[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.

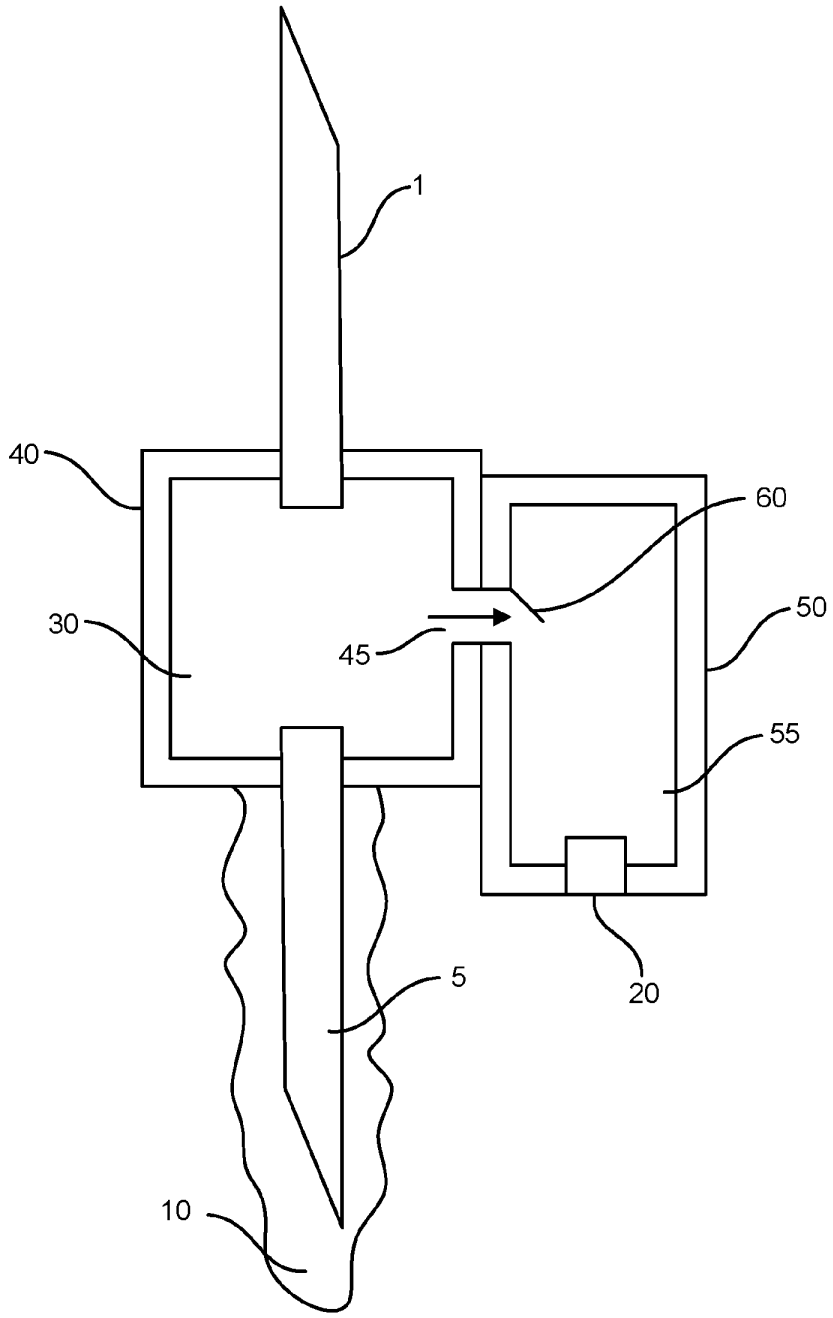


FIG. 1

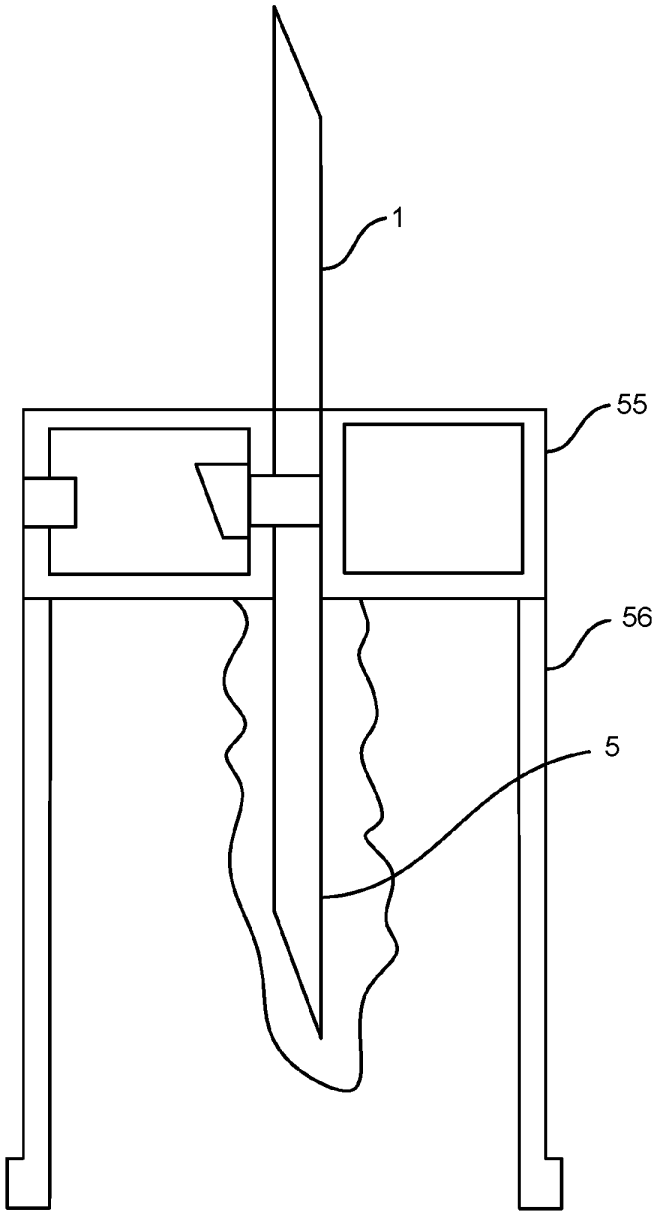


FIG. 2

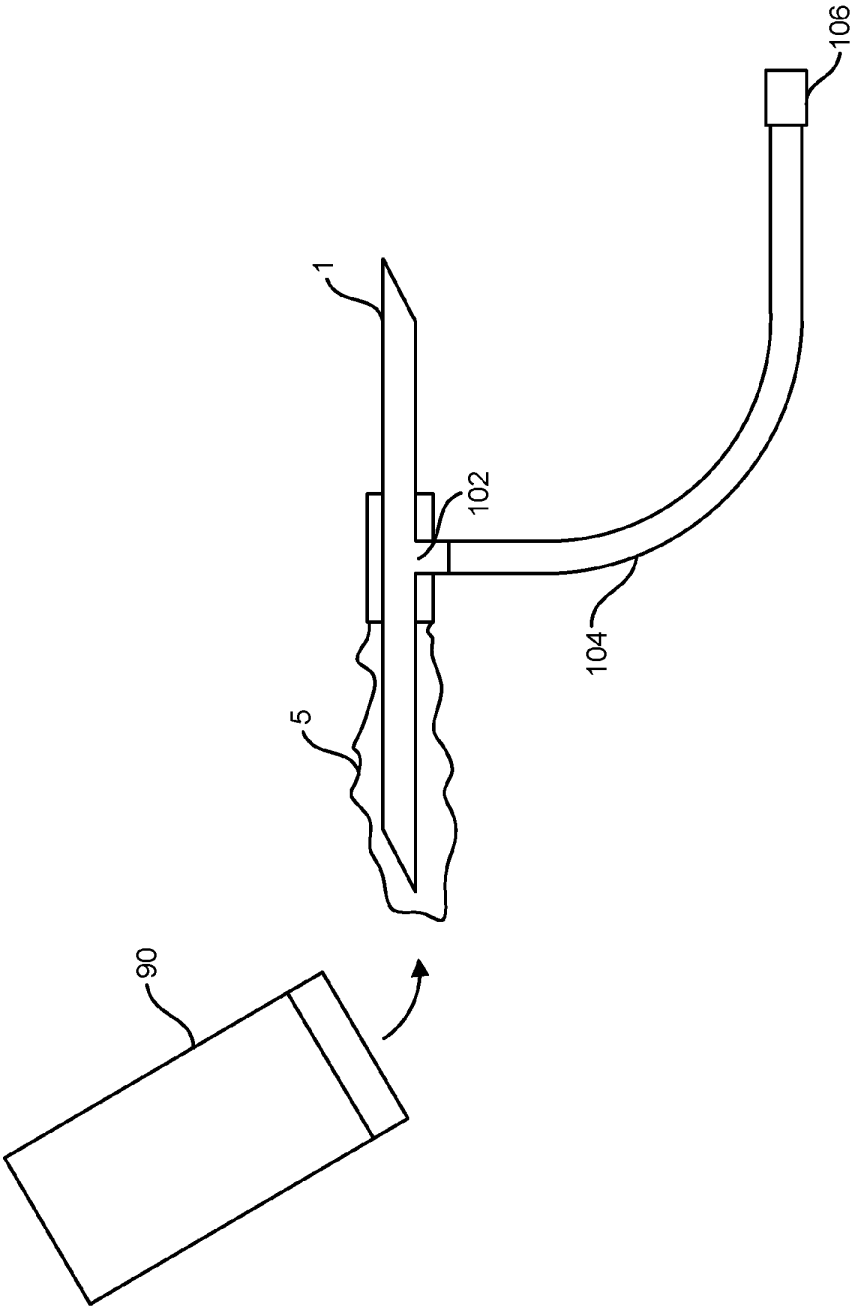


FIG. 3

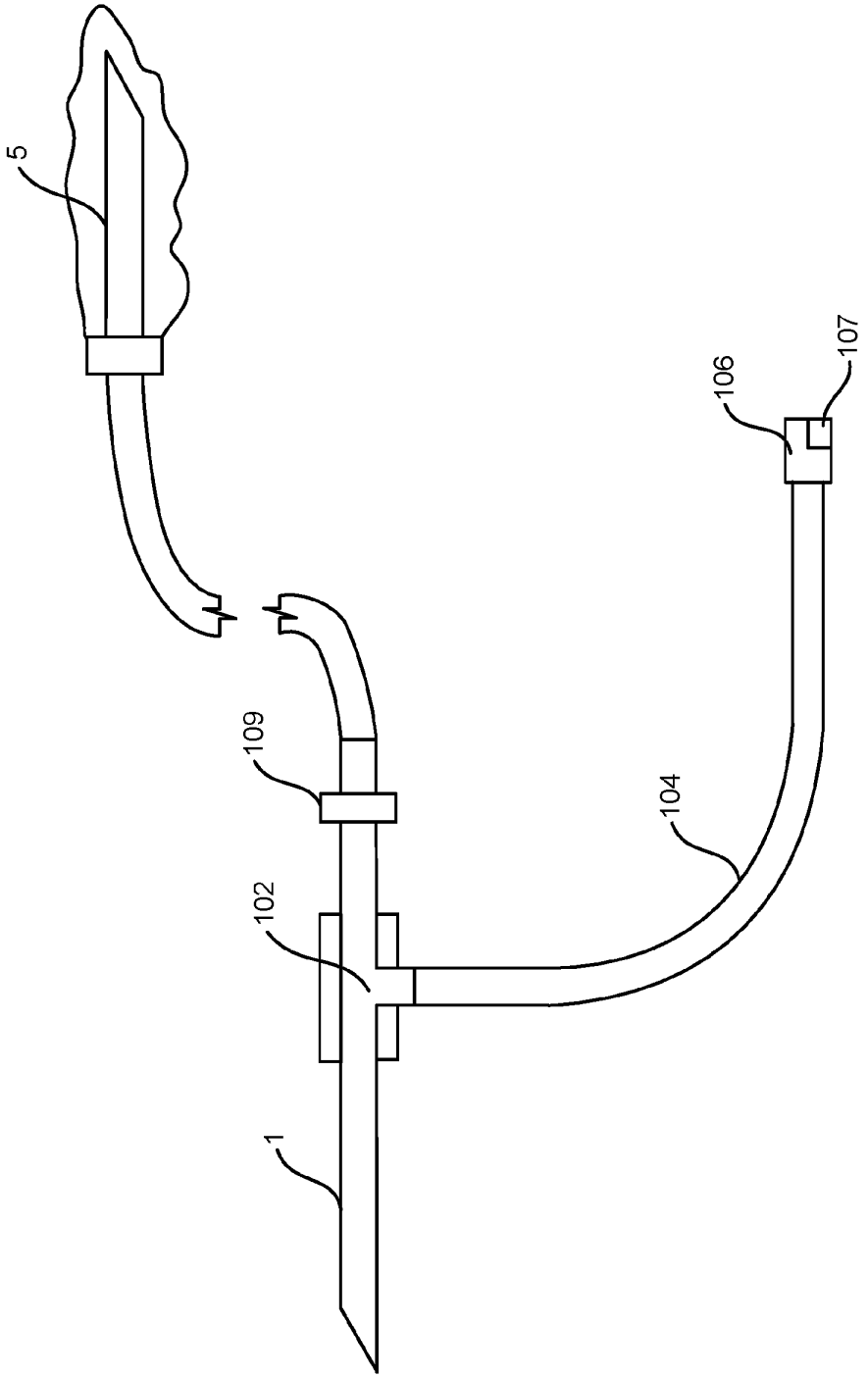


FIG. 4

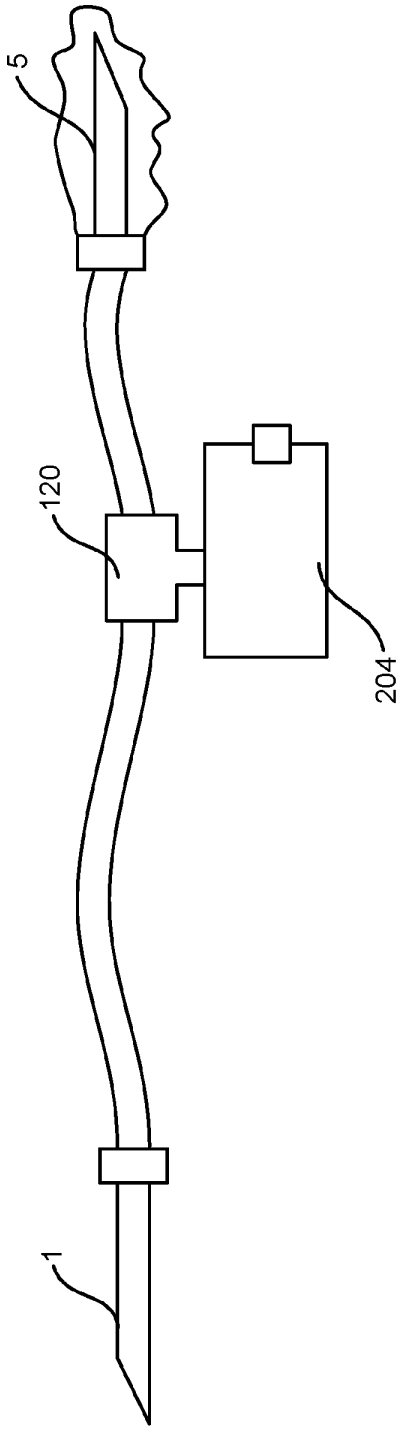


FIG. 5

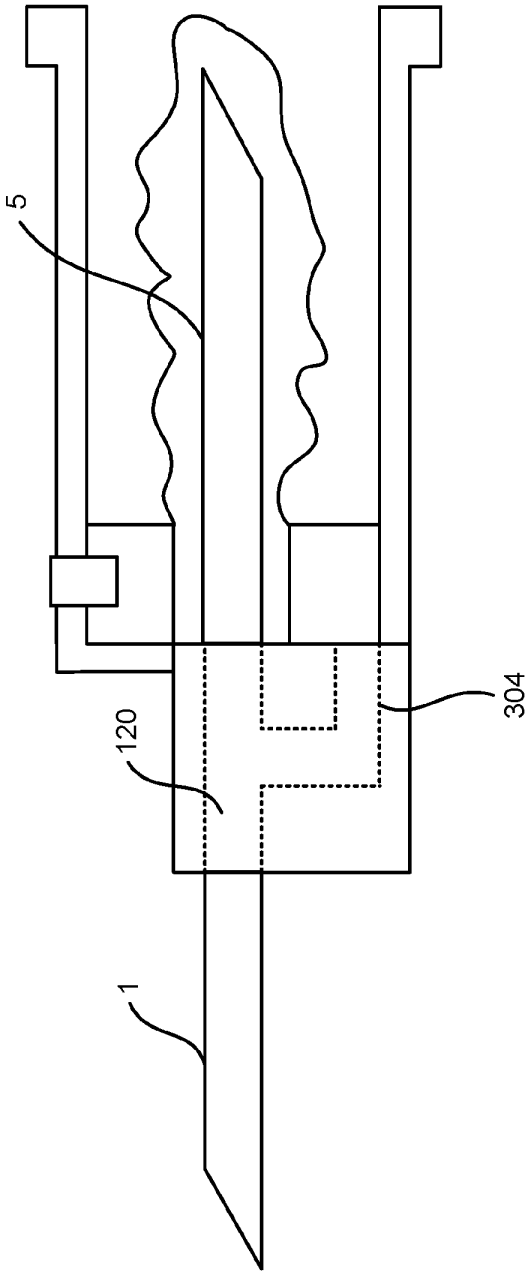


FIG. 6

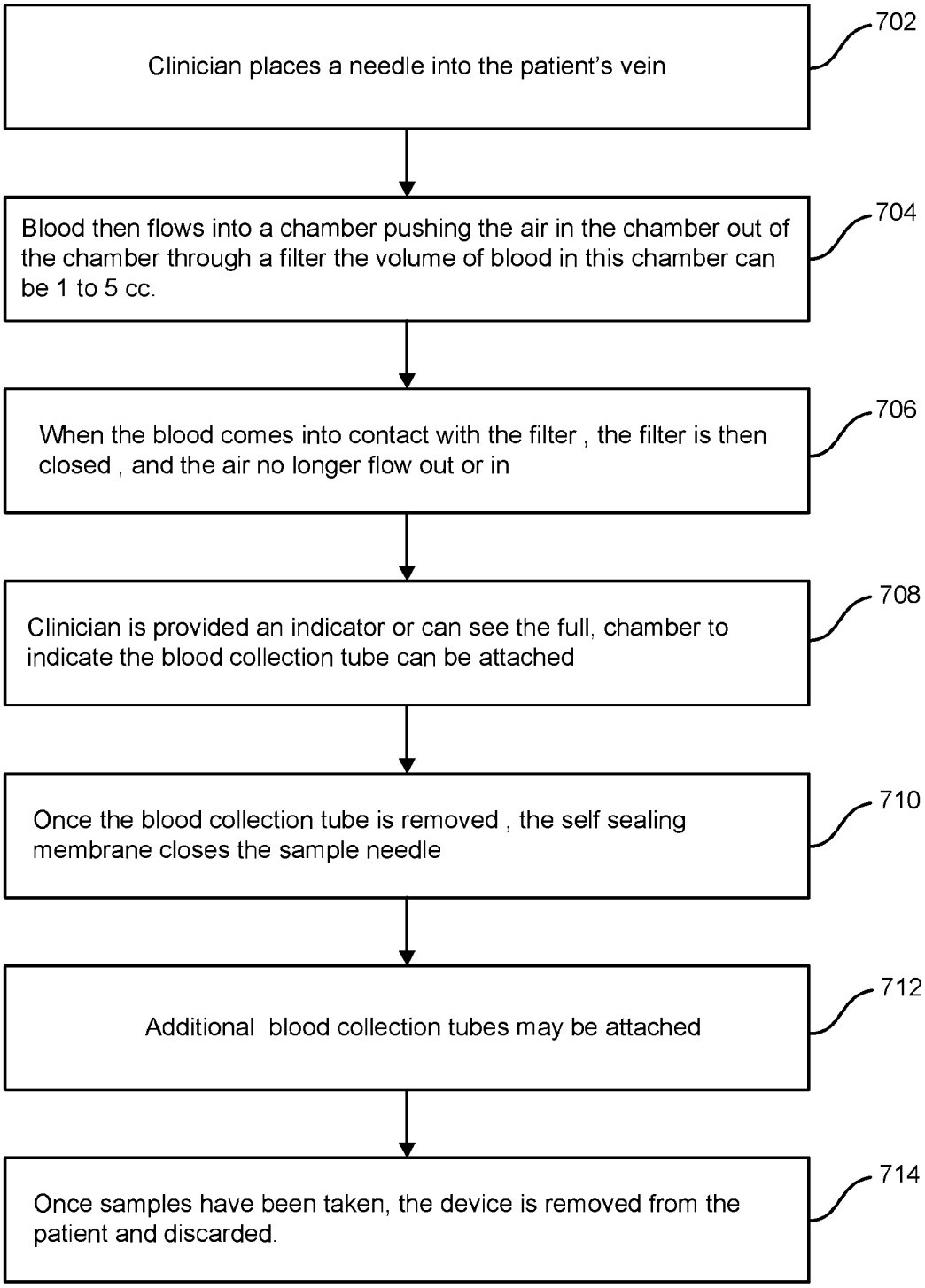

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air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

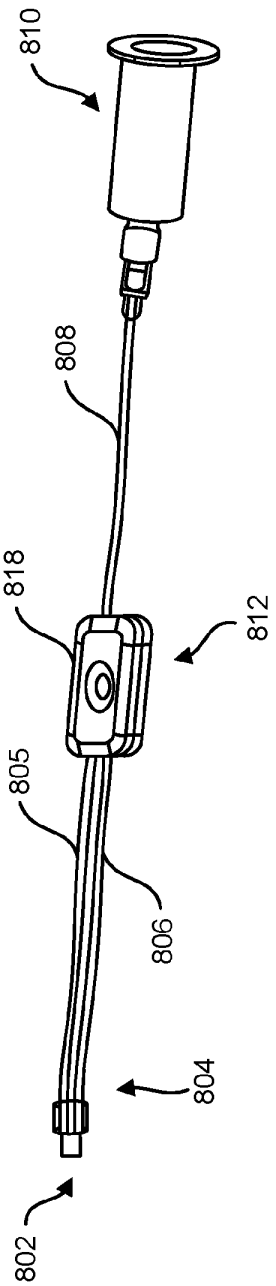


FIG. 8A

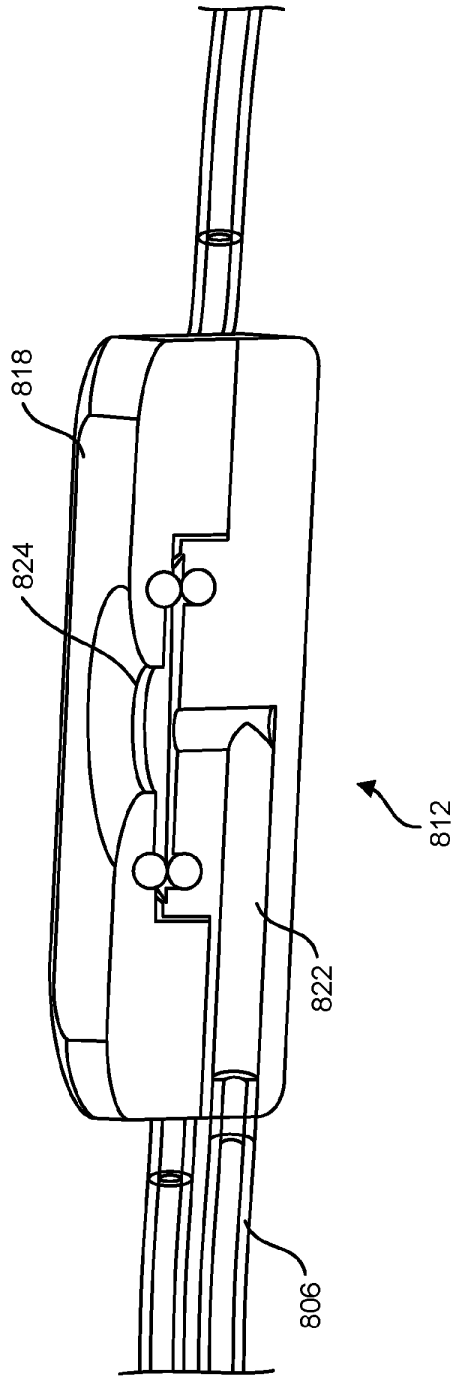


FIG. 8B

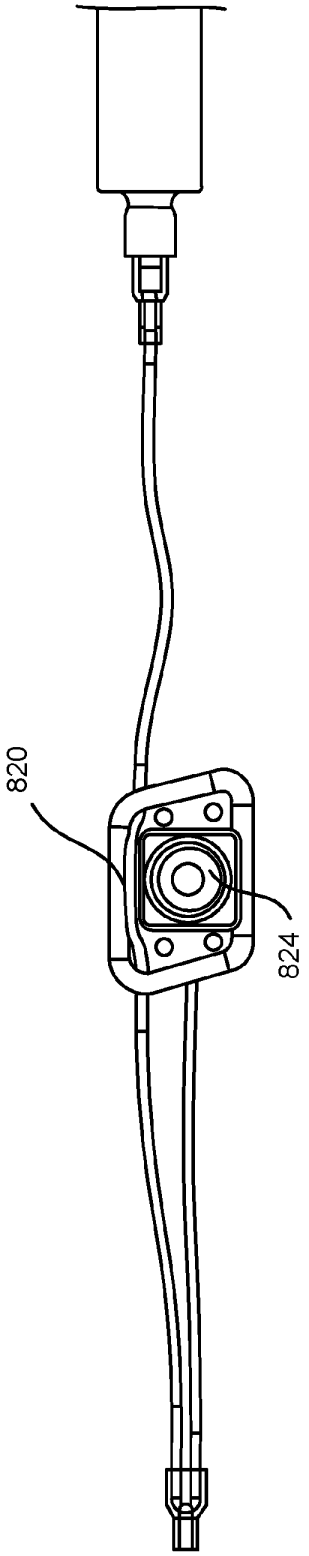


FIG. 8C

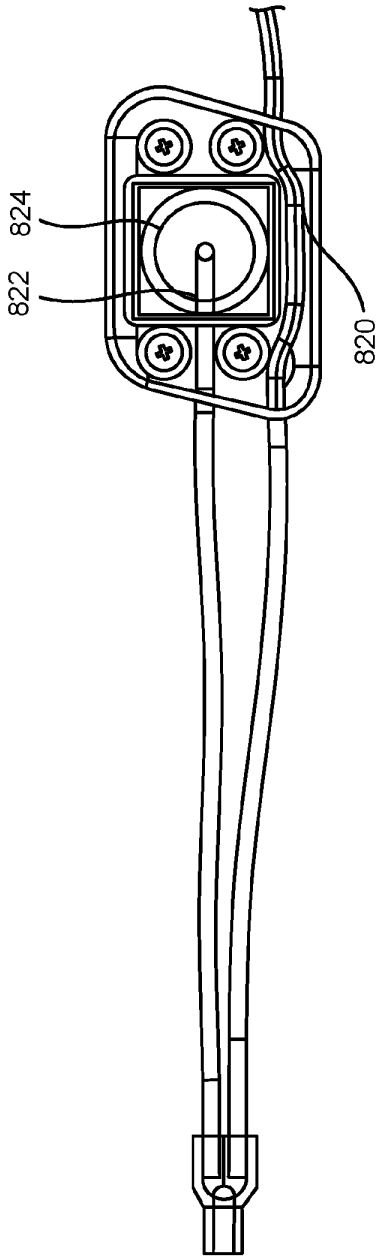


FIG. 8D

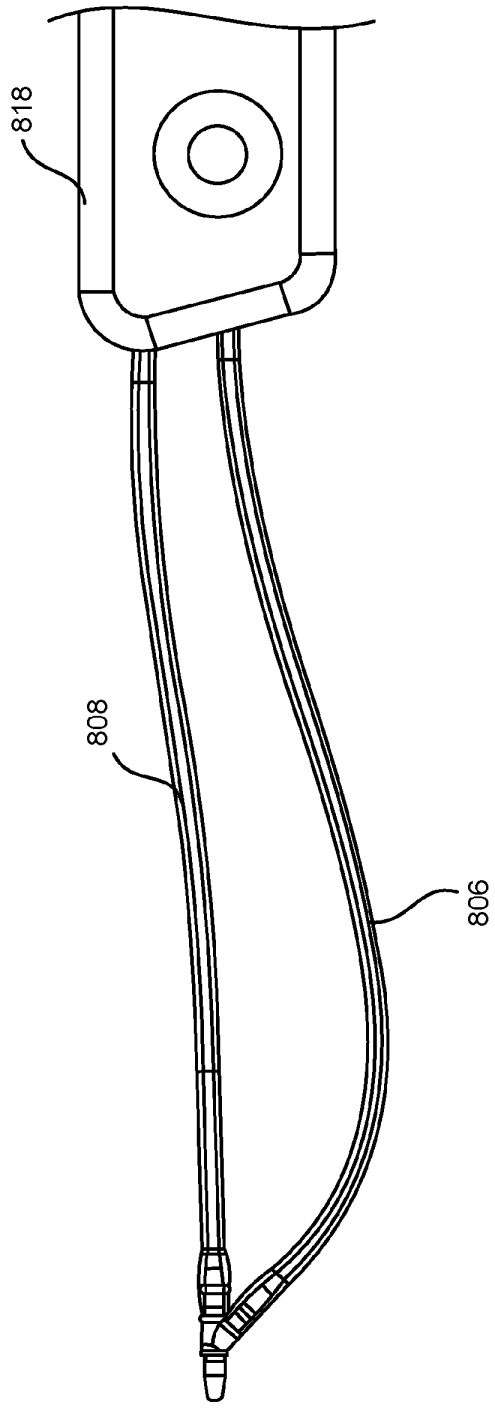


FIG. 8E

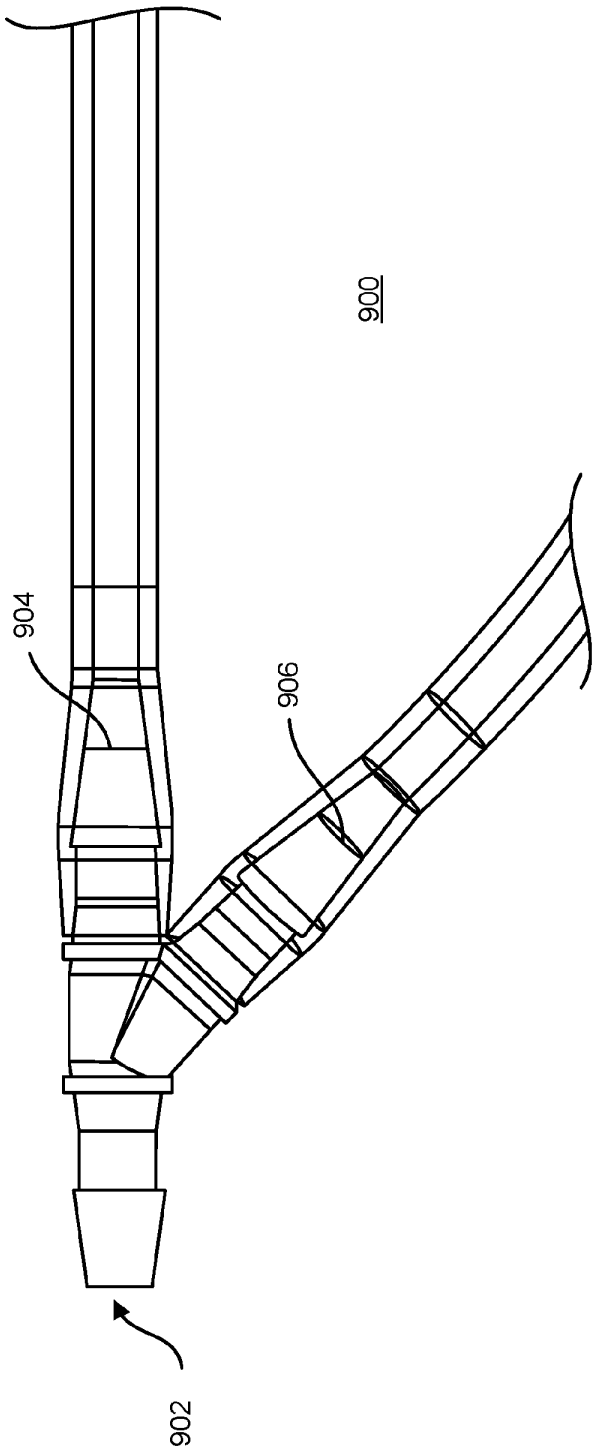


FIG. 9

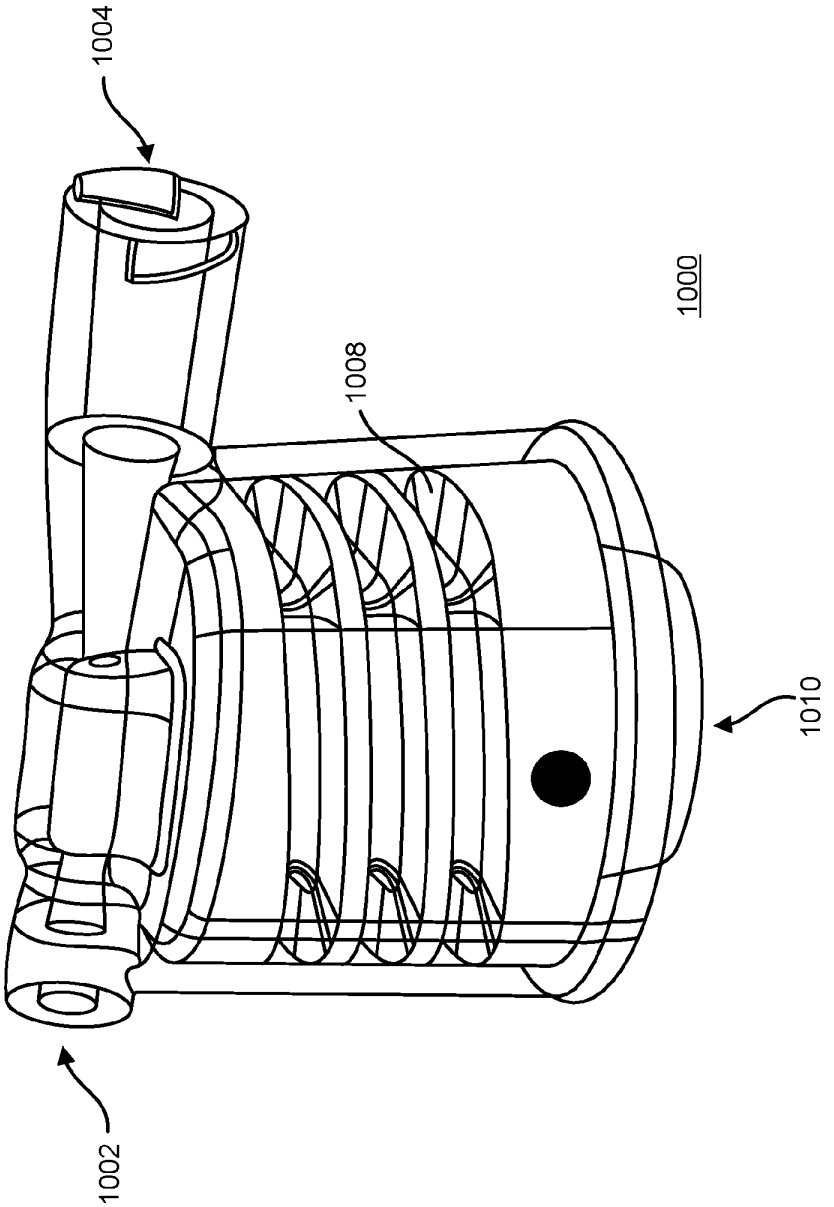


FIG. 10A

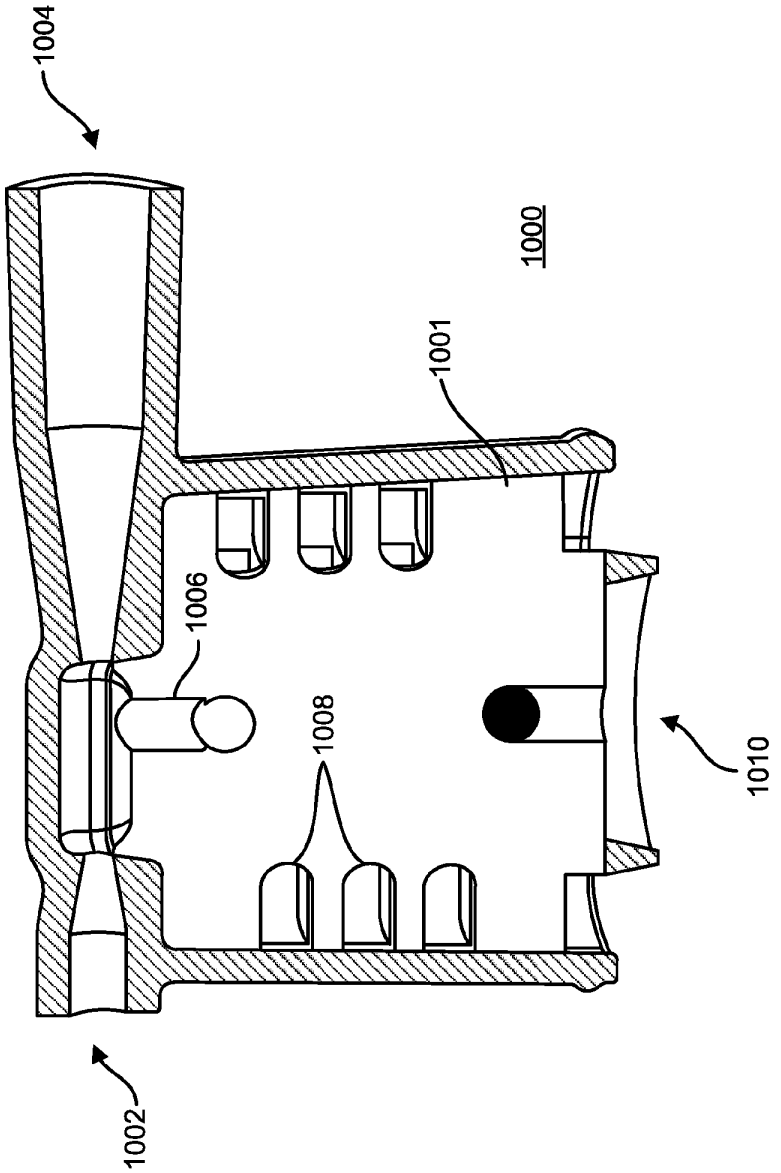


FIG. 10B

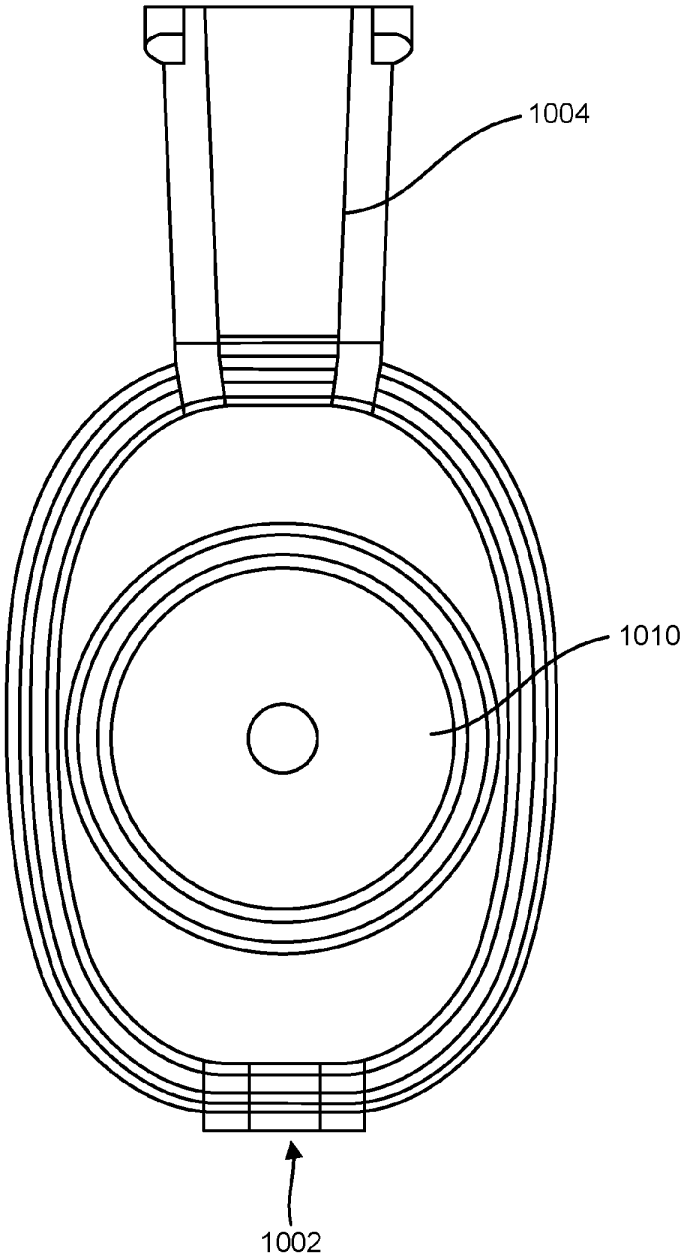


FIG. 10C

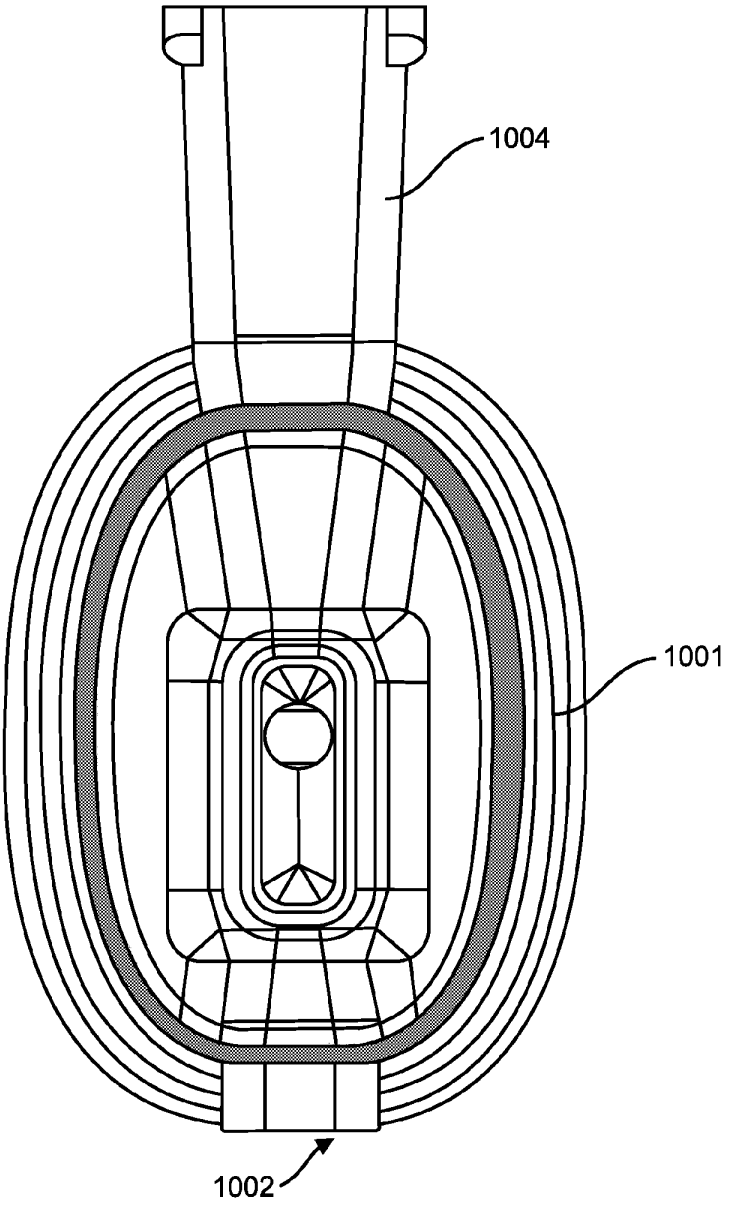


FIG. 10D

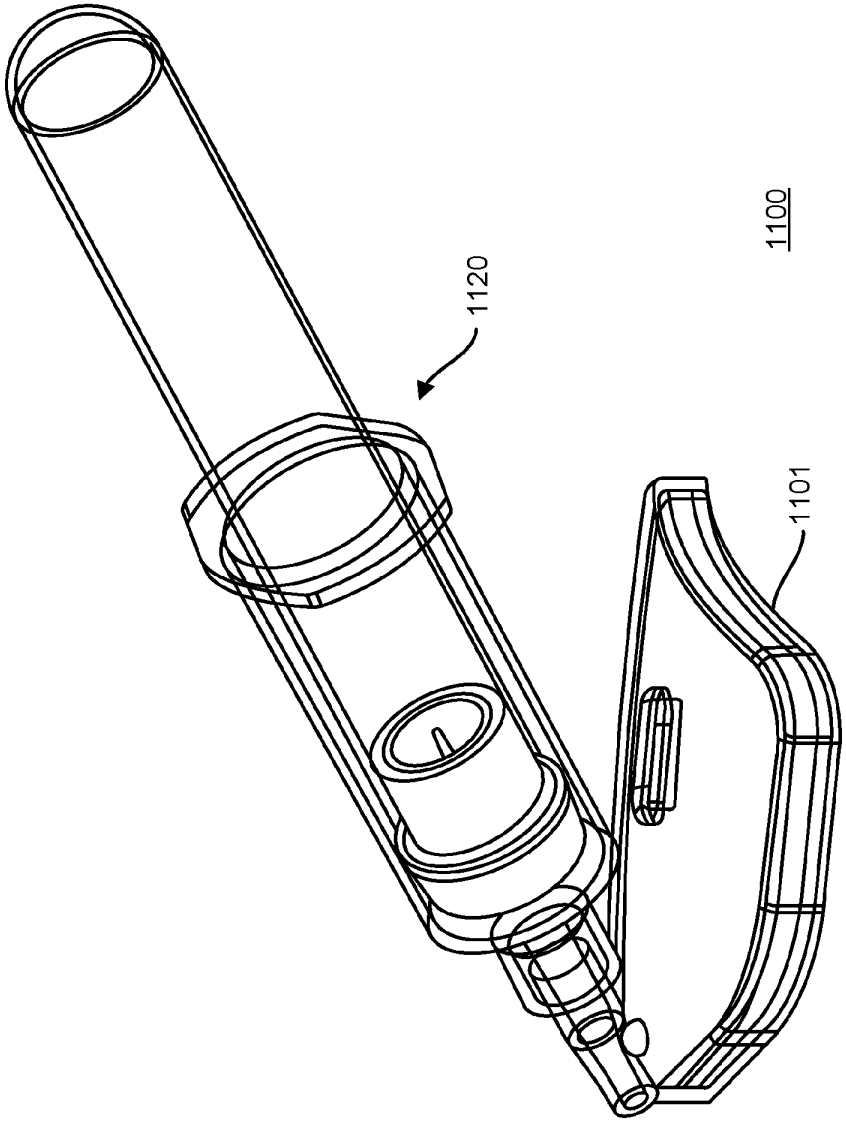


FIG. 11A

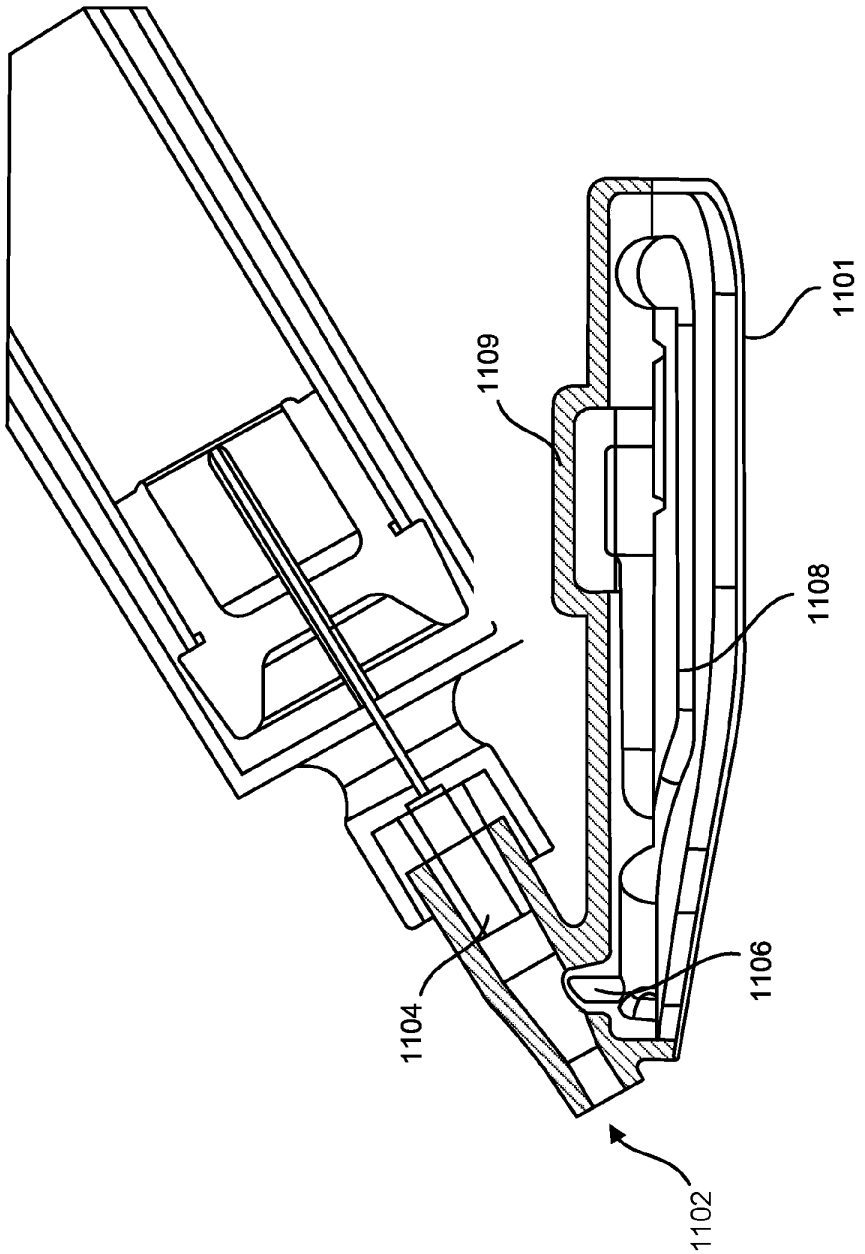


FIG. 11B

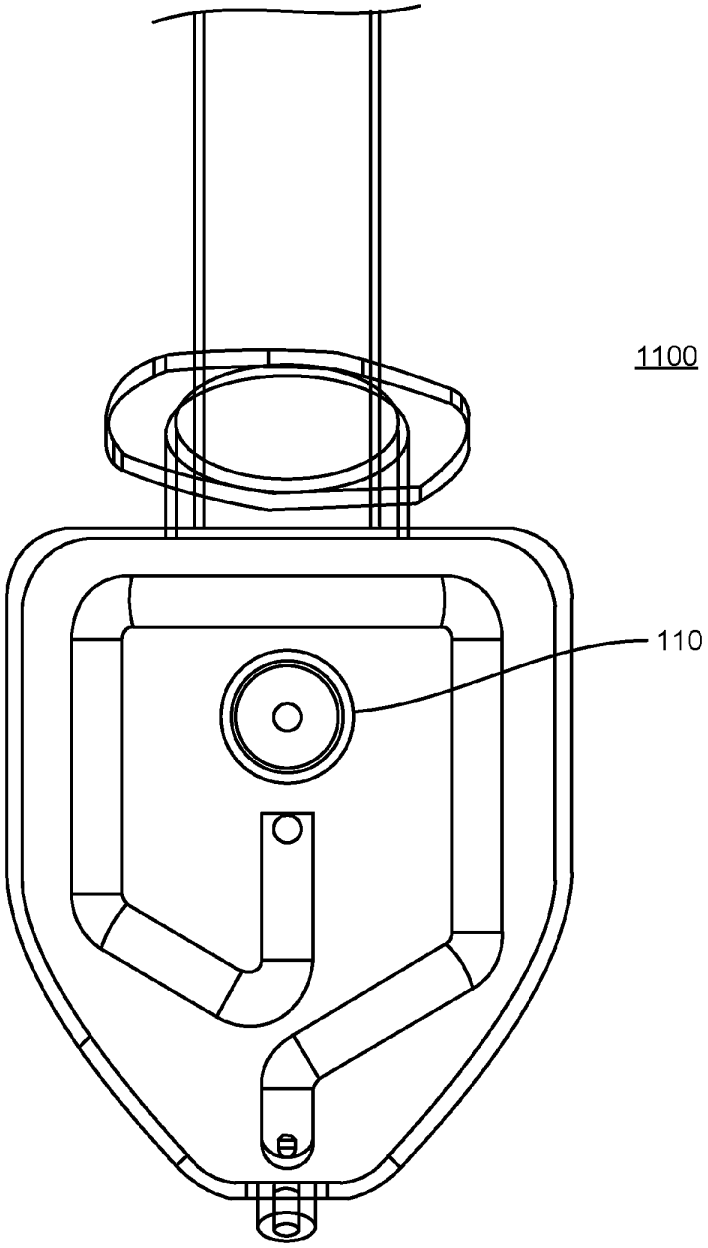


FIG. 11C

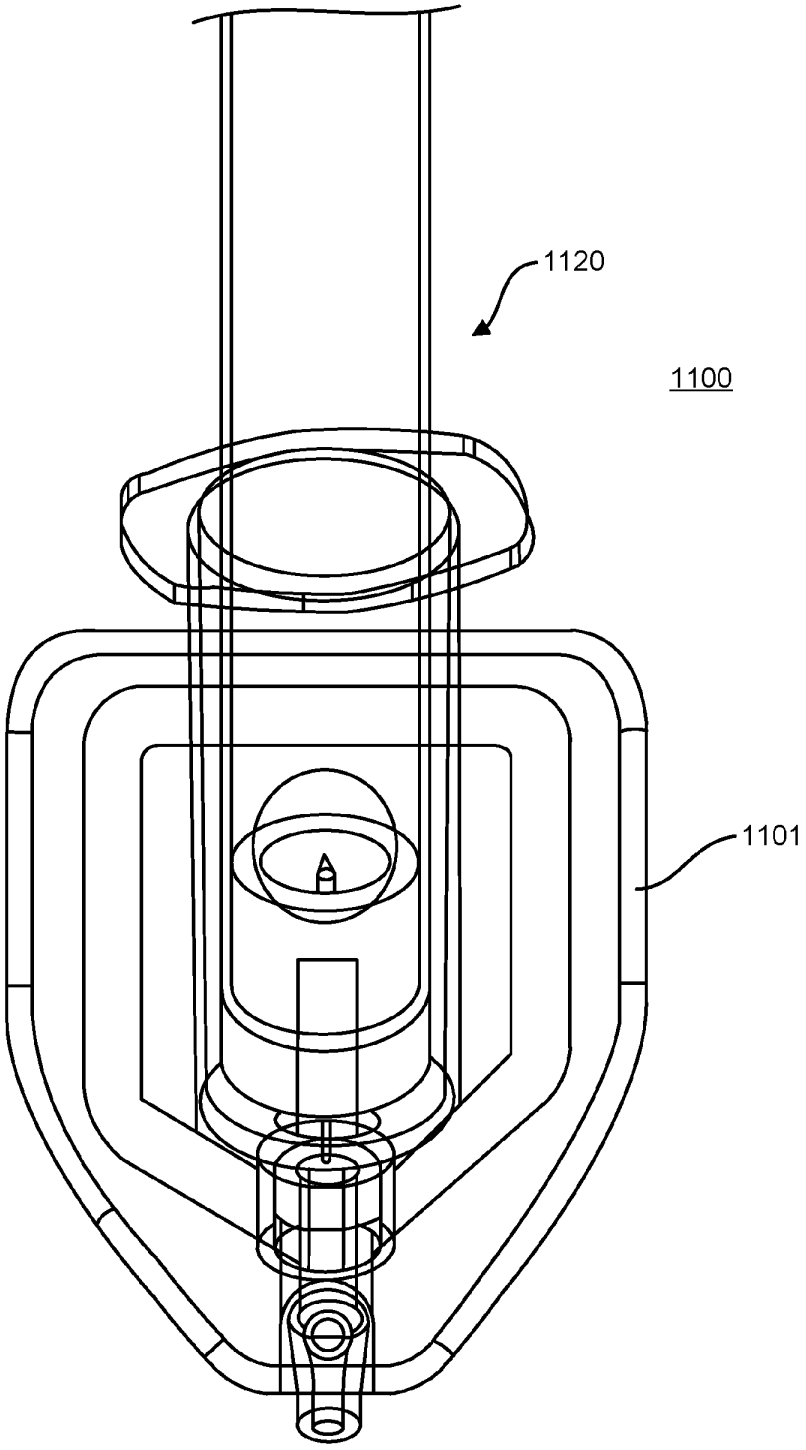


FIG. 11D

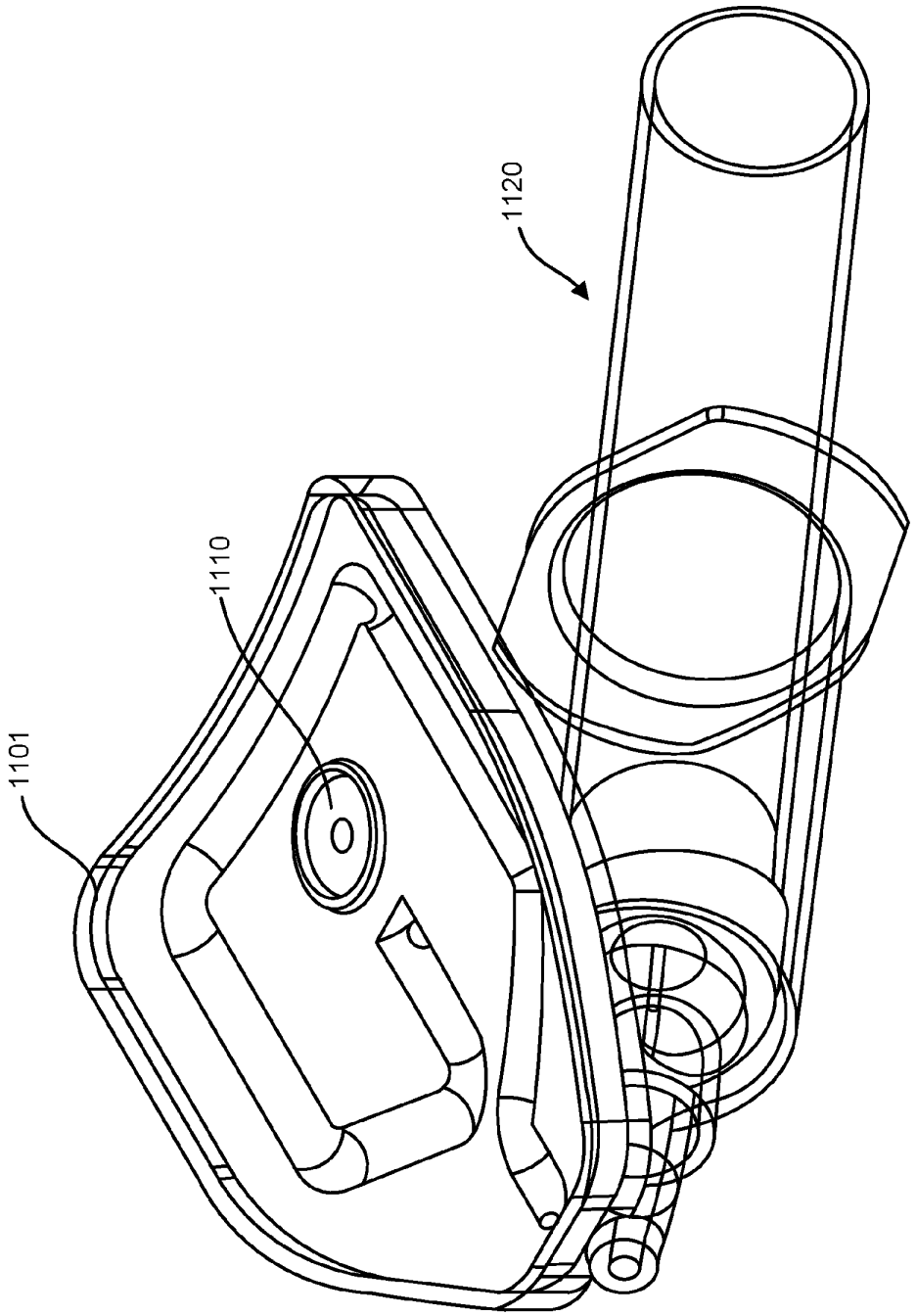


FIG. 11E

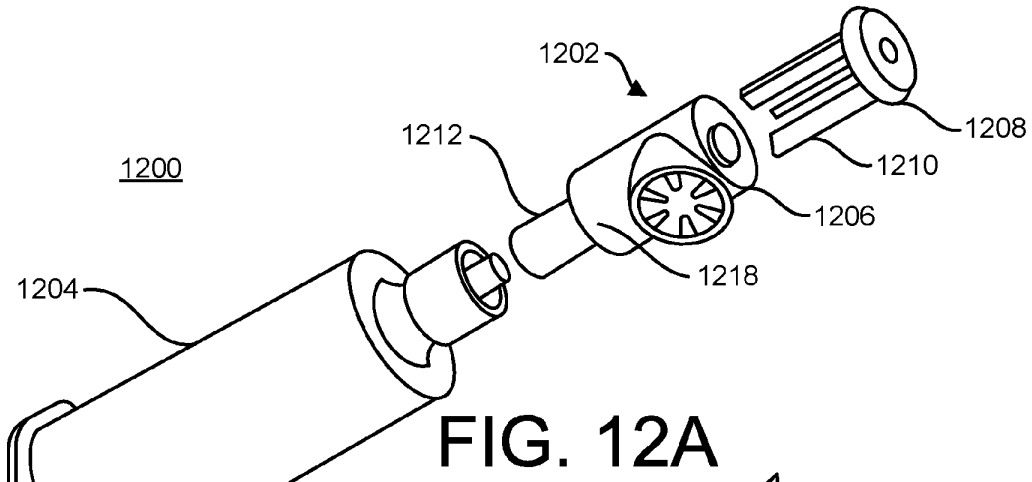


FIG. 12A

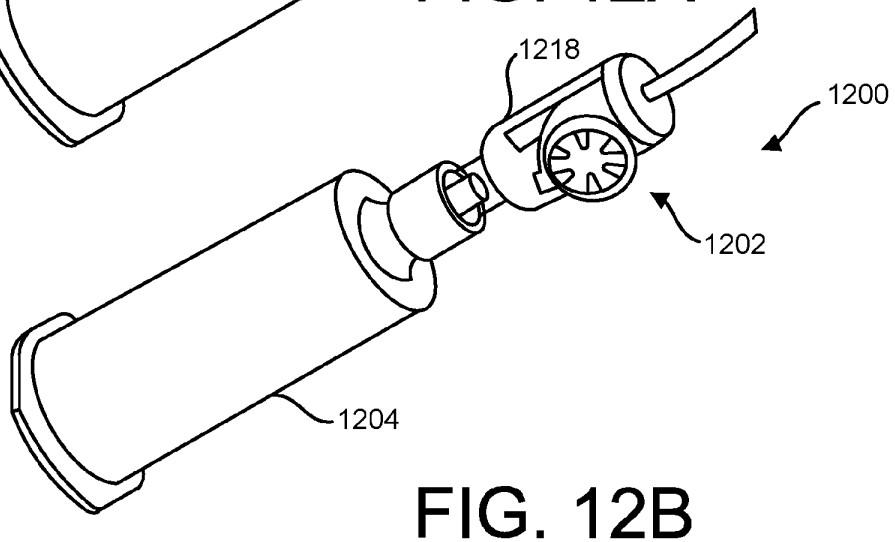


FIG. 12B

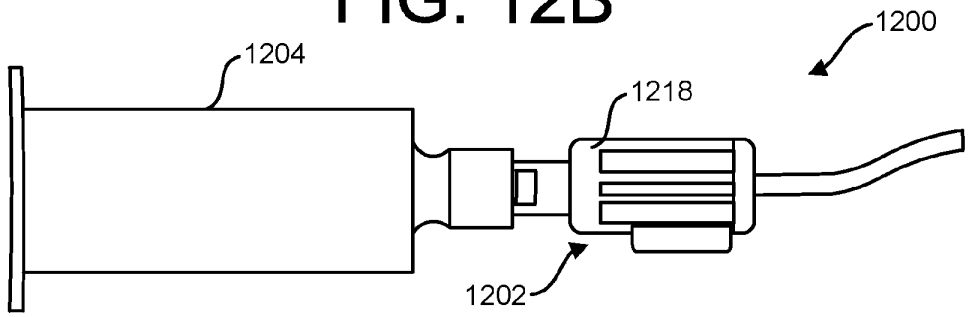


FIG. 12C

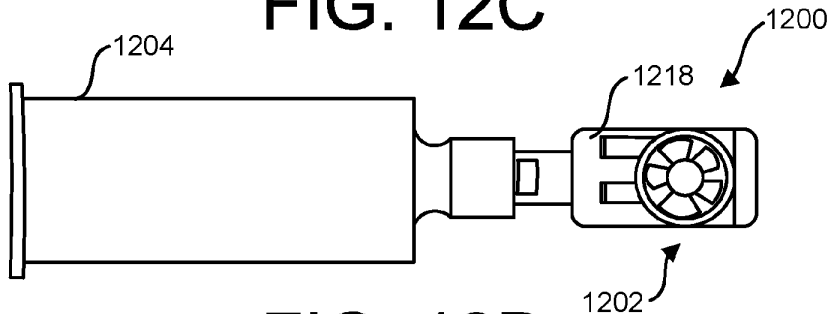


FIG. 12D

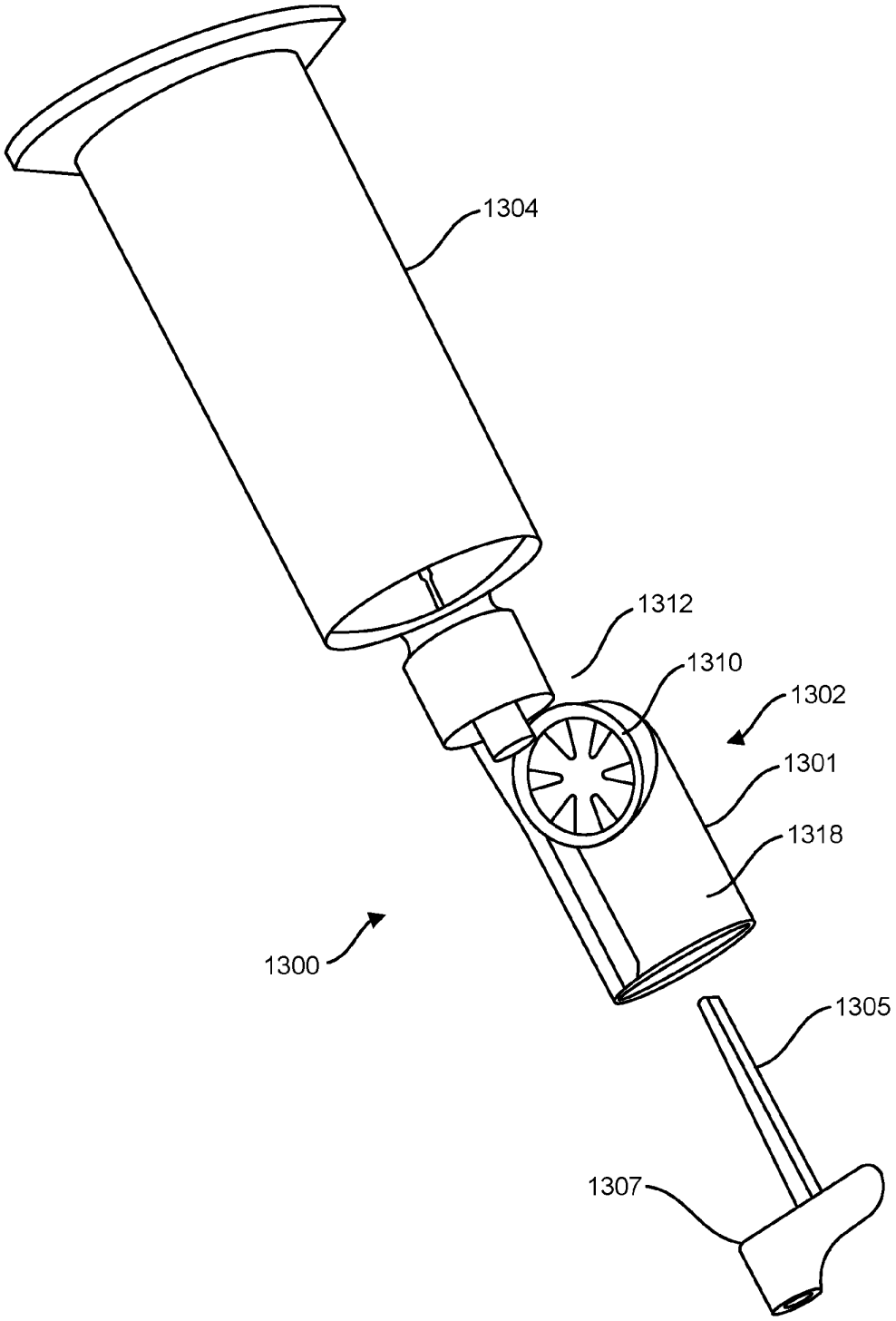


FIG. 13A

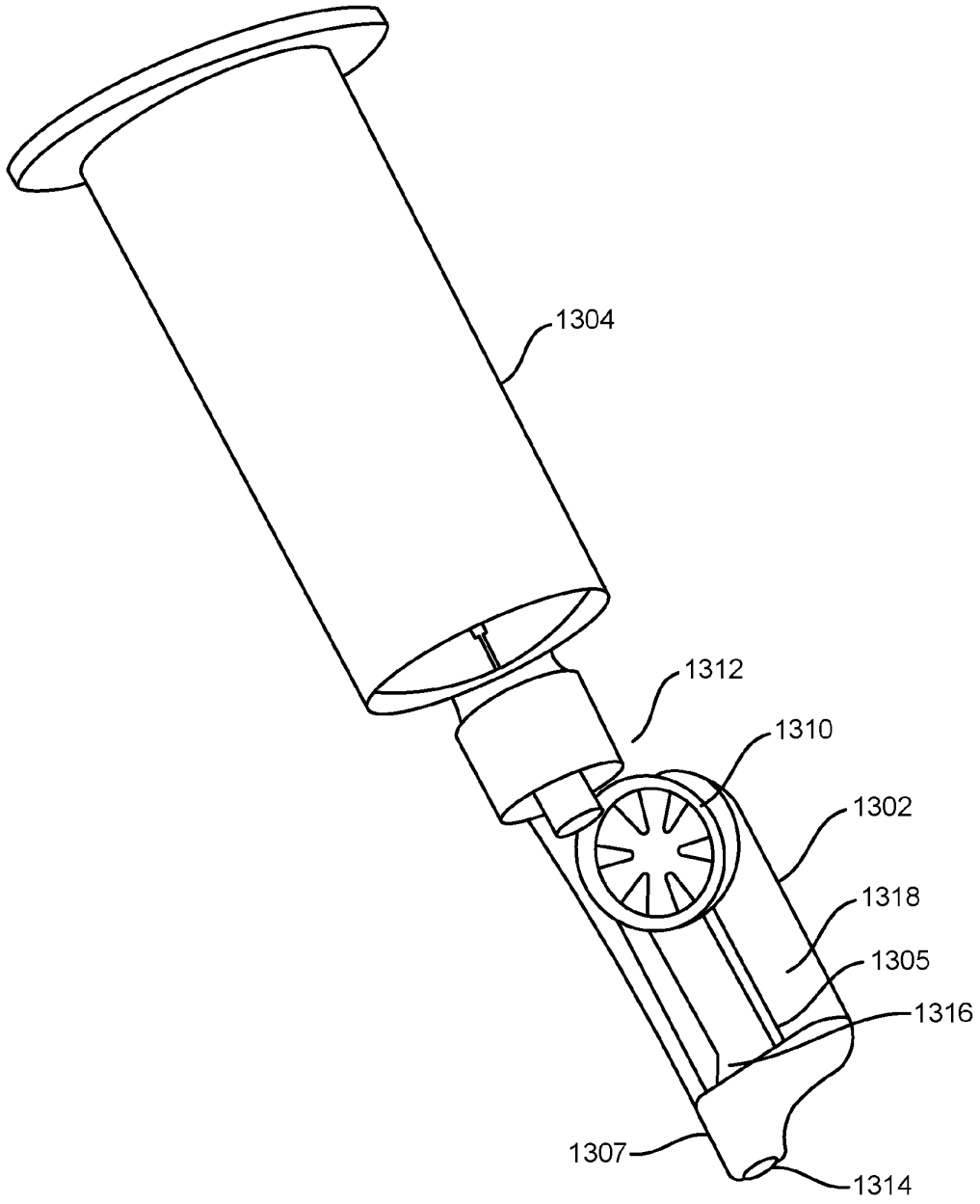


FIG. 13B

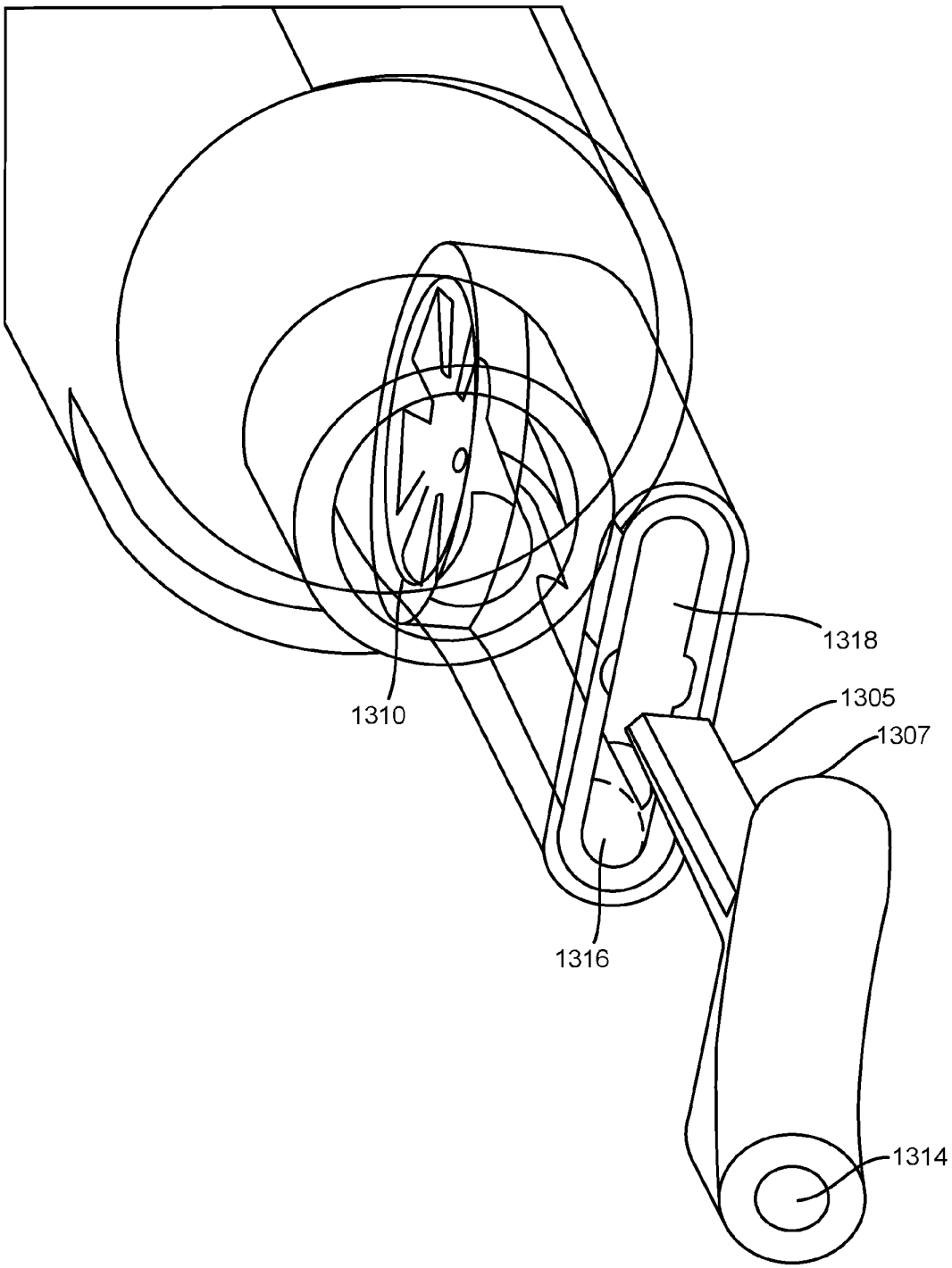


FIG. 13C

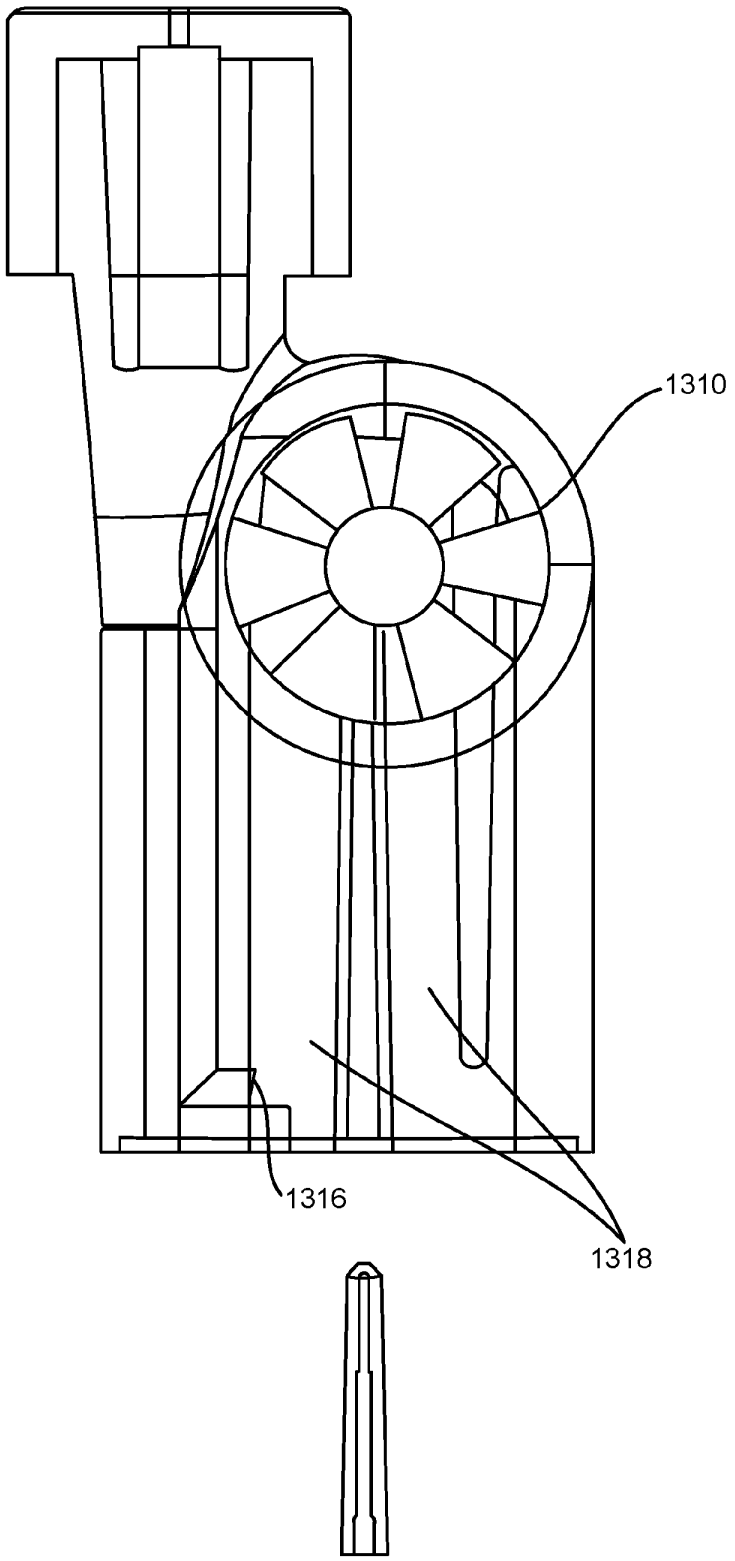


FIG. 13D

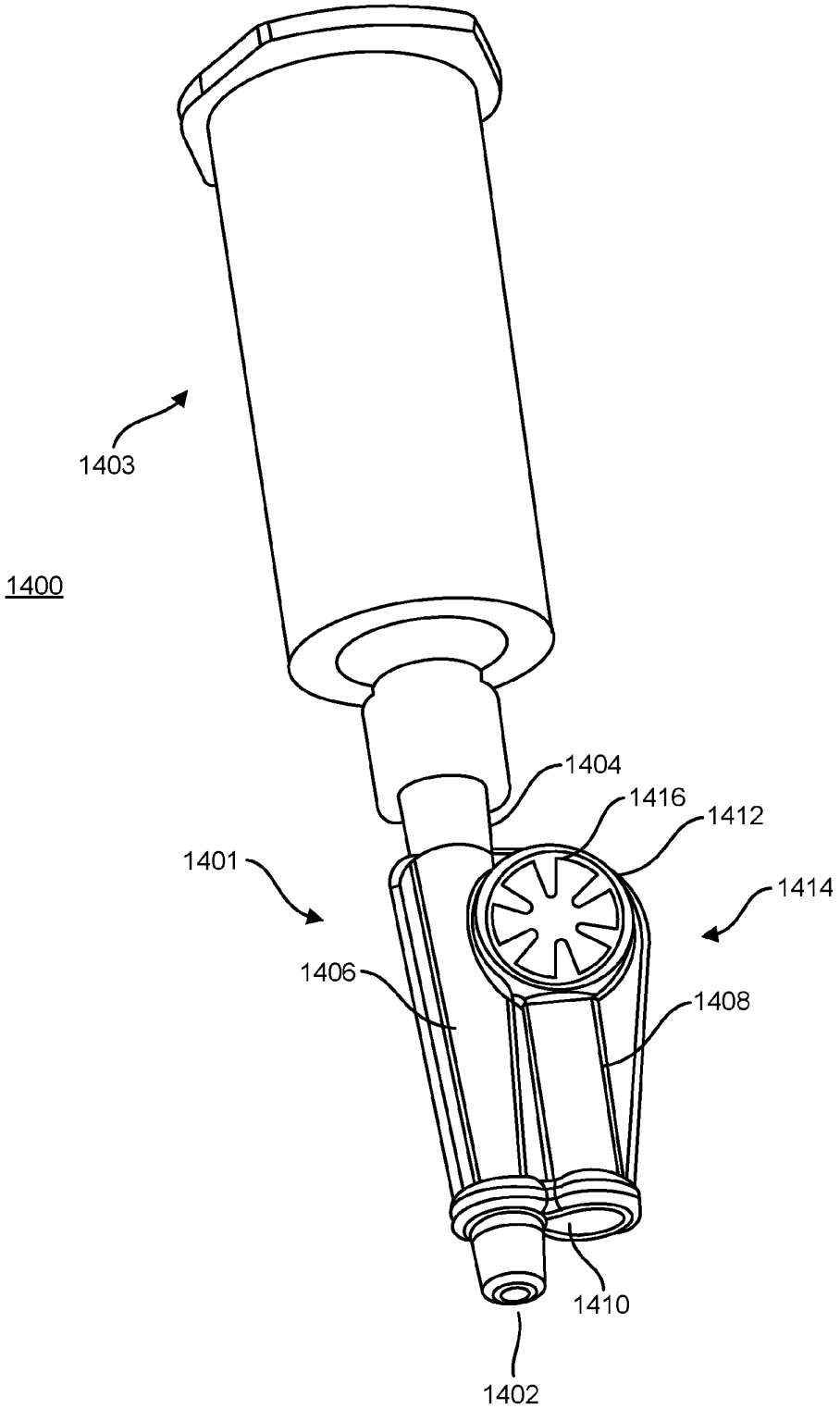


FIG. 14A

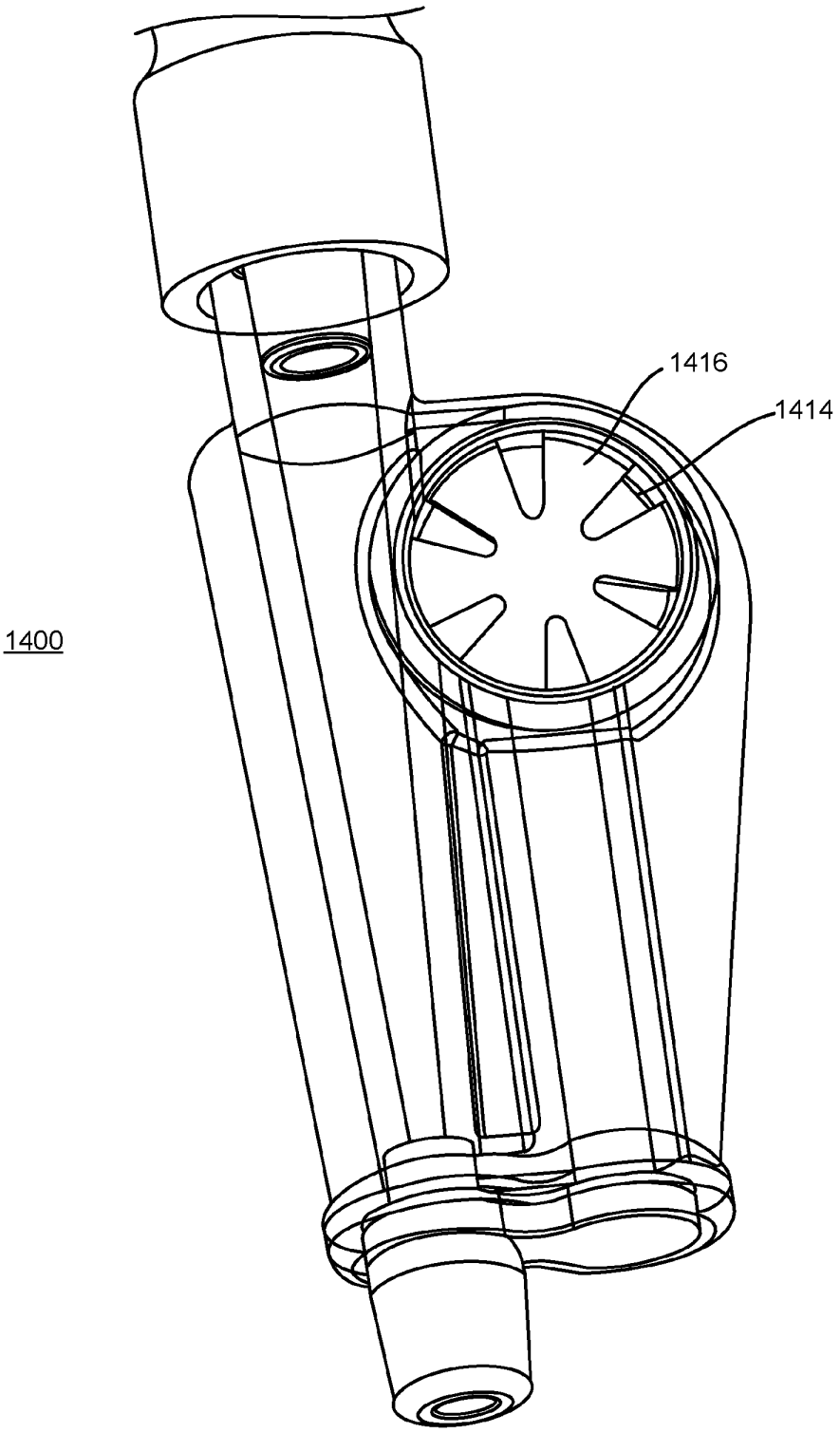


FIG. 14B

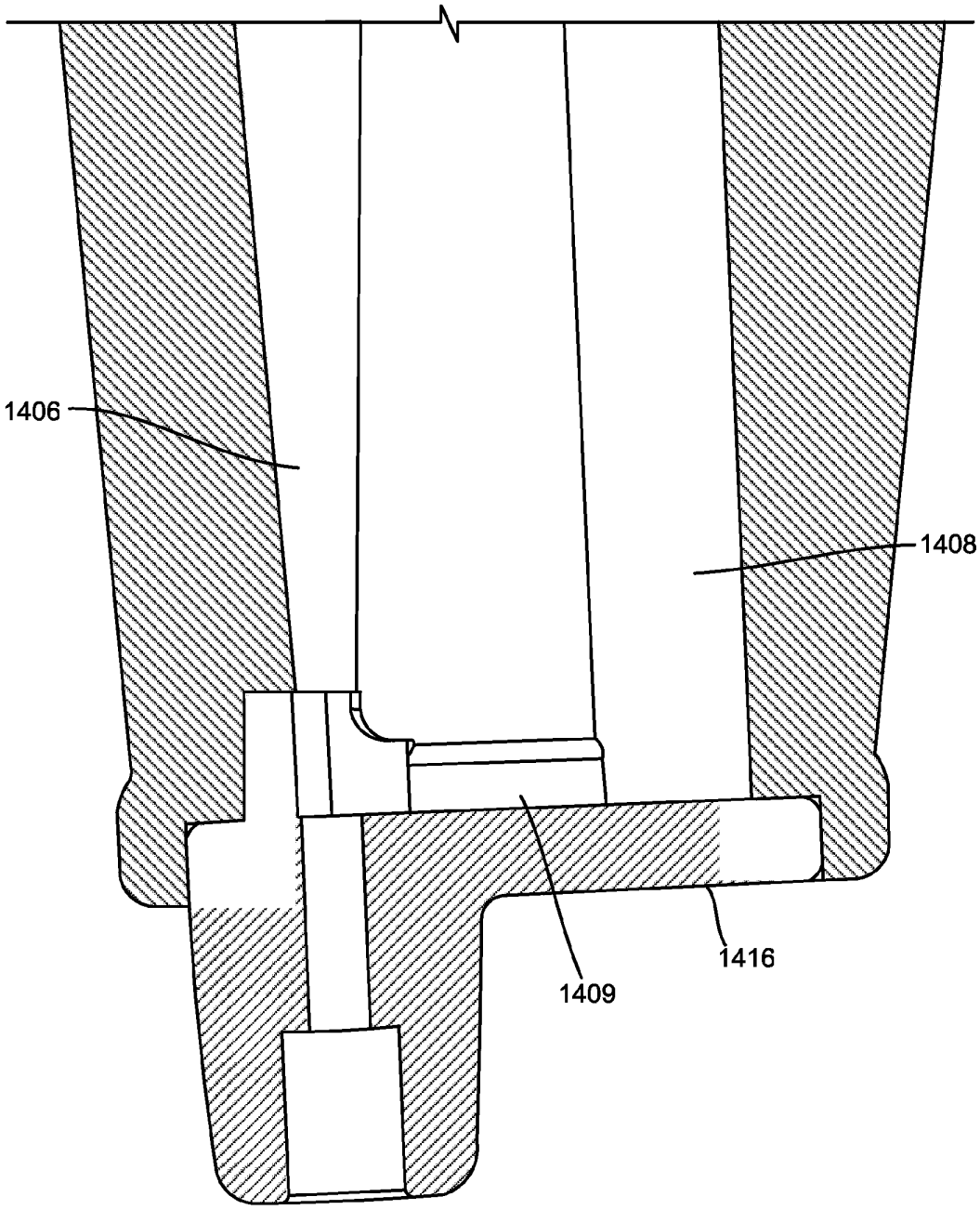


FIG. 14C

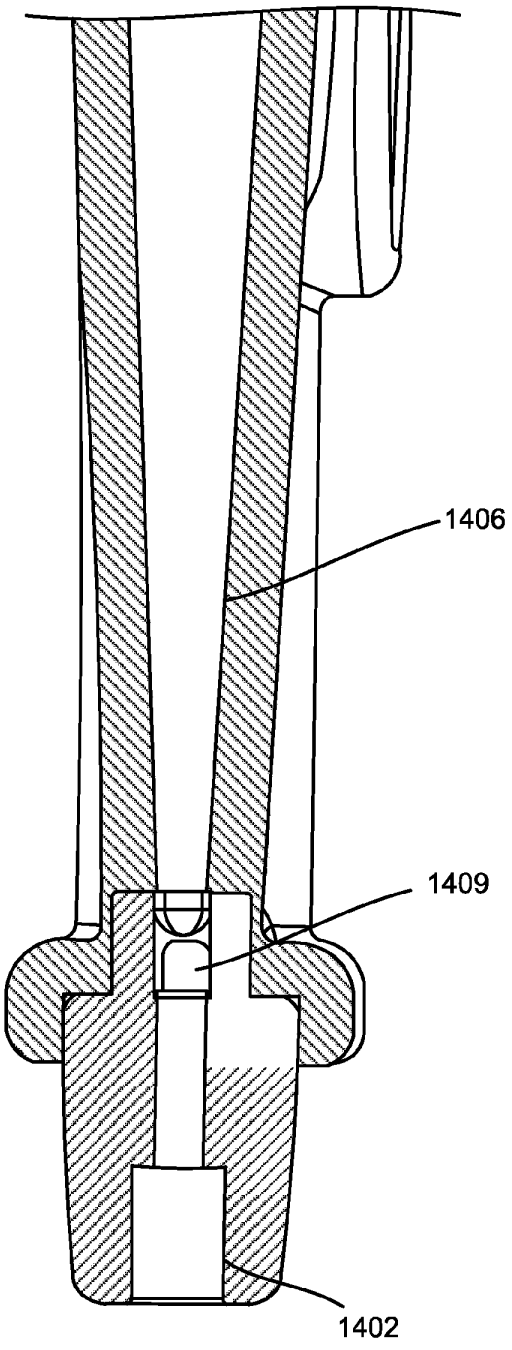


FIG. 14D

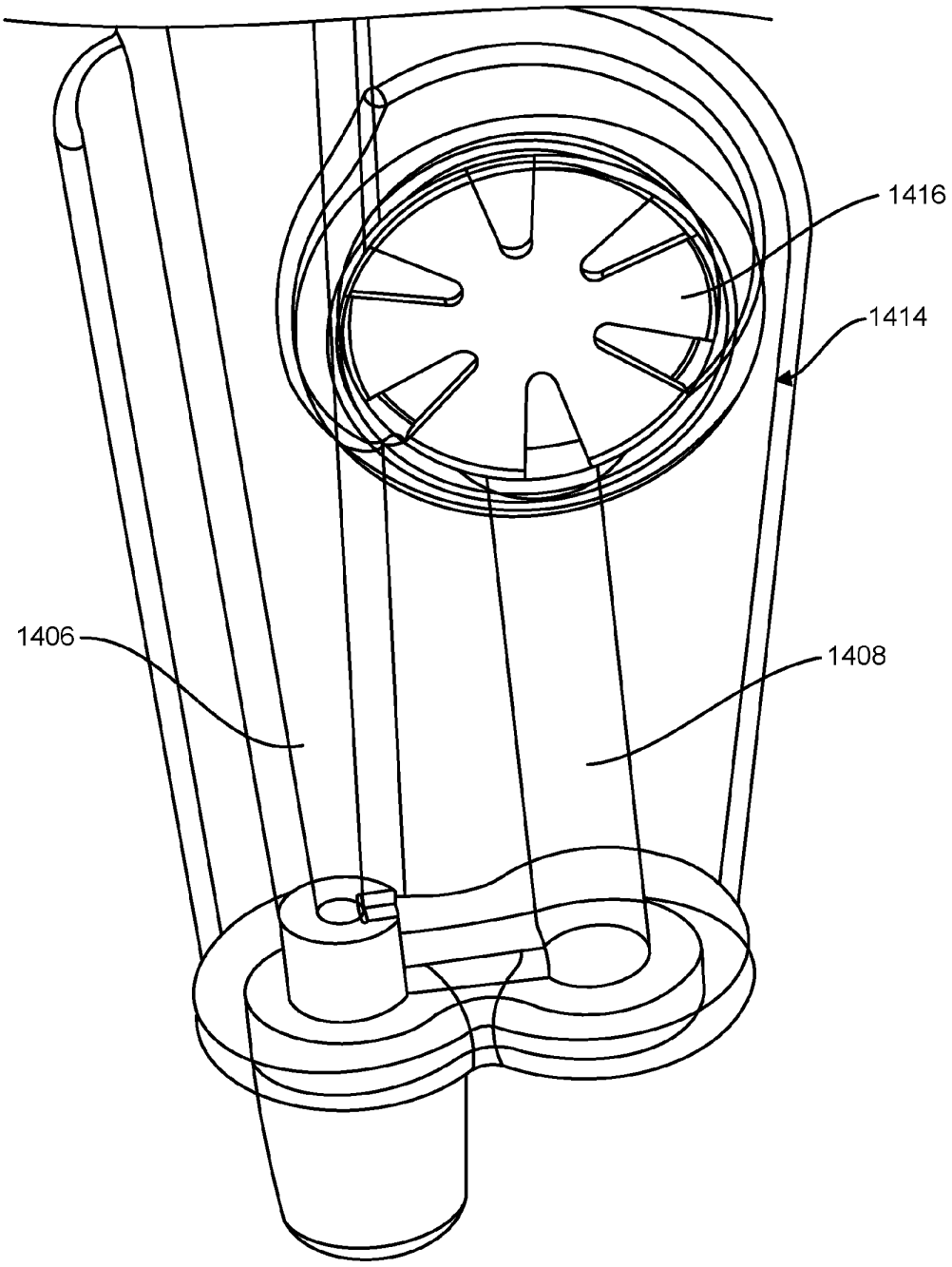


FIG. 14E

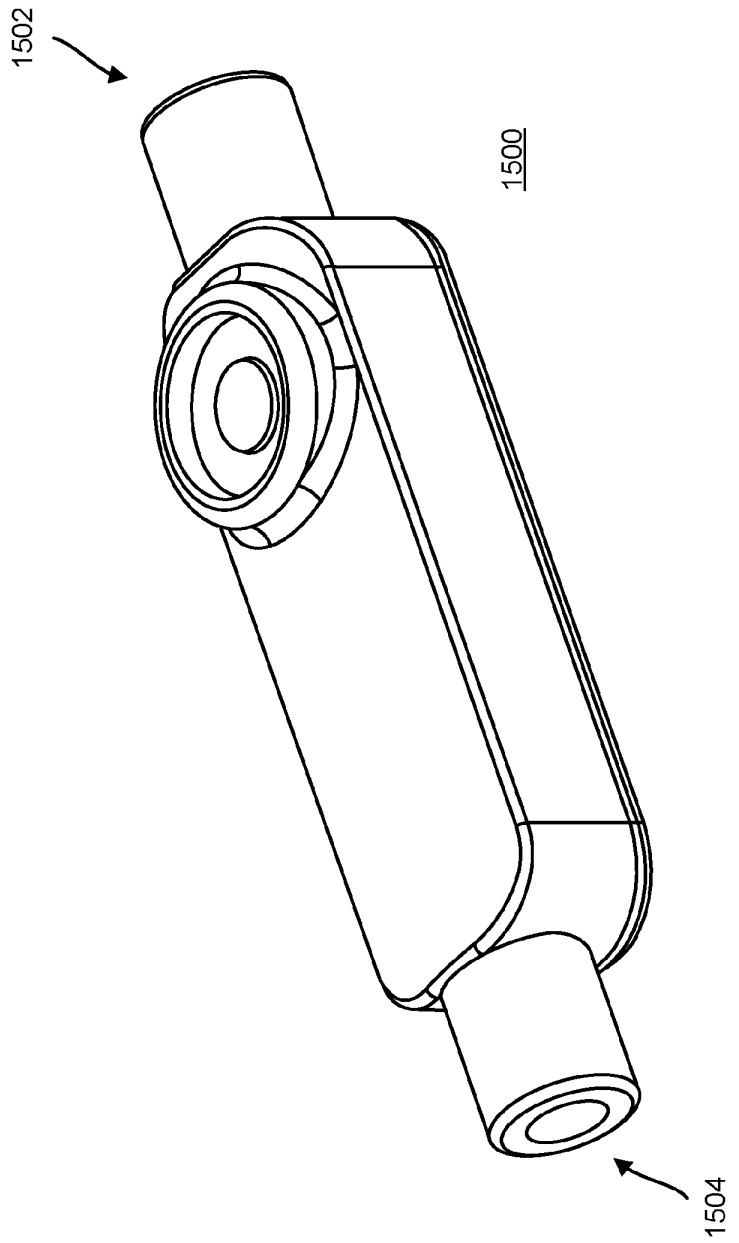


FIG. 15A

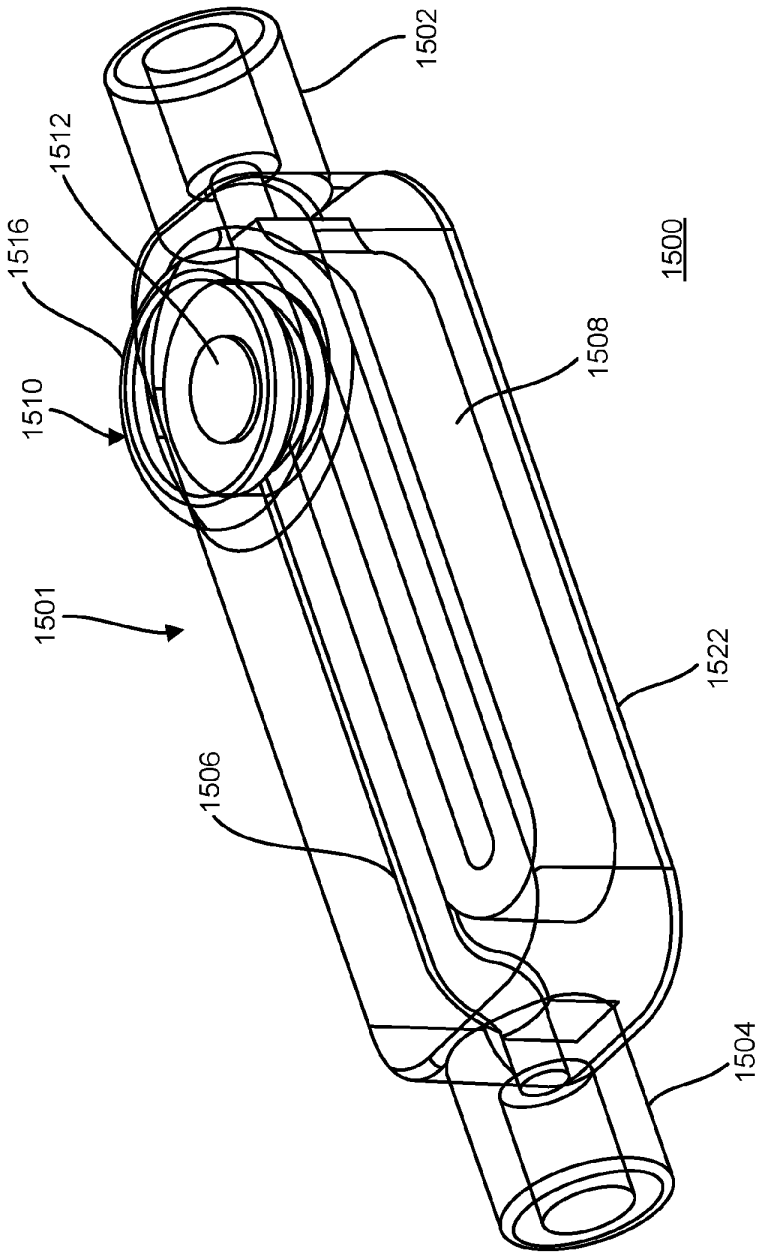


FIG. 15B

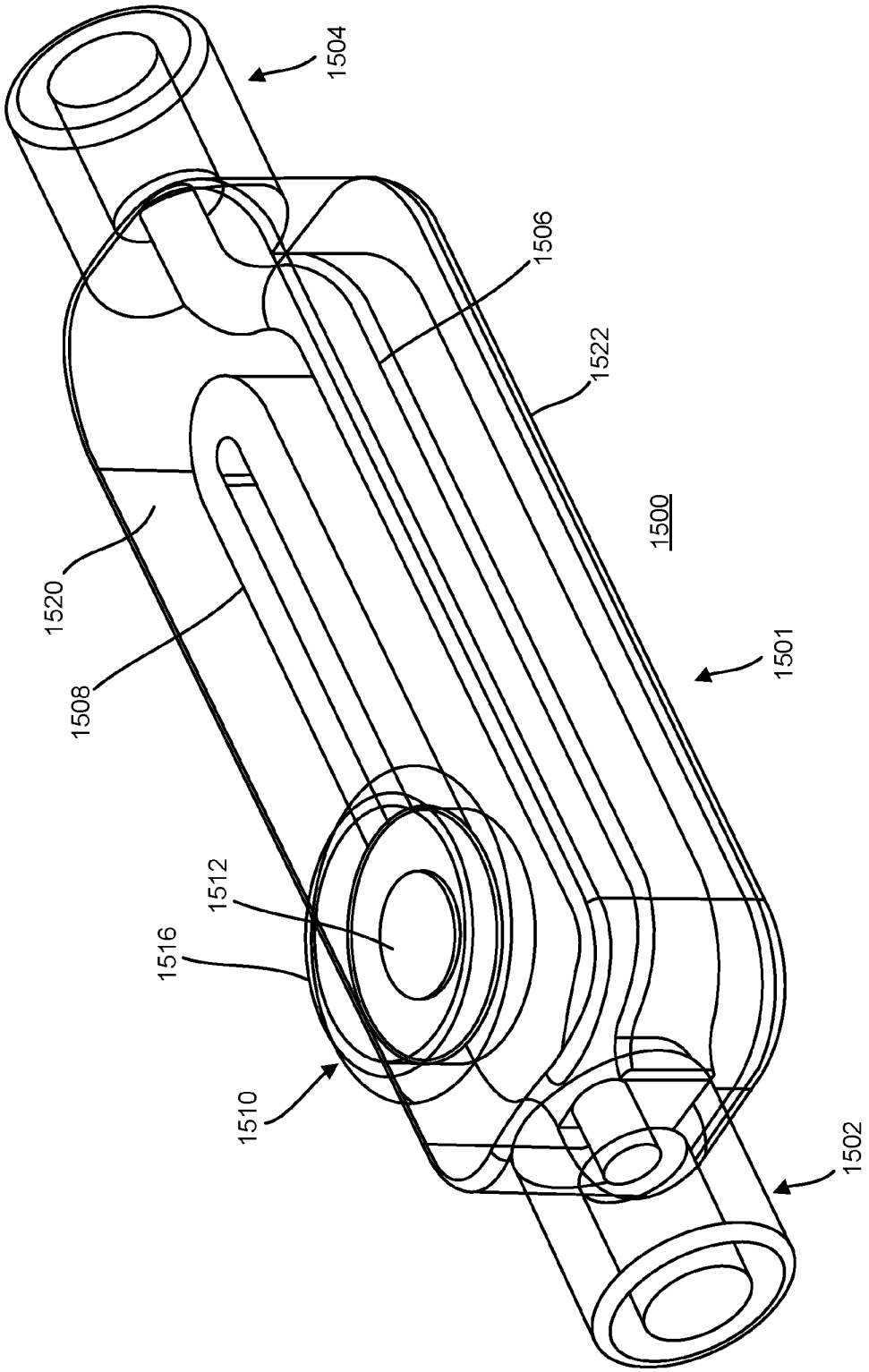


FIG. 15C

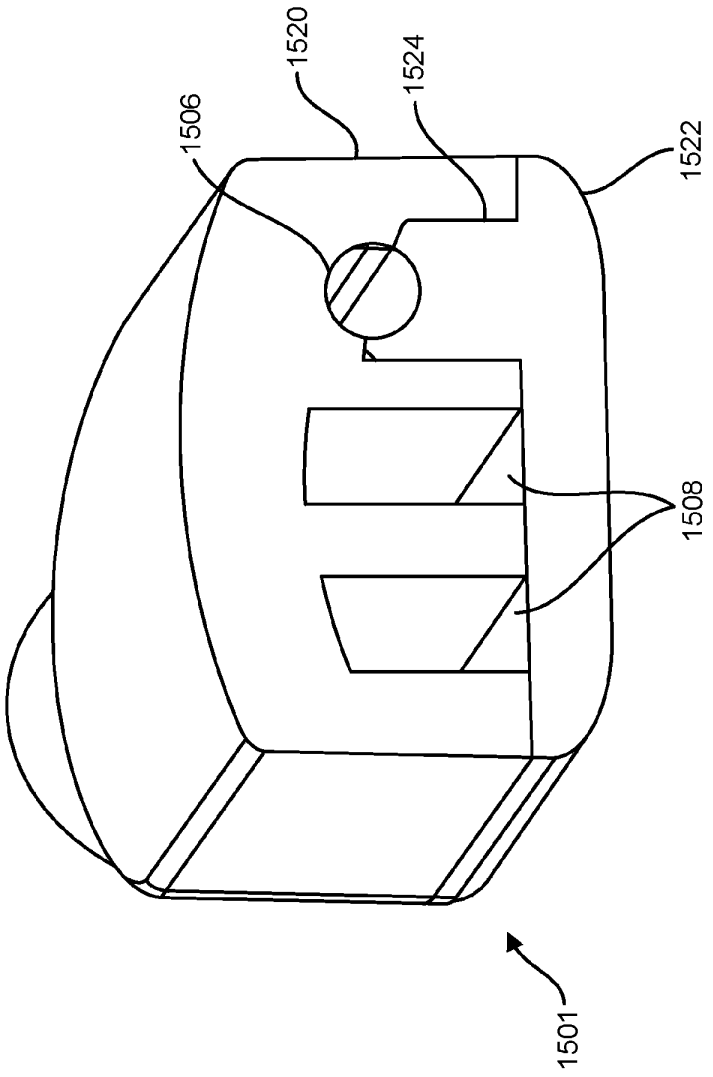


FIG. 15D

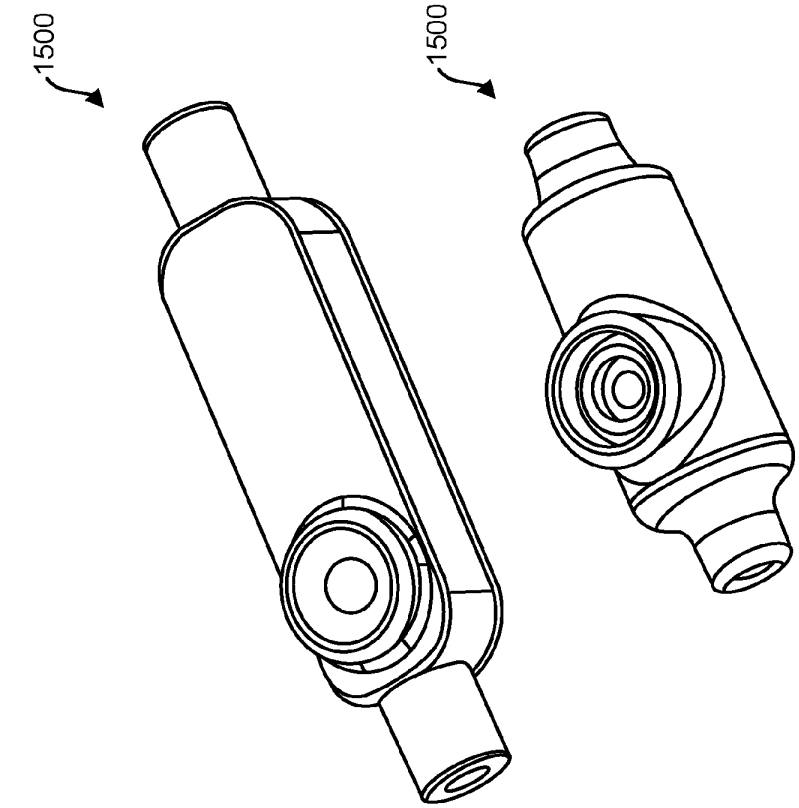


FIG. 15F

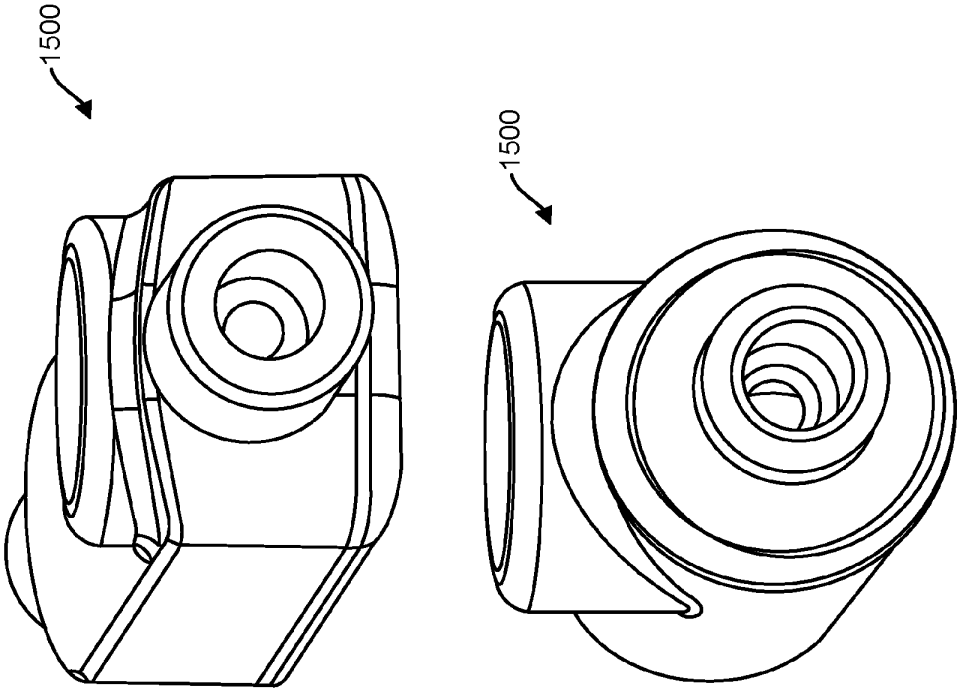


FIG. 15E

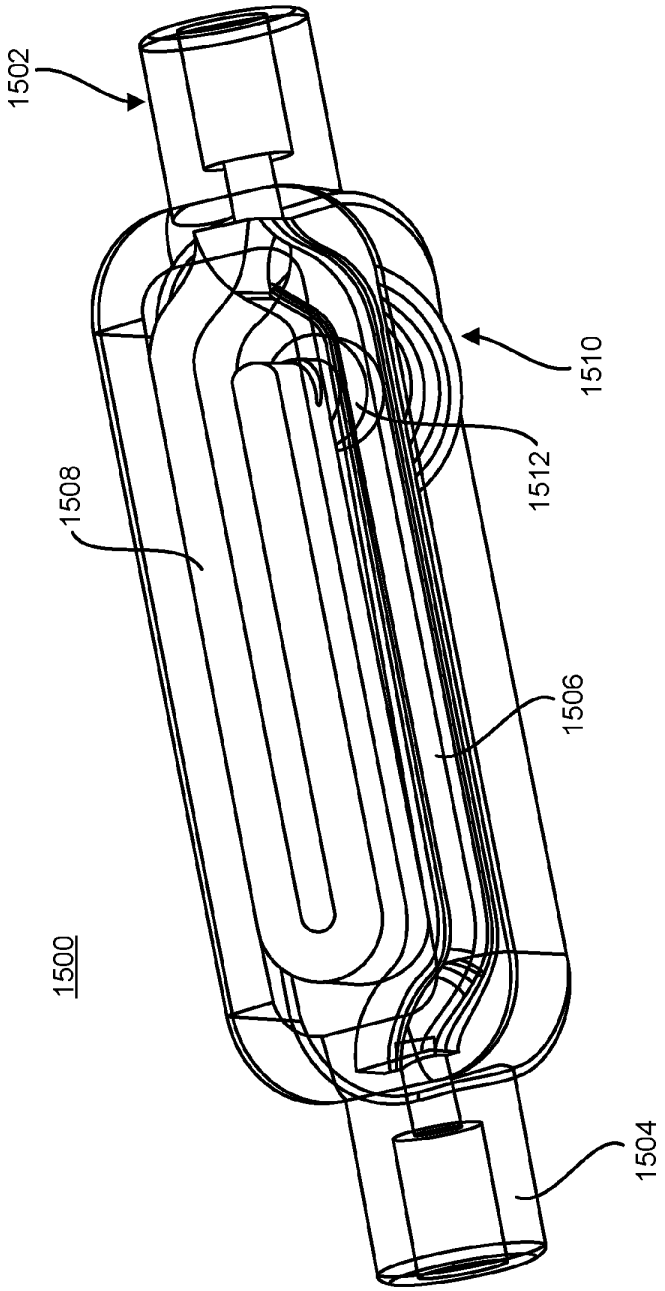


FIG. 15G

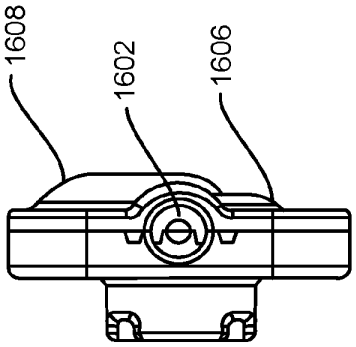


FIG. 16C

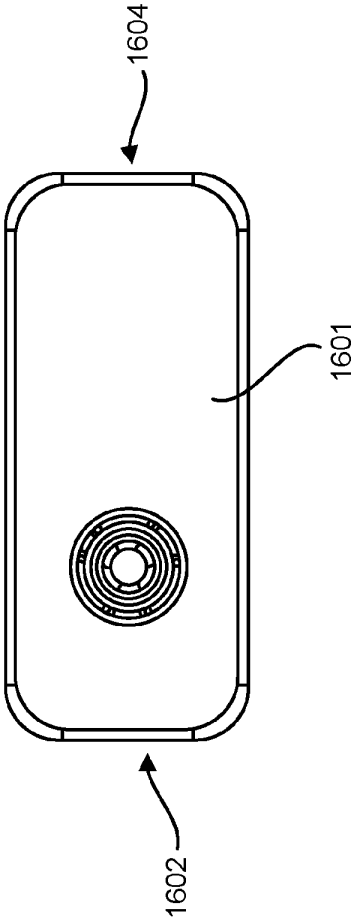


FIG. 16A

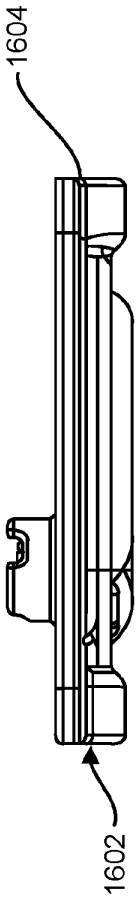


FIG. 16B

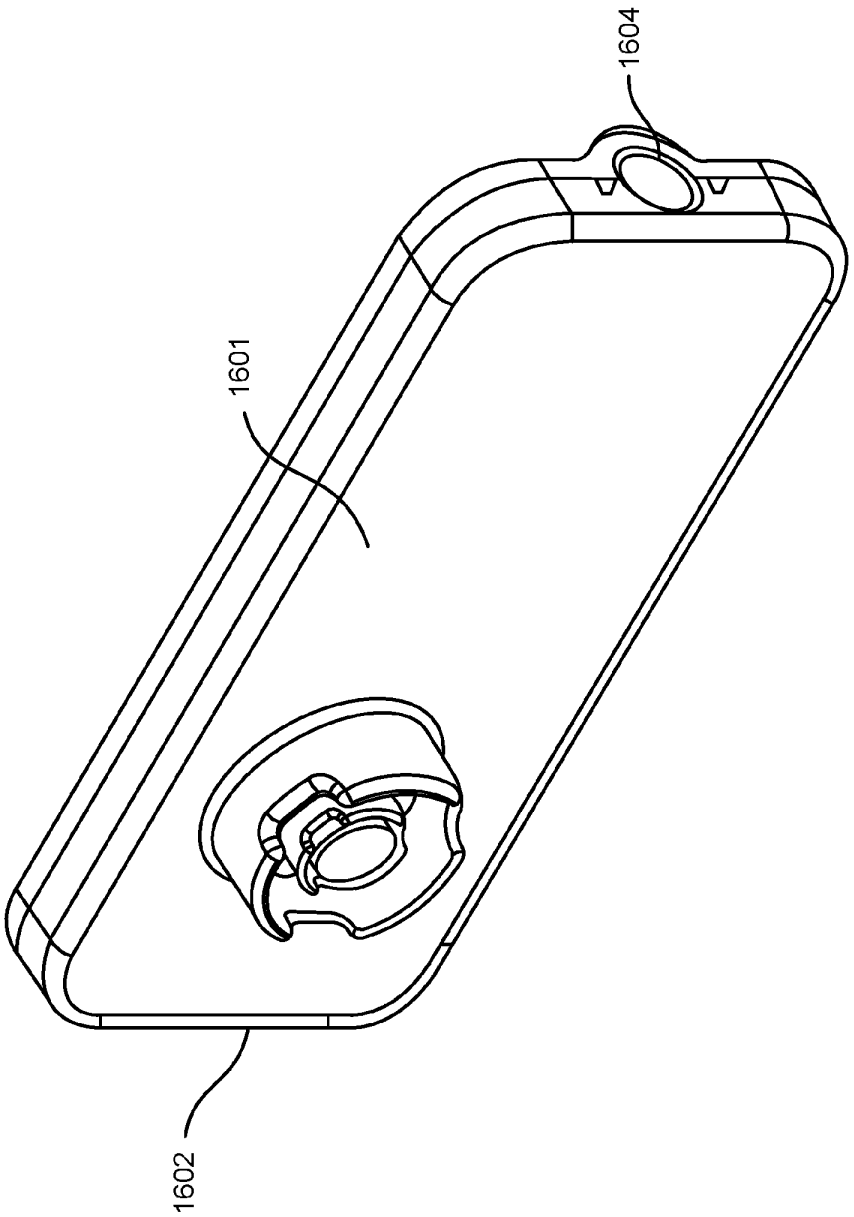


FIG. 16D

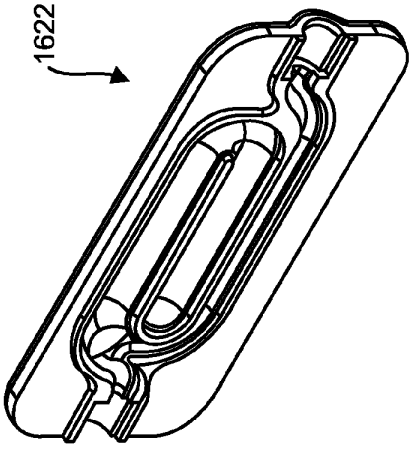


FIG. 17B



FIG. 17E

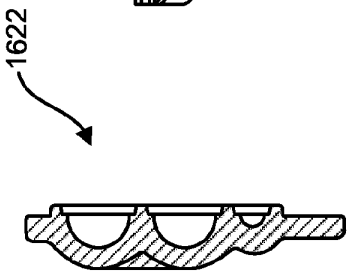


FIG. 17D

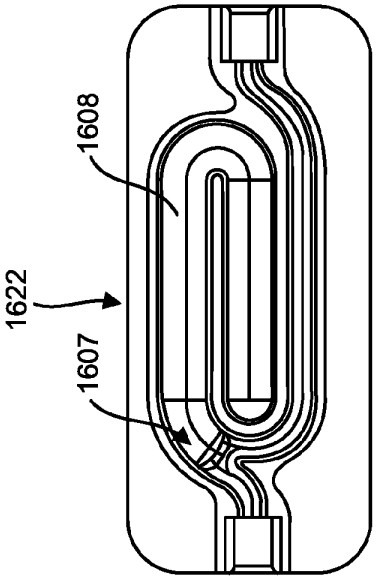


FIG. 17A

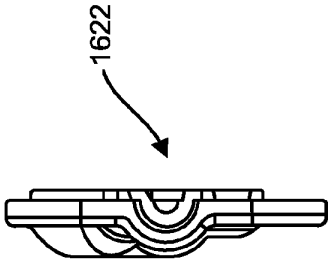


FIG. 17C

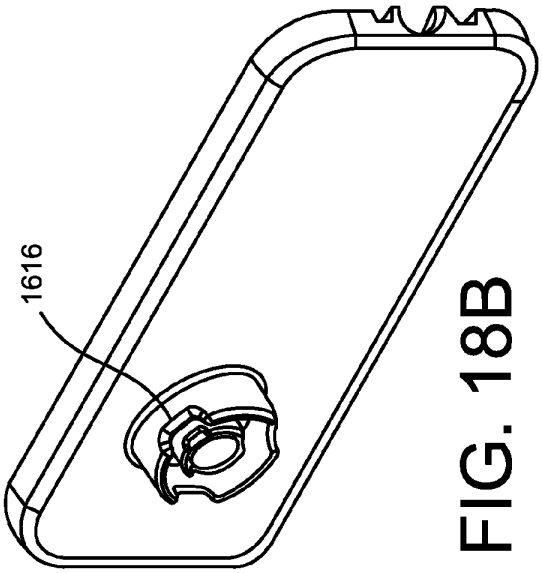


FIG. 18B

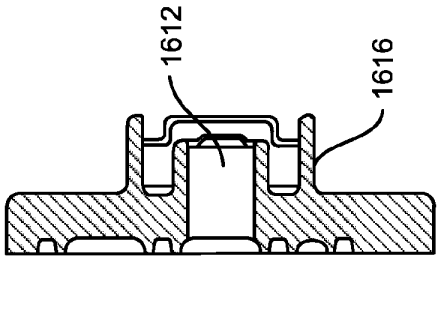


FIG. 18F

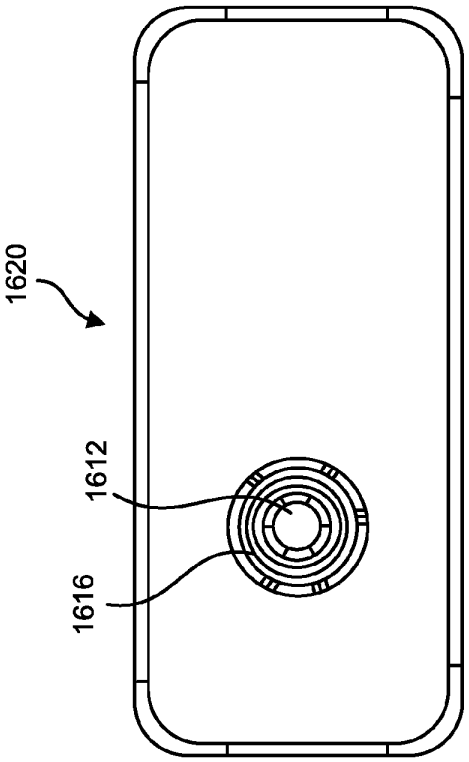


FIG. 18A

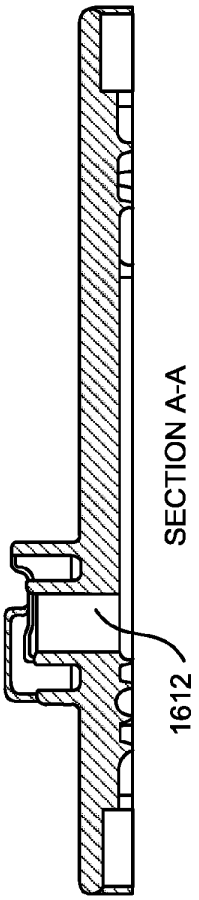


FIG. 18D

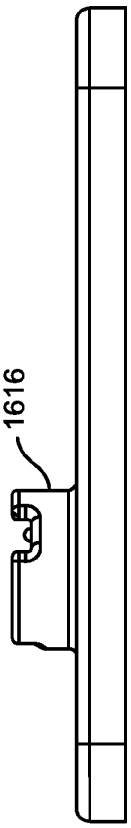


FIG. 18E

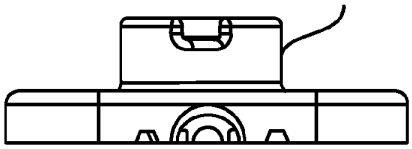


FIG. 18C

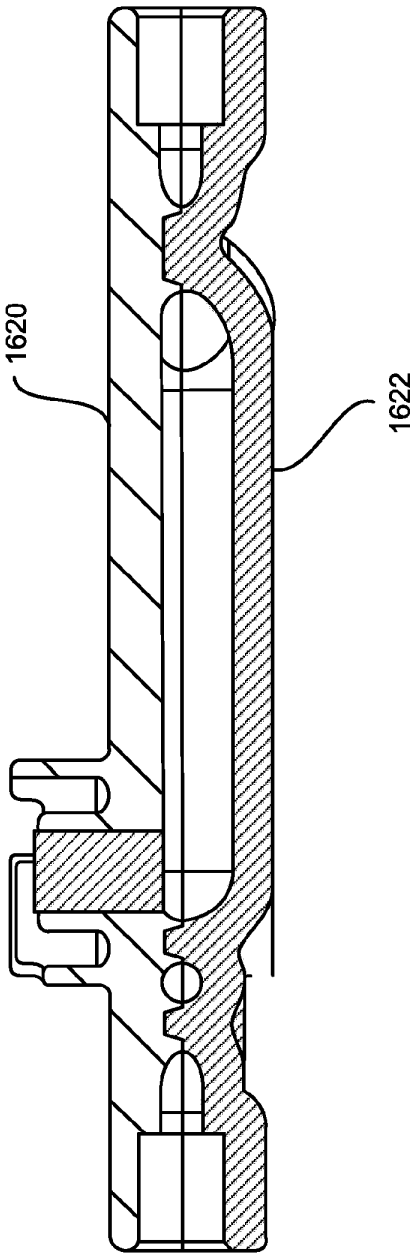


FIG. 19A

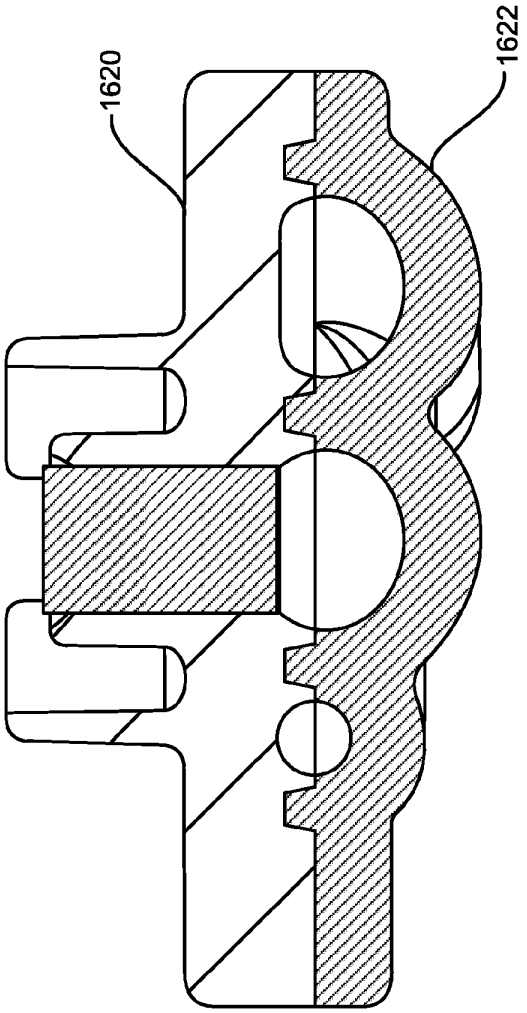


FIG. 19B

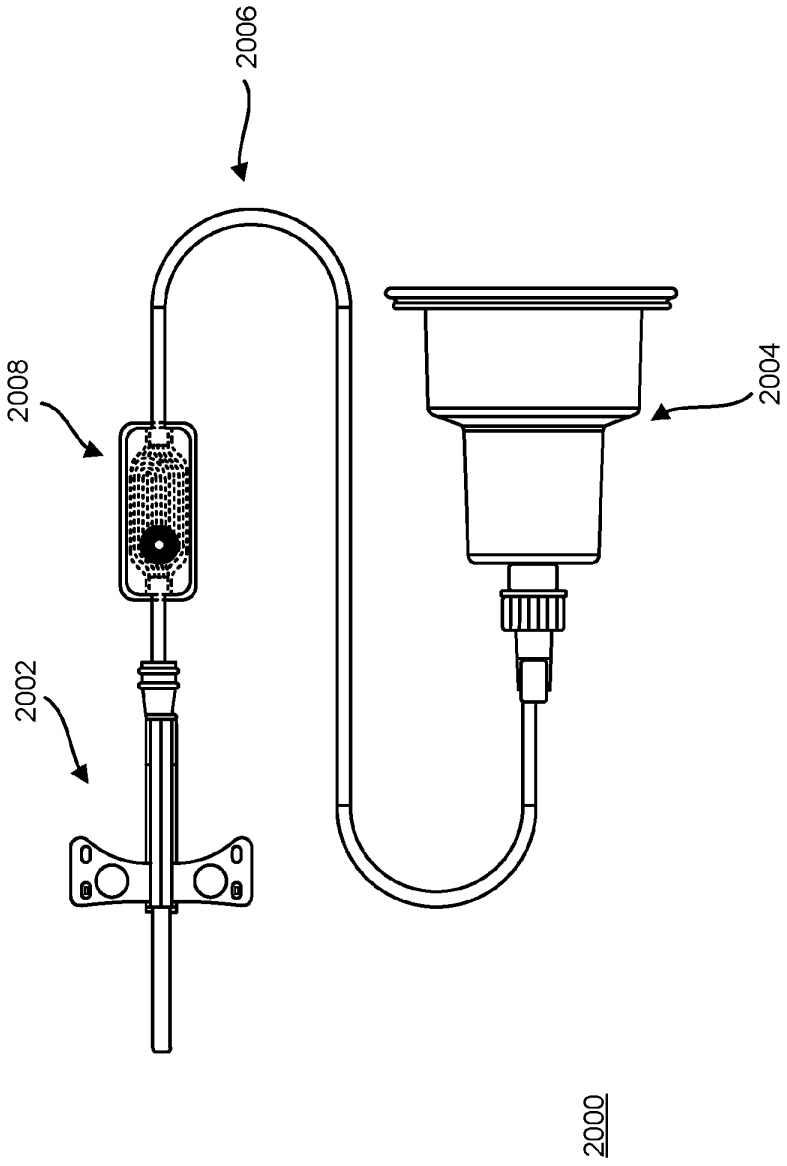


FIG. 20

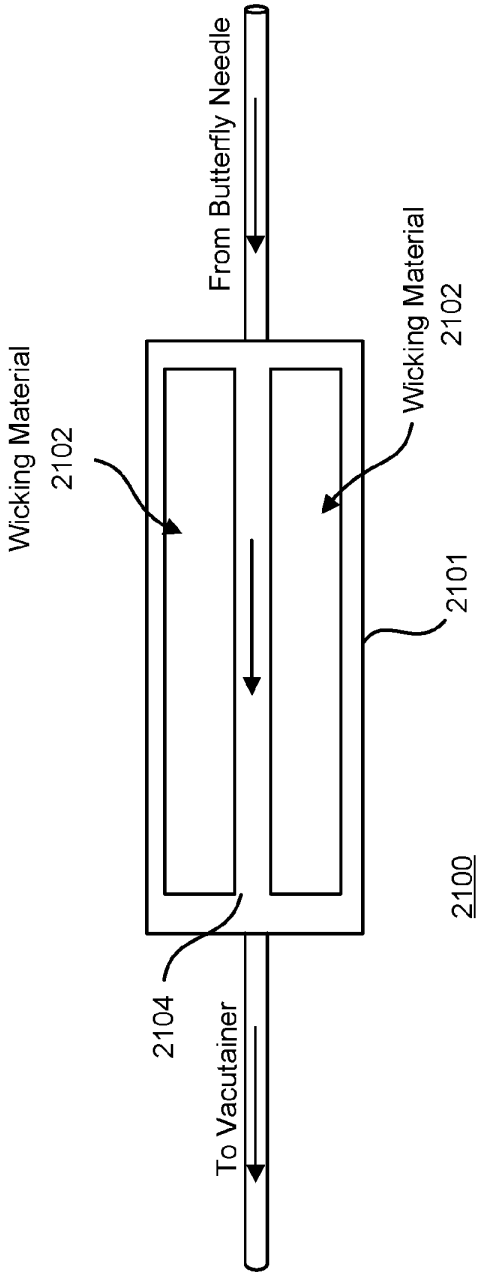

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

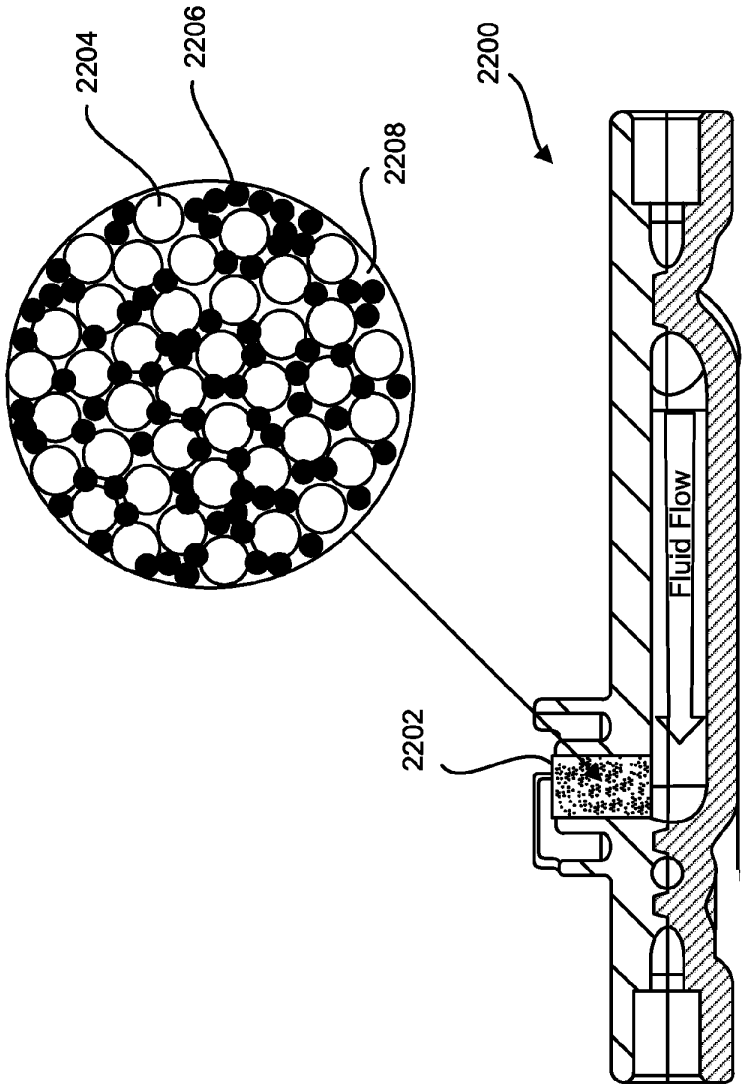


FIG. 22A

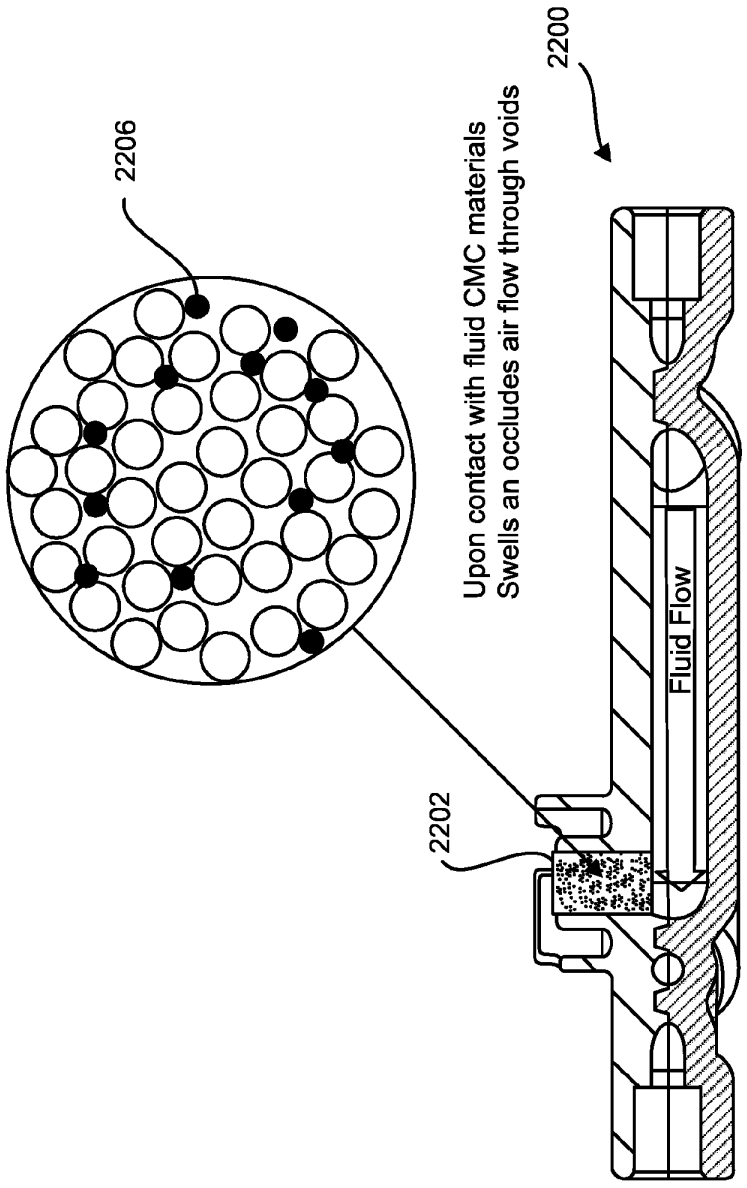

2200
2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
Fluid Flow
2202

FIG. 22B

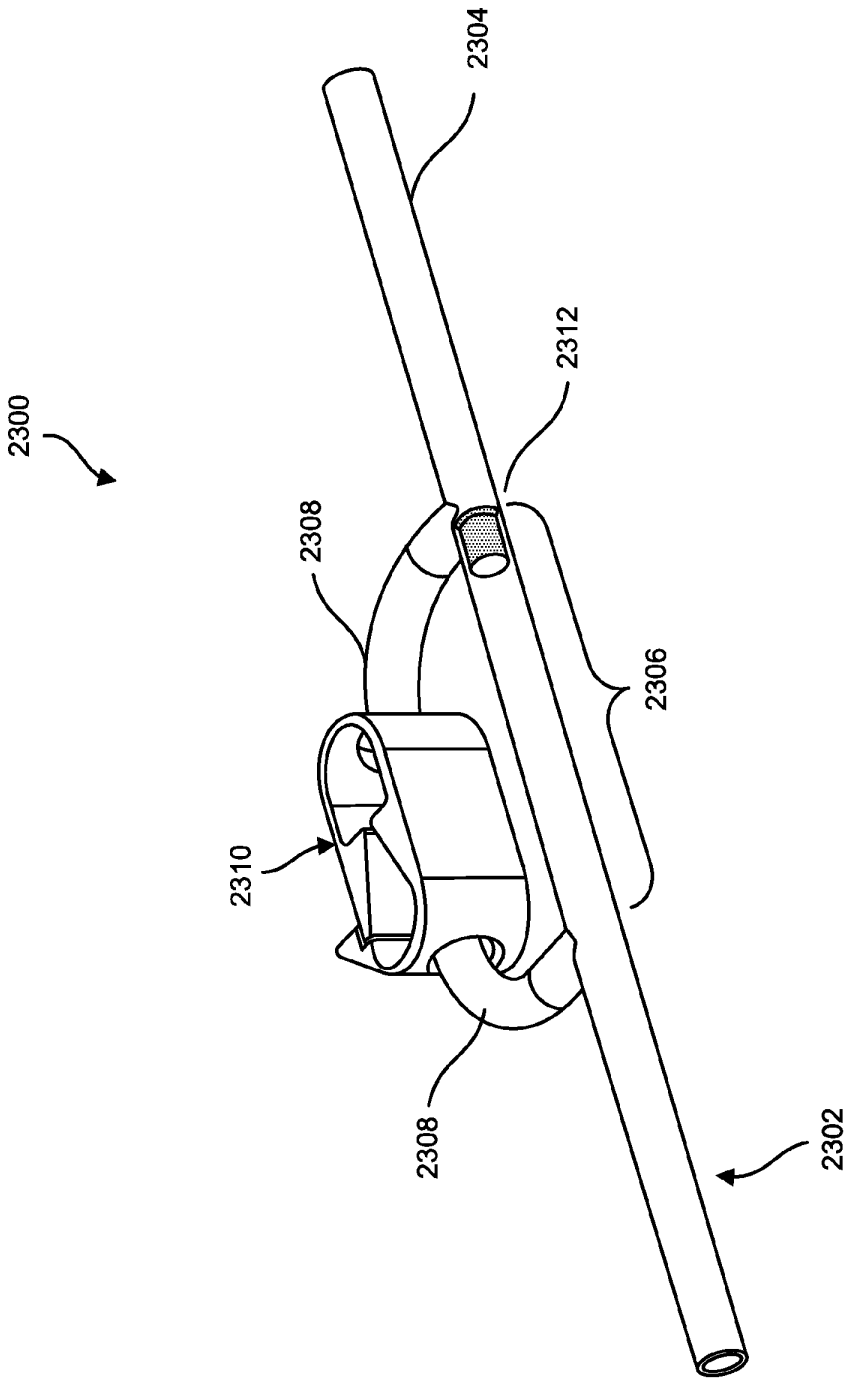


FIG. 23A

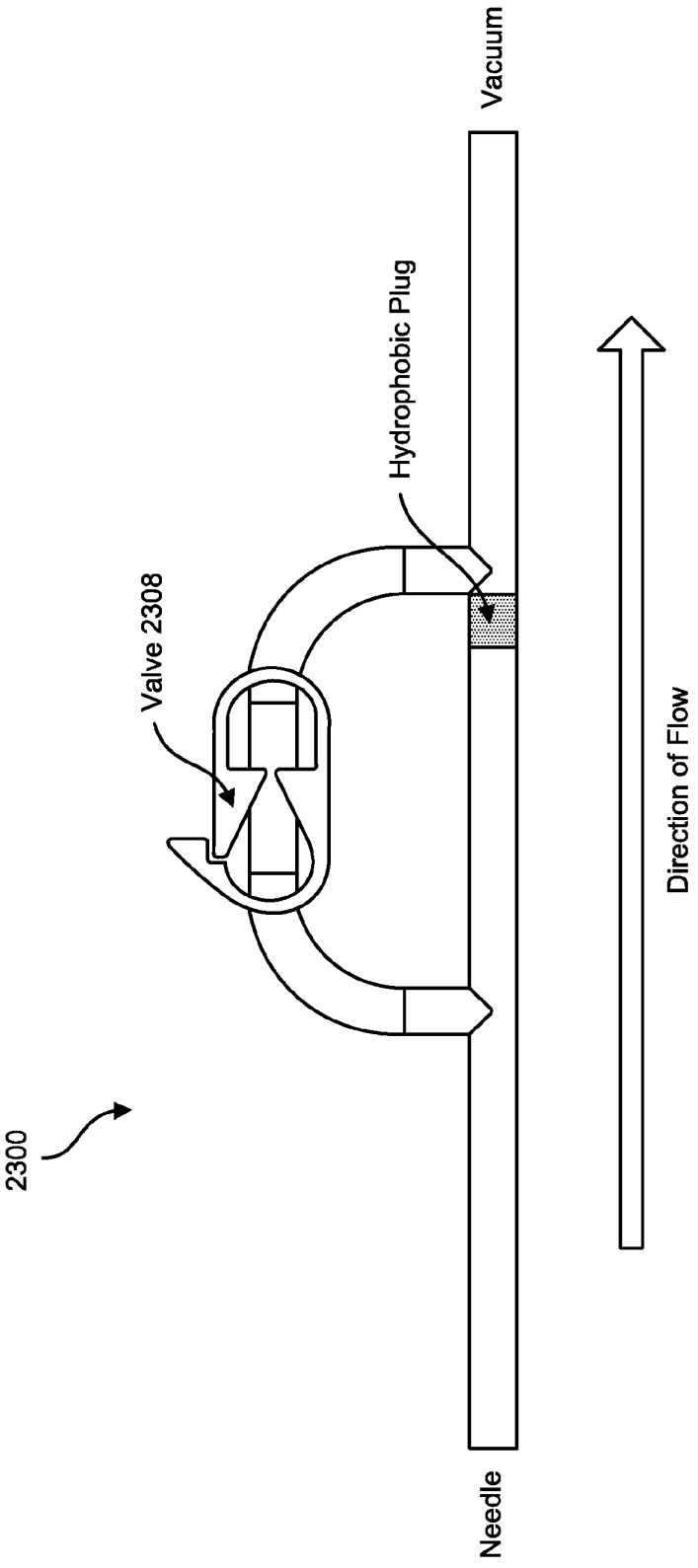

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

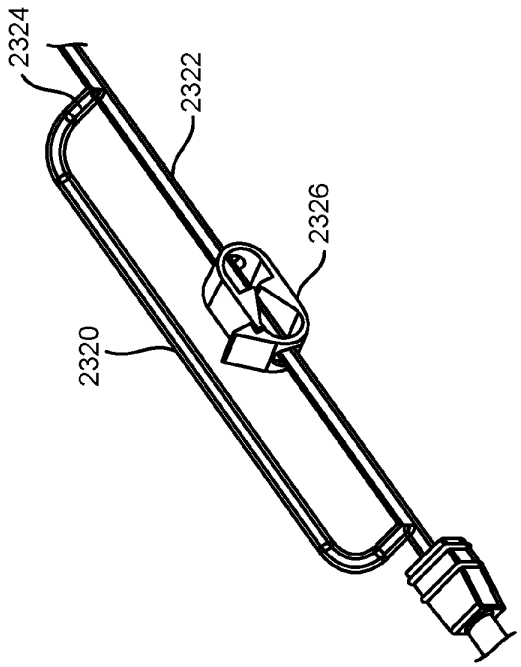


FIG. 23D

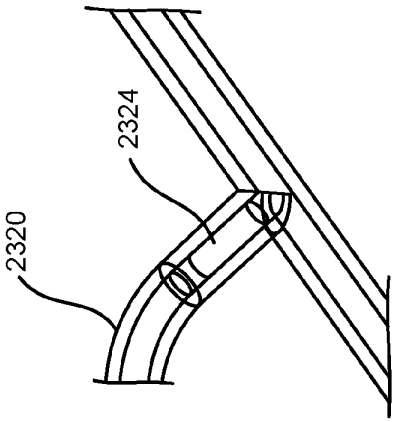


FIG. 23E

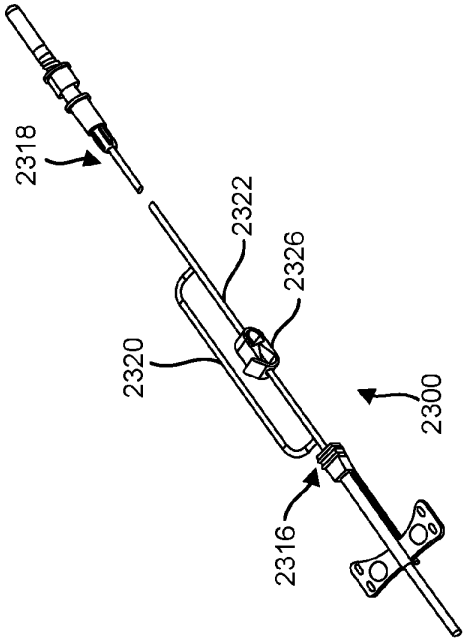


FIG. 23C

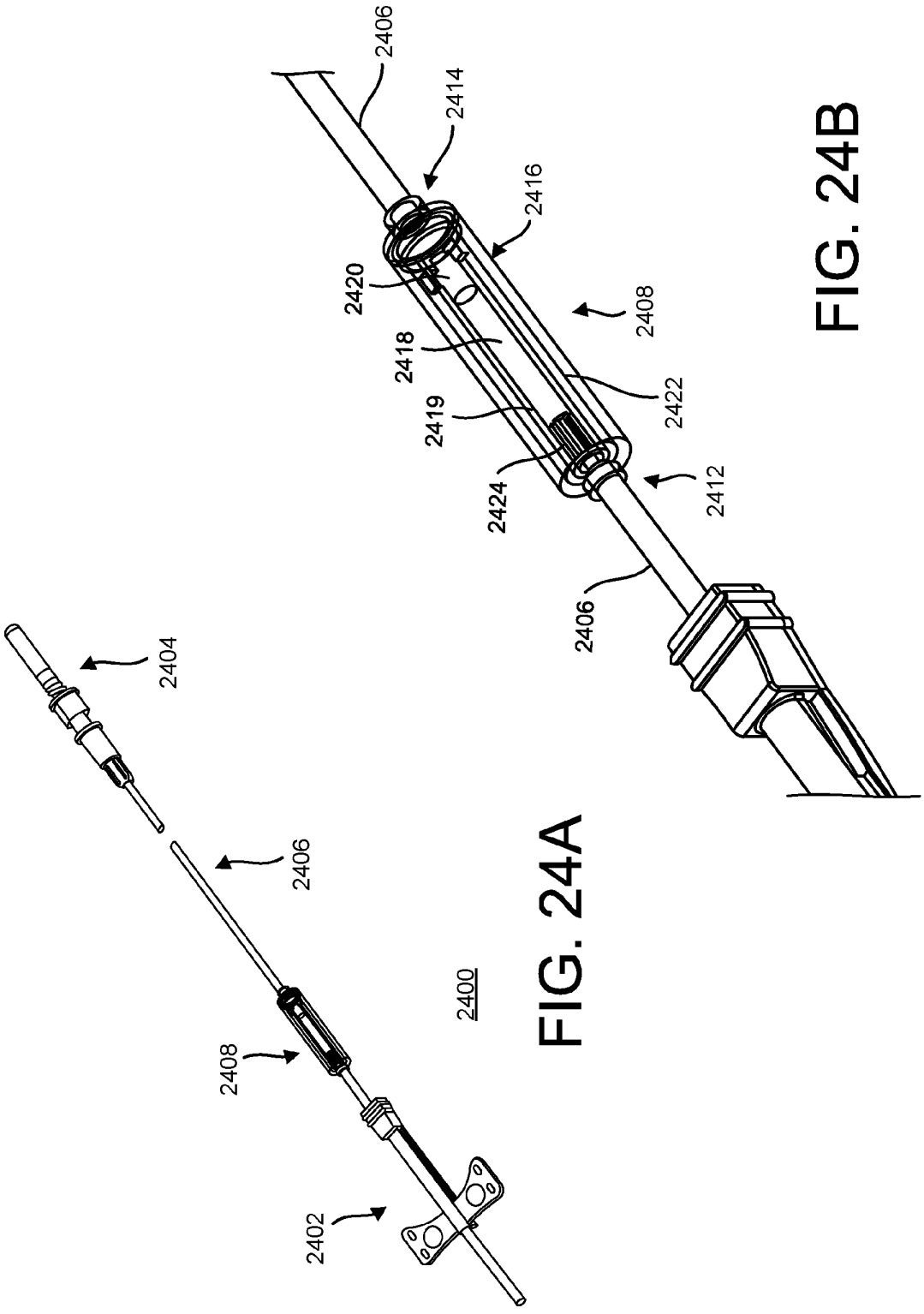


FIG. 24B

FIG. 24A

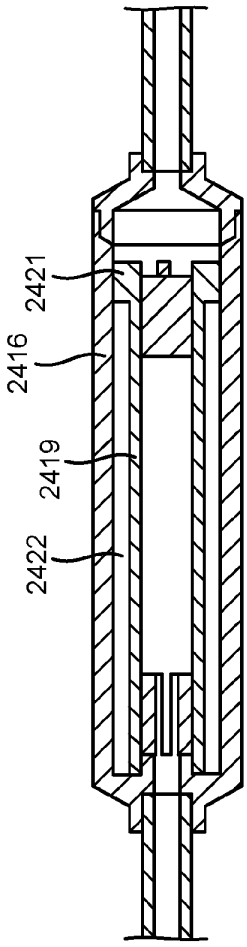


FIG. 24C

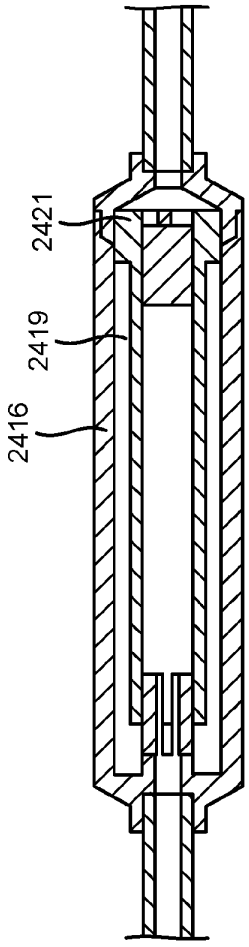


FIG. 24D

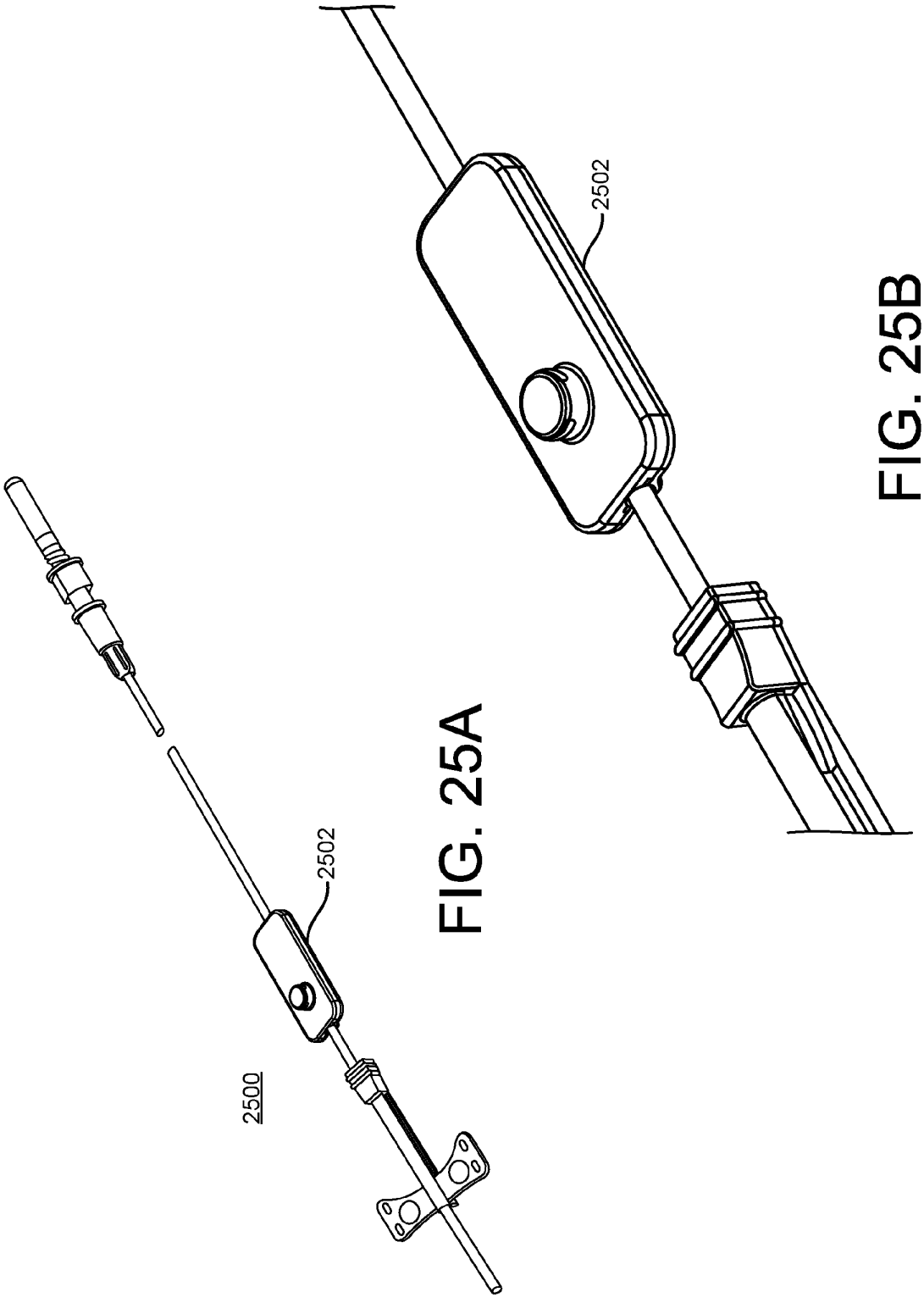


FIG. 25A

FIG. 25B

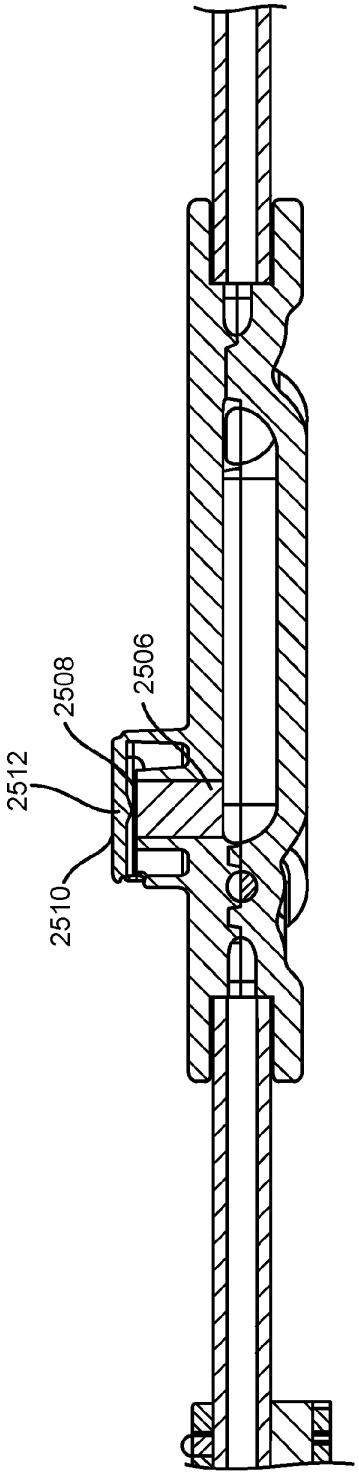


FIG. 25C

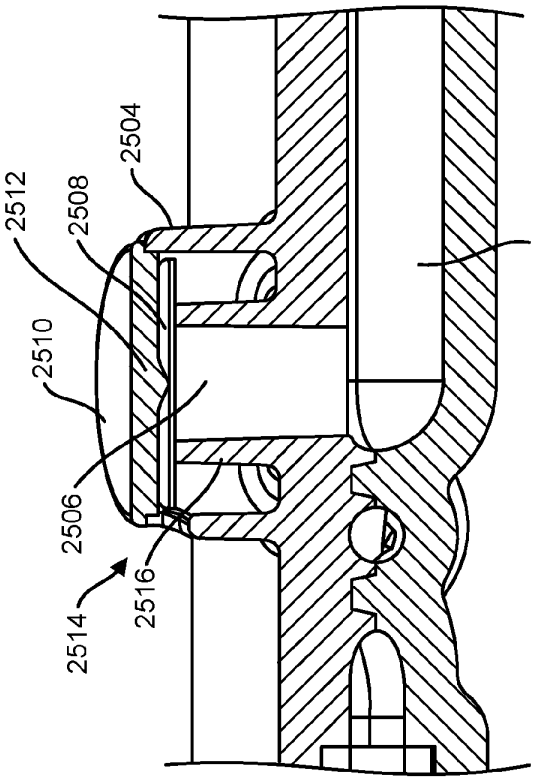


FIG. 25D

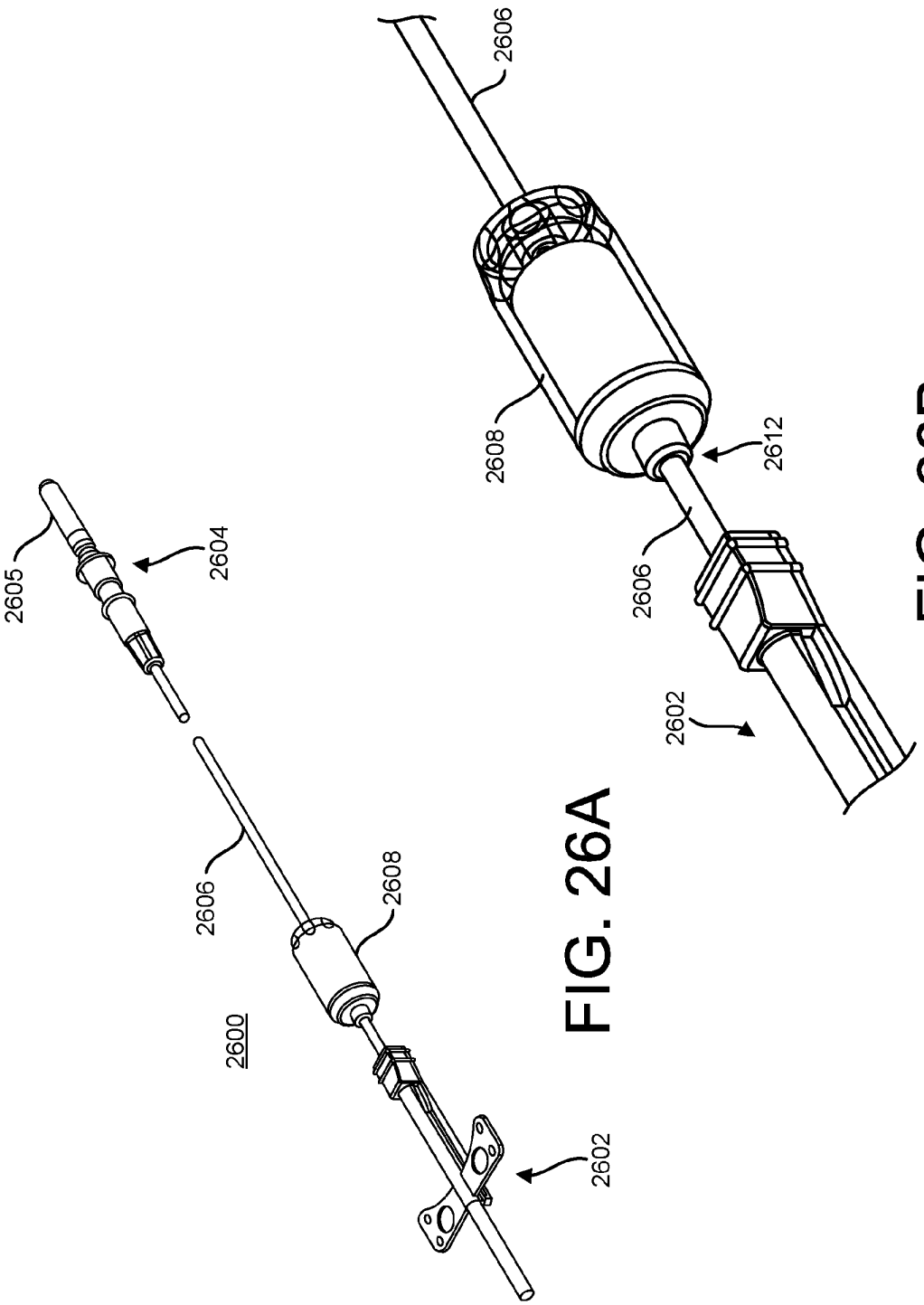


FIG. 26A

FIG. 26B

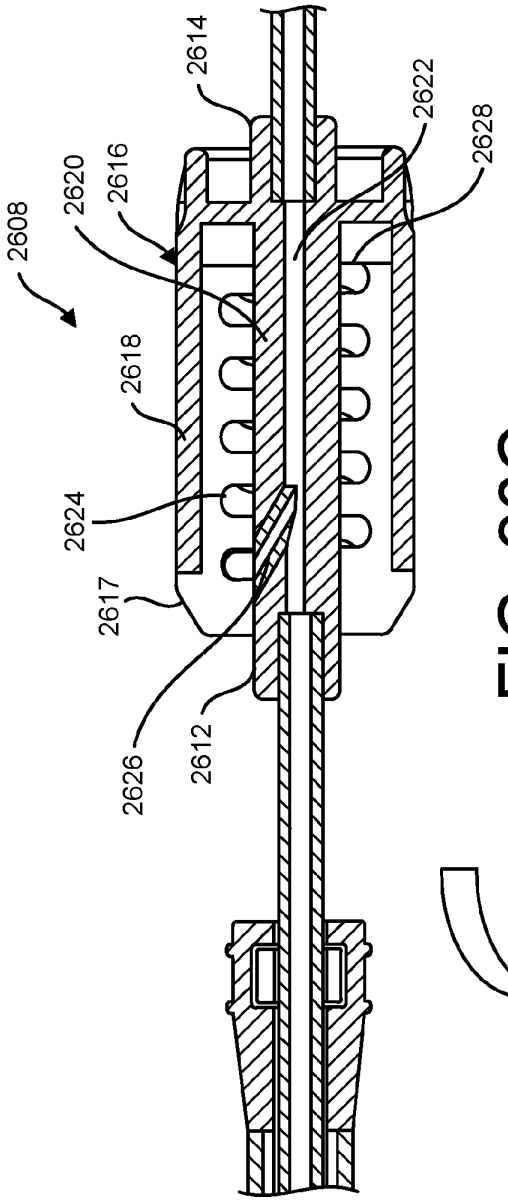


FIG. 26C

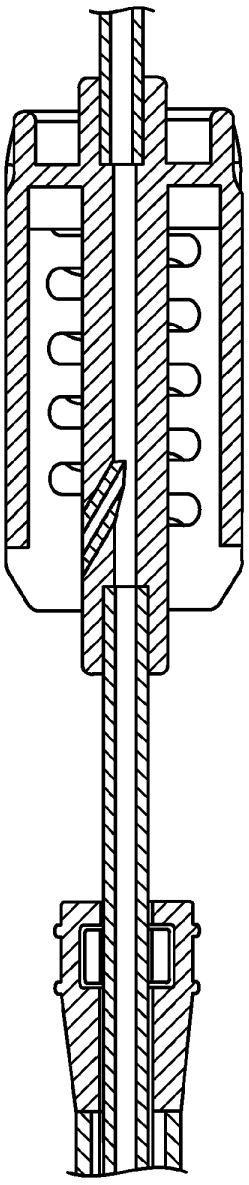


FIG. 26D

Replacement Sheet
58/69

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PCT/US2017/068569

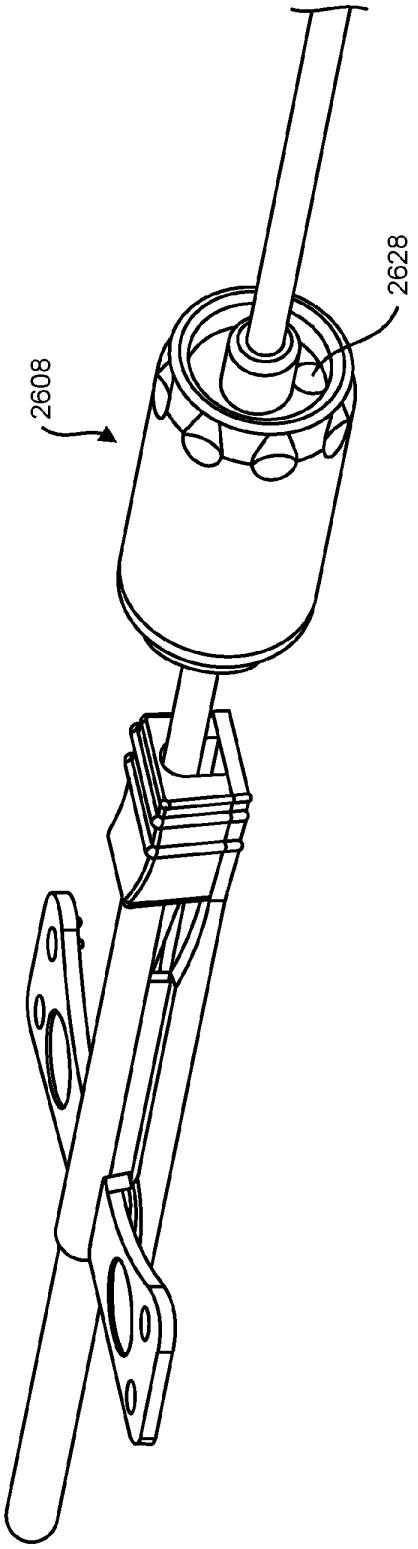


FIG. 26E

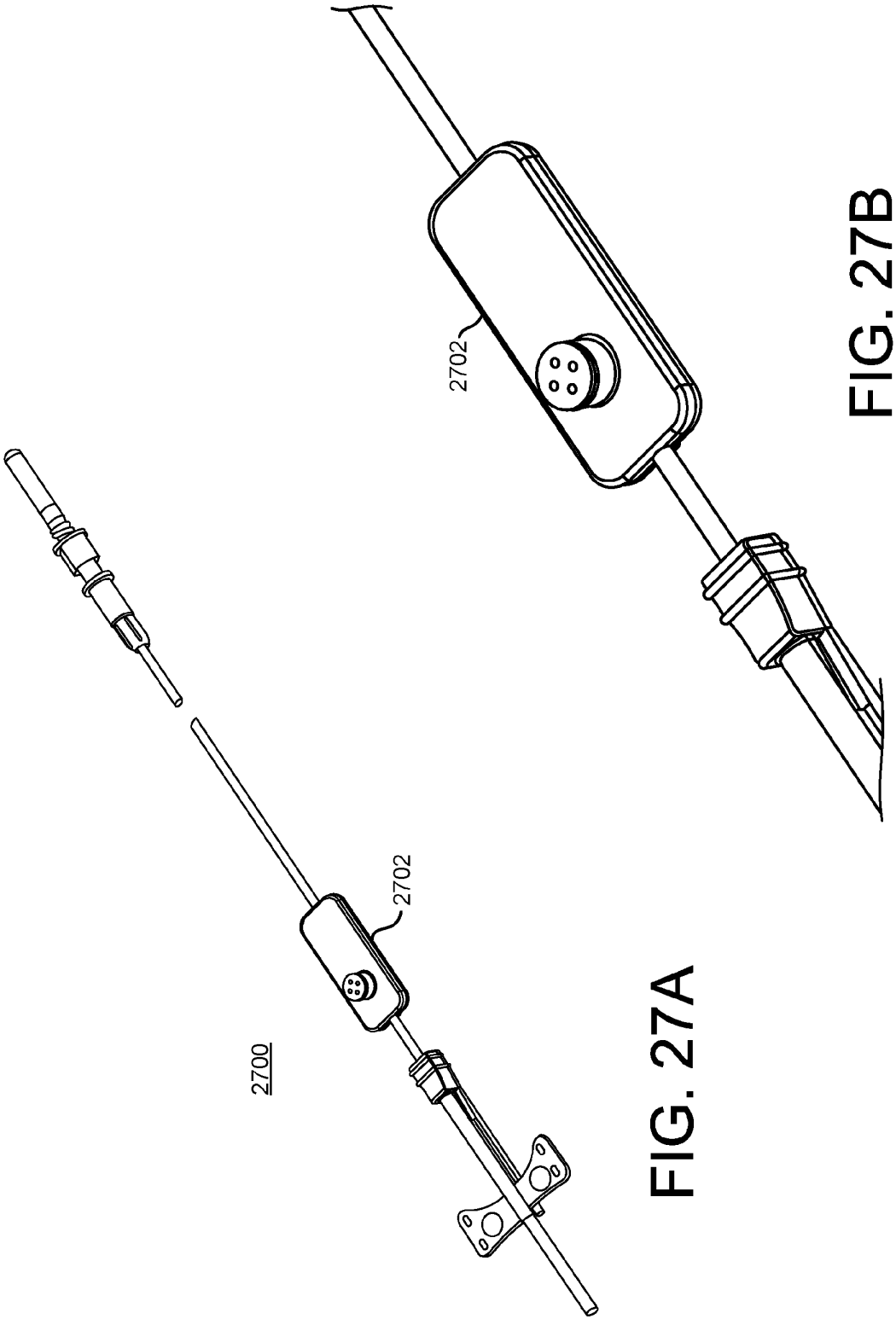


FIG. 27B

FIG. 27A

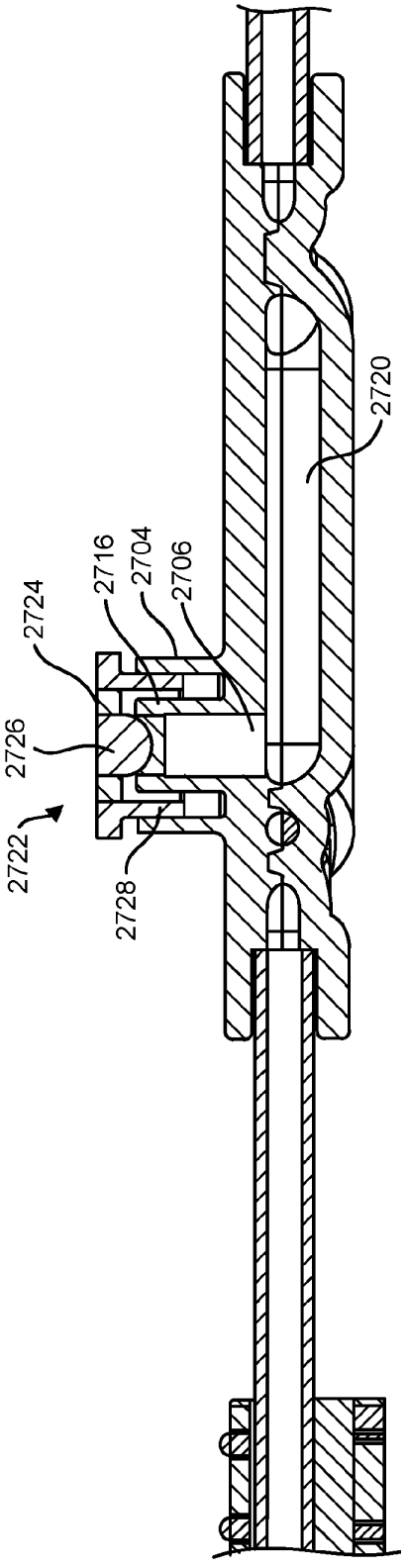


FIG. 27C

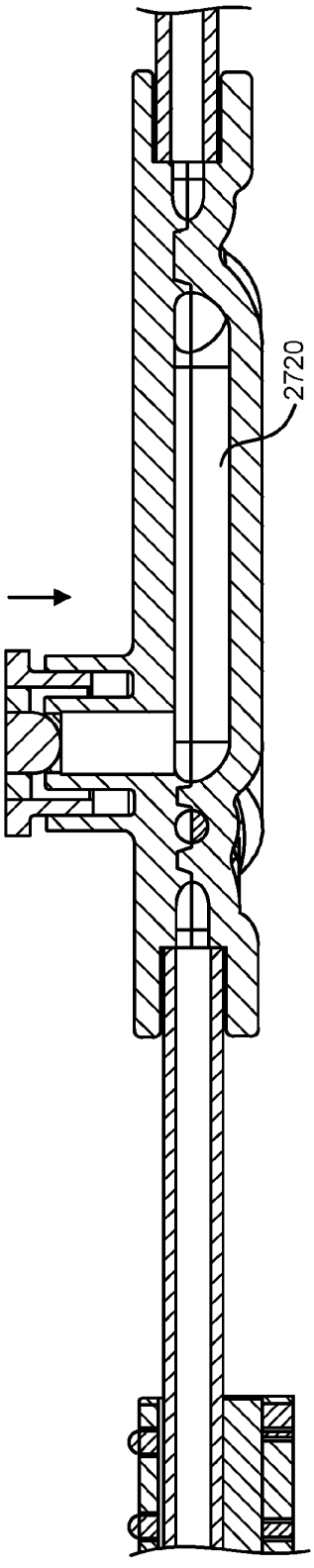


FIG. 27D

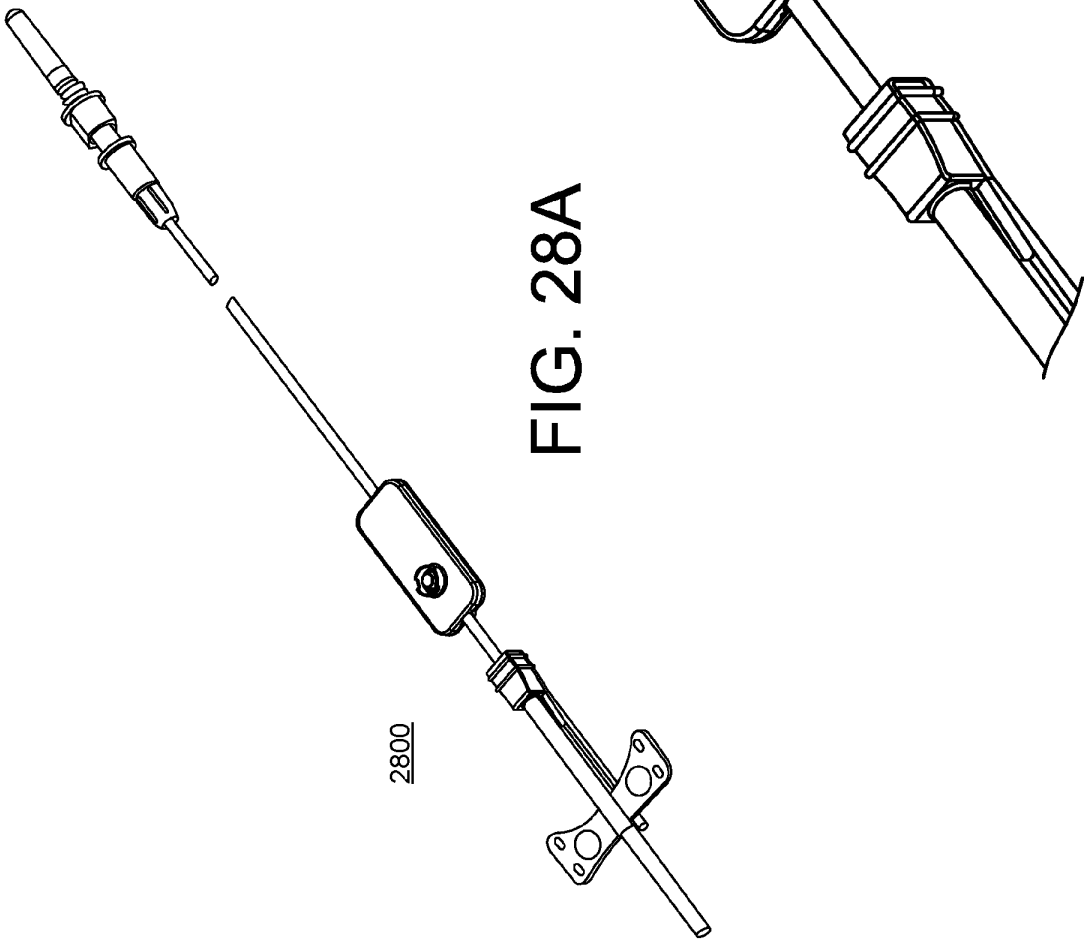


FIG. 28B

FIG. 28A

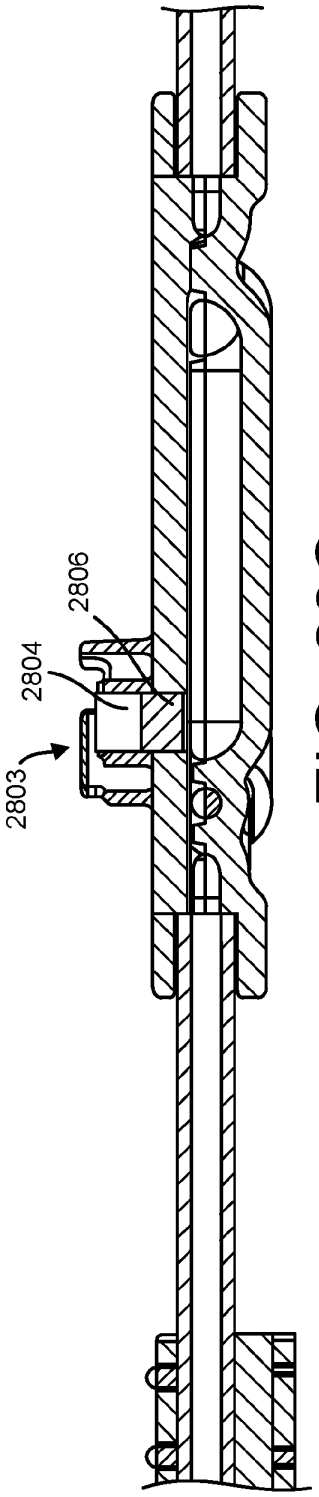


FIG. 28C

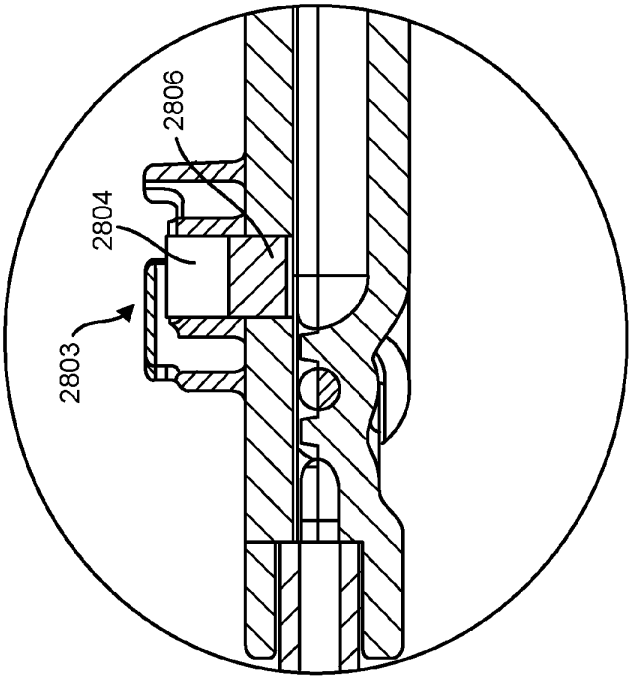


FIG. 28D

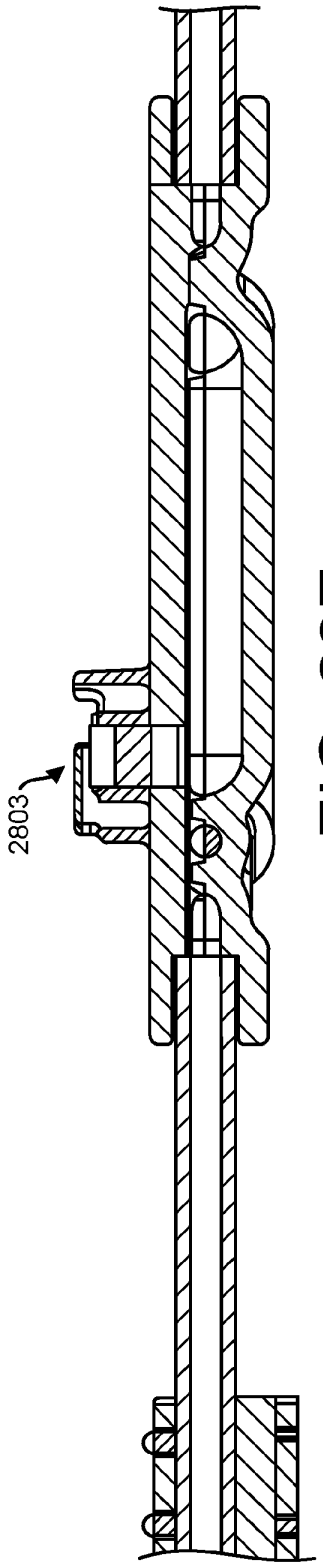


FIG. 28E

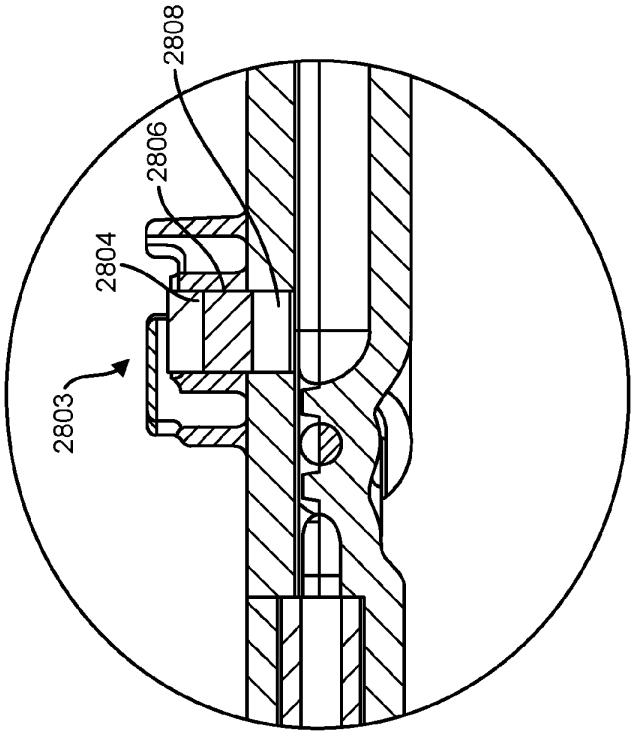


FIG. 28F

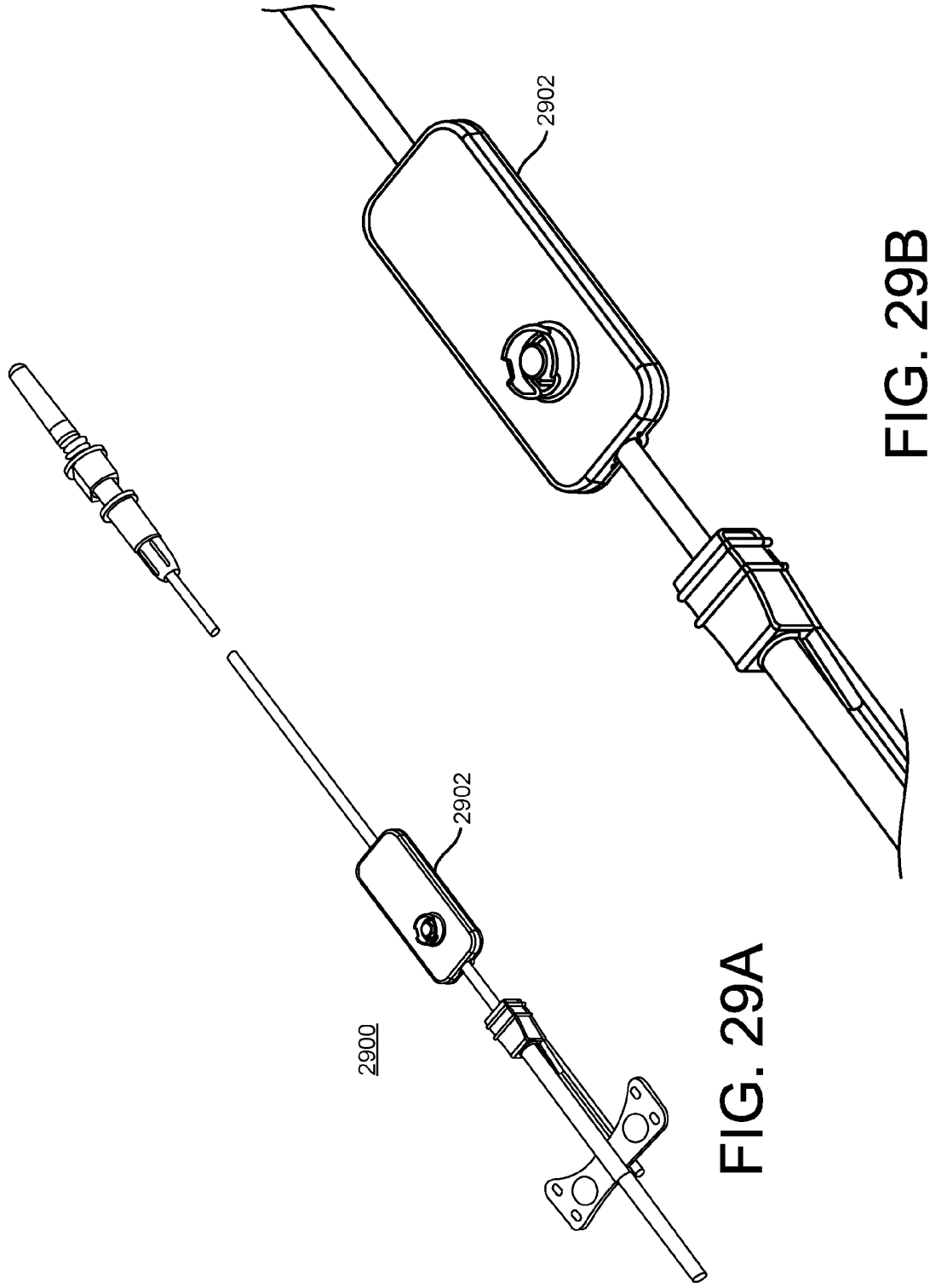


FIG. 29B

FIG. 29A

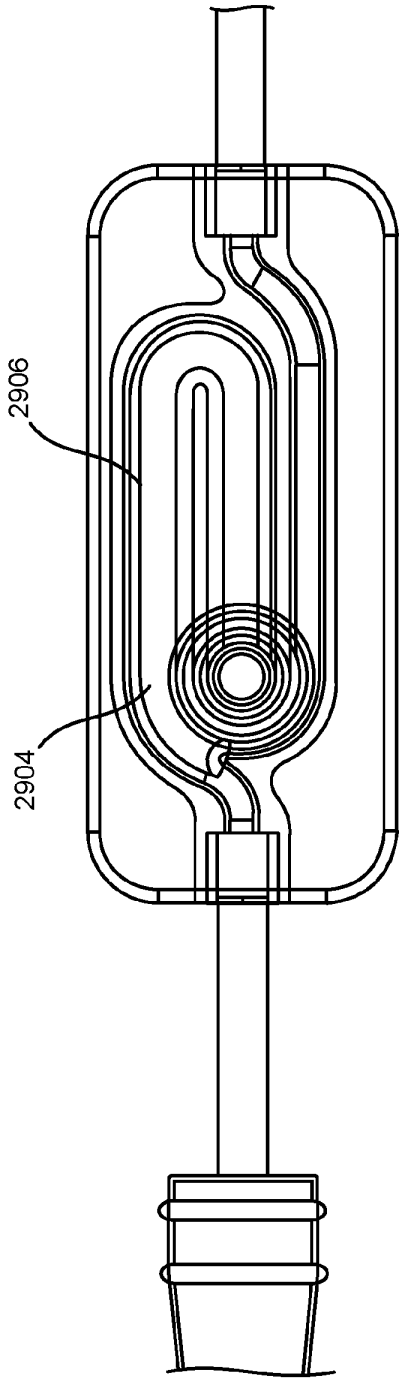


FIG. 29C

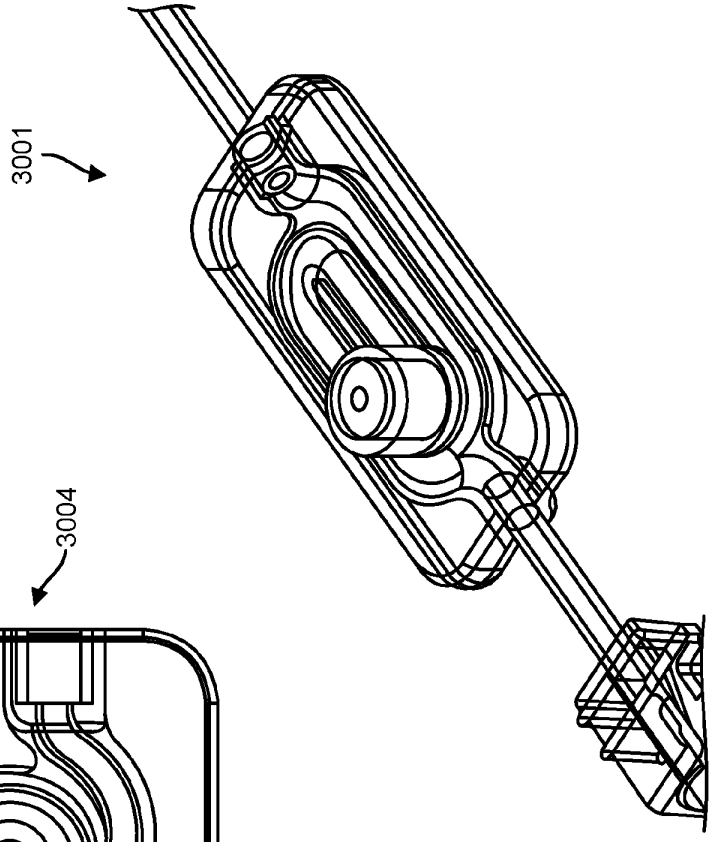


FIG. 30B

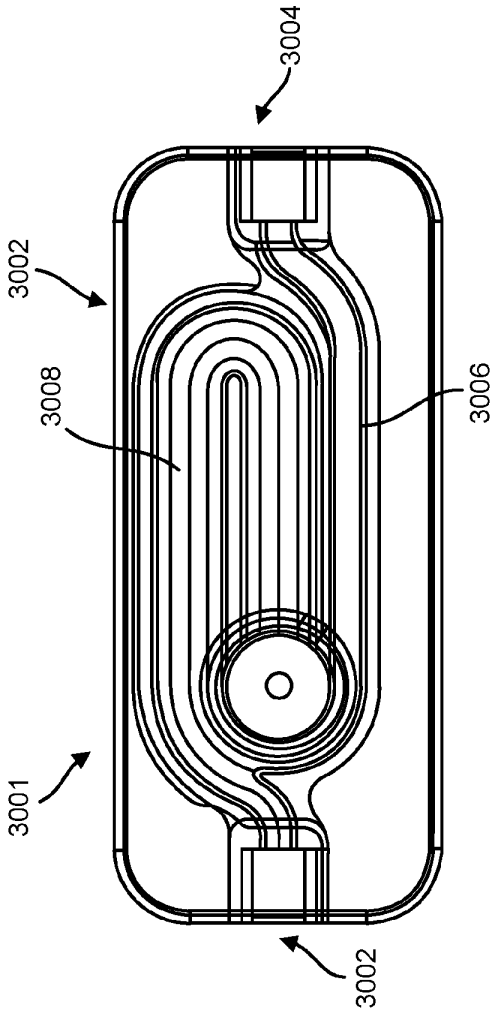


FIG. 30A

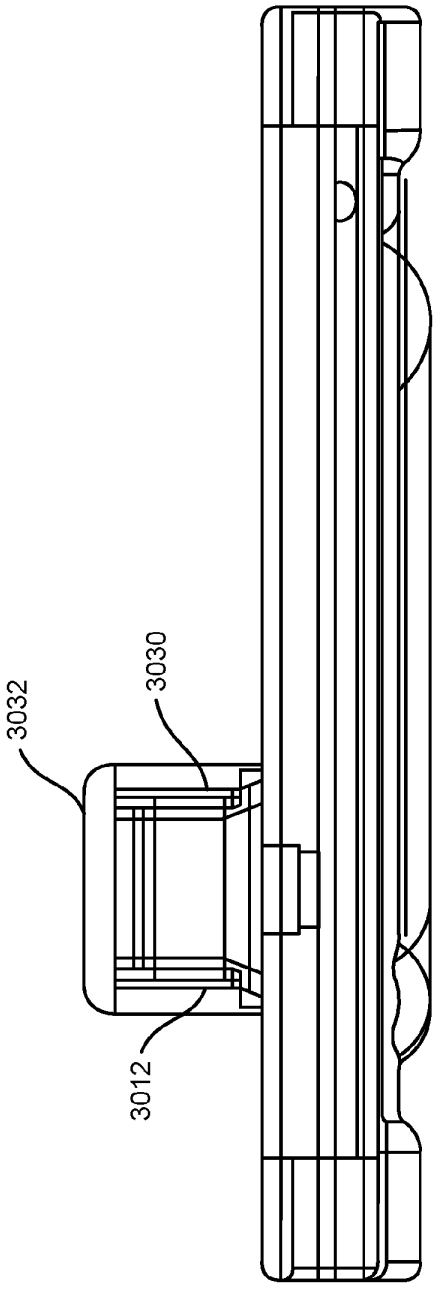


FIG. 30C

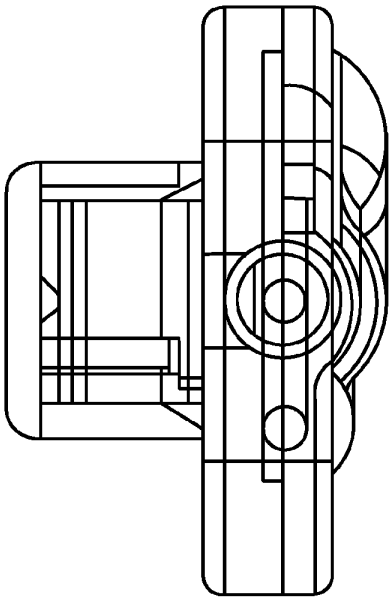


FIG. 30D

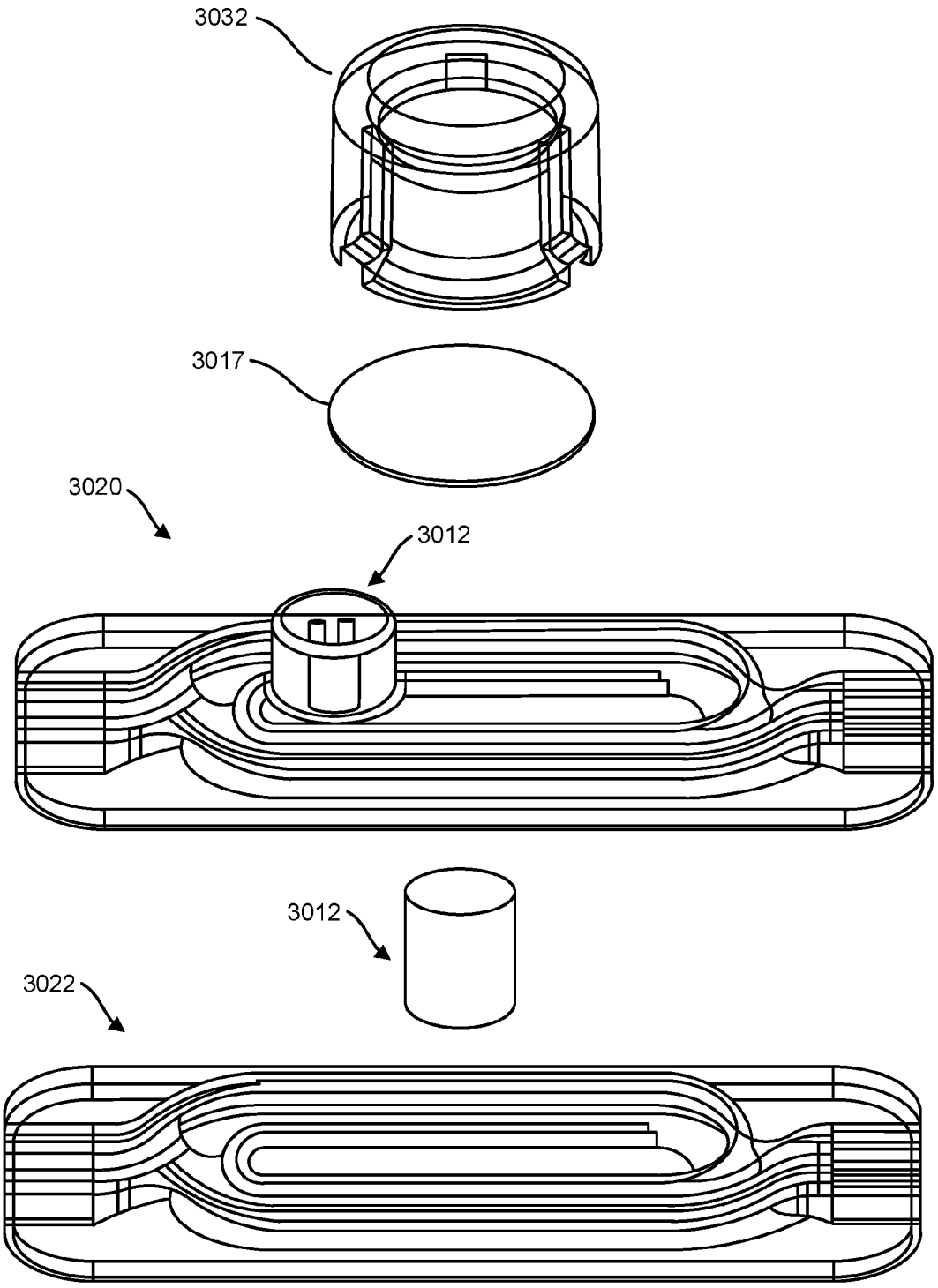


FIG. 30E

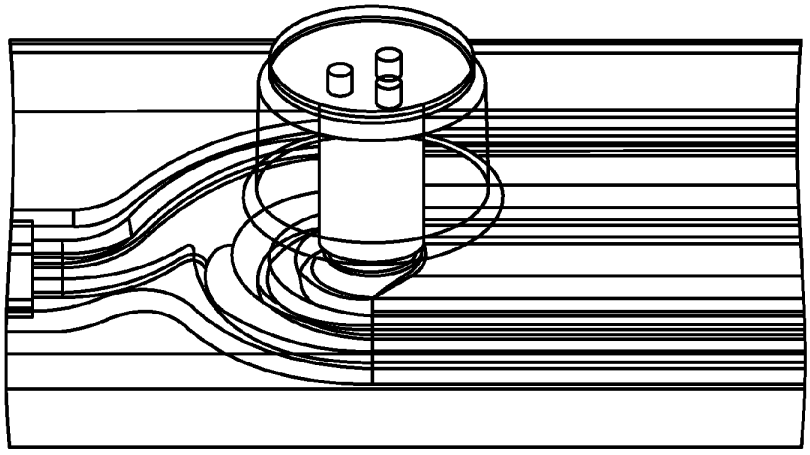


FIG. 30F

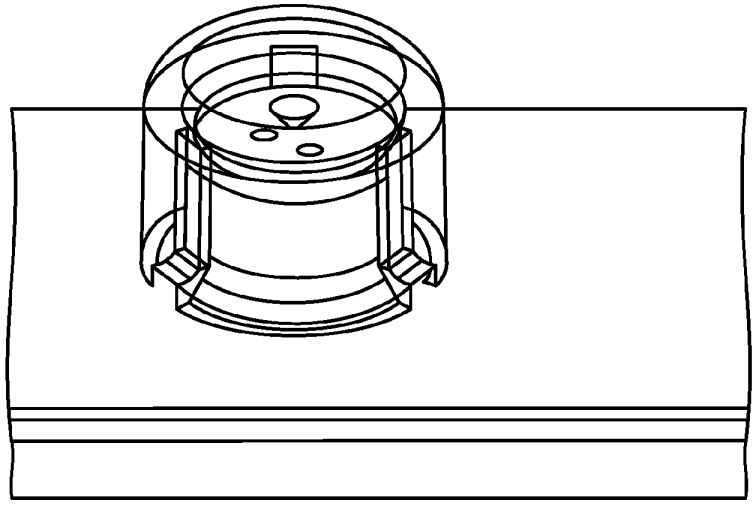


FIG. 30G

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 :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
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	
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		AU 2017216493 A1	07-09-2017
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		JP 6242386 B2	06-12-2017
		JP 2015519145 A	09-07-2015
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		US 2014155781 A1	05-06-2014
		US 2015351679 A1	10-12-2015
		WO 2013181352 A1	05-12-2013

Bibliographic data: WO2008101025 (A1) — 2008-08-21

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

Inventor(s): FRAZIER JOHN A [US]; BAK-BOYCHUK GREG [US]; WRIGHT MARK [US]; MCKEOWN MORGAN T [US] ± (FRAZIER, JOHN, A, ; BAK-BOYCHUK, GREG, ; WRIGHT, MARK, ; MCKEOWN, MORGAN, T)

Applicant(s): EDWARDS LIFESCIENCES CORP [US]; FRAZIER JOHN A [US]; BAK-BOYCHUK GREG [US]; WRIGHT MARK [US]; MCKEOWN MORGAN T [US] ± (EDWARDS LIFESCIENCES CORPORATION, ; FRAZIER, JOHN, A, ; BAK-BOYCHUK, GREG, ; WRIGHT, MARK, ; MCKEOWN, MORGAN, T)

Classification: **- international:** ***A61B5/15; A61M39/02; A61M39/04;*** *A61M1/02*
- cooperative: **A61B5/15003 (EP); A61B5/150236 (EP); A61B5/150244 (EP); A61B5/150305 (EP); A61B5/150992 (EP); A61B5/153 (EP); A61B5/154 (EP); A61B5/155 (EP); A61M1/0236 (EP); A61M39/045 (EP);** A61M2039/0202 (EP); A61M39/223 (EP)

Application number: WO2008US53871 20080213 Global Dossier

Priority number(s): US20070675578 20070215

Also published as: CA2678326 (A1) CN101631498 (A) EP2117431 (A1) US2008200837 (A1)

Abstract of WO2008101025 (A1)

A disposable, closed fluid sampling system for use with a medical conduit line (70), especially for taking blood samples from a pressure monitoring line. The conduit line (70) has at least one fluid sampling site (100, 102) interposed between a distal segment of tubing and a proximal segment of tubing. The system includes a disposable subsystem (96) having a bypass cannula (110) adapted to engage the sampling site, a reservoir (112) for drawing a prime volume of fluid past the sampling site, and a fluid sampling container (114). A 3-way stopcock (116) may connect the reservoir, bypass cannula, and sampling vessel for controlling the sampling procedure. The bypass cannula (110) may simultaneously place the subsystem into fluid communication with an inner chamber (136) of the sampling site and exclude the proximal segment of the conduit line. Alternatively, a stopcock immediately adjacent the sampling site in the proximal segment may be utilized. A method of using the system includes attaching the disposable subsystem, opening the reservoir to the distal segment while excluding the proximal segment, drawing a prime volume of fluid into the reservoir, opening the sampling vessel to the distal segment and drawing a sample, re-infusing the prime volume into the distal segment, and removing and discarding the subsystem. The

reservoir remains attached between the prime volume draw and re-infusion and is thus "closed."

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 August 2008 (21.08.2008)

PCT

(10) International Publication Number
WO 2008/101025 A1

(51) International Patent Classification:
A61B 5/15 (2006.01) *A61M 39/02* (2006.01)
A61M 39/04 (2006.01) *A61M 1/02* (2006.01)

(21) International Application Number:
PCT/US2008/053871

(22) International Filing Date:
13 February 2008 (13.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/675,578 15 February 2007 (15.02.2007) US

(71) Applicant *(for all designated States except US)*: **EDWARDS LIFESCIENCES CORPORATION** [US/US]; One Edwards Way, Irvine, CA 92614 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FRAZIER, John, A.** [US/US]; 3103 Roanoke Lane, Costa Mesa, CA 92626 (US). **BAK-BOYCHUK, Greg** [US/US]; 24842 Hidden Hills Road, Apt. #f, Laguna Niguel, CA 92677 (US). **WRIGHT, Mark** [US/US]; 826 Violet Court, Carlsbad, CA 80920 (US). **MCKEOWN, Morgan, T.** [US/US]; 19 Silkberry, Irvine, CA 92614 (US).

(74) Agents: **CARLIN, Gregory, J.** et al.; Edwards Lifesciences LLC, One Edwards Way, Irvine, CA 92614 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: DISPOSABLE, CLOSED BLOOD SAMPLING SYSTEM FOR USE IN MEDICAL CONDUIT LINE

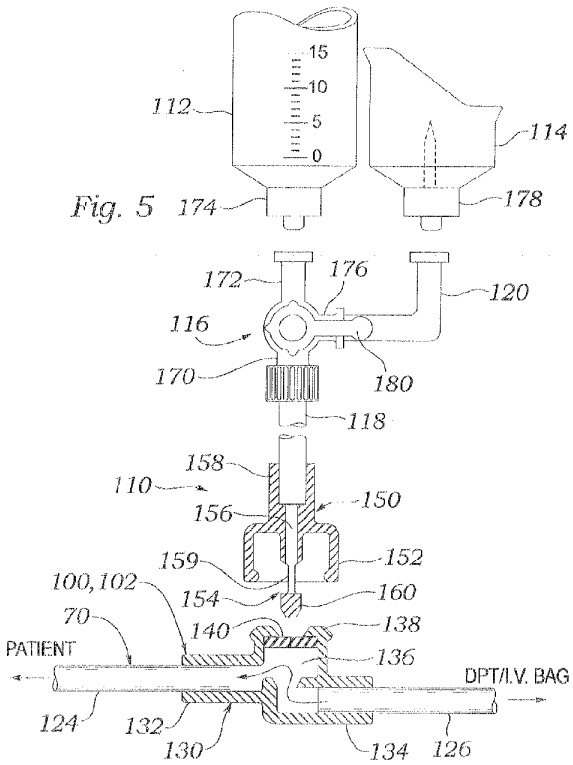


Fig. 5

(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."

WO 2008/101025 A1

FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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.

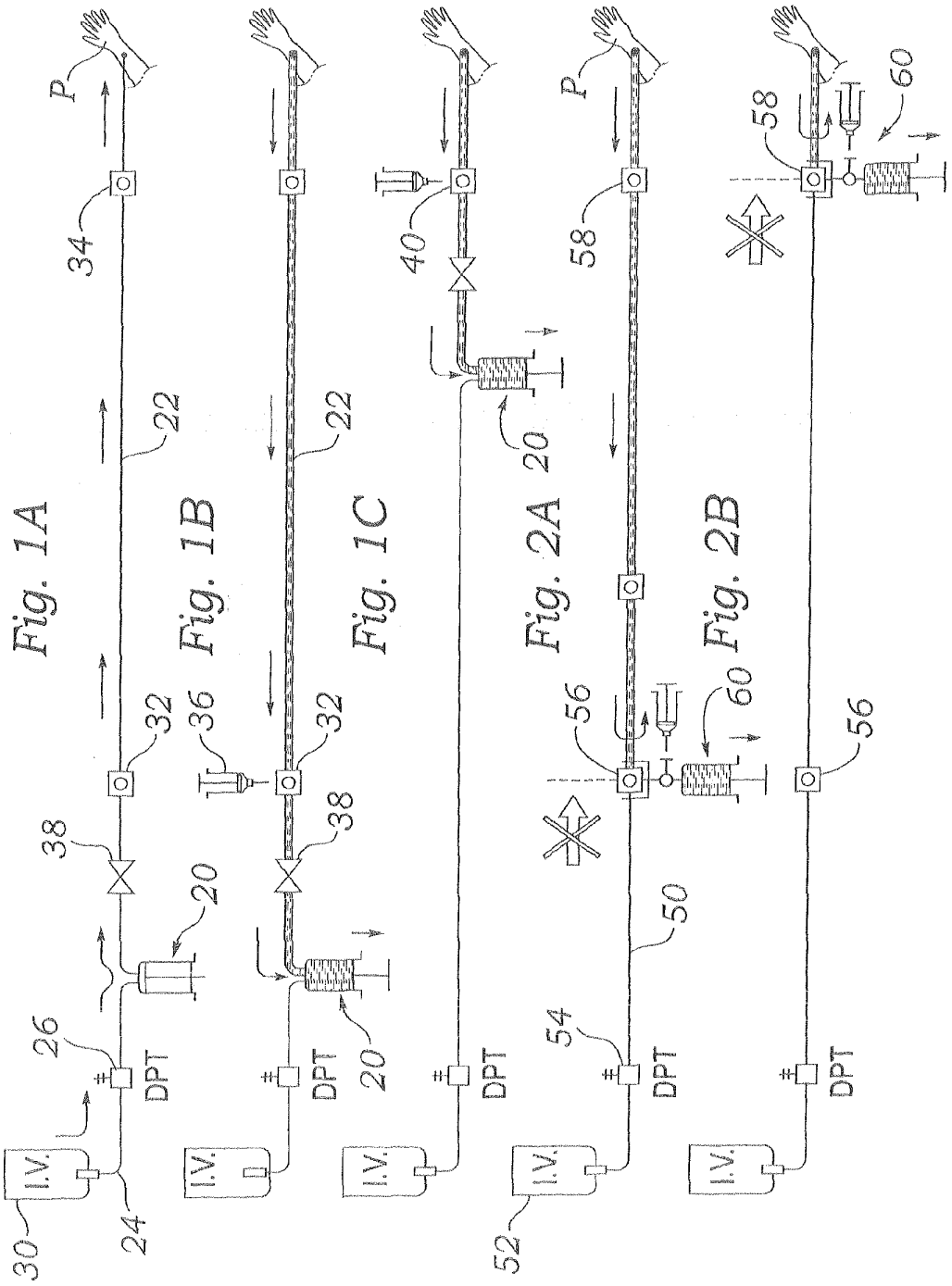
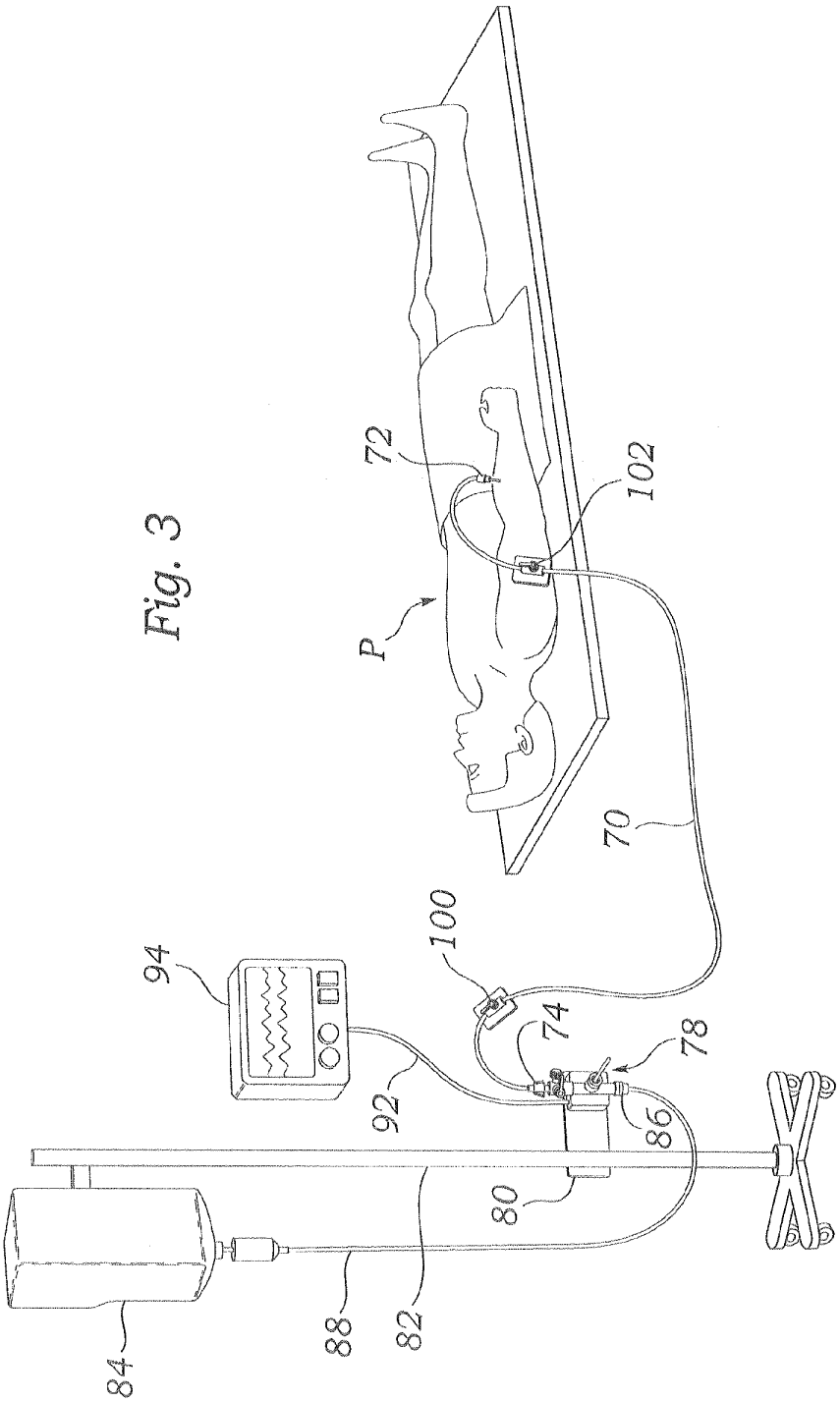

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Fig. 1B
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Fig. 1C
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Fig. 2A
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I.V.
Fig. 2B

Fig. 3



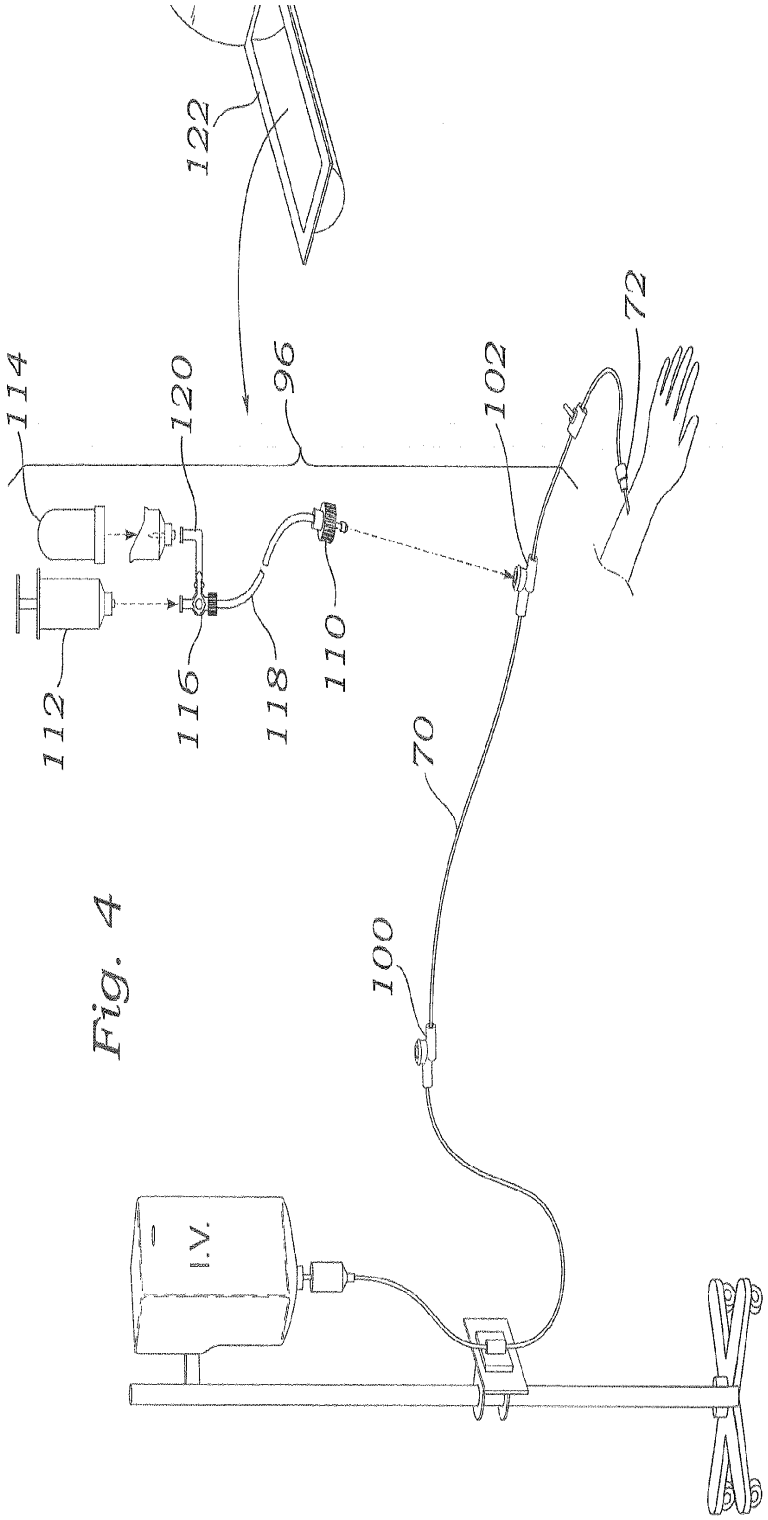


Fig. 4

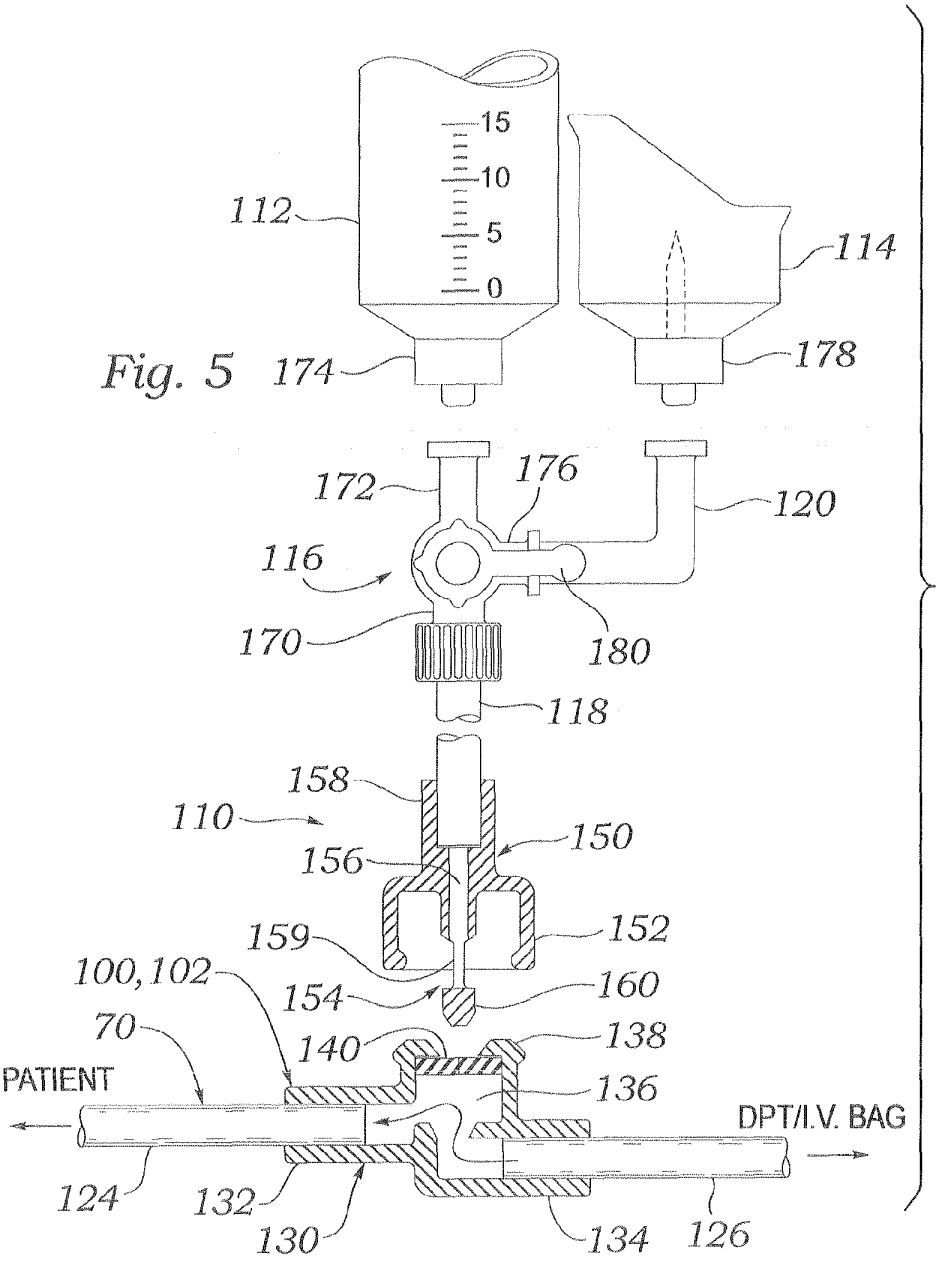

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DPT/I.V. BAG
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Fig. 5

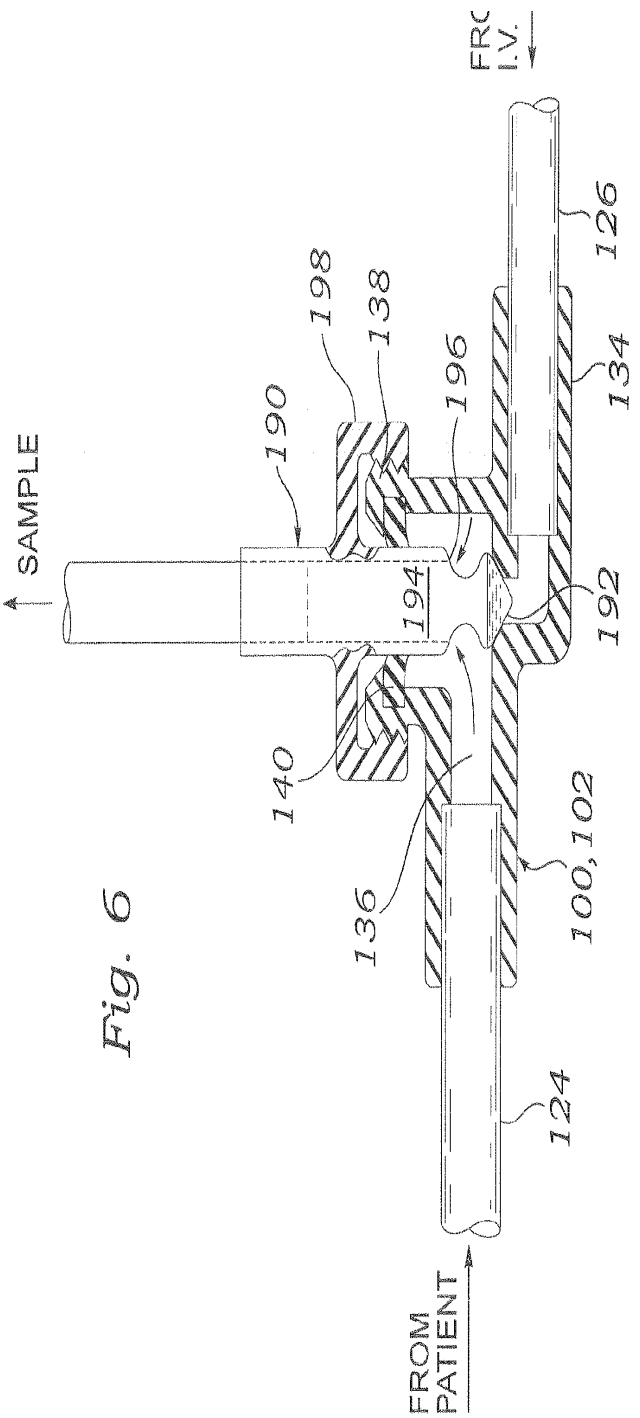

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I.V.
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FROM
PATIENT

Fig. 6

Fig. 7A

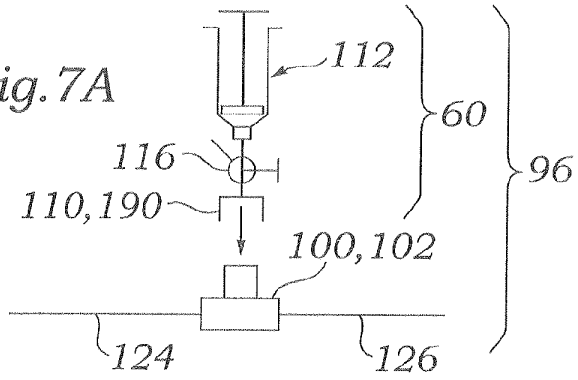


Fig. 7B

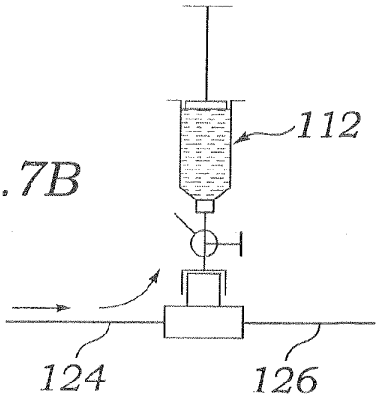


Fig. 7C

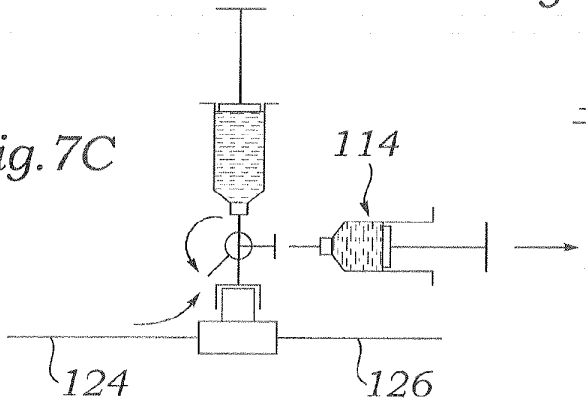


Fig. 7D

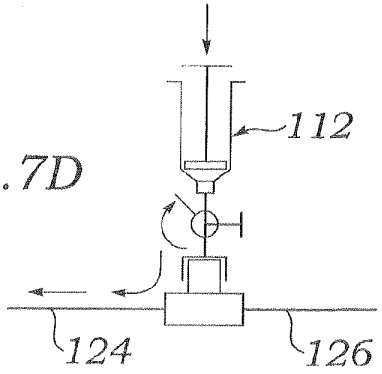


Fig. 7E

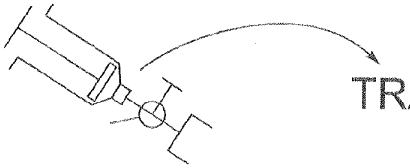




Fig.9A

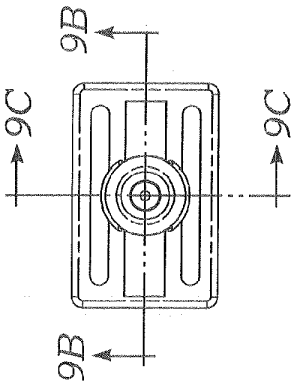


Fig.8B

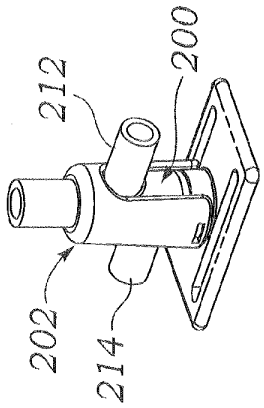


Fig.8A

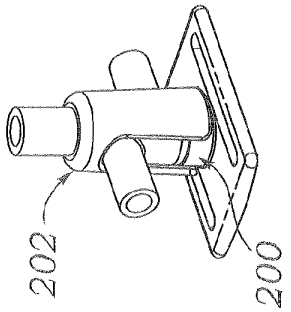


Fig.9C

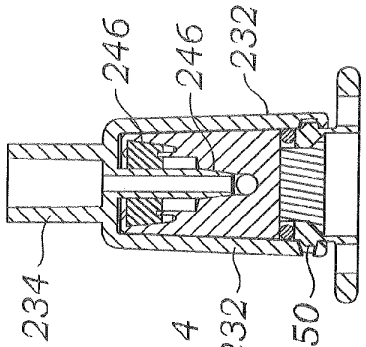


Fig.9B

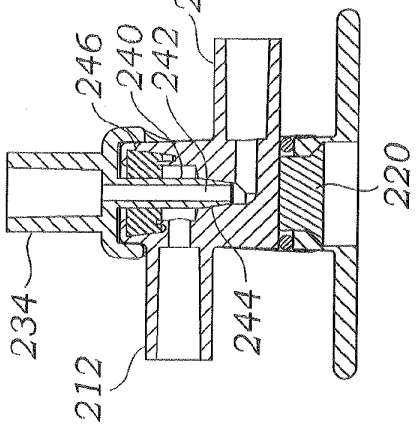


Fig.8C

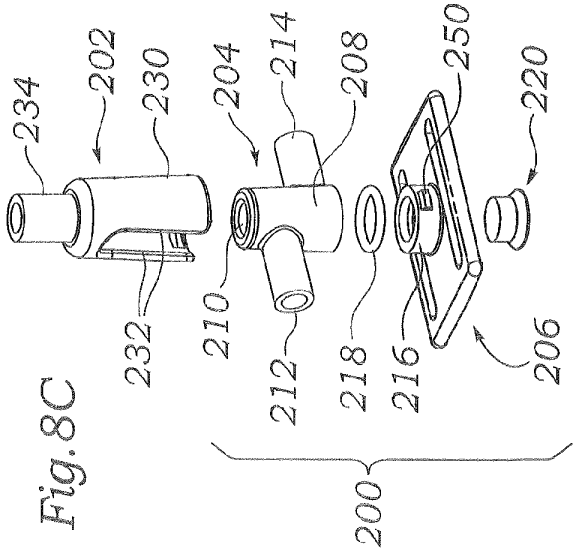


Fig. 10

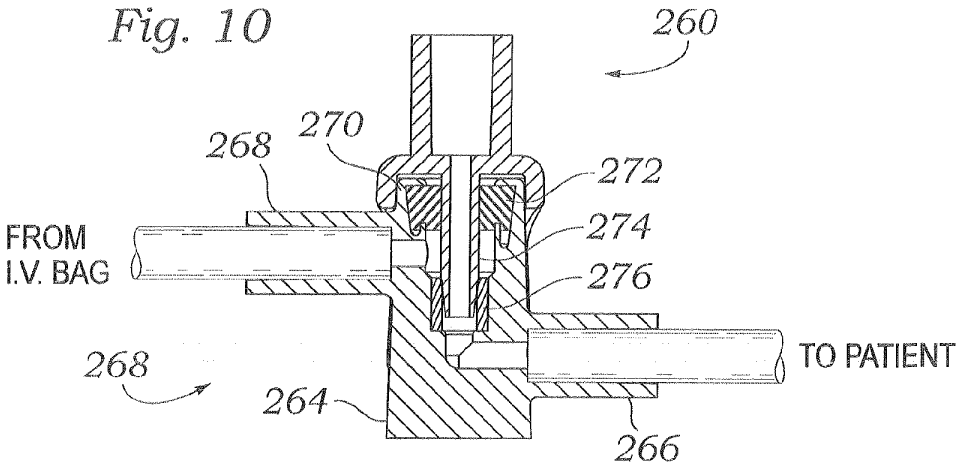

260
268
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272
274
276
FROM
I.V. BAG
TO PATIENT
268
264
266

Fig. 11

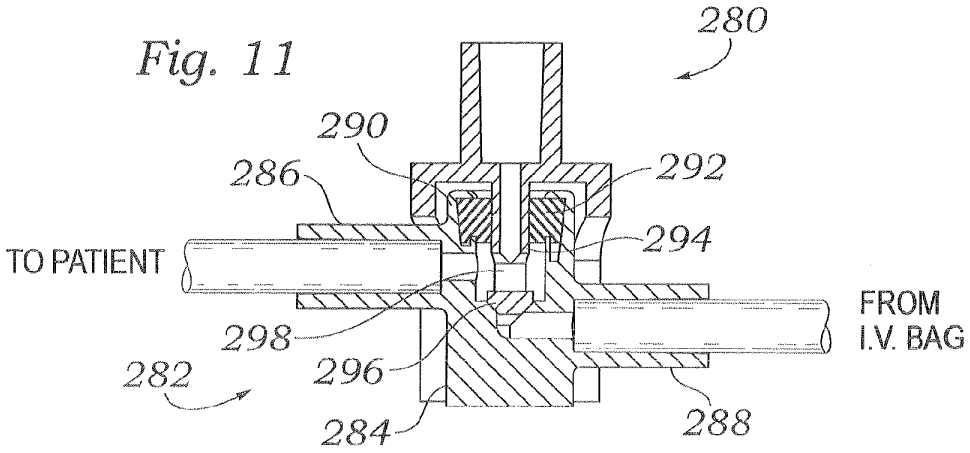

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294
TO PATIENT
FROM
I.V. BAG
298
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282
284
288

Fig. 12A

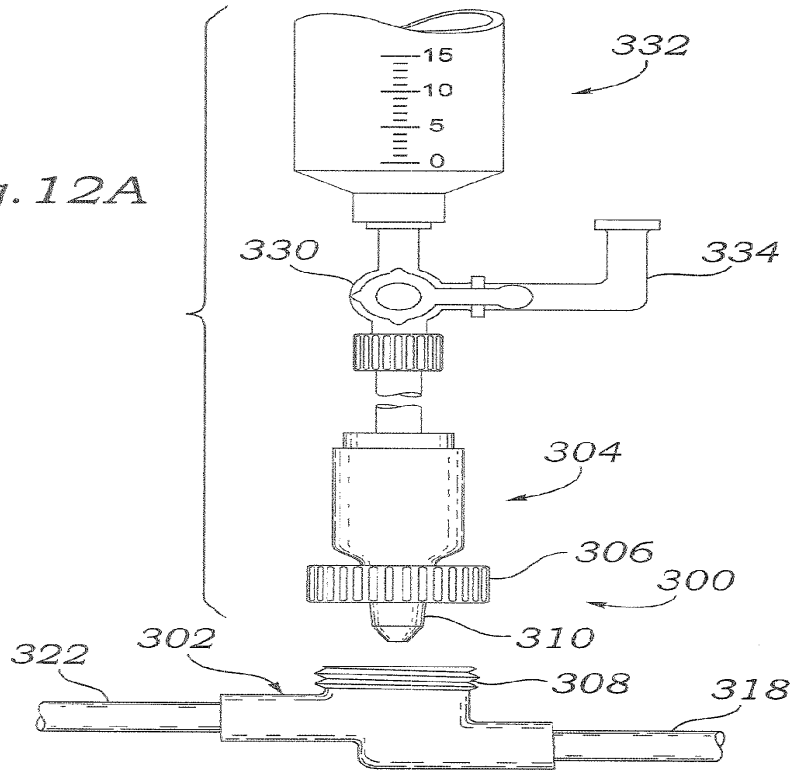
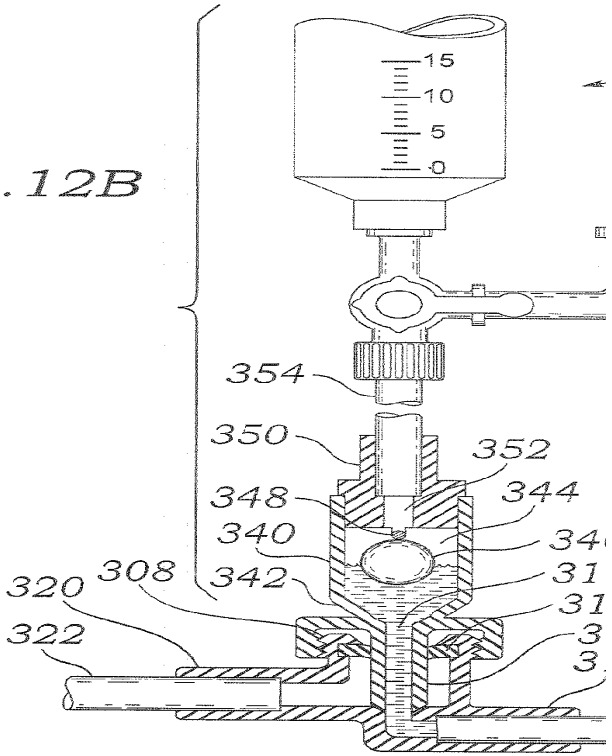


Fig. 12B



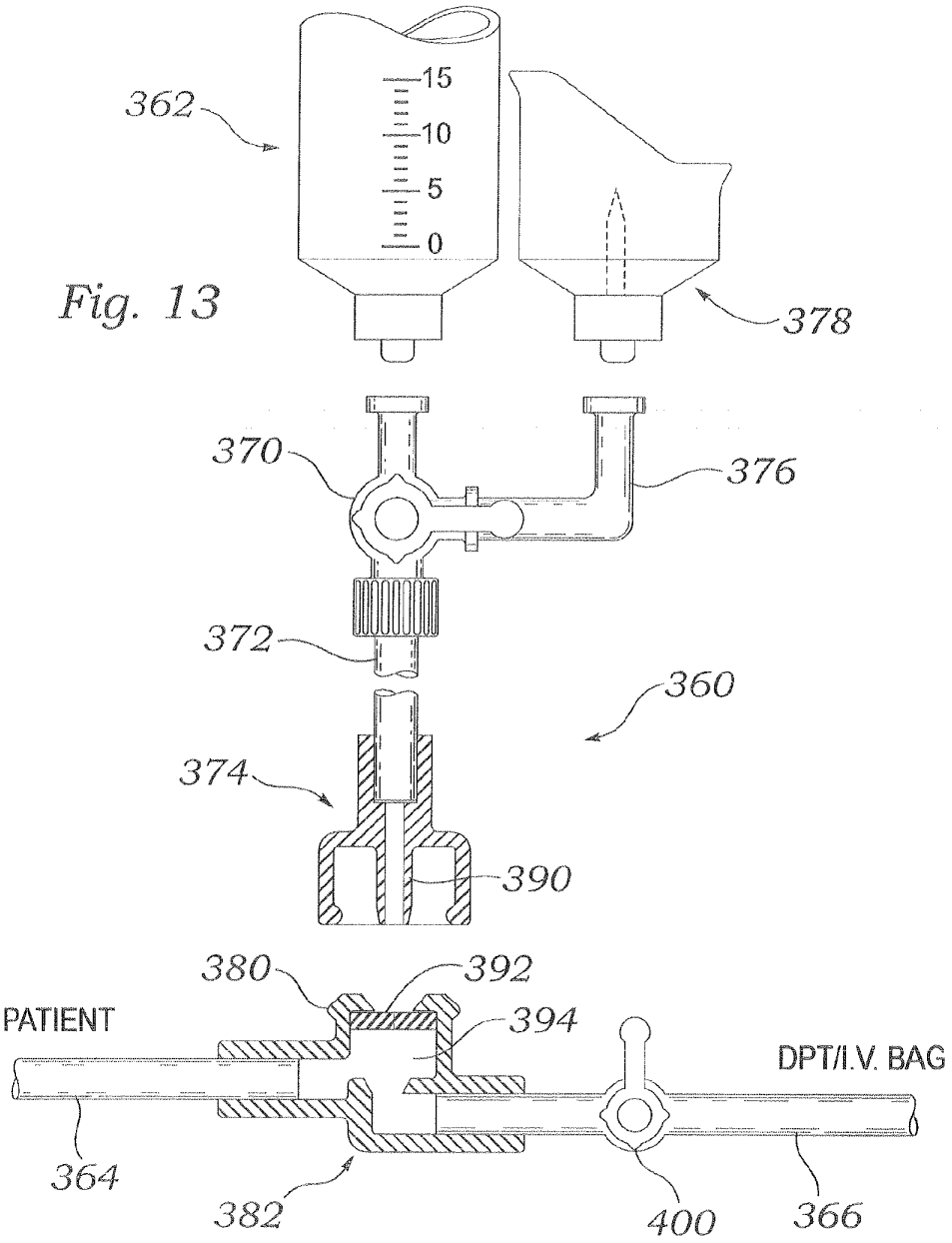

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Fig. 13

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.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2005)

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)

NCCLS simplifies the order of draw: a brief history.

Print

Title Annotation: *Clinical Issues; National Committee for Clinical Laboratory Standards, Phlebotomy*
Author: *Ernst, Dennis J.; Calam, Roger*
Geographic Code: *1USA*
Date: *May 1, 2004*
Words: *1926*
Publication: *Medical Laboratory Observer*
ISSN: *0580-7247*

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.

References

(1) Sun N, Knauf R. Cross contamination solved by technique. ASCP Summary Report. 1977;14(3):3.

(2) Calam R, Cooper M. Recommended "order of draw" for collecting blood specimens into additive-containing tubes. Clin Chem. 1982;28:1399.

(3) National Committee for Clinical Laboratory Standards. Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture. Approved Standard, H3-A2, Villanova, PA; 1991.

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(5) National Committee for Clinical Laboratory Standards. Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture. Approved Standard, H3-A4, Villanova, PA; 1998.

(6) McCall R, Tankersley C. Phlebotomy Essentials. 3rd ed. Lippincott Williams & Wilkins. Philadelphia, PA; 2003.

(7) Jacobsen R. Addressing "order of draw" in comparative calcium levels. MLO. 2001;33(12):6.

(8) National Committee for Clinical Laboratory Standards. Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture. Approved Standard, H3-A5, Wayne, PA; 2003.

RELATED ARTICLE: Alternatives to current order of draw

Some facilities have conducted internal studies that support a variation to NCCLS' order of draw. When reliable documentation supports an alternative order, the facility's protocol should take precedence. The Mayo Clinic in Rochester, MN, developed its own when it found that calcium levels drawn early in the order of draw can be significantly different than those drawn later in the order. Since immediate tourniquet removal is not always feasible (nor appropriate for ionized calcium collection), phlebotomists there follow an order of draw designed to protect against potentially erroneous calcium results, which includes a separate order of draw for syringes. In addition, tubes for trace-metal analysis are always first in order of draw at Mayo, since such specimens have been found to be contaminated by penetration of the sheathed back-end of the needle into any nontrace metal tube stoppers. Mayo's current order of draw is:

1. trace-metal collection tube (nonadditive)
2. gel separator tube (glass and plastic)
3. nongel serum tube (glass and plastic)
4. citrate tube
5. heparin tube
6. EDTA tube

7. oxalate/fluoride tube
8. ACD tube

Mayo also advocates a previous NCCLS order of dispensing from a syringe, i.e., tubes containing anticoagulants are dispensed first in order to minimize microclot formation in the syringe.

By Dennis J. Ernst, MT(ASCP), and Roger Calam, PhD, DABCC

Dennis J. Ernst, MT(ASCP), is director of the Center for Phlebotomy Education, editor of Phlebotomy Today, and an MLO editorial advisory board member. Roger Calam, PhD, is associate director of Clinical Chemistry at St. John Hospital and Medical Center, Detroit, MI. Both participated in the revision of the NCCLS venipuncture standard.

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JP 2009-131273

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bibliography close

(19) [Country of issue] Japan Patent Office (JP)

(12) [Type of publication] Published patent publication (A)

(11) [Publication number] JP 2009-131273 (P2009-131273A)

(43) [Published date]] June 18, 2009 (2009.6.18)

(54) [Title of Invention] Protease that activates blood coagulation factor VII

(51) [International Patent Classification]

C12Q 1/56 (2006.01)

A61K 38/43 (2006.01)

A61P 7/04 (2006.01)

A61P 43/00 (2006.01)

[FI]

C12Q 1/56 ZNA

A61K 37/48

A61P 7/04

A61P 43/00 111

[Request for examination] Yes

[Number of claims] 7

[Application form] OL

[Total number of pages] 25

(21) [Application number] Patent application 2009-57232 (P2009-57232)

(22) [Application date] March 11, 2009 (2009.3.11)

(62) [Indication of division] Division of Japanese Patent Application Hei 11-116411 [Original filing date] April 23, 1999 (1999.4.23)

(31) [Priority claim number] 19818495:6

(32) [Priority date] April 24, 1998 (1998.4.24)

(33) [Priority claiming country] Germany (DE)

(31) [Priority Claim number] 19851332:1

(32) [Priority date] November 6, 1998 (1998.11.6)

(33) [Country claiming priority] Germany (DE)

(31) [Priority claim number] 19851335:6

(32) [Priority date] November 6, 1998 (1998.11.6)

(33) [Priority claiming country] Germany (DE)

(31) [Priority claim number] 19851336:4

(32) [Priority date]] November 6, 1998 (1998.11.6)

(33) [Country claiming priority] Germany (DE)

(31) [Priority claim number] 19827734:2

(32) [Priority date] June 1998 22nd (1998.6.22)

(33) [Country claiming priority] Germany (DE)

(31) [Priority claim number] 19903693:4

(32) [Priority date] February 1, 1999 (1999.2.1)

(33) [Country claiming priority] Germany (DE)

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F term (reference)]
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wrap up close

(57) [Summary]
[Object] To discover a novel FVII-activating protease and its application.
SOLUTION: a) is inhibited by the presence of aprotinin, b) its activity is increased by calcium i ons and/or heparin or heparin analogues, and c) in SDS-PAGE, the molecular weight is reduce d in subsequent staining under non-reducing conditions. A protease that activates blood coag ulation factor VII, which exhibits one or more bands in the range of 50-75 kDa and, under red uced conditions, one or more bands in the molecular weight range of 10-35 kDa, as well as its The proenzyme is obtained from plasma or prothrombin complex (PPSB) concentrates by prior anion exchange chromatography followed by affinity chromatography using heparin or heparin analogues or dextran sulfate.

The present invention provides a test system for the qualitative and quantitative detection of said protease or its proenzyme, as well as a test system for its diagnostic application and said protease activating an amount of blood coagulation factor VII suitable for the lysis of fibrin-co ntaining thrombi. and/or pharmaceutical preparations containing the proenzyme thereof.
[Selection figure] None

The scope of the claims open —

1.

a) inhibited by the presence of aprotinin, b

) its activity is increased by calcium ions and/or heparin or heparin sulfate,

c) subsequent non-reducing conditions in SDS-PAGE shows one or more bands in the molecu lar weight range of 50-75 kDa by staining with , and in reducing conditions one band in the m olecular weight range of 40-55 kDa and one or more bands in the molecular weight range of 1 0-35 kDa. and

d) the band obtained in the reducing state in the molecular weight range 40-55 kDa in SDS-PAGE has the amino acid sequence: LLESLDP and the band obtained in the molecular weight r ange 10-35 kDa has the amino acid sequence: IYGGFKSTAGK. and/or

for the qualitative and quantitative detection of the proenzyme of said protease, the band ob tained in reducing conditions in SDS-PAGE has a molecular weight in the range of 60-65 kDa and contains the amino acid sequences: LLESLDP and IYGGFKSTAGK. In the test system, its p rotease activity is characterized by:

a) its activity to inactivate blood coagulation factor VIII/VIIIa or factor V/Va or b

) its activity to reduce blood clotting time in a comprehensive blood coagulation test or

c) its activity to activate the plasminogen activator or

d) its activity to activate FVII

.

2. The test system of claim 1

, wherein the activity of lowering blood clotting time comprises:

A test system measured by a) non-activated partial thromboplastin time (NAPTT) or

b) prothrombin time (PT) or

c) plasma recalcification time or

d) activated partial thromboplastin time (APTT) . 3. In the test system according to claims 1 and 2, the activity of activating and/or enhancing plasminogen activator comprises: a) single- chain urokinase PA (scuPA, single-chain urokinase plasminogen activator);) or b) a test system measuring by activation of single-chain tPA (sctPA, single-chain tissue plasminogen activator). 4. A test system according to any one of claims 1 to 3, which contains calcium ions in an amount of 0.001 mM or more. 5. a) inhibited by the presence of aprotinin, b) its activity increased by calcium ions and/or heparin or heparin sulfate, c) in SDS-PAGE with a molecular weight of 50 by subsequent staining under non-reducing conditions. showing one or more bands in the range of ~75 kDa, one band in the molecular weight range of 40-55 kDa and one or more bands in the molecular weight range of 10-35 kDa in the reduced state, and

and/or

Bands obtained in SDS-PAGE under reduced conditions are molecules in the range of 60-65 kDa

and wherein a mixture of the proenzyme of said protease containing the amino acid sequences: LLESLDP and IYGGFKSTAGK and a suitable proenzyme activator is used to test for prothrombin time-displaced tissue factor/thromboplastin.

6.

a) inhibited by the presence of aprotinin,

b) its activity is increased by calcium ions and/or heparin or heparin sulfate,

c) molecular weight 50 by subsequent staining in SDS-PAGE under non-reducing conditions. 1 or 2 or more bands in the range of ~75 kDa, in the reduced state 1 band in the molecular weight range of 40-55 kDa and 1 or 2 or more bands in the molecular weight range of 10-35 k

Da, and d

) The band obtained in the range of molecular weight 40-55 kDa under reducing conditions i n SDS-PAGE has the amino acid sequence: LLESLDP, the band obtained in the range of molec ular weight 10-35 kDa has the amino acid sequence: IYGGFKSTAGK, and/or

SDS- The bands obtained under reduced conditions in PAGE have molecular weights in the ra nge of 60-65 kDa and contain the amino acid sequences: LLESLDP and IYGGFKSTAGK. Assay system used for sex testing and quantification of single-chain plasminogen activator forms.

7.

A test system according to claims 1 to 6, wherein the plasminogen activator enhancing activi ty is

a) measured using a chromogen test or

b) A test system measuring the formation of plasmin itself or the lysis of fibrin clots brought about by plasmin in a coupling reaction in the presence of plasminogen.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to a protease for the activation of blood coagulation factor VII, methods for its isolation, detection and inactivation as well as pharmac eutical preparations comprising this protease. . BACKGROUND OF THE INVENTION The blood coagulation system consists of two different cascade-like pathways that activate blood clotting factors present in plasma. Depending on the induction mechanism, the intrinsic or extrinsic pa thway is preferentially used to initiate blood coagulation. [0003] When tissues are injured, t hromboplastin (tissue factor, TF and phospholipids) is exposed by the affected cells as starters of the extrinsic coagulation pathway. Membrane-localized thromboplastin can bind both blood coagulation factor VII (FVII) and circulating, activated FVII (FVIIa). In the presence of calciu m ions and lipids, this TF-FVIIa complex leads to binding of FX, which is converted to its activ ated form (FXa) by limited proteolysis. FXa then activates prothrombin to form thrombin, lead ing to the formation of fibrin, which ultimately causes wound closure. [0004] Further activati on of thromboplastin-binding FVII occurs initially by autocatalytic reactions, but especially aft er the initiation of the coagulation cascade it is supported by FXa and thrombin, leading in par ticular to a marked enhancement of the reaction cascade. [0005]

Administration of FVIIa or FVIIa-containing concentrates has been indicated for certain clinic al conditions. For example, in patients with hemophilia A who develop antibodies to FVIII as a result of administration of FVIII.
used the so-called FVIII alternative pathway activity (FEIBA) of FVIIa. Based on presently kno wn findings, FVIIa is well tolerated in this relationship, it does not produce thrombotic tendenc ies, and is sufficient to ensure that a limited but adequate degree of clotting occurs. Are suita ble. Recombinant FVIIa is already used therapeutically and prophylactically. FVII isolated from plasma can also be used after activation. Proteases such as thrombin can be used for this acti vation, however, these proteases themselves are capable of strongly activating blood clots an d may pose a thrombotic risk. For this reason, subsequent removal or inactivation of thrombin is necessary, resulting in losses. As a result of the thrombotic risk associated therewith, the us e of FXa or FIIa (thrombin) is often contraindicated and indicated only in emergencies, eg in c onnection with significant loss of blood and uncontrolled bleeding.
SUMMARY OF THE INVENTION
[
0006]
FVIIa is found in very low concentrations in the plasma of healthy individuals. Little is known so far about the formation and origin of FVIIa circulating in the blood. Traces of thromboplasti n expressed or released with cell destruction may play a role in this association. Factor XIIa, f or example, is known to cause activation of FVII under certain conditions, but the physiologica l relevance of this response has not yet been clarified.
[0007]
Surprisingly, a FVII-activating protease, distinct from all previously known proteases, has no w been discovered associated with the fractionation of human plasma and certain prothrombin complex concentrates. A study of this protease showed that it exhibited a particularly high am idolytic activity towards the peptide substrate S2288 (HD-isoleucyl-L-prolyl-L-arginine-pNA) fr om Chromogenix AB, Sweden. A special property of this protease is that its amidolytic activity is effectively inhibited by aprotinin. Other inhibitors such as the antithrombin III/heparin com plex are also suitable for its inhibition. On the other hand, its activity is increased by heparin and heparin-related substances such as heparin sulfate or dextran sulfate and calcium ions. Fi nally, it was found that this protease is capable of converting FVII to FVIIa in a time- and conc entration-dependent manner. This reaction is also inhibited by aprotinin. SUMMARY
OF THE INVENTION Accordingly , part of the subject matter of the present invention is that

a) aprotinin is inhibited by the presence and b) its activity is elevated by calcium ions and/or heparin or heparin-related substances. and c) in SDS-PAGE, subsequent staining in non-reducing conditions shows one or more bands in the molecular weight range of 50-75 kDa, and in reducing conditions one band in the molecular weight range of 40-55 kDa and molecular weight It is a protease that activates blood coagulation factor VII , exhibiting one or more bands ranging from 10 to 35 kDa . BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows protease concentration and inactivation of FVIII when protease and FVIII are incubated for a certain period of time.
FIG. 2 shows the inactivation of FVIII when the protease concentration is constant and FVIII is incubated for various times.
FIG. 3 shows the inactivation of FVIII when protease and FVIII are incubated with varying calcium concentrations in the mixture.
[Mode for carrying out the invention]
In the following

specification, the activated form of the protease is called "protease" and the non-activated form is called "proenzyme".
[0011]

This protease was further investigated and after concentration or isolation underwent a rapid loss of activity, which was observed in a solution containing 20 mM tris, 0.15 M NaCl, pH 7.5. Addition of albumin at a concentration of 0.1% also failed to prevent the activity of this protease from dropping to 50% after 1 hour at room temperature. On the other hand, very good stabilization of this protease was observed in solutions buffered to pH 6.5 with 50 mM sodium citrate. No or very little loss of activity was observed when the solution was adjusted to pH 4-7.2, preferably pH 5.0-7.0, even without the addition of specific stabilizers to the protease solution. However, it is expedient to add stabilizers to the solution, suitable stabilizers being, in addition to citrate, especially glutamate, amino acids such as arginine, glycine or lysine, calcium ions and sugars such as glucose, arabinose or An amount of 1 to 200 mmol/L, preferably 5 to 100 mmol/L of mannose can be mentioned. Effective stabilization is also achieved by the addition of glycols such as ethylene glycol or glycerol 5-80% by weight, preferably 10-60% by weight is used. In that case, the pH value of the stabilized solution should be between 4 and 9.
[0012]

The novel proteases, and also their proenzymes, are obtained by recombinant DNA methods or, for example, by production in the milk of suitable transgenic animals, in particular by fracti onation of plasma or prothrombin complex (PPSB) concentrates. can be done. The starting ma terial is then first subjected to anion exchange chromatography, followed by affinity chromato graphy of the eluate. Heparin or heparin-related substances immobilized on a matrix, such as heparin sulfate or dextran sulfate, are particularly suitable for affinity chromatography. Using such chromatographic methods, the novel proteases and/or proenzymes are selectively bound and can then be eluted again using known methods. The use of spacers can be recommended for coupling ligands to mattrex. A heparin-lysine matrix has been found to be particularly suit able for the isolation of novel proteases.

[0013]

In SDS-PAGE followed by staining, the proteases isolated by this method show one to severa l closely spaced bands in the molecular weight range of 55-75 kDa under non-reducing conditi ons. After reduction, one to several bands were observed in the molecular weight range of 15-35 kDa and one band was observed at 40-55 kDa. One additional band at 60-65 kDa was sho wn to constitute 5-10% of the total protein after scanning and quantitative evaluation, and th at non-activated proenzyme was also present. This result was supported by a suitable study u sing a monoclonal antibody directed against this protease. It was therefore concluded that the proenzyme of this protease could also be prepared, sterilized and used according to the meth od of the invention. Part of the subject matter of the present invention is therefore the proenz ymes of proteases that activate blood coagulation factor VII. The proportion of proenzyme is i ndicated by the 60-65 kDa band. Examples of suitable physiological activators of proenzymes correspond to amino acid sequences constituting the activation region of proenzymes, thrombi n, kallikrein or FVIIa, depending on their substrate specificity. Some of the properties of the novel protease mentioned above, namely the fact that it can be isolated from plasma or plasm a-derived prothrombin complex (PPSB) concentrates, inhibition of its amidolytic activity by ap rotinin and reduction and non-

reduction

The migration behavior described above in SDS-PAGE under both reducing conditions has bee n demonstrated by Hunfeld et al. 1999, 78: A42)

It recalls a protease isolated from a PPSB concentrate that has not been defined in detail. In t hat case, preparation was primarily accomplished using an aprotinin matrix. The activity has b een described as a thrombin-like activity as a result of the amidolytic cleavage of certain pepti de substrates. Hunfeld et al. found no effect on global coagulation parameters such as prothro mbin time, quick or platelet aggregation.

[0015]

N-terminal sequencing of the protease described by Hunfeld et al. shows that its cDNA is con sistent with that of the protein reported by Choi-Miura et al. (J. Biochem. 119:1157-1165, 19 96). In its primary structure, the corresponding protein exhibits homology with an enzyme na

med hepatocyte growth factor activating enzyme (HGFA). Two bands isolated from SDS-PAG E under reducing conditions were subjected to N-terminal sequencing and the following identit ies were established

. Molecular weight range of bands Amino acid sequence Reporter 10-35 kDa IYGGFK STAGK Present invention 30 kDa IYGGFKSTAG Hunfeld et al. 17 kDa IYGGFKSTAGK H Choi-Miura et al. 40-55 kDa LLESLDP Present invention

50 kDa SLDP Hunfeld et al.

57 kDa SLLESLDPWTPD Choi-Miura et al.

Nevertheless, at present it is still not possible to presume that these proteins are identical. In any event, none of the previously studied proteins described above have been reported to hav e FVIIa or other factor activating properties (see below).

[0017]

Based on its above-mentioned properties, the novel protease can be used diagnostically and therapeutically.

1

. Test Systems Using the Novel Proteases

The novel proteases can be used diagnostically in test reagents. Thus the presence of factor VII can be determined qualitatively and quantitatively in blood coagulation tests by adding no vel proteases.

Conversely

, the test system developed for measuring FVII activation can also be used for the detection and quantification of proteases. For this, the protease-containing solution is mixed with the FV II-containing solution and the FVIIa produced is quantified after an appropriate incubation tim e. This is for example Staclot(R) It can be performed using the FVIIa-rTF test (Stago/Boehring er Mannheim). Using the preferred procedure, this test is not limited to the concentration of F VII supplied. If the amount of protease in the form of a ratio of total protein is known, the rati o is: -

in a pure protease preparation, by the Kjeldahl method or other protein assays well known t o those skilled in the art, or

- can be determined using, for example, specific antibody-based antigen tests and suitable i mmunochemical assay methods such as ELISA, and then the specific activity of the protease p

reparation can be determined in a corresponding manner.

Surprisingly

, with further characterization of proteases, new properties have been discovered that allow additional measurements. Incubation of the proteases with blood coagulation factors VIII/VIII a and V/Va followed by quantification reveals that the blood coagulation factors are inactivate d in a manner independent of protease concentration and length of incubation. made rice field.

Another part of the subject matter of the present invention is therefore a novel test system for the qualitative and quantitative detection of proteases that activate blood coagulation fac tor VII, in which proteases are blood It can be quantified by its activity to inactivate coagulati on factor VIII/VIIIa or V/Va. This test system involves incubating a solution containing a prote ase with Factor VIII/VIIIa or Factor V/Va and determining the amount of residual Factor VIII/V IIIa or the amount of residual Factor V/Va by a conventional activity test. It is based on meas uring and then determining from this the amount of protease by comparison with a standard c urve. In carrying out this test, the incubation of the protease activity is inhibited by the additi on of limited amounts of aprotinin for a predetermined period of time, which has the advantag e that these concentrations do not affect the subsequent measurements of the test system. T he residual activity of the blood clotting factor is then determined by test methods well known to those skilled in the art. For this, the so-called Coamatic factor VIII test (Chromogenix AB), which mainly contains factors IX and X and quantifies the amount of FXa obtained by conversi on of a chromogenic substrate in the presence of a thrombin inhibitor, is used In terms of en abling (see description in [0007]), especially test systems have proven their worth. On the ot her hand, this amount is proportional to the amount of FVII or FVIIa. Determining the residua l FVIII activity then makes it possible to derive the concentration of protease present.

[0022]

Degradation of FVIII/FVIIIa or FV/FVa factors by proteolytic action can be clearly demonstrat ed by SDS-PAGE. Depending on how long the protease was incubated with, for example, the F VIII concentrate, the bands typical of FVIII disappear, while other new bands develop or the i ntensity of weaker bands increases. Thus, protease activity can also be correlated by quantifyi ng the attenuation or enhancement of a band, and thus can be quantitatively measured using, for example, protease preparations. Band intensities in SDS-PAGE electropherograms, or chan ges in band intensities by other electrophoretic methods, can be quantified using, for exampl e, a scanner and appropriate programs well known to those skilled in the art. Additionally, anti bodies to the blood clotting factors described above can be used in Western blots and can be employed for evaluation in the methods described above. Antibodies that specifically detect at tenuated bands or specifically developed bands are particularly suitable. In this connection, th ese antibodies can also be used to establish other immunochemical tests, such as ELISA.

[0023]

The proteolytic inactivation described for FVIII/FVIIIa is also observed when the protease is i ncubated with Factor V/Va, which exhibits some degree of structural homology with FVIII. De gradation can be monitored in a suitable activity test system and SDS-PAGE/Western blotting.
[0024]

Despite the inactivation of FV and FVIII, the addition of proteases to blood, platelet-rich plas ma or plasma at this time shortens the blood clotting time, i. It was found to exhibit gulent ac tivity. These test systems are understood to be, for example, non-activated partial thrombopla stin time (NAPTT), prothrombin time (PT) and recalcification time. These shortenings of time, measured for example in so-called coagulometers, by thrombus elastographs or otherwise in c hromogenic tests, correlate with the concentration of the procoagulant substance, so that the concentration of that substance in the sample is , can be inferred inversely using the calibratio n curve for blood clotting time. Concentrations of "FVII activators" can also be determined usi ng selected comprehensive coagulation tests.

"

FVII activator" also includes single-chain urokinase (scuPA, single-chain urokinase plasminog en activator), and single-chain tPA (sctPA, single-chain tissue

It has also been surprisingly found that it can provide an effective activator of plasminogen ac tivator), ie act as a plasminogen activator activator (PAA). The activity of activated PA can be measured, for example, using a chromogen. This property can therefore be used for the detec tion and quantification of "FVII activators". Activation of plasminogen activators can also be d etermined in coupling reactions in the presence of plasminogen, either by formation of plasmi n itself or by lysis of fibrin clots brought about by plasmin.

In summary

, therefore, it can be said that the protease can be incubated with a solution containing FVIII or FVIIIa and then the residual amount of FVIII/FVIIIa can be both detected and quantified by a suitable activity test. . Fv or Fva can be incubated with protease in the same manner and th e amount of Fv/Fva remaining can then be quantified. An unknown protease concentration ca n be quantitatively determined by comparing the increase in the amount of protease included in the test to a standard curve. Various comprehensive blood coagulation tests are likewise sui table for quantification, and protease concentrations are read from calibration curves based o n reduction of clotting times. The PAA activity of proteases can also be used for quantitation p urposes. A feature of these tests is that $CaCl_2$ is added to high concentrations of calcium, preferably >0.001 mM, particularly preferably >0.005 mM, suitable for FV and FVIII inactivation and PAA activity

.

It is particularly well exhibited when present in the form of As noted above, FV/FVIII inactivat ion is not enhanced by heparin or Only non-significant enhancement is observed. In contrast, PAA activity is stimulated in the presence of any substance, namely calcium and/or heparin or heparin-like substances. The protease-induced reaction can be performed in the presence of

a protease inhibitor, particularly heparin or a heparin-like substance (preferably in the presenc e of heparin) antithrombin III, C1-esterase inhibitor, α 2 -antiplasmin, inter-α-trypsin inhibitor or known inhibitors

. can be very efficiently attenuated or prevented by incubation with a low molecular weight pr otease inhibitor such as guanidinocaproic acid-p-ethoxycarbonylphenyl ester available under t he tradename FOY® . These substances can thus be used to stop the reaction, for example to accurately determine the incubation time or to further increase the specificity of the test. Red uction of free calcium ions in the mixture, for example with chelating agents, can also be used for this purpose. 2 . Stabilized preparations of Factors V and VIII

From the above observations regarding the proteolytic activity of novel proteases against blo od coagulation factors V and VIII, the problem of inhibiting the protease activity or attenuatin g its activity is due to the loss of production and the formation of fragments which are presum ably fragments of interfering proteins. occur to avoid All this is all the more important since F V and FVIII are usually prepared from cryoprecipitates obtained from plasma in the presence of calcium ions, the latter being required for maintenance of protein conformation. Another p art of the subject-matter of the present invention thus includes proteolytically formed Factor V and VIII fragments as a result of the fact that the proteases that activate blood coagulation Fa ctor VII are inhibited

.

is a stabilized preparation of free FV or FVIII. Further investigation revealed that the inactivati on of factors V and VIII by the proteases was particularly

It has been shown to occur efficiently in the presence of calcium ions at concentrations of 0.5 mM or higher, suggesting that the coagulation factor V or factor VIII preparations for inhibitio n of proteases that activate blood coagulation factor VII. Adjusting the concentration of calciu m ions to less than 1.0 mM, preferably less than 0.5 mM can effectively stabilize the Factor V and Factor VIII preparations. Although the factor V and factor VIII inactivating action of the pr otease is significantly reduced at these concentrations, the amount of calcium ions is still suffi cient to stabilize the conformation of the FV and FVIII molecules. The amount of calcium ions mentioned above should not be excessive not only in the final product, but also in the cryopre cipitate itself and in subsequent purification steps. Due to the aforementioned affinity of the protease or proenzyme for heparin and heparin-like substances, the protease/proenzyme can be isolated from FVIII- or FV-containing solutions by incubation with immobilized heparin or o ther immunological or affinity adsorbents

.

can be removed. Polyclonal or monoclonal antibodies, respectively antibody fragments, useful for the preparation of immunoadsorbents can be readily obtained by techniques known in the

art using all or part of the protease or proenzyme as the antigen.

However ,

in order to prevent proteolytic degradation of FV or FVIII, natural or synthetic protease inhibitors may optionally be used in addition to lowering the amount of calcium ions. Aprotinin, α2-Proteins such as antiplasmin, C1-esterase inhibitor or intertrypsin inhibitor can also be used as inhibitors. Low molecular weight substances known to those skilled in the art as synthetic serine protease inhibitors can also be used in this regard. Inhibitors such as antithrombin III, whose inhibitory potency is increased by heparin or heparinoids, can be added as well. Thus, although heparin by itself can increase the amidolytic activity of proteases on small chromogens, it was surprisingly found that it does not support the inactivation of FV/FVIII.

3

. Pharmaceuticals Comprising the Novel Proteases

The novel proteases and/or proenzymes can be used therapeutically.

They can be used alone or with substances that increase the activity of proteases, such as heparin or heparin-related substances, such as heparin sulfate, and/or calcium ions. In addition, factor VII can be added to this drug as well. The use of such agents that utilize their FVIII alternative pathway activity (FEIBA) is, for example, well tolerated due to the presence of, for example, antibodies against FVIII and/or FIX and/or FXI and/or contact phase proteins such as FXII. is present, or other types of missing conditions are present. In this context, FVII can be activated either in vitro, in plasma, in concentrated fractions, or by action on purified FVII. The novel blood clotting agents can also be used ex vivo for prevention of systemic bleeding or to stop bleeding.

[0034]

On the other hand, the observed inhibition of novel proteases by aprotinin or the inhibitors mentioned above can be used to develop drugs comprising protease inhibitors with reduced ability to clot blood. In addition to this, the novel proteases can also be used to identify physiological and non-physiological factors such as synthetic peptides that impair blood coagulation through their protease inhibitory action. Particularly efficiently transformed chromogenic substrates, such as the peptide sequence of S2288 (see above for details), can be used as a structural basis for this. If these preparations do not contain proteolytic activity, the addition of suitable inhibitors to the clot preparations may also be necessary during their preparation.

[0035]

As the protease was further characterized, properties were discovered that open up additional potential uses as so-called "Factor VII activator" proteases. single-stranded plasmid Incubation of a nogen activator, e.g., pro-urokinase (single-chain urokinase, sucPA, single-chain urokinase plasminogen activator) or sctPA (single-chain tissue plasminogen activator) results in the activation of these positive 'factor VII activators'. Resulting in activation of the minogen activator (PA). In this connection, the proteolysis of single-chain PA is limited, resulting in the formation of double-chain proteases, which are particularly suitable for plasminogen activa

tion. The plasmin produced is the effector of fibrinolysis, the physiological system involved in the dissolution of thrombi. PA, such as pro-urokinase or tPA, is an endogenous protein that is released on demand and, as is known, activated by plasmin or kallikrein (scuPA). The mechanism by which scuPA is activated in health has not yet been fully elucidated. The plasminogen activator is for therapeutic use as an isolated or recombinantly prepared protein in pharmaceutical preparations associated with thrombotic diseases or complications such as femoral vein thrombosis, myocardial infarction or stroke

.

can be done.

[0037]

The nature of the now discovered "Factor VII activator" allows the latter to be used for in vivo or ex vivo activation of plasminogen activators such as urokinase or sctPA. This activity also applies to the use of this protease, particularly in combination with single- or double-chain plasminogen activators or anticoagulants, as well for the prevention or treatment of thromboembolic disease. This potential use is consistent with the fact that proteases can also act in a procoagulant fashion. The question of which of the two responses takes precedence is presumably resolved by the availability of physiological substances. According to current knowledge, factor VII is moderately activated in plasma and is constantly maintained at a certain concentration so that sudden vascular injury can be dealt with immediately. On the other hand, tissue plasminogen activator as well as urokinase plasminogen activator are present in only nanogram quantities in 1 ml of plasma. Its concentration is elevated by secretion or synthesis of plasminogen activators only when fibrin deposition or thrombi occur, which are then activated locally, especially when they bind to thrombi, and then Activating plasminogen to exert their thrombolytic action. When single-chain PAs are present, their activation exceeds that of FVII, especially in a locally restricted manner, thereby allowing regulation to physiological conditions. Thus, this protease also modulates hemostasis, thereby potentially applying to replacement with proteases and/or proenzymes in cases of congenital or acquired defect conditions.

[0038]

Another part of the subject matter of the present invention is therefore a pharmaceutical preparation consisting of an amount of blood coagulation factor VII-activating protease and/or its proenzyme form sufficient to lyse fibrin-containing thrombi. The formulation can also contain a single chain plasminogen activator (PA) and/or an anticoagulant. If a proenzyme is present, it may also be advantageous to use a suitable activating agent within or in conjunction with the pharmaceutical formulations described above.

[0039]

Since it has been found that the plasminogen activator potentiating action of the "FVII activator" is enhanced in particular by calcium and/or heparin and heparin-like substances such as dextran sulfate, soluble calcium salts and/or heparin Alternatively, pharmaceutical preparations containing heparin-like substances can be advantageously used for lysing fibrin-containing thr

ombi according to the present invention. In this context, the protease/proenzyme, alone or in combination with a single- or double-chain plasminogen activator, optionally exerts a specific affinity for the protease, thereby increasing plasma half-life. It can be used as an extended ca rrier material or as a mediator to the surface together with a material that increases its activit y.

[0040]

Pharmaceutical preparations consisting of blood coagulation factor VII-activating protease ca n be used for the treatment of diseases caused by fibrin-containing thrombi due to their specif ic fibrinolytic action. The fibrinolytic process is also involved in the wound healing process. In t his connection, the proteases and/or proenzymes can be administered intravenously or topical ly, subcutaneously, intradermally or intramuscularly or topically in the case of injuries or woun ds or bound to a suitable carrier matrix. . Both proteases/proenzymes isolated from body fluid s such as blood or plasma and recombinantly or transgenically prepared proteases/proenzyme s can be used in this context. The protease/proenzyme is also suitable as a component of so-c alled fibrin glues, which must not contain substances that inhibit the protease/proenzyme, suc h as aprotinin. In this case, the clot-shortening action of proteases is utilized. The above pro teases/proenzymes can be used for congenital or acquired hemostatic defects, (generalized) b leeding episodes, various thrombosis-related complications

.

When used to treat bleeding, it is advantageous to add the protease/proenzyme together with FVIII and, if desired, further clotting factors.

4

. Method for Sterilizing FVII-Activating Protease

Being a protein isolated from human plasma, the novel protease and/or its proenzyme can o nly be used as a pharmaceutical preparation if it has been previously subjected to virus-inacti vating treatment. can do. The sterilization process is recognized as the most important proces s, especially for virus inactivation. However, the proteins to be processed require adequate sta bility to heating at about 60° C. for up to 10 hours. Optimal stabilizers must be determined se parately for each protein and their concentrations optimized.

In the case of novel proteases and/or their proenzymes, the conditions for stabilizing protein s in non-sterilized solutions have already been described above. A slightly acidic pH has prove n to be particularly advantageous in this case. However, novel proteases and/or their proenzy mes typically lose 50% or more of their original activity upon sterilization under these conditio ns. The sterilization of the pharmaceutical formulations comprising the novel proteases and/ or their proenzymes is carried out by subjecting the preparation to a

) pH range 3.5-8.0, preferably pH range 4.0-6.8; and/or c) one added sugar or combinatio n of different sugars at a total concentration of 0.01 mol/L or more, preferably 0.05 mol/L or more . 05 g/ml or more, preferably 0.2 g/ml or more; and/or d) one or more substances cap able of forming a complex with added calcium ions such as citric acid, oxalic acid, ethylenedia

minetetraacetic acid, etc. Preparing in the presence ensures optimum stabilization results. Additives such as albumin, Haemaccel® ′ heparin and heparinoids, glycerol , glycols and polyethylene glycols can be used separately or mixed together. After sterilization is complete, sugars, amino acids and other additives added as stabilizers can be reduced or completely removed from the preparation using methods well known to those skilled in the art. The results of the sterilization process are shown in Examples 12 and 13. [Example]

Example 1

Activation of FVII by the proteases prepared was demonstrated using the Staclot® FVIIa-rTF test system (Stago/Boehringer Mannheim) . This detection system has the specific property that preformed activated FVII (FVIIa) can only be used to inhibit the extrinsic coagulation pathway.

It is based on (recombinant) soluble tissue factor (rTF). This allows the actual content of FVIIa to be accurately determined, as opposed to using intact tissue factor.

Activation experiments were

performed using isolated FVII (Enzyme Research Labs). This FVII itself contains traces of FVIIa since it was isolated from human plasma. The concentration was adjusted to 0.05 IU/ml of FVII by dilution with buffer. FVII was incubated with test substances for 10 minutes at room temperature and then tested for true FVIIa content. FVIIa content was quantified using a standard curve constructed in parallel.

In preliminary

experiments, not described here, aprotinin completely inhibited the activity of the prepared protease at the concentrations used, but had no direct effect on FVIIa and showed no direct effect on the FVIIa-rTF test system. It was confirmed that there was no significant effect on

The results listed below relate in each case to triplicate measurements. That is, the following experiments were set up as follows.

1

. FVII:

Non-activated FVII was used as a control assay. It already contains traces of FVIIa (see abov

e) in the order of 10 mIU/ml of FVIIa.

2

. FVII+Aprotinin:

In this assay, FVII was incubated in the presence of aprotinin and the FVIIa-rTF assay was u sed to demonstrate that FVIIa itself was not inhibited nor was the test affected by the aprotini n used. This was confirmed (by comparison with Assay 1).

[0050]

3. Protease + FVII (incubation) then addition of aprotinin:

Result: FVIIa 18 mIU/ml

In this case the protease was given time to activate FVIIa. Aprotinin was added only to wash out the protease, after 10 minutes of incubation. The resulting FVIIa was quantified by the FV IIa-rTF assay. Thus, subtracting the basal value of FVIIa (assay 1), 8 mIU/ml of FVIIa was for med by the activity of the protease under the conditions chosen.

4

. Protease + aprotinin then addition of FVII:

Results: FVIIa 11 mIU/ml

In this assay the protease was inhibited with aprotinin prior to contact with FVII. Neither sub sequent incubation with FVII nor subsequent quantification of FVIIa resulted in a significant in crease in FVIIa content (the range of variation in the assay, ie 11 and 10 mIU/ml in assay 1, i s not considered significant).

5

. Protease:

Results: FVIIa 0 mIU/ml

This assay demonstrated that the protease itself had no effect on the FVIIa-rTF test system at the concentrations chosen.

In summary, from the above

- the described proteases activate FVII;

- the activation of FVII by proteases occurs "directly", i.e. independently of the presence of r TF;

- FVII activation is inhibited by aprotinin; aprotinin itself has no significant effect on the test system;

is concluded. Example 2 This example illustrates how FVII is activated in a reaction that is in dependent of the concentration of protease and the time the protease is incubated with FVII . The test system and reagents were selected to correspond to those described in Example 1. In the first series of experiments, the initially introduced FVII was preincubated (5 min at roo m temperature) with protease-containing solutions at various dilutions (1:5, 1:10 and 1:20), f ollowed by aprotinin (a protease inhibiting) and subsequently tested for their FVIIa content in the FVIIa-rTF assay. Again, a parallel assay in which the protease was inhibited by aprotinin b efore contacting with FVII served as a control. Results are given as activation factors. ie x ti

mes the value measured in the control assay described above. Assay: protease + FVII, incub ation, + aprotinin Control: protease + aprotinin, incubation + FVII

[Table 1]

プロテアーゼ溶液の希釈度	活性化係数	
	アッセイ	対 照
1：5	2.6	1.0
1：10	2.0	1.0
1：20	1.6	1.0

From this it is concluded that FVII is activated by proteases in a protease concentration-depe ndent manner. It was also demonstrated that FVII was activated by proteases in a manner t hat was independent of the length of incubation when the co-reactant concentration was kept constant

.

When equal volumes of a solution containing 0.2 IU/ml FVII and a 1:10-diluted protease solut ion were incubated together, aprotinin was added (to stop activation) after a corresponding pe riod of incubation, followed by: of FVIIa content was obtained.

[Table 2]

インキュベーションの長さ	活性化係数
0 分	1.0
2.5 分	1.3
5.0 分	2.0
10.0 分	2.8
40.0 分	＞3.8

From this it is concluded that FVII is activated in a time-dependent manner by proteases. Ex ample 3 This example will be used to demonstrate that protease activation of FVII is enhanc

ed by the presence of calcium ions and heparin

. 25 µl of protease-containing solution was added to 50 µl of

- buffer (control)
- 15 mM $CaCl_2$
- heparin 50 USP units/ml -

Pathromtin (lipid mixture, aliquot dissolved according to manufacturer's instructions) for 5 minutes at room temperature, then 150 µl of tris/NaCl buffer (pH 8). .2) and 25 µl of chromogenic substrate S2288 (3 mM), followed by measurement of absorbance over time at 405 nm (37° C.). Activation factors (x-fold) relative to buffer controls are shown in the table below. [Table 3]

アッセイ	活性化係数（緩衝液対照に対する倍数x）
緩衝液対照	1.0
＋$CaCl_2$	3.6
＋ヘパリン	2.6
＋脂質	0.9
＋$CaCl_2$＋ヘパリン	4.3
＋$CaCl_2$＋脂質	3.3
＋ヘパリン＋脂質	2.7
＋$CaCl_2$＋ヘパリン＋脂質	3.7

Under the conditions used in this example, a significant increase in protease activity can be observed in the presence of calcium ions and/or heparin. Example 4 In each case a solution containing 10, 1 or 0.1 µg/ml of protease was mixed with 25 µl of FVII (2 IU/ml) followed by 25 µl of CaCl 2 (25 mM) and

25 µl of Pathromtin® (Dade Behring GmbH) was added. After incubation for 0, 3, 10 and 20 minutes at 37° C., the reaction was stopped by adding 400 µl of aprotinin (500 KIU/mg). A sample to which aprotinin was added first was used as a control. Each sample was diluted in tris buffer/BSA. In each case 50 µl of this solution were mixed with 50 µl of the factor reagent [mainly consisting of FIXa, FX and thrombin inhibitors, modified according to the Cosmatic® $^{F}_{VIII}$ test, Chromogenix AB] and incubated at 37° C. for 10 minutes. 50 µl of substrate (eg S2765, Na-Cbo-D-Arg-Gly-Arg-pNA) was added, followed by the addition of 50 µl of acetic acid (5

0%) to stop the reaction after a defined time of incubation, OD 405 nm was then measured. A s tandard curve of FVIII was used to determine the concentrations in the samples. Results :

In the first assay, the protease incubation time with FVIII (2 IU/ml) was kept constant (10 m in), but the protease concentration was varied (0.1, 1 and 10 µg/ml). The reaction was stoppe d and the residual concentration of active FVIII was determined. Increasing protease concentr ations resulted in a corresponding inactivation of FVIII (Fig. 1).

The protease content of samples can be quantified using a suitable standard curve.

In the second assay, the concentration of protease was held constant (10 µg/ml), FVIII (2 I U/ml) and incubation time were varied. A significant decrease in the residual concentration of active FVIII was observed with increasing incubation time (Fig. 2).

Example 5 The effect of "FVII activator

" on factor V activity was examined.

25 µl of protease-containing solution (0-100 µg/ml) was incubated with 50 µl of FV (5 IU/ml) and 25 µl of $CaCl_2$ (0-20 min), then 400 µl of buffer containing 100 KIU/ml aprotinin was add ed. .

In both cases, 100 µl of each incubation assay was then incubated with 100 µl of FV-deficien t plasma for 1 minute at 37° C., then 200 µl of Thromborel S® were added, mixed and clottin g time was measured using a Schnitger & Gross coagulometer . was measured. Residual activity of FV was determined.

result:

[Table 4]

プロテアーゼ濃度 (µg/ml)	FVの残留活性 プロテアーゼとFVのインキュベート時間(分) 0	10	20
10	93	91	100
30	100	93	28
100	100	29	13

This example demonstrates that FV was inactivated by proteases over time. Example 6 The effect of "FVII activators" on blood clotting

times in a so-called global test was investigated using a Schnitger & Gross coagulometer. All the difference values given correspond to a shortened blood clotting time by this amount. NAPTT (non-activated partial thromboplastin time) protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml. 100 μl of each of these solutions were incubated with 100 μl of citrated plasma (from standard plasma pools or individual donors) and 100 μl of Pathromtin® for 2 minutes at 37° C., followed by addition of 100 μl of ^{25} mM $CaCl_2$ followed by blood. Clotting times were measured. Differences between these measurements and the corresponding blood clotting times obtained using buffer instead of protease were determined.

[Table 5]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(213秒)	0	13	20	42	43
1	0	20	33	42	41
2	0	27	31	45	47
3	0	13	14	23	29
4	0	18	37	51	50
5	0	25	49	54	46

Addition of the FVII activator resulted in a concentration-dependent shortening of NAPTT. Plasma Calcium Reprecipitation Time Protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml

. 100 μl of each of these solutions were incubated with 100 μl of citrated plasma (either from standard plasma pools or from individual donors) at 37° C. for 1 minute, then 100 μl of 25 mM $CaCl_2$ were added and clotting times were measured . Differences between these measurements and the corresponding blood clotting times obtained using buffer instead of protease were determined.

[Table 6]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(283秒)	0	17.2	15.1	30.5	50.4
1	0	29.8	51.7	60.3	90.1
2	0	25.2	51.7	69.5	101.3
3	0	28.0	—	39.0	74.6
4	0	27.3	42.7	55.6	91.8
5	0	44.3	69.1	101.2	134.2

PT (prothrombin time)

protease-containing solutions were diluted with buffer to 100, 30, 10 and 3 μg/ml . 100 μl of each of these solutions is incubated with 100 μl of citrated plasma (either from standard plasma pools or from individual donors) at 37° C. for 1 minute, then 200 μl of Thromborel S® (Dade Behring GmbH) are added, followed by blood clotting time was measured.

Differences between these measurements and the corresponding blood clotting times obtained using buffer instead of protease were determined.

[Table 7]

	血液凝固時間の差（緩衝液－サンプル、秒）				
	プロテアーゼ濃度（μg／ml）				
サンプル番号	0	3	10	30	100
標準ヒト血漿(13.6秒)	0	1.0	1.7	1.5	2.4
1	0	0.7	1.3	2.4	2.7
2	0	0.3	0.4	1.7	3.1
3	0	0.4	0.7	1.5	1.8
4	0	0.1	0.7	1.8	3.1
5	0	0.3	0.5	1.2	2.8

Example 7 The

plasminogen activator activating action of "FVII activator" was examined using single-chain urokinase (scuPA) and single-chain tPA (sctPA).

Assay:

0.1 ml PA solution (20 μg/ml scuPA or 100 μg/ml sctPA) + 0.1 ml

test buffer or

100 U/ml heparin in test buffer or

20 mM $CaCl_2$

in test buffer + 0.5 ml test buffer + 0.1 ml test buffer

1 ml protease/sample (increasing concentrations; 2-10 μg/ml scuPA

or 50-200 μg/ml sctPA)

incubation at 37° C.

+ 0.1 ml aprotinin at 100 KIU/ml in test buffer

2 min incubation at 37° C.

+ 0.1 ml For the substrate S-2444 (3 mM)

control, aprotinin is first introduced instead of plasminogen activator (PA) prior to the first in cubation, and so on through each case. On the other hand, PA was not added thereafter until i t was added instead of aprotinin.

The difference in measurements (Δ) $\Delta OD_{405\ nm}$ was measured optically. The control values obtained were subtracted from the sample/protease values and in this way the PA activity pro duced by the PAA activity was measured (mIU/min).

Results

:

Activation of scuPA (20 μg/ml scuPA, 2-10 μg/ml "FVII activator")

[Table 8]

A．刺激物質：なし

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	25	60	117
5	79	179	165
10	186	449	517

B．刺激物質：ヘパリン

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	190	332	425
5	330	455	458
10	417	462	460

C．刺激物質：$CaCl_2$

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） FVIIアクティベーター（μg／ml）		
	2	5	10
2	255	370	401
5	338	424	438
10	416	445	448

The table illustrates the fact that scuPA is activated in a manner that depends on the concentration of the "FVII activator" and the length of incubation. At the same time, both heparin and calcium showed a stimulatory effect on the activation of PA induced by proteases. Activation of scuPA (100 µg/ml sctPA, 50-200 µg/ml "FVII activator") The turnover rate of activated tPA is only increased by a factor of 3-4 compared to the tPA proenzyme
. (In the case of uPA it increases by a factor of 1000-1500), so high concentrations of the two co-reactants had to be chosen in order to obtain an analyzable measurement signal.

[Table 9]

A.

インキュベーション時間（分）	得られたＰＡ活性（ΔｍＩＵ／分） ＦＶＩＩアクティベーター(200μg／ml)
1	10.2
2	16.8
5	38.8
10	60.2
20	73.3

B. 「ＦＶＩＩアクティベーター」の濃度依存性(インキュベーション、時間：20分、37℃）、刺激物質：ヘパリン（100IU/ml）

ＦＶＩＩアクティベーター（μg／ml）	ＰＡ活性(ΔmIU／分)
50	33.6
100	51.0
200	71.9

C. 刺激物質（インキュベーション、時間：20分、37℃）

刺激物質	ＰＡ活性(ΔmIU／分)
なし	5.9
$CaCl_2$	25.3
ヘパリン	63.8

The table demonstrates that sctPA was also activated in a protease concentration- and incubation time-dependent manner. Both heparin and calcium ions showed a stimulatory effect on the ability of the 'FVII activator' to activate PA. Example 8 Two FVIII-containing solutions, one essentially free of von Willebrand Factor and the other containing vWF, were incubated in the presence of the protease described above and calcium. Residual FVIII activity was measured by a chromogen test after a predetermined time and correlated with a protease-free control assay. For this, 25 µl of a solution containing 0.1 IU/ml of FVIII were treated with an equ

al volume of protease solution (μg/ml) and the whole was mixed with 25 μl of CaCl 2 (25 mM) . After incubation at 37° C. for 0, 5, 10 and 20 minutes, it was treated in each case with 400 μl of a solution containing 200 KIU/ml aprotinin in order to terminate the proteolytic activity o f the protease. Preliminary experiments have shown that this concentration of aprotinin has n o significant interfering effect on the FVIII activity test (assays 1+3) described below. In Assa y 2, the protease was incubated with aprotinin prior to contact with FVIII and then manipulate d as described above.

In each case 50 μl of the stopped sample (or after further dilution) were then treated with s o-called factor reagents, consisting mainly of FIX, FX and thrombin inhibitors, and incubated a t 37° C. for 10 minutes . Addition of 50 μl of chromogenic substrate which is cleaved by activa ted FX was followed by incubation for 5 minutes before adding 50 μl of acetic acid (50%) to st op the reaction and ΔOD 405 nm was measured . FVIII activity (mIU) was determined using a s tandard curve prepared from FVIII concentrates and constructed using the dilution series inclu ded in the test.

FVIII activity is

expressed as a percentage of the control to which no protease was added.

result:

[Table 10]

	FVIII活性(%)			
	インキュベーション時間(分)			
アッセイ	0	5	10	20
1. FVIII	97	27	11	<1
2. FVIII／アプロチニン	98	97	97	96
3. FVIII／vWF	98	16	14	1

In the presence of CaCl 2 (6.25 mM in this case), FVIII was inactivated by proteases in a len gth-of-incubation-dependent manner. vWF did not protect FVIII from inactivation by protease s. Inhibition of the protease with aprotinin prior to contact with FVIII prevented inactivation of the former.

Example

9

In this series of experiments, Example 1/Assay 1 was performed, but in this case the calcium concentration in the mixture of protease and FVIII was varied. For this, $CaCl_2$ was added from a calcium stock solution to the final concentrations shown in FIG.

Results:

Approximately 50% FVIII remains under these conditions when the calcium concentration in the assay is reduced to less than 1 mM. Below 0.5 mM calcium the residual percentage is greater than 60% (Fig. 1). Example 10 The effect of "FVII activators" on blood clotting times in a so-called global

test was investigated by thrombus elastography. Changes in shear elasticity or strength of associated clots were recorded continuously using a Hilgard TEG meter (from Hellige). The so-called r and k values, the time from the onset of blood arrest and from the onset of clotting reaction respectively, for citrated plasma the time of recalcification to the TEG curve extends up to 1 mm and the r value The time from the end point to the curve extended to 20 mm (clotting time). [0074]

For this, 150 µl aliquots of blood or plasma from 5 donors were in each case incubated at 37° C. for 2 minutes in the measurement cuvette, then 50 µl of sample (protease) were added and mixed. 100 µl of 25 mM $CaCl_2$ was added to initiate the reaction. The final concentration of "FVII activator" in the assay was 15 µg/ml. Reduction in r time was measured for assays containing buffer instead of sample.

result:

[Table 11]

血液番号	サンプル	r時間(分)	k時間(分)	r＋k時間(分)
1	プロテアーゼ	5.2	3.4	8.6
1	緩衝液	7.8	5.6	13.4
2	プロテアーゼ	5.2	5.1	10.3
2	緩衝液	6.8	7.1	13.9
3	プロテアーゼ	4.0	5.2	9.2
3	緩衝液	6.5	6.3	12.8
4	プロテアーゼ	4.5	4.8	9.3
4	緩衝液	4.8	6.0	10.8
5	プロテアーゼ	4.2	3.8	8.0
5	緩衝液	7.0	5.8	12.8

血漿番号	サンプル	r時間(分)
1	プロテアーゼ	9.0
1	緩衝液	11.3
2	プロテアーゼ	9.2
2	緩衝液	12.5
3	プロテアーゼ	9.5
3	緩衝液	9.6
4	プロテアーゼ	8.2
4	緩衝液	12.1
5	プロテアーゼ	9.7
5	緩衝液	14.1

This

example demonstrates that in almost all cases the addition of protease causes a marked red uction in blood clotting time. In the example shown here the fibrinolytic effect of the "FVII acti vator" was hidden in the background. The reason for this is that in "normal subjects" the conc entration of plasminogen activator in plasma is in the nanogram range and has no effect on in vitro coagulation tests. Example 11 Protease FVIII alternative

pathway activity was demonstrated by the following experimental assays. That is, thrombus elastography was used as a measurement technique. The r time was evaluated (see Example 10). Whole blood samples were incubated with monoclonal antibodies known to inhibit FVIII a ctivity (antibodies against FVIII) in order to stimulate the presence of natural FVIII inhibitors. Samples were compared to a whole blood sample control (buffer instead of Mab). FE of protea se

IB activity was tested by adding protease (17 μg/ml final concentration) to Mab-inhibited whol e blood samples. Additionally, protease was added to the samples to determine the effect of t he protease itself on rtime.

Results

:

[Table 12]

	r時間
全血対照	8.0
全血＋ｍＡｂ	11.0
全血＋ｍＡｂ＋プロテアーゼ	8.0
全血＋プロテアーゼ	3.5

The rtime prolongation caused by the anti-FVIII mAb was again normalized by the presence of the protease, demonstrating the FEIB activity of the protease. As already demonstrated ab ove, the protease itself shortened the blood clotting time. Example 12 To a solution containin g 50 μg/ml FVII-activating protease was added the following substances to the corresponding final concentrations

. 25 mM sodium citrate 25 mM HEPES 100 mM arginine 0.75 g/ml sucrose This solution was divided into portions and in each case aliquots were adjusted to different pH values from 5.0 to 8.6 and then heated to 60° C. for 10 hours. bottom. The activity of the heated protea se solution was measured by the chromogenic assay, recording deamidation of the chromogen ic substrate S2288 (HD-Ile-Pro-Arg-pHA x 2HCl, Chromogenix AB, Sweden) over time. The act ivity was expressed as a percentage of aliquots measured in parallel without heating. Results

:

[Table 13]

アッセイ	活性(%)
出発原料	100
pH5.0	76
pH5.5	65
pH6.1	81
pH6.5	50
pH7.1	43
pH7.5	46
pH8.1	46
pH8.6	32

This series of experiments showed that stabilization, especially in the acidic pH range, markedly inactivated proteases.
decreased sharply. The slight "breakthrough" at pH 5.5 can be explained by the fact that the isoelectric point of the protease lies in this range. Sodium citrate prevents the >50% loss of activity that occurs in the preferred pH range. Example 13 The assay at pH 6.1 (Example 1) showed the best stabilization of the protease
. Therefore, various activities were tested and evaluated at pH 6.0 as described in Example 1.
The following final concentrations were set and the protease concentration was 50 μg/ml. 50 mM sodium citrate/50 mM NaCl, pH 6.0 0.75 g/ml sucrose 100 mM glycine 100 mM arginine Results:

[Table 14]

アッセイ	活性(%)
出発原料	100
クエン酸ナトリウム／NaCl	54
クエン酸ナトリウム／NaCl／スクロース	85
クエン酸ナトリウム／NaCl／スクロース／グリシン	92
クエン酸ナトリウム／NaCl／スクロース／アルギニン	97

Addition of sucrose and one amino acid in each case demonstrated a significant stabilization of the protease.

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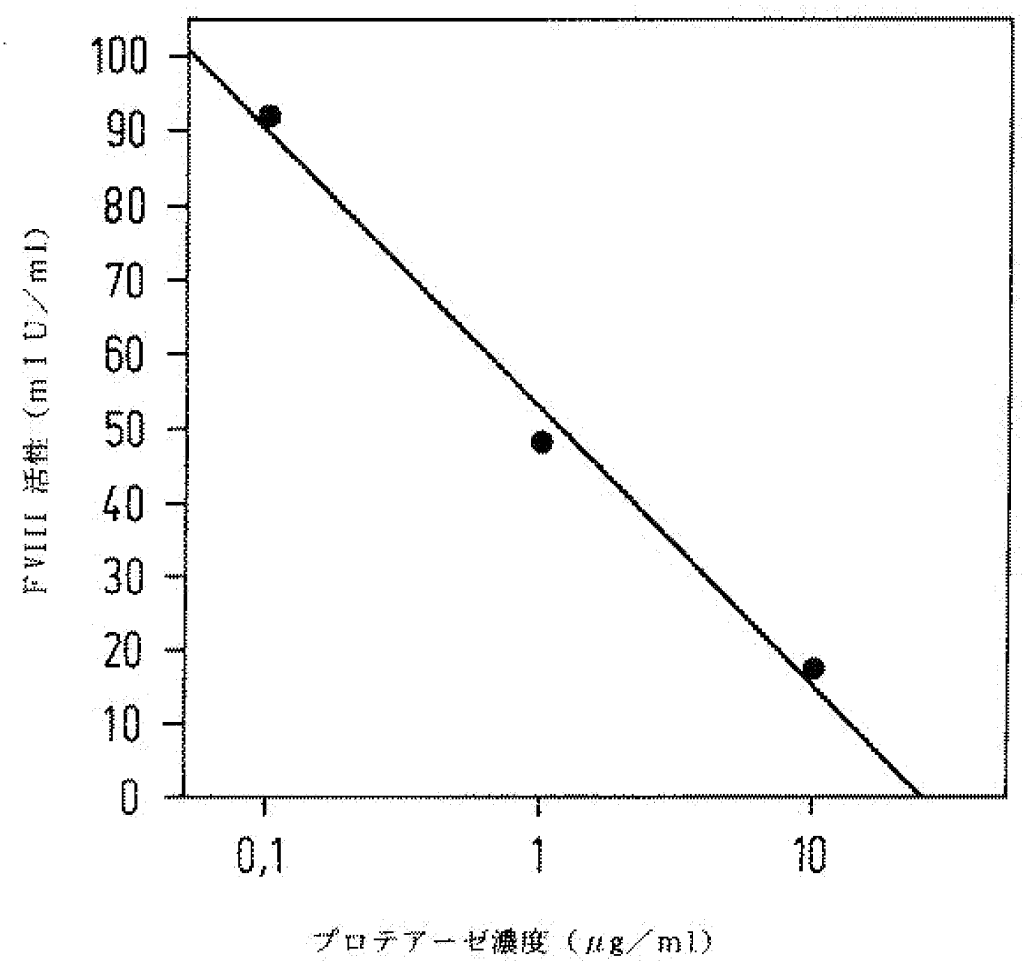


Figure 1

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(19)日本国特許庁(JP)　(12)公開特許公報(A)　(11)特許出願公開番号
特開2009-131273
(P2009-131273A)
(43)公開日　平成21年6月18日(2009.6.18)

(51)Int.Cl.			F I			テーマコード（参考）
C12Q	1/56	(2006.01)	C12Q	1/56	ZNA	4B063
A61K	38/43	(2006.01)	A61K	37/48		4C084
A61P	7/04	(2006.01)	A61P	7/04		
A61P	43/00	(2006.01)	A61P	43/00	111	

審査請求 有　請求項の数 7　OL　（全 25 頁）

(21)出願番号　特願2009-57232 (P2009-57232)
(22)出願日　平成21年3月11日 (2009.3.11)
(62)分割の表示　特願平11-116411の分割
原出願日　平成11年4月23日 (1999.4.23)
(31)優先権主張番号　19818495:6
(32)優先日　平成10年4月24日 (1998.4.24)
(33)優先権主張国　ドイツ(DE)
(31)優先権主張番号　19851332:1
(32)優先日　平成10年11月6日 (1998.11.6)
(33)優先権主張国　ドイツ(DE)
(31)優先権主張番号　19851335:6
(32)優先日　平成10年11月6日 (1998.11.6)
(33)優先権主張国　ドイツ(DE)
(31)優先権主張番号　19851336:4
(32)優先日　平成10年11月6日 (1998.11.6)
(33)優先権主張国　ドイツ(DE)

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(54)【発明の名称】血液凝固第ＶＩＩ因子を活性化するプロテアーゼ

(57)【要約】
【課題】　新規なFVII活性化プロテアーゼの発見とその応用。
【解決手段】　ａ）アプロチニンの存在によって阻害され、ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン類縁物質によってその活性が上昇し、またｃ）ＳＤＳ－ＰＡＧＥにおいて、以後の非還元状態での染色では分子量　５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量１０～３５ｋＤａの範囲の１個もしくは２個以上のバンドを示す、血液凝固第VII因子を活性化するプロテアーゼならびにそのプロ酵素は、血漿またはプロトロンビン複合体（ＰＰＳＢ）濃縮物から予め陰イオン交換クロマトグラフィーに付したのち、ヘパリンもしくはヘパリン類縁物質またはデキストラン硫酸を用いる親和性クロマトグラフィーによって得られる。
本発明は、上記プロテアーゼまたはそのプロ酵素の定性的および定量的検出、ならびにその診断的応用のための試験システムおよびフィブリン含有血栓の溶解に適当な量の血液凝固第VII因子を活性化する上記プロテアーゼおよび／またはそのプロ酵素を含有する医薬製剤が含まれる。
【選択図】　なし

【特許請求の範囲】
【請求項1】
ａ）アプロチニンの存在によって阻害され、
ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、
ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲に１個または２個以上のバンドを示し、そして
ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または
ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素の定性的および定量的検出のための試験システムにおいて、そのプロテアーゼ活性は、
ａ）血液凝固第VIII／VIIIａ因子もしくは第V／Ｖａ因子を不活性化するその活性または
ｂ）包括的血液凝固試験における血液凝固時間を低下させるその活性または
ｃ）プラスミノーゲンアクティベーターを活性化するその活性または
ｄ）FVIIを活性化するその活性
によって測定する試験システム。
【請求項2】
請求項１に記載の試験システムにおいて、血液凝固時間を低下させる活性は、
ａ）非活性化部分トロンボプラスチン時間（ＮＡＰＴＴ）または
ｂ）プロトロンビン時間（ＰＴ）または
ｃ）血漿カルシウム再沈着時間または
ｄ）活性化部分トロンボプラスチン時間（ＡＰＴＴ）
によって測定する試験システム。
【請求項3】
請求項１および２に記載の試験システムにおいて、プラスミノーゲンアクティベーターを活性化および／または増強する活性は、
ａ）一本鎖ウロキナーゼＰＡ（scuＰＡ、一本鎖ウロキナーゼプラスミノーゲンアクティベーター）または
ｂ）一本鎖 ｔＰＡ（sctＰＡ、一本鎖組織プラスミノーゲンアクティベーター）の活性化により測定する試験システム。
【請求項4】
請求項１～３に記載の試験システムにおいてカルシウムイオン０．００１ｍM以上の量を含む試験システム。
【請求項5】
ａ）アプロチニンの存在によって阻害され、
ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、
ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲の１個または２個以上のバンドを示し、そして
ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または

ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素と適当なプロ酵素アクティベーターの混合物をプロトロンビン時間置換組織因子／トロンボプラスチンの試験に使用するアッセイシステム。

【請求項6】

ａ）アプロチニンの存在によって阻害され、

ｂ）カルシウムイオンおよび／またはヘパリンもしくはヘパリン硫酸によりその活性は上昇し、

ｃ）ＳＤＳ－ＰＡＧＥにおいて、それに続く非還元状態での染色により分子量５０～７５ｋＤａの範囲の１個もしくは２個以上のバンドを示し、還元状態では分子量４０～５５ｋＤａに１個のバンドおよび分子量１０～３５ｋＤａの範囲の１個または２個以上のバンドを示し、そして

ｄ）ＳＤＳ－ＰＡＧＥにおいて還元状態で分子量４０～５５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＬＬＥＳＬＤＰを有し、分子量１０～３５ｋＤａの範囲に得られるバンドはアミノ酸配列：ＩＹＧＧＦＫＳＴＡＧＫを有するプロテアーゼ、および／または

ＳＤＳ－ＰＡＧＥにおいて還元状態で得られるバンドは６０～６５ｋＤａの範囲の分子量を有し、アミノ酸配列：ＬＬＥＳＬＤＰおよびＩＹＧＧＦＫＳＴＡＧＫを含有する前記プロテアーゼのプロ酵素と適当なプロ酵素アクティベーターの混合物を、プラスミノーゲンアクティベーターの機能性の試験ならびに一本鎖プラスミノーゲンアクティベーター型の定量に使用するアッセイシステム。

【請求項7】

請求項１～６に記載の試験システムにおいて、プラスミノーゲンアクティベーターを増強する活性は、

ａ）色素原試験を用いて測定するかまたは

ｂ）プラスミノーゲンの存在下におけるカップリング反応でプラスミン自体の形成もしくはプラスミンによってもたらされるフィブリン凝血の溶解で測定する試験システム。

【発明の詳細な説明】

【技術分野】

【0001】

本発明は血液凝固第VII因子の活性化のためのプロテアーゼ、それを単離、検出および不活性化する方法ならびにこのプロテアーゼからなる医薬製剤に関する。

【背景技術】

【0002】

血液凝固系は、血漿中に存在する血液凝固因子を活性化する２つの異なるカスケード様経路から構成される。その誘導機構によって、内因系または外因系経路が血液凝固の開始に優先的に使用される。

【0003】

組織が傷害された場合、トロンボプラスチン（組織因子、ＴＦとリン脂質）が外因性凝血経路のスターターとして冒された細胞により暴露される。膜局在性のトロンボプラスチンは、血液凝固第VII因子（ＦVII）および循環する、活性化ＦVII（ＦVIIａ）の両者を結合することができる。カルシウムイオンおよび脂質の存在下に、このＴＦ－ＦVIIａ複合体はＦＸの結合を招き、これは限定された蛋白分解によってその活性化型（ＦＸａ）に変換される。続いてＦＸａはプロトロンビンを活性化してトロンビンを形成させることにより、フィブリンの形成を招来し、それによって最終的に創傷の閉鎖が起こる。

【0004】

トロンボプラスチン結合ＦVIIの更なる活性化は最初は自触反応によって起こるが、特に、凝血カスケードの開始後には、それはＦＸａおよびトロンビンによって支持され、特に反応カスケードの著しい強化を招くことになる。

【0005】

ＦVIIａまたはＦVIIａ含有濃縮物の投与はある種の臨床状態に適用されている。たとえば、血友病Ａに冒されＦVIII投与の結果としてＦVIIIに対する抗体が発生している患者で

は、ＦＶＩＩａのいわゆるＦＶＩＩＩ副経路活性（ＦＥＩＢＡ）が用いられる。現時点で分かっている所見によれば、ＦＶＩＩａはこの関係で十分な耐容性を有し、それは血栓傾向を生じることはなく、限られているが適切な程度の凝血が起こることを保証するのに適している。組換えＦＶＩＩａは既に治療的におよび予防的に使用されている。血漿から単離されたＦＶＩＩはまた、活性化されてから用いることもできる。トロンビンのようなプロテアーゼをこの活性化に使用できるが、しかしながら、これらのプロテアーゼは、それら自体凝血を強力に活性化することが可能で、血栓の危険を招くことがある。この理由から、以後のトロンビンの除去または不活性化が必要であり、損失を生じることになる。それに伴う血栓の危険の結果として、多くの場合、ＦＸａもしくはＦＩＩａ（トロンビン）の使用は禁忌とされ、緊急時、たとえば血液の著しい喪失および止血不能の出血の関連でのみ適用される。

【図面の簡単な説明】

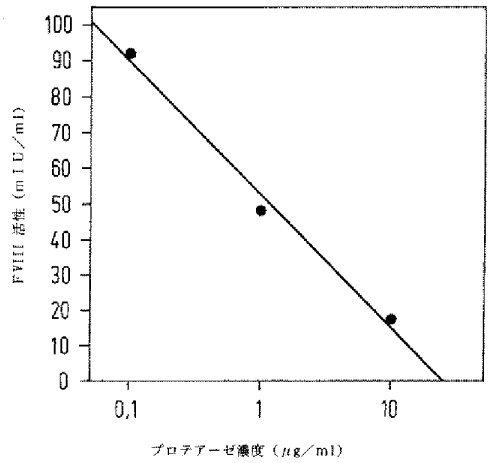
【0009】

【図1】プロテアーゼとＦＶＩＩＩを一定時間インキュベートした場合のプロテアーゼ濃度とＦＶＩＩＩの不活性化を示す。

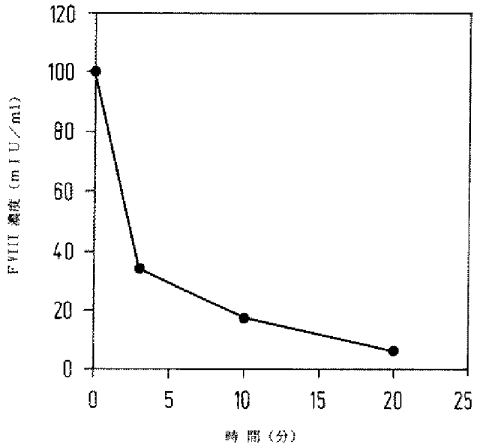
【図2】プロテアーゼ濃度を一定とし、ＦＶＩＩＩを様々な時間インキュベートした場合のＦＶＩＩＩの不活性化を示す。

【図3】プロテアーゼとＦＶＩＩＩを混合物中におけるカルシウム濃度を変動させインキュベートした場合のＦＶＩＩＩの不活性化を示す。

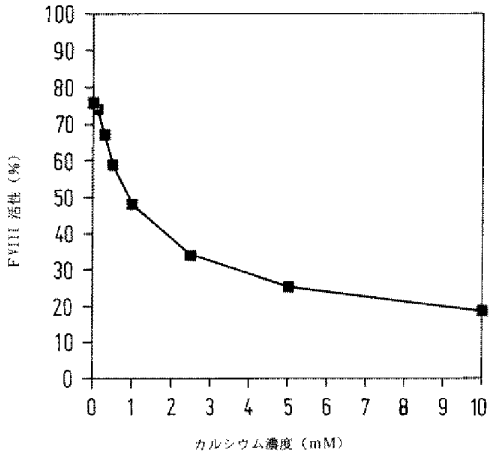
【図1】


100
90
80
70
60
50
40
30
20
10
0
FVIII 活性（mIU/ml）
0,1
1
10
プロテアーゼ濃度（μg/ml）

【図2】



【図3】


100
90
80
70
60
50
40
30
20
10
0
FVIII 活性（%）
0 1 2 3 4 5 6 7 8 9 10
カルシウム濃度（mM）

(31)優先権主張番号　19827734:2
(32)優先日　　平成10年6月22日(1998.6.22)
(33)優先権主張国　　ドイツ(DE)
(31)優先権主張番号　19903693:4
(32)優先日　　平成11年2月1日(1999.2.1)
(33)優先権主張国　　ドイツ(DE)

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Ｆターム(参考)　4B063 QA05　QQ36　QQ79　QQ95　QQ97　QR16　QR48　QR67　QR82　QX01
4C084 AA02　AA07　BA03　BA44　CA62　DC14　NA14　ZA532 ZC022

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 April 2014 (17.04.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/058945 A1

(51) International Patent Classification:
A61M 5/168 (2006.01)

(21) International Application Number:
PCT/US2013/063975

(22) International Filing Date:
9 October 2013 (09.10.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/712,468 11 October 2012 (11.10.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: SYSTEMS AND METHODS FOR DELIVERING A FLUID TO A PATIENT WITH REDUCED CONTAMINATION

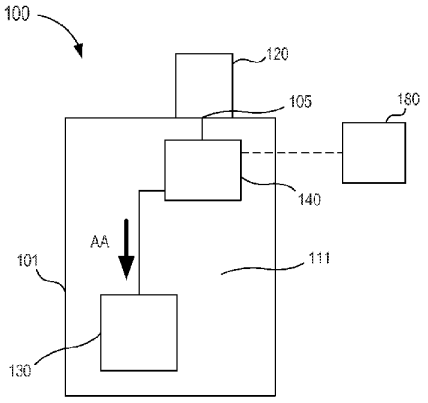


FIG. 1

(57) Abstract: An apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing includes an inlet port removably coupled to the cannula assembly and defines an inner volume. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a volume of bodily fluid from a patient. The flow control mechanism is at least partially disposed in the inner volume. The actuator is operably coupled to the flow control mechanism and is configured to move the flow control mechanism between a first configuration, in which bodily fluid can flow, via a fluid flow path defined by the flow control mechanism, from the cannula assembly, through the inlet port and into the fluid reservoir, to a second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

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SYSTEMS AND METHODS FOR DELIVERING A FLUID TO A PATIENT WITH REDUCED CONTAMINATION

Cross-Reference to Related Applications

[1001] This application claims priority to and the benefit of U.S. Provisional Patent Application Serial No. 61/712,468, filed October 11, 2012, entitled, "Systems and Methods for Delivering a Fluid to a Patient with Reduced Contamination," the disclosure of which is incorporated herein by reference in its entirety.

Background

[1002] Embodiments described herein relate generally to delivering a fluid to a patient, and more particularly to devices and methods for delivering a parenteral fluid to a patient with reduced contamination from microbes or other contaminants exterior to the body and/or the fluid source, such as dermally residing microbes.

[1003] Human skin is normally habituated in variable small amounts by certain bacteria such as coagulase-negative Staphylococcus species, Proprionobacterium acnes, Micrococcus species, Streptococci Viridans group, Corynebacterium species, and Bacillus species. These bacteria for the most part live in a symbiotic relationship with human skin but in some circumstances can give rise to serious infections in the blood stream known as septicemia. Septicemia due to these skin residing organisms is most often associated with an internal nidus of bacterial growth at the site of injured tissue, for example a damaged, scarred heart valve, or a foreign body (often an artificial joint, vessel, or valve). Furthermore, there are predisposing factors to these infections such as malignancy, immunosuppression, diabetes mellitus, obesity, rheumatoid arthritis, psoriasis, and advanced age. In some instances, these infections can cause serious illness and/or death. Moreover, these infections can be very expensive and difficult to treat and often can be associated with medical related legal issues.

[1004] In general medical practice, blood is drawn from veins (phlebotomy) for two main purposes; (1) donor blood in volumes of approximately 500mL is obtained for the treatment of anemia, deficient blood clotting factors including platelets and other medical conditions; and (2) smaller volumes (e.g., from a few drops to 10mL or more) of blood are obtained for testing purposes. In each case, whether for donor or testing specimens, a fluid communicator (e.g., catheter, cannula, needle, etc.) is used to penetrate and enter a vein (known as venipuncture) enabling withdrawing of blood into a tube or vessel apparatus in the desired

amounts for handling, transport, storage and/or other purposes. The site of venipuncture, most commonly the antecubital fossa, is prepared by cleansing with antiseptics to prevent the growth of skin residing bacteria in blood withdrawn from the vein. It has been shown venipuncture needles dislodge fragments of skin including hair and sweat gland structures as well as subcutaneous fat and other adnexal structures not completely sterilized by skin surface antisepsis. These skin fragments can cause septicemia in recipients of donor blood products, false positive blood culture tests and other undesirable outcomes. Furthermore, methods, procedures and devices are in use, which divert the initial portion of venipuncture blood enabling exclusion of these skin fragments from the venipuncture specimen in order to prevent septicemia in recipients of donor blood products, false positive blood culture tests and other undesirable outcomes.

[1005] Venipuncture is also the most common method of accessing the blood stream of a patient to deliver parenteral fluids into the blood stream of patients needing this type of medical treatment. Fluids in containers are allowed to flow into the patient's blood stream through tubing connected to the venipuncture needle or through a catheter that is placed into a patient's vasculature (e.g. peripheral IV, central line, etc.). During this process, fragments of incompletely sterilized skin can be delivered into the blood stream with the flow of parenteral fluids and/or at the time of venipuncture for introduction and insertion of a peripheral catheter. These fragments are undesirable in the blood stream and their introduction into the blood stream of patients (whether due to dislodging of fragments by venipuncture needle when inserting a catheter or delivered through tubing attached to needle or catheter) is contrary to common practices of antisepsis. Further, these microbes can be associated with a well-known phenomenon of colonization by skin residing organisms of the tubing and tubing connectors utilized to deliver parenteral fluids. The colonization is not typically indicative of a true infection but can give rise to false positive blood culture tests, which may result in unnecessary antibiotic treatment, laboratory tests, and replacement of the tubing apparatus with attendant patient risks and expenses. Furthermore, the risk of clinically significant serious infection due to skin residing organisms is increased.

[1006] As such, a need exists for improved fluid transfer devices, catheter introduction techniques and devices, as well as methods for delivering a parenteral fluid to a patient that reduce microbial contamination and inadvertent injection of undesirable external microbes into a patient's blood stream.

Summary

[1007] Devices and methods for delivering a fluid to a patient and/or introducing a peripheral catheter with reduced contamination from dermally residing microbes or other contaminants exterior to the body and/or an external fluid source are described herein. In some embodiments, an apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes an inlet port removably coupled to the cannula assembly. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient. The flow control mechanism is at least partially disposed in the inner volume and is configured to move relative to the housing between a first configuration and a second configuration. The flow control mechanism defines a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration. The actuator is operably coupled to the flow control mechanism to move the flow control mechanism from the first configuration, in which the inlet port is placed in fluid communication the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

Brief Description of the Drawings

[1008] FIGS. 1 and 2 are schematic illustrations of a fluid transfer device according to an embodiment.

[1009] FIG. 3 is a schematic illustration of a fluid transfer device according to an embodiment.

[1010] FIG. 4 is a perspective view of a fluid transfer device according to an embodiment.

[1011] FIG. 5 is an exploded view of the fluid transfer device of FIG. 4.

[1012] FIG. 6 is a cross-sectional view of the fluid transfer device taken along the line X_1-X_1 in FIG. 4, in a first configuration.

[1013] FIG. 7 is an enlarged view of a portion of the fluid transfer device labeled as region **A** in FIG. 6.

[1014] FIGS. 8 and 9 are cross-sectional views of the fluid transfer device taken along the line X_1-X_1 in FIG. 4, in a second and third configuration, respectively.

[1015] FIG. 10 is a side view of the fluid transfer device of FIG. 4 in a fourth configuration.

[1016] FIG. 11 is a perspective view of a fluid transfer device according to an embodiment.

[1017] FIG. 12 is an exploded view of the fluid transfer device of FIG. 11.

[1018] FIGS. 13 and 14 are cross-sectional views of the fluid transfer device taken along the line X_2-X_2 in FIG. 11, in a first and second configuration, respectively.

[1019] FIG. 15 is a side view of the fluid transfer device of FIG. 11 in a third configuration.

[1020] FIG. 16 is a perspective view of a fluid transfer device according to an embodiment.

[1021] FIG. 17 is an exploded view of the fluid transfer device of FIG. 16.

[1022] FIG. 18 is a cross-sectional perspective view of a housing included in the fluid transfer device taken along the line X_4-X_4 in FIG. 17.

[1023] FIG. 19 is a cross-sectional perspective view of a portion of a flow control mechanism included in the fluid transfer device taken along the line X_5-X_5 in FIG. 17.

[1024] FIG. 20 is a cross-sectional view of the fluid transfer device taken along the line X_3-X_3 in FIG. 16, in a first configuration.

[1025] FIG. 21 is a front view of the fluid transfer device of FIG. 16 in a second configuration.

[1026] FIG. 22 is a cross-sectional view of the fluid transfer device taken along the line X_3-X_3 in FIG. 16, in the second configuration.

[1027] FIG. 23 is a side view of the fluid transfer device of FIG. 16 in a third configuration.

[1028] FIG. 24 is a perspective view of a fluid transfer device according to an embodiment.

[1029] FIG. 25 is an exploded view of the fluid transfer device of FIG. 24.

[1030] FIG. 26 is a cross-sectional perspective view of a fluid reservoir included in the fluid transfer device taken along the line X_7-X_7 in FIG. 25.

[1031] FIG. 27 is a cross-sectional perspective view of a flow control mechanism included in the fluid transfer device taken along the line X_8-X_8 in FIG. 25.

[1032] FIGS. 28-30 are cross-sectional views of the fluid transfer device taken along the line X_6-X_6 in FIG. 24, in a first, second, and third configuration, respectively.

[1033] FIG. 31 is a perspective view of a fluid transfer device according to an embodiment.

[1034] FIG. 32 is an exploded view of the fluid transfer device of FIG. 31.

[1035] FIGS. 33 and 34 are cross-sectional views of the fluid transfer device taken along the line X_9-X_9 in FIG. 31, in a first configuration and a second configuration, respectively.

[1036] FIG. 35 is a perspective view of a fluid transfer device according to an embodiment.

[1037] FIG. 36 is an exploded view of the fluid transfer device of FIG. 35.

[1038] FIG. 37 is a cross-sectional view of the fluid transfer device taken along the line X_{10}-X_{10} in FIG. 35, in a first configuration.

[1039] FIG. 38 is a front view of the fluid transfer device of FIG. 35 in a second configuration.

[1040] FIG. 39 is a cross-sectional view of the fluid transfer device taken along the line X_{10}-X_{10} in FIG. 35, in the second configuration.

[1041] FIG. 40 is a flowchart illustrating a method of delivering a fluid to a patient using a fluid transfer device according to an embodiment.

Detailed Description

[1042] Devices and methods for delivering a fluid to a patient with reduced contamination from dermally residing microbes or other contaminants exterior to the body are described herein. In some embodiments, an apparatus includes a cannula assembly, a housing, a fluid reservoir, a flow control mechanism, and an actuator. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes an inlet port configured to be removably coupled to the cannula assembly. The fluid reservoir is fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient. The flow control mechanism is at least partially disposed in the inner volume and is configured to move relative to the housing between a first configuration and a second configuration. The flow control mechanism defines a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration. The actuator is operably coupled to the flow control mechanism to move the flow control mechanism from the first configuration, in which the inlet port is placed in fluid communication the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

[1043] In some embodiments, a device for delivering a fluid to a patient with reduced contamination includes a housing, a fluid reservoir, and a flow control mechanism. The housing has a proximal end portion and a distal end portion and defines an inner volume therebetween. The housing includes a first port configured to be removably coupled to a cannula assembly, and a second port configured to be fluidically coupled to a fluid source. The fluid reservoir is fluidically coupleable to the cannula assembly and configured to receive and isolate a predetermined volume of bodily fluid withdrawn from the patient. The flow control mechanism is at least partially disposed in the inner volume of the housing and is configured to move between a first configuration and a second configuration. When in the first configuration, the first port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through the first port and to the fluid reservoir. When in the second configuration, the fluid reservoir is fluidically isolated

from the cannula assembly and fluid can flow from the fluid source, in the second port, through the flow control mechanism, out the first port and to the cannula assembly.

[1044] In some embodiments, a method of delivering a fluid to a patient using a fluid transfer device includes establishing fluid communication between the patient and the fluid transfer device. Once in fluid communication, a predetermined volume of a bodily fluid is withdrawn from the patient. The predetermined volume of bodily fluid is transferred to a fluid reservoir. The fluid transfer device is fluidically isolated from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir. The method further includes establishing fluid communication between the patient and a fluid source with the fluid transfer device.

[1045] In some embodiments, an apparatus includes a housing, a cannula assembly, a flow control mechanism, and a fluid reservoir. The flow control mechanism is configured to move relative to the housing between a first configuration and a second configuration. The cannula assembly is coupled to the housing and fluidically coupled to the fluid reservoir when the flow control mechanism is in the first configuration. The fluid reservoir is fluidically isolated from the cannula assembly when the flow control mechanism is in a second configuration such that the cannula assembly can be fluidically coupled to an external fluid reservoir and/or an external fluid source.

[1046] As referred to herein, "bodily fluid" can include any fluid obtained from a body of a patient, including, but not limited to, blood, cerebrospinal fluid, urine, bile, lymph, saliva, synovial fluid, serous fluid, pleural fluid, amniotic fluid, and the like, or any combination thereof.

[1047] As used herein, the term "set" can refer to multiple features or a singular feature with multiple parts. For example, when referring to set of walls, the set of walls can be considered as one wall with distinct portions, or the set of walls can be considered as multiple walls. Similarly stated, a monolithically constructed item can include a set of walls. Such a set of walls can include, for example, multiple portions that are in discontinuous from each other. A set of walls can also be fabricated from multiple items that are produced separately and are later joined together (e.g., via a weld, an adhesive or any suitable method).

[1048] As used in this specification, the words "proximal" and "distal" refer to the direction closer to and away from, respectively, a user who would place the device into

contact with a patient. Thus, for example, the end of a device first touching the body of the patient would be the distal end, while the opposite end of the device (e.g., the end of the device being manipulated by the user) would be the proximal end of the device.

[1049] FIGS. 1 and 2 are schematic illustrations of a fluid transfer device 100 according to an embodiment, in a first and second configuration, respectively. Generally, the fluid transfer device 100 (also referred to herein as "transfer device") is configured to facilitate the insertion of a piercing member (e.g., a needle, a trocar, a cannula, or the like) into a patient to withdrawal and isolate a predetermined amount of bodily fluid from the patient containing, for example, dermally residing microbes. The fluid transfer device 100 is further configured to facilitate the delivery of parenteral fluid to the patient that does not substantially contain, for example, the dermally residing microbes. In other words, the transfer device 100 is configured to transfer and fluidically isolate the predetermined amount of bodily fluid, including dermally residing microbes dislodged from a venipuncture, within a collection reservoir and deliver parenteral fluids to the patient that are substantially free from the dislodged dermally residing microbes and/or other undesirable external contaminants.

[1050] The transfer device 100 includes a housing 101, a cannula assembly 120, a fluid reservoir 130, a flow control mechanism 140, and an actuator 180. The housing 101 can be any suitable shape, size, or configuration and is described in further detail herein with respect to specific embodiments. As shown in FIG. 1, the housing 101 defines an inner volume 111 that can movably receive and/or movably house at least a portion of the flow control mechanism 140, as described in further detail herein. A portion of the housing 101 can be, at least temporarily, physically and fluidically coupled to the cannula assembly 120. For example, in some embodiments, a distal end portion of the housing 101 can include an inlet port 105 or the like configured to physically and fluidically couple to a lock mechanism (not shown in FIGS. 1 and 2) included in the cannula assembly 120. In such embodiments, the lock mechanism can be, for example, a Luer-Lok® or the like that can engage the port. In some embodiments, the housing 101 can be monolithically formed with at least a portion of the cannula assembly 120. In other words, in some embodiments, the inlet port 105 can be monolithically formed with a portion of the cannula assembly 120 to define a fluid flow path between a portion of the housing 101 the cannula assembly 120. In this manner, a portion of the housing 101 can receive a bodily fluid from and/or deliver a parenteral fluid to a patient via a cannula included in the cannula assembly 120, as described in further detail herein.

[1051] The cannula assembly 120 can be any suitable configuration. For example, in some embodiments, the cannula assembly 120 includes an engagement portion and a cannula portion (not shown in FIGS. 1 and 2). In such embodiments, the engagement portion can physically and fluidically couple the cannula assembly 120 to the housing 101 (e.g., it can be the lock mechanism physically and fluidically coupled to the inlet port 105 as described above). The cannula portion can be configured to be inserted into a portion of a patient to deliver a fluid to or receive a fluid from the patient. For example, in some embodiments, the cannula portion can include a distal end with a sharp point configured to pierce a portion of the patient to dispose the cannula portion, at least in part, within a vein of the patient. In other embodiments, a piercing member (e.g., a lumen defining needle) can be movably disposed within the cannula assembly 120 to facilitate the insertion of the cannula portion 120 into the portion of the patient.

[1052] As shown in FIG. 1, the housing 101 can house and/or define the fluid reservoir 130. Similarly stated, in some embodiments, the fluid reservoir 130 can be disposed within and/or at least partially defined by the inner volume 111 of the housing 101. The fluid reservoir 130 can be configured to receive a predetermined amount of the bodily fluid and fluidically isolate the bodily fluid from a volume outside the fluid reservoir 130, as described in further detail herein. While shown in FIGS. 1 and 2 as being disposed within the inner volume 111 of the housing 101, in some embodiments, the fluid reservoir 130 can be disposed substantially outside the housing 101. In such embodiments, the fluid reservoir 130 can be physically and fluidically coupled to a portion of the housing 101. For example, in some embodiments, the fluid reservoir 130 can be coupled to an outlet port (not shown in FIGS. 1 and 2). In other embodiments, the fluid reservoir 130 can be operably coupled to the housing 101 via an intervening structure, such as, for example, a Luer-Lok® and/or flexible sterile tubing. In still other embodiments, the fluid reservoir 130 can be monolithically formed with at least a portion of the housing 101.

[1053] The flow control mechanism 140 included in the transfer device 100 is disposed, at least partially, within the inner volume 111 of the housing 101 and can be moved between a first configuration (FIG. 1) and a second configuration (FIG. 2). The flow control mechanism 140 can be any suitable mechanism configured to control or direct a flow of a fluid. For example, in some embodiments, the flow control mechanism 140 can include a valve (e.g., a check valve or the like) that allows a flow of a fluid in a single direction. In

other embodiments, a valve can selectively control a flow of a fluid in multiple directions. In still other embodiments, the flow control mechanism 140 can define one or more lumens configured to selectively receive a flow of a fluid. In such embodiments, the flow control mechanism 140 can be moved relative to the housing 101 to selectively place a lumen in fluid communication with a portion of the transfer device 100 (e.g., the housing 101, the cannula assembly 120, and/or the fluid reservoir 130). For example, in some embodiments, a portion of the flow control mechanism 140 can be movably disposed, at least temporarily, within the cannula assembly 120 to selectively place the fluid reservoir 130 in fluid communication with the cannula assembly 120. In some embodiments, the portion of the flow control mechanism 140 can include a piercing member such as, for example, a needle configured to extend beyond a distal end of the cannula assembly 120 (not shown in FIGS. 1 and 2) to pierce the skin of a patient and facilitate the insertion of the cannula assembly 120 into a vein of the patient.

[1054] In some embodiments, the transfer device 100 can include an actuator 180 operably coupled to the flow control mechanism 140 and configured to move the flow control mechanism 140 between the first and the second configuration. For example, in some embodiments, the actuator 180 can be a push button, a slider, a toggle, a pull-tab, a handle, a dial, a lever, an electronic switch, or any other suitable actuator. In this manner, the actuator 180 can be movable between a first position corresponding to the first configuration of the flow control mechanism 140, and a second position, different from the first position, corresponding to the second configuration of the flow control mechanism 140. In some embodiments, the actuator 180 can be configured for uni-directional movement. For example, the actuator 180 can be moved from its first position to its second position, but cannot be moved from its second position back to its first position. In this manner, the flow control mechanism 140 is prevented from being moved to its second configuration before its first configuration, as described in further detail herein.

[1055] In use, the flow control mechanism 140 can be in the first configuration to place the fluid reservoir 130 in fluid communication with the cannula assembly 120, as indicated by the arrow AA in FIG. 1. In this manner, the fluid reservoir 130 can receive a flow of bodily fluid that can include dermally residing microbes dislodged during a venipuncture event (e.g., when the cannula assembly 120 and/or the flow control mechanism 140 pierces the skin of the patient). In some embodiments, the fluid reservoir 130 can be configured to

receive a predetermined volume of the bodily fluid. With a desired amount of bodily fluid transferred to the fluid reservoir 130, a user (e.g., a doctor, physician, nurse, technician, phlebotomist, etc.) can manipulate the actuator 180 to move the flow control mechanism 140 from the first configuration to the second configuration. For example, the flow control mechanism 140 can be in the first configuration when the flow control mechanism 140 is in a distal position relative to the housing 101 (FIG. 1) and the actuator 180 can move the flow control mechanism 140 in a proximal direction relative to the housing 101 to place the flow control mechanism in the second configuration, as indicated by the arrow BB in FIG. 2. Moreover, when in the second configuration, the flow control mechanism 140 no longer facilitates the fluidic coupling of the fluid reservoir 130 to the cannula assembly 120. Thus, the fluid reservoir 130 is fluidically isolated from the cannula assembly 120.

[1056] While shown in FIGS. 1 and 2 as being moved in the proximal direction (e.g., in the direction of the arrow BB), in other embodiments, the actuator 180 can move the flow control mechanism 140 between the first configuration and the second configuration in any suitable manner or direction. For example, in some embodiments, the flow control mechanism 140 can be moved in a rotational motion between the first configuration and the second configuration. In other embodiments, the flow control mechanism 140 can be moved in a transverse motion (e.g., substantially perpendicular to the direction of the arrow BB). In such embodiments, the rotational or transverse motion can be such that the flow control mechanism 140 selectively defines one or more fluid flow paths configured to receive a fluid from a patient or to deliver a fluid to the patient, as described in further detail herein.

[1057] In some embodiments, the movement of the flow control mechanism 140 to the second configuration can substantially correspond to a physical and fluidic decoupling of at least a portion of the housing 101 from the cannula assembly 120 such that an external fluid reservoir 199 (e.g., also referred to herein as "fluid source") can be physically and fluidically coupled to the cannula assembly 120. For example, as shown in FIG. 2, in some embodiments, the housing 101 can be moved in the proximal direction (e.g., in the direction of the arrow BB) to be physically and fluidically decoupled from the cannula assembly 120. In some embodiments, the proximal movement of the flow control mechanism 140 urges the housing 101 to move in the proximal direction. In other embodiments, a user (e.g., a physician, phlebotomist, or nurse) can move the housing 101 in the proximal direction. In this manner, the external fluid reservoir 199 can be fluidically coupled to the cannula

assembly 120. Expanding further, with the predetermined amount of bodily fluid transferred to the fluid reservoir 130, the external fluid reservoir 199 can be fluidically coupled to the cannula assembly 120 to deliver a flow of a parenteral fluid that is substantially free from dermally residing microbes dislodged during the venipuncture event, as indicated by the arrow CC in FIG. 2. Similarly stated, the dermally residing microbes that are dislodged during the venipuncture event can be entrained in the flow of the bodily fluid delivered to the fluid reservoir 130. Thus, when the flow control mechanism 140 is moved to the second configuration and the fluid reservoir 130 is fluidically isolated from the cannula assembly 120, the external fluid reservoir 199 can deliver the flow of parenteral fluid substantially free from dermally residing microbes.

[1058] While the housing 101 is shown in FIG. 2 as being moved in the proximal direction such that the external fluid reservoir 199 can be physically and fluidically coupled to the cannula assembly 120, in other embodiments, a housing need not be decoupled from a cannula assembly. For example, FIG. 3 is a schematic illustration of a transfer device 200 according to an embodiment. The transfer device 200 includes a housing 201, a cannula assembly 220, a fluid reservoir 230, and a flow control mechanism 240.

[1059] As shown in FIG. 3, the housing 201 includes a proximal end portion 202 and a distal end portion 203 and defines an inner volume 211 therebetween. The distal end portion 203 can be physically and fluidically coupled to the cannula assembly 220, as described above in reference to FIG. 1. For example, in some embodiments, the distal end portion 203 can include an inlet port 205 (also referred to herein as "first port") or the like that can be physically and fluidically coupled to the cannula assembly 220. The proximal end portion 202 includes an outlet port 206 (also referred to herein as "second port") that can be physically and fluidically coupled to an external fluid reservoir 299. The external fluid reservoir 299 can be any suitable fluid reservoir and can be coupled to the second port 206 via an adhesive, a resistance fit, a mechanical fastener, any number of mating recesses, a threaded coupling, and/or any other suitable coupling or combination thereof. For example, in some embodiments, the external fluid reservoir 299 can be substantially similar to known fluid reservoirs configured to deliver a parenteral fluid (e.g., a fluid source). In some embodiments, the external fluid reservoir 299 is monolithically formed with the second port 206. In still other embodiments, the external fluid reservoir 299 can be operably coupled to the second port 206 via an intervening structure (not shown in FIG. 3), such as, for example,

a flexible sterile tubing. More particularly, the intervening structure can define a lumen configured to place the external fluid reservoir 299 in fluid communication with the second port 206.

[1060] The housing 201 can house or define at least a portion of the fluid reservoir 230. Similarly stated, the fluid reservoir 230 can be at least partially disposed within the inner volume 211 of the housing 201. The fluid reservoir 230 can receive and fluidically isolate a predetermined amount of the bodily fluid, as described above in reference to FIGS. 1 and 2. Similarly, the flow control mechanism 240 is at least partially disposed within the inner volume 211 of the housing 201 and can be moved between a first configuration and a second configuration. More specifically, the flow control mechanism 240 defines a first lumen 246 that fluidically couples the cannula assembly 220 to the fluid reservoir 230 when the flow control mechanism 240 is in the first configuration and a second lumen 247 that fluidically couples the cannula assembly 220 to the external fluid reservoir 299 when the flow control mechanism 240 is in the second configuration.

[1061] In use, the flow control mechanism 240 can be placed in the first configuration to fluidically couple the cannula assembly 220 to the fluid reservoir 230 via the first lumen 246. In this manner, a flow of a bodily fluid can be delivered to the fluid reservoir 230, as indicated by the arrow DD in FIG. 3. More specifically, the bodily fluid can flow from the cannula assembly 220, through the first port 205 (e.g., the inlet port) and into the fluid reservoir 230. As described above in the previous embodiment, the flow of the bodily fluid can contain dermally residing microbes dislodged by a venipuncture event (e.g., the insertion of a portion of the cannula assembly 220 into a vein of the patient).

[1062] With a predetermined amount of bodily fluid disposed within the fluid reservoir 230, the flow control mechanism 240 can be moved (e.g., by an actuator and/or manual intervention from the user) to the second configuration to fluidically isolate the fluid reservoir 230 from the cannula assembly 220. More specifically, the flow control mechanism 240 can be moved from the first configuration to fluidically isolate the first lumen 246 from the cannula assembly 220 and/or the fluid reservoir 230, thereby fluidically isolating the fluid reservoir 230 from the cannula assembly 220. In addition, the movement of the flow control mechanism 240 to the second configuration can place the second lumen 247 in fluid communication with the cannula assembly 220 and the outlet port 206 (e.g., the second port) disposed at the proximal end portion 202 of the housing 201. Thus, the external fluid

reservoir 299 can be fluidically coupled (as described above) to the second port 206 to deliver a flow of parenteral fluid to the patient via the second lumen 247 and the cannula assembly 220, as indicated by the arrow EE. For example, the flow of parenteral fluid can flow from the external fluid reservoir 299 (e.g., a fluid source), in the second port 206, through the second lumen 247 defined by the flow control mechanism 240, out the first port 205 and to the cannula assembly 220 to be delivered to the patient. Moreover, the flow of the parenteral fluid is substantially free from dermally residing microbes and/or other undesirable external contaminants.

[1063] In some embodiments, the transfer device 200 can be configured such that the first amount of bodily fluid needs to be conveyed to the fluid reservoir 230 before the transfer device 200 will permit the flow of the parenteral fluid to be conveyed through the transfer device 200 to the patient. In this manner, the transfer device 200 can be characterized as requiring compliance by a health care practitioner regarding the collection of the predetermined amount of bodily fluid prior to the delivery of the parenteral fluid. Similarly stated, the transfer device 200 can be configured to prevent a health care practitioner from delivering the parenteral fluid to the patient without first diverting or transferring the predetermined amount of bodily fluid to the fluid reservoir 230. In this manner, the health care practitioner is substantially prevented from introducing (whether intentionally or unintentionally) bodily surface microbes and/or other undesirable external contaminants into, for example, the flow of the parenteral fluid and/or the blood stream of the patient. In other embodiments, the fluid transfer device 200 need not include a forced-compliance feature or component.

[1064] FIGS. 4-10 illustrate a transfer device 300 according to an embodiment. The transfer device 300 includes a housing 301, a cannula assembly 320, a fluid reservoir 330, a flow control mechanism 340, and an actuator 380. The transfer device 300 can be any suitable shape, size, or configuration. For example, while shown in FIG. 4 as being substantially cylindrical, the transfer device 300 can be square, rectangular, polygonal, and/or any other non-cylindrical shape. Moreover, any portion of the transfer device 300 can include any feature or finish configured to enhance the ergonomics of the transfer device 300. For example, the housing 301 can include a portion configured to form a grip configured to be engaged by a user's hand.

[1065] The housing 301 includes a proximal end portion 302 and a distal end portion 303 and defines an inner volume 311 therebetween (see e.g., FIG. 6). As shown in FIG. 5, the proximal end portion 302 of the housing 301 includes a protrusion 304 that selectively engages a portion of the fluid reservoir 330, as described in further detail herein. The distal end portion 303 of the housing 301 is coupled to a port 305. More specifically, the port 305 can be coupled to the distal end portion 303 in any suitable manner such as, for example, via a friction fit, a threaded coupling, a mechanical fastener, an adhesive, any number of mating recesses, and/or any combination thereof. In other embodiments, the port 305 can be monolithically formed with the housing 301. Moreover, the port 305 can be coupled to the distal end portion 303 of the housing 301 such that a seal member 316 is disposed between the port 305 and a distal wall 308 of the housing 301. In this manner, when the port 305 is coupled to the housing 301, the seal member 316 can engage the distal wall 308 of the housing 301 and the port 305 to selectively form a substantially fluid tight seal, as described in further detail herein.

[1066] As shown in FIG. 6, the port 305 is removably coupled to a lock mechanism 321 of the cannula assembly 320. The lock mechanism 321 of the cannula assembly 320 can be, at least temporarily, coupled to the port 305 to selectively place the housing 301 in fluid communication with the cannula assembly 320. For example, in some embodiments, the lock mechanism 321 can be a Luer-Lok® that receives a portion of the port 305 to physically and fluidically couple the cannula assembly 320 to the housing 301. In other embodiments, the lock mechanism 321 and the port 305 can be removably coupled in any suitable manner.

[1067] As shown in FIGS. 5 and 6, the fluid reservoir 330 defines an inner volume 333 between a proximal end portion 331 and a distal end portion 332. More specifically, the inner volume 333 is closed at the proximal end portion 331 of the fluid reservoir 330 such that at the proximal end, the inner volume 333 is fluidically isolated from a volume outside the fluid reservoir 330. Conversely, the distal end portion 332 of the fluid reservoir 330 is open such that at the distal end, the inner volume 333 can be in fluid communication with a volume outside the fluid reservoir 330. The distal end portion 332 of the fluid reservoir 330 is movably disposed about the proximal end portion 302 of the housing 301, as shown in FIG. 6. Similarly stated, the proximal end portion 302 of the housing 301 is movably disposed within the inner volume 333 defined by the fluid reservoir 330 such that the inner volume 311 defined by the housing 301 is in fluid communication with the inner volume 333 of the fluid

reservoir 330. Moreover, the distal end portion 332 of the fluid reservoir 330 includes a protrusion 335 that can be placed in contact with the protrusion 304 disposed at the proximal end portion 302 of the housing 301 to substantially limit the movement of the fluid reservoir 330 relative to the housing 301, as described in further detail herein.

[1068] The flow control mechanism 340 included in the transfer device 300 is at least partially disposed within the inner volume 311 of the housing 301 and is configured to be moved between a first configuration and a second configuration. Expanding further, the flow control mechanism 340 is in the first configuration when disposed in a distal position relative to the housing 301 (see e.g., FIG. 6) and is in the second configuration when disposed in a proximal position relative to the housing 301 (see e.g., FIG. 9). As shown in FIGS. 6 and 7, the flow control mechanism 340 includes a first member 341 and a second member 360. The first member 341 includes a proximal end portion 342 and a distal end portion 343 and defines a lumen 346 therethrough. The first member 341 can be any suitable shape, size, or configuration. For example, as shown in FIG. 5, the first member 341 can be substantially cylindrical and can have a diameter substantially corresponding to the diameter of the inner volume 311 of the housing 301.

[1069] The second member 360 of the flow control mechanism 340 includes a proximal end portion 361 and a distal end portion 362 and defines a lumen 363 therethrough. As shown in FIG. 6, at least a portion of the second member 360 is movably disposed within the cannula assembly 320. More specifically, the second member 360 can be substantially cylindrical and can have a diameter substantially corresponding to the inner diameter of the cannula 324 included in the cannula assembly 320. As shown in the enlarged view of FIG. 7, the proximal end portion 361 of the second member 360 is configured to extend through the port 305 and the seal member 316 (described above), and through an opening 309 defined in the distal wall 308 to allow the second member 360 to be coupled to the first member 341. Expanding further, the proximal end portion 361 of the second member 360 is disposed within the lumen 346 defined by the first member 341. In some embodiments, the proximal end portion 361 of the second member 360 can form a friction fit with the walls of the first member 341 that define the lumen 346, thereby coupling the second member 360 to the first member 341. In other embodiments, the second member 360 can be coupled to the first member 341 via an adhesive or the like.

[1070] The distal end portion 362 of the second member 360 is configured to extend beyond a distal end of the cannula 324 included in the cannula assembly 320, when the flow control mechanism 340 is in the first configuration. Furthermore, the distal end portion 362 of the second member 360 can include a sharp point that can facilitate the insertion of the transfer device 300 (e.g., the flow control mechanism 340 and the cannula assembly 320) into a portion of a patient. For example, the distal end portion 362 of the second member 360 can be used to access a vein of the patient and facilitate the introduction of the cannula 324 into the vein. Moreover, with the cannula 324 and the distal end portion 362 of the second member 360 disposed within the vein of the patient the transfer device 300 can be configured to transfer a portion of a bodily fluid from the patient to the fluid reservoir 330 to prevent injection of dislodged dermally residing microbes that have been incompletely sterilized by surface antisepsis and/or other undesirable external contaminants.

[1071] As shown in FIG. 8, the transfer device 300 can be moved to a second configuration to begin a flow of bodily fluid (e.g., blood) from the patient to the transfer device 300. More specifically, the fluid reservoir 330 can be moved in the proximal direction relative to the housing 301 to place the transfer device 300 in the second configuration, as indicated by the arrow FF. The arrangement of the fluid reservoir 330 and the housing 301 is such that the proximal motion of the fluid reservoir 330, relative to the housing 301, increases the inner volume 333 defined by the fluid reservoir 330. Expanding further, the proximal end portion 302 of the housing 301 can be disposed within the inner volume 333 of the fluid reservoir 330 such that the protrusion 304 engages an inner surface of the fluid reservoir 330 to define a substantially fluid tight seal. In addition, the protrusion 335 of the fluid reservoir 330 can be placed in contact with the protrusion 304 of the housing 301 to limit the proximal motion of the fluid reservoir 330 relative to the housing 301. In this manner, the proximal motion of the fluid reservoir 330 relative to the housing 301 increases the collective volume of both the inner volume 311 defined by the housing 301 and the inner volume 333 of the fluid reservoir 330.

[1072] The increase of volume introduces a negative pressure within the inner volume 333 of the fluid reservoir 330 and within the inner volume 311 of the housing 301. Therefore, with the cannula 324 and the second member 360 of the flow control mechanism 340 disposed within the vein of the patient, the negative pressure urges a flow of bodily fluid (e.g., blood) through the lumen 363 and 346 defined by the second member 360 and first

member 341 of the flow control mechanism 340, respectively. As indicated by the arrow GG in FIG. 8, the bodily fluid can flow through the lumen 363 and 346 of the flow control mechanism 340 and enter the collective volume formed and/or defined by the inner volume 311 of the housing 301 and the inner volume 333 of the fluid reservoir 330.

[1073] As shown in FIG. 9, when a predetermined amount of bodily fluid is disposed within the fluid reservoir 330, the flow control mechanism 340 can be moved to its second configuration (e.g., the proximal position relative to the housing 301) to place the transfer device 300 a third configuration. More specifically, the flow control mechanism 340 includes a spring 349 that is in contact with the distal wall 308 of the housing 301 and the distal end portion 343 of the first member 341 included in the flow control mechanism 340. As shown in FIGS. 6-8, the spring 349 is maintained in a compressed configuration while the transfer device 300 is in the first and second configuration. As shown in FIG. 9, when the spring 349 is allowed to expand, the spring 349 exerts a force to move the flow control mechanism 340 in the proximal direction, as indicated by the arrow HH. In some embodiments, the expansion of the spring 349 can be in response to the actuator 380. The actuator 380 can be any suitable mechanism configured to selectively interact with the spring 349 such as, for example, a push button. In other embodiments, the actuator 380 can be a slider, a pull-tab, a lever, a toggle, an electronic switch, or the like.

[1074] The proximal motion of the flow control mechanism 340 can be such that both the first member 341 and the second member 360 of the flow control mechanism 340 are disposed within the collective volume defined by the fluid reservoir 330 and the housing 301. Similarly stated, the spring 349 moves the flow control mechanism 340 in the proximal direction a sufficient distance to move the distal end portion 362 of the second member 360 through the port 305, the seal member 316, and the distal wall 308 to be disposed within the housing 301. Furthermore, the seal member 316 can be configured such that as the distal end portion 362 passes beyond the distal wall 308 of the housing 301, the seal member 316 acts to seal the opening 309 through which the second member 360 was disposed. Thus, when the flow control mechanism 340 is completely disposed within the collective volume defined by the housing 301 and the fluid reservoir 330 (e.g., the combination of the inner volume 311 and the inner volume 333, respectively), the seal member 316 seals the distal end portion 303 of the housing 301 and the fluid reservoir 330 is substantially fluidically isolated from the cannula assembly 320.

[1075] With the fluid reservoir 330 fluidically isolated from the cannula assembly 320, the transfer device 300 can be placed in a fourth configuration, as shown in FIG. 10. More specifically, the housing 301 and the fluid reservoir 330 can be collectively moved in the proximal direction such that the port 305 is physically decoupled from the lock mechanism 321 of the cannula assembly 320, as indicated by the arrow II. In this manner, the fluid reservoir 330 can contain and fluidically isolate a portion of the bodily fluid (e.g., blood) that includes, for example, dermally residing microbes dislodged during the venipuncture event (e.g., the insertion of the distal end portion 362 of the second member 360 of the flow control mechanism 340). Furthermore, with the port 305 decoupled from the lock mechanism 321 of the cannula assembly 320, the cannula assembly 320 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 10) that can deliver a flow of a parenteral fluid that is substantially free from the dermally residing microbes.

[1076] While the fluid reservoir 330 is shown in FIGS. 4-10 as being disposed about a portion of the housing 301, in some embodiments, a transfer device can include a fluid reservoir the is substantially enclosed within a housing. For example, FIGS. 11-15 illustrate a transfer device 400 according to an embodiment. The transfer device 400 includes a housing 401, a cannula assembly 420, a fluid reservoir 430, a flow control mechanism 440, and an actuator 480. As shown in FIGS. 11 and 12, the overall size and shape of the transfer device 400 can be substantially similar to the overall size and shape of the transfer device 300 described above in reference to FIG. 4. In addition, the cannula assembly 420, the flow control mechanism 440, and the actuator 480 can be substantially similar in form and function to the cannula assembly 320, the flow control mechanism 340, and the actuator 380 included in the transfer device 300, described above in reference to FIGS. 4-10. Therefore, the cannula assembly 420, the flow control mechanism 440, and the actuator 480 are not described in further detail herein.

[1077] The housing 401 of the transfer device 400 includes a proximal end portion 402 and a distal end portion 403 and defines an inner volume 411 therebetween. More specifically, the housing 401 is substantially closed at the proximal end portion 402 such that at the proximal end, the inner volume 411 is fluidically isolated from a volume outside the housing 401. The distal end portion 403 of the housing 401 is coupled to a port 405. The port 405 is substantially similar to the port 305 described above, and can be coupled to the distal end portion 403 of the housing 401 such that a seal member 416 is disposed between

the port 405 and a distal wall 408 of the housing 401. In this manner, the seal member 416 can form a substantially fluid tight seal between the distal wall 408 and the port 405 (described in detail with reference the port 305 shown in FIGS. 6 and 7). Furthermore, the port 405 can be configured to removably couple the housing 401 to the cannula assembly 420. For example, the port 405 can be, at least temporarily, physically and fluidically coupled to a lock mechanism 421 included in the cannula assembly 420. In this manner, the housing 401 and the cannula assembly 420 can be selectively placed in fluid communication.

[1078] The fluid reservoir 430 included in the transfer device 400 is movably disposed within the inner volume 411 defined housing 401. More specifically, the fluid reservoir 430 is configured to move within the housing 401 between a first configuration (FIG. 13) and a second configuration (FIG. 14). The fluid reservoir 430 defines an inner volume 433 between a proximal end portion 431 and a distal end portion 432. The inner volume 433 is configured to selectively receive at least a portion of the flow control mechanism 440. Furthermore, the flow control mechanism 440 can moved between a first position and a second position to move the fluid reservoir 430 between the first configuration and the second configuration, as described in further detail herein.

[1079] As shown in FIG. 13, the flow control mechanism 440 is in the first position when disposed in a distal position relative to the housing 401. While in the first position, a first member 441 of the flow control mechanism 440 is completely contained within the inner volume 433 and a second member 460 is configured to extend from the first member 441 through the distal end portion 432 of the fluid reservoir 430. The second member 460 of the flow control mechanism 460 further extends through the housing 401 and the port 405 to be at least partially disposed within the cannula assembly 420 (as described above in detail with reference to the second member 360 shown in FIGS. 6 and 7). In this manner, a distal end portion 462 of the second member 460 can extend beyond a cannula 424 of the cannula assembly 420 to facilitate the insertion of the cannula 424 into a portion of a patient. Moreover, with the distal end portion 462 of the second member 460 disposed within the portion of the patient, a lumen 463 defined by the second member 460 and a lumen 446 defined by the first member 441 can place the fluid reservoir 430 in fluid communication with the portion of the patient.

[1080] In use, the transfer device 400 can be moved from the first configuration (FIG. 13) to the second configuration (FIG. 14) to facilitate the flow of a bodily fluid (e.g., blood) into

the fluid reservoir 430. More specifically, the flow control mechanism 440 includes a mechanical actuator 449 (e.g., a spring) that is in contact with the distal wall 408 of the housing 401 and the first member 441 of the flow control mechanism 440. As shown in FIG. 13, the mechanical actuator 449 is maintained in a compressed configuration while the transfer device 400 is in the first configuration. Similarly stated, the flow control mechanism 440 is in the first position relative to the housing 401 when the mechanical actuator 449 is in the compressed configuration. As shown in FIG. 14, when the mechanical actuator 449 is allowed to expand, the mechanical actuator 449 exerts a force to move the flow control mechanism 440 in the proximal direction, as indicated by the arrow JJ. In some embodiments, the expansion of the mechanical actuator 449 can be in response to an actuation of the actuator 480.

[1081] The proximal motion of the flow control mechanism 440 moves within the inner volume 433 to place the first member 441 in contact with the proximal end portion 441 of the fluid reservoir 430. In this manner, the flow control mechanism 440 urges the proximal end portion 431 of the fluid reservoir 430 to move in the direction of the arrow JJ (e.g., the proximal direction). Moreover, the distal end portion 432 of the fluid reservoir 430 can be coupled to the distal wall 408 of the housing 401 such that as the proximal end portion 431 moves in the proximal direction, the fluid reservoir 430 expands. Similarly stated, the fluid reservoir 430 can form a bellows in which the proximal motion of the flow control mechanism 440 moves the fluid reservoir 430 from a compressed configuration (e.g., the first configuration) to an expanded configuration (e.g., the second configuration).

[1082] The movement of the proximal end portion 431 relative to the distal end portion 432 increases the inner volume 433 defined by the fluid reservoir 430 and introduces a negative pressure within the inner volume 433. Moreover, with the lumen 446 of the first member 441 and the lumen 463 of the second member 460 in fluid communication with the fluid reservoir 430, at least a portion of the negative pressure is transferred through the flow control mechanism 440. Therefore, while the flow control mechanism 440 is being moved to the second position (FIG. 14), the negative pressure urges a flow of bodily fluid (e.g., blood) through the lumen 463 and 446 defined by the second member 460 and first member 441 of the flow control mechanism 440, respectively. Expanding further, as shown in FIG. 14, the proximal motion of the flow control mechanism 440 is such that the second member 460 is retracted to a proximal position relative to the distal wall 408 of the housing 401. Prior to

being disposed in the proximal position relative to the distal wall 408, however, the lumen 463 is maintained in fluid communication with the portion of the patient via the cannula 424. In this manner, the flow control mechanism 440 transfers the bodily fluid to the fluid reservoir 430 while being moved in the proximal direction and prior to being disposed in the second position. Thus, when the second member 460 is retracted to the proximal position relative to the distal wall 408, the flow control mechanism 440 has transferred a predetermined amount of bodily fluid to the fluid reservoir 430 and the seal member 416 can act to fluidically isolate the fluid reservoir 430. Similarly stated, the flow control mechanism 440 is configured to transfer the predetermined amount of bodily fluid to the fluid reservoir 430 concurrently with the proximal motion of both the flow control mechanism 440 and the fluid reservoir 430.

[1083] With the fluid reservoir 430 fluidically isolated from the cannula assembly 420, the transfer device 400 can be placed in a third configuration, as shown in FIG. 15. More specifically, the housing 401 and the fluid reservoir 430 can be collectively moved in the proximal direction to physically decouple the port 405 from the lock mechanism 421 of the cannula assembly 420, as indicated by the arrow KK. In some embodiments, the actuator 480 can facilitate the decoupling of the port 405 from the lock mechanism 421. In other embodiments, a second actuator (not shown) can be engaged to decouple the port 405 from the lock mechanism 421. In other embodiments, an actuator need not be engaged to decouple the port 405 from the lock mechanism 421.

[1084] With the port 405 decoupled from the lock mechanism 421, the fluid reservoir 430 can contain and fluidically isolate a portion of the bodily fluid (e.g., blood) that includes, for example, dermally residing microbes dislodged during the venipuncture event (e.g., the insertion of the distal end portion 462 of the second member 460 of the flow control mechanism 440). Furthermore, with the port 405 decoupled from the lock mechanism 421, the cannula assembly 420 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 15) that can deliver a flow of a parenteral fluid that is substantially free from the dermally residing microbes, as described above.

[1085] While the fluid reservoir 430 is shown in FIGS. 11-15 as being disposed within the inner volume 411 of the housing 401, in some embodiments, a fluid reservoir can be physically and fluidically coupled to a portion of the transfer device. For example, FIGS. 16-23 illustrate a transfer device 500 according to an embodiment. The transfer device 500

includes a housing 501, a cannula assembly 520, a flow control mechanism 540, and an actuator mechanism 580. As shown in FIGS. 16 and 17, the overall size and shape of the transfer device 500 can be substantially similar to the overall size and shape of the transfer device 300 described above in reference to FIG. 4. In other embodiments, the overall size and shape of the transfer device 500 can be square, rectangular, polygonal, and/or any other non-cylindrical shape. In addition, the cannula assembly 520 can be substantially similar in form and function to the cannula assembly 320 included in the transfer device 300, described above in reference to FIGS. 4-10. Therefore, the cannula assembly 520 is not described in further detail herein.

[1086] As shown in FIG. 18, the housing 501 of the transfer device 500 includes a proximal end portion 502 and a distal end portion 503 and defines an inner volume 511 therebetween. The housing 501 is substantially closed at the proximal end portion 502 such that at the proximal end, the inner volume 511 is fluidically isolated from a volume outside the housing 501. The distal end portion 503 of the housing 501 includes a distal wall 508 that defines an opening 509 configured to receive, at least temporarily, a portion of the flow control mechanism 540, as described in further detail herein. The housing 501 further defines an actuator chamber 510 configured to receive at least a portion of the actuator mechanism 580. As shown in FIG. 18, the walls of the housing 501 can be arranged such that the actuator chamber 510 is a bore with a centerline that is substantially perpendicular to a centerline defined by the inner volume 511.

[1087] Referring back to FIG. 17, the actuator mechanism 580 includes a first actuator member 581 and a second actuator member 585. As described in further detail herein, the actuator mechanism 580 can be moved between a first configuration (see e.g., FIG. 16) and a second configuration (see e.g., FIG. 21). The first actuator member 581 can be rotatably coupled to the walls of the housing 501 defining the actuator chamber 510. Similarly stated, the first actuator member 581 is configured to be disposed substantially outside the housing 501 and can be rotatably coupled to the walls of the housing 501 that define the actuator chamber 510. The first actuator member 581 includes an engagement portion 582 and a port 583 configured to be physically and fluidically coupled to a fluid reservoir, as described in further detail herein.

[1088] As shown in FIG. 19, the second actuator member 585 can be substantially cylindrical and is configured to be disposed within the actuator chamber 510 defined by the

housing 501. The second actuator member 585 defines a lumen 587 and a flow control channel 588. The lumen 587 is configured to be in fluid communication with the port 583 of the first actuator member 581. In this manner, the lumen 587 and the port 583 can receive a flow of a bodily fluid when the actuator mechanism 580 is in the first configuration, as described in further detail herein. The flow control channel 588 is configured to receive at least a portion of the flow control mechanism 540 when the actuator mechanism 580 is placed in the second configuration, as described in further detail herein.

[1089] The flow control mechanism 540 included in the transfer device 500 is at least partially disposed within the inner volume 511 of the housing 501 and is configured to be moved between a first position and a second position. Expanding further, the flow control mechanism 540 is in the first position when disposed in a distal position relative to the housing 501 (see e.g., FIG. 20) and is in the second position when disposed in a proximal position relative to the housing 501 (see e.g., FIG. 22). As shown in FIGS. 17 and 20, the flow control mechanism 540 includes a first member 541 and a second member 560. The first member 541 includes a proximal end portion 542 and a distal end portion 543 and defines a lumen 546 therethrough. The first member 541 can be any suitable shape, size, or configuration. For example, as shown in FIG. 17, the first member 541 can be substantially cylindrical with the proximal end portion 542 having a first diameter that substantially corresponds to the diameter of the flow control channel 588 defined by the second actuator member 585. As shown in FIG. 20, the first member 541 can be configured such that when the flow control mechanism 540 is in the first position, the lumen 546 defined by the first member 541 is in fluid communication with the lumen 587 defined by the second actuator member 585, as described in further detail herein.

[1090] The distal end portion 543 of the first member 541 can have a second diameter, smaller than the first diameter, substantially corresponding to an inner diameter of a lock mechanism 521 included in the cannula assembly 520. For example, in some embodiments, the distal end portion 543 can extend through the opening 509 defined by the distal wall 508 of the housing 501 to be disposed within the lock mechanism 521. In some embodiments, the distal end portion 543 can form a friction fit with an inner surface of the lock mechanism 521 to removably couple the flow control mechanism 540 to the cannula assembly 520. Furthermore, with the proximal end portion 542 of the first member 541 disposed in a proximal position relative to the distal wall 508 and with the diameter of the proximal end

portion 542 substantially larger than the diameter of the opening 509, the flow control mechanism 540 operatively couples the housing 501 to the cannula assembly 520.

[1091] The second member 560 of the flow control mechanism 540 includes a proximal end portion 561 and a distal end portion 562 and defines a lumen 563 therethrough. As shown in FIG. 20, at least a portion of the second member 560 is movably disposed within a cannula 524 of the cannula assembly 520. As described above with respect to the flow control mechanism 340, the proximal end portion 561 of the second member 560 is configured to extend through the lock mechanism 521 to be coupled to the first member 541. Expanding further, the proximal end portion 561 of the second member 560 is disposed within the lumen 546 defined by the first member 541. The distal end portion 562 of the second member 560 is configured to extend beyond a distal end of the cannula 524 included in the cannula assembly 520, when the flow control mechanism 540 is in the first configuration. In this manner, the second member 560 can facilitate the insertion of the transfer device 500 into a portion of a patient (e.g., the distal end can include a sharp point) and can further facilitate a transfer of a bodily fluid from the patient to a fluid reservoir (e.g., via the lumen 563).

[1092] For example, as shown in FIG. 20, the transfer device 500 can be in a first configuration when the flow control mechanism 540 is in the first position and the actuator mechanism 580 is in its first configuration. In this manner, the second member 560 of the flow control mechanism 540 and the cannula 524 of the cannula assembly 520 can be inserted into a portion of the patient, such as a vein, to place the transfer device 500 in fluid communication with the portion of the patient. Furthermore, a fluid reservoir (not shown in FIGS. 16-23) can be physically and fluidically coupled to the port 583 of the second actuator member 581. The arrangement of the flow control mechanism 540 and the actuator mechanism 580 is such that when the fluid reservoir is physically and fluidically coupled to the port 583, the fluid reservoir is in fluid communication with the lumen 587 defined by the second actuator member 585 and the two lumen 546 and 563 defined by the first member 541 and the second member 560 of the flow control mechanism 540, respectively. In some embodiments, the fluid reservoir can be, for example, a Vacutainer®. In such embodiments, the fluid reservoir can define a negative pressure such that when fluidically coupled to the port 583, the fluid reservoir introduces a suction force within the portion of the patient (e.g., via the lumen 587, 546, and 563). In this manner, a portion of the suction force can urge a

flow of bodily fluid through the lumen 563, 546, and 587 and into the fluid reservoir, as indicated by the arrow LL in FIG. 20. Moreover, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the flow control mechanism 540 and the cannula 524) become entrained therein and are transferred to the fluid reservoir.

[1093] With a predetermined amount of bodily fluid transferred to the fluid reservoir, the fluid reservoir can be decoupled from the port 583 (e.g., physically and fluidically or only fluidically). In this manner, a user can engage the first actuator member 581 to move the actuator mechanism 580 to its second configuration and thereby place the transfer device in a second configuration. For example, as indicated by the arrow MM in FIG. 21, the user (e.g., a physician, a nurse, a phlebotomist, etc.) can rotate the first actuator member 581 in a clockwise direction relative to the housing 501.

[1094] The actuator mechanism 580 is such that the rotation of the first actuator member 581 urges the second actuator member 585 to also rotate relative to the housing 501. In this manner, a centerline defined by the flow control channel 587 is rotated from a first configuration in which the centerline is substantially perpendicular to the centerline defined by the inner volume 511 to a second configuration in which the centerline is substantially parallel to the centerline of the inner volume 511. Similarly stated, the second actuator member 585 is rotated such that the centerline defined by the flow control channel 587 is aligned with the centerline defined by the inner volume 511.

[1095] As shown in FIG. 22, the rotation of the actuator mechanism 580 toward the second configuration can facilitate the movement of the flow control mechanism 540 from the first position toward the second position. More specifically, the flow control mechanism 540 includes a spring 549 that is disposed about the distal end portion 543 of the first member 541 and is in contact with the distal wall 508 of the housing 501 and a surface of the first member 541. The spring 549 is maintained in a compressed configuration while the transfer device 500 is in the first configuration. For example, as shown in FIG. 20, a proximal surface of the first member 541 of the flow control mechanism 540 can be in contact with a surface of the second actuator mechanism 585 such that the second actuator mechanism 585 prevents proximal movement of the flow control mechanism 540. When the actuator mechanism 580 is moved to the second configuration and the flow control channel 587 is aligned with the inner volume 511 (as described above), however, the proximal surface of the first member

541 is no longer in contact with the surface of the second actuator member 585 and the spring 549 is allowed to expand.

[1096] The expansion of the spring 549 exerts a force on the first member 541 of the flow control mechanism 540 to move the flow control mechanism 540 in the proximal direction, as indicated by the arrow NN in FIG. 22. In this manner, the flow control mechanism 540 can pass through the flow control channel 587 defined by the second actuator member 585 to be disposed in the second position (e.g., the distal position). The proximal motion of the flow control mechanism 540 is such that both the first member 541 and the second member 560 of the flow control mechanism 540 are disposed within the inner volume 511 defined by the housing 501. Similarly stated, the spring 549 moves the flow control mechanism 540 in the proximal direction a sufficient distance to move the distal end portion 562 of the second member 560 through the opening 509 defined by the distal wall 508 to be disposed within the housing 501.

[1097] As shown in FIG. 23, with the flow control mechanism 540 disposed within the housing 501, the distal end portion 543 of the first member 541 is no longer disposed within the lock mechanism 521 of the cannula assembly 520. In this manner, the housing 501 is physically and fluidically decoupled from the cannula assembly 520 and can be moved away from the cannula assembly 520, as indicated by the arrow OO in FIG. 23. Furthermore, with the housing 501 decoupled from the lock mechanism 521, the cannula assembly 520 can be physically and fluidically coupled to an external fluid reservoir (not shown in FIG. 23) that can deliver a flow of a parenteral fluid to the portion of the patient that is substantially free from the dermally residing microbes.

[1098] While the transfer devices described above are configured to include a cannula assembly that is physically and fluidically decoupled from a portion of the transfer device to receive a parenteral fluid, in some embodiments, a transfer device can include a cannula assembly configured to remain physically coupled to a portion of the transfer device. For example, FIGS. 24-30 illustrate a transfer device 600 according to an embodiment. The transfer device 600 includes a housing 601, a cannula assembly 620, a fluid reservoir 630, and a flow control mechanism 640. In use, the transfer device 600 can be moved between a first, a second, and a third configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes.

[1099] As shown in FIGS. 24 and 25, the housing 601 includes a proximal end portion 602 and a distal end portion 603 and defines an inner volume 611 therebetween. The proximal end portion 602 is substantially open such that the inner volume 611 can selectively receive the fluid reservoir 630 and at least a portion of the flow control mechanism 640. In addition, the proximal end portion 602 includes a protrusion 604 configured to engage a portion of the flow control mechanism 640, as described in further detail herein.

[1100] The distal end portion 603 of the housing 601 includes a distal port 605 and a reservoir seat 618. The reservoir seat 618 is configured to engage, at least temporarily, a portion of the fluid reservoir 630, as described in further detail herein. The distal port 605 is configured to be physically and fluidically coupled to a lock mechanism 621 included in the cannula assembly 620. For example, in some embodiments, the lock mechanism 621 can be a Luer-Lok® configured to receive the port 605. In other embodiments, the port 605 and the lock mechanism 621 can be coupled in any suitable manner such as, for example, a threaded coupling, a friction fit, or the like. In still other embodiments, the port 605 and the lock mechanism 621 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 620 to the housing 601. With the lock mechanism 621 coupled to the port 605, the inner volume 611 of the housing 601 is in fluid communication with a cannula 624 included in the cannula assembly 620, as further described herein.

[1101] As described above, the fluid reservoir 630 is disposed within the inner volume 611 of the housing 601. More particularly, the fluid reservoir 630 is movably disposed within the inner volume 611 between a first position in which the fluid reservoir 630 is in a distal position relative to the housing 601 (see e.g., FIG. 28) and a second position in which the fluid reservoir 630 is in a proximal position relative to the housing 601 (see e.g., FIG. 30). As shown in FIG. 26, the fluid reservoir 630 includes a proximal end portion 631 and a distal end portion 632 and defines an inner volume 633 therebetween. The proximal end portion 631 includes a flange 634 and a protrusion 635 and defines a set of openings 636. Furthermore, the proximal end portion 631 of the fluid reservoir 630 is substantially open to receive a portion of the flow control mechanism 640. In this manner, the proximal end portion 631 is configured to engage, interact, or otherwise correspond with a portion of the flow control mechanism 640, as further described herein.

[1102] The distal end portion 632 of the fluid reservoir 630 includes a valve seat 637. The valve seat 637 includes a port 638 and receives a valve 639 (see e.g., FIG. 28-30). The

valve seat 637 is selectively disposed about the reservoir seat 618 of the housing 601, as described in further detail herein. The valve 639 can be any suitable valve such as, for example, a check valve or the like. In this manner, the distal end portion 632 can be selectively placed in fluid communication with the inner volume 611 when the fluid reservoir 630 is disposed within the housing 601, as described in further detail herein.

[1103] As described above, the flow control mechanism 640 can be at least partially disposed within the housing 601. More particularly and as shown in FIG. 27, the flow control mechanism 640 includes an engagement portion 645 configured to be disposed outside the housing 601 and a plunger portion 650 configured to be at least partially disposed within the inner volume 611 defined by the housing 601. As described in further detail herein, the engagement portion 645 can be engaged by a user to move the flow control mechanism 640 between a first configuration and a second configuration.

[1104] The plunger portion 650 of the flow control mechanism 640 is configured to extend in a distal direction from a surface of the engagement portion 645. The plunger 650 includes a first surface 652, a second surface 655, a protrusion 653, a first seal member 658, and a second seal member 659. As shown in FIG. 27, the plunger portion 650 is substantially cylindrical and defines a channel 651 that receives, for example, a cannula 664 that defines a lumen 646. More particularly, the cannula 664 is configured to be disposed within an opening 654 defined by the first surface 652 to place the lumen 646 in fluid communication with an inner volume 656 defined between the first surface 652 and the second surface 655. The plunger 650 is further configured to define a set of openings 657 that can selectively place the inner volume 656 in fluid communication with a portion of the housing 601, as described in further detail herein.

[1105] In use, the transfer device 600 can be moved between a first configuration (FIG. 28), a second configuration (FIG. 29), and a third configuration (FIG. 30). Referring to FIG. 28, while in the first configuration, the cannula 624 of the cannula assembly 620 can be inserted into a portion of a patient to place the cannula 624 in fluid communication with, for example, a vein. In some embodiments, the cannula 624 can include a sharp point at a distal end such that the cannula 624 can pierce the portion of the patient. In other embodiments, the cannula assembly 620 can include a trocar (not shown) to facilitate the insertion of the cannula 624. As described above, the cannula assembly 620 is physically and fluidically coupled to the port 605 of the housing 601 such that when the cannula 624 is placed in fluid

communication with the vein of the patient, the port 605 is concurrently placed in fluid communication with the vein. With the port 605 in fluid communication with the portion of the patient (e.g., the vein), a user (e.g., a physician, nurse, technician, or the like) can engage the engagement portion 645 of the flow control mechanism 640 to place the transfer device 600 in the second configuration.

[1106] As shown in FIG. 29, the transfer device 600 is placed in the second configuration when the plunger portion 650 of the flow control mechanism 640 is moved within the fluid reservoir 630 from a first position (e.g., a distal position) to a proximal position (e.g., a proximal position), as indicated by the arrow PP. More specifically, the transfer device 600 includes a spring 649 configured to engage the protrusion 604 of the housing 601 and the flange 634 of the fluid reservoir 630 to maintain the fluid reservoir 630 in the first position while the flow control mechanism 640 is moved to its second position. Similarly, stated the flow control mechanism 640 is moved in a proximal direction relative to the fluid reservoir 630.

[1107] In addition, the first seal member 658 can engage an inner surface of the fluid reservoir 630 such that the proximal movement of the flow control mechanism 640 produces a negative pressure within a portion of the inner volume 633 of the fluid reservoir 630 (e.g., the portion of the inner volume 633 that is disposed distally relative to the first seal member 658). In this manner, the negative pressure introduces a suction force that can be operable placing the valve 639 in an open configuration. Thus, with the cannula 624 and the port 605 in fluid communication with the portion of the patient (e.g., the vein), a flow of bodily fluid (e.g., blood) can pass through the valve 639 and enter the inner volume 633 of the fluid reservoir 630, as indicated by the arrow QQ.

[1108] As shown in FIG. 29, the proximal movement of the flow control mechanism 640 relative to the fluid reservoir 630 is configured to stop when the flow control mechanism 640 is in the second position (e.g., the proximal position). More specifically, the protrusion 635 of the fluid reservoir 630 can engage the protrusion 653 of the plunger portion 650 to limit the proximal movement of the flow control mechanism 640 relative to the fluid reservoir 630. Furthermore, when the flow control mechanism 640 is in the second position relative to the fluid reservoir 630, the openings 657 of the plunger portion 650 are in fluid communication with the openings 636 defined by the fluid reservoir 630. Thus, the inner volume 656 defined by the plunger portion 650 of the flow control mechanism 640 is placed in fluid

communication with the inner volume 611 of the housing 601, as described in further detail herein.

[1109] With the transfer device 600 in the second configuration, a flow of a predetermined amount of bodily fluid can be transferred to the inner volume 633 of the fluid reservoir 630 that can include, for example, dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 624 into the vein and/or otherwise accessing the vasculature of the patient). In addition, when the predetermined amount of bodily fluid is transferred to the inner volume 633 of the fluid reservoir 630, the valve 639 can be placed in a closed configuration. For example, in some embodiments, the transfer of the predetermined amount of bodily fluid can be such that the negative pressure within the inner volume 633 is brought into equilibrium with the pressure of the vein, thus allowing the valve 639 to move to the closed configuration. In other embodiments, the valve 639 can be manually actuated by user interference (e.g., engagement of an actuator, a switch, a button, a toggle, or the like). In this manner, the bodily fluid disposed in the inner volume 633 between the first seal member 658 and the distal end portion 632 of the fluid reservoir 630 can be fluidically isolated from a volume outside the inner volume 633. Expanding further, the first seal member 658 prevents a flow of the bodily fluid in the proximal direction and the valve 639, being in the closed configuration, prevents a flow of the bodily fluid in the distal direction. Thus, the predetermined amount of bodily fluid is fluidically isolated from a volume outside the inner volume 633 of the fluid reservoir 630 defined between the first seal member 658 and the distal end portion 632.

[1110] As indicated by the arrow RR in FIG. 30, the user can continue to move the flow control mechanism 640 in the proximal direction to place the transfer device 600 in the third configuration. More specifically, with the protrusion 653 of the flow control mechanism 640 in contact with the protrusion 635 of the fluid reservoir 630, the proximal movement of the flow control mechanism 640 is such that the flow control mechanism 640 and the fluid reservoir 630 move, concurrently, in the proximal direction relative to the housing 601. Furthermore, the proximal movement is such that the valve seat 637 is moved in the proximal direction relative to the reservoir seat 618. Similarly stated, the proximal movement of the fluid reservoir 630 is such that the valve seat 637 is no longer disposed about the reservoir seat 618 of the housing 601. In this manner, the port 605 is placed in fluid communication with the inner volume 611 of the housing 601.

[1111] With the transfer device 600 in the third configuration, an external fluid source (not shown in FIG. 30) can be placed in fluid communication with a portion of the transfer device 600 to transfer a flow of parenteral fluid to the portion of the patient. For example, in some embodiments, the transfer device 600 can include a proximal lock mechanism 613 that can physically and fluidically couple the transfer device 600 to the external fluid source. The proximal lock mechanism 613 can be any of those described herein. In this manner, the external fluid source can deliver a flow of parenteral fluid to the lumen 646, as indicated by the arrow SS. Moreover, with the lumen 646 in fluid communication with the inner volume 656 defined between the first surface 652 and the second surface 655, the flow of the parenteral fluid can pass through the openings 657 defined by the plunger portion 650 of the flow control mechanism 640. In addition, the first seal member 658 and the second seal member 659 can act to define a fluid flow path that directs the flow of the parenteral fluid to the openings 636 defined by the fluid reservoir 630. In this manner, the flow of parenteral fluid can pass through the openings 636 of the fluid reservoir 630 to enter the inner volume 611 defined by the housing 601. Similarly stated, upon exiting the openings 636, the parenteral fluid can flow within the inner volume 611 defined by the housing 601 and outside of the fluid reservoir 630, as indicated by the arrows SS. Expanding further, the parenteral fluid can flow within the housing 601 in the distal direction and enter the port 605 to transfer the flow parenteral fluid to the cannula assembly 620. Therefore, the external fluid source can deliver a flow of parenteral fluid to the patient that is fluidically isolated from the predetermined amount of bodily fluid disposed in the fluid reservoir 630 and is thus, substantially free from dermally residing microbes and/or other undesirable external contaminants.

[1112] In some embodiments, user intervention maintains the transfer device 600 in the third configuration. Expanding further and as described above, the proximal movement of the fluid reservoir 630 is such that a portion of the force applied by the user (e.g., the physician, nurse, technician, or the like) to move the flow control mechanism 640 and fluid reservoir 630 is used to move the spring 649 to a compressed configuration. In such embodiments, the removal of the portion of the force would allow the spring 649 to expand and thereby move the fluid reservoir 630 in the distal direction. In other embodiments, a transfer device can include a catch, protrusion, latch or the like configured to maintain the spring in the compressed configuration.

[1113] While the transfer device 600 is shown in FIGS. 24-30 as including a fluid reservoir 630, in other embodiments, a transfer device can include a flow control mechanism with an integrated fluid reservoir. For example, FIGS. 31-34 illustrate a transfer device 700 according to an embodiment. The transfer device 700 includes a housing 701, a cannula assembly 720, and a flow control mechanism 740. In use, the transfer device 700 can be moved between a first configuration and a second configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes and/or other undesirable external contaminants.

[1114] As shown in FIGS. 31 and 32, the housing 701 includes a proximal end portion 702 having a proximal port 706 and a distal end portion 703 having a distal port 705. The proximal port 706 is configured to be physically and fluidically coupled to an external fluid source, as described in further detail herein. The distal port 705 is configured to be physically and fluidically coupled to a lock mechanism 721 included in the cannula assembly 720. For example, in some embodiments, the lock mechanism 721 can be a Luer-Lok® configured to receive the distal port 705. In other embodiments, the distal port 705 and the lock mechanism 721 can be coupled in any suitable manner such as, for example, a threaded coupling, a friction fit, or the like. In still other embodiments, the distal port 705 and the lock mechanism 721 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 720 to the housing 701. With the lock mechanism 721 coupled to the distal port 705, the distal port 705 is placed in fluid communication with a cannula 724 included in the cannula assembly 720, as further described herein.

[1115] The housing 701 defines an inner volume 711 and a set of recess 710. The inner volume 711 is configured to receive at least a portion of the flow control mechanism 740. As shown in FIG. 31, the set of recesses 710 are defined by the housing 701 in a perpendicular orientation relative to the proximal port 706 and distal port 705. Similarly stated, the recesses 710 are perpendicular to a centerline defined by the proximal port 706 and the distal port 705. In this manner, a portion of the flow control mechanism 740 can extend through the recesses 710 when the flow control mechanism 740 is disposed within the inner volume 711 of the housing 701, as described in further detail herein.

[1116] The flow control mechanism 740 defines a first lumen 746, a second lumen 747, and a fluid reservoir 730. The first lumen 746 extends though a portion of the flow control

mechanism 740 and is in fluid communication with the fluid reservoir 730. Similarly stated, the first lumen 746 extends through a portion of the flow control mechanism 740 to selectively place the fluid reservoir 730 in fluid communication with a volume substantially outside of the flow control mechanism 740, as described in further detail herein. As shown in FIG. 33, the second lumen 747 extends through the flow control mechanism 740 and is fluidically isolated from the fluid reservoir 730. In this manner, the second lumen 747 can be selectively placed in fluid communication with the proximal port 706 and the distal port 705 of the housing 701 to deliver a flow of parenteral fluid, as described in further detail herein.

[1117] The flow control mechanism 740 has a circular cross-sectional shape such that when the flow control mechanism 740 is disposed within the inner volume 711, a portion of the flow control mechanism 740 forms a friction fit with the walls of the housing 701 defining the inner volume 711. For example, in some embodiments, the flow control mechanism 740 is formed from silicone and has a diameter larger than the diameter of the inner volume 711. In this manner, the diameter of the flow control mechanism 740 is reduced when the flow control mechanism 740 is disposed within the inner volume 711. Thus, the outer surface of the flow control mechanism 740 forms a friction fit with the inner surface of the walls defining the inner volume 711. In other embodiments, the flow control mechanism 740 can be any suitable elastomer configured to deform when disposed within the inner volume 711 of the housing 701.

[1118] In use, while in the first configuration, the cannula 724 of the cannula assembly 720 can be inserted into a portion of a patient to place the cannula 724 in fluid communication with, for example, a vein. In some embodiments, the cannula 724 can include a sharp point at a distal end such that the cannula 724 can pierce the portion of the patient. In other embodiments, the cannula assembly 720 can include a trocar (not shown) to facilitate the insertion of the cannula 724. As described above, the cannula assembly 720 is physically and fluidically coupled to the distal port 705 of the housing 701 such that when the cannula 724 is placed in fluid communication with the vein of the patient, the distal port 705 is placed in fluid communication with the vein.

[1119] As shown in FIG. 33, when the transfer device 700 is in the first configuration, the first lumen 746 of the flow control mechanism 740 is in fluid communication with the distal port 705 of the housing 701. In this manner, the fluid reservoir 730 defined by the flow control mechanism 740 is placed in fluid communication with the vein of the patient and can

rcccivc a flow of a bodily fluid (c.g., blood). Morcovcr, with thc flow control mcchanism 740 forming a friction fit with the inner surface of the housing 701 (as described above), the flow control mechanism 740 and the housing 701 can form a substantially fluid tight seal about an inlet of the first lumen 746. In this manner, the cannula assembly 720, the distal port 705, and the first lumen 746 collectively define a flow path configured to deliver a flow of bodily fluid from the portion of the patient to the fluid reservoir 730, as indicated by the arrow TT. In addition, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 724) are entrained in the flow of bodily fluid and are transferred to the fluid reservoir 740.

[1120] With a desired amount of bodily fluid transferred to the fluid reservoir 730, a user can engage the transfer device 700 to move the transfer device 700 from the first configuration to the second configuration. In some embodiments, the desired amount of bodily fluid transferred to the fluid reservoir 730 is a predetermined amount of fluid. For example, in some embodiments, the transfer device 700 can be configured to transfer bodily fluid until the pressure within the fluid reservoir 730 is equilibrium with the pressure of the portion of the body in which the cannula 724 is disposed (e.g., the vein). In some cmbodimcnts, at lcast a portion of thc flow control mcchanism 740 can bc transparcnt to allow visualization of the bodily fluid flowing into the fluid reservoir 730. The flow control mechanism 740 can include indicators (e.g., 0.1 mL, 0.5 mL, 1 mL, 1.5 mL, 2 mL, 3 mL, 4 mL, 5 mL, etc. graduation marks) to the user can visualize the volume of bodily fluid that has been received in the fluid reservoir 730.

[1121] As shown in FIG. 34, the transfer device 700 can be moved from the first configuration to the second configuration by moving the flow control mechanism 740 in the direction of the arrow UU. In this manner, the first lumen 746 is fluidically isolated from the distal port 705. While not shown in FIGS. 31-34, the first lumen 746 can include a valve or seal configured to fluidically isolate the bodily fluid disposed within the fluid reservoir 730 from a volume outside the flow control mechanism 740. In some embodiments, the valve can be, for example, a one-way check valve. Thus, the fluid reservoir 730 can receive the flow of fluid from a volume outside the fluid reservoir 730 but prevent a flow of fluid from the fluid reservoir 730.

[1122] When moved to the second configuration, the second lumen 747 defined by the flow control mechanism 740 is placed in fluid communication with the distal port 705 and the

proximal port 706 of the housing 701. As described above, the proximal port 706 can be physically and fluidically coupled to an external fluid source (not shown in FIGS. 31-34) such that when the transfer device 700 is in the second configuration, the proximal port 706, the second lumen 747, the distal port 705, and the cannula assembly 720 collectively define a fluid flow path. In this manner, the transfer device 700 can facilitate the delivery of a flow of parenteral fluid from the external fluid source to the portion of the patient (e.g., the vein), as indicated by the arrow VV in FIG. 34. Expanding further, with the predetermined amount of bodily fluid fluidically isolated within the fluid reservoir 730, the transfer device 700 can facilitate the delivery of the flow of parenteral fluid to the patient that is substantially free from, for example, the dermally residing microbes dislodged during the venipuncture event.

[1123] While the flow control mechanism 740 is shown in FIGS. 31-34 as including the integrated fluid reservoir 730, in other embodiments, a transfer device can be configured to be physically and fluidically coupled to an external fluid reservoir. For example, FIGS. 35-39 illustrate a transfer device 800 according to an embodiment. As shown in FIGS. 35 and 36, the transfer device 800 includes a housing 801, a cannula assembly 820, and a flow control mechanism 880. In use, the transfer device 800 can be moved between a first configuration and a second configuration to receive a predetermined amount of a bodily fluid from a patient and to deliver a flow of a parenteral fluid to the patient that is substantially free from, for example, dermally residing microbes.

[1124] The housing 801 includes a proximal end portion 802, a distal end portion 803, and defines an inner volume 811. The inner volume 811 can receive at least a portion of the flow control mechanism 880 and the actuator 880, as further described herein. As shown in FIG. 37, the distal end portion 803 of the housing 801 defines a distal port 805 and the proximal end portion 802 of the housing 801 defines a first proximal port 806, and a second proximal port 807. The distal port 805, the first proximal port 806, and the second proximal port 807 are configured to be in fluid communication with the inner volume 811 defined by the housing 801.

[1125] The distal port 805 is configured to receive a distal cannula 817. The distal cannula 817 (e.g., a lumen defining cannula) is configured to be physically and fluidically coupled to a port 822 included in the cannula assembly 820. The port 822 can be any suitable port. For example, in some embodiments, the distal cannula 817 and the port 822 can be coupled via an adhesive or the like to fixedly couple the cannula assembly 820 to the housing

801. With the port 822 of the cannula assembly 820 coupled to the distal cannula 817 and with the distal cannula 817 coupled to the distal port 805, the distal port 805 is in fluid communication with a cannula 824 included in the cannula assembly 820, as further described herein.

[1126] The first proximal port 806 and the second proximal port 807 are configured to receive a first proximal cannula 812 and a second proximal cannula 814, respectively (e.g., lumen defining cannulas). Furthermore, the first proximal cannula 812 is physically and fluidically coupled to a first lock mechanism 813 that can further be physically and fluidically coupled to an external fluid reservoir (not shown in FIGS. 35-39). Similarly, the second proximal cannula 814 is physically and fluidically coupled to a second lock mechanism 815 that can further be physically and fluidically coupled to an external fluid source (not shown in FIGS. 35-39). In this manner, the cannula assembly 820, the external fluid reservoir (not shown), and the external fluid source (not shown) can be selectively placed in fluid communication with the inner volume 811 defined by the housing 801, as described in further detail herein.

[1127] Referring back to FIG. 36, the actuator mechanism 880 includes an engagement portion 882 and an activation surface 884. The activation surface 844 is configured to contact, mate, or otherwise engage the flow control mechanism 840. The engagement portion 882 can be engaged by a user to rotate the actuator mechanism 880 relative to the housing 801 to move the transfer device 800 between a first configuration and a second configuration, as described in further detail herein.

[1128] The flow control mechanism 840 defines a first lumen 846 and a second lumen 847 and is disposed within the inner volume 821 defined by the housing 801. The flow control mechanism 840 defines a circular cross-sectional shape such that when the flow control mechanism 840 is disposed within the inner volume 821, a portion of the flow control mechanism 840 forms a friction fit with the walls of the housing 801 defining the inner volume 821, as described in detail above. The flow control mechanism 840 is operably coupled to and/or otherwise engages the actuator 880. For example, in some embodiments, the actuator mechanism 880 can be coupled to the flow control mechanism 840 via a mechanical fastener and/or adhesive. In other embodiments, the actuator mechanism 880 and the flow control mechanism 840 can be coupled in any suitable manner. Therefore, the flow control mechanism 840 is configured to move concurrently with the actuator mechanism 880

when the actuator mechanism 880 is rotated relative to the housing 801. In this manner, the flow control mechanism 840 can be moved to place the first lumen 846 or the second lumen 847 in fluid communication with the distal port 805, the first proximal port 806, and/or the second proximal port 807, as described in further detail herein.

[1129] In use, while in the first configuration, the cannula 824 of the cannula assembly 820 can be inserted into a portion of a patient to place the cannula 824 in fluid communication with, for example, a vein. In some embodiments, the cannula 824 can include a sharp point at a distal end such that the cannula 824 can pierce the portion of the patient. In other embodiments, the cannula assembly 820 can include a trocar (not shown) to facilitate the insertion of the cannula 824. As described above, the cannula assembly 820 is physically and fluidically coupled to the distal port 805 of the housing 801 such that when the cannula 824 is placed in fluid communication with the vein of the patient, the distal port 805 is placed in fluid communication with the vein.

[1130] Furthermore, a user (e.g., a physician, a nurse, a technician, or the like) can engage the transfer device 800 to physically and fluidically couple the first lock mechanism 813 to an external fluid reservoir (not shown). The external fluid reservoir can be any suitable reservoir. For example, in some embodiments, the external fluid reservoir can be a BacT/ALERT® SN or a BacT/ALERT® FA, manufactured by BIOMERIEUX, INC. In this manner, the external fluid reservoir can define a negative pressure within an inner volume of the reservoir. Therefore, when the flow control mechanism 840 is in the first configuration, a negative pressure differential introduces a suction force within the first proximal cannula 812, the first lumen 846 defined by the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820. In this manner, the first proximal cannula 812, the first lumen 846 defined by the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820 collectively define a fluid flow path configured to transfer a flow of a bodily fluid to the external fluid reservoir, as indicated by the arrow WW in FIG. 37. In addition, the flow of bodily fluid can be such that dermally residing microbes dislodged during a venipuncture event (e.g., the insertion of the cannula 824) are entrained in the flow of bodily fluid and are transferred to the external fluid reservoir.

[1131] As shown in FIG. 38, in some embodiments, the magnitude of the suction force can be modulated by moving the actuator mechanism 880 in the direction of the arrow XX. For example, in some instances, it can be desirable to limit the amount of suction force

introduced to a vein. In such instances, the user can move the actuator mechanism 880 and the flow control mechanism 840 to reduce the size of the fluid pathway (e.g., an inner diameter) between the distal port 805 of the housing 801 and the first lumen 846 of the flow control mechanism 840, thereby reducing the suction force introduced into the vein of the patient.

[1132] With the desired amount of bodily fluid transferred to the external fluid reservoir, a user can engage the actuator mechanism 880 to move the transfer device 800 from the first configuration to the second configuration. In some embodiments, the desired amount of bodily fluid transferred to the external fluid reservoir is a predetermined amount of fluid. For example, in some embodiments, the transfer device 800 can be configured to transfer bodily fluid until the pressure within the external fluid reservoir is equilibrium with the pressure of the portion of the body in which the lumen-defining device is disposed (e.g., the vein), as described above. In some embodiments, at least a portion of the external fluid reservoir can be transparent to allow visualization of the bodily fluid flowing into the fluid reservoir. The external fluid reservoir can include indicators (e.g., 0.1 mL, 0.5 mL, 1 mL, 1.5 mL, 2 mL, 3 mL, 4 mL, 5mL, etc. graduation marks to accommodate identification of diversion volumes ranging from just a few drops or centiliters of blood to a larger volumes) so the user can visualize the volume of bodily fluid that has been received in the external fluid reservoir.

[1133] The transfer device 800 can be moved from the first configuration to the second configuration by further moving the actuator mechanism 880 in the direction of the arrow XX in FIG. 38. As the actuator mechanism 880 is moved from the first configuration toward the second configuration, the actuator mechanism 880 rotates the flow control mechanism 840 toward its second configuration. In this manner, the first lumen 846 is fluidically isolated from the distal port 805 and the first proximal port 806 and the external fluid reservoir can be physically and fluidically decoupled from the transfer device 800. In addition, the second lumen 847 defined by the flow control mechanism 840 is placed in fluid communication with the distal port 805 and the second proximal port 807, as shown in FIG. 39.

[1134] With the transfer device in the second configuration, the second proximal lock mechanism 815 can be physically and fluidically coupled to the external fluid source (not shown in FIGS. 35-39). In this manner, the second proximal cannula 814, the second lumen 847 of the flow control mechanism 840, the distal cannula 817, and the cannula assembly 820 collectively define a fluid flow path. Thus, the transfer device 800 can facilitate the delivery

of a flow of parenteral fluid from the external fluid source to the portion of the patient (e.g., the vein), as indicated by the arrow YY in FIG. 39. Expanding further, with the predetermined amount of bodily fluid transfer to the external fluid reservoir and with the external fluid reservoir decoupled from the transfer device 800, the transfer device 800 can facilitate the delivery of the flow of parenteral fluid to the patient that is substantially free from, for example, the dermally residing microbes dislodged during the venipuncture event or otherwise introduced to the fluid flow path to the patient.

[1135] FIG. 40 is a flowchart illustrating a method 990 of delivering a fluid to a patient using a fluid transfer device, according to an embodiment. The method 990 includes establishing fluid communication between the patient and the fluid transfer device, at 991. The fluid transfer device can be any of those described herein. As such, the fluid transfer device can include a cannula assembly or the like that can be inserted percutaneously to place the fluid transfer device in fluid communication with the patient (e.g., inserted into a vein of the patient). More specifically, in some embodiments, the cannula assembly of the fluid transfer device can include a sharpened distal end configured to pierce the skin of the patient. In other embodiments, the transfer device can include a flow control mechanism that can include a sharpened distal end portion that is configured to extend beyond a distal end portion of the cannula assembly to pierce the skin of the patient. For example, in some embodiments, the fluid transfer device can include a flow control mechanism that is substantially similar to the flow control mechanism 340 of the transfer device 300 described above with reference to FIGS. 4-10.

[1136] With the cannula assembly in fluid communication with the patient, a predetermined volume of a bodily fluid is withdrawn from the patient, at 991. For example, in some embodiments, the fluid transfer device can include a flow control mechanism, such as those described above, that can be moved between a first configuration and a second configuration. In some embodiments, flow control mechanism can be configured to define a fluid flow path between, for example, the cannula assembly and a fluid reservoir included in and/or fluidically coupled to the fluid transfer device. In other embodiments, any portion of fluid transfer device can define at least a portion of the fluid flow path. For example, the fluid transfer device can include a housing or the like that can define at least a portion of the fluid flow path. Thus, the predetermined volume of the bodily fluid is transferred to the fluid reservoir, at 993. In some embodiments, the predetermined volume of the bodily fluid can

include, for example, dermally residing microbes that were dislodged during, for example, the venipuncture event (e.g., inserting the cannula assembly into the patient).

[1137] Once the predetermined volume of bodily fluid is disposed in the fluid reservoir, the fluid transfer device is fluidically isolated from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir, at 994. For example, in some embodiments, once the predetermined volume of bodily fluid is disposed in the fluid reservoir, the fluid transfer device can be physically and/or fluidically decoupled from the fluid reservoir. In other embodiments, the flow control mechanism (as described above) can be moved from the first configuration to the second configuration to fluidically isolate the fluid reservoir from a volume outside of the fluid reservoir. For example, in some embodiments, the flow control mechanism can define a lumen or the like that can define a fluid flow path between the cannula assembly and the fluid reservoir when in the first configuration. In such embodiments, the flow control mechanism can be transitioned (e.g., moved, rotated, and/or otherwise reconfigured) from the first configuration to the second configuration in which the lumen is removed from fluid communication with the cannula assembly and/or the fluid reservoir, thereby fluidically isolating the fluid reservoir from the cannula assembly. In some embodiments, the flow control mechanism can be configured to transition from the first configuration to the second configuration automatically once the predetermined volume of bodily fluid is disposed in the fluid reservoir.

[1138] With the fluid reservoir fluidically isolated from at least a portion of the fluid transfer device, fluid communication is established between the patient and a fluid source via the fluid transfer device, at 995. For example, in some embodiments, the fluid source can be operably coupled to the fluid transfer device to place the fluid source in fluid communication with at least a portion of the fluid transfer device. In some embodiments, the flow control mechanism (described above) can define a second lumen that can place the fluid source in fluid communication with the cannula assembly when in the second configuration. In other embodiments, with the fluid reservoir decoupled from the fluid transfer device that fluid source can be placed in fluid communication with the cannula assembly via any other portion of the fluid transfer device (e.g., a portion of a housing and/or the like). In this manner, a fluid can flow from the fluid source, through the fluid transfer device and into the patient. Moreover, by fluidically isolating the predetermined volume of bodily fluid the flow of fluid

from the fluid source can be substantially free of contaminants such as, for example, the dermally residing microbes, as described above.

[1139] While various embodiments have been described above, it should be understood that they have been presented by way of example only, and not limitation. Where methods and steps described above indicate certain events occurring in certain order, those of ordinary skill in the art having the benefit of this disclosure would recognize that the ordering of certain steps may be modified and that such modifications are in accordance with the variations of the invention. Additionally, certain of the steps may be performed concurrently in a parallel process when possible, as well as performed sequentially as described above. Additionally, certain steps may be partially completed before proceeding to subsequent steps.

[1140] While various embodiments have been particularly shown and described, various changes in form and details may be made. For example, while the actuator 580 is shown and described with respect to FIG. 21 as being rotated in a single direction, in other embodiments, an actuator can be rotated in a first direction (e.g., in the direction of the arrow MM in FIG. 21) and a second direction, opposite the first. In such embodiments, the rotation in the second direction can be configured to move a transfer device through any number of configurations. In other embodiments, the rotation of the actuator in the second direction can be limited.

[1141] Although various embodiments have been described as having particular features and/or combinations of components, other embodiments are possible having any combination or sub-combination of any features and/or components from any of the embodiments described herein.

[1142] The specific configurations of the various components can also be varied. For example, the size and specific shape of the various components can be different from the embodiments shown, while still providing the functions as described herein. More specifically, the size and shape of the various components can be specifically selected for a desired rate of bodily fluid flow into a fluid reservoir or for a desired rate of parenteral fluid flow into the patient.

Claims

1. An apparatus, comprising:

a cannula assembly;

a housing including a proximal end portion and a distal end portion and defining an inner volume therebetween, the housing having an inlet port configured to be removably coupled to the cannula assembly;

a fluid reservoir fluidically coupled to the housing and configured to receive and isolate a first volume of bodily fluid withdrawn from the patient;

a flow control mechanism at least partially disposed in the inner volume of the housing and configured to move relative to the housing between a first configuration and a second configuration, the flow control mechanism defining a fluid flow path between the cannula assembly and the fluid reservoir in the first configuration; and

an actuator operably coupled to the flow control mechanism and configured to move the flow control mechanism from the first configuration in which the inlet port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through inlet port via the fluid flow path and to the fluid reservoir, to the second configuration, in which the fluid reservoir is fluidically isolated from the cannula assembly.

2. The apparatus of claim 1, wherein the flow control mechanism includes a fluid communicator configured to be moved from a first position to a second position to place the flow control mechanism in the second configuration.

3. The apparatus of claim 2, wherein the fluid communicator is configured to extend through the inlet port and beyond the distal end portion of the housing in the first position.

4. The apparatus of claim 2, wherein the fluid communicator is retracted into the inner volume of the housing in the second position.

5. The apparatus of claim 1, wherein the flow control mechanism includes a first member movably disposed in the inner volume of the housing, and a second member coupled to the first member and configured to extend through the inlet port and beyond the distal end portion of the housing in the first configuration.

6. The apparatus of claim 5, wherein the first member includes a proximal end portion and a distal end portion, and defines a lumen therethrough.

7. The apparatus of claim 6, wherein the second member includes a proximal end portion and a distal end portion, and defines a lumen therethrough.

8. The apparatus of claim 7, wherein the proximal end portion of the second member is configured to be disposed in the lumen defined by the first member.

9. The apparatus of claim 7, wherein the distal end portion of the second member is configured to extend beyond a distal end of the cannula assembly when the flow control mechanism is in the first configuration.

10. The apparatus of claim 9, wherein the second member is a needle configured to be inserted into the patient

11. The apparatus of claim 1, wherein the cannula assembly is removably coupled to the housing.

12. The apparatus of claim 1, wherein the flow control mechanism includes a spring configured to expand and move the flow control mechanism from the first configuration to the second configuration.

13. The apparatus of claim 12, wherein the actuator is configured to release the spring from a compressed state when actuated by a user.

14. The apparatus of claim 1, wherein the fluid reservoir is movably coupled to the housing and configured to be moved from a first position to a second position, the movement from the first position to the second position configured to create a negative pressure in the fluid reservoir.

15. The apparatus of claim 1, wherein the fluid reservoir is movably disposed within the inner volume of the housing, the fluid reservoir including a proximal end portion and a

distal end portion and defining an inner volume therebetween, the inner volume configured to selectively receive at least a portion of the flow control mechanism.

16. The apparatus of claim 15, wherein the proximal end portion of the fluid reservoir is configured to move relative to the distal end portion of the fluid reservoir to increase the inner volume defined by the fluid reservoir and create a negative pressure within the inner volume.

17. The apparatus of claim 1, wherein the fluid reservoir is movably disposed within the inner volume of the housing and configured to move from a first configuration to a second configuration to create a negative pressure in the fluid reservoir.

18. The apparatus of claim 17, wherein the actuator is configured to move the fluid reservoir from the first configuration to the second configuration when actuated by a user.

19. The apparatus of claim 1, wherein the actuator includes an outlet port configured to be fluidically coupled to the fluid reservoir.

20. The apparatus of claim 19, wherein the actuator defines a lumen configured to allow fluid communication between the fluid flow path and the outlet port when the flow control mechanism is in the first configuration.

21. The apparatus of claim 20, wherein the actuator is configured to rotate from a first position in which bodily fluid can flow from the flow control mechanism, through the outlet port and to the fluid reservoir, to a second position, in which the flow control mechanism is placed in the second configuration and the fluid reservoir is fluidically isolated from the cannula assembly.

22. A device for delivering a fluid to a patient with reduced contamination, the device comprising:

a housing including a proximal end portion and a distal end portion and defining an inner volume therebetween, the housing having a first port configured to be removably coupled to a cannula assembly, and a second port configured to be fluidically coupled to a fluid source;

a fluid reservoir fluidically couplcablc to a cannula assembly and configured to receive and isolate a predetermined volume of bodily fluid withdrawn from the patient; and

a flow control mechanism at least partially disposed in the inner volume of the housing and configured to move relative to the housing between a first configuration in which the first port is placed in fluid communication with the fluid reservoir such that bodily fluid can flow from the cannula assembly, through first port and to the fluid reservoir, and a second configuration in which (a) the fluid reservoir is fluidically isolated from the cannula assembly, and (b) fluid can flow from the fluid source, in the second port, through the flow control mechanism, out the first port and to the cannula assembly.

23. The device of claim 22, wherein the fluid reservoir is disposed in the inner volume of the housing and is at least partially defined by the flow control mechanism.

24. The device of claim 23, wherein the fluid reservoir includes an inlet port configured to be fluidically coupled to the first port of the housing.

25. The device of claim 24, further comprising a valve disposed in the inlet port of the fluid reservoir.

26. The device of claim 25, wherein the valve is a check valve.

27. The device of claim 24, wherein the fluid reservoir is configured to move relative to the housing from a first position in which the inlet port is fluidically coupled to the first port of the housing, to a second position in which the inlet port is fluidically isolated from the first port of the housing.

28. The device of claim 22, wherein the flow control mechanism includes a first sealing member and a second sealing member spaced apart from the first sealing member, the first sealing member at least partially defining the fluid reservoir.

29. The device of claim 28, wherein the flow control mechanism is configured to move the first sealing member and the second sealing member from a first position to a second position to place the flow control mechanism in the second configuration.

30. The device of claim 29, wherein the movement of the first sealing member from the first position to the second position is configured to create a negative pressure in the fluid reservoir.

31. The device of claim 22, wherein the fluid reservoir is defined by the flow control mechanism.

32. The device of claim 31, wherein the fluid reservoir includes an inlet port configured to be fluidically coupled to the first port of the housing in the first configuration, and fluidically isolated from the first port of the housing in the second configuration.

33. The device of claim 22, wherein the flow control mechanism defines a lumen, the lumen configured to be fluidically isolated from the first port and the second port of the housing in the first configuration, and in fluid communication with the first port and the second port of the housing in the second configuration such that fluid can flow from the fluid source, in the second port of the housing, through the lumen of the flow control mechanism, and out the first port of the housing.

34. The device of claim 22, wherein the flow control mechanism is configured to rotate from a first position in which the flow control mechanism is in the first configuration, to a second position in which the flow control mechanism is placed in the second configuration.

35. A method of delivering a fluid to a patient using a fluid transfer device, the method comprising:

establishing fluid communication between the patient and the fluid transfer device;

withdrawing a predetermined volume of a bodily fluid from the patient;

transferring the predetermined volume of the bodily fluid to a fluid reservoir;

fluidically isolating the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir; and

establishing fluid communication between the patient and a fluid source with the fluid transfer device.

36. The method of claim 35, whereby sequestering the predetermined volume of the bodily fluid in the fluid reservoir establishes a sterile fluid flow path between the fluid source and the patient.

37. The method of claim 35, wherein the fluid transfer device includes a flow control mechanism, the method further comprising:

disposing the flow control mechanism in a first configuration prior to withdrawing the predetermined volume of bodily fluid from the patient, the first configuration establishing fluid communication between the patient and the fluid reservoir.

38. The method of clam 37, further comprising:

after the predetermined volume of bodily fluid has been transferred the fluid reservoir, moving the flow control mechanism to a second configuration, the second configuration establishing fluid communication between the fluid source and the patient.

39. The method of claim 38, wherein the flow control mechanism is automatically moved from the first configuration to the second configuration after the predetermined volume of bodily fluid has been transferred to the fluid reservoir.

40. The method of claim 35, further comprising:

delivering fluid from the fluid source to the patient.

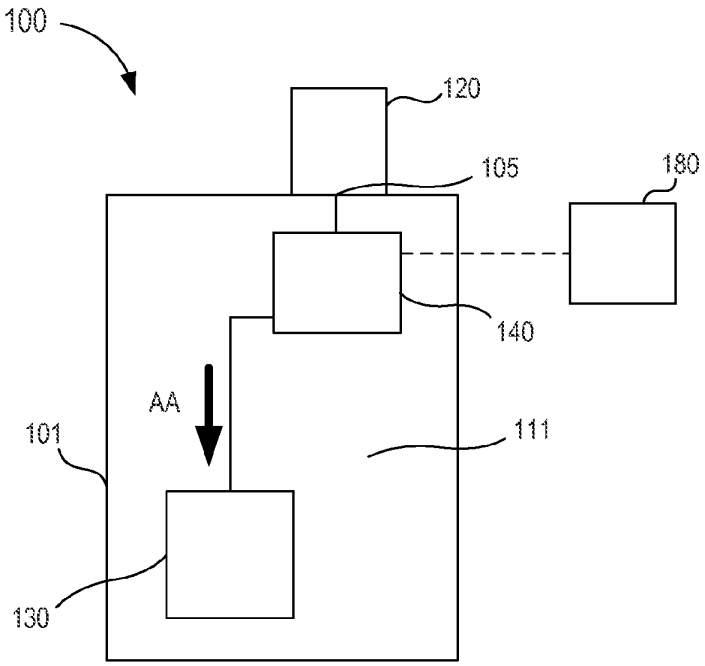

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FIG. 1

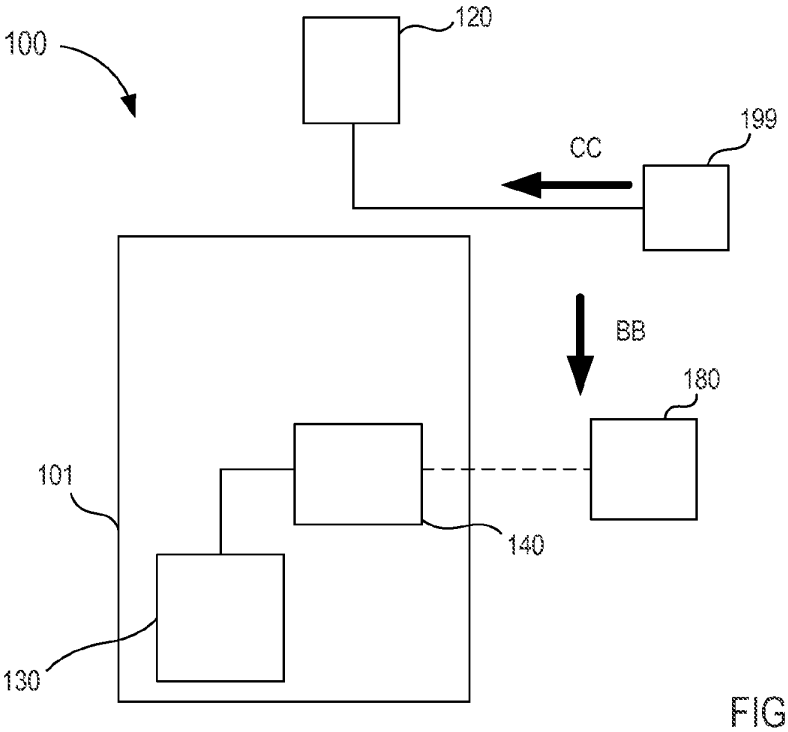

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FIG. 2

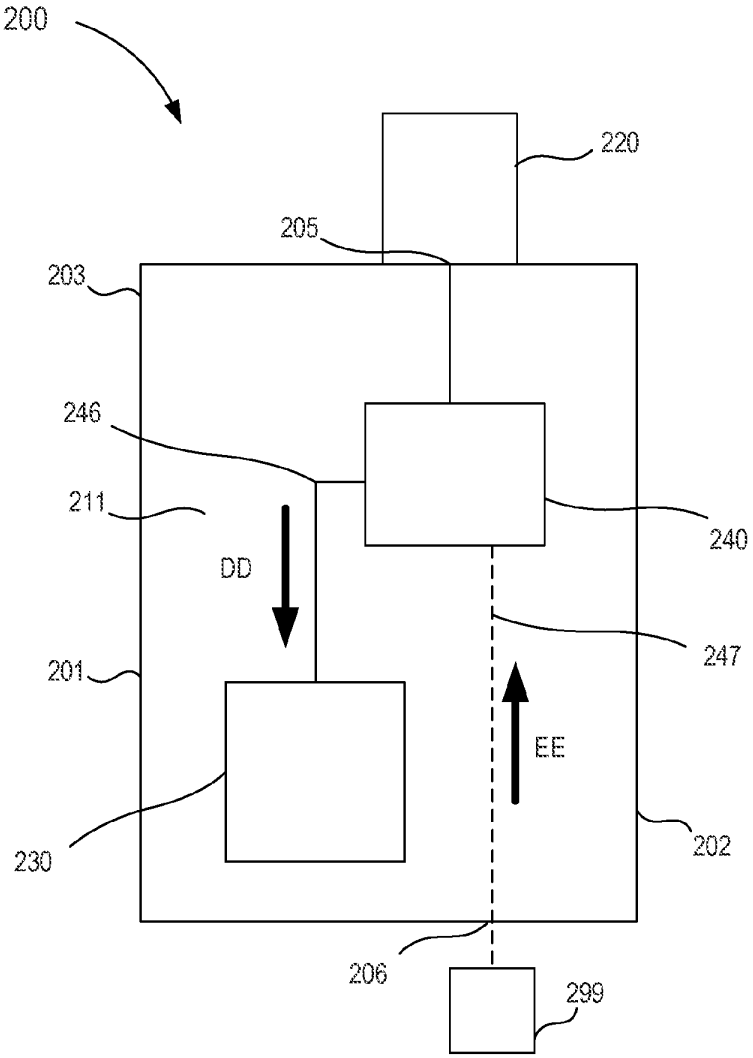


FIG. 3

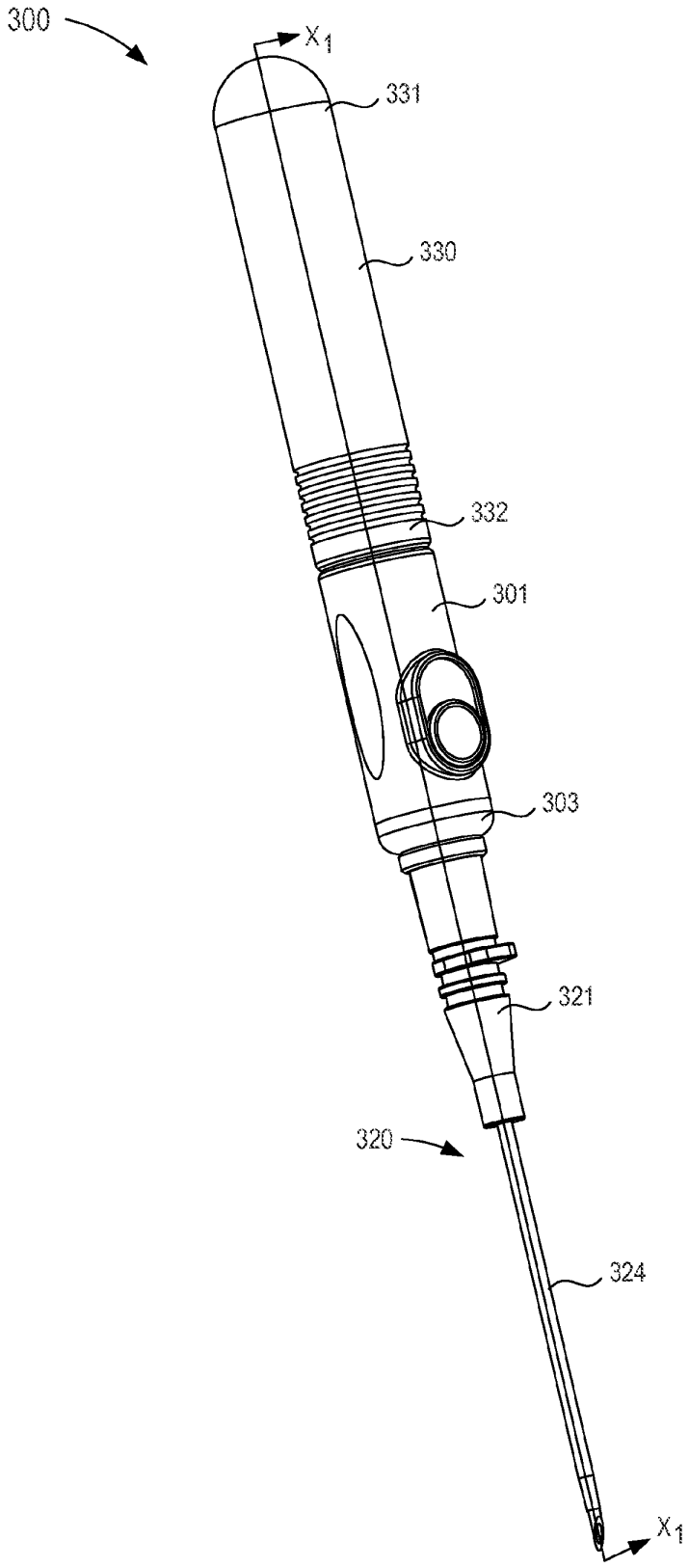


FIG. 4

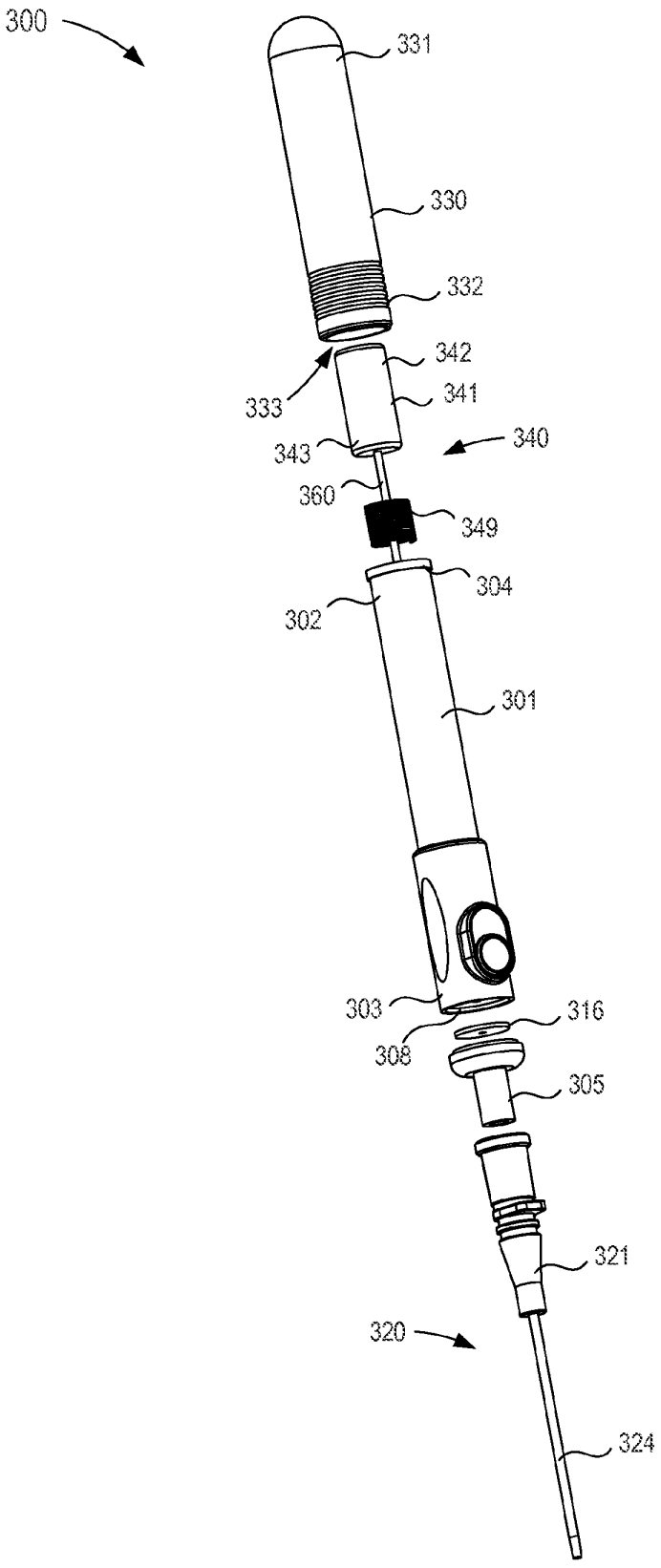

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FIG. 5

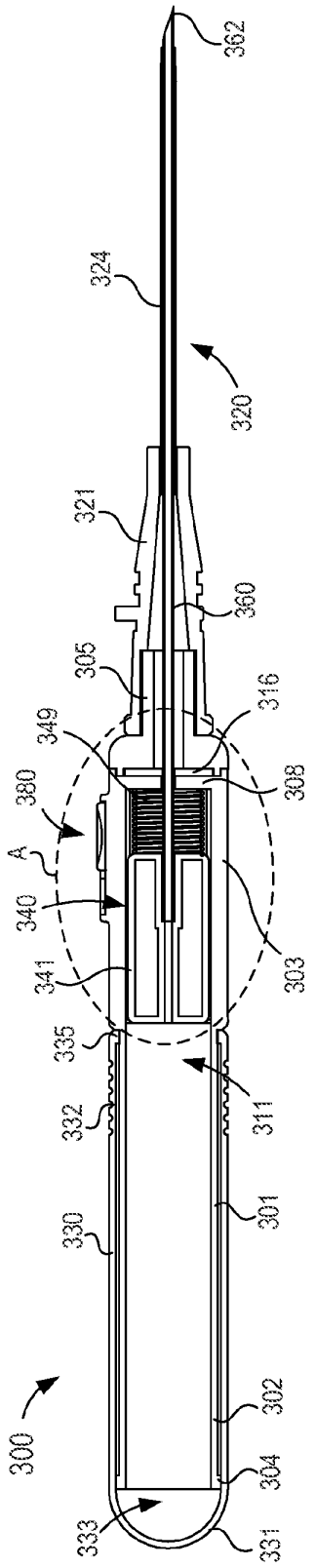

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FIG. 6

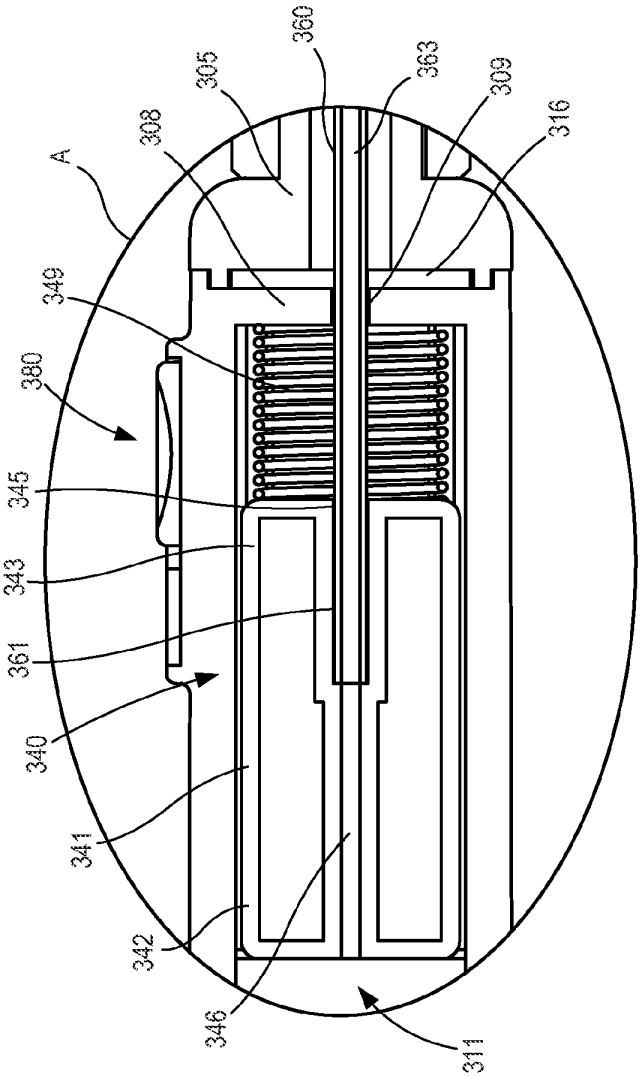

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FIG. 7

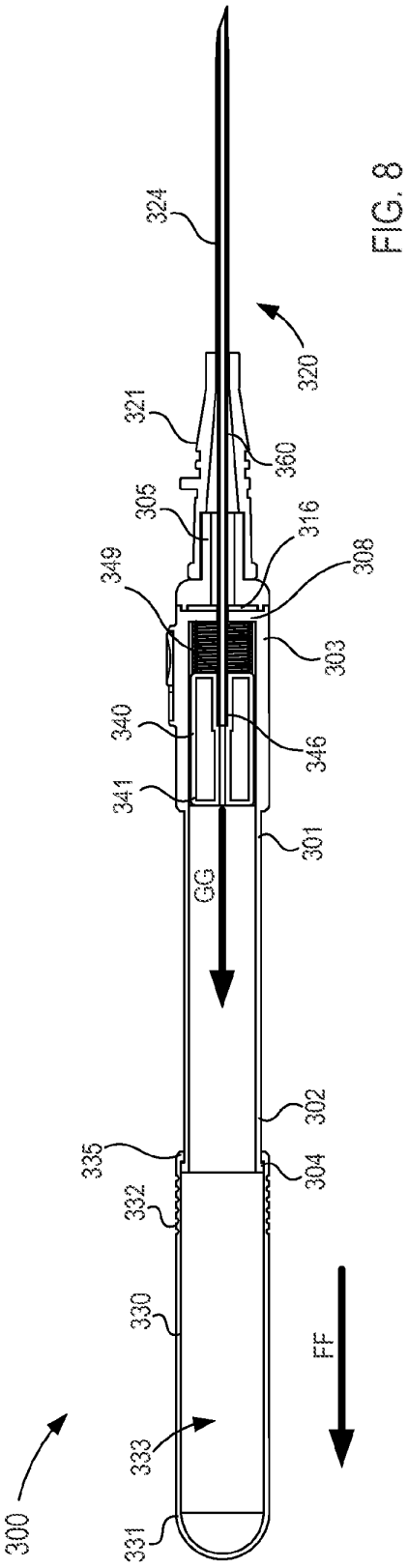

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FIG. 8

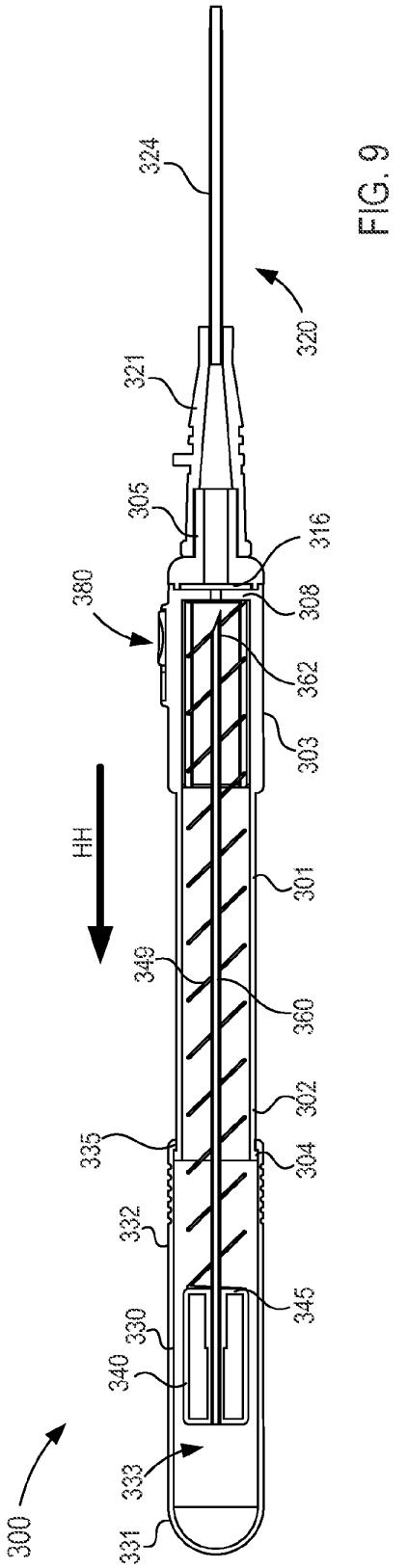

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FIG. 9

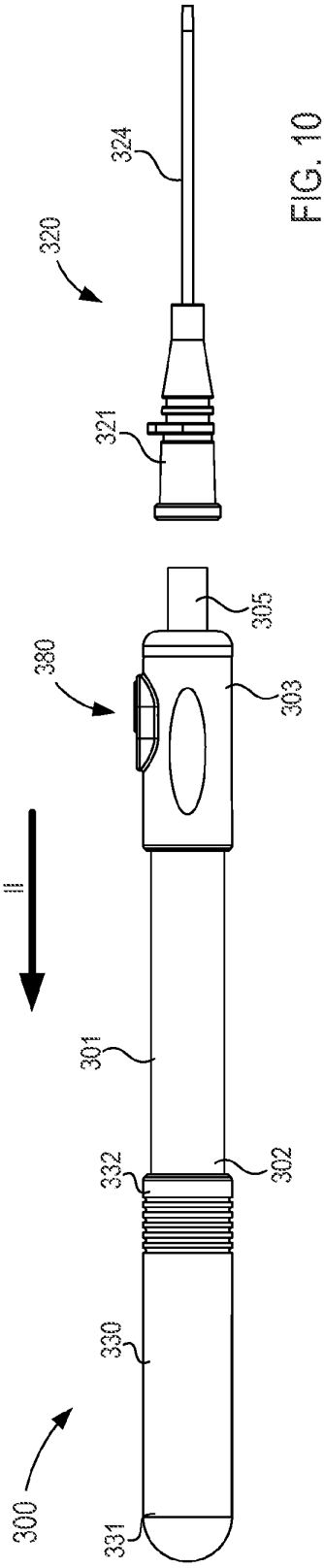


FIG. 10

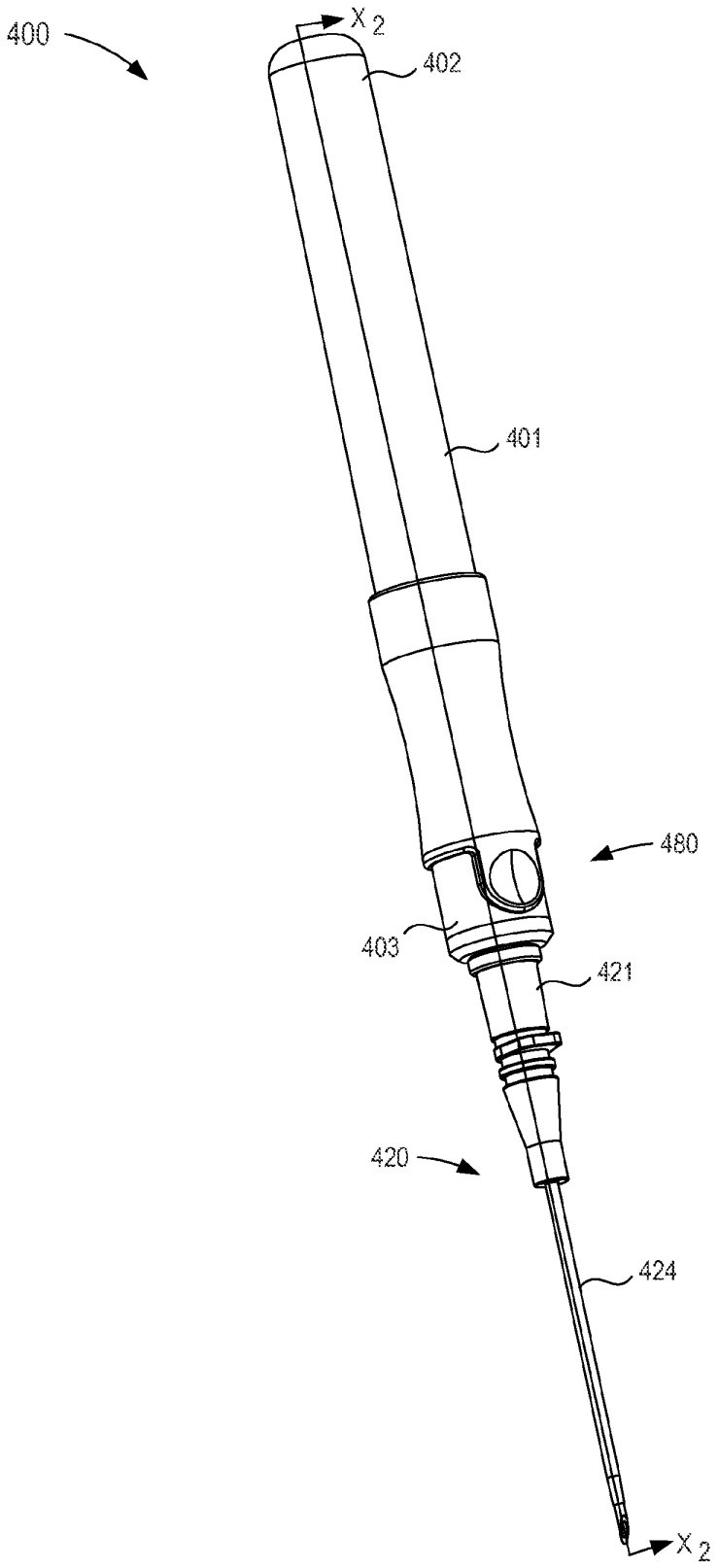


FIG. 11

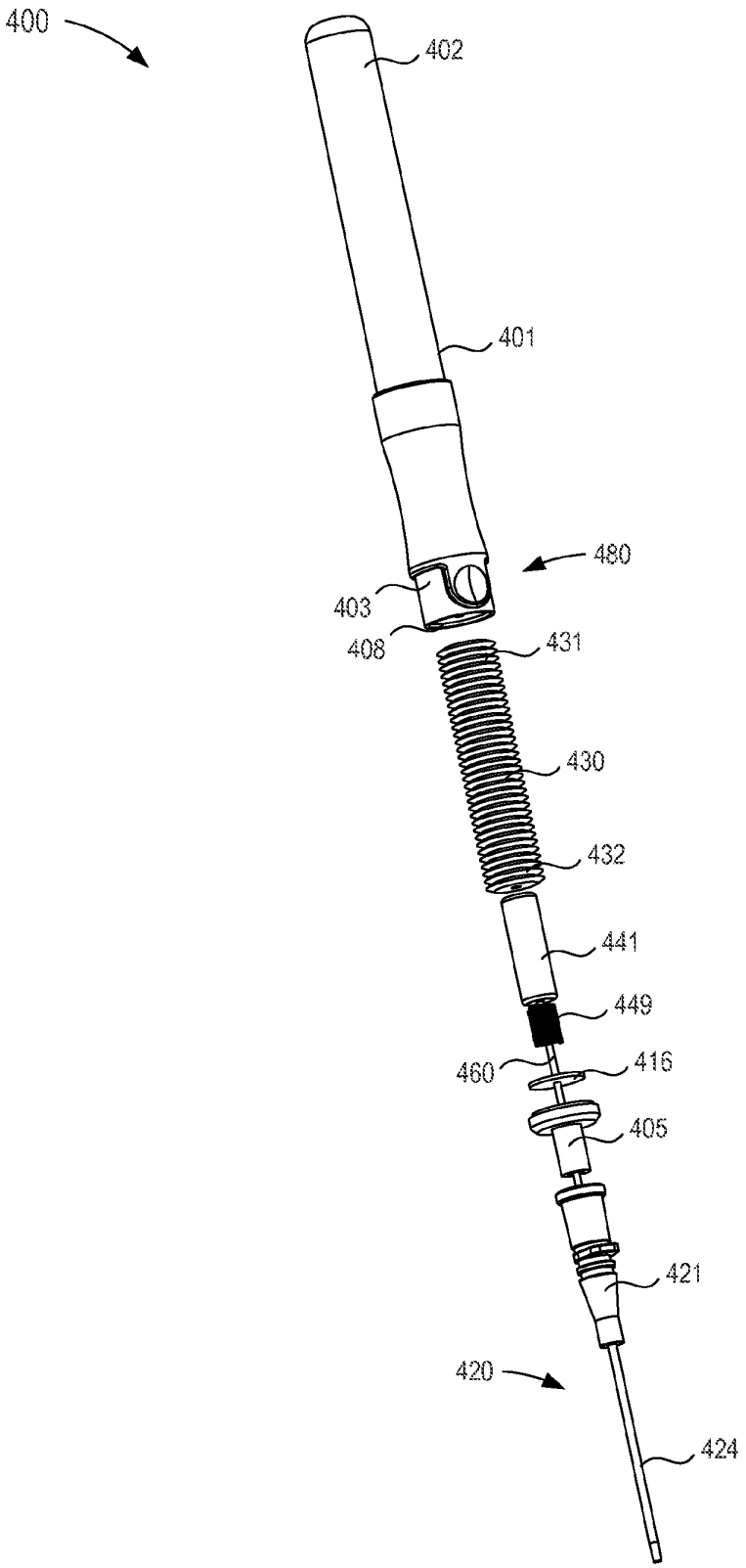

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FIG. 12

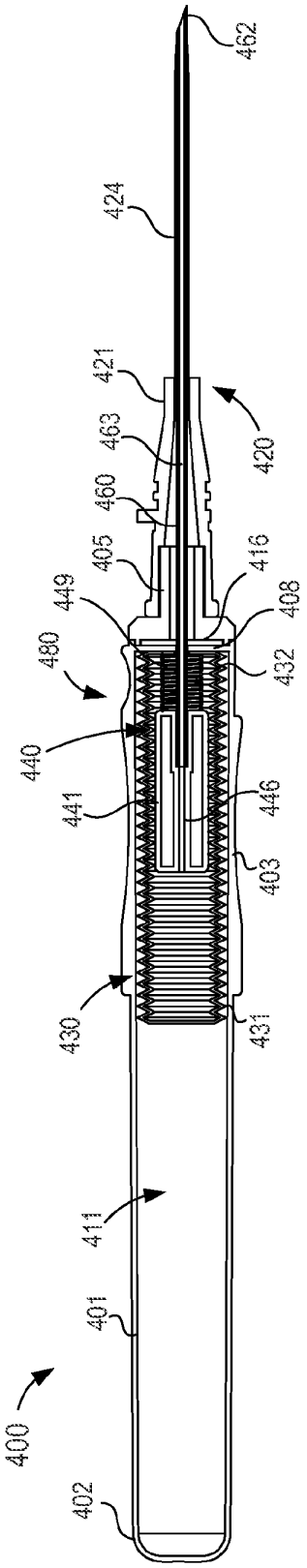

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FIG. 13

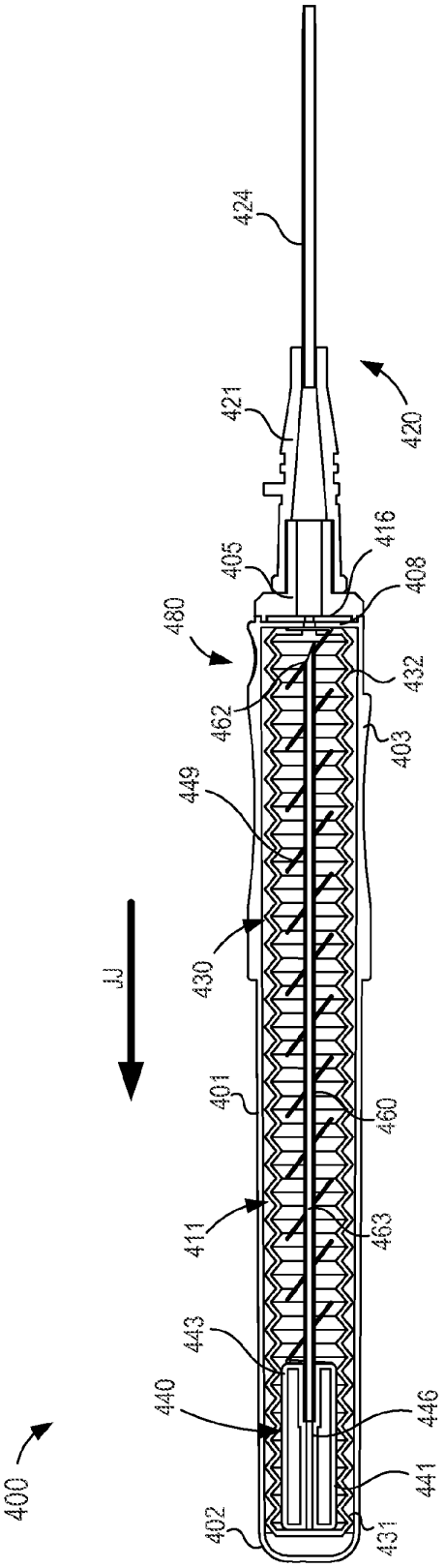

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FIG. 14

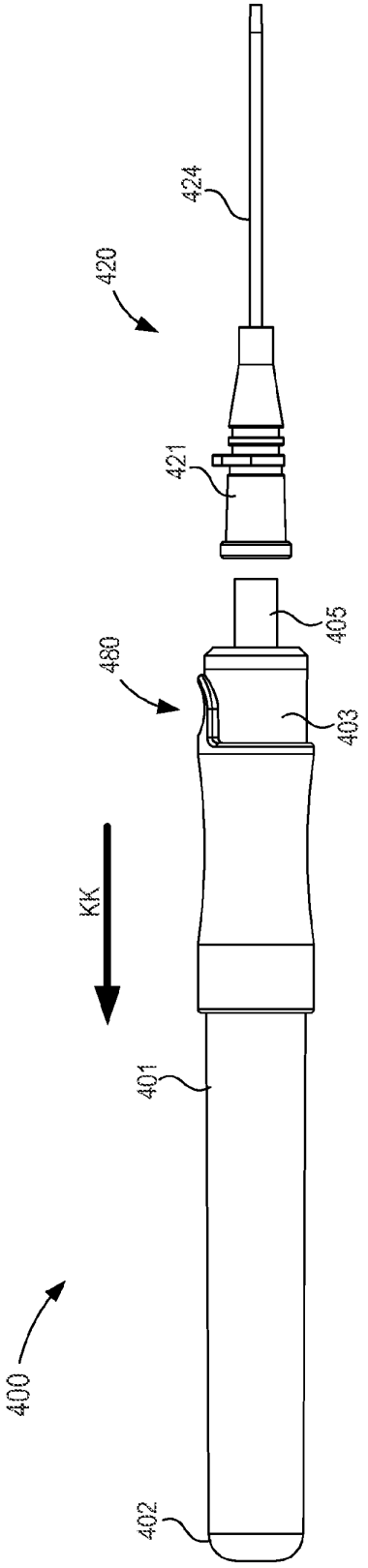


FIG. 15

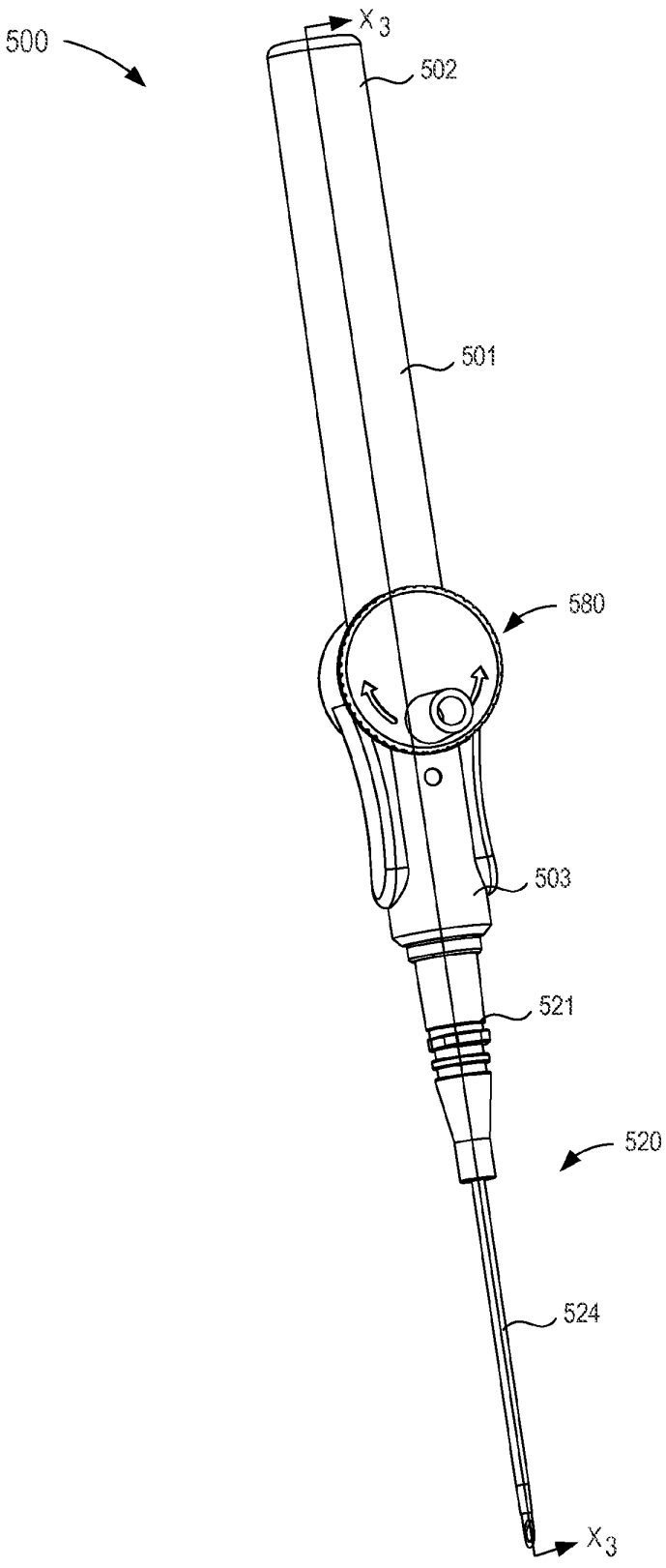


FIG. 16

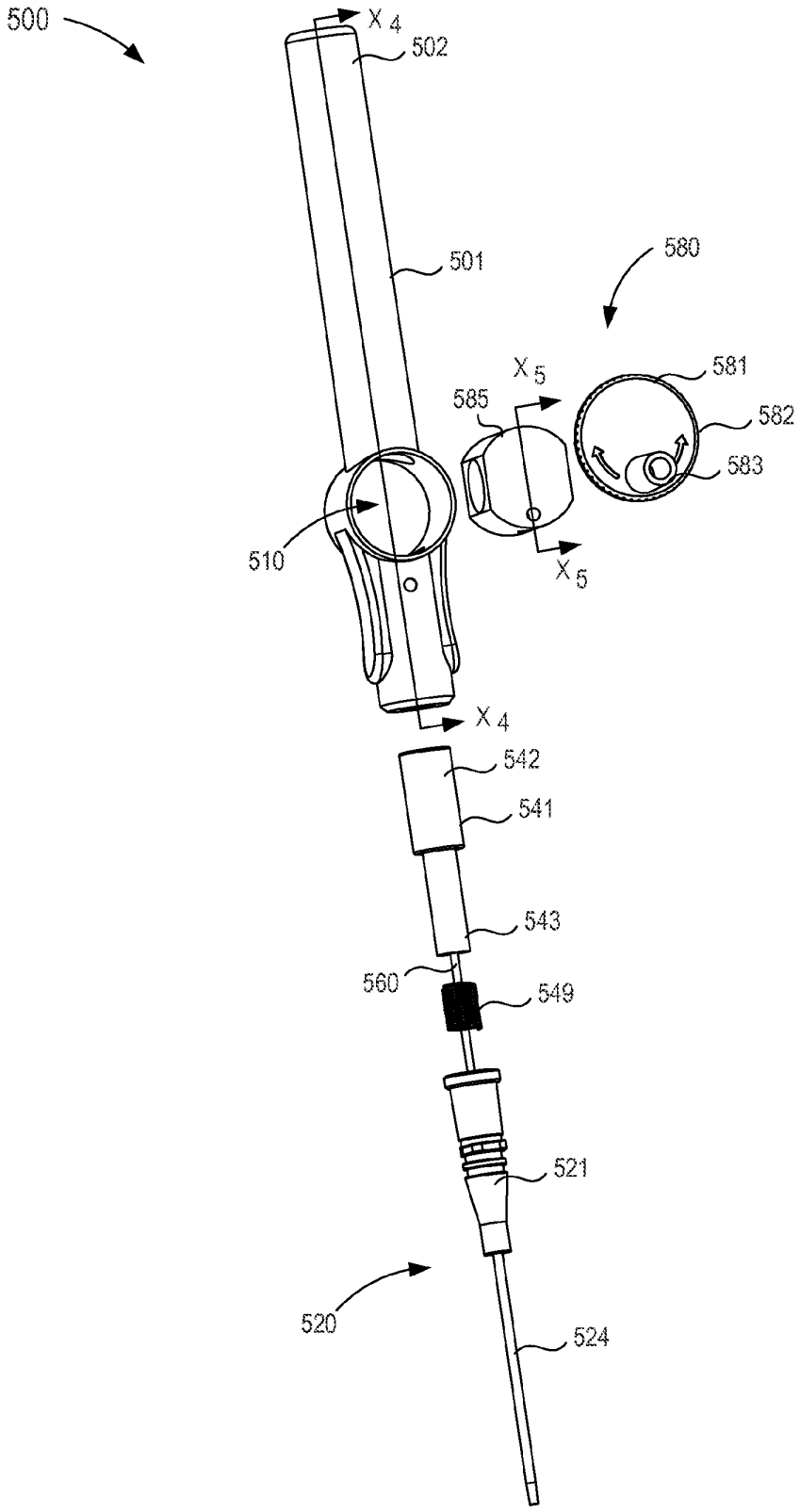

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X 5
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FIG. 17

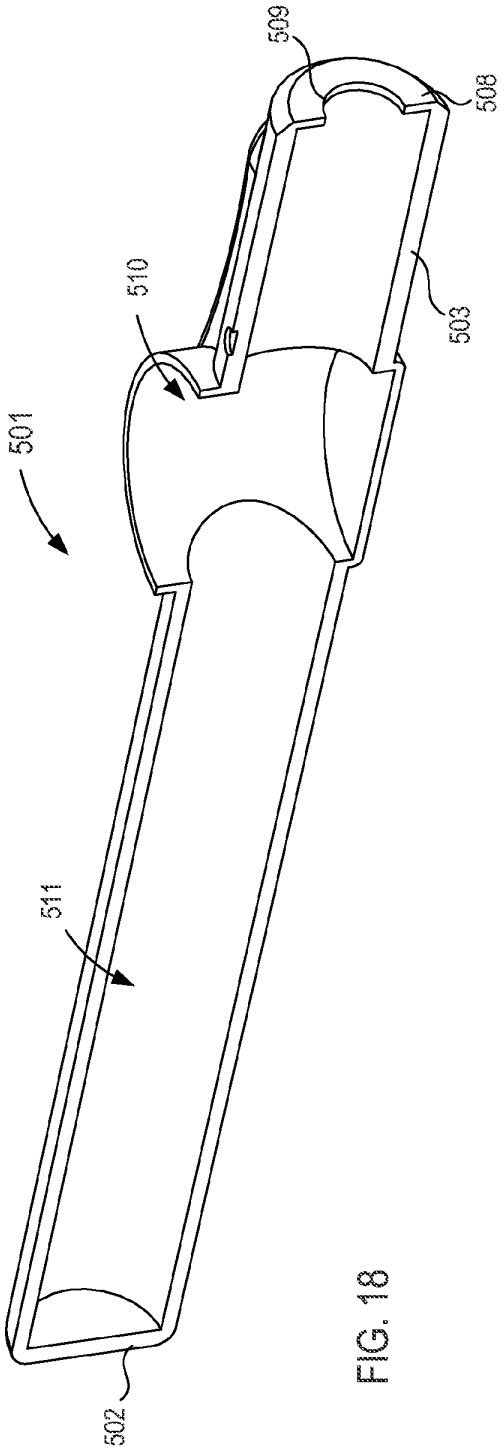


FIG. 18

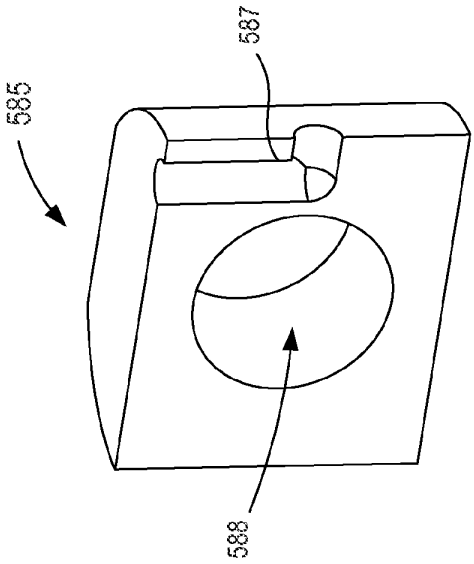


FIG. 19

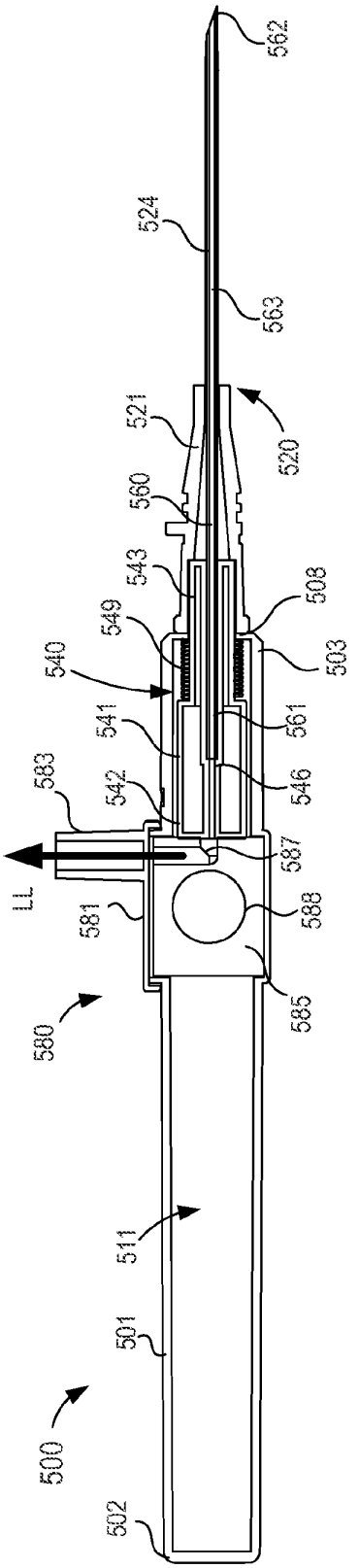

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FIG. 20

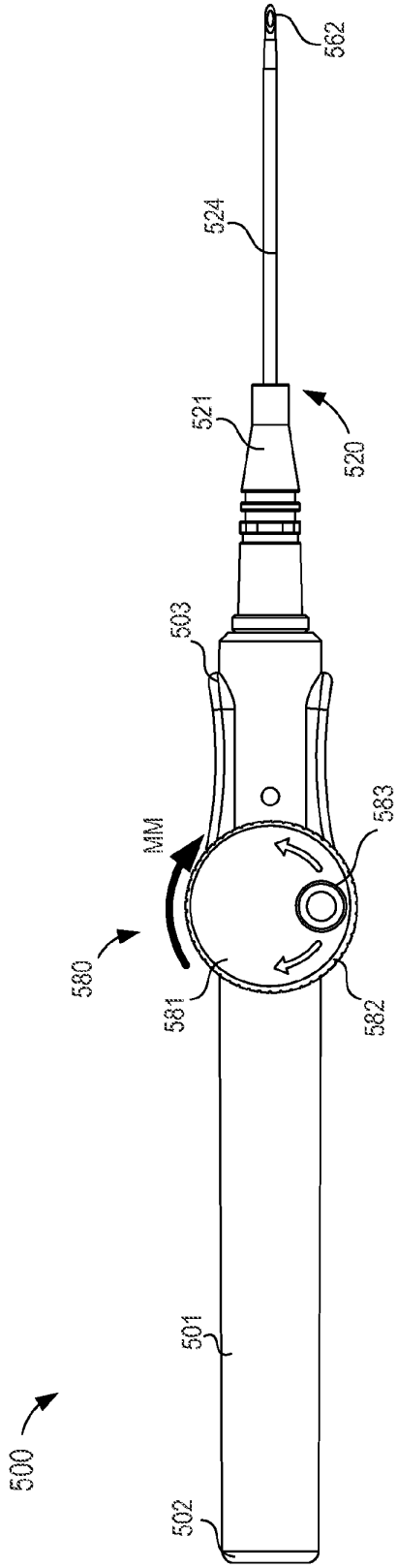

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FIG. 21

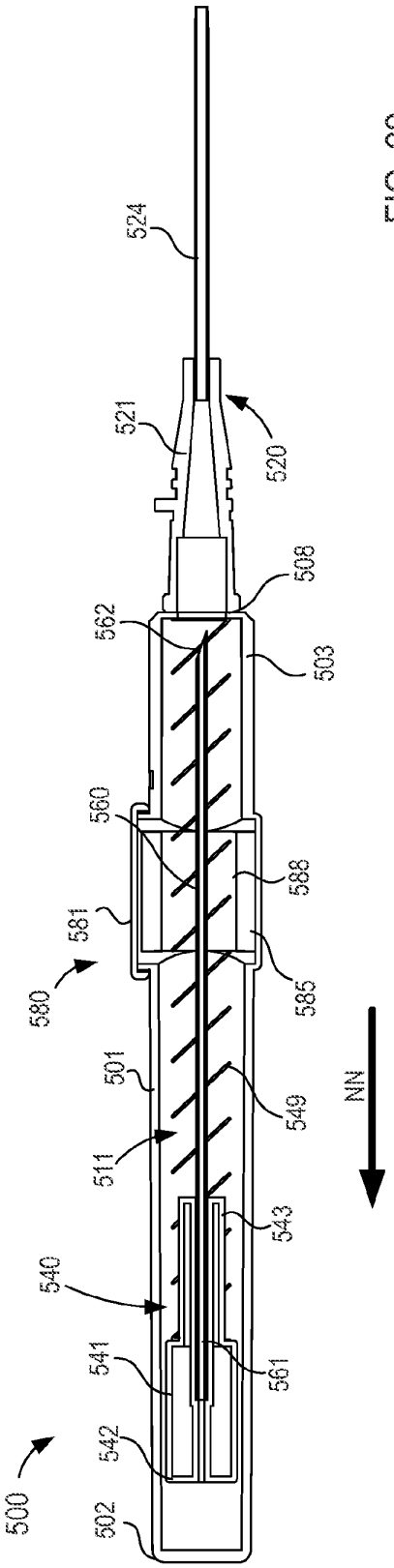

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FIG. 22

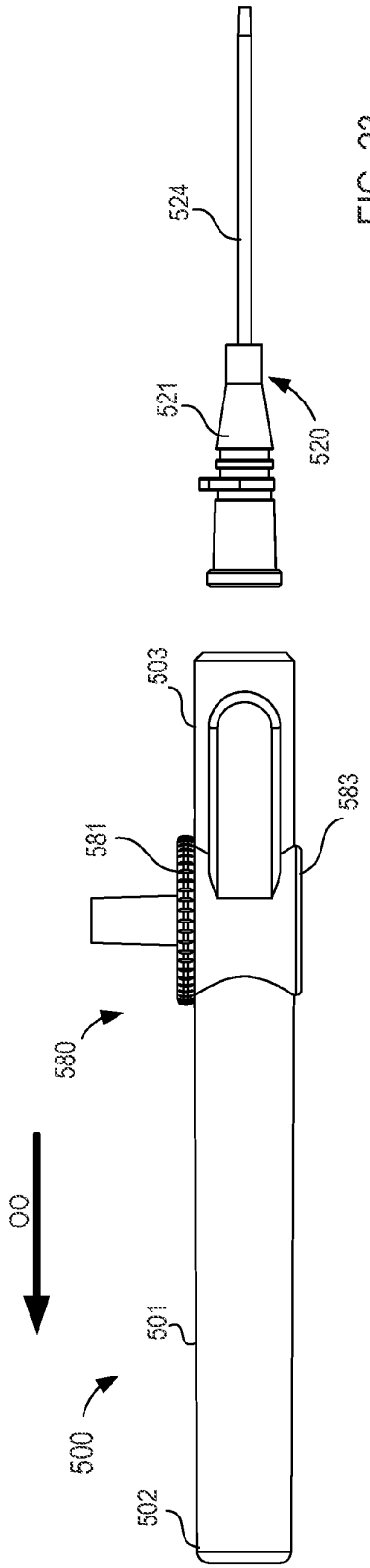

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FIG. 23

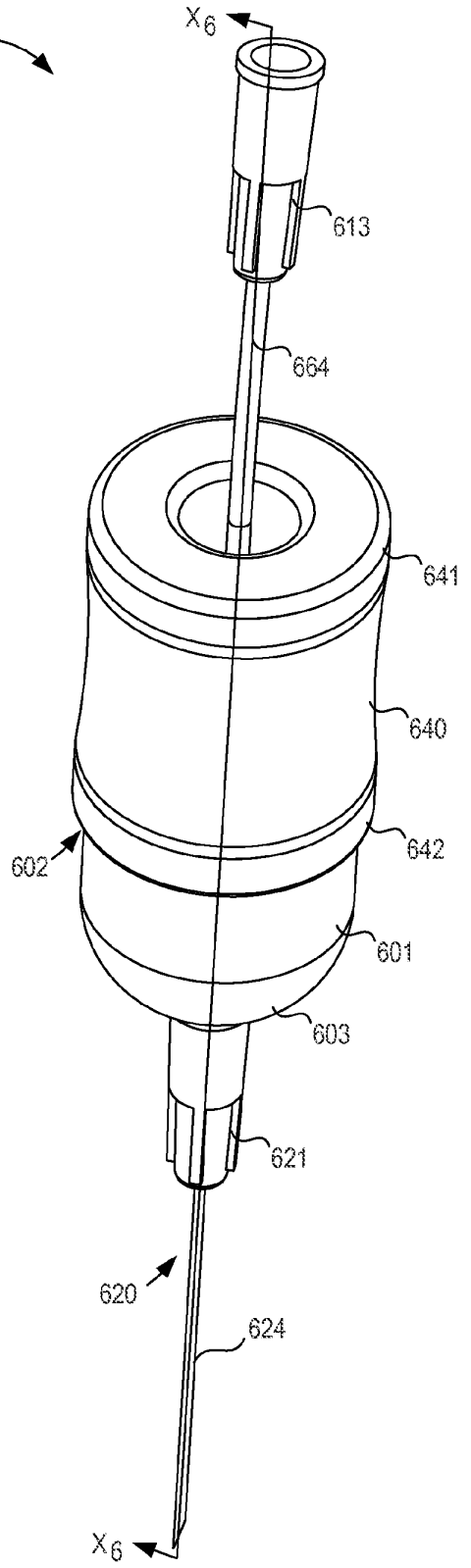


FIG. 24

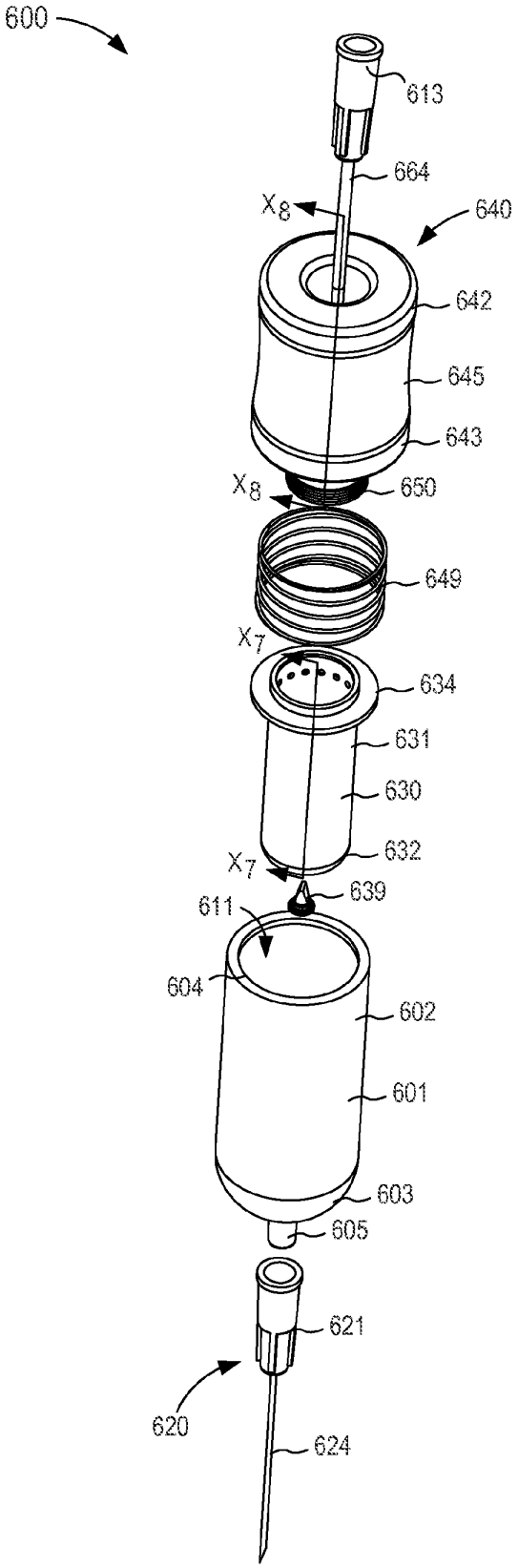

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FIG. 25

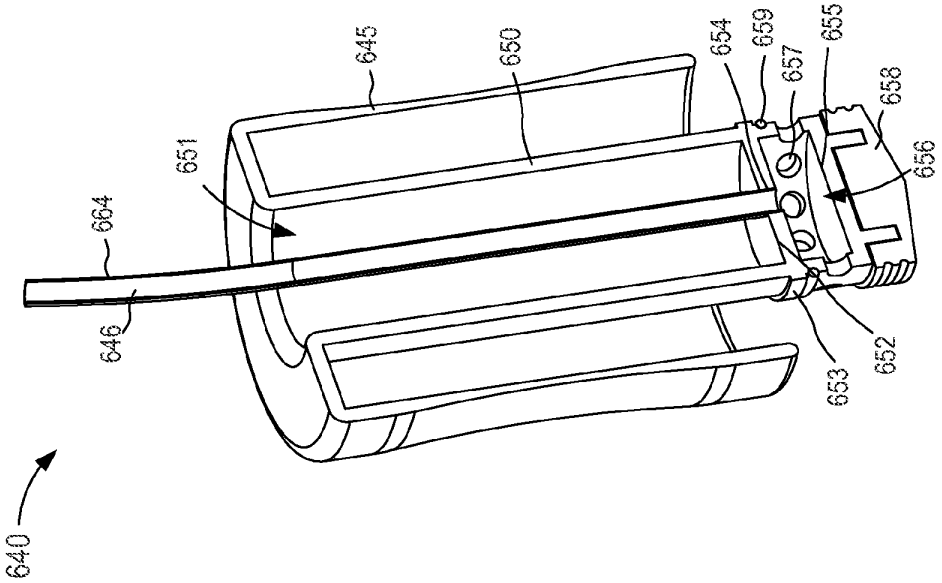

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FIG. 27

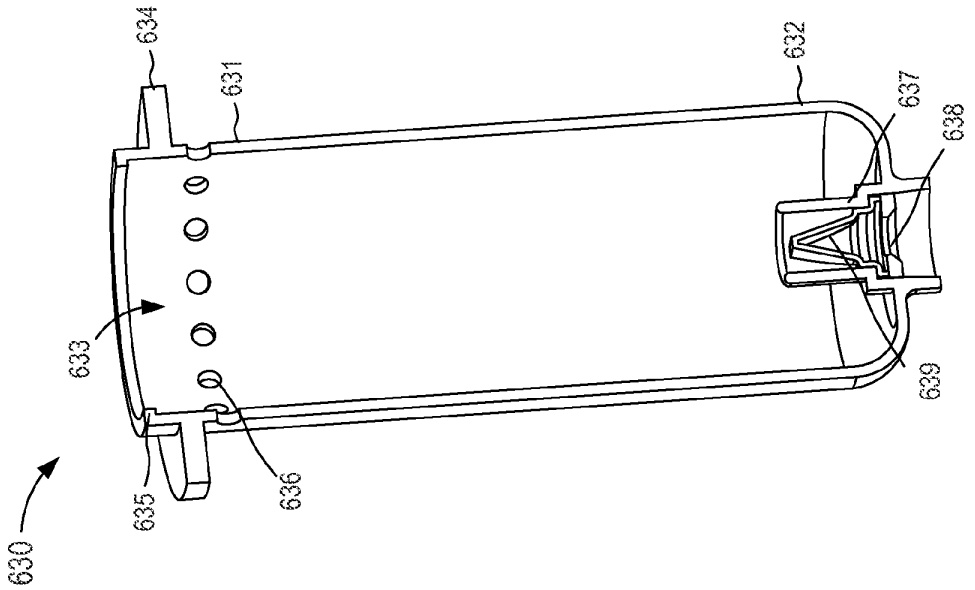

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FIG. 26

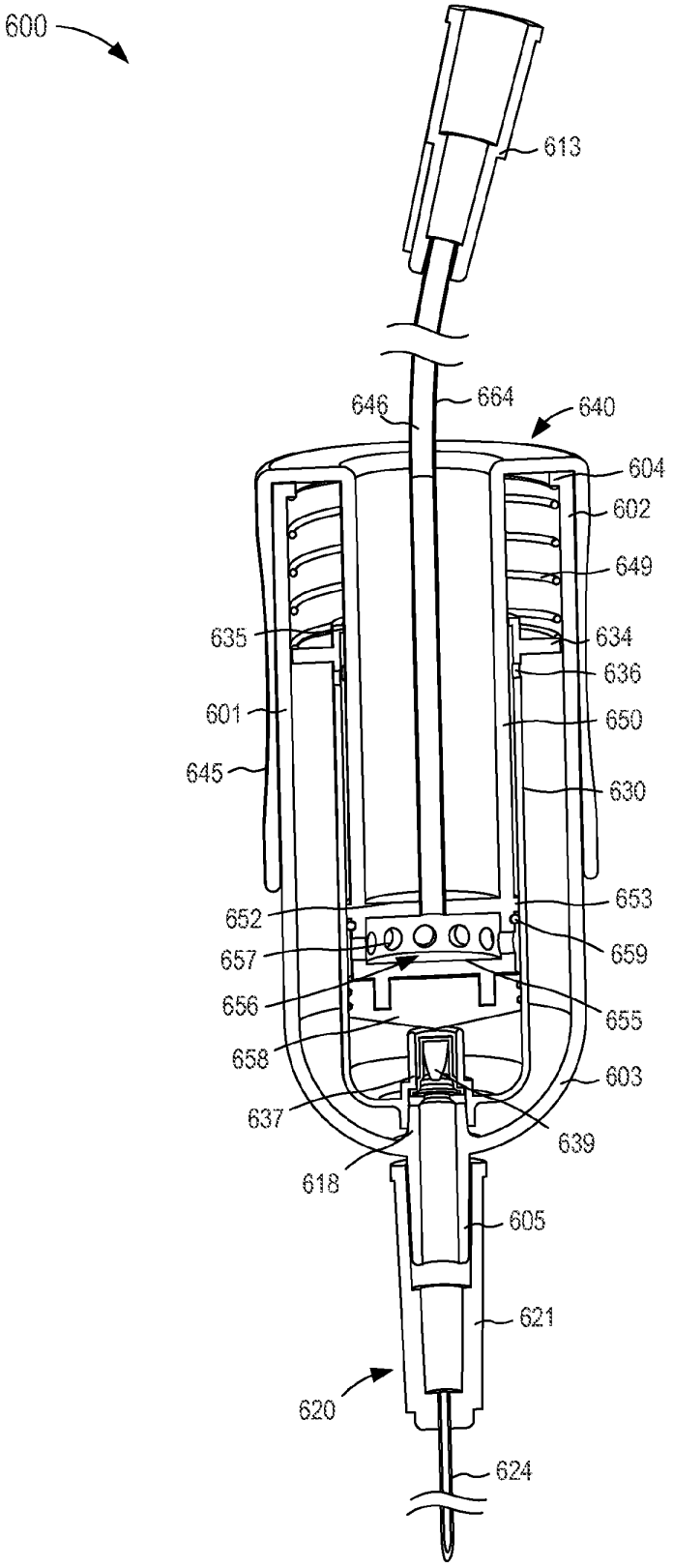

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FIG. 28

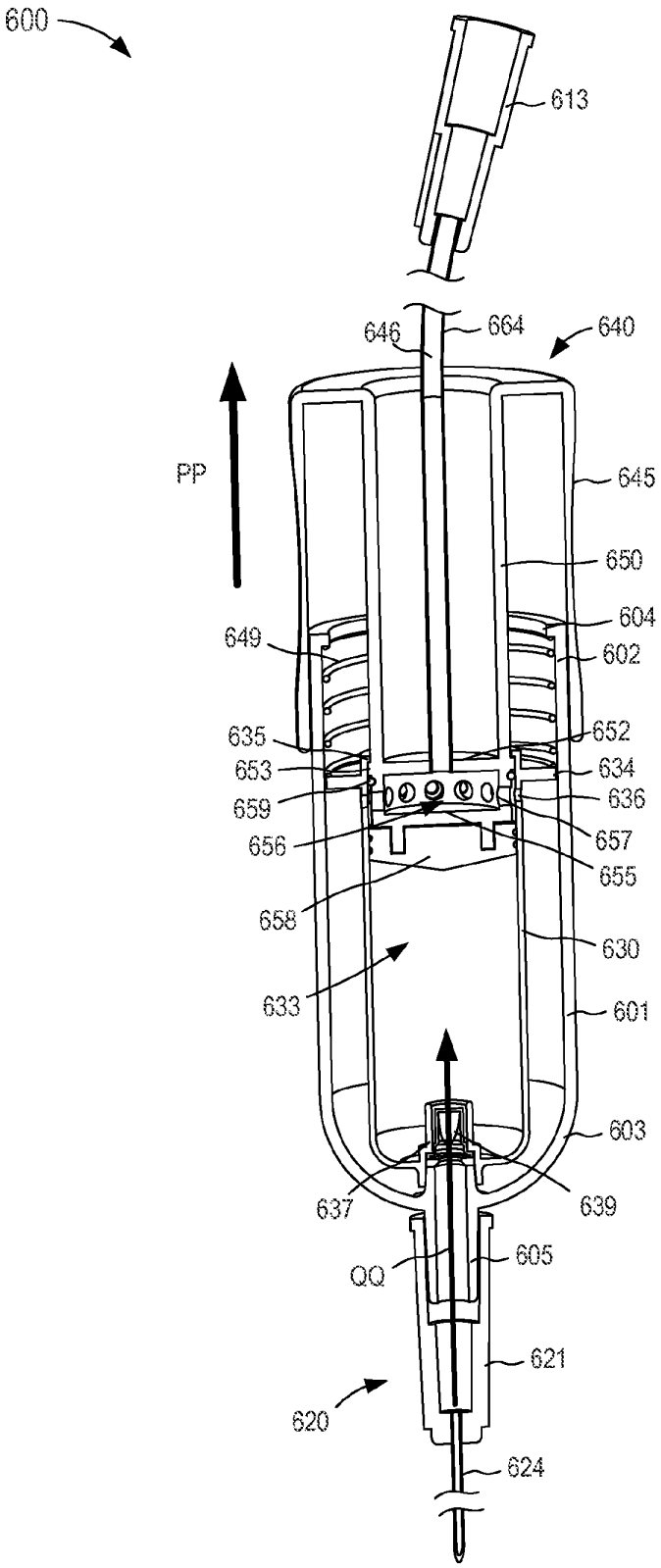

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FIG. 29

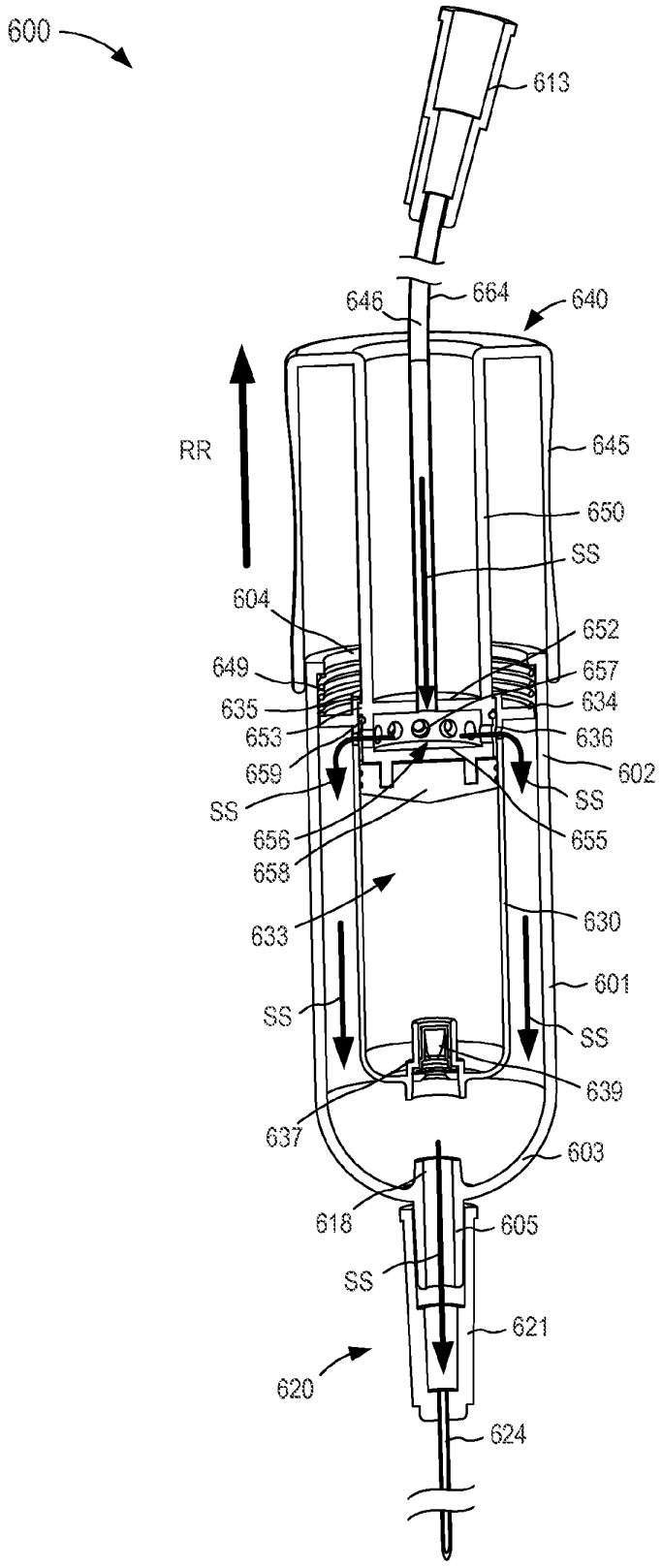

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FIG. 30

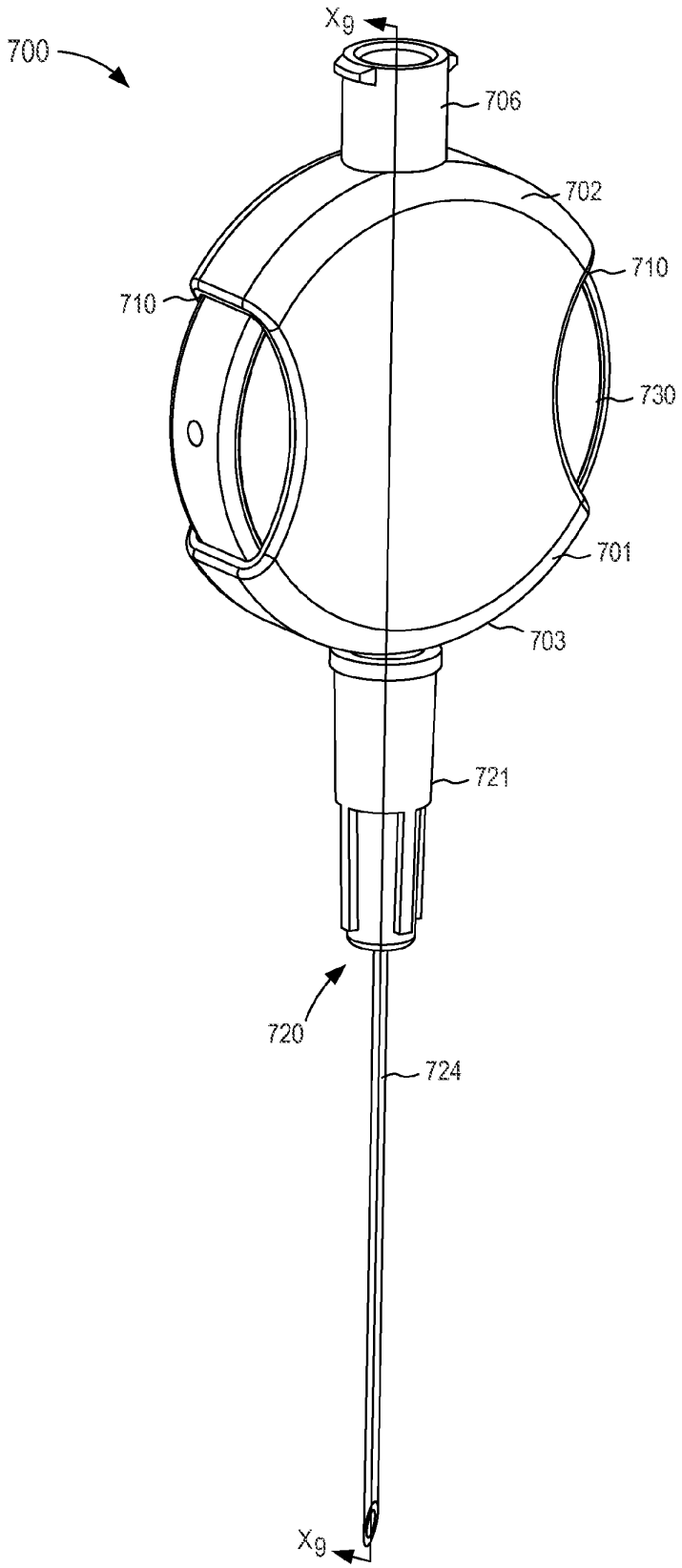


FIG. 31

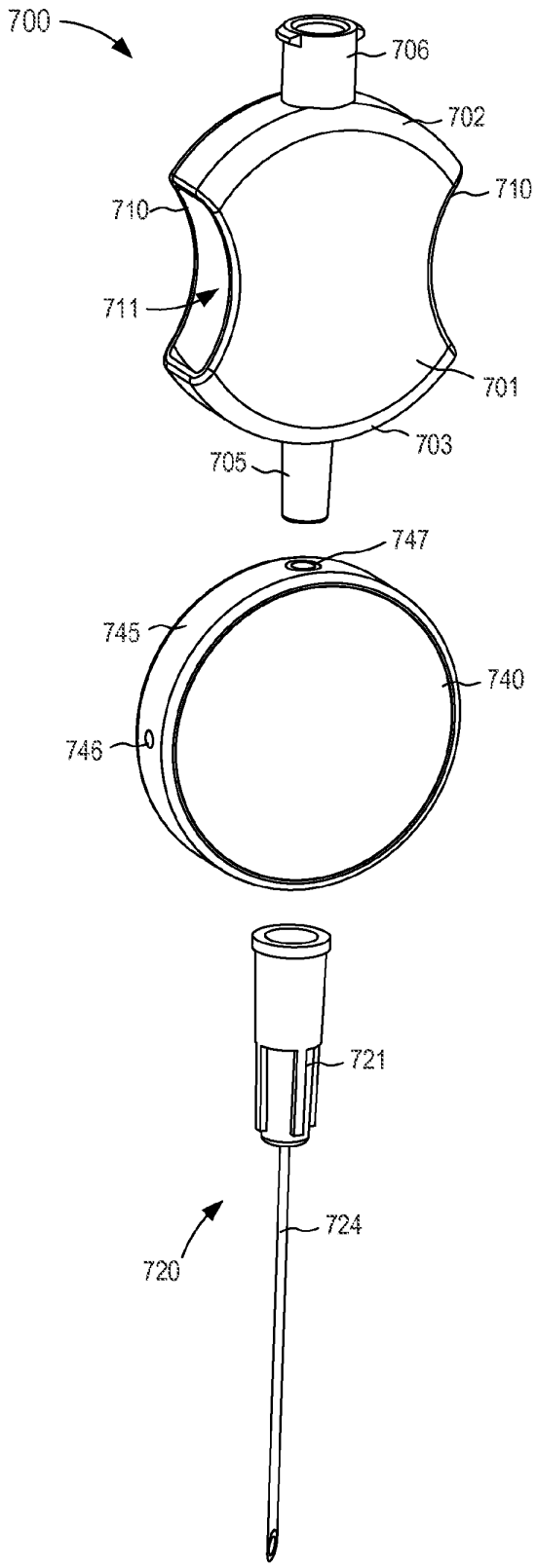


FIG. 32

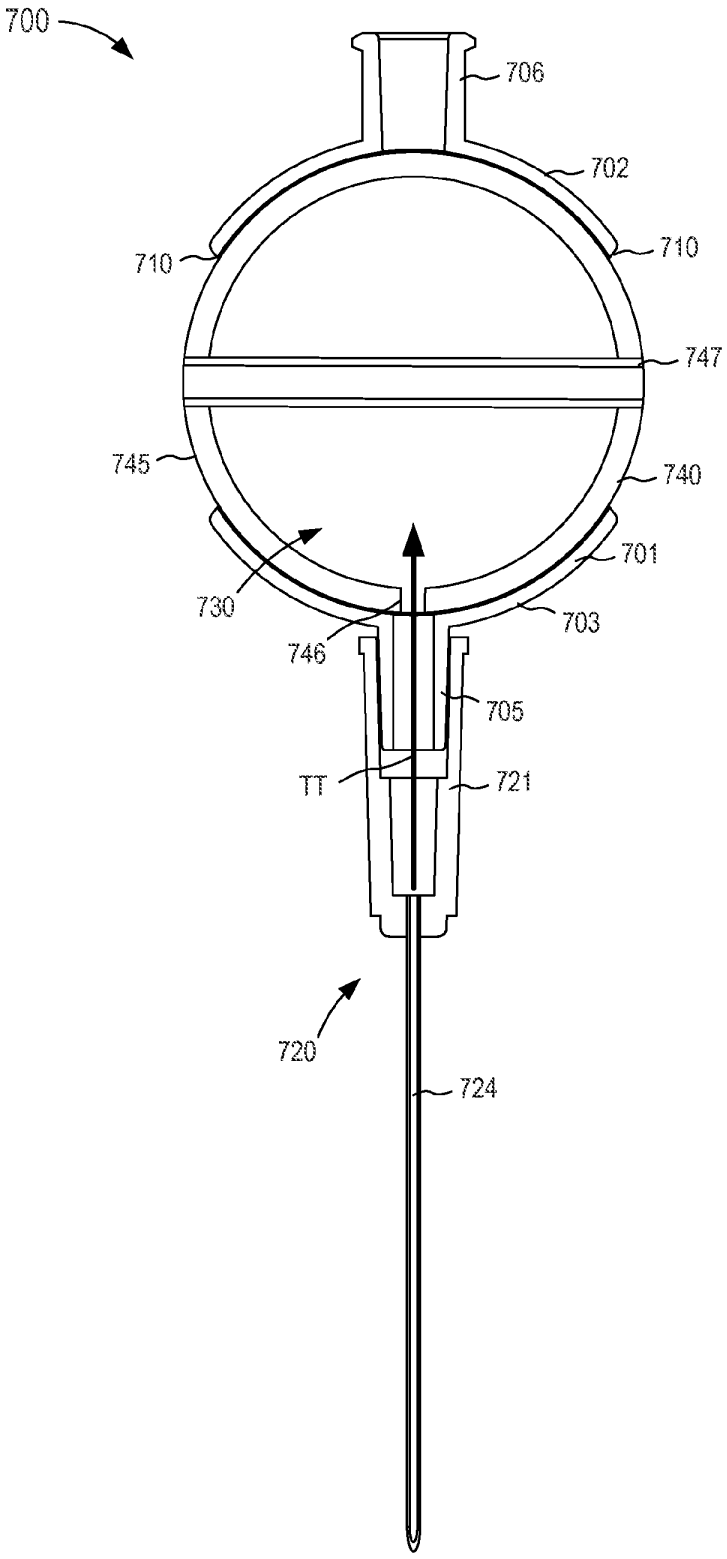

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FIG. 33

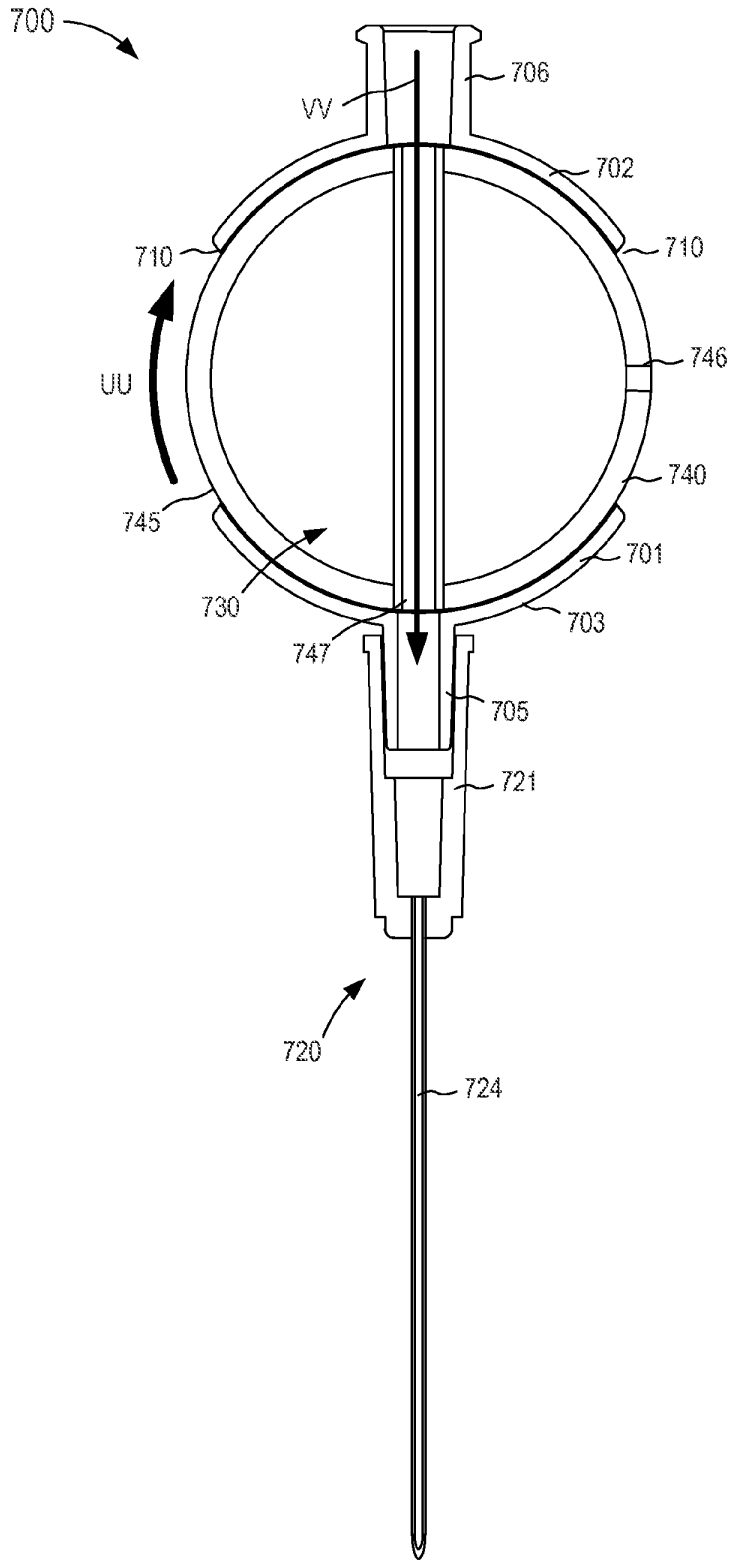

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FIG. 34

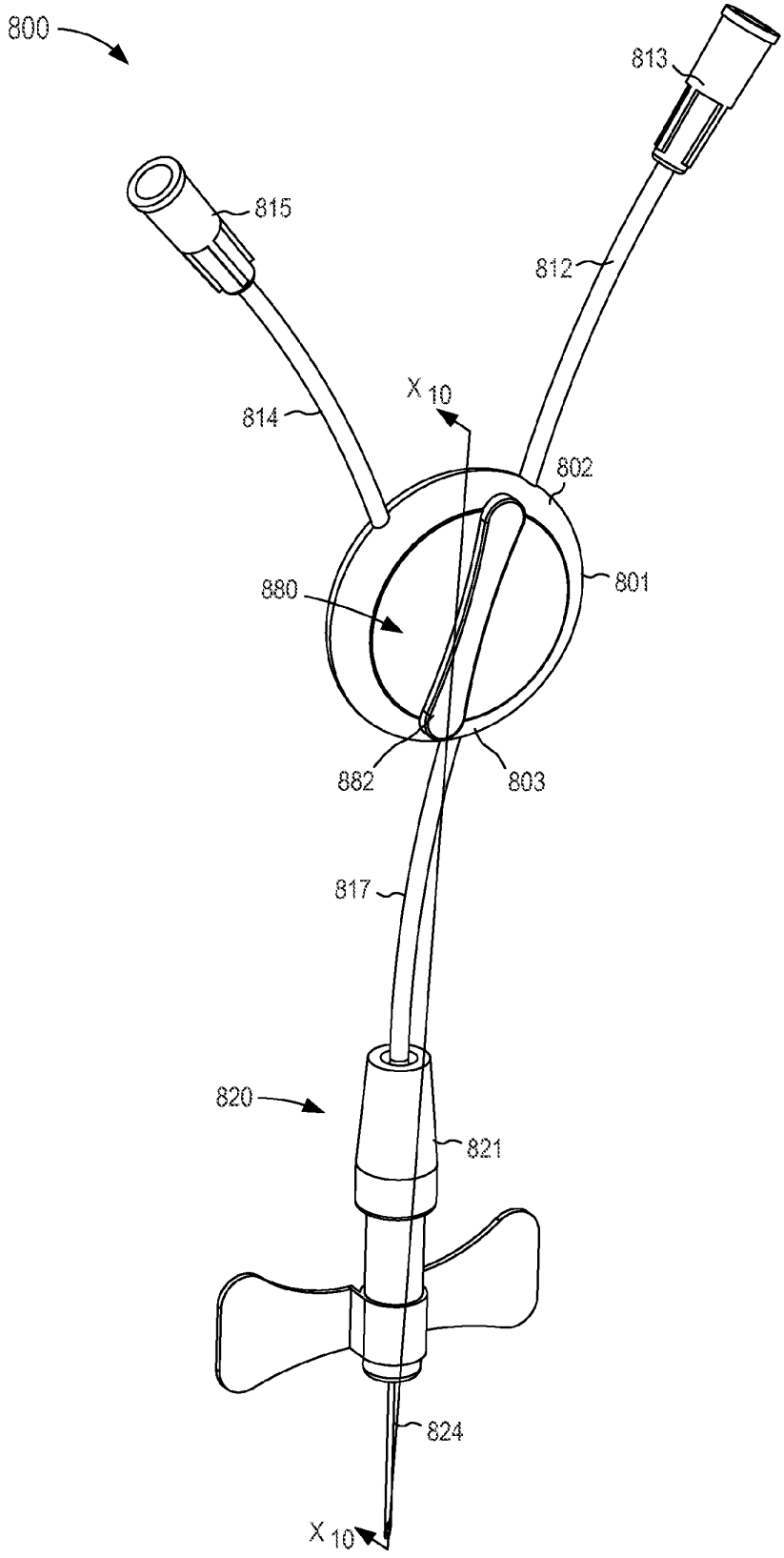


FIG. 35

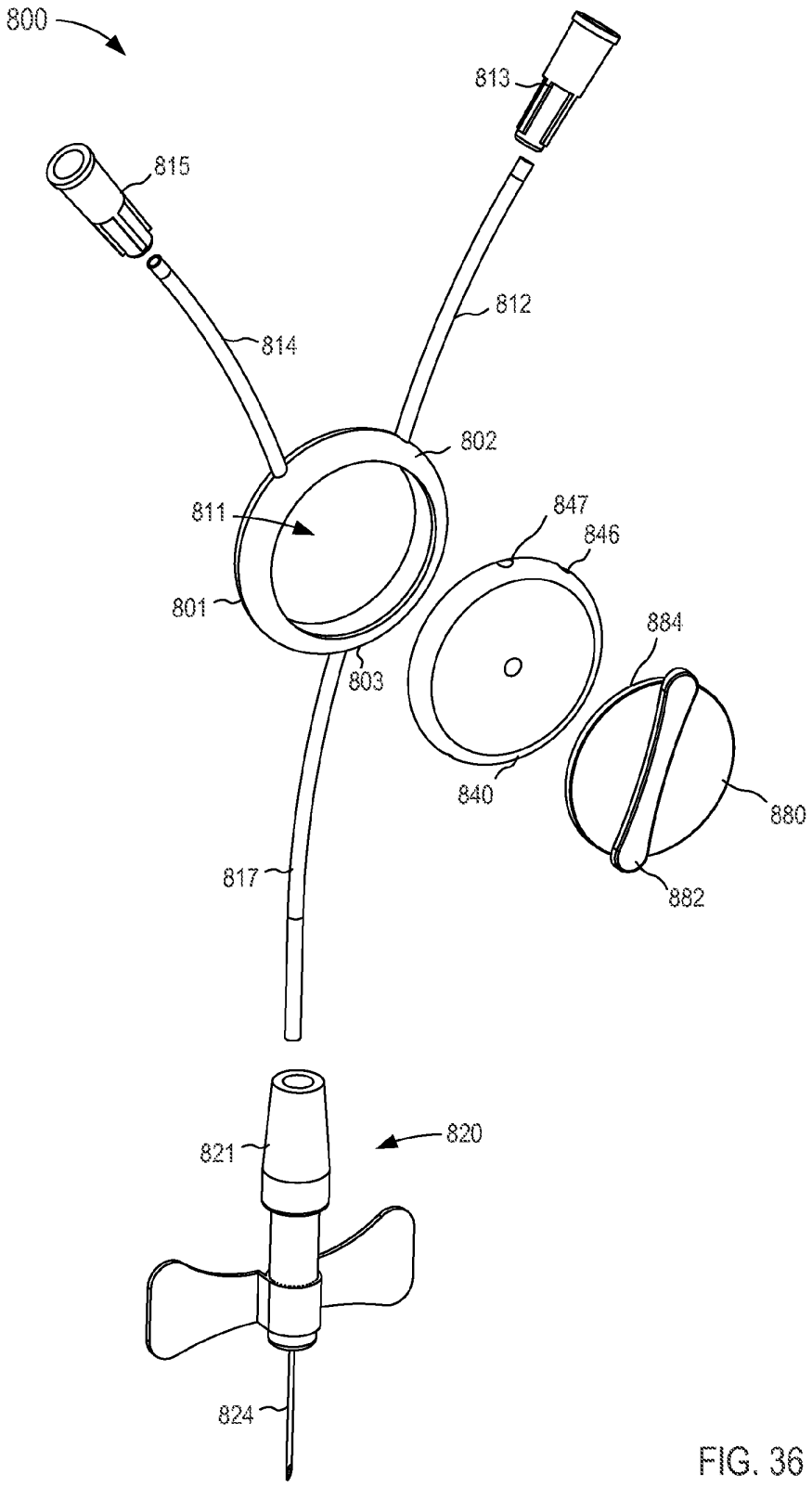

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FIG. 36

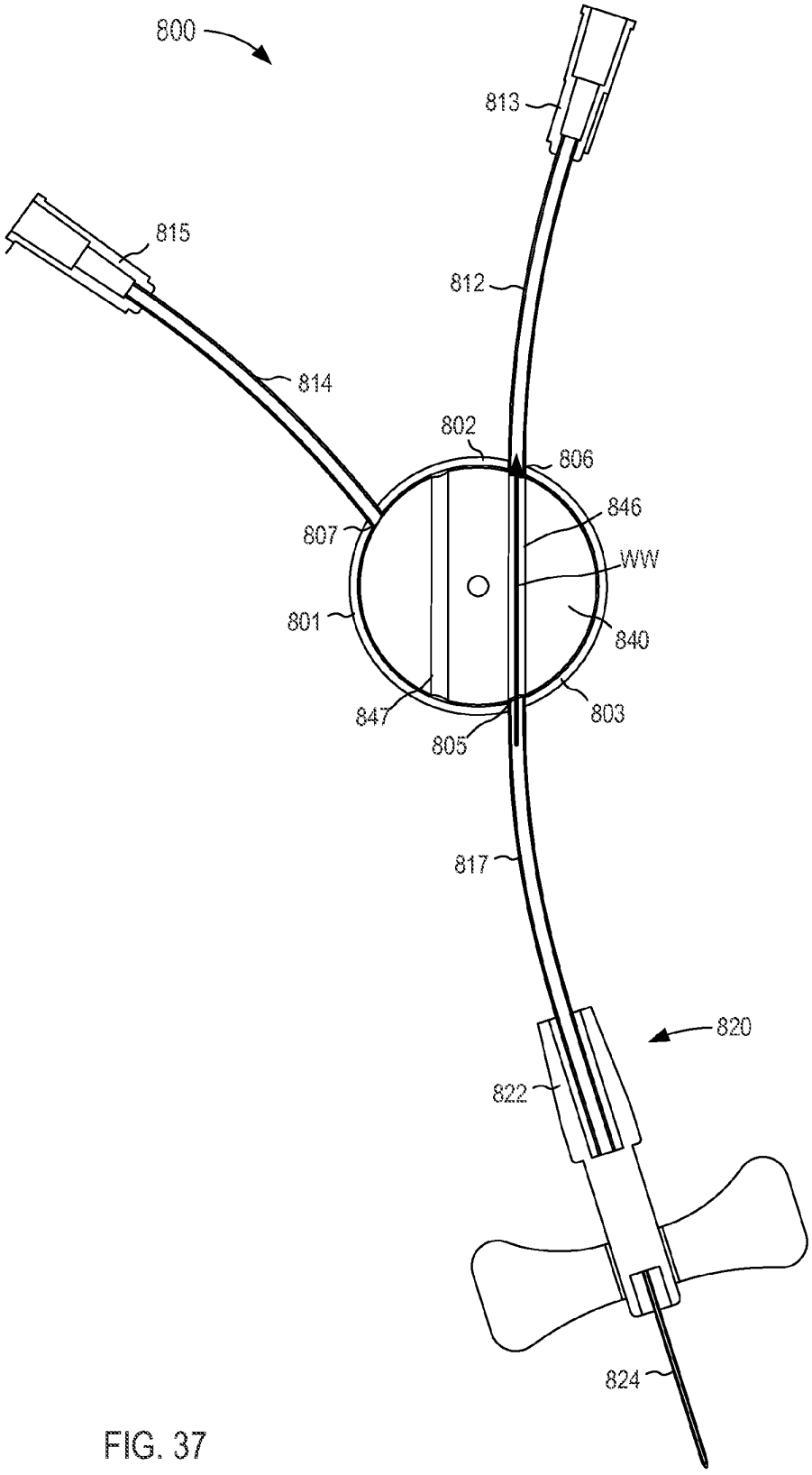

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FIG. 37

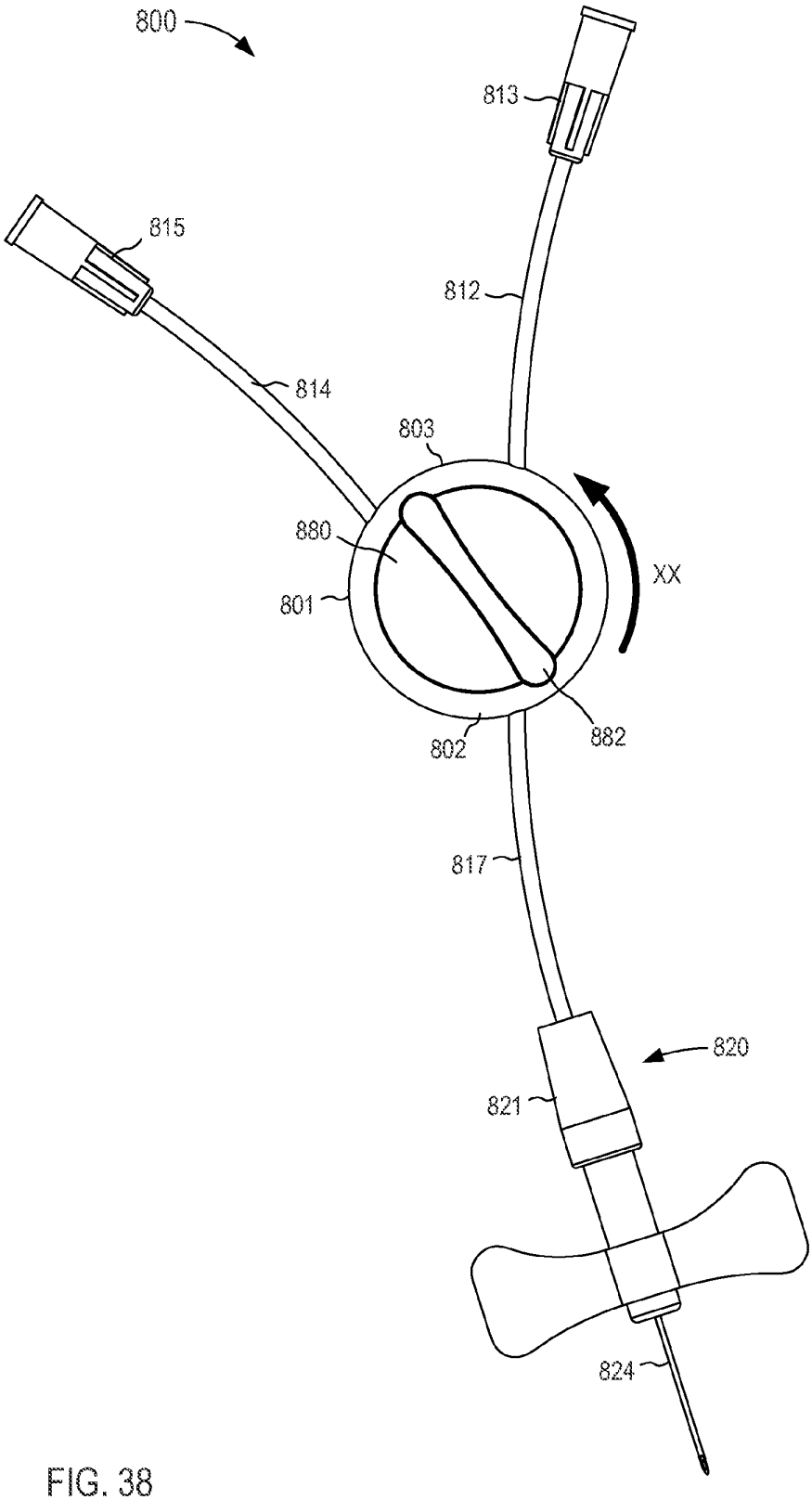


FIG. 38

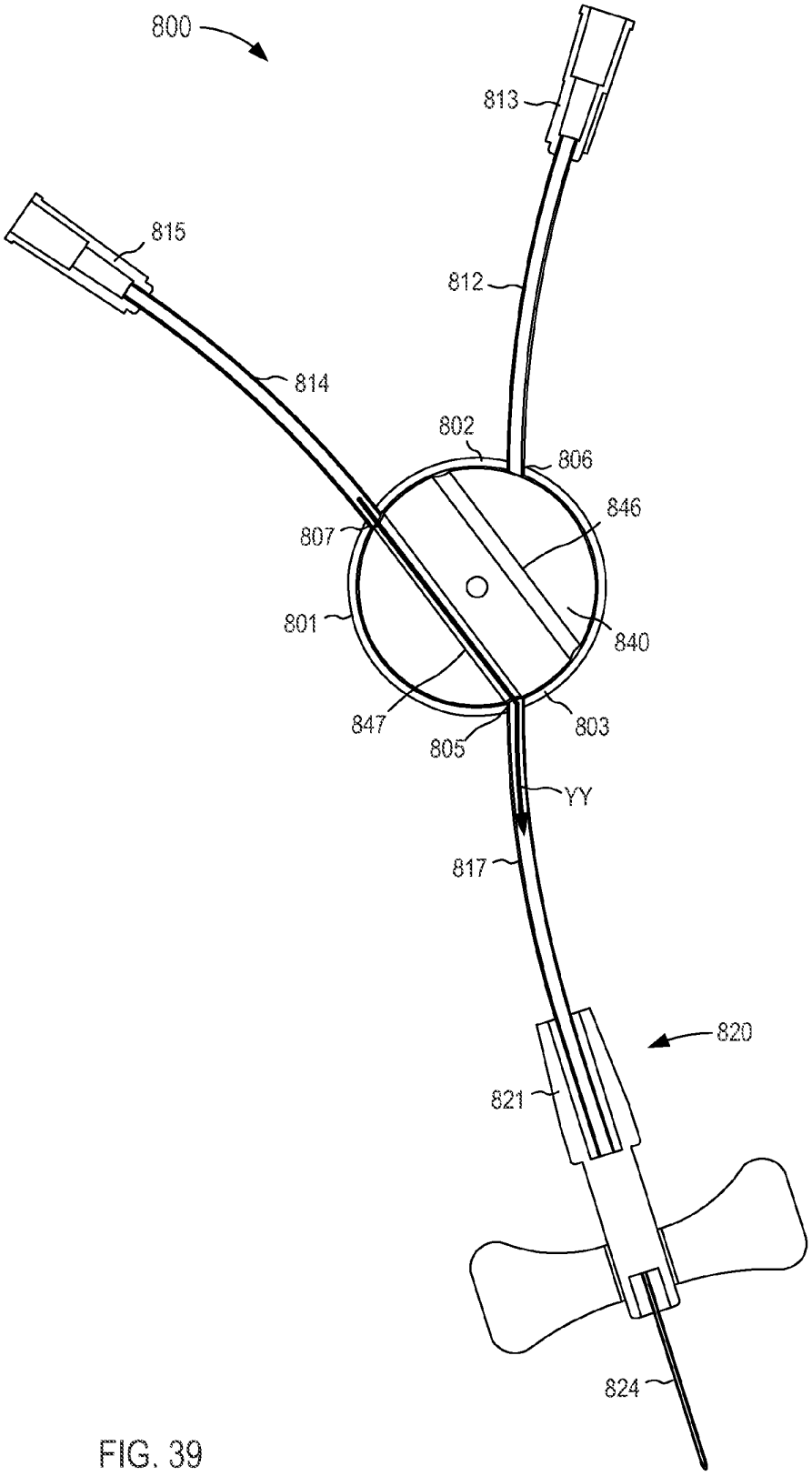

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FIG. 39

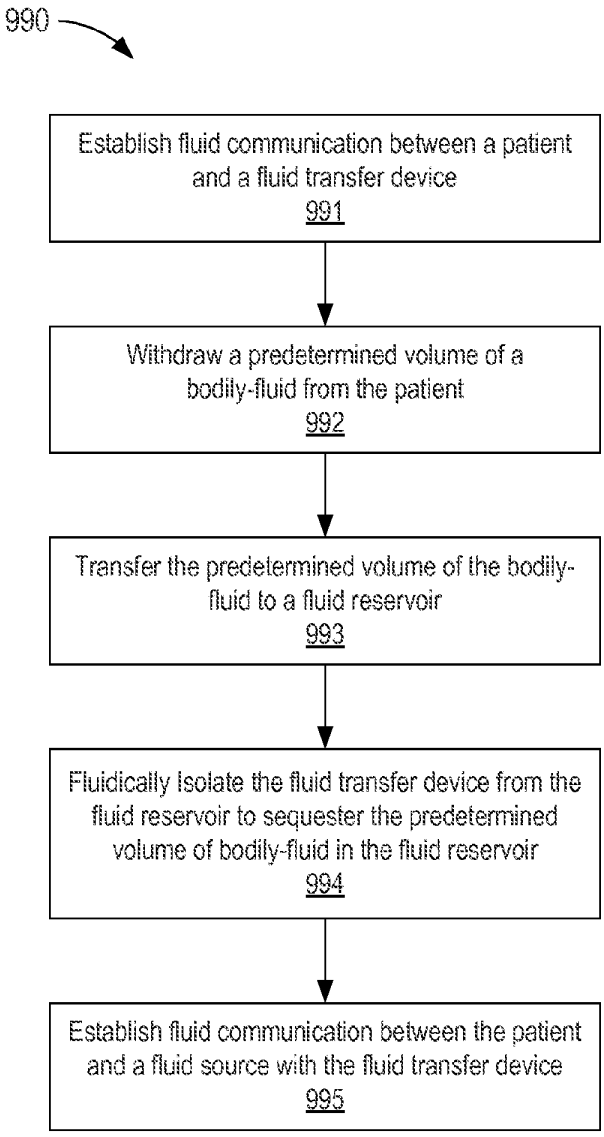

990
Establish fluid communication between a patient and a fluid transfer device
991
Withdraw a predetermined volume of a bodily-fluid from the patient
992
Transfer the predetermined volume of the bodily-fluid to a fluid reservoir
993
Fluidically isolate the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily-fluid in the fluid reservoir
994
Establish fluid communication between the patient and a fluid source with the fluid transfer device
995

FIG. 40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/063975

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 5/155 (2014.01)
USPC - 600/575
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61B 5/15, 5/155; A61M 1/00, 5/00, 5/31, 5/32, 5/178, 5/315, 25/06; B01L 3/14 (2014.01)
USPC - 600/573, 575, 576, 577, 578, 579; 604/110, 164.01, 164.08, 191, 228, 246, 403, 411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61B 5/1405, 5/1427, 5/1428 (2013.01)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0306601 A1 (SHAW et al) 10 December 2009 (10.12.2009) entire document	1-30, 33, 34
Y	US 2012/0215131 A1 (PATTON) 23 August 2012 (23.08.2012) entire document	1-30, 33, 34
Y	US 5,573,510 A (ISAACSON) 12 November 1996 (12.11.1996) entire document	14-18, 23-27
Y	US 4,988,339 A (VADHER) 29 January 1991 (29.01.1991) entire document	14-17, 28-30
Y	US 2002/0193751 A1 (THEEUWES et al) 19 December 2002 (19.12.2002) entire document	22-30, 33, 34
Y	US 6,016,712 A (WARDEN et al) 25 January 2000 (25.01.2000) entire document	26
Y	US 2003/0208151 A1 (KRAUSE et al) 06 November 2003 (06.11.2003) entire document	33

☐ Further documents are listed in the continuation of Box C. ☐

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

Date of the actual completion of the international search	Date of mailing of the international search report
06 March 2014	20 MAR 2014
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/063975

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

SEE CONTINUATION SHEET ATTACHED

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-34

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2013/063975

CONTINUATION OF BOX III

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-34 are drawn to an apparatus.

Group II, claims 35-40 are drawn to a method of delivering a fluid to a patient using a fluid transfer device.

The inventions listed as Groups I - II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I, housing including a proximal end portion and a distal end portion; a fluid reservoir fluidically coupled to the housing; and a flow control mechanism, are not present in Group II; and the special technical features of Group II, establishing fluid communication between the patient and the fluid transfer device; fluidically isolating the fluid transfer device from the fluid reservoir to sequester the predetermined volume of bodily fluid in the fluid reservoir, are not present in Group I.

Further, Groups I and II share the technical features of a fluid reservoir fluidically coupled and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient.
However, these technical features do not represent a contribution over the prior art. Specifically, US 2011/0306853 A1 to Black et al teaches a body fluid sampling system (10; Abstract; Fig. 2A) comprising a fluid reservoir (18) fluidically coupled to an array of microchannels (16; para. [00060]) and configured to receive and isolate a first volume of bodily fluid withdrawn from a patient (paras. [0061] and [0062]).

Since none of the special technical features of the Groups I - II inventions is found in more than one of the inventions, unity is lacking.

Anaesth Intens Care 1993, 21, 20-23

Hazards of Bacterial Contamination of Blood Products

T. GOTTLIEB*

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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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Accepted for publication August 25, 1992.

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platelet recipients.[4] Subacute parasitic infections with plasmodia (malaria) and with trypanosoma (Chagas' disease) are frequent causes of blood transfusion transmission in the tropics and in South America.

Bacteraemia may follow recovery from an episode of bacterial gastroenteritis, particularly after infection with *Yersinia enterocolitica* and salmonella sp.[5,6] In a review of seven cases of yersinia transfusion reactions, four patients had preceding diarrhoea within four weeks of transfusion and one had concomitant diarrhoea. However, two patients gave no history of diarrhoeal symptoms. Asymptomatic bacteraemia was usual at the time of donation.

Transient bacteraemia may follow procedures such as dental work. The bacteraemia is usually of a very short duration, not exceeding 30 minutes, unless endocarditis ensues. In such instances the micro-organisms comprise oral streptococci and anaerobes. These are generally of lesser virulence and are unlikely to survive refrigeration compared with gram-negative bacteria.

EXOGENOUS BACTERIA

In this instance bacteria enter blood through some defect in the usual collection practice. Most commonly contamination occurs through inadequate skin preparation.[1,3,7] Less frequently bacteria may colonise collection tubing as occurred in an outbreak of serratia infection.[8] Contamination may occur during storage. An episode of sepsis due to *Pseudomonas cepacia* followed port contamination after the thawing of platelets in a water bath.[9]

A review of UK reports of exogenous post-transfusion sepsis documented 14 episodes between 1980-89.[10] Of these, ten were due to "environmental" pseudomonads (eight were *Pseudomonas fluorescens*) and eight of the ten patients died. Of the many organisms that may colonise skin surfaces, pseudomonas species, serratia, flavobacteria etc, are notable in that they can survive paltry disinfection or may actually be present in the disinfectant solution. These gram-negative isolates are associated with more severe transfusion reactions compared with gram-positive species such as coagulase-negative staphylococci and viridans streptococci.

The increase in notification of bacterial infections is paralleled by the increase in demand for platelet transfusion. Storage at room temperature enhances bacterial proliferation. In many cases bacteria are grown on culture without clinical disease: in these the bacteria are usually skin saprophytes such as pro-*Pionibacterium acnes* or corynebacterium species, often referred to as "diphtheroids". However any of a large number of both gram-positive and negative organisms have been isolated in episodes of sepsis.

Following refrigeration most gram-positive bacteria will not survive. Moreover these are often present in low number and are usually destroyed by host defences—complement, lysosyme and other opsonins. By contrast, gram-negative, psychrophilic (cold-loving) bacteria will survive refrigeration.

PSYCHROPHILIC BACTERIA

Bacteria can be divided into thermophiles growing at $>50°C$, mesophiles, and psychrophiles capable of growth at $<5°C$. The latter organisms prefer growth at room temperature but will survive refrigeration. At 5°C metabolism is significantly reduced and growth occurs at a slow linear rate. After prolonged storage, between one and three weeks, there is sufficient build-up of bacteria or endotoxin to cause a severe transfusion reaction. Alternately once blood is rewarmed these organisms will re-establish their usual logarithmic growth within two to four hours.[1] Metabolic enzymes with optimal activity at room temperature will be switched on. This highlights the need for proper storage and transportation of blood.

The psychrophile most commonly associated with transfusion reactions is *Yersinia enterocolitica*. Other species encountered include enterobacter, klebsiella species, pseudomonas species especially *P. fluorescens* and *P. putida*, and *E. coli*.

Yersinia enterocolitica

Yersinia belongs to the enterobacteriaceae and is a facultative anaerobe. It is usually a zoonotic organism and is transmitted to humans via the food chain, especially from contaminated pork as well as from water and milk. Yersinia lacks siderophores necessary to scavenge iron when bound to transferrin. As they require exogenous free iron, their growth and virulence is enhanced in the presence of iron overload states such as haemachromatosis, cirrhosis and following the use of desferrioxamine.

Gastroenteritis is the usual presentation of yersinia infection. When bacteraemia occurs, symptoms may range from endotoxic shock to an asymptomatic carrier state. Numerous examples of yersinia blood transfusion infection have been reported including several from Australia.[1-3,5,10-16] Diarrhoea may precede blood donation by 8-30 days, however yersinia is rarely cultured from the donor's stool. A rise in yersinia antibodies can however be detected in the donor. In most reports transfused blood had been stored for more than three weeks prior to transfusion.

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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.

Received 30 August 1996; revised 6 June 1997.
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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Clinical Infectious Diseases 1997; 25:1066–70
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1058–4838/97/2505–0020$03.00

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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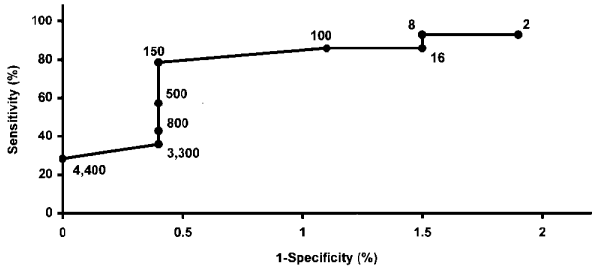


Figure 1. Receiver operating characteristic curve for ratio of bacterial counts in culture of the blood withdrawn from the catheter and culture of blood from a peripheral vein. The numbers on the curve are respective cutoffs in the differential blood cultures.

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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Received 6.24.05 | Revisions Received 7.26.05 | Accepted 7.27.05

Bacterial Contamination of Platelets for Transfusion: Recent Advances and Issues

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DOI: 10.1309/167948JY25TMY611

- Bacterial contamination of blood products has emerged as a serious problem in transfusion medicine in the past 20 years and is second only to ABO-mismatch in causing transfusion-associated death.
- Data from 1985 - 1999 showed that 11% (77/694) of transfusion-associated fatalities reported to the FDA were caused by bacterially contaminated products leading to sepsis.
- As platelets are stored at room temperature, and in a large volume of plasma and a bag that allows oxygen diffusion, it is platelet products that are the most frequently implicated in transfusion-associated fatalities due to bacterial contamination.

The transfusion medicine community has attempted to reduce the amount of bacterial contamination in the blood supply by several methods including improved skin disinfection prior to donation, removal of the skin plug with diversion of the first 10 cc of the collection, ongoing donor screening, and analysis/culture of the donated product. Even with these measures in place, several fatalities due to septic reactions associated with transfusion have occurred and been reported. At the time of this writing, the exact "residual risk" of bacterial contamination is not known.

While packed red blood cell units can be contaminated by bacteria, the fact that they are *not* stored at room temperature and are not in a medium containing a large amount of plasma, leads the incidence of sepsis following transfusion of these units to be much less frequent. For a discussion of pRBC bacterial contamination, the first 3 references are recommended to the reader.[1-3] Below, the authors focus on the risks, strategies, and regulations regarding bacterial contamination of platelet products and its mitigation.

Estimates of Prevalence and Incidence

Prior to routine culturing of platelet units, which became universal following implementation AABB Standard 5.1.5.1 (discussed in more detail below), the estimated numbers of bacterially contaminated units, transfusion-associated septic reactions and deaths were usually made retrospectively based on reported or published reactions and sequelae.

By 2000, it was generally held that between 1:1,000 and 1:4,000 units[3-8] were contaminated with bacteria; the estimate of 1:2,000 to 3,000 became commonly accepted. Sepsis due to bacterial contamination was less common and estimated to occur in 1:20,000 to 1:85,000 units.[8] Estimates at the number of deaths due to this transfusion related complication were more difficult to elucidate.

In 2001, Yomtovian and colleagues estimated that 500 to 750 "severe and possibly fatal" events occurred annually.[4] Other estimates of this figure are more on the order of 100 to 150 deaths per year.[9,10] (The estimated risk of bacterially contaminated red cell units was significantly lower (approximately 1:500,000)[11] and approximately 10 to 1,000 times greater than the combined risk of transfusing HIV, HBV, HCV, and HTLV.[11]

Sources of Bacterial Contamination

Occult donor bacteremia and contamination of the product during collection have been the main avenues for entry of bacteria and have been the focus of prevention efforts. Gram-positive skin flora, introduced to the unit during collection, are the most common contaminates identified in retrospective analysis of platelet units.[12] Three reporting systems have suggested that 70% of contaminates isolated were gram-positive bacteria, while 80% of fatalities due to transfusion-related sepsis were caused by gram-negative organisms.[13-15] This finding was also observed in a recent review of the American Red Cross (ARC) experience with pretransfusion culturing of apheresis-derived platelets (ADP) between March and December 2004 (discussed in detail below).[16] This data showed that gram-positive organisms are implicated in approximately 4/5 of the cases. Gram-negative bacteria comprise the other 20%; however, they account for 40% of deaths due to septic transfusion reactions. Burns and colleagues recently published an extensive list of primary reports of clinically significant sepsis attributed to platelet transfusion from a PubMed literature search of all published cases.[17]

Due to the clinical significance of bacterial contamination, much effort has been made over the years to improve disinfection of skin at the phlebotomy site including the discontinuation of "green soap." Additionally, diversion of the skin plug produced by the needle as it passes through the skin, away from the bag into a pouch used for other viral testing, has been instituted nationwide in the United States. Despite these efforts, bacterial contamination of products continued(s) to be observed and skin flora continued(s) to be the most frequently cultured organisms.

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Asymptomatic donor bacteremia is the reason seemingly healthy volunteers may be allowed to donate while infectious, leading to bacterial contamination of blood products. In this case, even stringent donor screening will not catch this potential source of bacterial contamination. There are many examples of donors who unknowingly donate blood while bacteremic. For example, a case of transfusion associated *Staphylococcus aureus* platelet contamination has been reported in a blood donor who had undergone a tooth extraction 3 hours prior to donation, and was likely the result of transient bacteremia.[12] Haimowitz and colleagues discovered *Streptococcus bovis* at 11.4 hours after incubation of a platelet product donated by an asymptomatic female. After being informed of the result and despite negative follow up blood cultures, she underwent colonoscopy and a 3 cm mass was noted and removed.[18] Jafari and colleagues reported a case of *Salmonella* sepsis transmitted via platelet transfusion to 2 recipients from an asymptomatic donor who upon retrospective questioning reported that he had fever, abdominal pain, diarrhea, and hematochezia 13 days *prior* to donation. The donor owned a pet boa constrictor. The snake was thought to have been colonized with *Salmonella* and the original source of the infection.[19] Finally, there have been several cases of pRBC transfusion-associated *Yersinia enterolitica* septicemia in which many of the donors retrospectively reported diarrhea in the days preceding donation.[20]

An Open Letter to the Blood Community and AABB Standard 5.1.5.1

Physicians concerned that the risk from infected units was too high and that there were technologies that could address the issue at least in part wrote an "open letter" to the transfusion medicine community urging implementation of a method to stem this complication.[21] In 2003, AABB Standard 5.1.5.1 was released after considerable discussion, debate, and a public comment period. To be implemented within 1 year, the Standard read, "The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components."

At that time and presently, there were no FDA-approved tests for unit-by-unit bacteria screening at the time and point of transfusion. In addition, it was known that more than 15 tests *could* be used but none met "optimal" criteria including sensitivity and specificity, cost:efficacy, and logistical considerations affecting product supply and outdating. Thus, AABB was in an unenviable position of introducing a standard without guidance (at that time) as to *how* to implement it. **Table 1** below (adapted from reference 22) lists the tests capable of detecting bacteria and some comments regarding each.

Clinical Relevance

Typically at the time of collection, the level of contamination is relatively low (between 1 to 10 colony forming units (CFU)/mL.[2,3] However, once the product is inoculated, the bacteria can proliferate to levels of 10^6/mL or greater.[3] This amount of bacteria transfused during a short period of time can cause bacteremia, fever, chills, hypotension, nausea, vomiting, diarrhea, and oliguria, which may progress to sepsis and ultimately multi-system organ failure and death. Alternatively, the transfusion of contaminated cellular blood products may produce no symptoms or long-term clinical consequences. The severity of the reaction depends on: 1) the species of bacteria present, 2) the inoculum, 3) the rate of bacterial propagation, and 4) underlying disease, leukocyte count, the status of the immune system, and receipt of concomitant antibiotics in the recipient.[3] Gram-negative bacteria tend to cause more severe reactions due to the presence of endotoxin produced by these organisms. While causing only one-fifth of the cases, gram-negative bacteria have been reported to account for 40% of deaths due to septic transfusion reactions.[12,16]

Table 1_Description of Tests Capable of Detecting Bacteria

Methodology	Comments
Culture-based methodology: BacT/ALERT 3D Automated Microbial Detection System (bioMérieux, Durham, NC)	Detects CO_2 production by bacteria; FDA approved for quality control; Semi-closed system; Detects 5-10 CFU/mL (12-26 hr incubation);4 mL required
Culture-based methodology: (Pall eBDS, Pall Corporation, East Hills, NY)	Measures O_2 consumption by bacteria; FDA approved for quality control; Completely closed system; Requires 5-6 mL (concentrated to 2-3 mL)
DNA/RNA-based amplification and non-amplification, Chemiluminescence systems	Highly sensitive and specific; Requires highly conserved target by all bacteria or multiple primers and large inoculum; In experimental use only
Tests detecting changes in metabolic parameters or physical elements (glucose concentration, pH, platelet swirling)	Low sensitivity and specificity; Platelet concentration of the sample can affect results; Can be used at point of issue; Validation and QC difficult
Flow or static cytometry: (Scansystem, Hemosystem, Marseilles, France [laser-based, solid-phase cytometry])	Recently approved in Europe; Rapid (30 hr incubation and 90 min test time); Acceptable sensitivity and specificity; Requires reagent antibody to highly conserved common antigen or multiple reagent antibodies; 3 mL required
Bacterial cell wall component detection systems: (Platelet PGD test, Verax Biomedical, Worcester, MA)	Rapid (20 minutes); Lateral flow format; Sensitivity (10^3 to 10^4) in preliminary trial; 0.5 mL required; In experimental use only
Dielectrophoretic method: (Cell Analysis, Slough, United Kingdom)	Recently approved in Europe; Rapid (30 min); Sensitivity (10^3 to 10^5) in preliminary trial; 1 mL required
Gram stain	Requires a high level of contamination; Low sensitivity at lower concentrations; Can be used at point of issue; Validation and QC difficult
Endotoxin detection	Requires a high level of contamination; Low sensitivity at lower concentrations

Adapted from Reference 22.

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Strategies for the Mitigation of Contaminated Blood Products

As previously stated, detection strategies show variable sensitivity and specificity. Measuring abnormal glucose concentrations, low pH, microscopic examination of gram-stained specimens, and platelet swirling characteristics have been less useful due to low sensitivity and specificity. However, these methods have the advantage of being able to be used at the time and point of transfusion, are less expensive and use equipment commonly available.

Automated culture-based systems used for years in the hospital setting for detection of bacteremia in blood cultures obtained from patients were implemented by many of the nation's blood collection systems. Principally, they detect CO_2 generation or O_2 consumption by bacteria. Some of the limitations of culture-based systems are relatively insensitive at low levels of bacterial contamination causing false negative results, long incubation times for slow-growing bacteria, false positive results, high cost and the need for capital investment.[24-26] Holme and colleagues have recently shown that modifications to the Pall eBDS system have attempted to minimize these limitations.[29] While feasible for apheresis-derived platelets (ADP), culture based methods are not considered feasible for each whole blood-derived platelet (WBP) unit at the time of collection because of the high cost. Thus, those centers and services that used ADP could comply more easily and effectively with the new standard than those who used WBP, and converting entire systems from ADP to WBP was in-and-of-itself costly and met with resistance due to standard of care, cost, and availability concerns.

Apheresis Derived (ADP) Versus Whole Blood Derived Platelets (WBP)

Even before the implementation of Standard 5.1.5.1, the use of ADP had increased (52% to 99% of total transfused products per Ness and colleagues from 1987-1998) likely in part due to concern by some authorities about bacterial contamination.[8] Indeed, Ness and colleagues concluded that the rate of septic transfusion reactions due to WBP was 5.39 times higher than ADP (95% CI, 1.89, 12.9). Dykstra and colleagues found that the rate of bacterial contamination in ADP and WBP was identical (P=1.0); however, when platelet concentrates were pooled, the risk increased by 5 fold.[7]

Despite the apparent advantages of using ADP, maintaining adequate inventories and simultaneously providing adequate bacterial contamination testing is still a challenge due to the time it takes for the culture. Many experts have considered the effect and possibility of extending the expiration date to 7 days. In order to have a licensed 7 day ADP, clinical tests of the platelets, storage and medium will be required as will demonstration of bacteria detection and an acceptable rate of "residual risk." In order to allow the use of WBP with cost effective and optimal bacterial detection performance, 2 alternatives can be considered, but both are in clinical development and thus are not available. These include: 1) a 5 or 7 day "pooled and stored" WBP where a culture-based system could be used as a single test on a pre-storage pooled product, and 2) the approval of a effective test that could be used at the point and time of transfusion and which would be rapid enough for most clinical situations.

Residual Risk in "Tested" Components

Despite the strategies described above, bacterial contamination continues to be observed, although markedly reduced, and fatal consequences have been reported. As there was no standardized or required system in place to determine the true incidence of the morbidity and mortality caused by septic platelet units prior to the implementation of AABB Standard 5.1.5.1, it is impossible to determine with accuracy the effect of the standard in terms of percent improvement or reduction in adverse events. Some relevant data are available however.

From March 1, 2004 through December 31, 2004, approximately 350,000 units from 87,000 voluntary donors at 36 regional centers were cultured by the American Red Cross. Two hundred nineteen were initially positive, 67 were confirmed on re-sampling for an overall confirmed positive rate of 0.019% or 1:5,234 as compared to published reports of 1:2,000 to 3,000. Initially, 4 to 5 mL from each unit was transferred through a sterile docking device at least 24 hours after collection and used to inoculate BacT/ALERT BPA aerobic culture bottles. Confirmation of a positive blood culture bottle was performed by taking a new sample from product, inoculating a new BacT/ALERT aerobic culture bottle and if positive, performing bacterial isolation and identification. Eighty percent of the confirmed positive cases were gram-positive bacteria, mainly *Staphylococcus* (46.3%) and *Streptococcus* (26.9%) species. Serratia was the most commonly isolated gram-negative bacteria (n=4). Seventy-two percent of gram-negative organisms were identified within the first 12 hours of inoculation (personal communication; ARC). No patient transfused with an unconfirmed positive product had a septic transfusion reaction.

Three fatal cases and 2 non-fatal cases of transfusion-associated sepsis in platelet recipients have occurred since the standard was adopted. The first 2 cases were reported in MMWR.[27] The first case was that of a 74-year-old man who received 1 pool of 5 platelet concentrates. The pooled unit was tested by a pH method and found to be acceptable. After a hypotensive reaction, *S. aureus* was cultured from both the patient's blood and the platelet bag and by pulsed-field gel electrophoresis (PFGE) were identical. The second case was a 79-year-old man who was transfused a single platelet pheresis unit. The unit was tested by an automated culture system using a standard method. One hour after transfusion the patient had shortness of breath, chills, and fever. *S. lugdenensis* was cultured from both the patient's blood and the platelet bag and by PFGE were identical. The final case of fatality [presented to the Advisory Committee on Blood Safety (1/25/2005)] was a premature infant who received 2 doses of a single platelet pheresis. The unit was tested by a manual culture. The patient had symptoms consistent with sepsis. The platelet unit was then recultured and found to be growing *Serratia marcescens*. The patient's cultures were negative, but the cultures were taken after antibiotic therapy was initiated. One of the non-fatal cases was a BacT/ALERT failure of an apheresis platelet unit.[16]

Using numbers that are estimates only, and recognizing the limitations therein, a residual risk figure may be on the order of 3 to 6 fatal cases per year following the administration of approximately 2 million platelet doses per year (*The reader is asked to note that the true number of transfused platelet doses per year in the United States has not been established with certainty. While as many as 9 million units are given, the proportion of ADP vs. WBP is not known, nor is the number of WBP pooled into a dose*). Therefore, an incidence figure of approximately 1 fatality per approximately 500,000 tested doses may be posited. This is

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likely to be grossly inaccurate due to the lack of validated data, suboptimal test methods for WBP, and reporting and assumptions used. If one uses the figures given earlier in this report of 100 to 150 deaths annually (pre-standard implementation) and a residual as high as 6, then the improvement has been about 95%. Again, this number is a gross estimate, which will likely be revised with the collection of additional data. Though the "improvement rate" seems excellent, a residual risk of fatality incidence of 1:500,000 may be judged unacceptable by some, and thus other means of improving upon this complication may be warranted.

Pathogen Reduction (Inactivation)

Pathogen reduction is the term given to a number of technologies that prevent pathogens from replicating and thus prevent them from causing disease following transfusion. Methods under investigation (some are in use in Europe) use a variety of compounds including methylene blue, riboflavin and solvent-detergent treatment. In addition, a number of photodynamic processes use psoralen-based chemicals followed by ultraviolet light to inactivate bacteria and viruses by preventing replication and transcription of nucleic acids. This latter method has been extensively tested for bacterial reduction in platelet products. Gram-positive and gram-negative bacteria have been shown in three preclinical trials to be sensitive to pathogen inactivation (reviewed in reference 28). The main disadvantage of pathogen inactivation is that no method is equally effective for all organisms and these methods may be especially ineffective for spore-forming organisms.[28] The advantage is that this is a proactive method for bacterial reduction and has the potential to be as effective for known pathogens as it is for emerging pathogens.

Ongoing Issues

Bacterial contamination of blood products was, and may continue to be, a serious health risk to transfusion recipients. While we believe substantial improvement has been made, though difficult to accurately quantify, some level of residual risk appears to exist. Systems to help quantify this residual risk need to be implemented and/or strengthened. In addition, there is some evidence to suggest that the implementation of Standard 5.1.5.1 has caused a significant reduction in platelet availability, delay in their release to hospital transfusion services, and/or a declination in WBP use which may have added to the overall cost of platelet provision and transfusion. In order to address these issues, rapid and cost-effective tests need to be developed and approved for use at the time and point of transfusion. Alternatively, and with the use of a validated bacterial detection test, prestorage pooling may be "allowed" and thus lead to a state of equipoise between ADP and WBP safety and therefore use. An effective method or methods for bacterial detection and limitation will likely allow the extension of either ADP or pooled and stored WBP to 7 or perhaps even 8 days, thus likely improving the logistical and availability issues currently surrounding this valuable human resource. Finally, the adoption of pathogen reduction technologies in Europe and their approval in the United States may abrogate any residual or evolving risk.

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KUR-MAG-DE005188

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

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

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

WO 2017/019552 (Art. 153(3) EPÜ).

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

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

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

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

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

(19) World Intellectual Property Organization
International Bureau

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

WIPO | PCT

(10) International Publication Number
WO 2017/019552 A1

(51) International Patent Classification:
A61B 5/15 (2006.01) *A61B 5/154* (2006.01)
A61B 5/153 (2006.01)

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

(22) International Filing Date:
22 July 2016 (22.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/196,797	24 July 2015 (24.07.2015)	US
62/238,636	7 October 2015 (07.10.2015)	US
62/318,194	4 April 2016 (04.04.2016)	US
15/140,448	27 April 2016 (27.04.2016)	US
15/140,443	27 April 2016 (27.04.2016)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

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

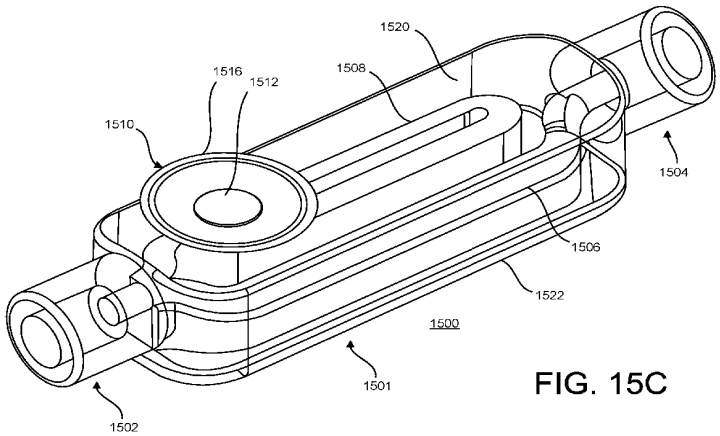


FIG. 15C

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

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

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

BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

1. A blood sequestration device comprising;

an inlet port;

an outlet port;

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

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

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

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

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

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

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

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

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

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

an inlet port connected with the patient needle;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

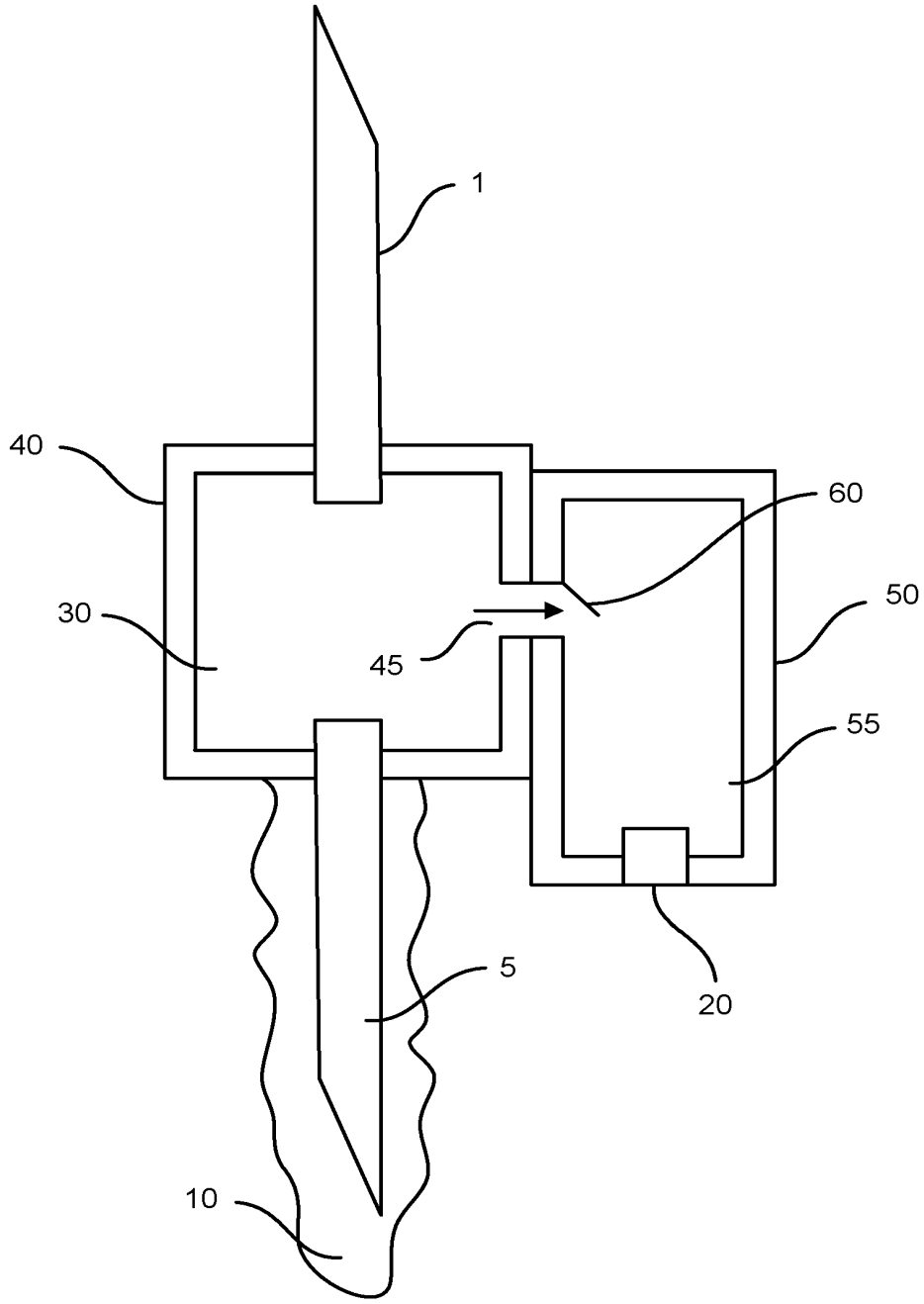


FIG. 1

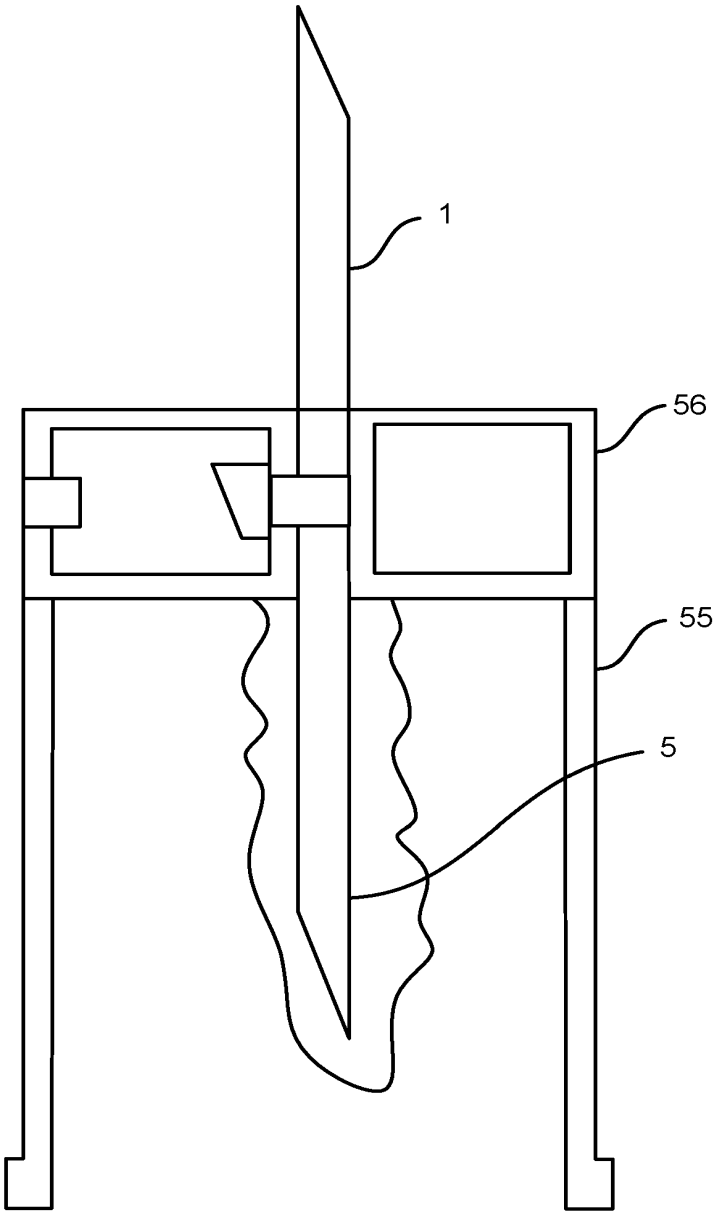


FIG. 2

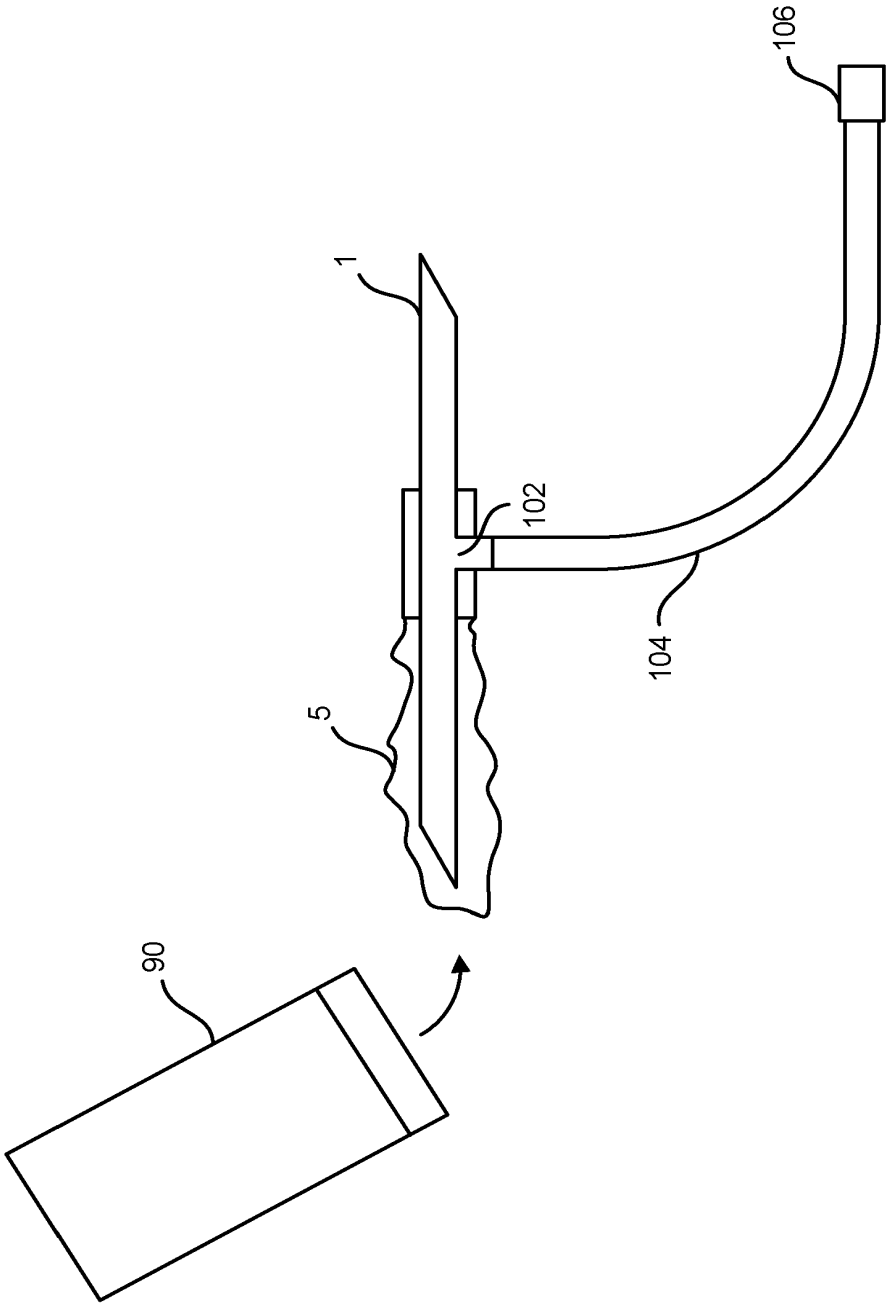


FIG. 3

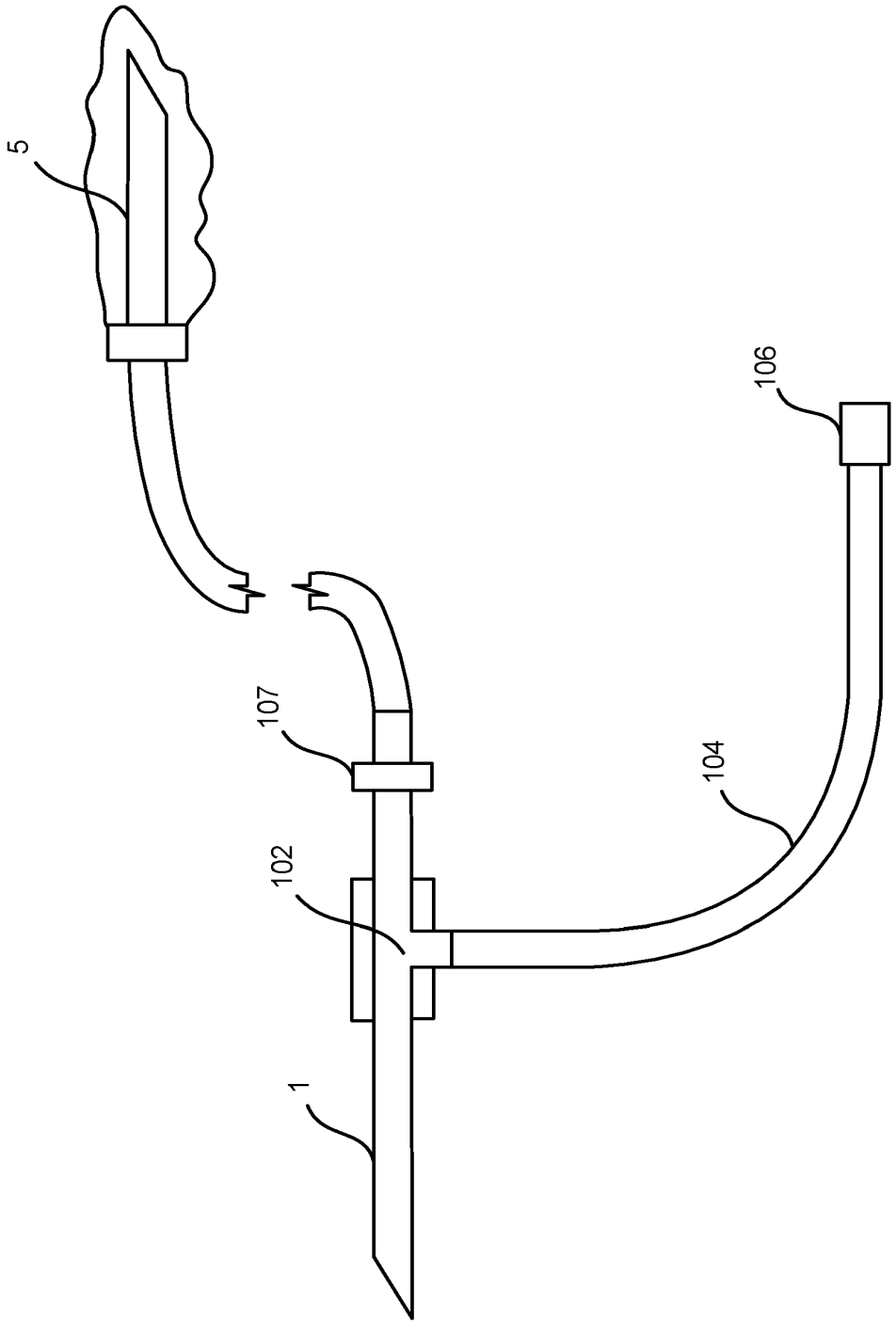


FIG. 4

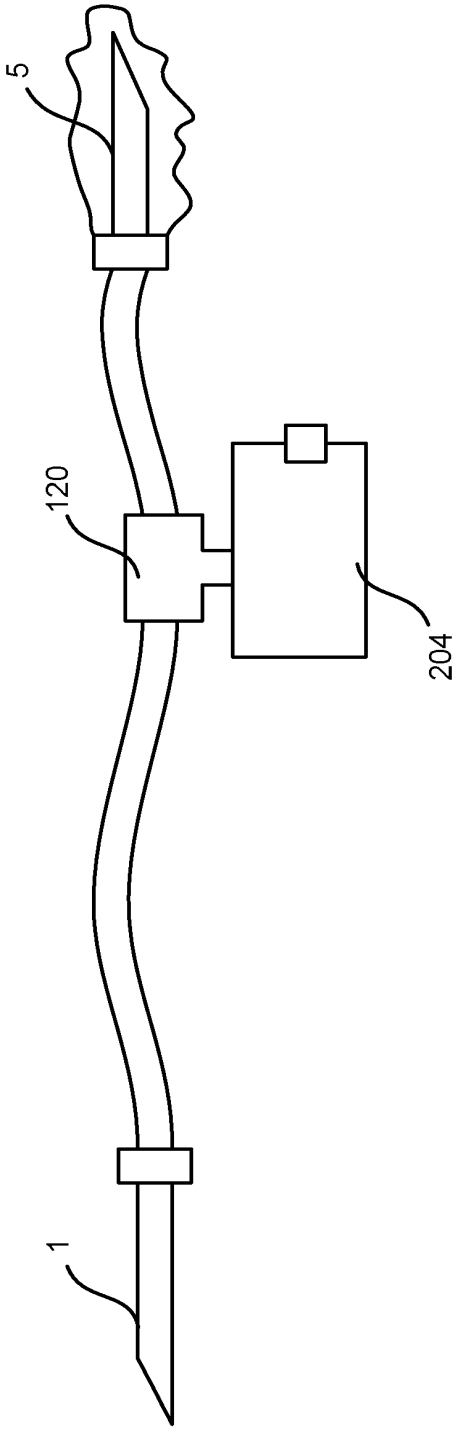


FIG. 5

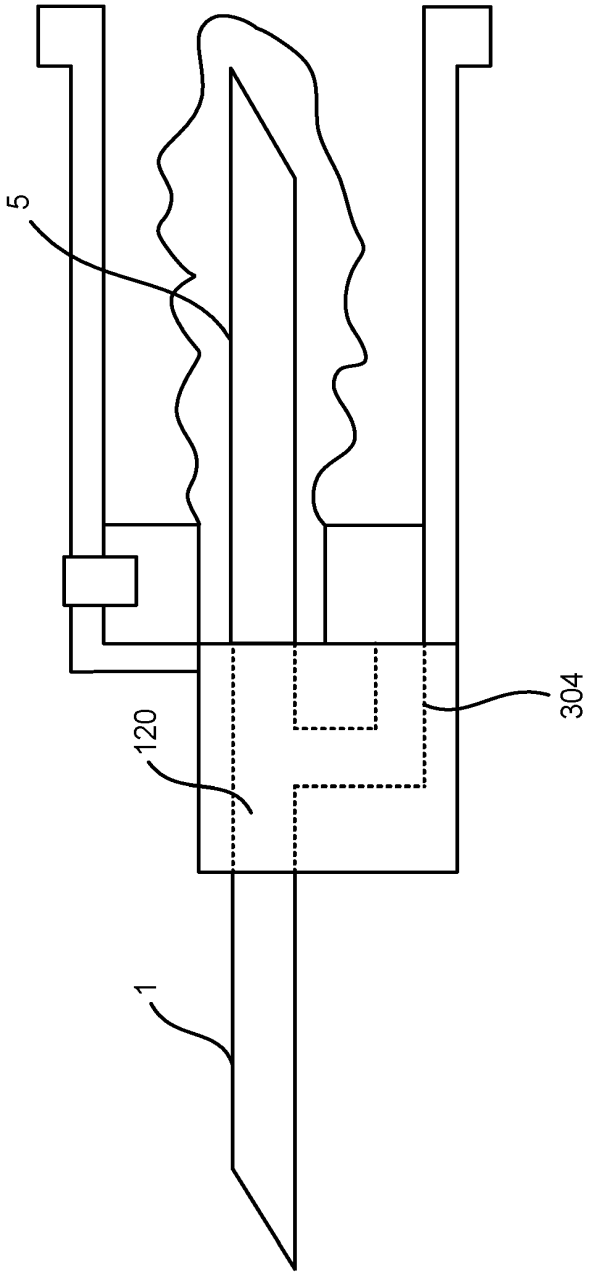


FIG. 6

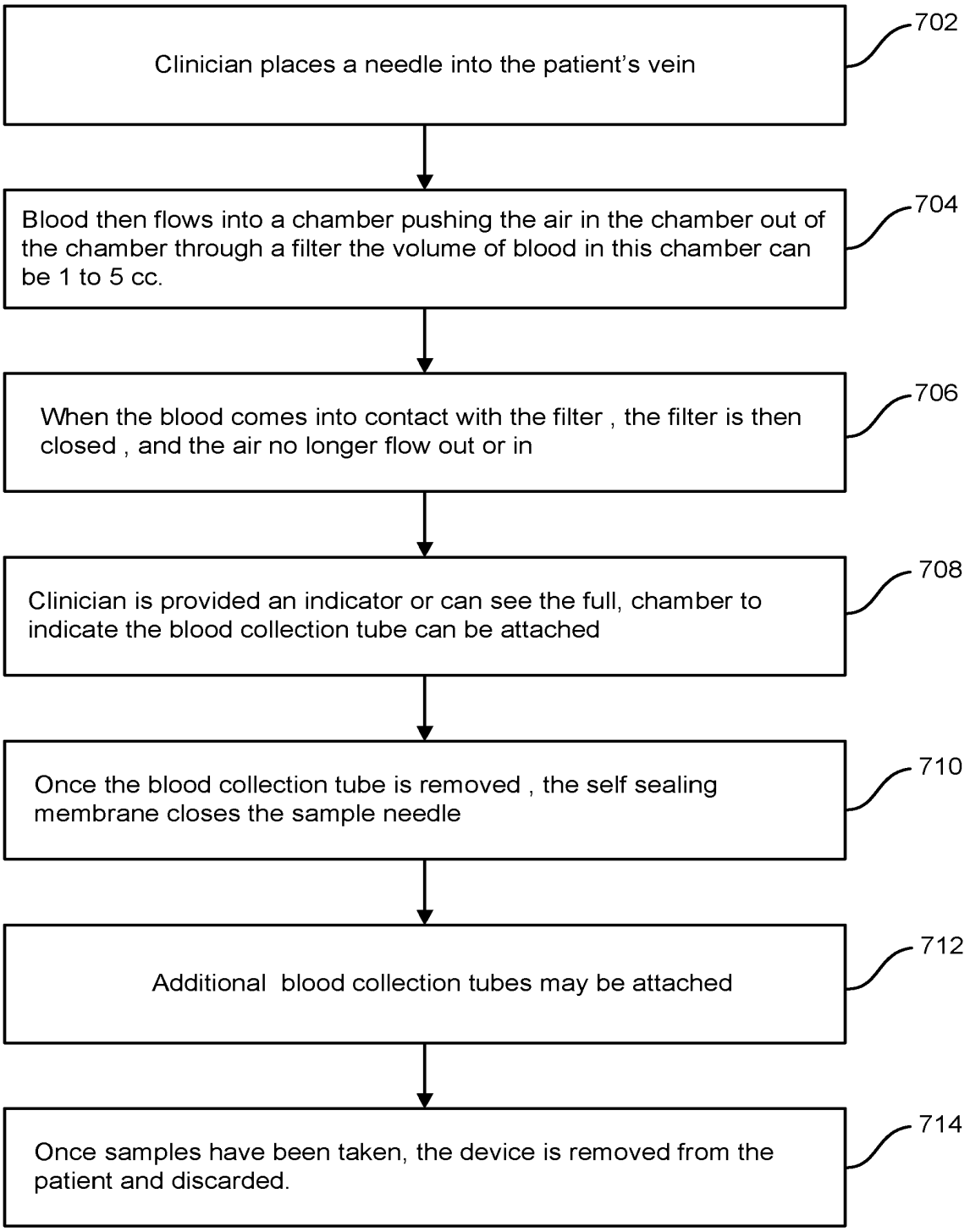
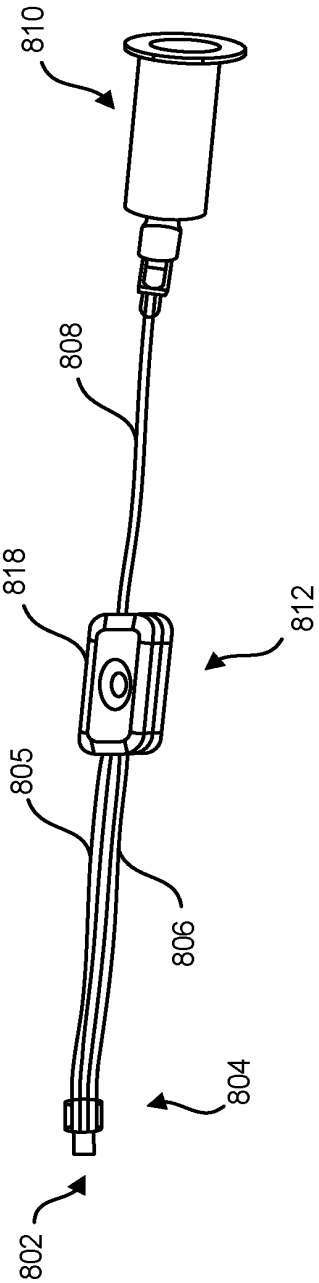

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air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

FIG. 7



800

FIG. 8A

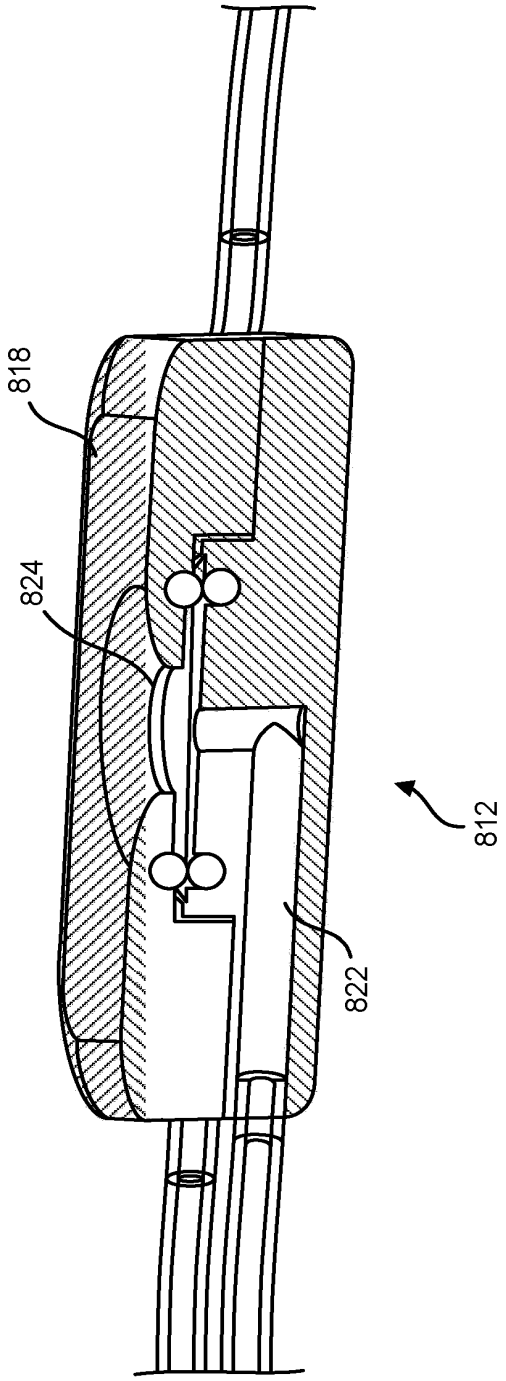


FIG. 8B

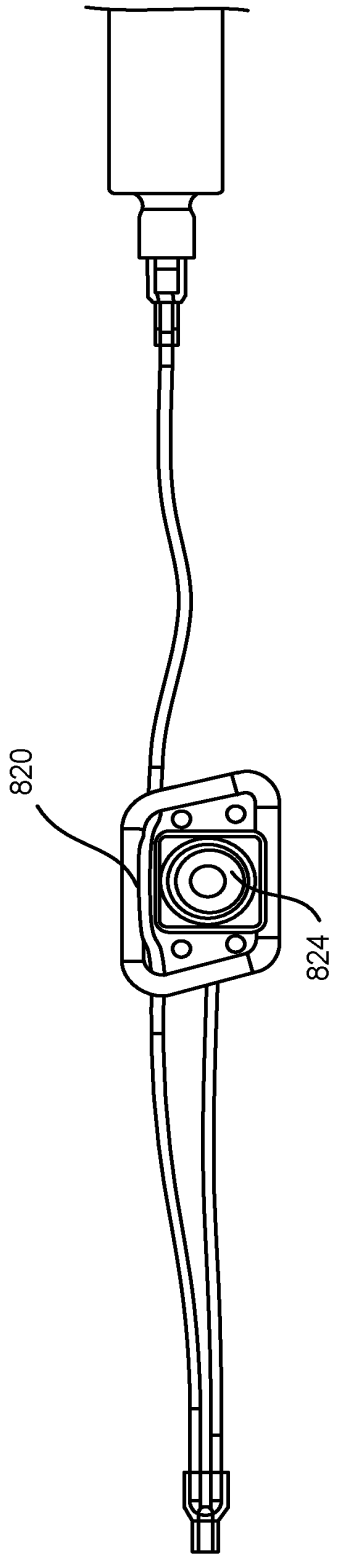


FIG. 8C

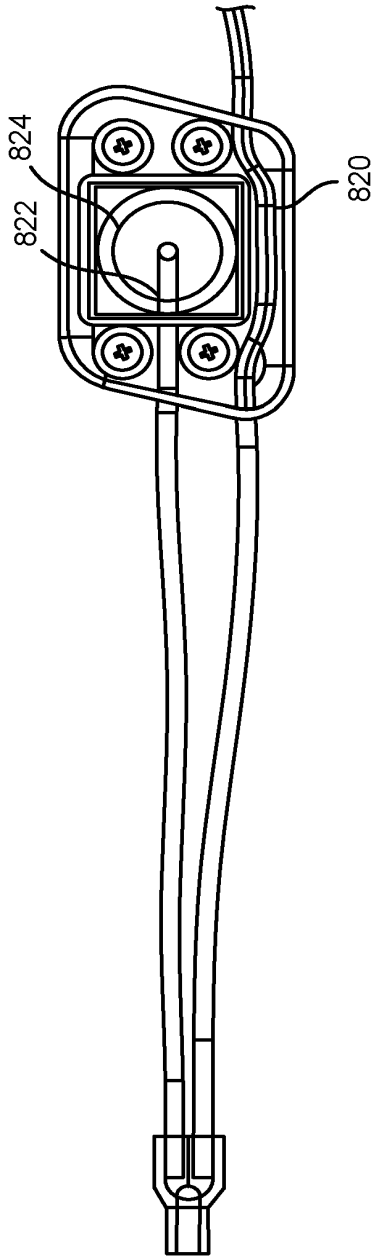


FIG. 8D

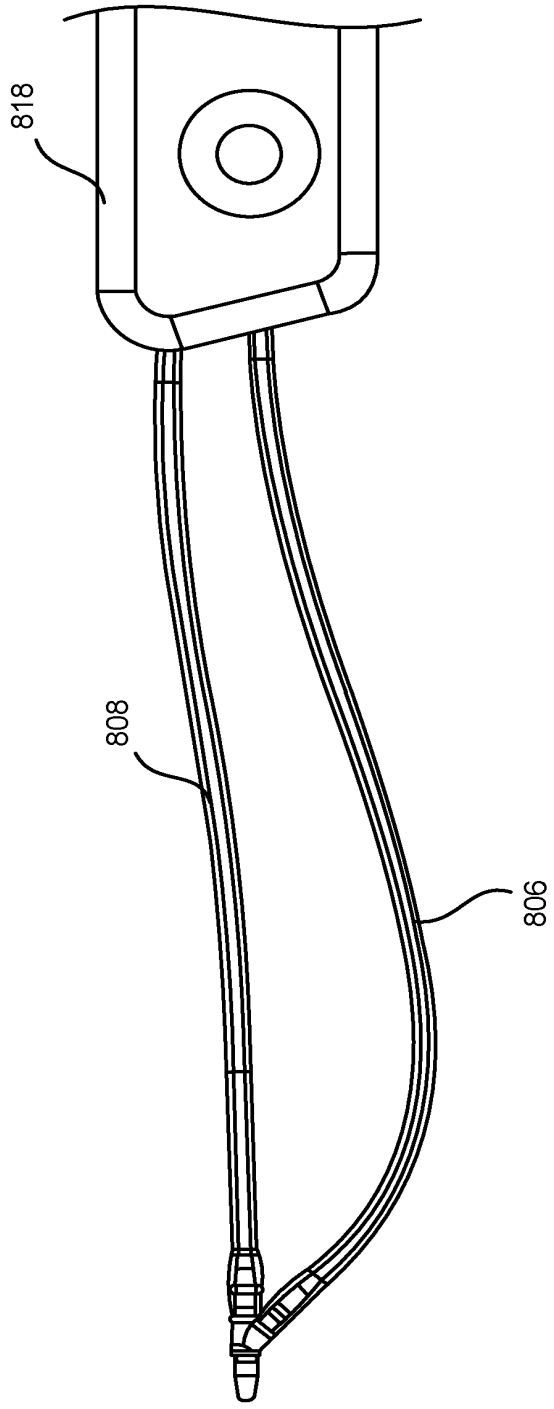


FIG. 8E

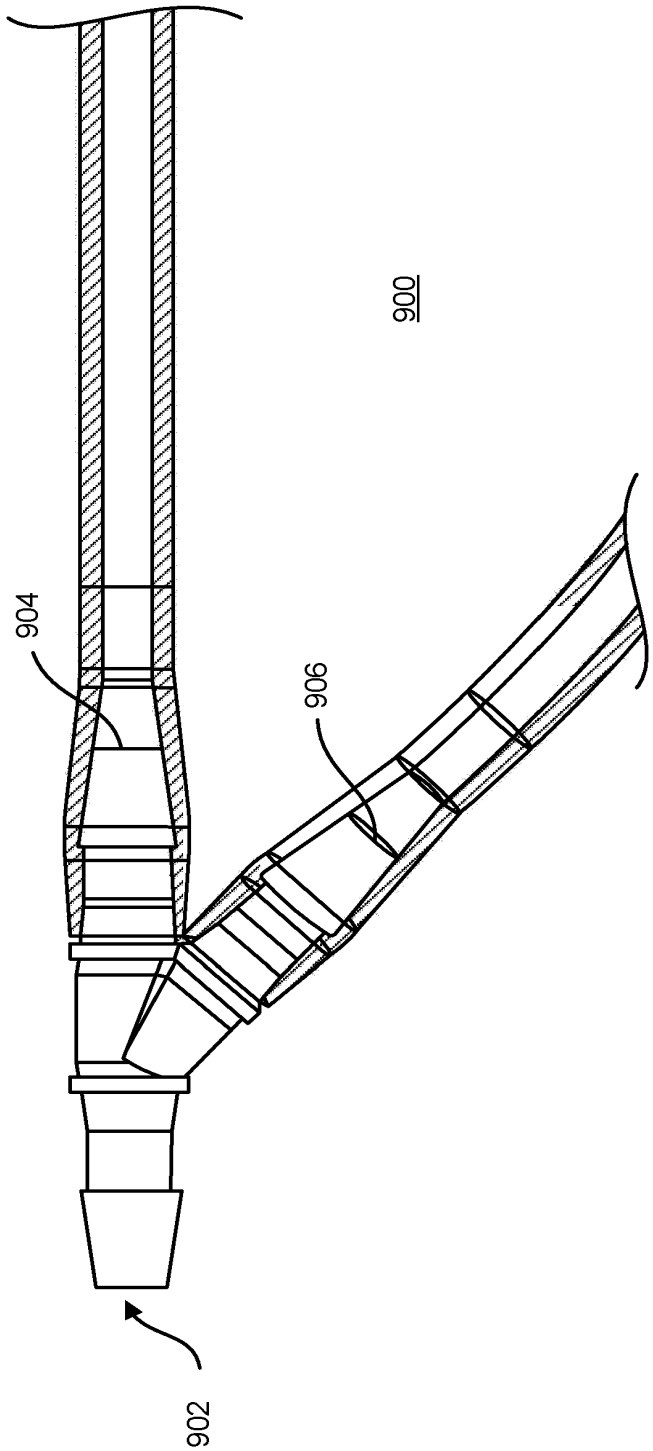


FIG. 9

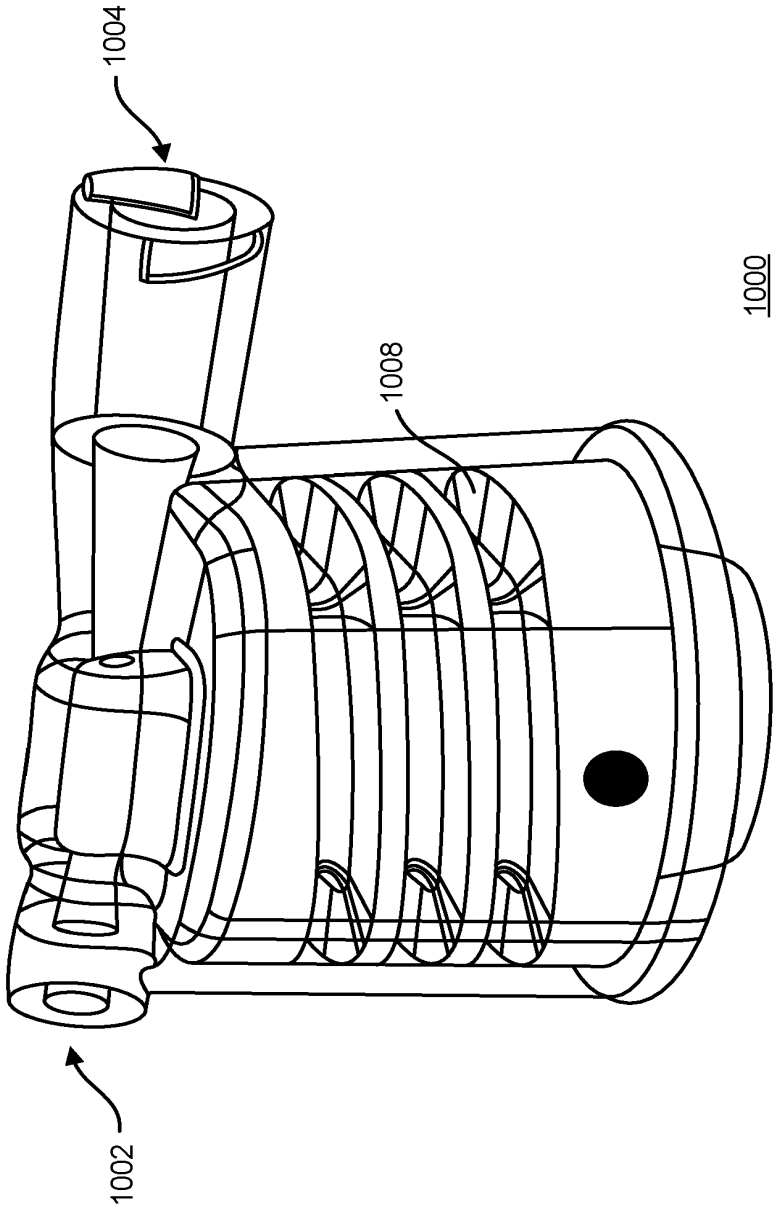


FIG. 10A

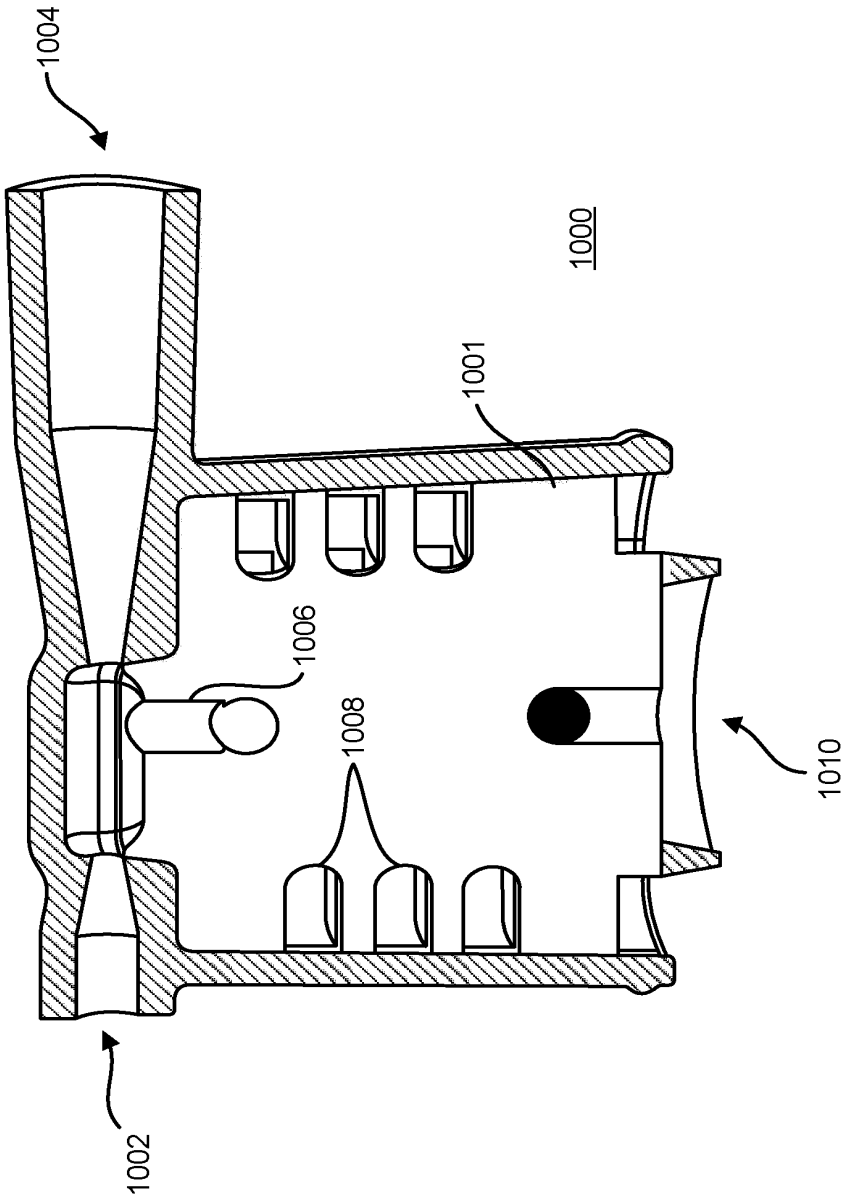


FIG. 10B

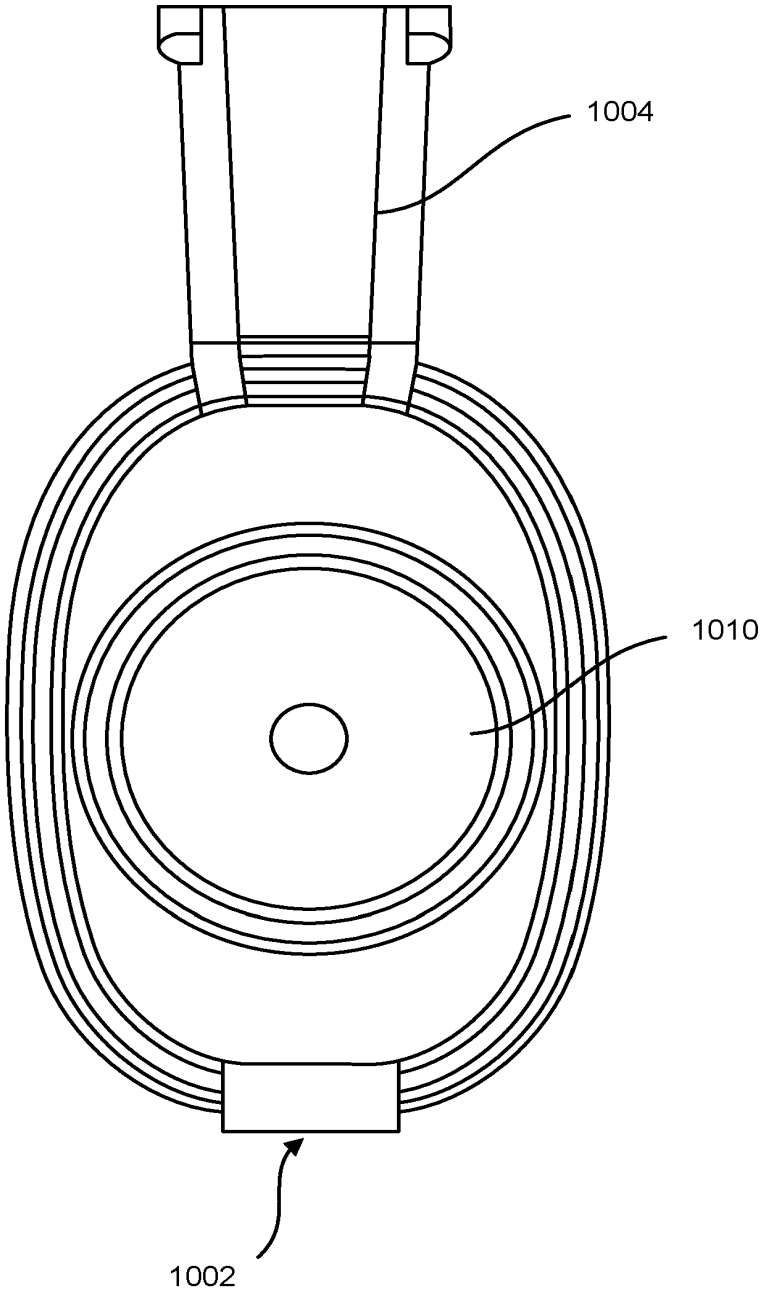


FIG. 10C

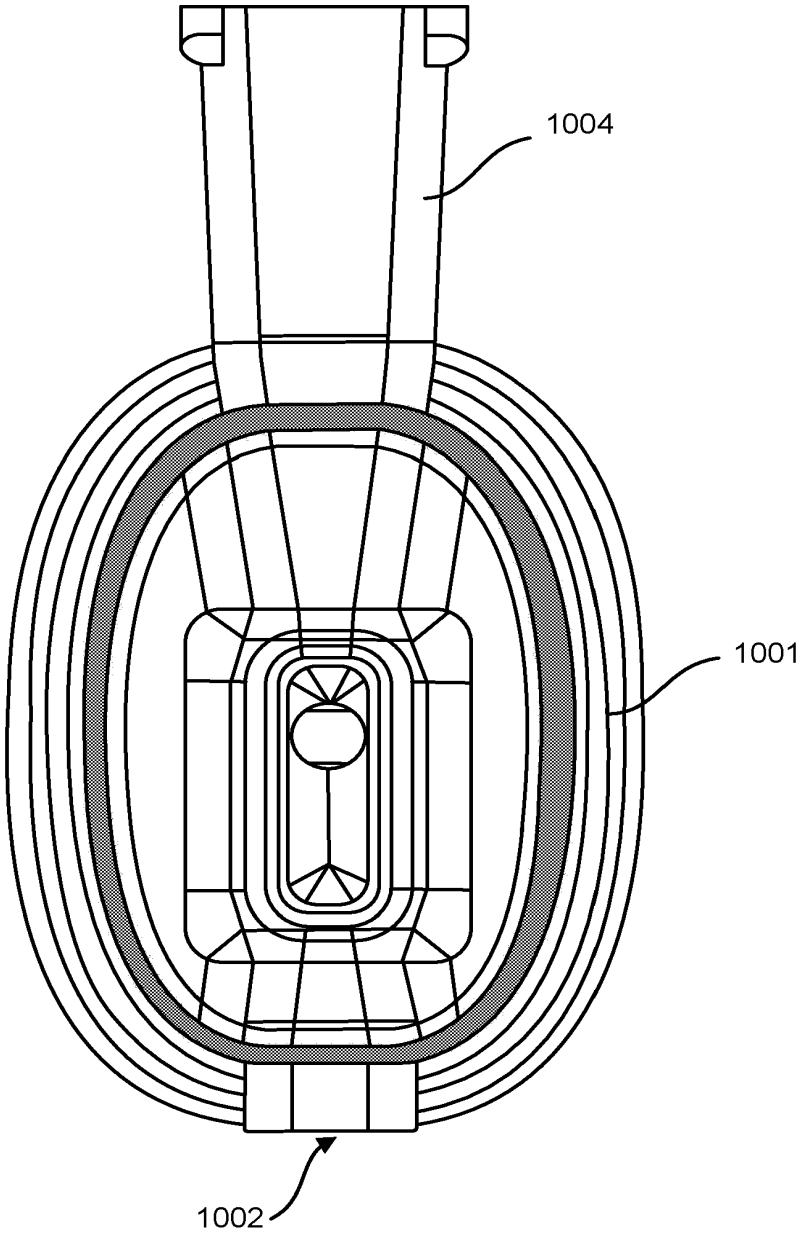


FIG. 10D

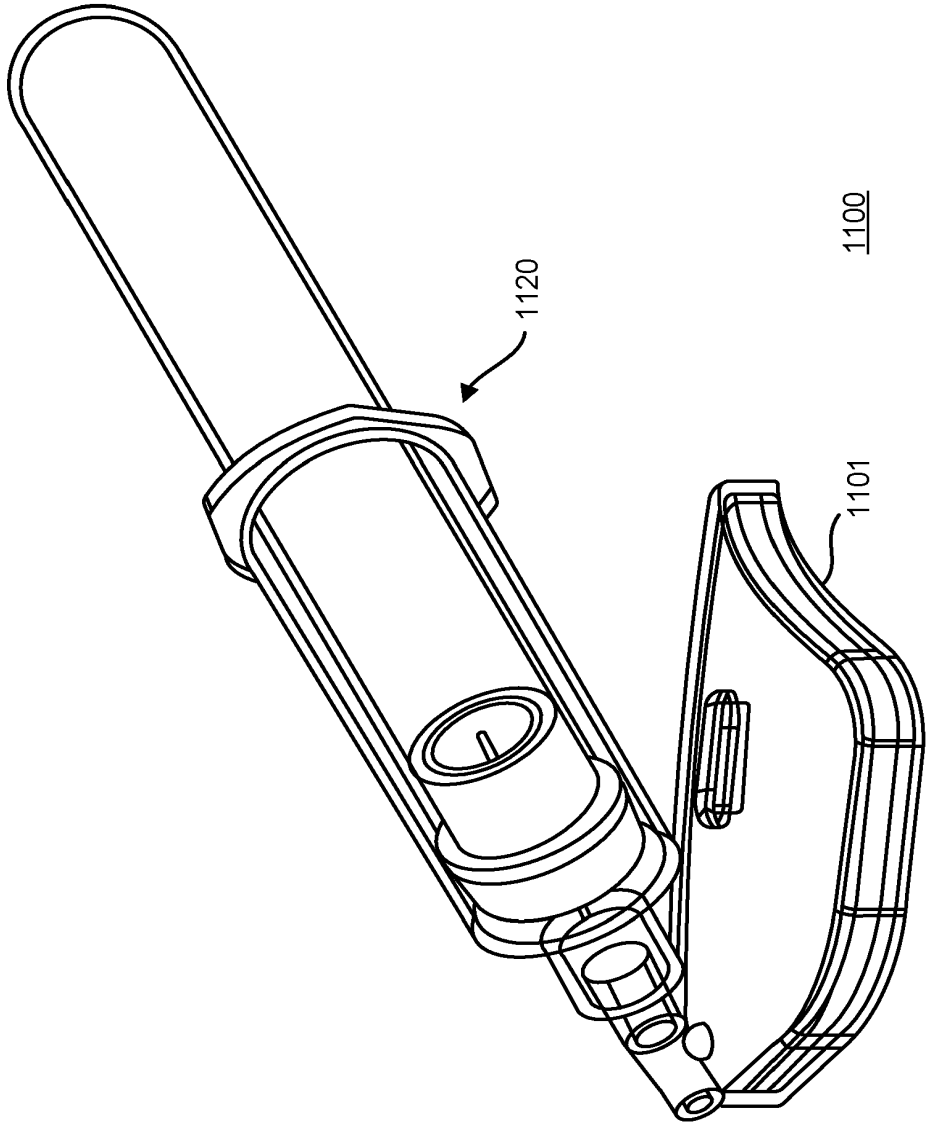


FIG. 11A

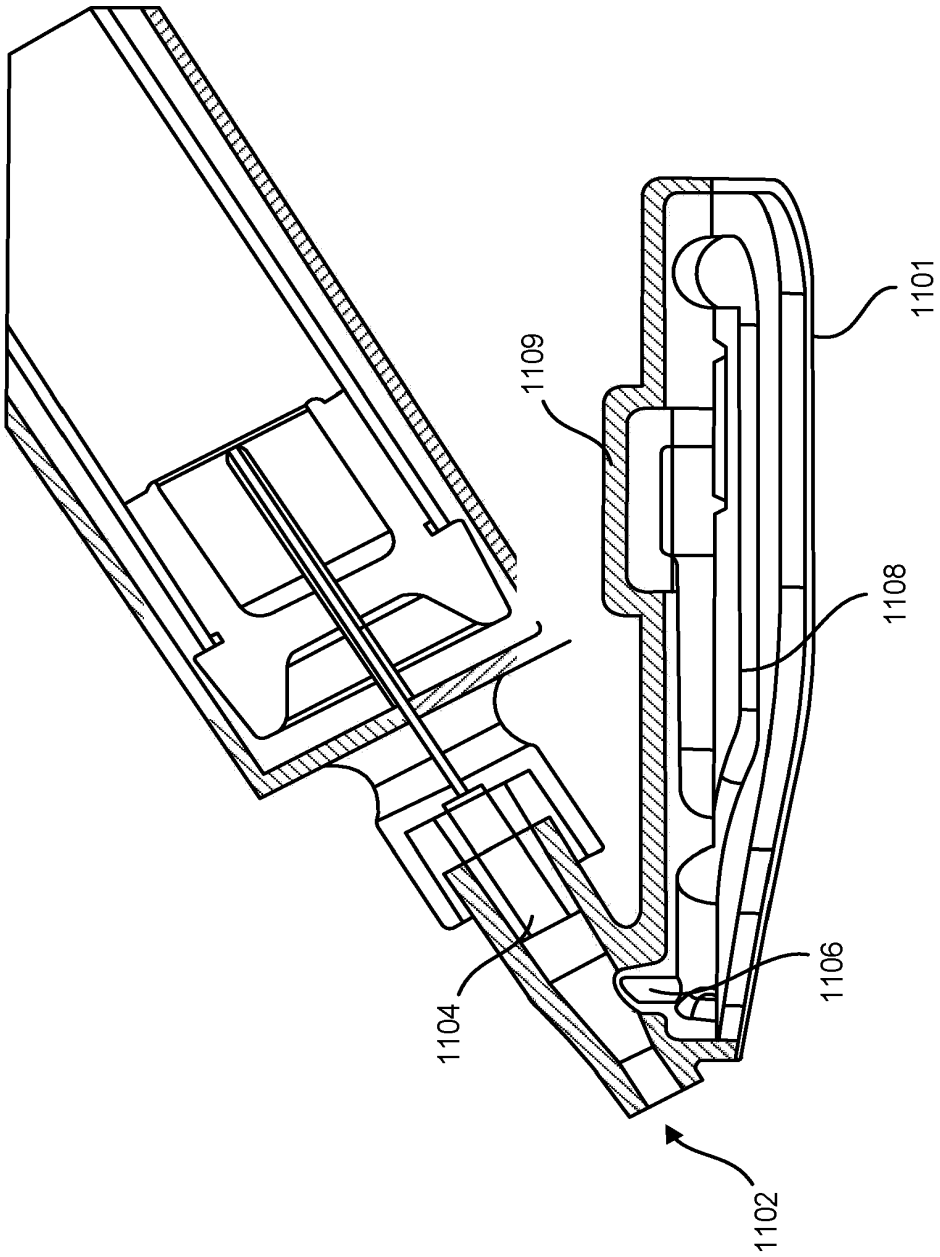


FIG. 11B

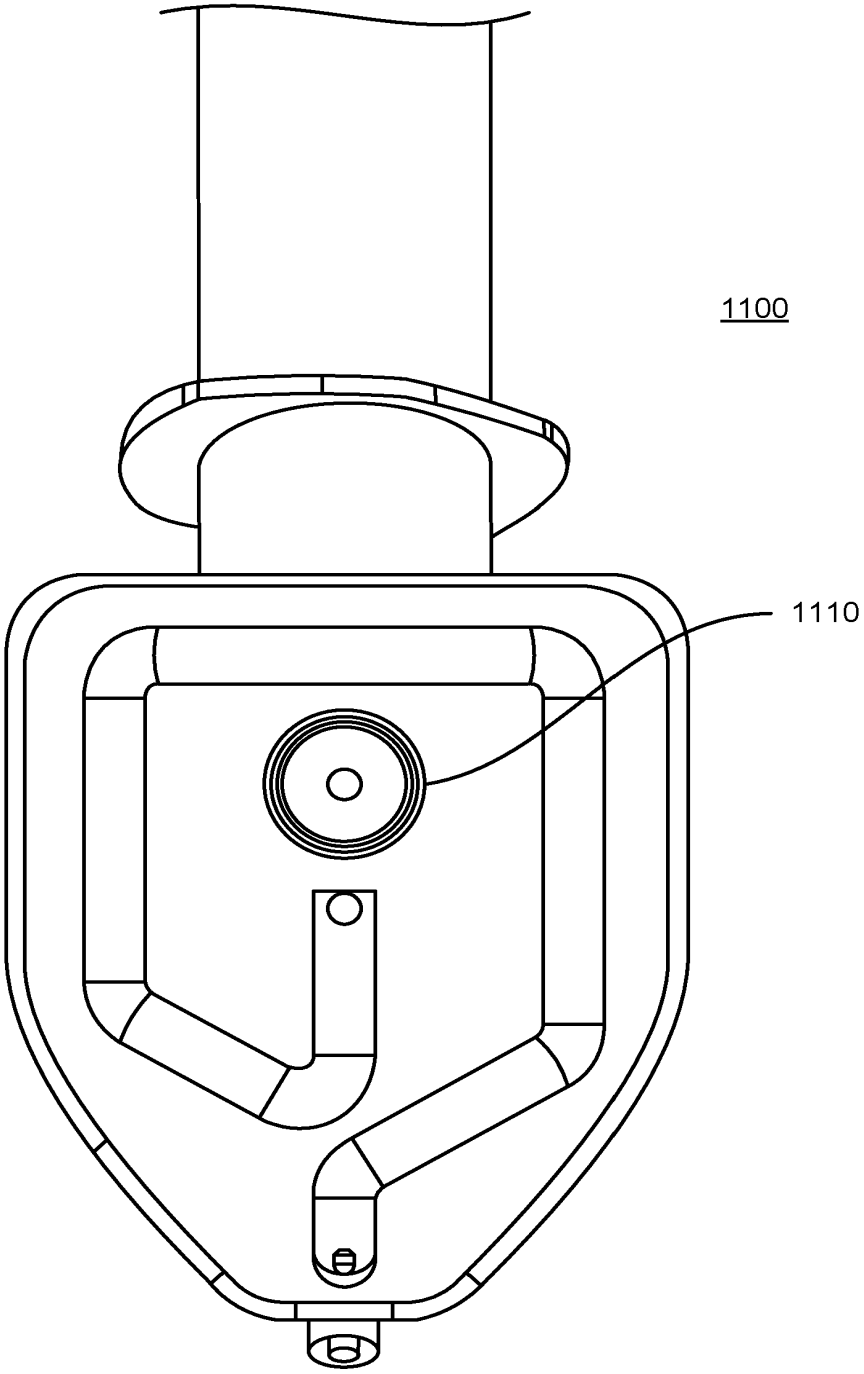


FIG. 11C

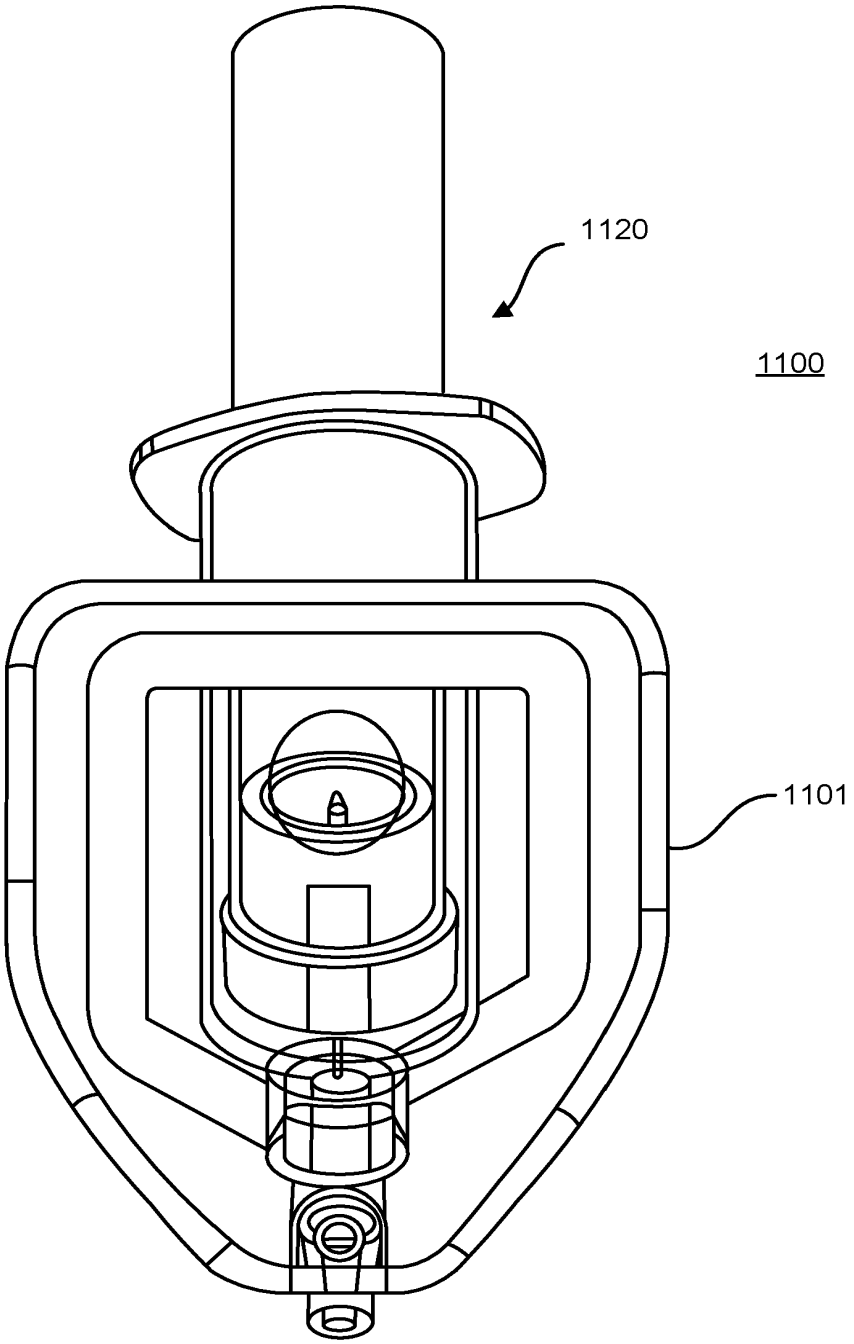


FIG. 11D

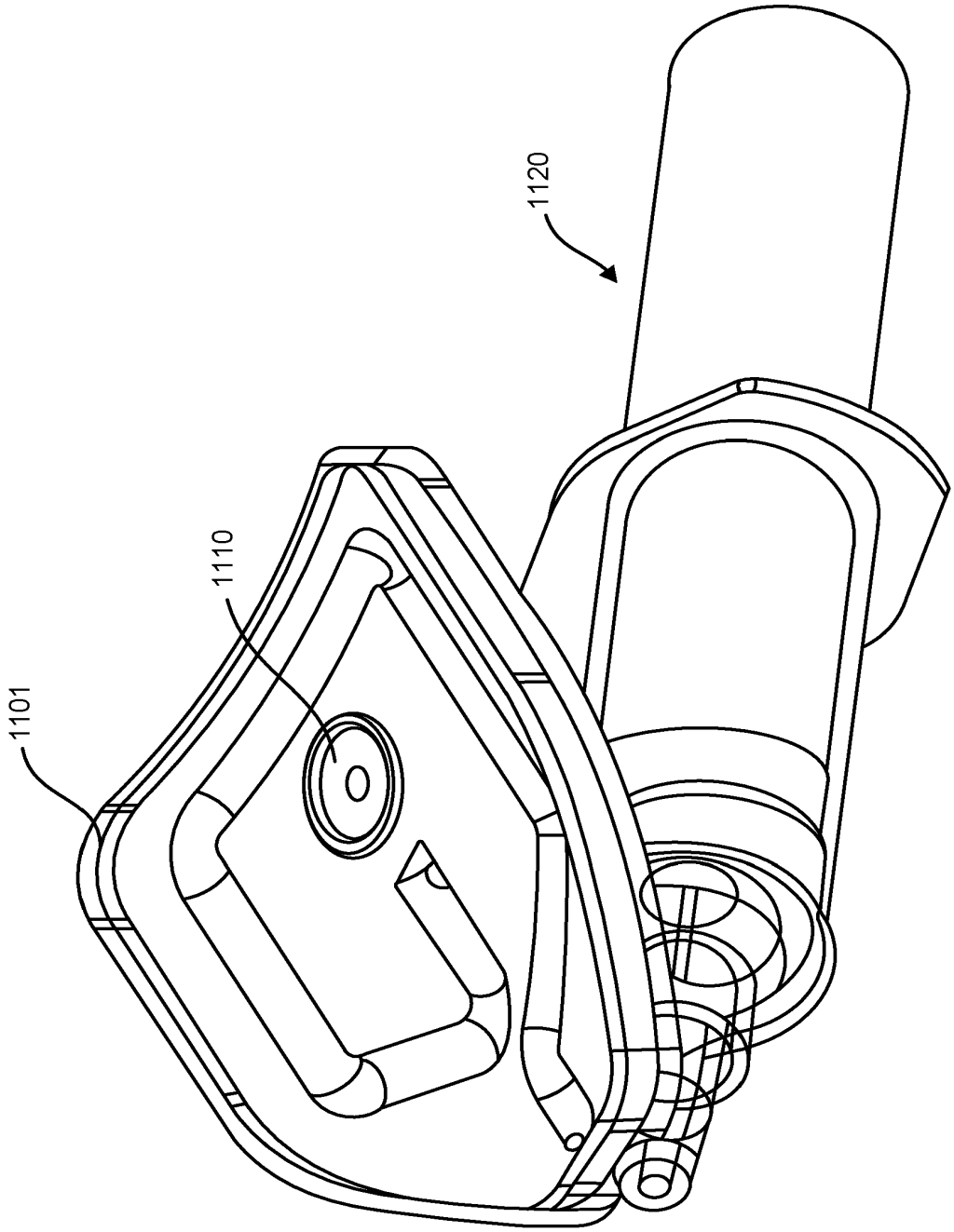


FIG. 11E

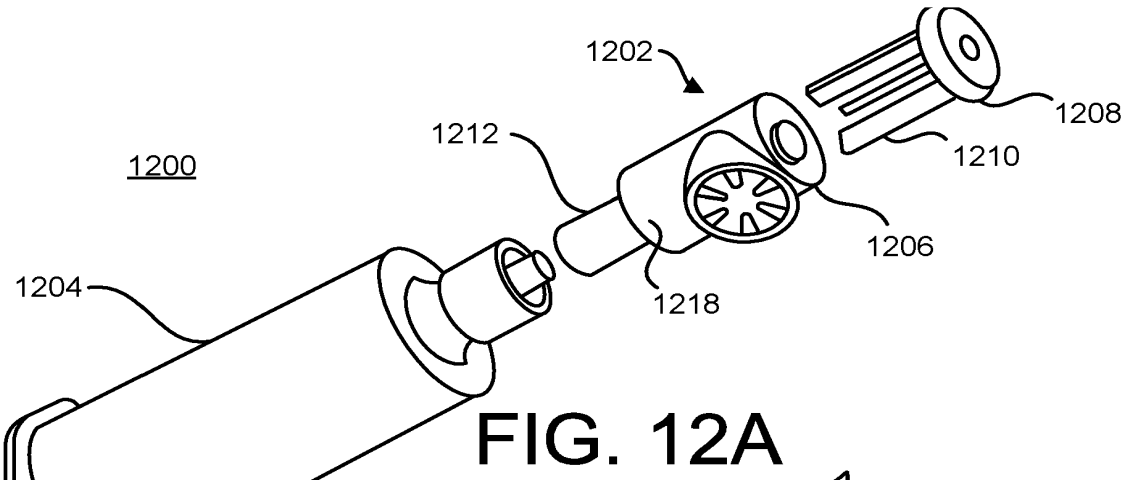


FIG. 12A

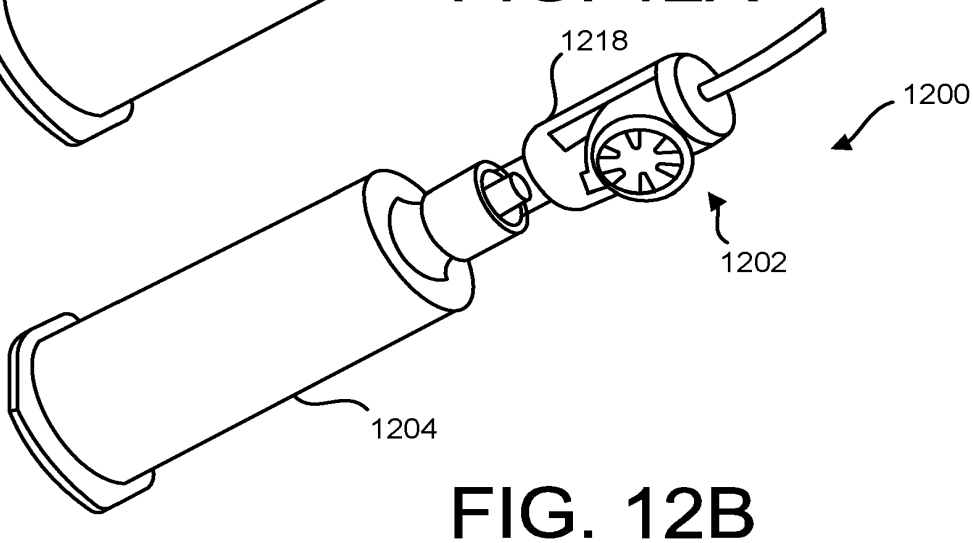


FIG. 12B

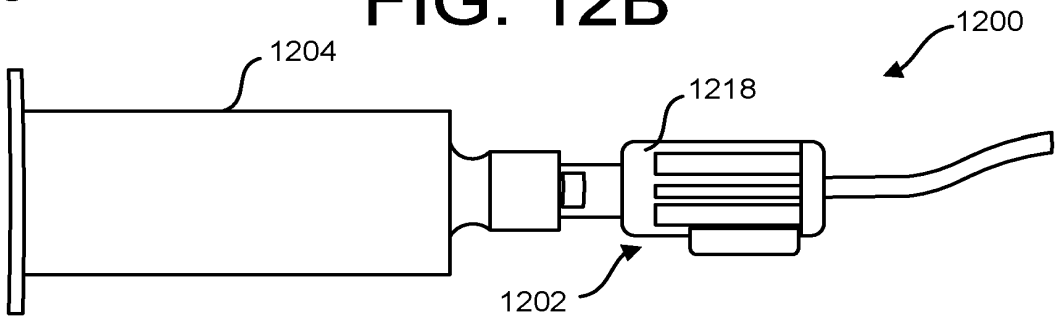


FIG. 12C

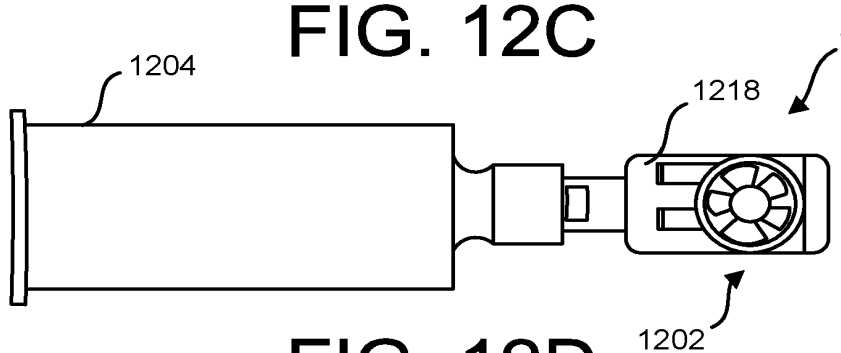


FIG. 12D

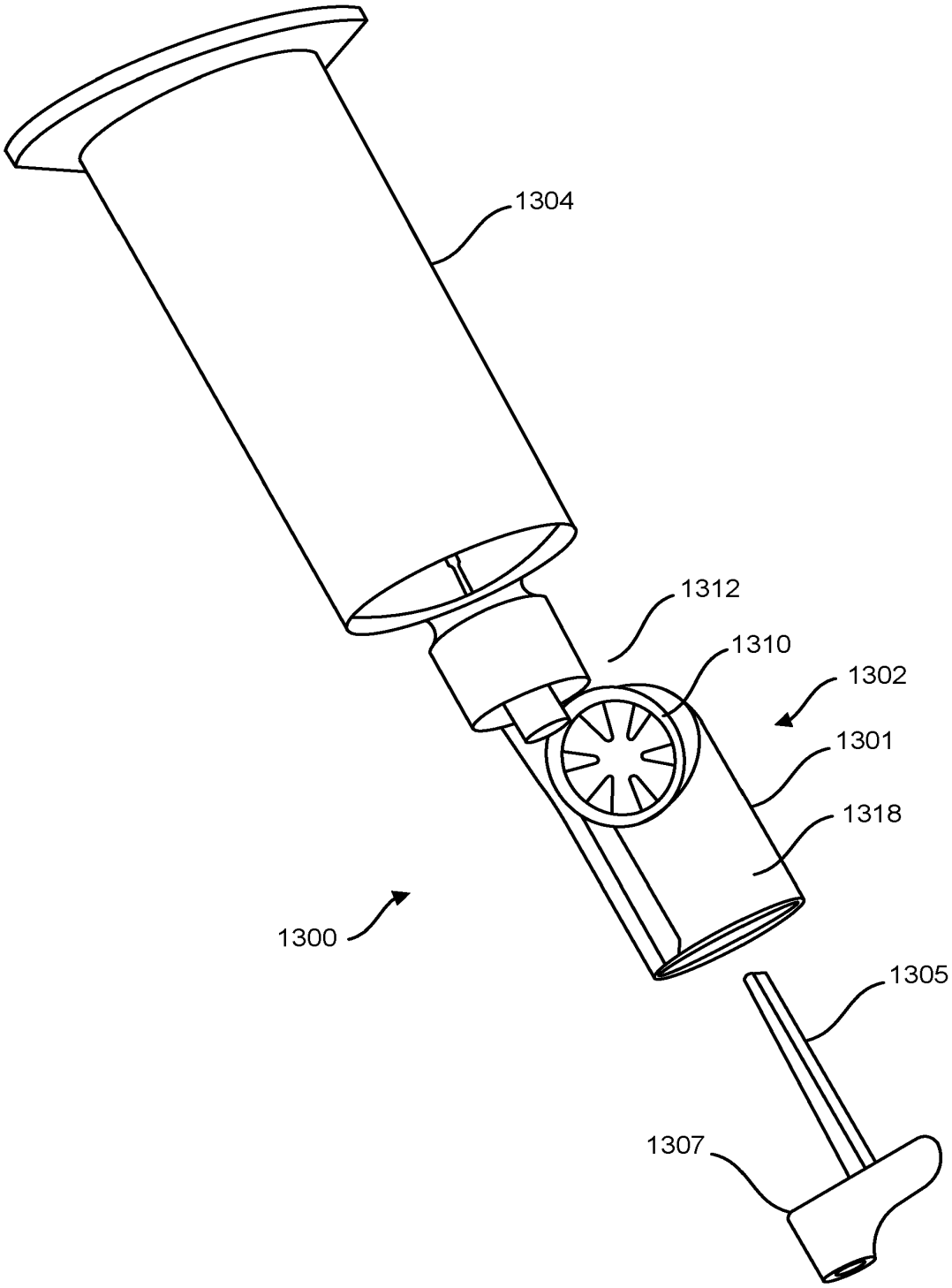


FIG. 13A

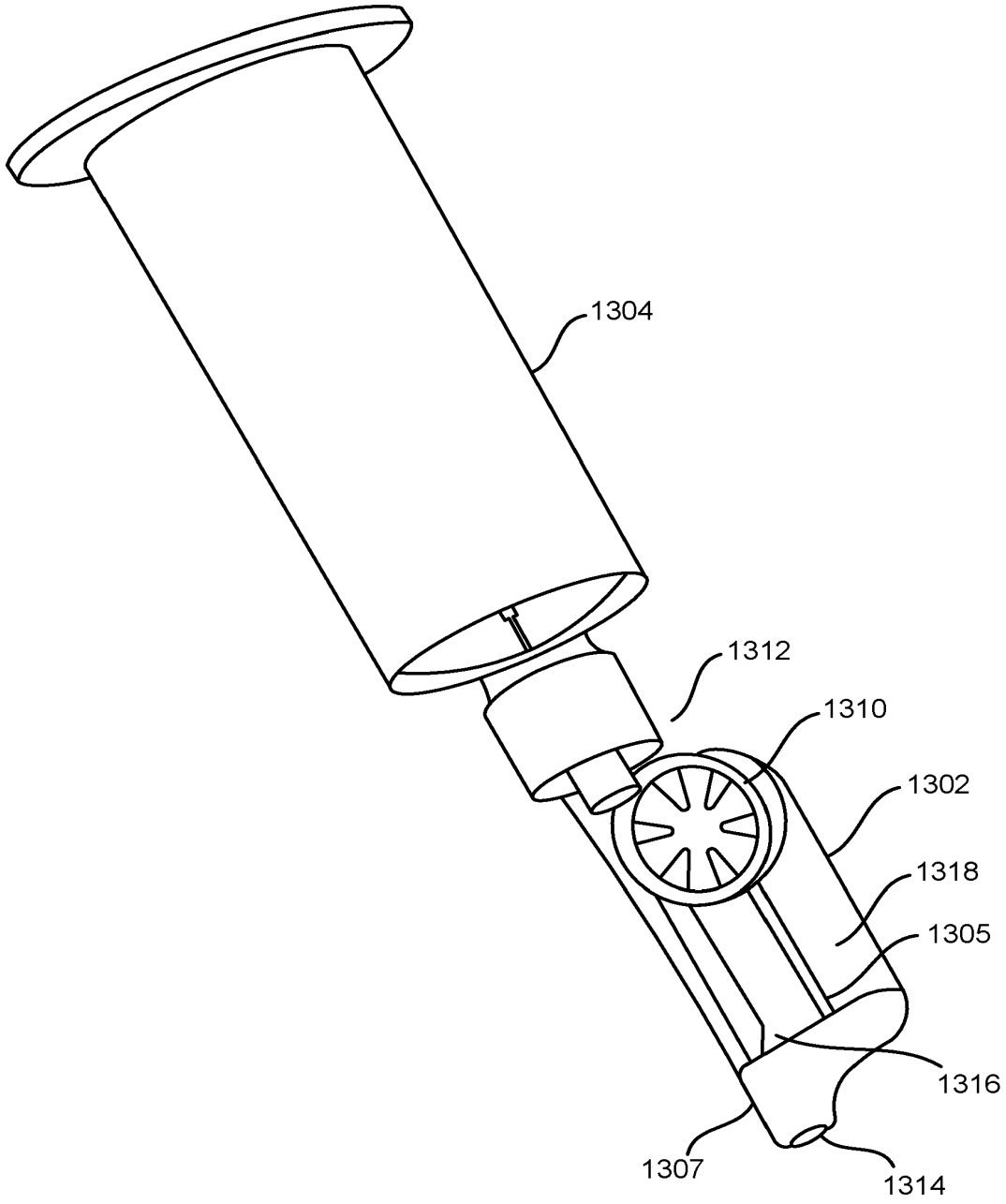


FIG. 13B

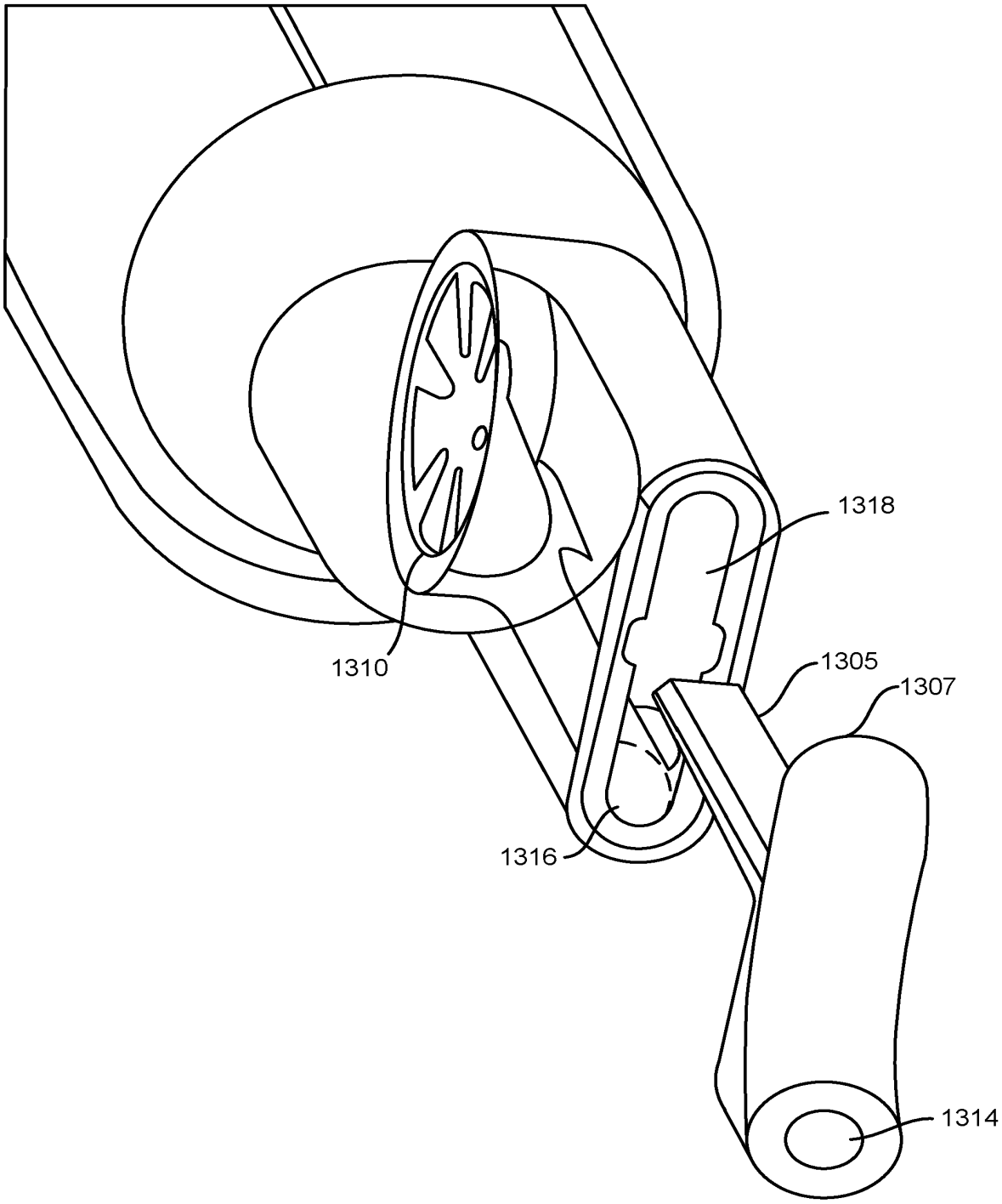


FIG. 13C

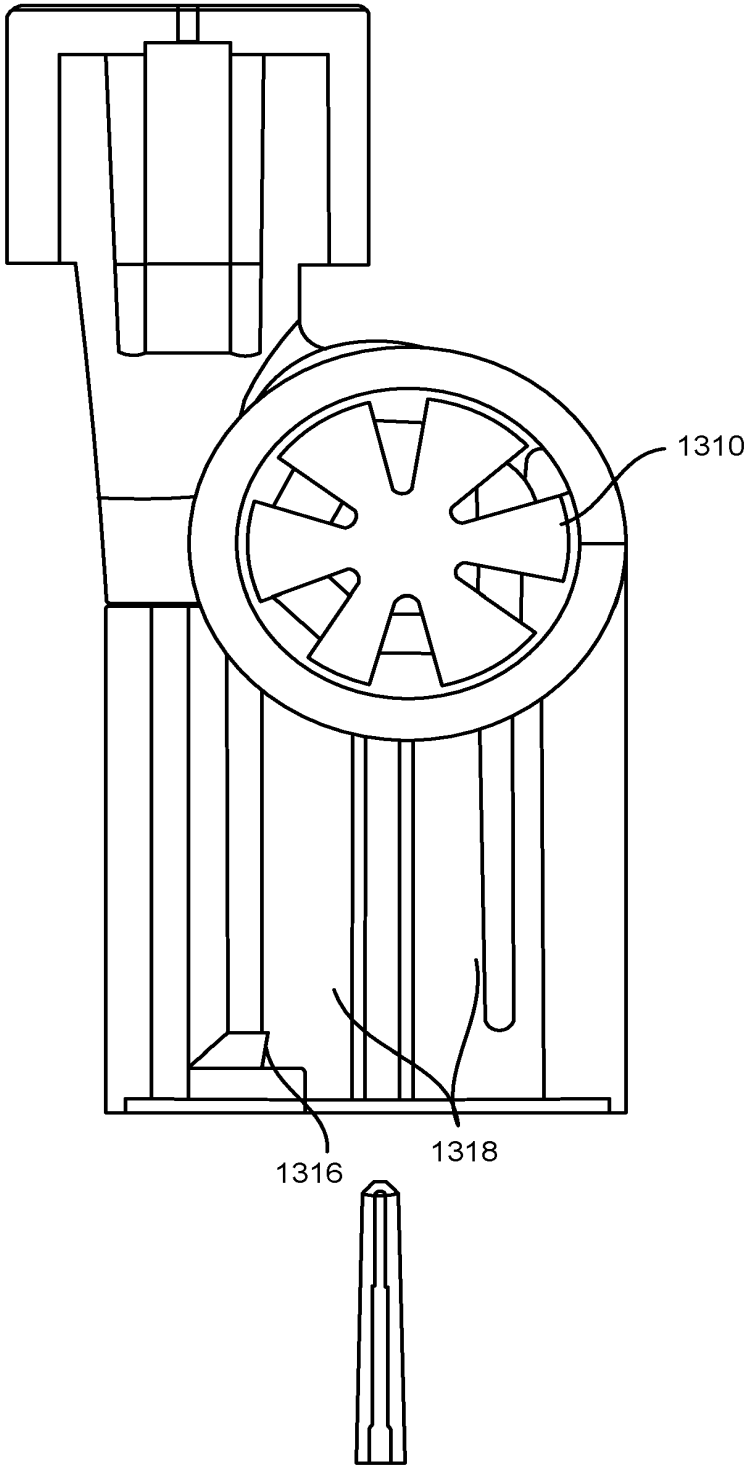


FIG. 13D

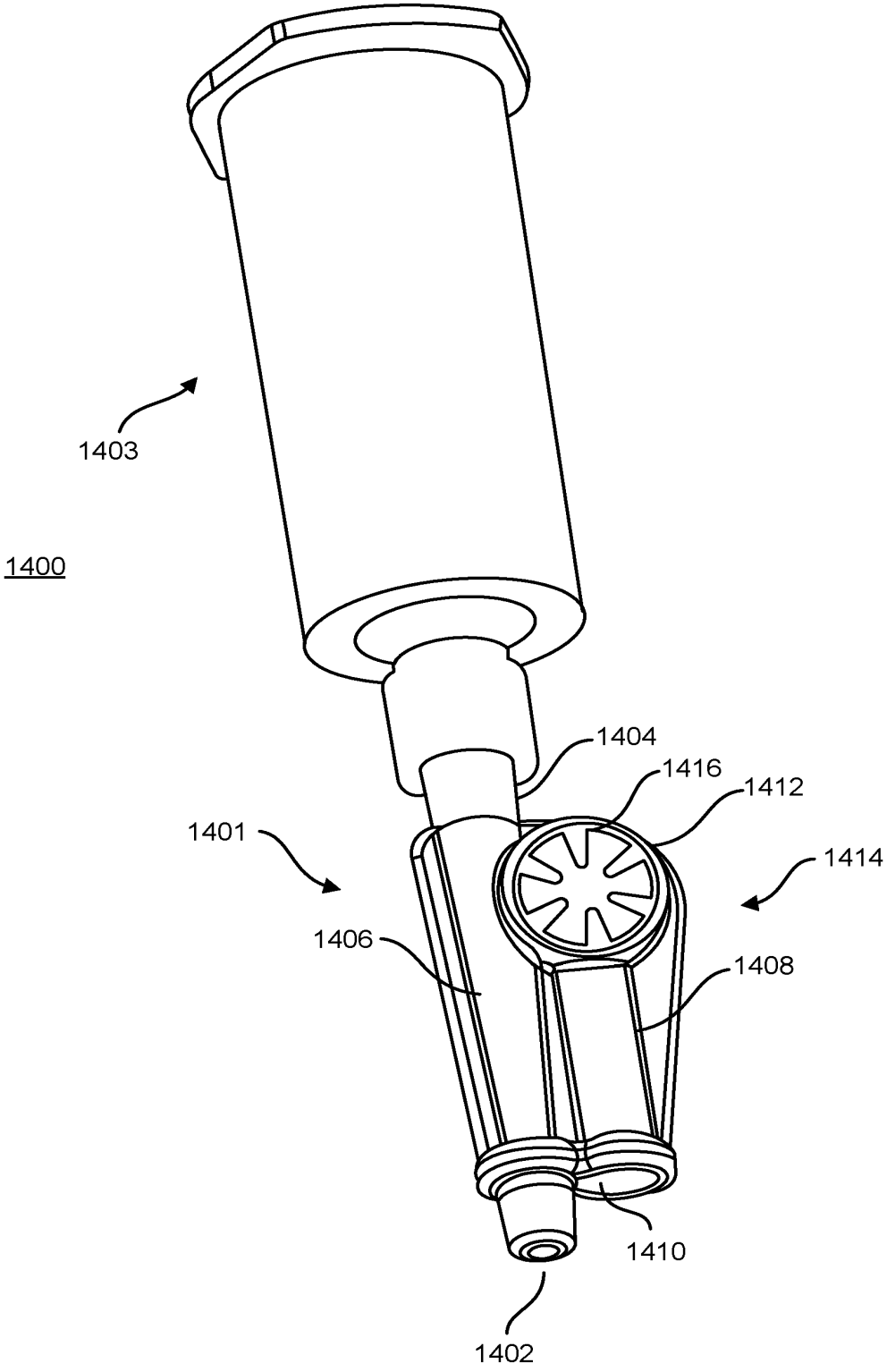


FIG. 14A

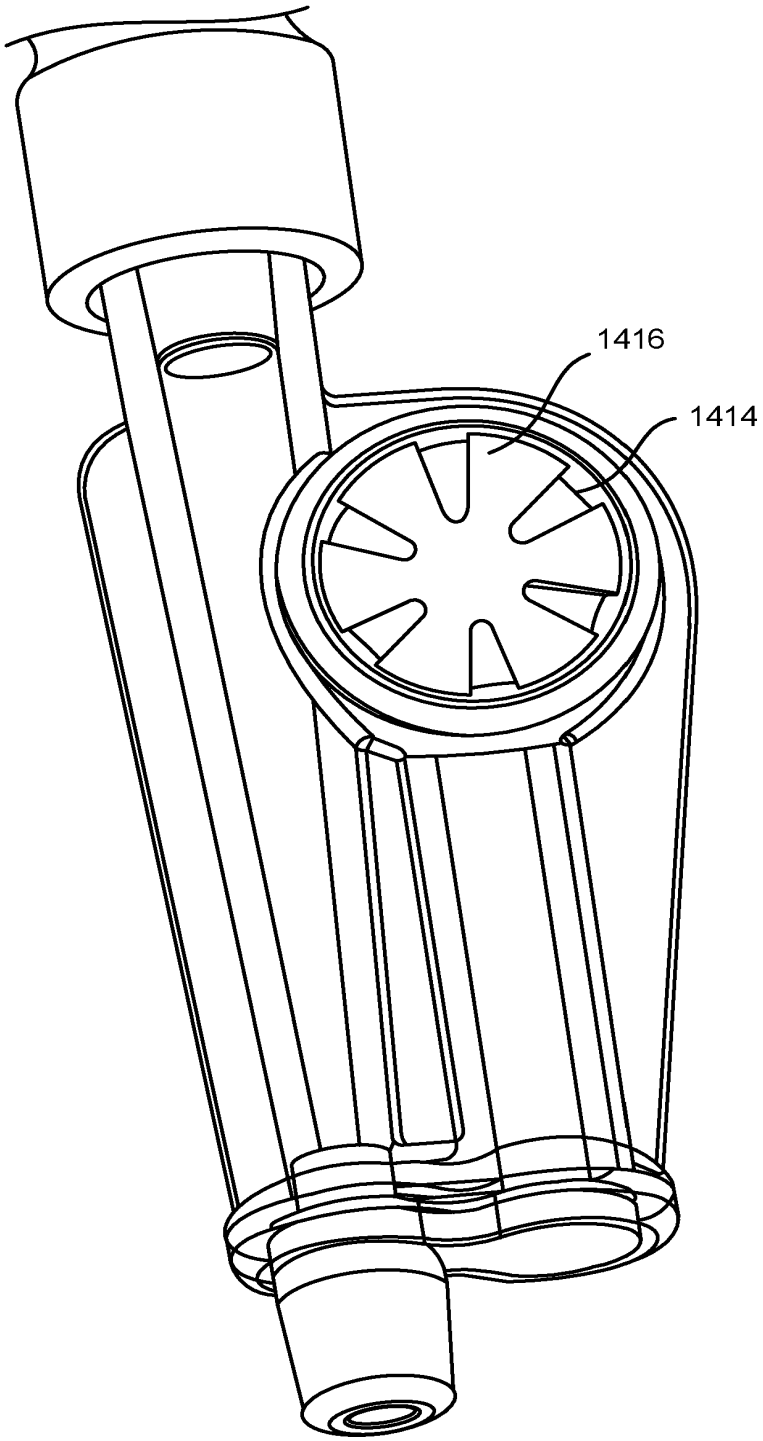


FIG. 14B

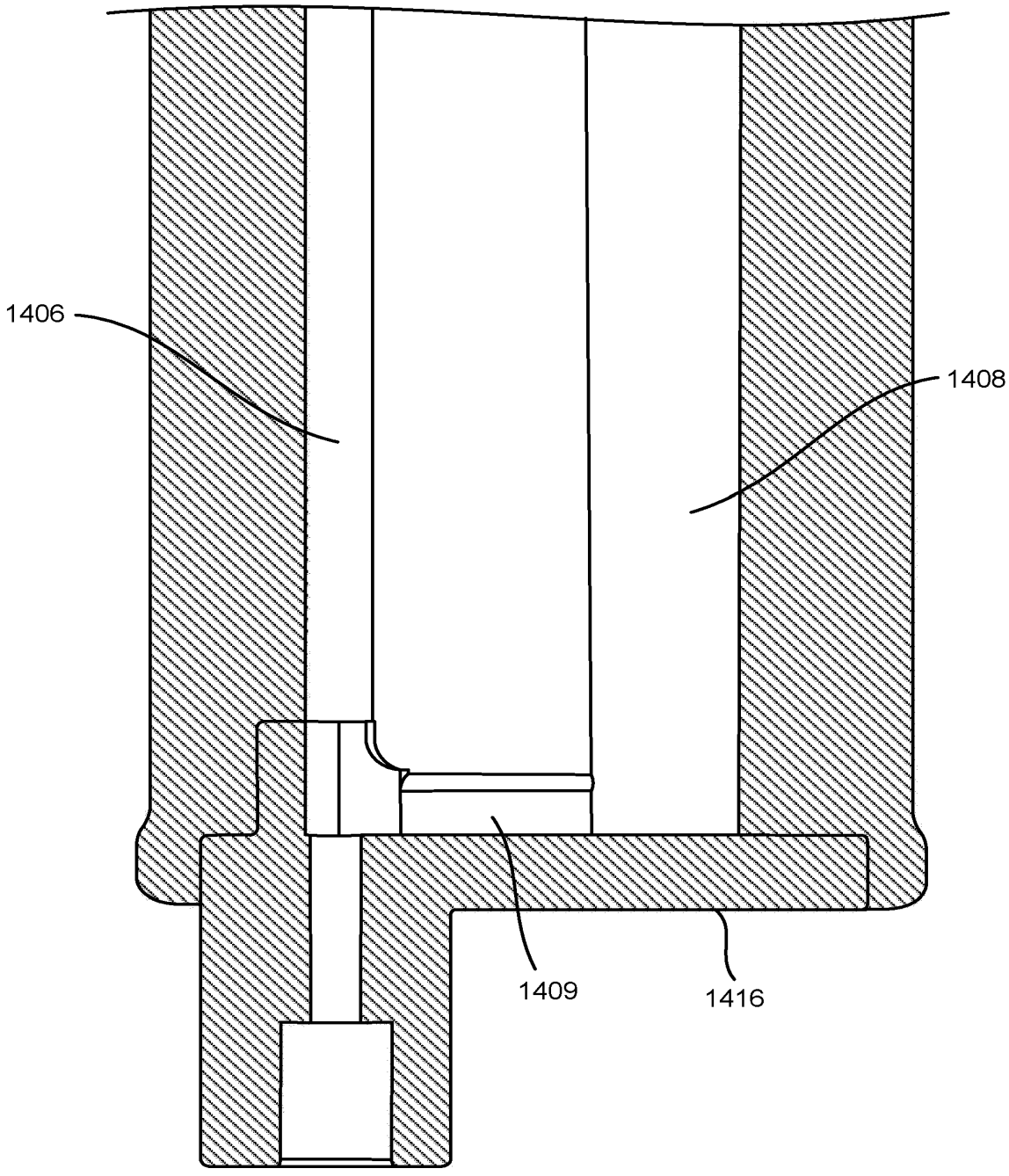


FIG. 14C

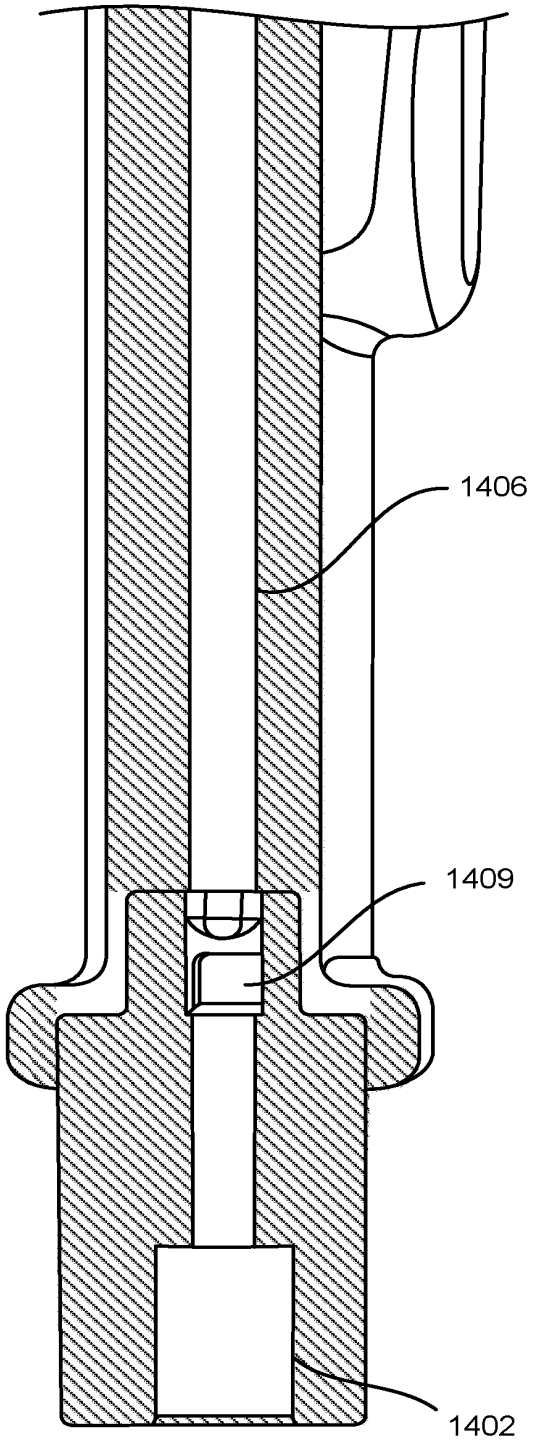


FIG. 14D

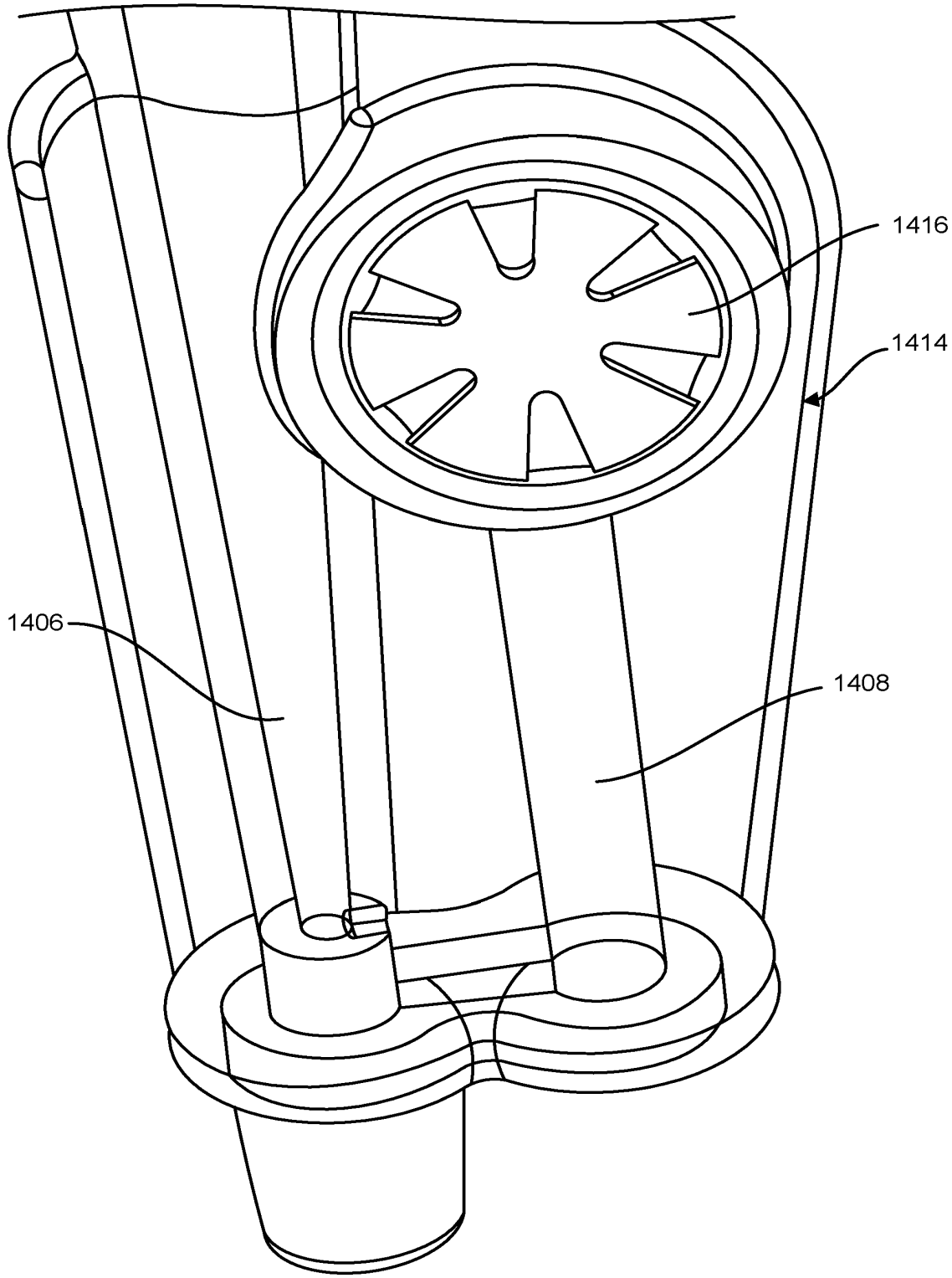


FIG. 14E

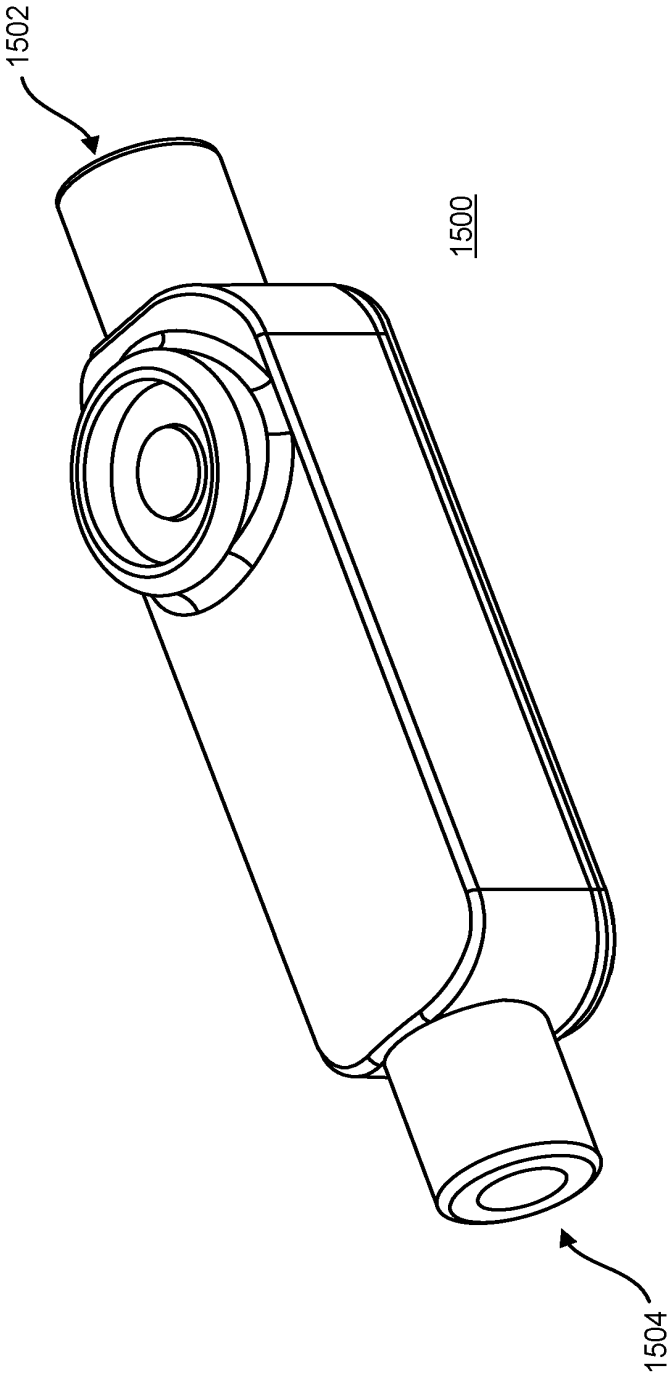


FIG. 15A

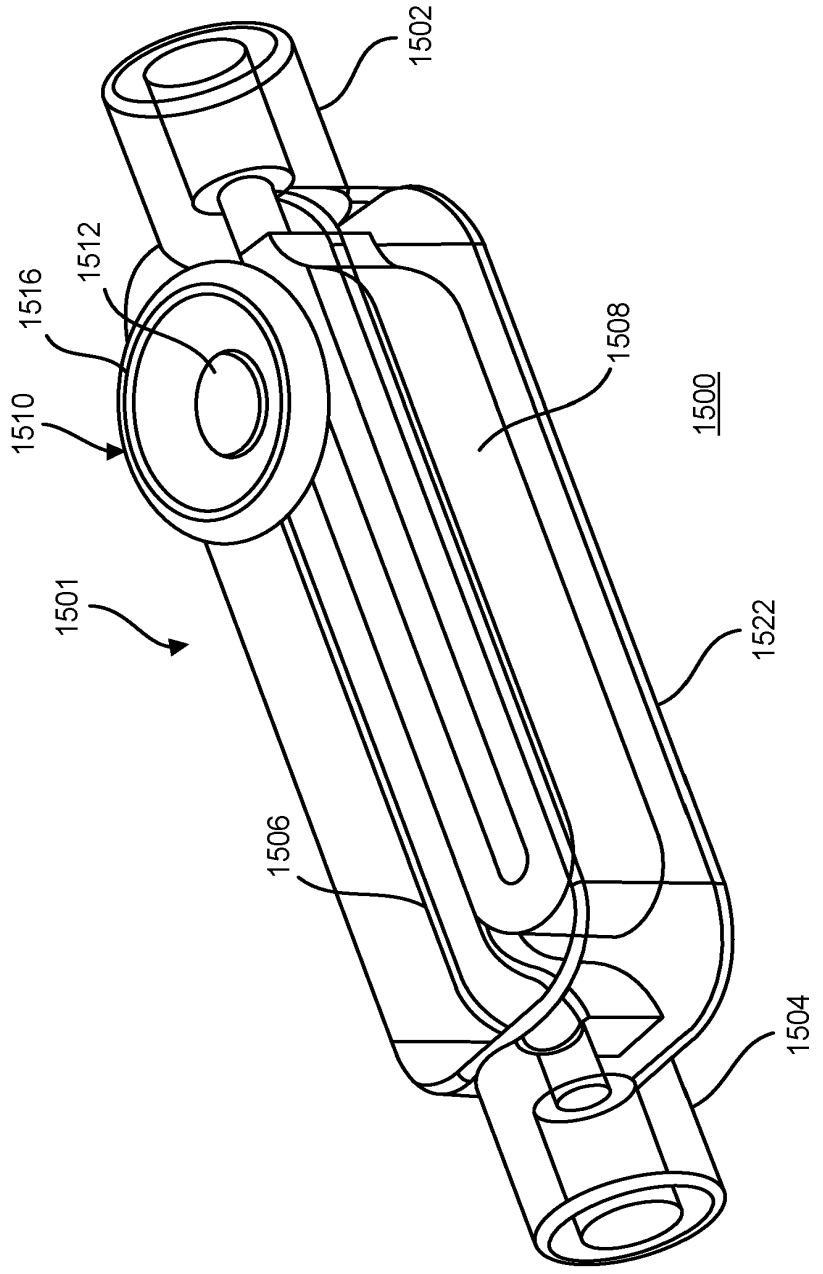


FIG. 15B

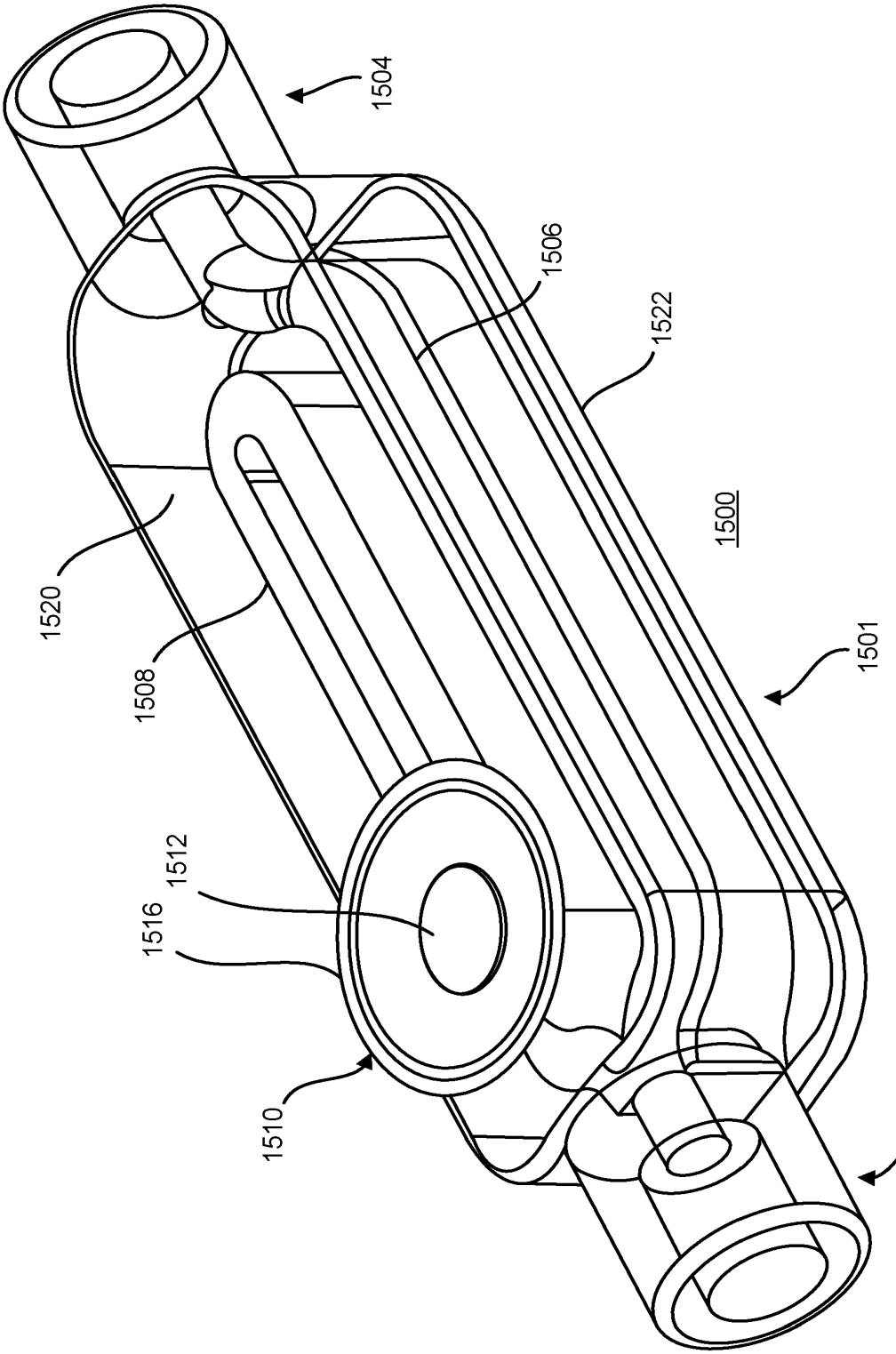


FIG. 15C

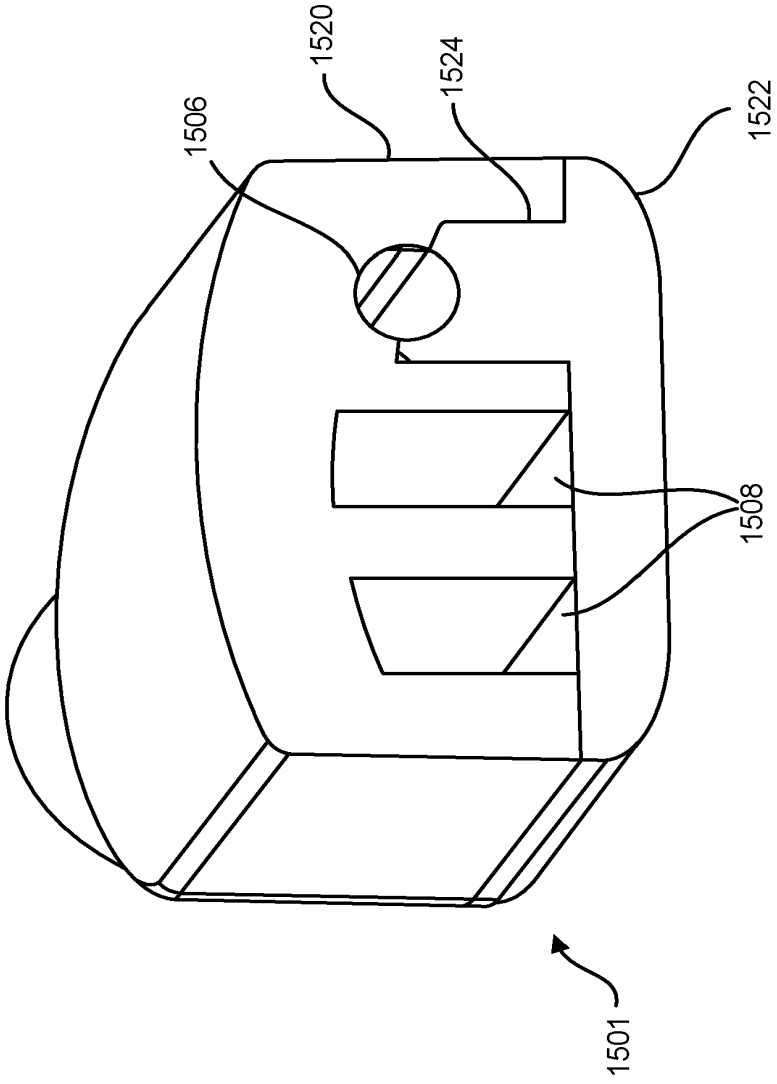


FIG. 15D

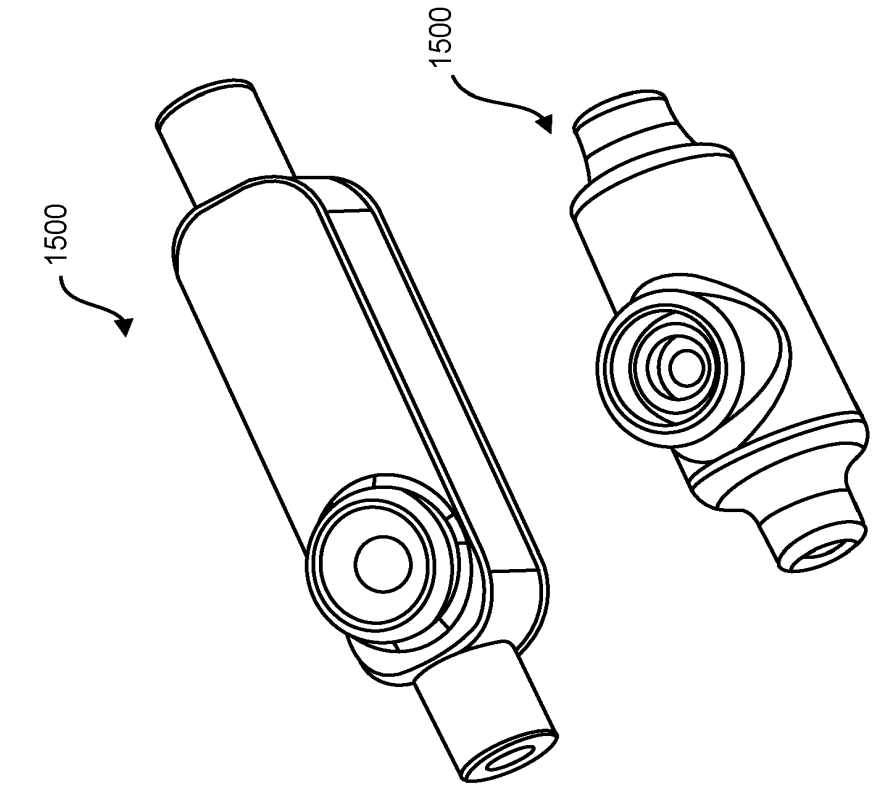


FIG. 15F

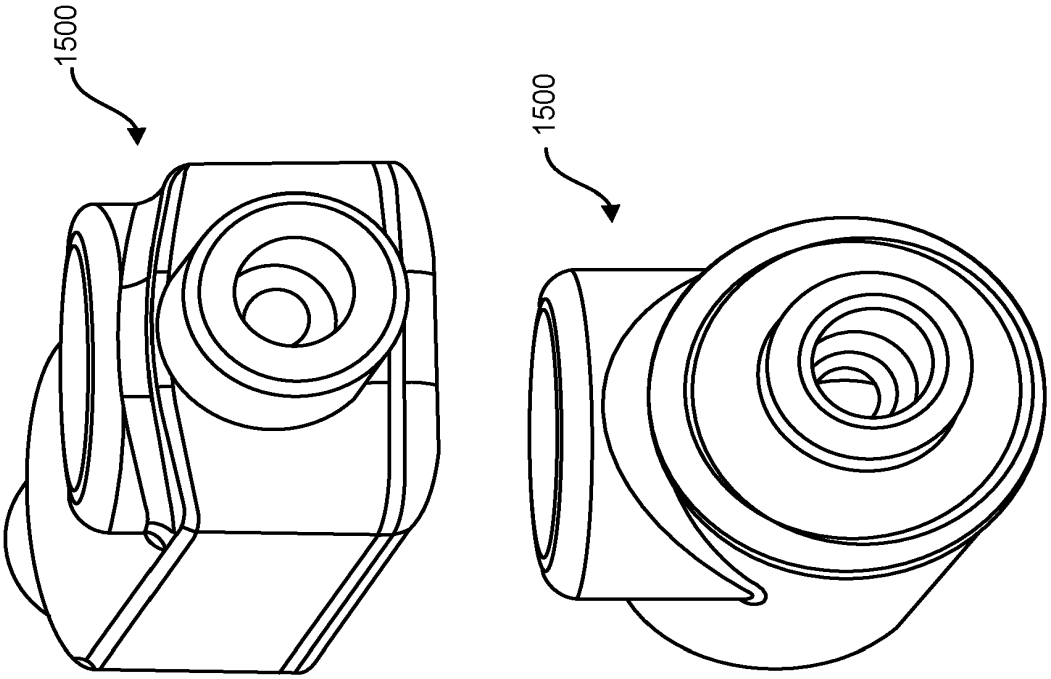


FIG. 15E

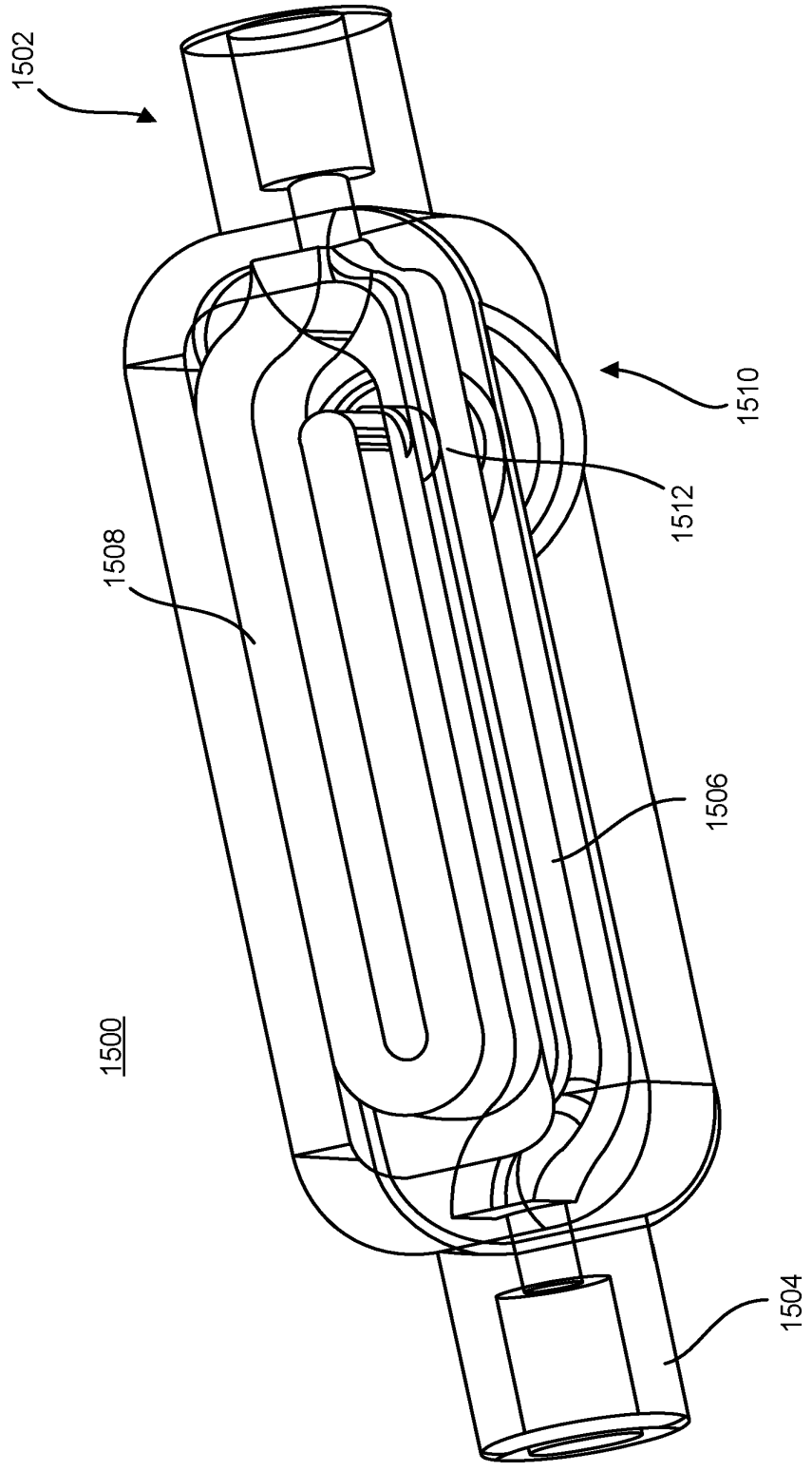


FIG. 15G

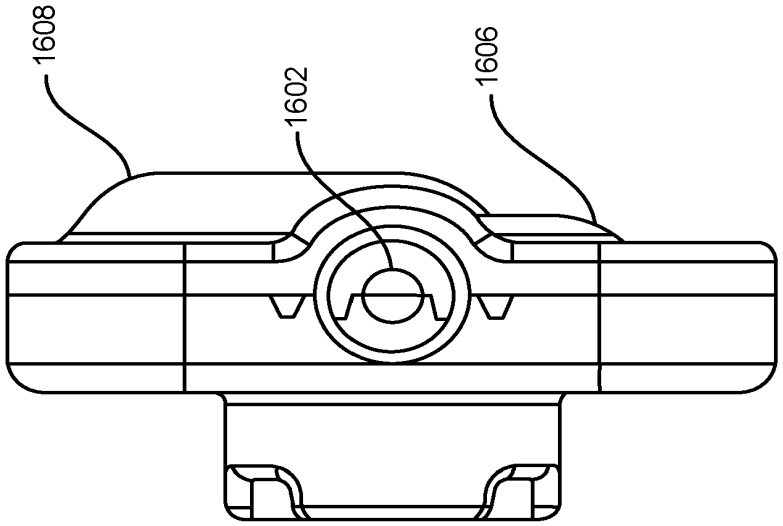


FIG. 16C

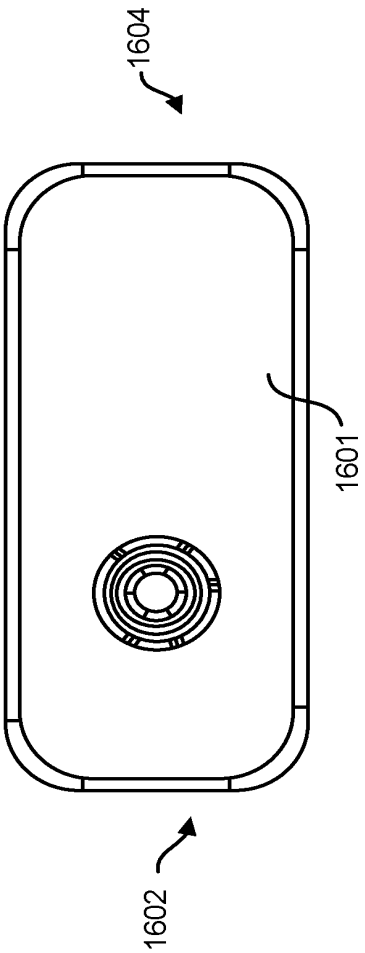


FIG. 16A

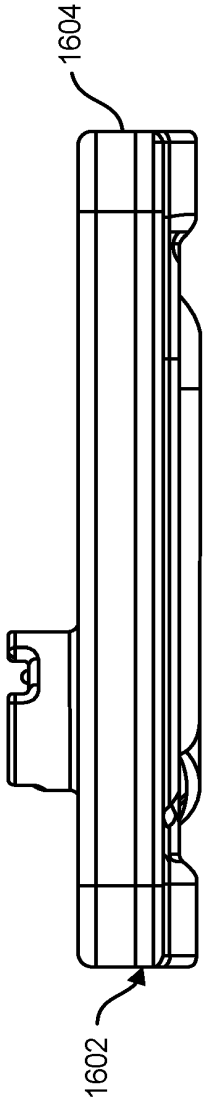


FIG. 16B

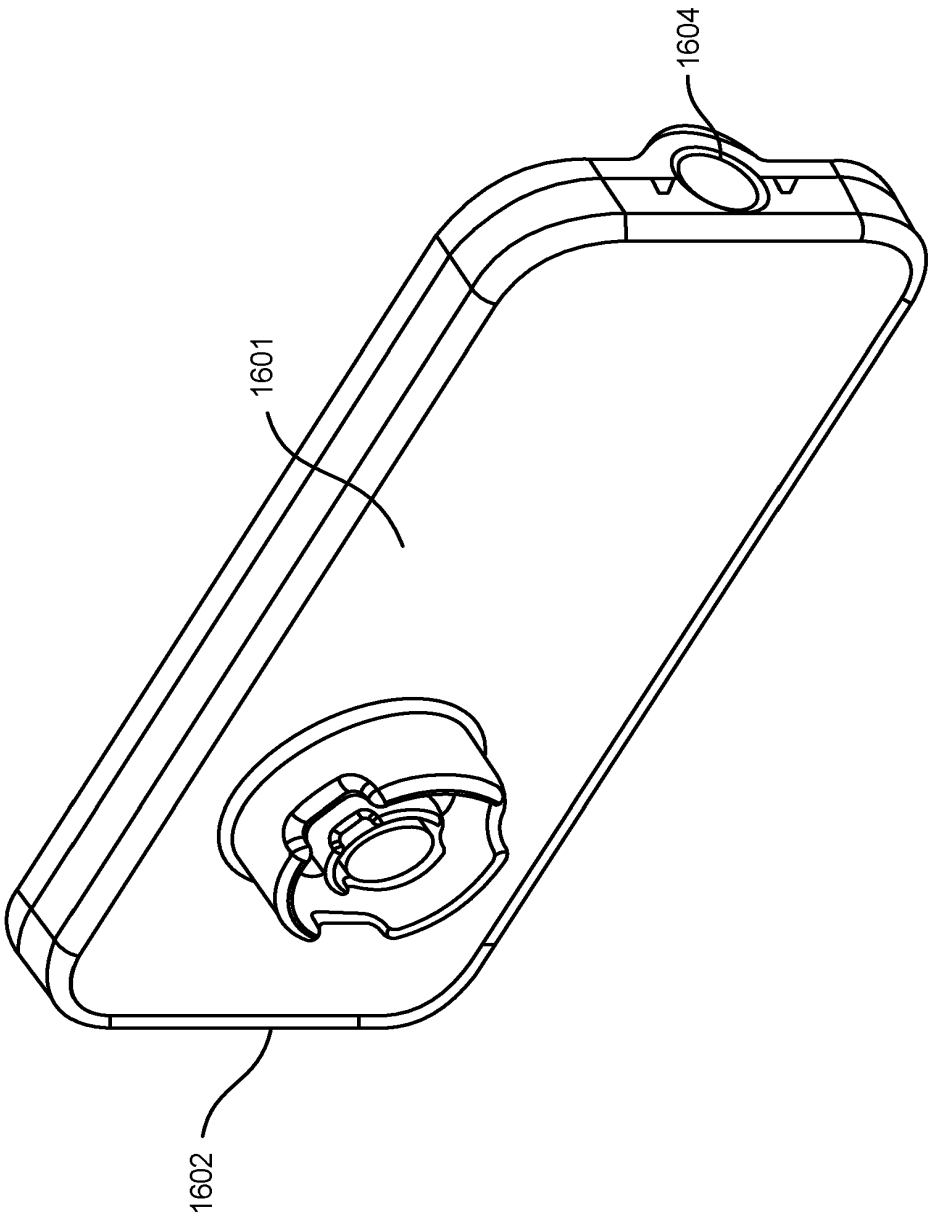


FIG. 16D

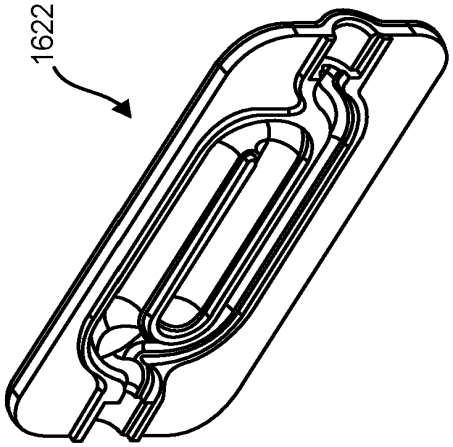


FIG. 17B

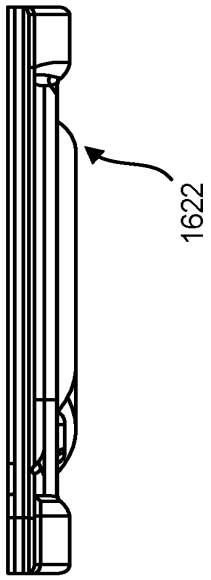


FIG. 17E

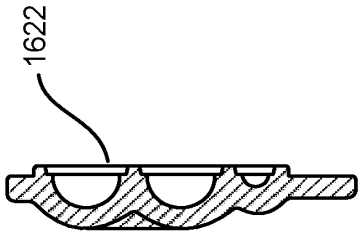


FIG. 17D

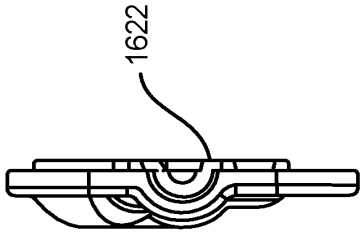


FIG. 17C

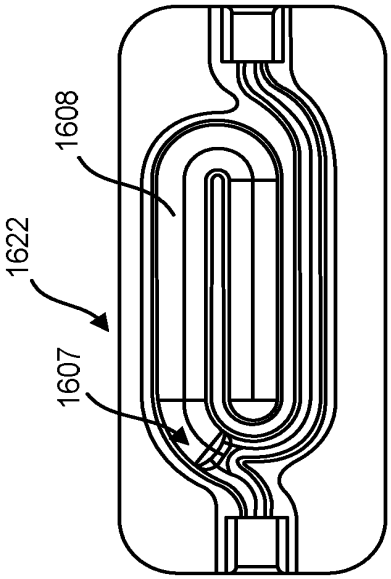


FIG. 17A

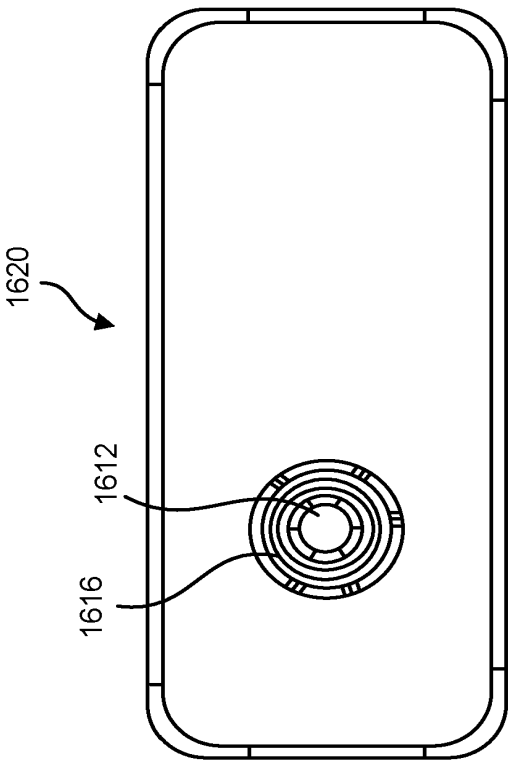


FIG. 18A

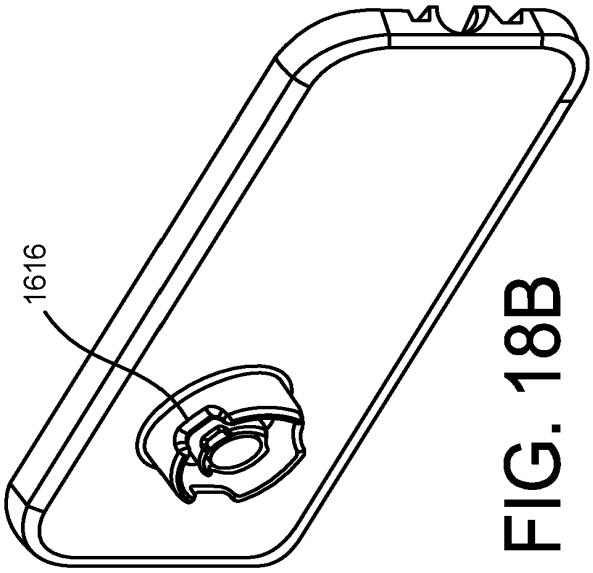


FIG. 18B

FIG. 18C

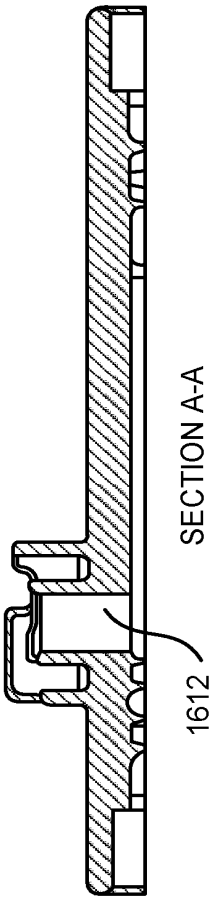


FIG. 18D

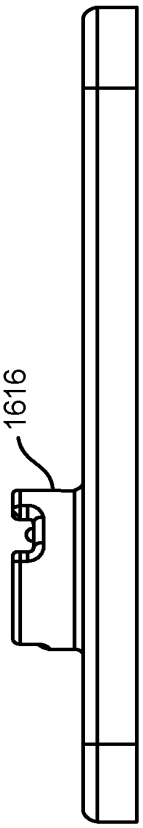


FIG. 18E

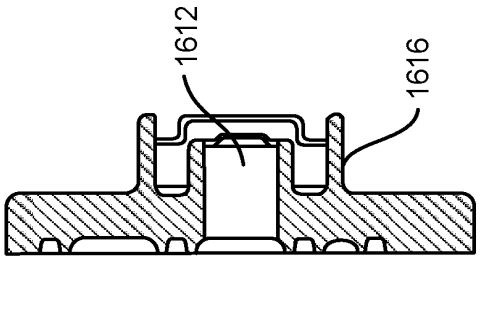


FIG. 18F

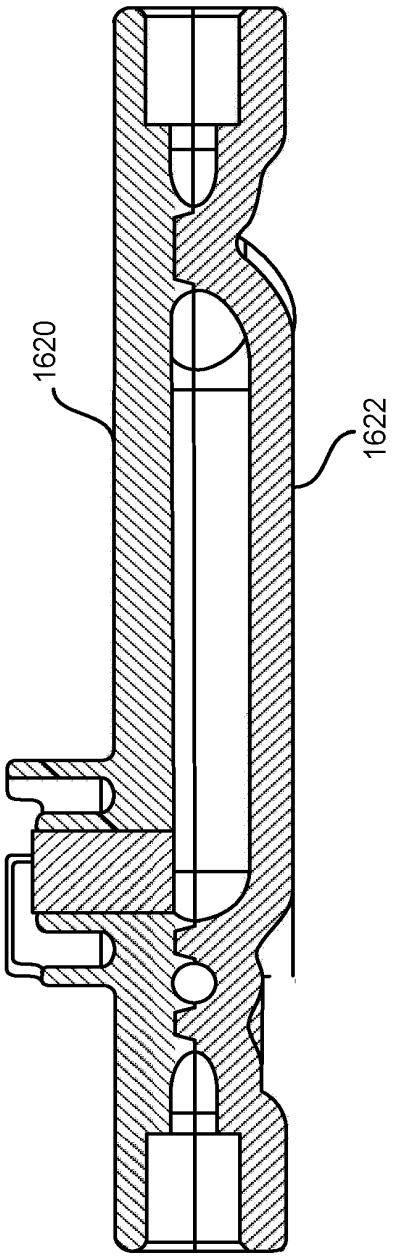


FIG. 19A

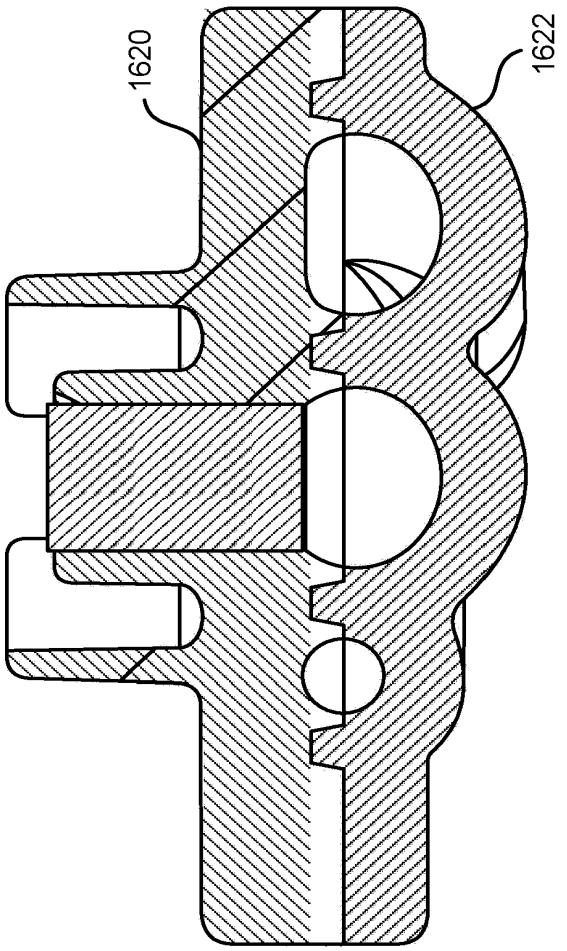


FIG. 19B

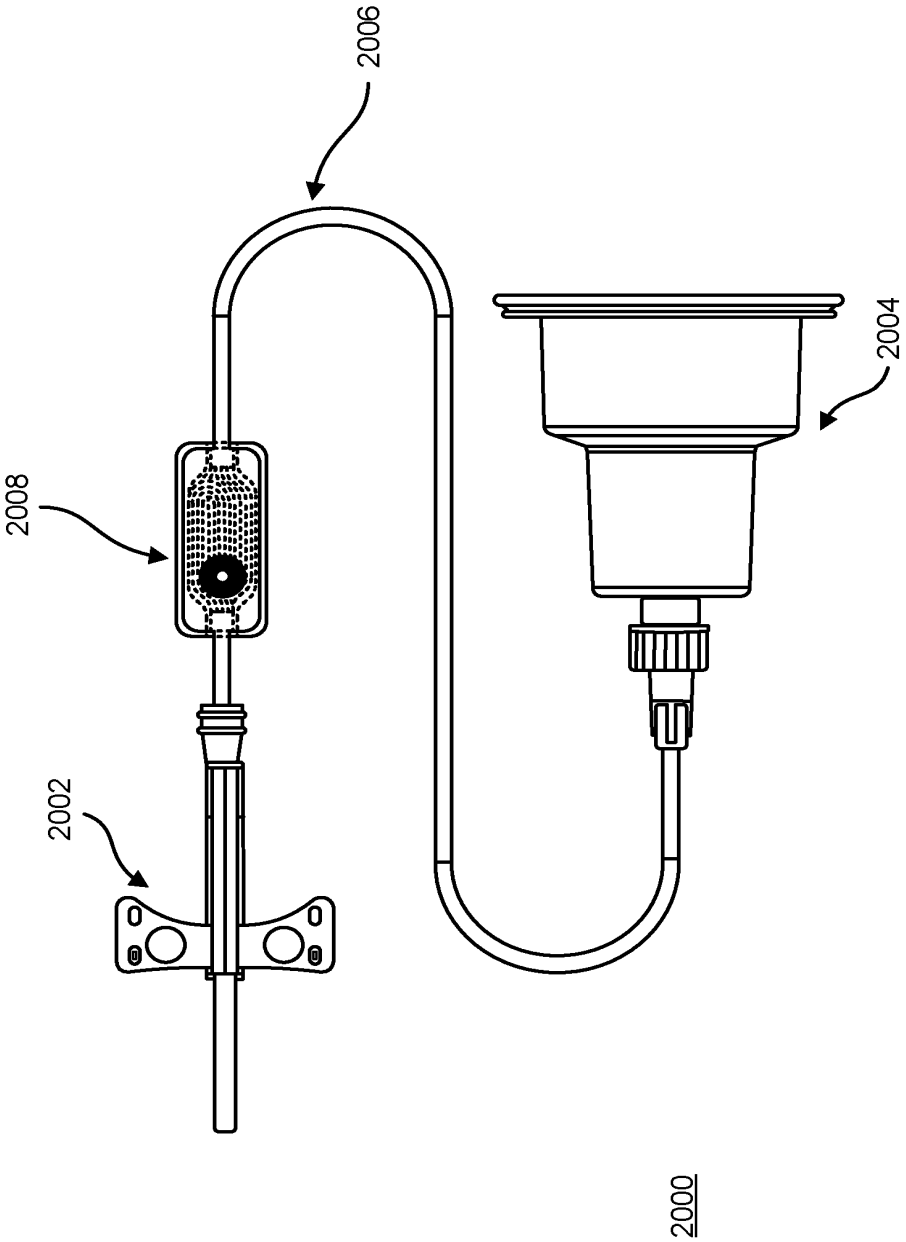


FIG. 20

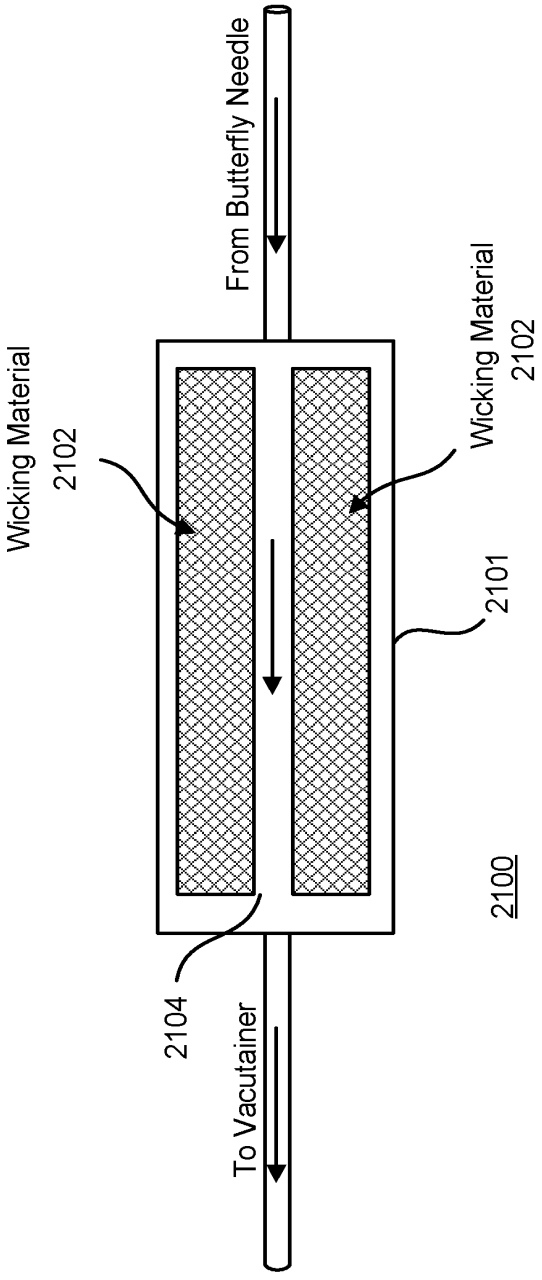

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

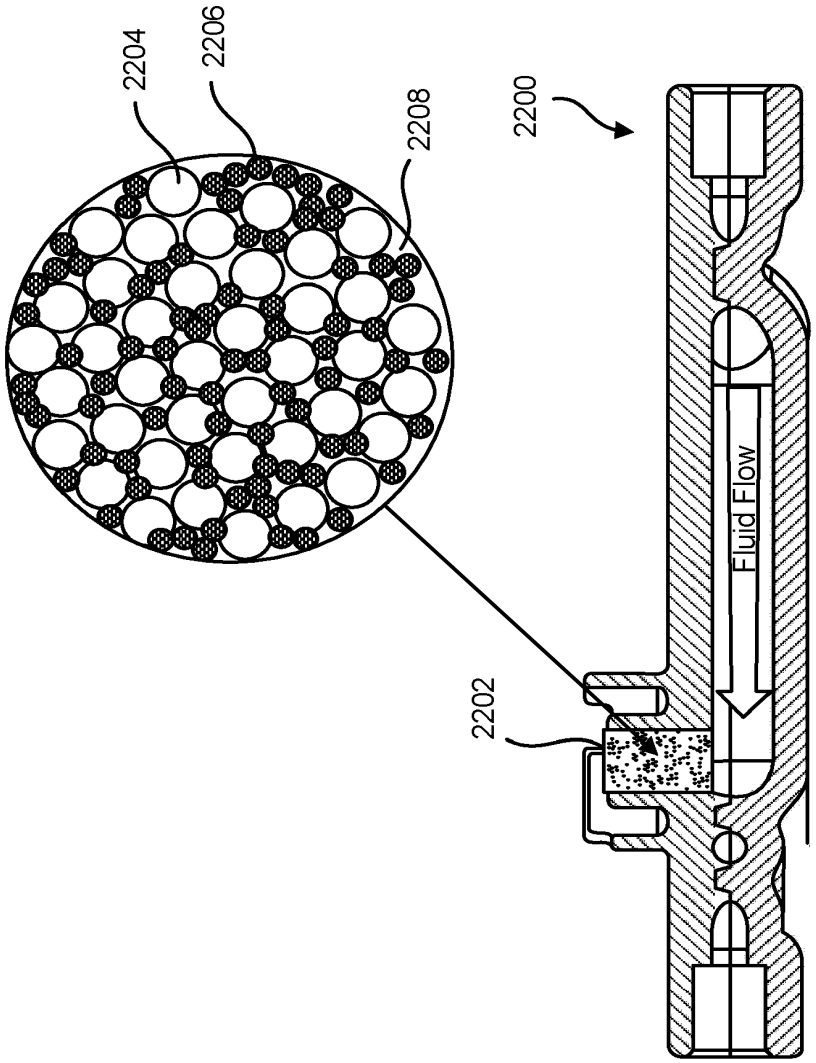


FIG. 22A

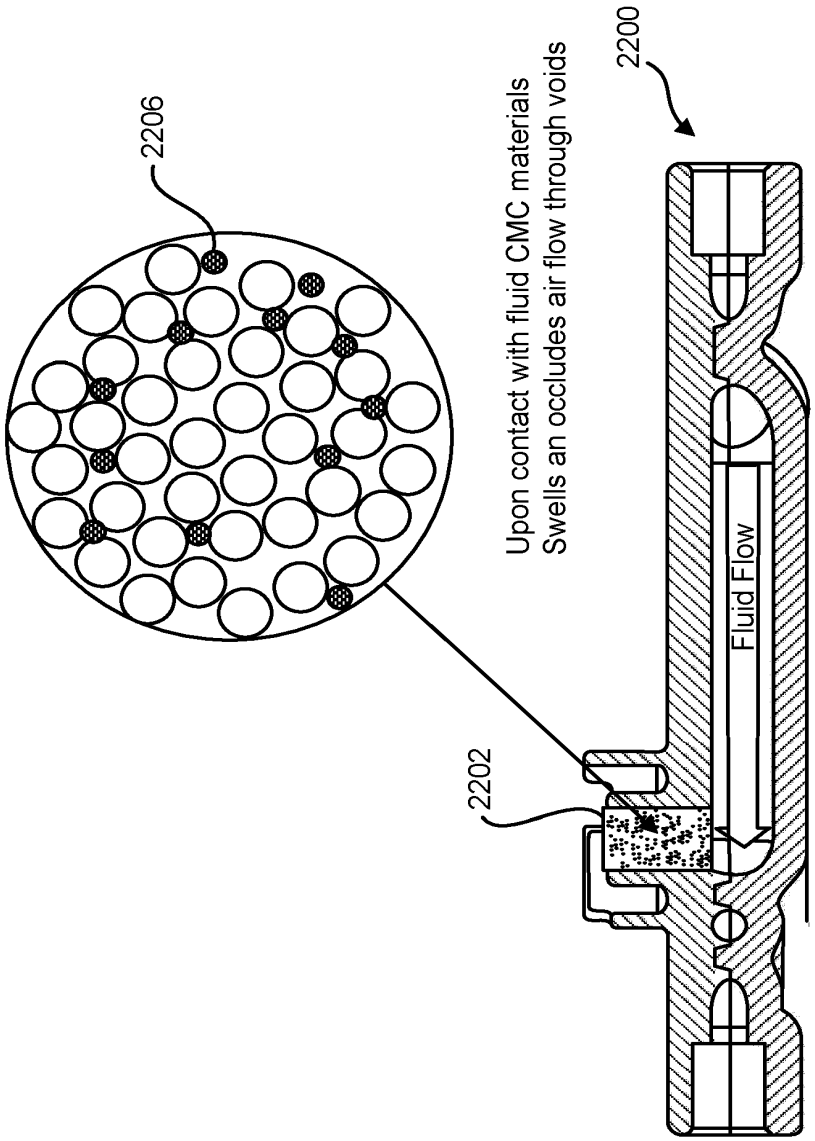

2206
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
2200
2202
Fluid Flow

FIG. 22B

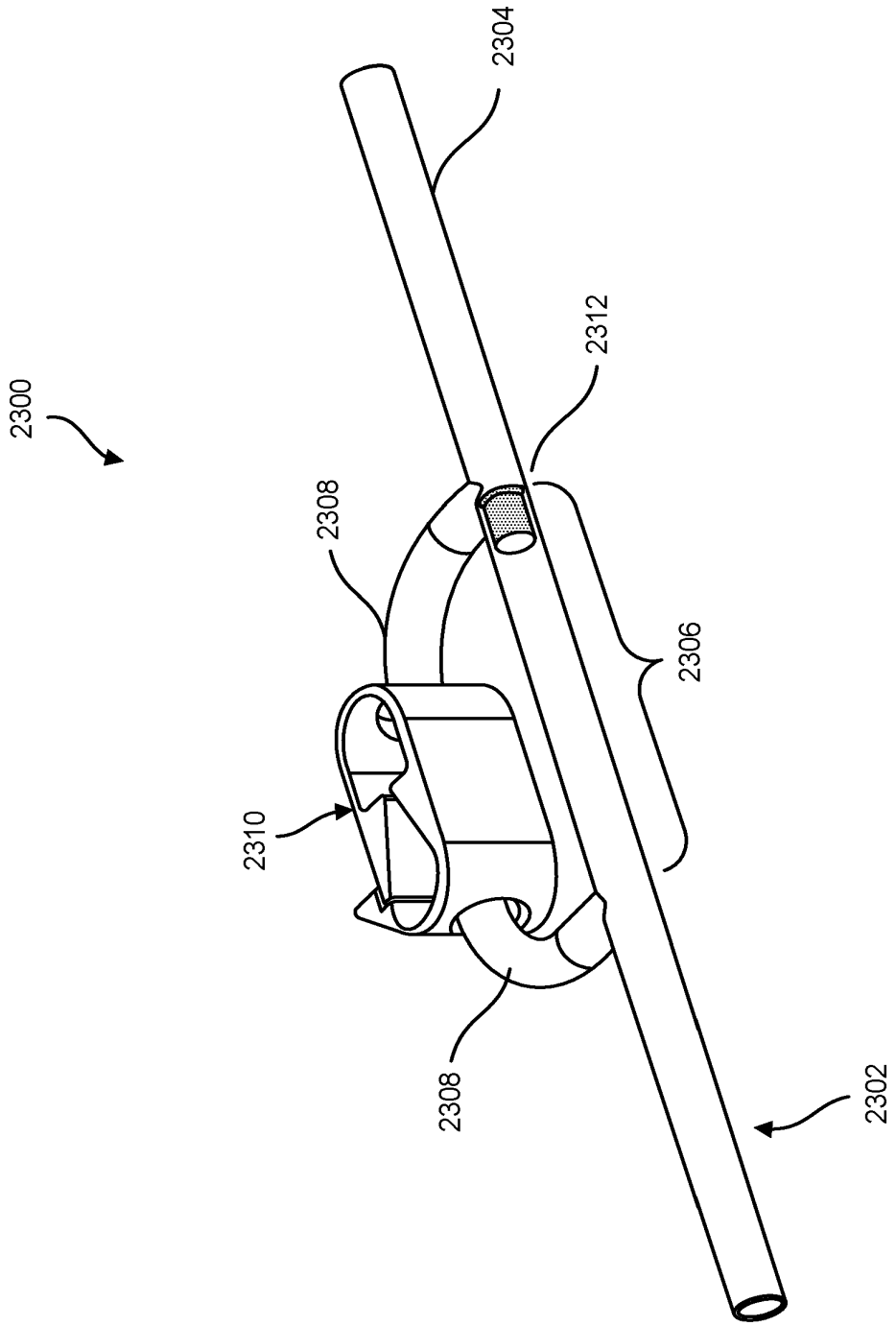


FIG. 23A

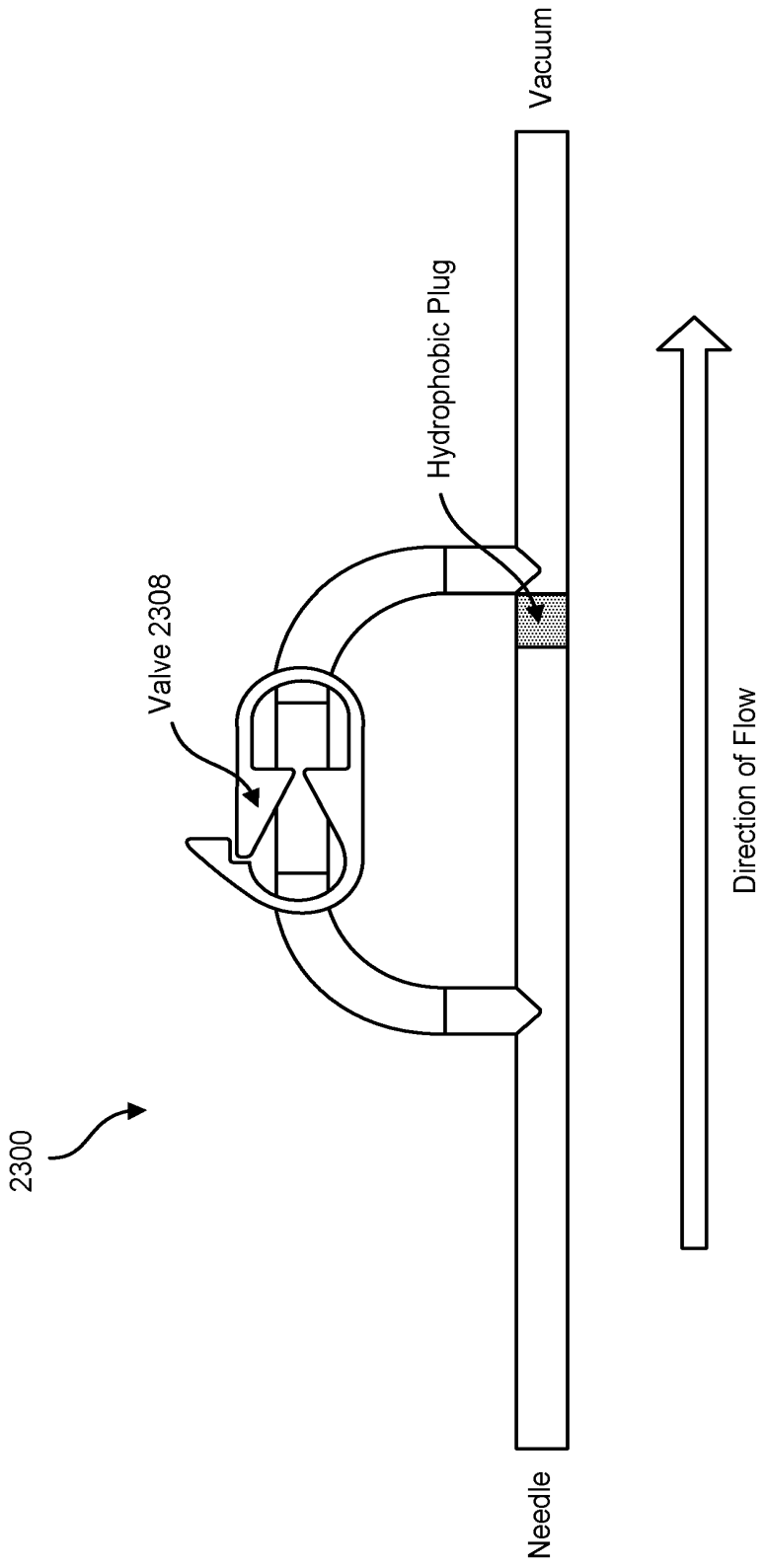

Vacuum
Hydrophobic Plug
Valve 2308
2300
Needle
Direction of Flow

FIG. 23B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

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

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

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

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/043709

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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

2

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/043709

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011162772 A1	29-12-2011	NONE	
US 2009227953 A1	10-09-2009	US 2009227953 A1	10-09-2009
		US 2010262038 A1	14-10-2010
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JP H08257018 A	08-10-1996	NONE	
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US 2013317391 A1	28-11-2013	US 2013317391 A1	28-11-2013
		US 2015099996 A1	09-04-2015
		US 2015351678 A1	10-12-2015

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

Bibliographic data: DE10038026 (A1) — 2001-02-22

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

Inventor(s):

Applicant(s): ZIERDEN PETER [DE] ± (ZIERDEN, PETER)

Classification:
- **international:** ***A61B5/15;*** (IPC1-7): A61B5/15; A61M1/00
- **cooperative:** **A61B5/15003 (EP)**; **A61B5/150152 (EP)**; **A61B5/150389 (EP)**; **A61B5/150503 (EP)**; **A61B5/150656 (EP)**; **A61B5/150732 (EP)**; **A61B5/153 (EP)**; **A61B5/155 (EP)**; A61B5/150748 (EP)

Application number: DE20001038026 20000802

Priority number(s): DE20001038026 20000802 ; DE19992013417U 19990806

Also published as: DE29913417 (U1)

Abstract of DE10038026 (A1)

The blood extractor has a housing (1) with a hollow needle (10) extending through the wall of the patients blood vessel (B) to aspirate blood from it. The needle can move between a retracted position in which it is behind the surface of the housing and an extended position in which the end of the needle extends from the housing.

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DESCRIPTION DE10038026A1

[0001]

13 The invention relates to a device for removing blood from a blood vessel of the type corresponding to the preamble of claim 1.

[0002]

18 Such devices always comprise a hollow needle that is beveled at one end for penetrating the skin, the tissue lying between the skin and the vessel and the vessel wall, and which is usually equipped with a coupling at its other end, which is used to attach a container with a volume for receiving the blood taken .

[0003]

25 To generate the suction required for taking blood, it is known to design the containers as a piston/cylinder arrangement, after the hollow needle has been inserted into the blood vessel and the container has been coupled, the piston is actuated manually to increase the volume of the vessel.

[0004]

32 The disadvantage of this device is that the patient can only prick the hollow needle into the blood vessel with considerable skill and practice if the person performing the puncture is almost painless for the patient.

35 Furthermore, when the plunger is actuated manually, the needle cannot usually be kept completely still, which means that the needle in the puncture area stretches or even injures the skin, the underlying tissue and the vessel wall, which regularly causes pain to the patient.

[0005]

41 For the latter reason, it is also known to pre-evacuate the vessels that have the volume for receiving the blood taken and to seal them with a closure or

43 Equip valve assembly, which is opened when coupled to the hollow needle, so that the blood to be removed is sucked into the volume of the container without requiring additional manual operation of the device.

[0006]

49 This measure prevents the risk of "wobbly pain" caused by the manual operation of the piston, but the disadvantage is that the insertion of the hollow needle, the subsequent coupling of the pre-evacuated vessel and the frequently necessary replacement of a full container with an empty one In turn, absorption of the blood removed leads to undesired movements of the needle which are painful for the patient.

[0007]

57 It is therefore the object of the invention to provide a device which allows blood to be taken from a blood vessel in a manner that is less painful for the patient.

[0008]

62 This object is solved by the invention presented in claim 1.

[0009]

66 Because in the device according to the invention the hollow needle can be moved between a retracted position, in which the hollow needle remains at least essentially within the outer contours of the housing of the device, and an extended position, in which the end of the hollow needle to be inserted into the blood vessel is pushed out of the housing by one certain length protrudes, is displaceably arranged, and that means are provided with which the hollow needle can be displaced from its retracted to its extended position, it is no longer necessary for the insertion of the needle that both the guide and the displacement during the insertion process of the needle must be accomplished by the person taking the blood sample.

74 Rather, the housing only needs to be positioned at the point on the body where the blood is to be taken and the means for extending the needle then activated.

76 The risk of "wobbling" during insertion of the hollow needle is therefore significantly reduced.

77 Since the means for moving the hollow needle can also be designed in such a way that it can be moved from its retracted to its extended position at high speed and the puncture process therefore only lasts a very short time, the pain associated with taking blood is reduced again.

80 Another advantage is that the high penetration speed of the needle reduces the pressure required in the blood vessel to prevent the vessel walls from collapsing when the needle is inserted, which is usually achieved by applying a pressure cuff, thereby reducing the risk of extravascular bruising.

[0010]

87 The means with which the hollow needle can be displaced from its retracted into its extended position preferably have an arrangement which exerts an elastic force on the hollow needle acting in the direction of the retracted towards the extended position.

90 In order to carry out the puncture, the hollow needle is then first moved into its retracted position, held in this position by suitable means, for example a locking device, and after the device has been brought to the suitable point on the body, by releasing the means, for example the locking moved to its extended position, with the tip of the hollow needle penetrating the blood vessel.

[0011]

98 In terms of its design, the arrangement for generating the elastic force can have a compression spring.

[0012]

103 However, it is also possible to generate the elastic force with the help of a compressed air reservoir or in a completely different way.

[0013]

108 The pain associated with taking blood from the patient can be further reduced if the housing of the device includes at least one internal volume for receiving the blood taken from the patient.

110 As a result of this measure, a coupling of a vessel for receiving blood taken after the puncture has been made is superfluous, so that "shaking pains" are prevented.

[0014]

115 If existing, commercially available containers are to continue to be used, an embodiment of the device according to the invention is recommended in which the housing includes an adapter arrangement for connecting at least one commercially available container for receiving the blood taken.

119 With this configuration, depending on the requirements, either a plurality of containers can be connected to the adapter at the same time or--if this is not desired or possible--a plurality of containers can also be connected one after the other.

[0015]

125 The means for sucking the blood through the interior of the hollow needle preferably include a negative pressure in the at least one interior volume compared to the outside environment.

127 This negative pressure can be generated, for example, by the inner volume being pre-evacuated and the interior of the hollow needle communicating with the inner volume in its extended position, in other words: only when the hollow needle is in the extended position is its interior connected to the pre-evacuated inner volume.

[0016]

134 However, it is also possible to provide means that only generate the negative pressure when the hollow needle is moved from its retracted to its extended position, to provide a manually or automatically actuated piston/cylinder device, or to bring about the negative pressure in any other way.

[0017]

141 Irrespective of the manner in which the negative pressure for sucking the blood is brought about, there are considerable advantages for the application if the device is designed in such a way that the negative pressure is applied to the hollow needle when it penetrates the blood vessel.

145 This measure effectively prevents painful extravascular bruising (hematoma) as a result of taking blood, which is regularly the case when blood can escape past the hollow needle from the blood vessel into the adjacent tissue during blood taking.

148 Because the suction in this preferred embodiment of the invention already exists when the hollow needle enters the blood vessel, blood that would otherwise have gotten into the tissue is also sucked out, even if the opening of the hollow needle is not completely into the vessel has penetrated or partially exited the opposite vessel wall.

152 As a further consequence, in this embodiment the "penetration depth" of the tip of the hollow needle for carrying out the blood withdrawal method does not have to be specified as precisely as hitherto, which also makes it easier for the user to take the blood.

[0018]

158 For handling the device according to the invention, it is particularly advantageous to provide the side part of the housing from which the hollow needle protrudes in its extended position with at least one contact surface via which the device is supported on the body surface of a patient during use.

162 To carry out the removal process, the device then only needs to be placed on a suitable part of the body and the displacement process of the hollow needle started.

[0019]

167 Tests have shown that the blood sampling process can be carried out particularly reliably and with little pain if the at least one contact surface is designed in such a way that when the device is supported on the body surface of the patient, the hollow needle forms an angle of between 5° and 30° with respect to the body surface in the support area - depending on the thickness of the tissue located between the vessel wall through which the hollow needle is intended to penetrate and the support surface.

[0020]

176 The device according to the invention can be used particularly variably when the at least one contact surface is designed in such a way that the angle that the hollow needle forms with the body surface during the removal process can be adjusted.

[0021]

182 In order to prevent the blood vessel intended for the removal process from being pushed away to the side when the device is put on, in a particularly preferred embodiment of the device according to the invention a recess is provided in the at least one contact surface, into which the blood vessel can at least partially bulge and thus from is positioned on the lateral boundary surfaces of the recess.

[0022]

190 If blood from a patient is used to carry out various diagnostic or

191 Therapy method required, so it is advantageous to provide a plurality of internal volumes separated from one another or an adapter arrangement for connecting a plurality of containers for receiving blood taken.

[0023]

197 The inner volumes or the containers can then optionally communicate with one another in series or also in parallel.

[0024]

202 In the drawing, exemplary embodiments of the invention are shown schematically.

203 Show it:

[0025]

207 1 shows a detail and diagrammatic view of a first exemplary embodiment of a device according to the invention in a longitudinal section, with the hollow needle being in its retracted position;

[0026]

212 FIG. 2 shows the same embodiment in the same view as in FIG. 1, but with the hollow needle being in its extended position; FIG.

[0027]

217 FIG. 3--in a detail--the same exemplary embodiment as in FIG. 1 in a partially sectional plan view (view A in FIG. 1);

[0028]

222 FIG. 4 shows another embodiment of a device according to the invention in a view corresponding to FIG. 3;

[0029]

227 5--schematically and in detail--an exemplary embodiment corresponding to FIGS. 1 to 3 of a device according to the invention during a removal process in a view in the direction of the blood vessel used for blood removal;

[0030]

233 6 - schematically - different positions of the beveled end of the hollow needle relative to the position of the blood vessel;

[0031]

238 7 shows an embodiment of a device according to the invention, which comprises a plurality of volumes communicating with one another in series for receiving blood that has been taken (schematic);

[0032]

244 8 shows an embodiment of a device according to the invention in a view corresponding to FIG

[0033]

248 9 shows an embodiment of a device according to the invention in a view corresponding to FIGS. 7 and 8, which has an adapter plate for connecting two external containers for receiving blood that has been taken.

[0034]

254 The embodiment of a device according to the invention, denoted as 100 as a whole in FIGS. 1 to 3 and shown only partially and schematically in these figures, comprises a housing 1, which in its interior has two internal volumes 3, 4 fluidically connected to one another via a channel 2 for receiving blood.

258 The housing 1 has, on its end face 5 pointing downwards in FIG. 1, a housing extension 6, the end 7 of which shown at the bottom in FIG. 1 is open.

[0035]

263 The interior 8 of the housing extension 6 serves to accommodate a hollow needle arrangement designated as a whole by 9, which essentially consists of the actual hollow needle 10 directed towards the open end 7 and a hollow needle carrier 11 serving to slidably mount the hollow needle arrangement 9 in the interior 8 of the housing extension 6 , which cooperates with the inner lateral surface 12 of the housing extension 6 at least approximately in a sealing manner.

[0036]

271 With its end face 13 facing away from the hollow needle 10 , the hollow needle carrier 11 is supported on a rigid contact surface 15 of the housing 1 via a pretensioned spiral spring 14 .

[0037]

276 A locking device 16 is used to lock the hollow needle arrangement 9 against the compressive force of the coil spring 14 in the retracted position.

[0038]

281 The hollow needle arrangement 9 has an inner channel 18 which extends from the tip 19 of the hollow needle 10 to a lateral opening 20 in the hollow needle carrier 11 .

[0039]

286 Furthermore, in the side wall of the housing extension 6 shown on the right in FIG.

[0040]

290 To move the hollow needle 10 from its retracted position shown in FIG. 1 to its extended position shown in FIG. 2, the locking device 16 is moved in such a way that the contact surface 17 is released.

293 Due to the force exerted by the spiral spring 14 on the hollow needle arrangement 9, the latter snaps down according to FIG.

295 In this position, the inner channel 18 communicates with the channel 21 via the opening 22 so that the inner volumes 3 and 4 communicate with the inner channel 18 of the hollow needle and blood can flow through the channels 18, 21 and 2 into the inner volumes 3, 4.

[0041]

301 As can also be seen from FIG.

[0042]

305 As illustrated in FIG. 6, blood can only be taken if the hollow needle 10 penetrates just deep enough into the patient's tissue that its tip does not stop before penetrating the wall of the blood vessel B (see

308 6a)), nor does the area of the hollow needle 10 which is bevelled towards the tip 19 project completely through the blood vessel B (cf.

310 Fig. 6e)).

[0043]

314 In order to be able to adapt the "penetration depth" of the tip 19 of the hollow needle 10 required for blood sampling to the individual requirements, a cuff 24 is provided on the housing extension 6, which is displaceably mounted in the direction of arrow P, with which the effective length of the housing extension 6 and thus the penetration depth the tip 19 of the hollow needle 10 can be changed.

319 The cuff 24 and the housing extension 6 can be equipped with locking means, not shown in the drawing, with which the cuff 24 can be locked in three different basic positions in which the penetration depth is adapted to the conditions usual in children, normal-weight adults or overweight adults .

[0044]

326 Extravascular bruising is also effectively prevented in end positions of the hollow needle 10 in which the tip 19 has not fully penetrated the blood vessel B (Fig. 6b)) or has partially penetrated the opposite wall of the blood vessel B (Fig. 6d)), since the negative pressure for sucking out the blood is already applied to the hollow needle as soon as it has entered the vessel.

[0045]

334 In principle, it is possible for the hollow needle 10 to pierce the blood vessel B essentially perpendicularly to its course.

336 However, such a procedure presupposes that the "penetration depth" must be predetermined almost exactly.

338 In order to avoid this, it is advisable to take the sample at an angle α between the hollow needle 10 and the blood vessel B, which is in the range between 5° and 30°.

340 For this purpose, the exemplary embodiment of the invention shown in FIGS. 1 and 2 has contact surfaces 25, through which the desired angle α is specified.

342 In the exemplary embodiments shown in the drawing, the angle α is fixed.

343 However, it is also within the scope of the invention to design the contact surfaces so variably that the angle α can be changed depending on the intended use of the device.

[0046]

348 As already described and shown again in detail in FIG. 1, a spiral spring 14 can be used to generate the force that drives the hollow needle arrangement from its retracted into its extended position.

351 However, as shown schematically in FIG. 4, it is also possible to provide a compressed air reservoir 26 between the end face 13 and the contact surface 15 or other means suitable for effecting an elastic force for propulsion.

[0047]

357 In order to prevent the vessel from which blood is to be taken from migrating laterally when the device 100 is placed on and the removal process thereby being frustrated, in a preferred embodiment of the invention a recess 27 is provided in the contact surfaces, into which the blood vessel B after the device 100 has been placed on the skin, it is at least partially pressed in and the blood vessel B is thus fixed laterally in the position required for taking blood (see Fig.

363 5).

[0048]

367 As illustrated in FIGS. 7 to 9, devices 100 according to the invention can be equipped in different ways with volumes for taking up blood that has been taken.

369 Thus, several volumes 28, 29, 30--three in FIG.

[0049]

373 It is also possible, as shown in FIG. 8, to provide inner volumes 31, 32, 33 which are arranged

parallel to one another and are correspondingly filled approximately at the same time as one another.

[0050]

379 To generate the negative pressure required for filling, the volumes 28 to 33 can be pre-evacuated, or the negative pressure required in them can take place in any other way, for example by connecting the volumes to a piston/cylinder unit, an external pump, etc.

382 In order to avoid extravascular bruising, it is only essential that the negative pressure has already been generated when the tip 19 of the hollow needle 10 penetrates into the vessel.

[0051]

387 In the exemplary embodiment shown in FIG. 9, the volumes 34, 35 provided for receiving the blood removed are arranged externally and designed as piston/cylinder units 36/37 in such a way that the pistons 36 can be displaced into the cylinder 37 by manually operable piston rods 38 .

391 To attach the piston/cylinder unit 36/37 to this device, which is designated as a whole by 200, an adapter arrangement 39 is used, from which the housing extension 206 in turn extends downward according to FIG.

394 The hollow needle arrangement 209 and the channels 202 correspond in their technical design and function to the hollow needle arrangement 9 and the channels 2 as they are described with reference to FIGS. 1 to 3 and therefore do not require any special discussion at this point.

397 Reference List

[0052]

401 The blood is taken in the device according to FIG. 9 in a manner already described with reference to FIGS. 1 to 3, whereby by pulling out the piston rods 38 into the position shown in FIG Cylinder 37 are held against the action of the negative pressure created prior to the needle propelling and penetrating the blood vessel.

1

408 Housing2 Channel3 Internal volume4 Internal volume5 Front side6 Housing extension7 End8 Interior9 Hollow needle arrangement10 Hollow needle11 Hollow needle carrier12 Inner lateral surface13 Front side14 Spiral spring15 Contact surface .16 Locking device17 Contact surface18 Inner channel19 Tip20 Opening21 Channel22 End23 Stop24 Cuff25 Contact surface26 Compressed air reservoir27 Recess28 Volume29 Volume30 Volume31 Volume32 Volume33 Volume34 volume 35 volume 36 piston 37 cylinder 38 piston rod 39 adapter assembly 40 locking projections 100 device 206 housing extension 209 hollow needle assembly 202 channels H skin B Blood vessel A view P arrow

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CLAIMS DE10038026A1

1.

13 Device for taking blood from a blood vessel (B), with a housing (1), with a hollow needle (10) that can be inserted through the blood vessel wall into the interior of the blood vessel (B), and with means for sucking the blood through the interior of the hollow needle, characterized in that the hollow needle (10) moves between a retracted position, in which the hollow needle (10) remains at least substantially within the outer contours of the housing, and an extended position, in which the end (19) to be inserted into the blood vessel (B) the hollow needle (10) protrudes from the housing by a length, and in that means are provided with which the hollow needle (10) can be displaced from its retracted to its extended position.

2.

24 Device according to Claim 1, characterized in that the means for displacing the hollow needle (10) from its retracted to its extended position comprise an arrangement which acts on the hollow needle (10) in a direction from the retracted to the extended position exert an acting elastic force.

3.

31 Device according to Claim 2, characterized in that the arrangement has a compression spring (14).

4.

36 Device according to Claim 2 or 3, characterized in that the arrangement has a compressed air reservoir (26).

5.

41 Device according to one of Claims 1 to 4, characterized in that the housing (1) comprises at least one internal volume (3, 4, 28-35) for receiving blood which has been removed.

6.

46 Device according to one of Claims 1 to 4, characterized in that the housing (1) comprises an adapter arrangement (39) for the connection of at least one container, the internal volume (34, 35) of which is used to hold the blood taken.

7.

52 Device according to Claim 5 or 6, characterized in that the means for sucking the blood through the interior of the hollow needles (10) comprise a negative pressure in the at least one interior volume (3, 4, 28-35) compared to the external environment.

8.

58 Device according to Claim 7, characterized in that the inner volume (3, 4, 28-35) is pre-evacuated and that the interior of the hollow needle (10) communicates with the inner volume (3, 4, 28-35) in its extended position.

9.

64 Device according to Claim 7, characterized in that means are provided which generate the negative pressure in the inner volume (3, 4, 28-35) when the hollow needle (10) is moved from its retracted to its extended position.

10.

70 Device according to Claim 9, characterized in that means for generating the negative pressure are a piston arrangement which is connected to the hollow needle (10) and which generates a negative pressure in a cylinder arrangement when the hollow needle (10) is moved into its extended position, and means which, in the extended Position of the hollow needle (10) connects the interior of the cylinder with the interior volume (3, 4, 28-35) for receiving the blood.

11.

78 Device according to one of Claims 1 to 10, characterized in that the side part of the housing (1) from which the hollow needle (10) protrudes in its extended position has at least one contact

surface (25) for supporting the device during use on the body surface of a patient.

12.

84 Device according to Claim 11, characterized in that the at least one contact surface (25) is designed in such a way that when the device is supported on the body surface of the patient, the hollow needle (10) forms an angle α to the body surface in the support area in the range between 5° and 30° includes.

13.

91 Device according to Claim 12, characterized in that the at least one contact surface (25) is designed such that the angle α between the hollow needle (10) and the body surface when the device is supported on the patient's body surface is adjustable.

14.

97 Device according to one of Claims 11 to 13, characterized in that the contact surface (25) has at least one recess (27) for fixing the blood vessel (B) used for taking blood.

15.

102 Device according to one of Claims 1 to 14, characterized in that the device comprises a plurality of separate inner volumes (3, 4, 28-33) for receiving the blood taken or an adapter arrangement (39) for connecting several containers for receiving blood taken includes.

16.

108 Device according to Claim 15, characterized in that the internal volumes (28, 29, 30) or the containers communicate with one another in series.

17.

113 Device according to Claim 15, characterized in that the inner volumes (31, 32, 33) or the containers communicate with one another in parallel.

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENT- UND MARKENAMT

(12) **Offenlegungsschrift**

(10) **DE 100 38 026 A 1**

(51) Int. Cl.[7]:
A 61 B 5/15
A 61 M 1/00

(21) Aktenzeichen: 100 38 026.3
(22) Anmeldetag: 2. 8. 2000
(43) Offenlegungstag: 22. 2. 2001

DE 100 38 026 A 1

(66) Innere Priorität:
299 13 417. 2 06. 08. 1999

(71) Anmelder:
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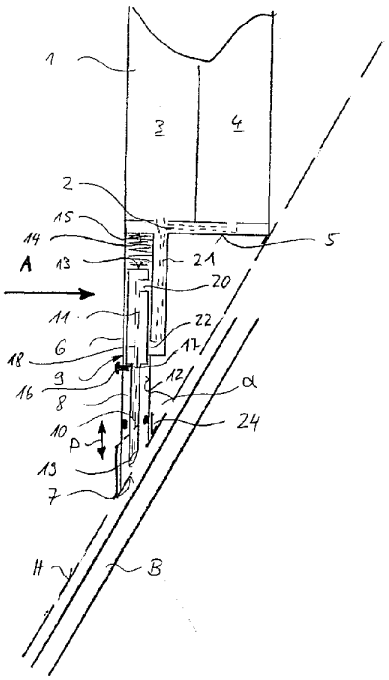
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Erfinder wird später genannt werden

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) Vorrichtung zur Entnahme von Blut aus einem Blutgefäß

(57) Die Vorrichtung umfaßt ein Gehäuse mit einer durch die Blutgefäßwandung ins Innere des Blutgefäßes einführbaren Hohlnadel und Mittel zum Saugen des Blutes durch das Innere der Hohlnadel.
Zwecks Blutentnahme aus einem Blutgefäß in für den Patienten weniger schmerzhafter Weise ist die Hohlnadel zwischen einer zurückgezogenen Position, in der die Hohlnadel zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß einführende Ende der Hohlnadel aus dem Gehäuse um eine Länge hervorragt, verlagerbar angeordnet. Ferner sind Mittel vorgesehen, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist.



DE 100 38 026 A 1

Beschreibung

Die Erfindung bezieht sich auf eine Vorrichtung zur Entnahme von Blut aus einem Blutgefäß der dem Oberbegriff des Anspruchs 1 entsprechenden Art.

Derartige Vorrichtungen umfassen stets eine zur Durchdringung der Haut, des zwischen Haut und Gefäß liegenden Gewebes sowie der Gefäßwandung einenends angeschrägte Hohlnadel, die an ihrem anderen Ende meist mit einer Kupplung ausgestattet ist, welche dem Ansetzen eines ein Volumen zur Aufnahme des entnommenen Blutes aufweisenden Behälters dient.

Zur Erzeugung des zur Blutentnahme erforderlichen Soges ist es bekannt, die Behältnisse als Kolben/Zylinderanordnung auszugestalten, wobei nach erfolgtem Einstich der Hohlnadel in das Blutgefäß und Ankuppeln des Behältnisses der Kolben manuell im Sinne einer Vergrößerung des Gefäßvolumens betätigt wird.

Nachteilig ist bei dieser Vorrichtung, daß ein für den Patienten nahezu schmerzloses Einstechen der Hohlnadel in das Blutgefäß nur bei erheblichem Geschick und erheblicher Übung der den Einstich vornehmenden Person möglich ist. Weiterhin kann bei manueller Betätigung des Kolbens die Nadel in der Regel nicht vollständig ruhig gehalten werden, was dazu führt, daß die Nadel im Einstechbereich die Haut, das darunter liegende Gewebe und die Gefäßwandung dehnt oder sogar verletzt, was regelmäßig zu Schmerzbeeinträchtigungen des Patienten führt.

Aus letzterem Grunde ist es ebenfalls bekannt, die das Volumen zur Aufnahme des entnommenen Blutes aufweisenden Gefäße vorzuevakuieren und in ihrem mit der Kupplung der Hohlnadel zu verbindenden Bereich mit einer Verschluß- bzw. Ventilanordnung auszustatten, die beim Ankuppeln an die Hohlnadel geöffnet wird, so daß das zu entnehmende Blut in das Volumen des Behältnisses eingesaugt wird, ohne daß es hierzu einer zusätzlichen manuellen Betätigung der Vorrichtung bedarf.

Durch diese Maßnahme wird die Gefahr, durch die manuelle Betätigung des Kolbens hervorgerufener "Wackelschmerzen" zwar verhindert, nachteilig ist jedoch, daß das Einstechen der Hohlnadel, das anschließende Ankuppeln des vorevakuierten Gefäßes und das in häufigen Fällen notwendige Auswechseln eines vollen gegen einen leeren Behälter zur Aufnahme des entnommenen Blutes wiederum zu unerwünschten, für den Patienten schmerzhaften Bewegungen der Nadel führt.

Es ist daher die Aufgabe der Erfindung, eine Vorrichtung zu schaffen, welche eine Blutentnahme aus einem Blutgefäß in für den Patienten weniger schmerzhafter Weise ermöglicht.

Diese Aufgabe wird durch die in Anspruch 1 wiedergegebene Erfindung gelöst.

Dadurch, daß bei der erfindungsgemäßen Vorrichtung die Hohlnadel zwischen einer zurückgezogenen Position, in der die Hohlnadel zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses der Vorrichtung verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß einzuführende Ende der Hohlnadel aus dem Gehäuse um eine bestimmte Länge hervorragt, verlagerbar angeordnet ist, und daß Mittel vorgesehen sind, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, ist es zum Einstechen der Nadel nicht mehr erforderlich, daß während des Einstechvorganges sowohl die Führung, als auch die Verlagerung der Nadel von der die Blutabnahme durchführenden Person bewerkstelligt werden muß. Vielmehr braucht das Gehäuse lediglich an der Stelle des Körpers, an der die Blutabnahme erfolgen soll, positioniert und anschließend die Mittel zum Ausfahren der Nadel

aktiviert zu werden. Die Gefahr des "Wackelns" während des Einstiches der Hohlnadel ist daher erheblich verringert. Da zudem die Mittel zur Verlagerung der Hohlnadel derart ausgebildet sein können, daß diese mit hoher Geschwindigkeit aus ihrer zurückgezogenen in ihre ausgefahrene Position erfolgt und damit der Einstichvorgang nur eine sehr kurze Zeit dauert, ist der mit der Blutentnahme verbundene Schmerz abermals reduziert. Weiterhin ist vorteilhaft, daß durch die hohe Eindringgeschwindigkeit der Nadel der in dem Blutgefäß zum Verhindern des Kollabierens der Gefäßwandungen beim Einstechen der Nadel erforderliche Druck der meist durch Anlegen einer Druckmanschette bewerkstelligt wird, verringert ist, wodurch das Risiko paravasaler Blutergüsse reduziert ist.

Die Mittel, mit denen die Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, weisen vorzugsweise eine Anordnung auf, die auf die Hohlnadel eine in Richtung der zurückgezogenen auf die ausgefahrene Position wirkende, elastische Kraft ausüben. Zur Durchführung des Einstiches wird die Hohlnadel dann zunächst in ihre zurückgezogene Position verlagert, in dieser durch geeignete Mittel, beispielsweise einer Verriegelungseinrichtung, gehalten, und, nachdem die Vorrichtung an die geeignete Stelle des Körpers gebracht wurde, durch Lösen der Mittel, beispielsweise der Verriegelung, in ihre ausgefahrene Position gebracht, wobei die Spitze der Hohlnadel in das Blutgefäß eindringt.

In ihrer konstruktiven Ausgestaltung kann die Anordnung zur Erzeugung der elastischen Kraft eine Druckfeder aufweisen.

Es ist jedoch ebenfalls möglich, die elastische Kraft mit Hilfe eines Druckluftreservoirs oder auch in einer gänzlich anderen Weise zu erzeugen.

Der mit der Blutentnahme für den Patienten verbundene Schmerz kann nochmals verringert werden, wenn das Gehäuse der Vorrichtung mindestens ein Innenvolumen zur Aufnahme des dem Patienten entnommenen Blutes umfaßt. Durch diese Maßnahme wird ein Ankuppeln eines Gefäßes zur Aufnahme entnommenen Blutes nach erfolgtem Einstich überflüssig, so daß "Wackelschmerzen" verhindert werden.

Sollen bereits vorhandene, handelsübliche Behälter weiterhin Verwendung finden, so empfiehlt sich eine Ausführungsform der erfindungsgemäßen Vorrichtung, bei der das Gehäuse eine Adapteranordnung zum Anschluß mindestens eines handelsüblichen Behälters zur Aufnahme entnommenen Blutes umfaßt. Durch diese Ausgestaltung können an den Adapter je nach Anforderungen entweder mehrere Behälter gleichzeitig, oder – falls dies nicht erwünscht oder möglich ist – auch mehrere Behälter nacheinander angeschlossen werden.

Die Mittel zum Saugen des Blutes durch das Innere der Hohlnadel umfassen vorzugsweise einen Unterdruck in dem mindestens einen Innenvolumen gegenüber der äußeren Umgebung. Dieser Unterdruck kann beispielsweise dadurch erzeugt werden, daß das Innenvolumen vorevakuiert ist und das Innere der Hohlnadel in ihrer ausgefahrenen Position mit dem Innenvolumen kommuniziert, mit anderen Worten: daß erst in der ausgefahrenen Position der Hohlnadel die Verbindung deren Inneren mit dem vorevakuierten Innenvolumen erfolgt.

Es ist jedoch ebenfalls möglich, Mittel vorzusehen, die den Unterdruck erst beim Verlagern der Hohlnadel aus ihrer zurückgezogenen in ihre ausgefahrene Position erzeugen, eine manuell oder automatisch betätigbare Kolben/Zylindereinrichtung vorzusehen oder den Unterdruck auf eine beliebige andere Weise zu bewerkstelligen.

Unabhängig davon, auf welche Weise der Unterdruck

zum Saugen des Blutes bewirkt wird, ergeben sich für die Anwendung erhebliche Vorteile, wenn die Vorrichtung derart ausgebildet ist, daß der Unterdruck an der Hohlnadel anliegt, wenn diese in das Blutgefäß eindringt. Durch diese Maßnahme wird nämlich wirkungsvoll verhindert, daß infolge der Blutentnahme schmerzhafte paravasale Blutergüsse (Hämatome) entstehen, was regelmäßig dann der Fall ist, wenn während der Blutentnahme Blut an der Hohlnadel vorbei aus dem Blutgefäß in das angrenzende Gewebe austreten kann. Dadurch, daß der Sog bei dieser bevorzugten Ausführungsform der Erfindung bereits beim Eindringen der Hohlnadel in das Blutgefäß besteht, wird auch Blut, was ansonsten in das Gewebe gelangt wäre, abgesaugt, und zwar selbst dann, wenn die Öffnung der Hohlnadel nicht vollständig in das Gefäß eingedrungen oder teilweise aus der gegenüberliegenden Gefäßwandung wieder ausgetreten ist. Als weitere Folge muß bei dieser Ausführungsform die "Eindringtiefe" der Spitze der Hohlnadel zur Durchführung des Blutentnahmeverfahrens nicht so exakt wie bislang vorgegeben werden, was die Blutentnahme auch dem Anwendungspersonal erleichtert.

Für die Handhabung der erfindungsgemäßen Vorrichtung ist es besonders vorteilhaft, das Seitenteil des Gehäuses, aus dem die Hohlnadel in ihrer ausgefahrenen Position herausragt, mit mindestens einer Anlagefläche zu versehen, über die sich die Vorrichtung während ihrer Verwendung auf der Körperoberfläche eines Patienten abstützt. Die Vorrichtung braucht zur Durchführung des Entnahmevorganges dann lediglich auf eine geeignete Körperstelle aufgesetzt und der Verlagervorgang der Hohlnadel in Gang gesetzt zu werden.

Versuche haben gezeigt, daß der Blutentnahmevorgang besonders zuverlässig und schmerzarm durchgeführt werden kann, wenn die mindestens eine Anlagefläche derart ausgestaltet ist, daß bei Abstützung der Vorrichtung auf der Körperoberfläche des Patienten die Hohlnadel zur Körperoberfläche im Abstützbereich einen Winkel im Bereich zwischen 5° und 30° – je nach Dicke des zwischen der Gefäßwandung, die die Hohlnadel durchdringen soll, und der Abstützfläche befindlichen Gewebes – einschließt.

Besonders variabel einsetzbar ist die erfindungsgemäße Vorrichtung dann, wenn die mindestens eine Anlagefläche derart ausgestaltet ist, daß der Winkel, den die Hohlnadel mit der Körperoberfläche während des Entnahmevorgangs einschließt, einstellbar ist.

Um zu verhindern, daß das jeweils für den Entnahmevorgang vorgesehene Blutgefäß beim Aufsetzen der Vorrichtung seitlich weggedrückt wird, ist bei einer besonders bevorzugten Ausführungsform der erfindungsgemäßen Vorrichtung eine Aussparung in der mindestens einen Anlagefläche vorgesehen, in die das Blutgefäß sich zumindest teilweise hereinwölben kann und somit von den seitlichen Begrenzungsflächen der Aussparung positioniert wird.

Wird Blut eines Patienten zur Durchführung verschiedener Diagnose- bzw. Therapieverfahren benötigt, so ist es von Vorteil, eine Mehrzahl voneinander getrennter Innenvolumina oder eine Adapteranordnung zum Anschluß mehrerer Behälter zur Aufnahme entnommenen Blutes vorzusehen.

Die Innenvolumina oder die Behälter können dann wahlweise seriell oder auch parallel miteinander kommunizieren.

In der Zeichnung sind Ausführungsbeispiele der Erfindung schematisch dargestellt. Es zeigen:

Fig. 1 – ausschnittsweise und schematisch – ein erstes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung in einem Längsschnitt, wobei sich die Hohlnadel in ihrer zurückgezogenen Position befindet;

Fig. 2 dasselbe Ausführungsbeispiel in derselben Ansicht wie in **Fig.** 1, wobei sich jedoch die Hohlnadel in ihrer ausgefahrenen Position befindet;

Fig. 3 – ausschnittsweise – dasselbe Ausführungsbeispiel wie in **Fig.** 1 in einer teilgeschnittenen Aufsicht (Ansicht A in **Fig.** 1);

Fig. 4 ein anderes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung in einer **Fig.** 3 entsprechenden Ansicht;

Fig. 5 – schematisch und ausschnittsweise – ein **Fig.** 1 bis 3 entsprechendes Ausführungsbeispiel einer erfindungsgemäßen Vorrichtung während eines Entnahmevorganges in einer Ansicht in Richtung des der Blutentnahme dienenden Blutgefäßes;

Fig. 6 – schematisch – verschiedene Positionen des abgeschrägten Endes der Hohlnadel relativ zur Lage des Blutgefäßes;

Fig. 7 eine Ausführungsform einer erfindungsgemäßen Vorrichtung, die mehrere seriell miteinander kommunizierende Volumina zur Aufnahme entnommenen Blutes umfaßt (schematisch);

Fig. 8 eine Ausführungsform einer erfindungsgemäßen Vorrichtung in einer **Fig.** 7 entsprechenden Ansicht, die mehrere parallel miteinander kommunizierende Innenvolumina zur Aufnahme entnommenen Blutes umfaßt sowie

Fig. 9 eine Ausführungsform einer erfindungsgemäßen Vorrichtung in einer **Fig.** 7 und 8 entsprechenden Ansicht, welche eine Adapterplatte zum Anschluß zweier externer Behältnisse zur Aufnahme entnommenen Bluts aufweist.

Die in den **Fig.** 1 bis 3 als Ganzes mit **100** bezeichnete, in diesen Figuren lediglich ausschnittsweise und schematisch dargestellte Ausführungsform einer erfindungsgemäßen Vorrichtung umfaßt ein Gehäuse **1**, welches in seinem Inneren zwei fluidisch über einen Kanal **2** miteinander verbundene Innenvolumina **3**, **4** zur Aufnahme entnommenen Blutes aufweist. Das Gehäuse **1** weist an seinen **Fig.** 1 nach unten weisenden Stirnseite **5** einen Gehäusefortsatz **6** auf, dessen in **Fig.** 1 unten dargestelltes Ende **7** offen ausgebildet ist.

Das Innere **8** des Gehäusefortsatzes **6** dient der Aufnahme einer als Ganzes mit 9 bezeichneten Hohlnadelanordnung, die im wesentlichen aus der zum offenen Ende **7** hin gerichteten eigentlichen Hohlnadel **10** und einem der verschiebbaren Lagerung der Hohlnadelanordnung **9** in dem Inneren **8** des Gehäusefortsatzes **6** dienenden Hohlnadelträger **11** besteht, der mit der inneren Mantelfläche **12** des Gehäusefortsatzes **6** zumindest annähernd abdichtend zusammenwirkt.

Mit seiner der Hohlnadel **10** abgewandten Stirnseite **13** stützt sich der Hohlnadelträger **11** über eine vorgespannte Spiralfeder **14** an einer starren Anlagefläche **15** des Gehäuses **1** ab.

Der Arretierung der Hohlnadelanordnung **9** gegen die Druckkraft der Spiralfeder **14** in der zurückgezogenen Position dient eine Arretiereinrichtung **16**, die in der zurückgezogenen Position der Hohlnadelanordnung **9** eine der Stirnseite **13** gegenüberliegende Anlagefläche **17** hintergreift.

Die Hohlnadelanordnung **9** weist einen Innenkanal **18** auf, der sich von der Spitze **19** der Hohlnadel **10** bis zu einer seitlichen Öffnung **20** des Hohlnadelträgers **11** erstreckt.

Ferner ist in der in **Fig.** 1 rechts dargestellten Seitenwandung des Gehäusefortsatzes **6** ein einenends in den Kanal **2** mündender Kanal **21** vorgesehen, dessen anderes Ende **22** in das Innere **8** des Gehäusefortsatzes **6** mündet.

Zur Verlagerung der Hohlnadel **10** aus ihrer in **Fig.** 1 dargestellten, zurückgezogenen Position in ihre in **Fig.** 2 dargestellte, ausgefahrene Position wird die Arretiereinrichtung **16** derart verlagert, daß die Anlagefläche **17** freigegeben wird. Durch die von der Spiralfeder **14** auf die Hohlnadelanordnung **9** ausgeübte Kraft schnellt letztere gemäß **Fig.** 2 nach unten, bis die Anlagefläche **17** an einem von der inneren Mantelfläche **12** nach innen ragenden Anschlag **23** anliegt und hierdurch der Verlagerungsweg begrenzt wird. In

dieser Position kommuniziert der Innenkanal **18** über die Öffnung **22** mit dem Kanal **21**, so daß die Innenvolumina **3** und **4** mit dem Innenkanal **18** der Hohlnadel kommunizieren und Blut durch die Kanäle **18**, **21** und **2** in die Innenvolumina **3**, **4** einströmen kann.

Wie ferner aus **Fig.** 2 ersichtlich ist, hat die Hohlnadel **10** mit ihrer Spitze **19** die Haut H im Bereich der Stelle, an der die Hohlnadel **10** in das Blutgefäß B eindringen soll, sowie eine Wandung des Blutgefäßes B durchsetzt.

Wie **Fig.** 6 veranschaulicht, ist eine Blutentnahme nur dann möglich, wenn die Hohlnadel **10** gerade so tief in das Gewebe des Patienten eindringt, daß ihre Spitze weder vor dem Durchdringen der Wandung des Blutgefäßes B zum Stillstand kommt (s. **Fig.** 6a)), noch der zur Spitze **19** hin angeschrägte Bereich der Hohlnadel **10** vollständig durch das Blutgefäß B hindurchragt (vgl. **Fig.** 6e)).

Um die zur Blutentnahme erforderliche "Eindringtiefe" der Spitze **19** der Hohlnadel **10** den individuellen Anforderungen anpassen zu können, ist an dem Gehäusefortsatz **6** eine in Richtung des Pfeiles P verschiebbar gelagerte Manschette **24** vorgesehen, mit der die wirksame Länge des Gehäusefortsatzes **6** und somit die Eindringtiefe der Spitze **19** der Hohlnadel **10** veränderbar ist. Die Manschette **24** und der Gehäusefortsatz **6** können mit in der Zeichnung nicht dargestellten Rastmitteln ausgestattet sein, mit denen sich die Manschette **24** in drei verschiedenen Grundstellungen arretieren läßt, bei denen die Eindringtiefe an die bei Kindern, normalgewichtigen Erwachsenen bzw. übergewichtigen Erwachsenen üblichen Verhältnisse angepaßt ist.

Paravasale Blutergüsse werden auch bei Endpositionen der Hohlnadel **10**, in denen die Spitze **19** nicht vollständig in das Blutgefäß B eingedrungen ist (**Fig.** 6b)) oder die gegenüberliegende Wandung des Blutgefäßes B teilweise durchdrungen hat (**Fig.** 6d)), wirksam verhindert, da der Unterdruck zum Absaugen des Blutes an der Hohlnadel bereits anliegt, sobald diese in das Gefäß eingedrungen ist.

Prinzipiell ist es zwar möglich, den Einstich der Hohlnadel **10** in das Blutgefäß B im wesentlichen senkrecht zu dessen Verlauf vorzunehmen. Eine derartige Vorgehensweise setzt jedoch voraus, daß die "Eindringtiefe" nahezu exakt vorbestimmt werden muß. Um dies zu vermeiden, empfiehlt es sich, die Entnahme unter einem Winkel α zwischen der Hohlnadel **10** und dem Blutgefäß B vorzunehmen, der im Bereich zwischen 5° und 30° liegt. Hierzu weist das in den **Fig.** 1 und 2 dargestellte Ausführungsbeispiel der Erfindung Anlageflächen **25** auf, durch die der gewünschte Winkel α vorgegeben ist. Bei den in der Zeichnung dargestellten Ausführungsbeispielen ist der Winkel α fest eingestellt. Es liegt jedoch ebenfalls im Rahmen der Erfindung, die Anlageflächen derart variabel auszugestalten, daß der Winkel α je nach vorgesehener Anwendungsweise der Vorrichtung veränderbar ist.

Wie bereits beschrieben und in **Fig.** 1 nochmals im einzelnen dargestellt, kann der Erzeugung der die Hohlnadelanordnung aus ihrer zurückgezogenen in ihre ausgefahrene Position vortreibenden Kraft eine Spiralfeder **14** dienen. Es ist – wie in **Fig.** 4 schematisch dargestellt – jedoch ebenfalls möglich, zum Vortrieb ein Druckluftreservoir **26** zwischen der Stirnseite **13** und der Anlagefläche **15** oder andere zur Bewirkung einer elastischen Kraft geeignete Mittel vorzusehen.

Um zu verhindern, daß das Gefäß, aus dem Blut entnommen werden soll, beim Aufsetzen der Vorrichtung **100** seitlich auswandert und der Entnahmevorgang hierdurch vereitelt wird, ist bei einer bevorzugten Ausführungsform der Erfindung in den Anlageflächen eine Aussparung **27** vorgesehen, in die sich das Blutgefäß B nach dem Aufsetzen der Vorrichtung **100** auf die Haut zumindest teilweise eindrückt und somit das Blutgefäß B seitlich in der für die Blutentnahme erforderlichen Position fixiert wird (s. **Fig.** 5).

Wie in den **Fig.** 7 bis 9 verdeutlicht, können erfindungsgemäße Vorrichtungen **100** in unterschiedlicher Weise mit Volumina zur Aufnahme entnommenen Blutes ausgestattet sein. So können mehrere – in **Fig.** 7 drei – Volumina **28**, **29**, **30** in dem Gehäuse **1** vorgesehen sein, die seriell miteinander kommunizieren und somit während des Entnahmevorganges nacheinander mit Blut gefüllt werden.

Ferner ist es möglich, wie in **Fig.** 8 dargestellt, parallel zueinander angeordnete Innenvolumina **31**, **32**, **33** vorzusehen, die dementsprechend etwa zeitparallel zueinander aufgefüllt werden.

Zur Erzeugung des zum Auffüllen erforderlichen Unterdrucks können die Volumina **28** bis **33** vorevakuiert sein, oder der in selbigen erforderliche Unterdruck kann auf eine beliebige andere Weise, beispielsweise durch Verbindung der Volumina mit einer Kolben/Zylindereinheit, einer externen Pumpe usw. erfolgen. Zur Vermeidung paravasaler Blutergüsse ist es lediglich wesentlich, daß der Unterdruck bereits erzeugt ist, wenn die Spitze **19** der Hohlnadel **10** in das Gefäß eindringt.

Bei dem in **Fig.** 9 dargestellten Ausführungsbeispiel sind die zur Aufnahme des entnommenen Blutes vorgesehenen Volumina **34**, **35** extern angeordnet und als Kolben/Zylindereinheiten **36/37** ausgebildet und zwar derart, daß die Kolben **36** durch manuell betätigbare Kolbenstangen **38** in den Zylinder **37** verlagerbar sind. Zur Anbringung der Kolben/Zylindereinheit **36/37** an dieser als Ganzes mit **200** bezeichneten Vorrichtung dient eine Adapteranordnung **39**, von der aus sich gemäß **Fig.** 9 wiederum nach unten der Gehäusefortsatz **206** erstreckt. Die Hohlnadelanordnung **209** und die Kanäle **202** entsprechen in ihrer technischen Ausgestaltung und Funktion der Hohlnadelanordnung **9** und den Kanälen **2**, so wie sie anhand der **Fig.** 1 bis 3 beschrieben sind und bedürfen daher an dieser Stelle keiner besonderen Erörterung.

Die Blutentnahme bei der Vorrichtung gemäß **Fig.** 9 erfolgt in einer anhand von **Fig.** 1 bis 3 bereits beschriebenen Weise, wobei durch Herausziehen der Kolbenstangen **38** in die in **Fig.** 9 dargestellte Position, in der die Kolben **36** durch Arretiervorsprünge **40** an der Innenwandung des Zylinders **37** gegen die Wirkung des Unterdrucks gehalten werden, selbiger vor dem Vorschnellen der Nadel und Eindringen in das Blutgefäß erzeugt wird.

Bezugszeichenliste

1 Gehäuse
2 Kanal
3 Innenvolumen
4 Innenvolumen
5 Stirnseite
6 Gehäusefortsatz
7 Ende
8 Inneres
9 Hohlnadelanordnung
10 Hohlnadel
11 Hohlnadelträger
12 innere Mantelfläche
13 Stirnseite
14 Spiralfeder
15 Anlagefläche
16 Arretiereinrichtung
17 Anlagefläche
18 Innenkanal
19 Spitze
20 Öffnung

21 Kanal
22 Ende
23 Anschlag
24 Manschette
25 Anlagefläche
26 Druckluftreservoir
27 Aussparung
28 Volumen
29 Volumen
30 Volumen
31 Volumen
32 Volumen
33 Volumen
34 Volumen
35 Volumen
36 Kolben
37 Zylinder
38 Kolbenstangen
39 Adapteranordnung
40 Arretiervorsprünge
100 Vorrichtung
206 Gehäusefortsatz
209 Hohlnadelanordnung
202 Kanäle
H Haut
B Blutgefäß
A Ansicht
P Pfeil

Patentansprüche

1. Vorrichtung zur Entnahme von Blut aus einem Blutgefäß (B),
mit einem Gehäuse (**1**),
mit einer durch die Blutgefäßwandung ins Innere des Blutgefäßes (B) einführbaren Hohlnadel (**10**),
und mit Mitteln zum Saugen des Bluts durch das Innere der Hohlnadel, **dadurch gekennzeichnet**,
daß die Hohlnadel (**10**) zwischen einer zurückgezogenen Position, in der die Hohlnadel (**10**) zumindest im wesentlichen innerhalb der Außenkonturen des Gehäuses verbleibt, und einer ausgefahrenen Position, in der das in das Blutgefäß (B) einzuführende Ende (**19**) der Hohlnadel (**10**) aus dem Gehäuse um eine Länge hervorragt, verlagerbar angeordnet ist, und
daß Mittel vorgesehen sind, mit denen die Hohlnadel (**10**) aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß die Mittel, mit denen die Hohlnadel (**10**) aus ihrer zurückgezogenen in ihre ausgefahrene Position verlagerbar ist, eine Anordnung umfassen, die auf die Hohlnadel (**10**) eine in Richtung von der zurückgezogenen auf die ausgefahrene Position wirkende, elastische Kraft ausüben.

3. Vorrichtung nach Anspruch 2, dadurch gekennzeichnet, daß die Anordnung eine Druckfeder (**14**) aufweist.

4. Vorrichtung nach Anspruch 2 oder 3, dadurch gekennzeichnet, daß die Anordnung ein Druckluftreservoir (**26**) aufweist.

5. Vorrichtung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Gehäuse (**1**) mindestens ein Innenvolumen (**3**, **4**, **28–35**) zur Aufnahme entnommenen Blutes umfaßt.

6. Vorrichtung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Gehäuse (**1**) eine Adapteranordnung (**39**) zum Anschluß mindestens eines Behälters umfaßt, dessen Innenvolumen (**34**, **35**) zur Aufnahme von entnommenem Blut dient.

7. Vorrichtung nach Anspruch 5 oder 6, dadurch gekennzeichnet, daß die Mittel zum Saugen des Blutes durch das Innere der Hohlnadeln (**10**) einen Unterdruck in dem mindestens einen Innenvolumen (**3**, **4**, **28–35**) gegenüber der äußeren Umgebung umfassen.

8. Vorrichtung nach Anspruch 7, dadurch gekennzeichnet, daß das Innenvolumen (**3**, **4**, **28–35**) vorevakuiert ist und daß das Innere der Hohlnadel (**10**) in ihrer ausgefahrenen Position mit dem Innenvolumen (**3**, **4**, **28–35**) kommuniziert.

9. Vorrichtung nach Anspruch 7, dadurch gekennzeichnet, daß Mittel vorgesehen sind, die beim Verlagern der Hohlnadel (**10**) aus ihrer zurückgezogenen in ihre ausgefahrene Position den Unterdruck in dem Innenvolumen (**3**, **4**, **28–35**) erzeugen.

10. Vorrichtung nach Anspruch 9, dadurch gekennzeichnet, daß Mittel zur Erzeugung des Unterdrucks eine mit der Hohlnadel (**10**) verbundene Kolbenanordnung, die beim Verlagern der Hohlnadel (**10**) in ihre ausgefahrene Position in einer Zylinderanordnung einen Unterdruck erzeugt, und Mittel, die in der ausgefahrenen Position der Hohlnadel (**10**) das Innere des Zylinders mit dem Innenvolumen (**3**, **4**, **28–35**) zur Aufnahme des Bluts verbindet, umfaßt.

11. Vorrichtung nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß das Seitenteil des Gehäuses (**1**), aus dem die Hohlnadel (**10**) in ihrer ausgefahrenen Position herausragt, mindestens eine Anlagefläche (**25**) zur Abstützung der Vorrichtung während ihrer Verwendung auf der Körperoberfläche eines Patienten aufweist.

12. Vorrichtung nach Anspruch 11, dadurch gekennzeichnet, daß die mindestens eine Anlagefläche (**25**) derart ausgestaltet ist, daß bei Abstützung der Vorrichtung auf der Körperoberfläche des Patienten die Hohlnadel (**10**) zur Körperoberfläche im Abstützbereich einen Winkel α im Bereich zwischen 5° und 30° einschließt.

13. Vorrichtung nach Anspruch 12, dadurch gekennzeichnet, daß die mindestens eine Anlagefläche (**25**) derart ausgestaltet ist, daß der Winkel α, den die Hohlnadel (**10**) mit der Körperoberfläche bei Abstützung der Vorrichtung auf der Körperoberfläche des Patienten aufweist, einstellbar ist.

14. Vorrichtung nach einem der Ansprüche 11 bis 13, dadurch gekennzeichnet, daß die Anlagefläche (**25**) mindestens eine Aussparung (**27**) zur Fixierung des der Blutentnahme dienenden Blutgefäßes (B) aufweist.

15. Vorrichtung nach einem der Ansprüche 1 bis 14, dadurch gekennzeichnet, daß die Vorrichtung eine Mehrzahl von einander getrennter Innenvolumina (**3**, **4**, **28–33**) zur Aufnahme des entnommenen Bluts umfaßt oder eine Adapteranordnung (**39**) zum Anschluß mehrerer Behälter zur Aufnahme entnommenen Blutes umfaßt.

16. Vorrichtung nach Anspruch 15, dadurch gekennzeichnet, daß die Innenvolumina (**28**, **29**, **30**) oder die Behälter seriell miteinander kommunizieren.

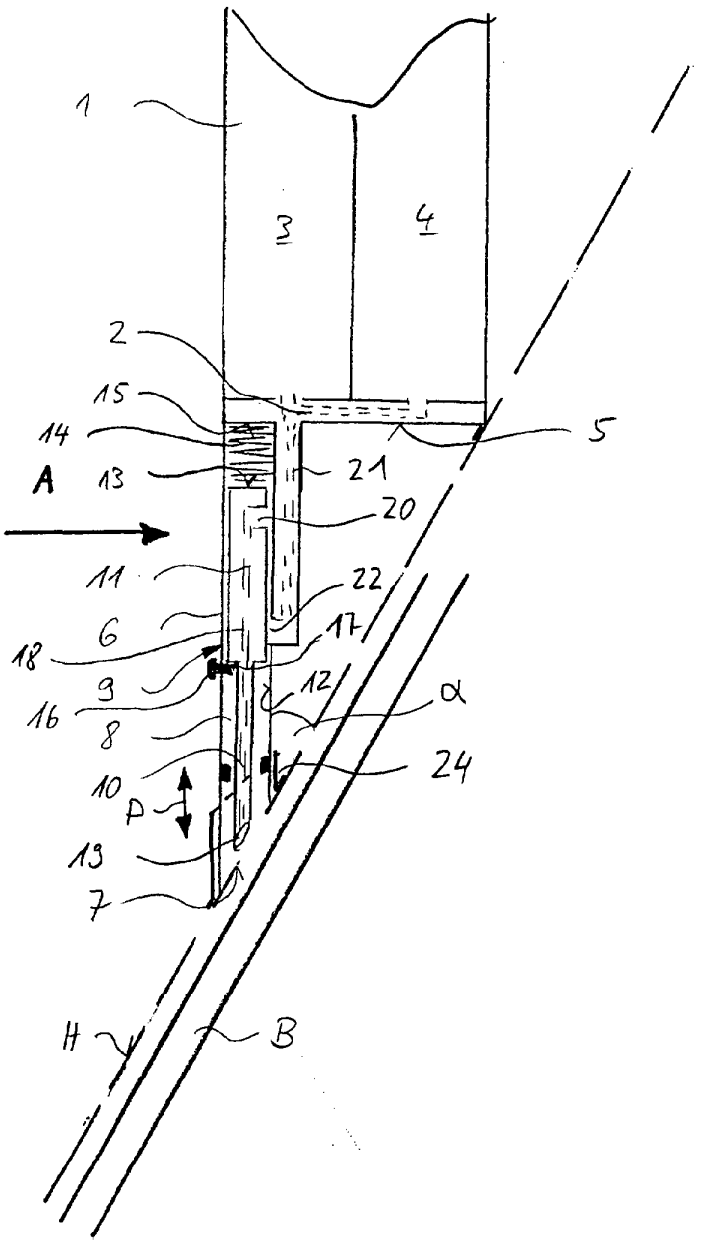
17. Vorrichtung nach Anspruch 15, dadurch gekennzeichnet, daß die Innenvolumina (**31**, **32**, **33**) oder die Behälter parallel miteinander kommunizieren.

Hierzu 6 Seite(n) Zeichnungen

- Leerseite -

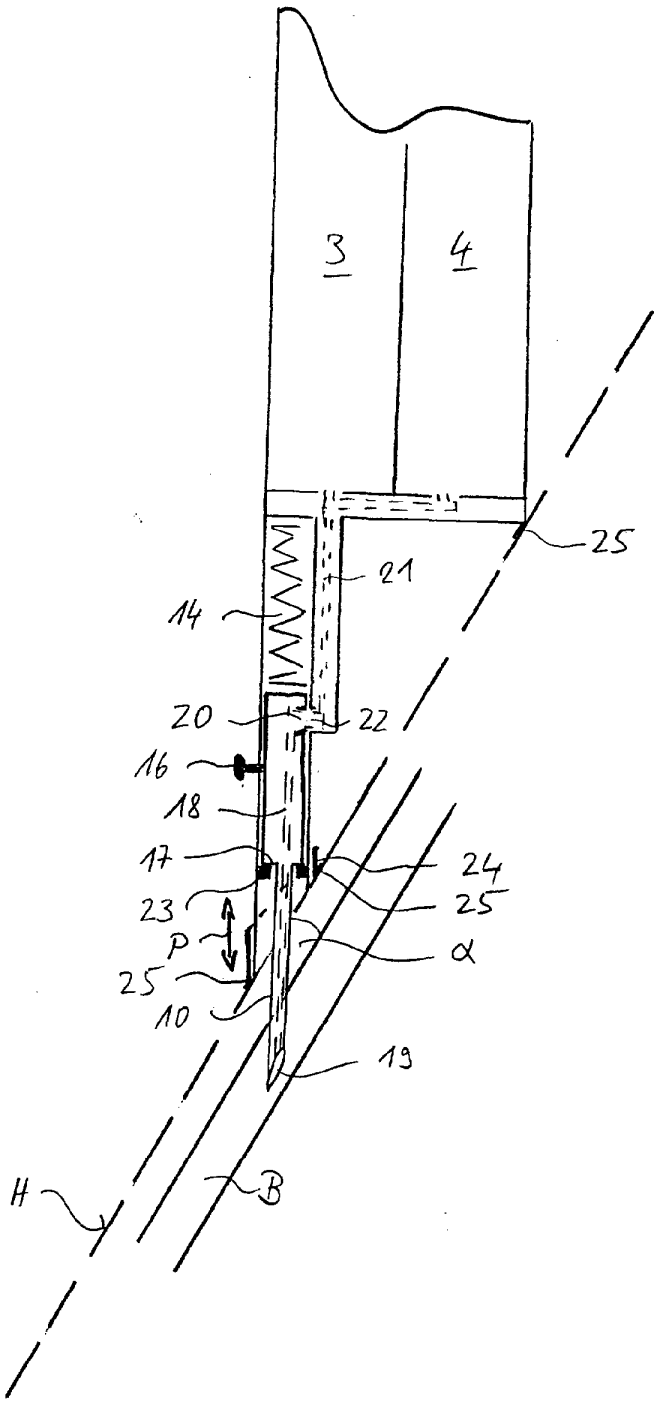
Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 1



Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 2



Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 3

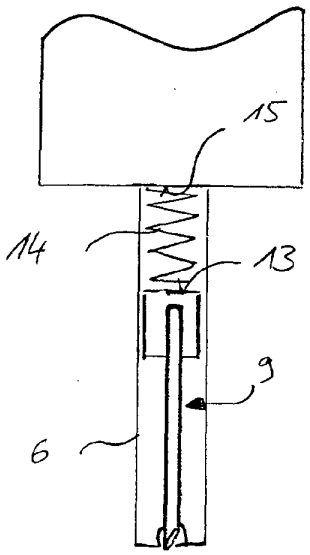
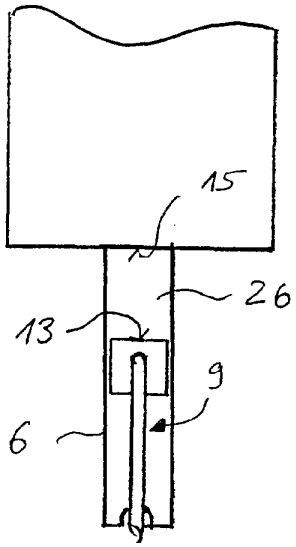


Fig. 4



Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 5

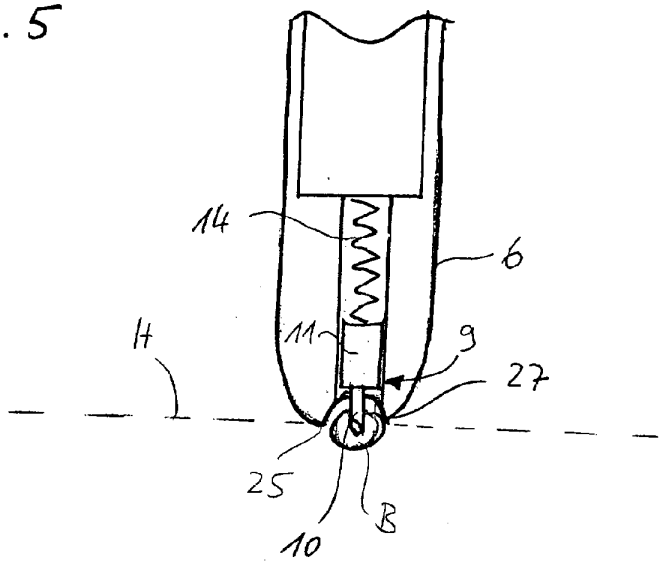
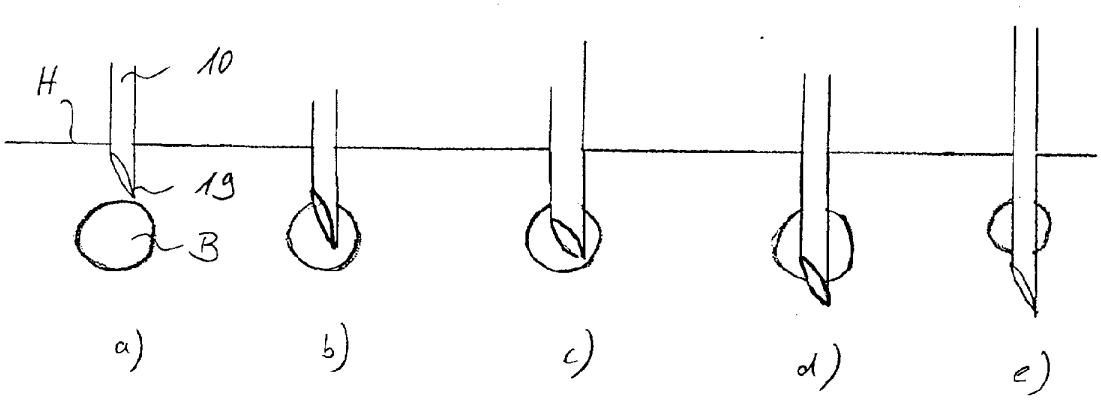


Fig. 6



Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 7

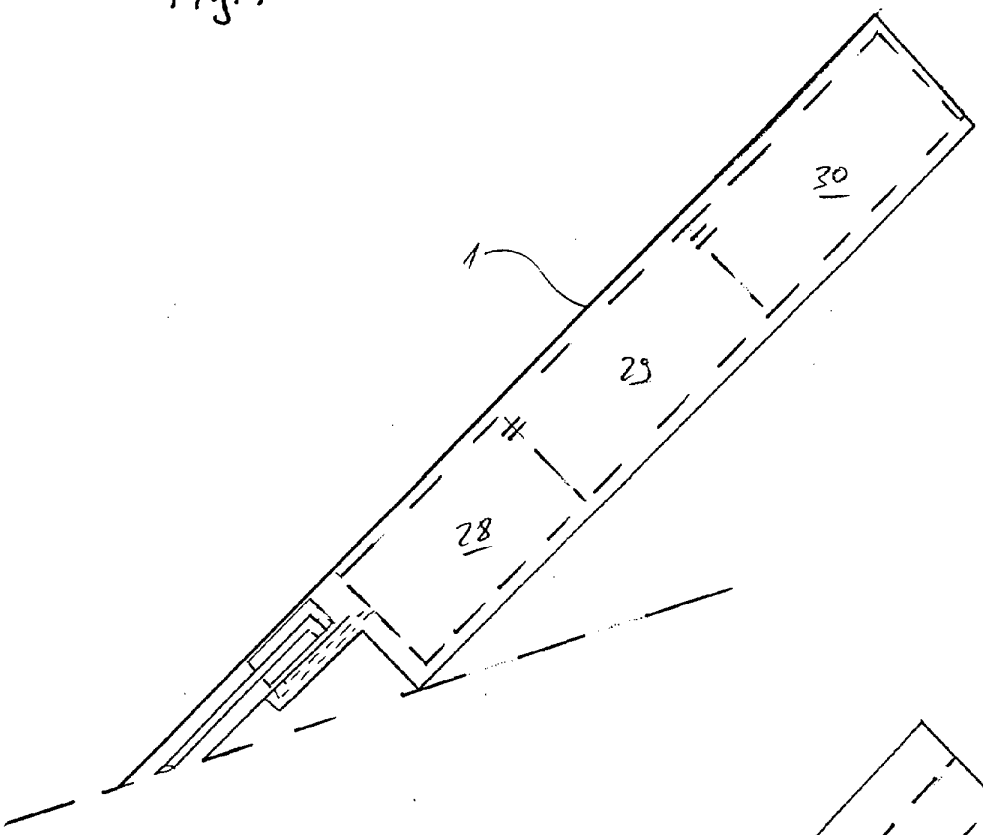
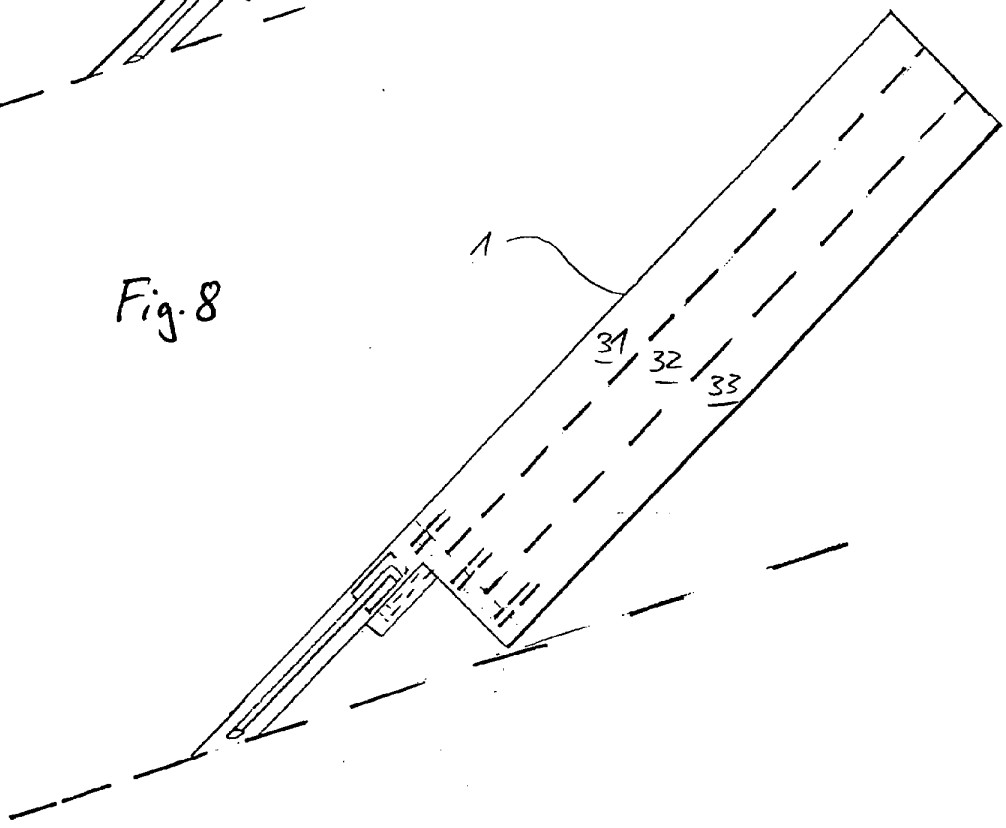
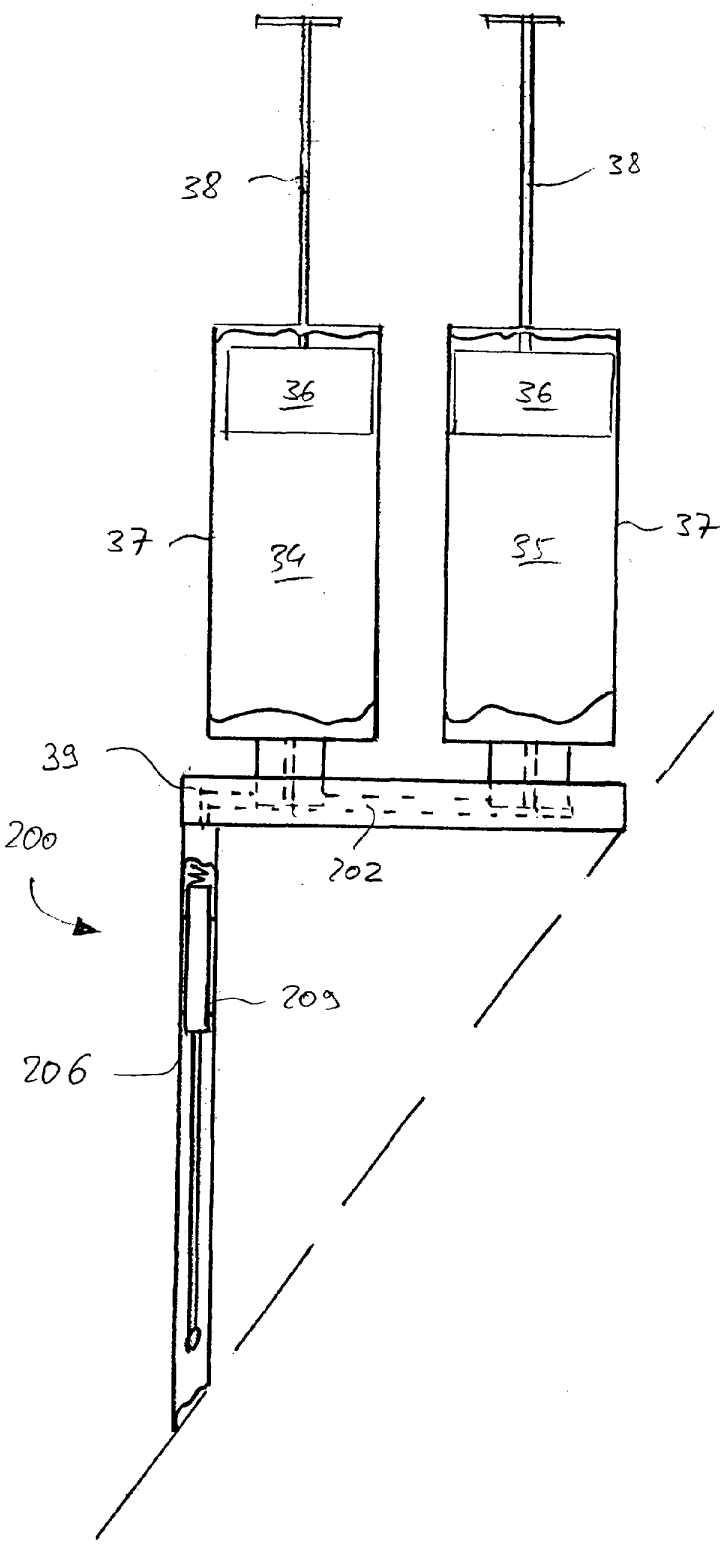


Fig. 8



Nummer: **DE 100 38 026 A1**
Int. Cl.[7]: **A 61 B 5/15**
Offenlegungstag: 22. Februar 2001

Fig. 9



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(19) [Country of issue] Japan Patent Office (JP)

(12) [Type of publication] Published patent publication (A)

(11) [Publication number] JP-A-2-224742

(43) [Published date] 1990 (1990) September 6

(54) [Title of invention] Improved blood sampling device

(51) [International patent classification 5th edition]

A61B 5/14 300 H

A61M 1/02 370

[FI]

A61B 5/14 300 H

A61M 1/02 370

[Request for examination] Unclaimed

[Total number of pages] 10

(21) [Application number] Japanese Patent Application Hei 1-338039

(22) [Filing date] December 26, 1989

(31)) [Priority claim number] 292490

(32) [Priority date] December 30, 1988

(33) [Priority claim country] United States of America (US)

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wrap up close —

(57) [Abstract] Since this gazette is application data before electronic filing, abstract data is n ot recorded.

The scope of the claims open —

Claims:
(1) In a coupling used by medical personnel in drawing and storing blood from a patient to ins ert the needle of the needle assembly into the patient to draw the blood sample, the coupling comprises first
and an elongated hollow shaft having a second end; and a
first portion of the shaft fixedly connecting the needle assembly to the shaft so that blood dra wn by the needle can be delivered to the shaft. and an adapter sleeve attached to a second e nd of said shaft for
connecting said shaft to a blood storage means,
for communicating blood received by said shaft; an opening connected to said shaft between an adapter sleeve and said connecting member and communicating with said connecting mem ber.
(2) The coupling of claim 1, further comprising means for blocking blood flow and exhausting air trapped within said shaft.
(3) intermediate the opening and the adapter sleeve, wherein the means for evacuating air re stricts blood flow from the shaft to the adapter sleeve while permitting air flow from the shaft to the adapter sleeve; 3. A coupling according to claim 2, comprising flow control means locat ed within said shaft of.
(4) The coupling of Claim 3, wherein said flow control means comprises a microporous hydrop hobic plug.
(5) The coupling of claim (4) further comprising needle guide means for guiding a needle coup

led to blood reservoir means through said plug and for coaxially fitting said needle with said s haft.

(6) The cup according to (2), further comprising blood storage means for temporarily storing a portion of blood drawn from a patient, said blood storage means being sealably connectable to said opening. ring.

(7) The coupling of claim (6), wherein said blood storage means comprises a syringe.

(8) Further comprising valve means fixedly positioned intermediate said opening and said shaf t for enabling selective communication between said shaft and said opening. coupling.

(9) The coupling of claim 2, further comprising means for sealing said opening.

(10) In a blood collection device used by medical personnel to withdraw and store a blood sa mple from a patient, needle means adapted to be inserted into the patient to withdraw the blo od

sample

; coupling means for connecting the means to the blood storage means,

said coupling means having first and second openings;and adapted to direct blood from said n eedle means to said first and second openings.

(11) The coupling of claim 10, further comprising means for blocking blood flow to exhaust air trapped within said coupling means.

(12) the means for evacuating air restricts blood flow from the needle means to the first openi ng while permitting air flow from the needle means to the first opening; 12. The blood collecti on device of claim 11, comprising flow control means positioned within said coupling means b etween said first and second openings.

(13) The blood collection device of Claim 12, wherein said flow control means comprises a mic roporous hydrophobic plug.

(14) The blood collection device of (13) further comprising needle guide means for guiding a n eedle coupled to blood reservoir means through said plug and coaxial with said coupling mean s.

(15) The method according to (14), further comprising blood storage means for temporarily st oring a portion of the blood drawn from the patient, said blood storage means being sealingly connectable to said second opening. A blood collection device as described.

(16) The blood collection device of (12), wherein said blood storage means comprises a syring e.

(17) The blood collection device of (12) further comprising means for sealing said second ope ning.

(18) further comprising valve means disposed intermediate said needle means and said secon d opening for enabling selective communication between said needle means and said second opening. The blood sampling device according to (12).

(19) said needle means is an elongate needle for insertion into a patient and leading from sai d needle to said coupling means;

13. The blood collection device of claim 12, comprising: a tube, said tube being generally tran sparent so that medical personnel can see blood being directed therethrough.

(20) A blood collection device for use by medical personnel in drawing and collecting blood sa mples from a patient, comprising needle means for drawing blood from a patient and coupling means for selectively connecting

blood

reservoir means to said needle means. wherein

said coupling means is secured to said needle means, said coupling means being positioned b etween said first opening and said needle means and a first opening for receiving blood storag e means; a hollow shaft, said coupling means further comprising a second opening for receivi ng blood storage means, said second opening being connected to said first opening and said n eedle; Mounted on the shaft between means,

the blood sampling device restricts the flow of blood from the shaft to the first opening, but re stricts the flow of blood from the shaft to the first opening.The blood collection device further comprising a flow control device located within the shaft intermediate the first and second ope nings to allow gas flow to the first opening.

(21) further comprising blood storage means for temporarily storing a portion of blood, said bl ood storage means being sealed to said second opening for receiving blood delivered from sai d needle means to said shaft; 21. A blood collection device according to claim 20, adapted for coupling.

(22) said blood storage means comprises a syringe having a blood storage chamber and a plu nger located within said blood storage chamber, said syringe sealing said blood storage chamb er to said second opening; 22. A blood collection device according to claim 21, further compri sing means for connecting with.

(23) The blood collection device of Claim 20, wherein said flow control means comprises a mic roporous hydrophobic plug.

(24) further comprising blood storage means for storing a blood sample, said blood storage m eans being sealingly attachable to said first opening for insertion through said plug, thereby 2 4. A blood collection device according to claim 23, comprising a needle adapted to lead blood f rom the shaft to said blood storage means.

(25) guiding means located within said shaft between said plug and said first opening for guidi ng said needle of said blood storage means through said plug and making said needle coaxial with said shaft; 25. The blood collection device of claim 24, further comprising:

(26) within said shaft between said flow control means and said first opening for guiding a ne edle coupled to said blood storage means through said flow control means and coaxial with sai d shaft; 21. A blood collection device according to claim 20, further comprising guide means l ocated at the .

(27) The blood collection device of Claim 20, further comprising valve means for selectively all owing communication between said shaft and said second opening.

(28) said needle means comprises a needle for insertion into a patient to withdraw a blood sa mple and an elongated tube for guiding blood withdrawn from a patient to said coupling mean s, said tube being flexible

; 21. A blood collection device according to claim 20, and wherein the blood being conducted by said tube is generally transparent so as to be visible to medical personnel.

(29) further comprising a syringe having a blood storage chamber and a plunger positioned wi thin the blood storage chamber, the syringe having means for sealingly connecting the blood s torage chamber to the second opening; 29. A blood collection device according to claim 28, fu rther comprising.

(30) The blood collection device of (11) further comprising cap means for sealing said second opening.

(31) in drawing and collecting a blood sample from a patientA blood collection device for use by medical personnel comprising a

first elongated needle member having an insertion end and an attachment end, said insertion end adapted for insertion into a patient, said first needle member comprising: has a coaxial p assageway for carrying blood drawn from a patient from the insertion end to the attachment e nd and includes a

needle receiving end, a mating end, and from the needle receiving end to the mating end. an d said mounting of said first needle member

such that blood drawn from a patient is conveyed by said first needle member to said first fe male connector. means for fixedly and sealingly connecting an end to a receiving end of said fi rst female connector; a

mating end; a mounting end; and a coaxial extending from said mating end to said mounting end. further comprising a first male connector having a passageway, wherein the mating end of the first male connector is adapted to receive blood conveyed to the first female connector by the first male connector;

first and second ends and a passage extending from the first end to the second end sealingly mated to the mating end of the first female connector; and wherein the first end of the tube i s connected to the attachment end of the first male connector such that blood received by the first male connector is carried by the tube. sealingly attached to the portion, the tube being fl exible and generally transparent so that blood received by the tube is visible to medical perso nnel;

Further comprising a coupling having an elongated hollow shaft and a connecting member att ached to a first end of said shaft, said coupling securing a second end of said tube to said cou pling. to sealably connect to a second end of the shaft, thereby conveying blood received by t he tube to the coupling, the coupling being attached to a second end of the shaft connecting t he shaft to blood storage means. and the coupling is fixedly attached to the shaft between the adapter sleeve and the connecting member such that blood received by the coupling flows int o and out of the second female connector. a plug communicatively further comprising a secon

d female connector in communication with said connecting member and positioned within said shaft of said coupling between said second female connector and said adapter sleeve; wherein said plug is adapted to allow gas to escape from said shaft to effectively block blood flow from said shaft to said adapter sleeve.

(32) a second needle member having an insertion end, a connecting end, a coaxial passageway extending from said insertion end to said connecting end, and a vacutainer means for storing blood drawn from a patient

; The vacutainer means is fixedly attached to the second needle member, the adapter sleeve is positioned such that the vacutainer means is press fit into the adapter sleeve, and the second 32. A blood collection device according to claim 31, wherein a needle member is configured to be inserted through said plug, thereby conveying blood received by said shaft of said coupling to said vacutainer means.

(33) located within said coupling between said plug and said adapter sleeve for guiding said second needle member to insert said second needle member into said plug coaxial with said coupling; 33. A blood collection device according to claim 32, further comprising a needle guide means for receiving the blood.

(34) needle guide means located within said coupling between said plug and said adapter sleeve for guiding a needle coupled to blood storage means for coaxial insertion of said needle into said coupling; 32. The blood collection device of claim 31, further comprising:

(35) further comprising cap means adapted to engage said second female connector and thereby seal said second female connector to prevent blood from flowing out of said second female connector; A blood sampling device according to claim (31).

(36) Further comprising a syringe for temporarily storing blood, said syringe having a blood storage chamber and a plunger located within said blood storage chamber, said syringe being in communication with said blood storage means. (31) adapted to mate with said second female connector such that blood received by said coupling is stored within said syringe.

(37) located within said coupling between said plug and said adapter sleeve for guiding said second needle member to insert said second needle member into said plug coaxial with said coupling; 37. A blood collection device according to claim 36, further comprising a needle guide means for receiving the blood.

(38) a second needle member having an insertion end, a connecting end, a coaxial passageway extending from said insertion end to said connecting end, and a vacutainer means for storing blood drawn from a patient

; The vacutainer means is fixedly attached to the second needle member, the adapter sleeve is positioned such that the vacutainer means is press fit into the adapter sleeve, and the second A needle member is configured to be inserted through said plug, thereby carrying blood received by said shaft of said coupling to said vacutainer means.38. The blood collection device of claim 37.

(39) The blood collection of claim (37) further comprising first, second and third cap means re

spectively sealing said first needle means, said second female connector and said adapter slee ve. Device.

(40) The blood collection device of claim (31) further comprising valve means coupled to said second female connector for selectively communicating between said second female connector and said shaft.

(41) needle means for withdrawing blood from a patient

and

temporarily storing a first blood portion withdrawn from the patient in a blood collection devic e used by medical personnel to withdraw and store a blood sample from a patient; syringe me ans and

coupling means sealingly connecting said needle means to said syringe means, said coupling means including flow control means for venting air trapped within said needle means and said coupling means. said coupling means further comprising adapter means adapted to receive bl ood storage means and direct blood to said coupling means for storage; A blood collection dev ice wherein the means are further configured to return said first blood portion to the patient.

(42) said coupling means comprises a coupling having an elongated hollow shaft, said couplin g means attached to a first end of said shaft fixedly connecting said needle means to said cou pling; further comprising a connecting member, said adapter means attached to a second end of said shaft, said coupling receiving said syringe means, said shaft between said adapter mea ns and said connecting member; 42. A blood collection device according to claim 41, further c omprising a connecting member fixedly attached to.

(43) The blood collection device of Claim 42, wherein said flow control means comprises a plu g positioned within said shaft of said coupling between said connecting member and said adap ter means.

(44) The blood collection device of Claim 43, wherein said plug comprises a microporous hydr ophobic plug.

(45) said needle means comprises a needle for insertion into a patient to withdraw a blood sa mple and an elongated tube for conducting blood withdrawn from the patient to said coupling, said tube being flexible; 44. A blood collection device according to claim 43, and wherein bloo d being conducted by said tube is generally transparent so as to be visible to medical personn el.

(46) drawing a first blood portion from the patient to fill the blood collection device while evac uating the air trapped in the blood collection device so that the anaerobic sample is not conta minated with air trapped in the blood collection means; An anaerobic sample is taken from th e patient after generally evacuating the trapped air from the blood collection device.A method of drawing

an anaerobic blood sample from a patient comprising the step of drawing a sample of blood fr om a patient.

(47) temporarily storing the first blood portion after drawing the first blood portion and

returning the first blood portion to the patient after drawing the anaerobic blood sample
; The method of claim (46), further comprising:
(48) withdrawing the first blood portion
further comprises coupling a coupling to a syringe, the coupling sealably coupled to a needle a ssembly
; inserting
the
needle assembly into the patient and coupling the inserted needle assembly and the coupling so that blood is directed through the needle assembly and into the coupling with the syringe a ttached
; evacuating trapped air,
connecting a vacutainer needle of a vacutainer to said vented coupling, said vacutainer needle being in communication with said inserted needle assembly, and a cup with said vacutainer at tached
.
48. The method of claim (47), comprising withdrawing said first blood portion from a ring into said syringe .
(49) wherein withdrawing the anaerobic blood sample comprises establishing blood flow betw een the needle assembly and the vacutainer after the first blood portion has been withdrawn; The method described in .
(50) The method of claim (48), wherein withdrawing the first blood portion into the syringe co mprises allowing blood to flow freely under the pressure of the patient's heart.

detailed description open ----

Description:
INDUSTRIAL APPLICABILITY
The present invention is directed to apparatus for taking a blood sample from a patient, and i n particular to apparatus for obtaining a blood sample from a patient in which the partial pres sure of gas within the sample is such that the blood pressure in the patient's body is An impro ved blood collection device is directed to receiving a blood sample so as to approximately equ al the gas partial pressure therein.
(PRIOR ART)
In the medical field, it is necessary to determine the in vivo gaseous equilibrium in the blood of a patient.
A medical worker will typically be concerned with the partial pressures of oxygen and carbon d

ioxide. They may also be concerned with ionic species whose activity is related to the gas bala nce in the blood, such as hydrogen ions and calcium ions.

In order for a blood sample to be valid for gas-in-blood analysis, the sample must be under a naerobic conditions, i.e., to prevent fluctuations in the partial pressure of the gas to be tested (when the blood is outside the patient's body). Must be collected to avoid exposure to gas.The major commercially available blood collection devices that must be present are largely unsatis factory in ensuring the integrity of anaerobic blood collection. An example of a conventional d evice uses a syringe and a vented plunger, where the syringe is removed from the patient unti l the correct blood volume is obtained from the patient by pulling on the vented plunger from no void in the barrel. Slowly withdraw the blood into the barrel of the However, these devices allow some exposure of the blood sample to the atmosphere. Some amount of ambient air will be contained within the barrel before the plunger moves. Thus, the initial portion of blood is e xposed to these gases, thereby changing the partial pressure of the gases contained in this ini tial sample. No means are provided for discarding the first portion of the drawn blood, so the entire sample would be contaminated.

Further, no means are provided to protect the medical personnel of the device against acciden tal bursting or exposure to contaminated blood during the course of the procedure when using the aforementioned device.

Other devices, such as the Becton and Dickenson Vacutainer and vacutainer attachments, hav e shown improved properties to protect medical personnel from exposure to drawn blood. Ho wever, these devices also. It allows some exposure of the first part of the blood sample to the atmosphere.

In addition to the shortcomings of the prior art described above, blood collection devices that provide means for flushing, i.e., injecting, for example, nutrients, medications, etc., into the b lood stream while permitting the collection of an anaerobic blood sample are currently lackin g. not known where.

Accordingly, it is desirable to provide a device for drawing an anaerobic blood sample from a p atient, and it is further desirable to provide a device for drawing a blood sample that can also inject a liquid into the patient's blood stream, i.e., a puncture. It is further desirable to provid e such a device that allows repeated blood sampling without the need for additional needle pl acement, and during scheduled interval sampling, i.e., during other subsequent blood samplin g. It would be desirable to provide a device for drawing blood samples that can be left in the p atient.

OBJECTS OF THE INVENTION

It is therefore an object of the present invention to provide a blood collection device for drawi ng an anaerobic blood sample from a patient.

It is also an object of the present invention to provide a blood collection device that can withd raw an initial contaminated blood sample portion and maintain complete anaerobicity in the re maining sample.

It is a further object of the present invention to provide a blood collection device that can inje ct an external liquid into the patient's blood stream.

It is a further object of the present invention to provide a blood sampling device that allows re peated blood sampling without the need for additional puncture or needle placement.

Yet another object of the present invention is to provide a blood collection device that can be l eft on the patient between scheduled intervals of collection, ie, other subsequent blood collect ions.

These and other objects of the present invention are met by providing a coupling for use by m edical personnel when drawing blood from a patient and storing it, which coupling draws the b lood sample. The coupling is particularly adapted for use with a needle assembly for injecting a needle into a patient. A coupling fixedly

connects the elongated hollow shaft and the needle assembly to the shaft for withdrawal by th e needle. a connecting member attached to the first end of the shaft that delivers blood to the shaft, and a coupling attached to the second end of the shaft that connects the shaft to variou s blood storage means. The adapter sleeve further comprises an opening coupled to the shaft intermediate the adapter sleeve and the connecting member, the opening being in communica tion with the opening such that blood received in the shaft communicates with the opening. In another embodiment

of the present invention, a device is provided for blocking blood flow and venting air trapped i n the shaft, in particular flow control means, such as microporous A hydrophobic plug is locate d in the shaft intermediate the opening and the adapter sleeve to restrict blood flow from the shaft to the adapter sleeve while allowing air flow from the shaft to the adapter sleeve. 6 In a nother embodiment of the invention, a valve is provided intermediate the shaft and the openi ng to allow selective communication between the shaft and the opening.

Other embodiments of the invention are particularly pointed out and distinctly claimed in the c laims. The invention, however, as to organization and method of implementation, will best be understood from the following detailed description when read with the accompanying drawing s in which: FIG.

DETAILED DESCRIPTION OF THE INVENTION

A cross-sectional view showing the improved blood collection device of the present invention i s provided in FIG. The blood sampling device comprises an elongated needle 100 having an in sertion end 102 adapted for insertion into a patient's blood stream (artery or vein). Needle 10 0 also has an attachment end 104 attached to first connecting member 106 via cylindrical sea l 108 . As is well known in the art, meter 100- has a coaxial passage extending from insertion end 102 to attachment end 104 that conducts blood drawn from the patient to first connectin g member 106. As shown in FIG.

Cylindrical seal 10B has a central opening 110 in which mounting end 104 of needle 100 is fix edly mounted. Additionally, the cylindrical seal 108 isIt is fixedly attached to needle receiving end 112 of member 106 . The second connecting member 114 has a mating end 116 adapted

to mate with the mating end 118 of the first connecting member 106 so that it is received by the first connecting member. rice field. Blood from leaflet 100 is directed to second connecting member 114 via mating joints 116,118.

First end 120 of tube 122 is sealingly attached to attachment end 124 of second connecting m ember 114 . A tube 122 is provided for carrying blood withdrawn from the patient through tub e 100 to coupling 126 . Tubing 122 allows the needle to be easily inserted into the patient's bl oodstream and, after insertion, the coupling 126 can be disengaged by medical personnel wit hout undue movement of the total 100 and causing discomfort to the patient. Preferably, the t ube 122 is flexible so as to be operable, and preferably transparent so that the medical perso nnel can visually observe the blood drawn from the patient.

The combination of needle 100, first connecting member 106, second connecting member 11 4, and tube 122 constitutes a needle assembly, readily available from needles, connecting me mbers, and tubes well known in the art. Can be assembled. - By way of example, the first and second connecting members 106 and 114 consist of male and female Luer connectors, as is w ell known in the art.

A coupling 126 is provided for connecting the second end 128 of the tube with each of the firs t and second blood storage means 130 and 132 . To this end, coupling 126 has a connecting member 134 with a central opening that receives second end 128 of tube 122 . Connecting m ember 134 is integrally connected to elongated hollow shaft 136 such that blood delivered to coupling 126 by tube 122 is received within shaft 136 . Adapter sleeve 138 is integrally conne cted to shaft 136 at the end opposite to the end to which connecting member 134 is connecte d. Adapter sleeve 138 is in communication with shaft 136 and is provided for receiving second blood storage means 132, as will be described more fully below.

Coupling 126 further includes an opening 140 integrally connected to shaft 136 intermediate a dapter sleeve 138 and connecting member 134 .

An opening 140 is provided for connecting first blood storage means 130 to shaft 136 of coupl ing 126 . A passageway 162 is provided in shaft 136 proximate opening 140 such that openin g 140 communicates with connecting member 134 . Accordingly, blood delivered to coupling 1 26 by tube 122 is conveyed via adapter sleeve 138 and opening 140 to first and second blood storage means 130 and 132 for storage.

Coupling 126 also has a plug 142 disposed within the shaft between adapter sleeve 138 and o pening 140 . Plug 142 is a fluid flow, e.g., porous plug, venting air trapped within connecting members 106, 114, tube 122, shaft 136, and opening 140 during the early stages of a blood c ollection procedure. It consists of control means. The plug 142 is thus adapted to restrict bloo d flow from the shaft 136 to the adapter sleeve 138 and allow air flow from the shaft to the a dapter sleeve. 142 consists of a microporous, hydrophobic plug, well known in the art. Howev er, those skilled in the art will appreciate that other liquid flow control means may be used in place of the preferred microporous hydrophobic plug 142 .

As previously mentioned, opening 140 is adapted to receive first blood storage means 130 .

A cap 144 is engageable with opening 140 to seal the opening from inadvertent blood loss, w hich often occurs when first blood storage means 130 is not connected to coupling 126 . Howe ver, in normal operation, cap 144 is removed from opening 140 and connects first blood stora ge means 130 thereto.

In a preferred embodiment of the present invention, the first blood storage means 130 compri ses a syringe of the type having a blood storage chamber 146 and a plunger 148 positioned w ithin the blood storage chamber 146 .

As is well known, in operation, plunger 148 is slowly withdrawn from blood storage chamber 1 46 so that blood enters the chamber. Blood storage means 130 further comprises connection means 150 for connecting blood storage means 130 to opening 140 . In a preferred embodim ent of the invention, opening 140 and connecting member 150 each comprise male and femal e luer connectors. However, it will be apparent to those skilled in the art that other connector members may be provided to sealingly connect first blood storage means 130 to coupling 126 .

In operation, the cap 144 is removed from the opening 140 and the blood reservoir means 13 0 is connected thereto.The blood is then withdrawn, or preferably allowed to flow freely under the pressure of the patient's heart. Meter 100 is inserted into the patient's blood stream so as to be able and delivered to shaft 136 via connecting members 106 , 114 and tubing 122 . Air trapped within connecting members 106, 114, tube 122, shaft 136 and opening 140 is displac ed by the patient's blood entering the flow passageway and vented through porous plug 142, as previously described. .

A first portion of the blood that is withdrawn or flows under cardiac pressure from the patient is exposed to trapped air before being ventilated.As it is exposed, it is generally contaminated and therefore not suitable for anaerobic blood sampling.

This first blood portion is thus withdrawn from the coupling 126 into the blood storage means 130 for temporary storage, while the anaerobic blood sample passes through the second bloo d storage means 132. to be received. After the anaerobic blood sample is received, the blood temporarily stored in blood storage means 130 is discarded or returned to the patient via tube 122 and meter 100 .

A second blood storage means 132 is connected to the coupling 126 via an adapter sleeve 13 8 for withdrawing an anaerobic blood sample. The second blood storage means 132 may com prise a Becton Dickenson vacutainer well known in the art. Blood storage means 132 has a blo od storage chamber 152 for receiving an anaerobic blood sample drawn from the patient. are doing. Needle 154 is sealingly connected to needle hub 156 and their assembly is connected t o blood storage chamber 152 via a compatible coupling 158 (commonly referred to as a vacut ainer adapter). Hermetically connected. Needle 154 has a seal to prevent communication with blood storage chamber 152, as is well known in the art. Additionally, as is well known in the a rt, blood storage chamber 152 is evacuated so as not to contain air that contaminates blood d rawn from the patient.

A compatible coupling 158 provides means for removing the seal from needle 154 in order to place needle 154 in communication with blood storage chamber 152 .

Adapter sleeve 138 has an internal adapter chamber 160 sized to snugly receive needle hub 1 56 . The length of adapter sleeve 138 and the position of plug 142 within shaft 136 is such th at blood reservoir 132 is fully inserted into adapter sleeve 138 and needle 154 passes through passageway 162 and second end 128 of tube 122 through plug 142 . is selected to lie betwee n A needle guide 164 is positioned within coupling 126 between adapter sleeve 138 and plug 142 to allow a needle to be inserted into coupling 126 coaxially with shaft 136 . Needle guide 164 receives needle 154 during insertion of blood reservoir 132 into coupling 126 and guides t he needle prior to needle insertion into plug 142 so that the needle is coaxial with shaft 136 . provided for positioning.

In operation, blood reservoir means 130 is connected to coupling 126 via opening 140 as prev iously described for collecting an anaerobic blood sample. The meter 100 is inserted into the p atient's bloodstream and air trapped inside the meter 100, connectors 106, 114, tubing 122 a nd coupling 126 is evacuated through plug 142 as previously described.Total 154 of blood stor age means 132 is then inserted through plug 142 and into coupling 126 so that it lies beyond passageway 162 near tube 122 . The contaminated air of the blood sample is removed so that any fraction of contaminated air that accumulates within needle 154 is exhausted through plu g 142, i.e., removed from coupling 126 prior to receiving the anaerobic blood sample. It is des irable to insert gauge 154 into coupling 126 prior to storing the portion in storage means 130 .

After the soot 154 is properly inserted into the coupling 126, the first portion of contaminated blood is drawn from the coupling 126 into the blood storage means 130 for temporary storag e. At this time, the seal on needle 154 is removed by compatible coupling 158, as is well kno wn in the art, so that the anaerobic blood sample is directed to blood reservoir 152. FIG.

To ensure that substantially all of the blood directed to blood storage chamber 152 is blood re ceived from tube 122 and not blood received from blood storage chamber 146 of blood storag e means 130, total 154 is connected to passageway 162. and tube 122 and near second end 128 of tube 122 in coupling 126 in shaft 136 .

In an alternative embodiment of the present invention, when receiving an anaerobic blood sa mple, a valve capable of substantially isolating a contaminated blood sample stored in blood s torage means 130 from shaft 136 during operation; Alternatively, it may be desirable to provi de other selective coupling means.

In addition to the cap 144, a plurality of caps or other sealing means may be provided for posi tioning the total 100 to seal the chamber 160 of the adapter sleeve 138, as is common in the medical industry.

Although only a few preferred embodiments of the novel blood collection device have been de scribed in detail herein, many modifications and variations will become readily apparent to tho se skilled in the art, both in the true scope and spirit of the invention. It is the intent of the ap

pended claims to cover all such improvements and modifications that fall within the scope of t he claims.

Brief description of the drawing open —

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a cross-sectional view of one of the improved blood collection devices of the pre sent invention.

100 Needle

106 First connecting member

114 Second connecting member

122 Tube

126 Coupling

130.132 Blood reservoir Means

134 ... Connection member

136 ... Shaft

138 ·

140 ·

142,

144,

146.

148

154

Adapter sleeve

opening

plug

cam

blood storage chamber plunger

needle



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(P0200)

Espacenet

Bibliographic data: JPH02224742 (A) — 1990-09-06

IMPROVED BLOOD SAMPLER

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Classification: **- international:** ***A61B5/15; A61B5/155; A61M1/02;*** (IPC1-7): A61B5/14; A61M1/02

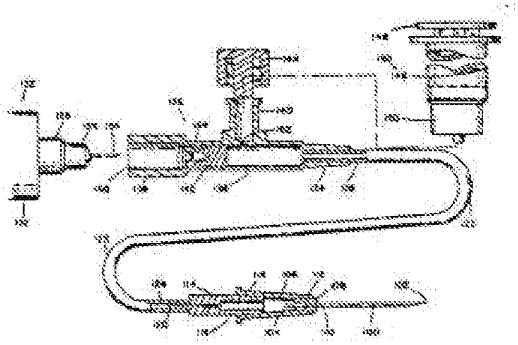
- cooperative: **A61B5/15003 (EP, US); A61B5/150992 (EP, US)**

Application number: JP19890338039 19891226

Priority number(s): US19880292490 19881230

Also published as: CA2002175 (A1) EP0376168 (A2) EP0376168 (A3) US5046509 (A)

Abstract of JPH02224742 (A)



PURPOSE: To keep completely anaerobic of the residual a blood sample, with the first sampled portion of contaminated blood removed, by fixedly coupling a slender hollow shaft and a needle assembly together, with a joint member mounted to the first end of a shaft and an adapter sleeve to the second end.

CONSTITUTION: Coupling 126 has joint member 134 which receives the second end 128 of tube 122. Adapter sleeve 138 is connected integrally to shaft 136 at an opposite end of the end to which the joint member 134 is connected. The adapter sleeve 138 communicates with the shaft 136 and receives second blood storage means 132. The coupling 126 has further opening 140 which is joined integrally to the shaft 136 between the adapter sleeve 138 and joint member 134. The blood delivered to the coupling 126 through tube 122 is transferred to the first and second blood storage means 130, 132 respectively for storage therein via the adapter sleeve 138 and opening 140.

⑲日本国特許庁(JP)　⑪特許出願公開

⑫公開特許公報(A)　平2-224742

⑤Int. Cl.[5]	識別記号	庁内整理番号
A 61 B 5/14	300 H	7831-4C
A 61 M 1/02	370	7180-4C

⑬公開　平成2年(1990)9月6日

審査請求　未請求　請求項の数 50　(全10頁)

⑤④発明の名称　改良された血液採取装置

⑳特　願　平1-338039

㉒出　願　平1(1989)12月26日

優先権主張　㉜1988年12月30日㉝米国(US)㉛292490

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明　細　書

1.発明の名称　改良された血液採取装置

2.特許請求の範囲

(1) 患者から血液を抜き取って貯蔵する際に医療作業員によって使用され、血液サンプルを抜き取るために針組立体の針を患者に挿入する、カップリングにおいて、

第1及び第2の端部を有する細長い中空シャフトと、

前記針組立体を前記シャフトに固定して連結し、それによって、前記針によって引き抜かれた血液を前記シャフトに送ることができる、前記シャフトの第1の端部に取り付けられた接続部材と、

前記シャフトを血液貯蔵手段に接続する、前記シャフトの第2の端部に取り付けられたアダプタースリーブと、

前記シャフトによって受け入れられた血液を連通させるため、前記アダプタースリーブと前記接続部材との間の前記シャフトに連結されて前記接続部材に連通している開口部と、から成るカップリング。

(2) 血液の流れを遮断して、前記シャフト内にたまった空気を排気する手段をさらに備える請求項(1)に記載のカップリング。

(3) 前記空気を排気する手段が、前記シャフトから前記アダプタースリーブへの空気の流れを可能にしつつ、シャフトからアダプタースリーブへの血液の流れを制限する、前記開口部と前記アダプタースリーブとの中間の前記シャフト内に位置している流れ制御手段から成る請求項(2)に記載のカップリング。

(4) 前記流れ制御手段が、微孔質疎水性プラグから成る請求項(3)に記載のカップリング。

(5) 血液貯蔵手段に結合している針を前記プラグを通して案内し、前記針を前記シャフトと同軸にする針案内手段をさらに備える請求項(4)に記載のカップリング。

(6) 患者から抜き取った血液の一部を一時的に貯蔵する血液貯蔵手段をさらに備え、前記血液貯蔵手段は、前記開口部に密封して連結可能である請求項(2)に記載のカップリング。

(7) 前記血液貯蔵手段が、注射器から成る請求項(6)に記載のカップリング。

(8) 前記シャフトと前記開口部との間の選択的な連通を可能にする、前記開口部と前記シャフトの中間に固定して配置されているバルブ手段をさらに備える請求項(2)に記載のカップリング。

(9) 前記開口部を密封する手段をさらに備える請求項(2)に記載のカップリング。

(10)患者から血液サンプルを抜き取って貯蔵するために医療作業員によって使用される血液採取装置において、

血液サンプルを抜き取るために、患者に挿入されるように適合している針手段と、

前記針手段を血液貯蔵手段に連結させるカップリング手段とを備え、

前記カップリング手段は、第1及び第2の開口部を有しており、前記針手段からの血液を前記第1及び第2の開口部に導くようになっている血液採取装置。

(11)血液の流れを遮断して、前記カップリング手段内にたまった空気を排気する手段をさらに備える請求項(10)に記載のカップリング。

(12)前記空気を排気する手段が、前記針手段から前記第1の開口部への空気の流れを可能にしつつ、前記針手段から前記第1の開口部への血液の流れを制限する、前記第1及び第2の開口部の間の前記カップリング手段内に位置している流れ制御手段から成る請求項(11)に記載の血液採取装置。

(13)前記流れ制御手段が、微孔質疎水性プラグから成る請求項(12)に記載の血液採取装置。

(14)血液貯蔵手段に結合している針を前記プラグを通して案内し、前記カップリング手段と同軸になる針案内手段をさらに備える請求項(13)に記載の血液採取装置。

(15)患者から抜き取った血液の一部を一時的に貯蔵する血液貯蔵手段をさらに備え、前記血液貯蔵手段は、前記第2の開口部に密封して連結可能である請求項(14)に記載の血液採取装置。

(16)前記血液貯蔵手段が、注射器から成る請求項(12)に記載の血液採取装置。

(17)前記第2の開口部を密封する手段をさらに備える請求項(12)に記載の血液採取装置。

(18)前記針手段と前記第2の開口部との間の選択的な連通を可能にする、前記針手段と前記第2の開口部の中間に配置されているバルブ手段をさらに備える請求項(12)に記載の血液採取装置。

(19)前記針手段が、患者に挿入する針と、前記針から前記カップリング手段へ導く、細長いチューブと、から成り、前記チューブは、医療作業員が導かれている血液を前記チューブを通して見ることができるように、概ね透明である請求項(12)に記載の血液採取装置。

(20)患者から血液サンプルを抜き取って集める際に医療作業員が使用する血液採取装置において、

患者から血液を抜き取る針手段と、

前記針手段に血液貯蔵手段を選択的に連結するカップリング手段と、を備え、

前記カップリング手段は前記針手段に固定されており、前記カップリング手段は、血液貯蔵手段を受け入れる第1の開口部と、前記第1の開口部と前記針手段との間にある中空のシャフトとを有しており、前記カップリング手段は、血液貯蔵手段を受け入れる第2の開口部をさらに備えており、前記第2の開口部は、前記第1の開口部と前記針手段の間の前記シャフトに取り付けられており、

前記血液採取装置は、前記シャフトから前記第1の開口部への血液の流れを制限するが、前記シャフトから前記第1の開口部への気体の流れを可能にする、前記第1及び第2の開口部の中間の前記シャフト内部に位置している流れ制御装置をさらに備える血液採取装置。

(21)血液の一部を一時的に貯蔵する血液貯蔵手段をさらに備え、前記血液貯蔵手段は、前記針手段から前記シャフトへ送られた血液を受け入れる、前記第2の開口部へ密封して連結されるようになっている請求項(20)に記載の血液採取装置。

(22)前記血液貯蔵手段が、血液貯蔵チャンバーと前記血液貯蔵チャンバー内に位置しているプラ

ンジャーとを有する注射器から成り、前記注射器は、前記血液貯蔵チャンバーを前記第２の開口部へ密封して連結する手段をさらに有している請求項(21)に記載の血液採取装置。

(23)前記流れ制御手段が、微孔質疎水性プラグから成る請求項(20)に記載の血液採取装置。

(24)血液サンプルを貯蔵する血液貯蔵手段をさらに有しており、前記血液貯蔵手段は、前記第１の開口部に密封して取り付け自在であって、前記プラグを通して挿入し、それによって、前記シャフトから前記血液貯蔵手段へ血液を導くようになっている針を有している請求項(23)に記載の血液採取装置。

(25)前記プラグを通して前記血液貯蔵手段の前記針を案内し、前記針を前記シャフトと同軸にする、前記プラグと前記第１の開口部との間の前記シャフト内に位置している案内手段をさらに備えている請求項(24)に記載の血液採取装置。

(26)前記流れ制御手段を通して前記血液貯蔵手段に結合している針を案内し、前記針を前記シャフトと同軸にする、前記流れ制御手段と前記第１の開口部との間の前記シャフト内に位置している案内手段をさらに備えている請求項(20)に記載の血液採取装置。

(27)前記シャフトと前記第２の開口部との間を選択的に連通できるように、バルブ手段をさらに備える請求項(20)に記載の血液採取装置。

(28)前記針手段が、血液サンプルを抜き取るために患者に挿入する針と、患者から抜き取られた血液を前記カップリング手段へ導く細長いチューブとを有し、前記チューブは可撓性を有し、かつ、前記チューブによって導かれている血液が医療作業員に見えるように概ね透明である請求項(20)に記載の血液採取装置。

(29)血液貯蔵チャンバーと該血液貯蔵チャンバー内に位置しているプランジャーとを有する注射器をさらに備え、前記注射器は、前記血液貯蔵チャンバーを前記第２の開口部へ密封して連結する手段をさらに備えている請求項(28)に記載の血液採取装置。

(30)前記第２の開口部を密封するキャップ手段をさらに備える請求項(11)に記載の血液採取装置。

(31)患者から血液サンプルを抜き取って集める際に医療作業員が使用する血液採取装置において、

挿入端部と取り付け端部を有する第１の細長い針部材を備え、前記挿入端部が患者に挿入するようになっており、前記第１の針部材が患者から抜き取られた血液を前記挿入端部から前記取付端部へ運ぶ同軸通路を有しており、

針受け入れ端部と、嵌合端部と、前記針受け入れ端部から前記嵌合端部へ延びる同軸通路と、を有する第１の雌コネクターと、

患者から抜き取られた血液が前記第１の針部材によって前記第１の雌コネクターに運ばれるように、前記第１の針部材の前記取り付け端部を前記第１の雌コネクターの受け入れ端部に固定してかつ密封自在に連結する手段と、

嵌合端部と、取り付け端部と、前記嵌合端部から前記取り付け端部へ延びる同軸通路を有する第１の雄コネクターをさらに備え、前記第１の雄コネクターの前記嵌合端部は、前記第１の雌コネクターへ運ばれた血液が前記第１の雄コネクターによって受け入れられるように、前記第１の雄コネクターの前記嵌合端部に密封自在に嵌合されており、

第１及び第２の端部と、前記第１の端部から前記第２の端部へ延びている通路とを有する細長いチューブをさらに備え、前記チューブの前記第１の端部は、前記第１の雄コネクターによって受け入れられた血液が前記チューブによって送られるように、前記第１の雄コネクターの前記取り付け端部に密封自在に取り付けられており、前記チューブは、可撓性を有し、かつ、前記チューブによって受け入れられた血液が医療作業員に見えるように概ね透明であり、

細長い中空のシャフトと、前記シャフトの第１の端部に取り付けられている接続部材とを有するカップリングをさらに備え、前記カップリングは、前記チューブの第２の端部を前記カップリングに固定して密封自在に連結し、それによって、前記チューブによって受け入れられた

血液を前記カップリングに送り、前記カップリングは、前記シャフトを血液貯蔵手段に接続する、前記シャフトの第２の端部に取り付けられたアダプタースリーブをさらに有し、前記カップリングは、前記アダプタースリーブと前記接続部材との間の前記シャフトに固定して取り付けられて、前記カップリングによって受け入れられた血液が前記第２の雌コネクターと連通するように、前記接続部材と連通している第２の雌コネクターをさらに有し、

前記第２の雌コネクターと前記アダプタースリーブとの間の前記カップリングの前記シャフト内に位置しているプラグをさらに備え、前記プラグは、気体を前記シャフトから逃がして前記シャフトから前記アダプタースリーブへ血液流れを有効に遮断するようになっている血液採取装置。

(32)挿入端部と、連結端部と、前記挿入端部から前記連結端部へ延びる同軸通路とを有する第２の針部材と、

患者から抜き取られた血液を貯蔵するバキュティナー手段とをさらに備え、前記バキュティナー手段は、前記第２の針部材に固定して取り付けられ、前記アダプタースリーブは、前記バキュティナー手段が前記アダプタースリーブの中へ圧入されるように、かつ、前記第２の針部材が前記プラグを通して挿入され、それによって前記カップリングの前記シャフトによって受け入れられた血液を前記バキュティナー手段へ運ぶように、形成されている請求項(31)に記載の血液採取装置。

(33)前記第２の針部材を案内して前記第２の針部材を前記カップリングと同軸の前記プラグへ挿入する、前記プラグと前記アダプタースリーブとの間の前記カップリング内に位置している針案内手段をさらに備えている請求項(32)に記載の血液採取装置。

(34)血液貯蔵手段に結合している針を案内して前記針を前記カップリングへ同軸に挿入する、前記プラグと前記アダプタースリーブとの間の前記カップリング内に位置している針案内手段をさらに備えている請求項(31)に記載の血液採取装置。

(35)前記第２の雌コネクターに係合しそれによって前記第２の雌コネクターから血液が流出するのを防止すべく前記第２の雌コネクターを密封するようになっているキャップ手段をさらに備える請求項(31)に記載の血液採取装置。

(36)一時的に血液を貯蔵する注射器をさらに備え、前記注射器は、血液貯蔵チャンバーと該血液貯蔵チャンバー内に位置するプランジャーとを有し、前記注射器は、前記血液貯蔵手段と連通していて、前記カップリングによって受け入れられた血液が前記注射器内に貯蔵されるように、前記第２の雌コネクターと嵌合するようになっている請求項(31)に記載の血液採取装置。

(37)前記第２の針部材を案内して前記第２の針部材を前記カップリングと同軸の前記プラグへ挿入する、前記プラグと前記アダプタースリーブとの間の前記カップリング内に位置している針案内手段をさらに備えている請求項(36)に記載の血液採取装置。

(38)挿入端部と、連結端部と、前記挿入端部から前記連結端部へ延びる同軸通路とを有する第２の針部材と、

患者から抜き取られた血液を貯蔵するバキュティナー手段とをさらに備え、前記バキュティナー手段は、前記第２の針部材に固定して取り付けられ、前記アダプタースリーブは、前記バキュティナー手段が前記アダプタースリーブの中へ圧入されるように、かつ、前記第２の針部材が前記プラグを通して挿入され、それによって前記カップリングの前記シャフトによって受け入れられた血液を前記バキュティナー手段へ運ぶように、形成されている請求項(37)に記載の血液採取装置。

(39)前記第１の針手段、前記第２の雌コネクター、及び前記アダプタースリーブを各々密封する、第１、第２及び第３のキャップ手段をさらに備える請求項(37)に記載の血液採取装置。

(40)前記第２の雌コネクターと前記シャフトとの間を選択的に連通する、前記第２の雌コネクターに連結されたバルブ手段をさらに備える請求項(31)に記載の血液採取装置。

(41)患者から血液サンプルを抜き取って貯蔵するために、医療作業員が使用する血液採取装置において、

患者から血液を抜き取る針手段と、

患者から抜き取った第1の血液部分を一時的に貯蔵する注射器手段と、

前記針手段を前記注射器手段へ密封自在に連結するカップリング手段とを備え、前記カップリング手段は、前記針手段と前記カップリング手段内にたまった空気を排気する流れ制御手段を有しており、前記カップリング手段は、血液貯蔵手段を受け入れて前記カップリング手段へ貯蔵のために血液を導くようになっているアダプター手段をさらに有しており、前記注射器手段と前記カップリング手段は、前記第1の血液部分を患者に戻すようにさらになっている血液採取装置。

(42)前記カップリング手段が、細長い中空シャフトを有するカップリングを備え、前記カップリング手段が、前記カップリングへ前記針手段を固定して連結する、前記シャフトの第1の端部に取り付けた接続部材をさらに有し、前記アダプター手段は、前記シャフトの第2の端部に取り付けられており、前記カップリングは、前記注射器手段を受け入れる、前記アダプター手段と前記接続部材との間の前記シャフトに固定して取り付けた接続部材をさらに有している請求項(41)に記載の血液採取装置。

(43)前記流れ制御手段が、前記接続部材と前記アダプター手段との間の前記カップリングの前記シャフト内に位置しているプラグから成る請求項(42)に記載の血液採取装置。

(44)前記プラグが微孔質疎水性プラグから成る請求項(43)に記載の血液採取装置。

(45)前記針手段が、血液サンプルを抜き取るために患者に挿入する針と、患者から抜き取られた血液を前記カップリングへ導く、細長いチューブとを有し、前記チューブは可撓性を有し、かつ、前記チューブによって導かれている血液が医療作業員に見えるように概ね透明である請求項(43)に記載の血液採取装置。

(46)前記血液採取装置にたまった空気を排気しながら患者から第1の血液部分を抜き取って前記血液採取装置を満たし、嫌気性サンプルが前記血液採取手段にたまった空気に汚染されないように、前記血液採取装置にたまった空気を概ね排気した後、患者から嫌気性サンプルを抜き取る、

ステップから成る患者から嫌気性血液サンプルを抜き取る方法。

(47)前記第1の血液部分を抜き取った後に、前記第1の血液部分を一時的に貯蔵し、

前記嫌気性血液サンプルを抜き取った後に、前記第1の血液部分を患者に戻す、

ステップをさらに含む請求項(46)に記載の方法。

(48)前記第1の血液部分を抜き取るステップが、

注射器にカップリングを連結するステップをさらに含み、前記カップリングは針組立体に密封自在に連結されており、

さらに、前記第1の血液部分を抜き取るステップが、

血液が前記針組立体を介して前記注射器を取り付けたカップリングの中に導かれるように、患者に前記針組立体を挿入し、

前記挿入された針組立体とカップリング内にたまった空気を排気し、

バキュティナーのバキュティナー針を前記通気されたカップリングに接続して、前記バキュティナー針を前記挿入された針組立体と連通させ、

前記バキュティナーを取り付けたカップリングから前記第1の血液部分を前記注射器の中に抜き取る、

ステップを含んでいる請求項(47)に記載の方法。

(49)前記嫌気性血液サンプルを抜き取るステップが、前記第1の血液部分が抜き取られた後で前記針組立体と前記バキュティナーとの間に血液の流れをつくるステップから成る請求項(48)に記載の方法。

(50)前記第1の血液部分を前記注射器へ抜き取るステップが、患者の心臓の圧力下で自由に血液

を流すステップから成る請求項(48)に記載の方法。

3.発明の詳細な説明

(産業上の利用分野)

本発明は、患者から血液サンプルを採取する装置に向けられたものであり、特に、サンプル内の気体分圧が、患者の生体内における血液内の気体分圧とほぼ等しくなるように、血液サンプルを受け取ることができる、改良された血液採取装置に向けられたものである。

(従来技術)

医療分野では、患者の血液内の、生体内における気体の平衡状態を決定することが必要である。医療作業員は、代表的には、酸素と二酸化炭素の分圧を気にかけるであろう。彼らは、また、例えば水素イオンやカルシウムイオンのような、活性が血液中の気体平衡に関連してくるイオンの種を気にかけるであろう。

血液サンプルを血液中の気体分析のために有効なものにするには、サンプルは、嫌気条件で、すなわち、検査すべき気体の分圧に変動が生ずるのを防止すべく血液が患者の体外の気体にさらされないように、採取されなければならない。現在市販されて利用できる主要な血液採取装置は、嫌気血液採取の完全性を保証しているという点では、概ね妥当であるとはいえない。従来装置の例としては、注射器及びベント式プランジャーが使用されており、バレル内の空隙がない状態からベント式プランジャーを引っ張ることによって、患者から正確な血液体積が得られるまで、患者から注射器のバレルの中に血液をゆっくりと抜き取る。しかしながら、これらの装置は、血液サンプルが外気にさらされるのをある程度許している。プランジャーが移動する前に、ある程度の外気量はバレル内に含有されるであろう。従って、血液の最初の部分はこれらの気体にさらされ、それによって、この最初のサンプルに含有している気体の分圧が変化する。抜き取られた血液のうち最初の部分を捨てる手段は提供されておらず、そのため、全サンプルが汚染されるであろう。

さらに、前述した装置を用いる際に、装置の医療作業員を、作業の途中で汚染された血液の偶発的な破裂や暴露に対して保護する手段も提供されていない。

ベクトンディケンソン(Becton and Dickenson)のバキュテイナー(Vacutainer)及びバキュテイナー付属装置のような他の装置は、抜き取られた血液に対する暴露から医療作業員を保護する、改良された特性を示している。しかしながら、これらの装置もまた、外気に対する血液サンプルの最初の部分の暴露を、ある程度許容してしまう。

前述した従来技術の欠点に加えて、嫌気性血液サンプルの採取を可能にしつつ、流し込み、すなわち血液の流れの中へ、例えば栄養剤や薬等を注入する手段を備える血液採取装置は、現在のところ知られていない。

従って、患者から嫌気性血液サンプルを抜き取る装置を提供することが望ましい。さらに、液体を患者の血液の流れに注入することもできる、血液サンプルを抜き取る装置を提供することがさらに望ましい。穿刺、すなわち針の配置を追加して行う必要のない、繰り返して血液を採取できる、前記装置を提供することがさらに望ましい。また、予定された区間の採取、すなわち他の引き続いて行なわれる血液の採取の間、患者に残してお

くことができる、血液サンプルを抜き取る装置を提供することが望ましい。

(発明の目的)

それゆえ、本発明の目的は、患者から嫌気性血液サンプルを抜き取る血液採取装置を提供することである。

また、本発明の目的は、最初の汚染された血液のサンプル部分を抜き取って、残りのサンプルにおける完全な嫌気性を維持できる、血液採取装置を提供することである。

さらに、本発明の目的は、外部の液体を患者の血液の流れの中に注入できる血液採取装置を提供することである。

さらに、本発明の目的は、穿刺、すなわち針の配置を追加して行なう必要のない、繰り返して血液を採取できる血液採取装置を提供することである。

さらに、本発明の別の目的は、予定された区間の採取、すなわち他の引き続いて行なわれる血液採取の間、患者に残しておくことができる血液採取装置を提供することである。

本発明の、これら及び他の目的は、患者から血液を抜き取ってこれを貯蔵するときに、医療作業員が使用するカップリングを提供することによって、かなえられる。このカップリングは、血液サンプルを引き出すべく、患者に針を注入する針組立体とともに使用するために、特に利用される。カップリングは、細長い中空シャフトと、針組立体を該シャフトに固定的に連結し、針によって引き出された血液をシャフトに送る、シャフトの第1の端部に取り付けられる接続部材と、から成る。カップリングは、シャフトを様々な血液貯蔵手段に接続する、シャフトの第2の端部に取りつけられたアダプタースリーブをさらに備えている。開口部が、アダプタースリーブと接続部材との中間のシャフトに連結されており、シャフトに受け入れられた血液がその開口部と連通するように、その開口部は、接続部材と連通している。

本発明の別の実施例では、血液の流れを遮断してシャフトにたまった空気を通気する装置が提提される。特に、流れ制御手段、例えば、微孔質の疎水性プラグが、シャフトからアダプタースリーブへの空気の流れを可能にしつつ、シャフトからアダプタースリーブへの血液の流れを制限するため、開口部とアダプタースリーブとの中間のシャフト内に位置している。本発明の他の実施例では、シャフトと開口部との選択的な連通を可能にするバルブが、シャフトと開口部との中間に設けられる。

本発明の他の実施例は、特許請求の範囲で特に示され、明瞭に請求される。しかしながら、本発明は、実施の構成や方法に関する限り、添付図面を参照して次の詳細な説明を読むことから最も良く理解できるであろう。

(実施例)

本発明の改良された血液採取装置を示す断面図が第1図に提供されている。血液採取装置は、患者の血液流れ(動脈あるいは静脈)内に挿入するようになった挿入端部102を有する細長い針100を備えている。針100は、さらに、円筒シール108を介して第1の接続部材106に取り付けられている取り付け端部104を有している。当業界で周知のように、針100は、患者から引き出された血液を第1の接続部材106へ導く、挿入端部102から取り付け端部104へ延びる同軸通路を有している。

円筒シール108は、内部に針100の取り付け端部104が固定して取り付けられている中央開口部110を有している。さらに、円筒シール108は、第1の接続部材106の針受け入れ端部112へ固定して取り付けられている。第2の接続部材114は、第1の接続部材106の嵌合端部118と嵌合するようになった嵌合端部116を有しており、その結果、第1の接続部材によって受け入れられた、針100からの血液は、嵌合接合116、118を介して第2の接続部材114に導かれる。

チューブ122の第1の端部120が、第2の接続部材114の取り付け端部124に密封して取り付けられている。チューブ122は、患者から引き出された血液を針100を介してカップリング126へ運ぶために設けられている。チューブ122は、針を患者の血液流れに容易に挿入可能であり、さらに、挿入後、針100に無用な動

きを与えて患者に不快感を生ぜしめることなく、医療作業員がカップリング１２６を操作可能となるように、可撓性であるのが好ましい。さらに、チューブ１２２は、医療作業員が患者から引き出された血液を視覚で観察できるように、透明であるのが好ましい。

針１００と、第１の接続部材１０６と、第２の接続部材１１４と、チューブ１２２との組合わせは、針組立体を構成し、当業界で周知の針、接続部材、及びチューブから容易に組立て可能である。一例として、第１及び第２の接続部材１０６及び１１４は、当業界で周知のように、雄及び雌のルエル(Luer)コネクターから成る。

カップリング１２６は、チューブの第２の端部１２８を、第１及び第２の血液貯蔵手段１３０及び１３２の各々と接続するために設けられている。この目的のために、カップリング１２６は、チューブ１２２の第２の端部１２８を受け入れる中央開口部を有する接続部材１３４を有している。接続部材１３４は、チューブ１２２によってカップリング１２６に送られる血液がシャフト１３６の内部に受け入れられるように、細長い中空シャフト１３６に一体に接続される。アダプタースリーブ１３８は、接続部材１３４が接続されている端部と反対側の端部でシャフト１３６に一体に接続されている。アダプタースリーブ１３８は、シャフト１３６と連通しており、後で完全に説明するように、第２の血液貯蔵手段１３２を受け入れるために設けられる。

カップリング１２６は、さらに、アダプタースリーブ１３８と接続部材１３４との中間のシャフト１３６に一体に接続されている開口部１４０を、さらに有している。開口部１４０は、第１の血液貯蔵手段１３０をカップリング１２６のシャフト１３６へ接続するために設けられる。通路１６２は、開口部１４０が接続部材１３４と連通するように、開口部１４０に近接してシャフト１３６に設けられている。従って、チューブ１２２によってカップリング１２６に送られてきた血液は、貯蔵のため、アダプタースリーブ１３８及び開口部１４０を経由して第１及び第２の血液貯蔵手段１３０及び１３２へ運ばれる。

カップリング１２６は、また、アダプタースリーブ１３８と開口部１４０との間のシャフト内に配置されたプラグ１４２を有している。プラグ１４２は、血液採取作業の初期の段階の間に、接続部材１０６、１１４、チューブ１２２、シャフト１３６、及び開口部１４０内にたまった空気を排気する、例えば、多孔質プラグのような液体流れ制御手段から成る。従って、プラグ１４２は、シャフト１３６からアダプタースリーブ１３８への血液の流れを制限して、シャフトからアダプタースリーブへの空気の流れを可能にするようになっている。本発明の好ましい実施例では、プラグ１４２は、当業界で周知の、微孔質の疎水性プラグから成る。しかしながら、他の液体流れ制御手段が、好ましい微孔質疎水性プラグ１４２の代わりに、用いることができることは、当業者には明らかであろう。

前述したように、開口部１４０は、第１の血液貯蔵手段１３０を受け入れるようになっている。キャップ１４４は、第１の血液貯蔵手段１３０がカップリング１２６に接続されていないときに、しばしばおこる不注意な血液損失から開口部を密封するため、開口部１４０と係合可能である。しかしながら、通常作業では、キャップ１４４は、開口部１４０から取り除かれ、そこに第１の血液貯蔵手段１３０を接続している。

本発明の好ましい実施例では、第１の血液貯蔵手段１３０は、血液貯蔵チャンバー１４６と、その血液貯蔵チャンバー１４６内に配置されたプランジャー１４８を有する形式の注射器から成る。周知のように、操作の際には、プランジャー１４８は、血液がチャンバー内に入るように、血液貯蔵チャンバー１４６からゆっくりと引き出される。血液貯蔵手段１３０は、さらに、血液貯蔵手段１３０を開口部１４０に接続するため、接続手段１５０を備えている。本発明の好ましい実施例では、開口部１４０と接続部材１５０は、各々、雄雌のルエルコネクターから成る。しかしながら、他のコネクター部材が第１の血液貯蔵手段１３０をカップリング１２６に密封して接続するために提供されることは、当業者には明らかであろう。

操作の際は、キャップ１４４は、開口部１４０から取り除かれて、そこに血液貯蔵手段１３０が接続される。次いで、血液が引き出され、あるいは好ましくは患者の心臓の圧力下で自由に流れることができるように、かつ、接続部材１０６、１１４及びチューブ１２２を介して、シャフト１３６に送られるように、患者の血液流れの中に針１００が挿入される。接続部材１０６、１１４、チューブ１２２、シャフト１３６及び開口部１４０内にたまった空気は、前述したように、流れ通路に入った患者の血液によって、置換され、多孔質プラグ１４２を介して通気される。引き出され、あるいは患者からの心臓の圧力下で流れる血液の第１の部分は、通気される前に、たまった空気にさらされるので、概ね汚染されており、それゆえ、嫌気性血液採取に適していない。従って、この第１の血液の部分は、一時的に貯蔵するために、血液貯蔵手段１３０の中へカップリング１２６から引き出され、一方、嫌気性血液サンプルは、第２の血液貯蔵手段１３２を介して受取られる。嫌気性血液サンプルが受取られた後、血液貯蔵手段１３０内に一時的に貯蔵された血液は、捨てられ、あるいは、チューブ１２２及び針１００を介して患者に戻される。

嫌気性血液サンプルを引き出すため、第２の血液貯蔵手段１３２がアダプタースリーブ１３８を介してカップリング１２６に接続されている。第２の血液貯蔵手段１３２は、当業界で周知のベクトン・ディケンソン・バキュティナーから成っていてもよい。血液貯蔵手段１３２は、患者から抜き取られた嫌気性血液サンプルを受け入れる血液貯蔵チャンバー１５２を有している。針１５４は、針ハブ１５６に密封して接続されており、それらの組立体は、適合性を有するカップリング１５８（普通は、バキュテイナーアダプターとして言及されている）を介して血液貯蔵チャンバー１５２に密封して接続されている。当業界で周知のように、針１５４は、血液貯蔵チャンバー１５２と連通することを防止するため、シールを有している。さらに、当業界で周知のように、血液貯蔵チャンバー１５２は、患者から抜き取られた血液を汚染する空気を含まないようにするため、排気されている。適合性を有するカップリング１５８は、針１５４を血液貯蔵チャンバー１５２と連通させて配置するため、針１５４からシールを取り除く手段を備えている。

アダプタースリーブ１３８は、針ハブ１５６をきちんと受け入れるような径でできた内部アダプターチャンバー１６０を有している。アダプタースリーブ１３８の長さとシャフト１３６内のプラグ１４２の位置は、血液貯蔵手段１３２がアダプタースリーブ１３８に完全に挿入され、針１５４がプラグ１４２を通って通路１６２とチューブ１２２の第２の端部１２８との間に位置するように、選択される。針がシャフト１３６と同軸になるようにカップリング１２６内に挿入されることを可能とするため、針ガイド１６４がアダプタースリーブ１３８とプラグ１４２との間のカップリング１２６内に配置されている。針ガイド１６４は、カップリング１２６内への血液貯蔵手段１３２の挿入の間、針１５４を受け入れて、かつ、針がシャフト１３６と同軸となるように、プラグ１４２への針の挿入前に針を位置決めするために、設けられている。

操作の際は、嫌気性血液サンプルを集めるために、血液貯蔵手段１３０が、前述した開口部１４０を介してカップリング１２６に連結される。針１００が患者の血液流れの中に挿入され、針１００、コネクター１０６、１１４、チューブ１２２及びカップリング１２６の内部にたまった空気が前述したようにプラグ１４２を介して排気される。次いで、血液貯蔵手段１３２の針１５４が、チューブ１２２の近傍の通路１６２を越えて位置するように、プラグ１４２を通してカップリング１２６内に挿入される。針１５４内にたまった汚染空気のどんなにわずかの部分でもプラグ１４２を介して排気されるように、すなわち、嫌気性血液サンプルを受け入れる前にカップリング１２６から取り除かれるように、血液サンプルの汚染された部分を貯蔵手段１３０内に貯蔵する前に、針１５４をカップリング１２６へ挿入することが望ましい。

針１５４がカップリング１２６内に適当に挿入された後、汚染された血液の第１の部分はカップ

リング１２６から一時貯蔵のため血液貯蔵手段１３０へ引き出される。このとき、針１５４のシールは、嫌気性血液サンプルが血液貯蔵１５２へ導かれるように、当業界で周知のように、適合性カップリング１５８によって除去される。血液貯蔵チャンバー１５２へ導かれた血液のほぼ全部がチューブ１２２から受け取った血液であって、血液貯蔵手段１３０の血液貯蔵チャンバー１４６から受け取った血液ではないようにするために、針１５４は、通路１６２とチューブ１２２との中間でかつ、チューブ１２２の第２の端部１２８の近傍の、シャフト１３６内のカップリング１２６内に位置していることが好ましい。

本発明の代わりの実施例では、嫌気性血液サンプルを受け取っているとき、血液貯蔵手段１３０内に貯蔵された汚染された血液サンプルを、操作中に、シャフト１３６からほぼ隔離することができるバルブ、あるいは他の選択性カップリング手段を備えることが望ましい。

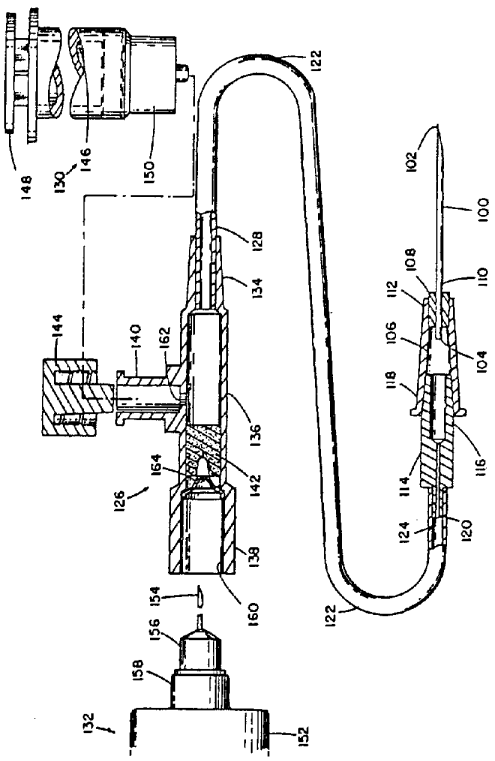
医療業界では普通となっているように、キャップ１４４に加えて、複数のキャップあるいは他のシール手段が、針１００に配置してアダプタースリーブ１３８のチャンバー１６０を密封するために設けられてもよい。

新規な血液採取装置の好ましい実施例のいくつかのみをここで詳細に説明したが、当業者には、多くの改良や変更が容易に明らかとなるであろう。本発明の真の範囲及び精神に入るこのようなすべての改良や変更を包含することが、特許請求の範囲の趣旨である。

4.図面の簡単な説明

第１図は、本発明の改良された血液採取装置の断面図を示す。

１００・・・・・針
１０６・・・・・第１の接続部材
１１４・・・・・第２の接続部材
１２２・・・・・チューブ
１２６・・・・・カップリング
１３０、１３２・血液貯蔵手段
１３４・・・・・接続部材
１３６・・・・・シャフト
１３８・・・・・アダプタースリーブ
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2010 (03.06.2010)

PCT

(10) International Publication Number
WO 2010/062734 A1

(51) International Patent Classification:
A61F 13/02 (2006.01) *A61P 7/04* (2006.01)
A61L 15/44 (2006.01)

(21) International Application Number:
PCT/US2009/063049

(22) International Filing Date:
3 November 2009 (03.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/110,698 3 November 2008 (03.11.2008) US
61/234,773 18 August 2009 (18.08.2009) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: BLOOD COAGULATION INDUCING POLYMER HYDROGEL

(57) Abstract: The present application is drawn to a synthetic, polymer hydrogel-based material, which is able to actively induce the body's natural hemostatic coagulation process in blood or acellular plasma. The present invention provides the development of a primary amine containing polymer hydrogel capable of inducing blood coagulation and delivering therapeutics for hemostatic or wound care applications, and a method of forming such a primary amine containing polymer hydrogel capable of inducing the blood coagulation process. The primary amine containing polymer hydrogel is able to achieve the same end result as biological-based hemostatics, without the innate risk of disease transmission or immunological response, and at a fraction of the price. Furthermore, due to its inherent hydrogel-based design the material has the capability of arresting blood loss while simultaneously delivering therapeutics in a controlled manner, potentially revolutionizing the way in which wounds are treated.

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BLOOD COAGULATION INDUCING POLYMER HYDROGEL

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional applications Serial Nos. 61/110,698, filed November 3, 2008 and 61/234,773, filed August 18, 2009, which are incorporated in their entireties by reference herein.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under CTS0640778 awarded by the National Science Foundation. The U.S. Government has certain rights in this invention.

TECHNICAL FIELD

[0003] The present invention relates to a polymer material capable of actively inducing the blood coagulation cascade while simultaneously delivering therapeutics in a controlled manner for application in the wound care field.

BACKGROUND

[0004] Technology capable of effectively controlling traumatic hemorrhaging does not exist. As a result, millions of people around the world are dying every year. Over 3,000,000 worldwide, 156,000 in the U.S. alone, die from trauma related injuries each year. Half will die before they reach the hospital, and 80% will die within 24 hours of hospital admission. Uncontrolled hemorrhaging, or blood loss, accounts for almost half of these deaths. Moreover, on the battlefield an astounding 85% of military mortalities are due to blood loss, a statistic that has remained mostly unchanged since the Vietnam War. Army medics, emergency medical technicians (E.M.T.) personnel, and other various emergency responders need a product capable of providing rapid and effective hemostasis until they can get their patients to the operating room. Once at the operating room, hemostatic products are still crucial to surgeons who must control bleeding to maintain the stability of their patient.

[0005] Current products are either exorbitantly expensive, ineffective, and/or have adverse side effects. There is a clear need for a hemostatic product which is inexpensive,

effective, with little to no adverse side effects and medics, emergency responders, and surgeons are all looking for a solution. Furthermore, there is currently no existing product or material on the market with the capability of providing rapid hemostasis along with simultaneous drug delivery. A product which could effectively stop blood loss while simultaneously delivering potentially life-saving therapeutics such as adrenaline or insulin in a regulated manner would have a multitude of applications from the battlefield to the operating room.

[0006] Death may occur in minutes after a traumatic injury due to blood loss. The body has natural mechanisms to control hemorrhaging yet these processes may be insufficient in cases of excessive hemorrhaging, defective due to medical conditions such as hemophilia, or compromised due to adverse effects of medication like Coumadin. The natural hemostatic response is not adequate to control major hemorrhaging due to traumatic injury, which is the main reason why such injuries, if gone untreated, are typically fatal. Administration of biologically derived blood products to augment the native hemostatic response and to maintain adequate oxygen delivery to the brain and vital organs, carries significant risks including disease transmission, infection, pulmonary dysfunction, and immune response. Furthermore, many people have deficiencies within their hemostatic response i.e. hemophilia, which prevent them from adequately stopping blood loss. Millions of people around the world suffer from bleeding disorders, and are unable to clot blood effetively. Current treatments are typically limited to clotting factor (Factor VIII, Factor II) replacement therapies, which are typically painful and exorbitantly expensive. There is a clear need for an inexpensive, painless alternative to current treatments. Whether the injury overwhelms the body's clotting response or the native response is deficient or compromised, an inexpensive, synthetic material which has the ability to induce clotting effectively, while simultaneously delivering therapeutics would undoubtedly revolutionize the way in which wounds are treated.

[0007] The field of hemostatic agents and materials has expanded dramatically within the last decade. This considerable expansion and evolution of the field, throughout the last decade has also been accompanied by tremendous diversification resulting in a multitude of hemostatic products now available on the market, each with their own advantages and disadvantages. The hemostatic products currently available on the market today are either biological-based or synthetic-based. Biological-based hemostatics are comprised of animal or "animal derived" substrates which are able to initiate, amplify, and/or assist the natural

coagulation response. Although they have excellent hemostatic effects and work via the promotion of the body's natural responses, they are incredibly expensive (up to $500 per application) and carry risks of disease infection and severe immunological response. Synthetic hemostatic agents are typically less expensive and immune inert yet often fail to effectively induce the coagulation cascade. Such synthetic agents are mainly designed to be mere physical obstructions to impede blood flow while providing a scaffold for the coagulation process to occur. A purely synthetic, polymer-based hydrogel material capable of effectively inducing the body's natural coagulation response has enormous potential within the field. Such a material is unique to the market in that it could be used to effectively stop bleeding while simultaneously delivering necessary therapeutics to a wound site.

SUMMARY OF THE INVENTION

[0008] The inventors of the present application have developed a purely synthetic, polymer hydrogel-based material, which is able to actively induce the body's natural hemostatic coagulation process in blood or acellular plasma. There is currently no polymer hydrogel-based, synthetic hemostatic agent with the capability of inducing the formation of a natural hemostatic matrix in the absence of platelets or blood cells. Since the material is able to induce the formation of a natural hemostatic plug in the absence of platelets or cells, it has enormous potential as a hemostatic agent in surgery, to treat trauma victims, and especially for patients with platelet disorders. The material is able to achieve the same end result as biological-based hemostatics, without the innate risk of disease transmission or immunological response, and at a fraction of the price. Furthermore, due to its inherent hydrogel-based design the material has the capability of arresting blood loss while simultaneously delivering therapeutics in a controlled manner, potentially revolutionizing the way in which wounds are treated.

[0009] The blood coagulation cascade may be activated via two distinct routes, the tissue factor pathway and the intrinsic pathway, also known as the contact activation pathway. Both pathways eventually result in the activation of a common pathway, which leads to the formation of a fibrin-based hemostatic clot Our research has shown that a material is able to induce the formation of fibrin via the tissue pathway factor Specifically, a positively charged polymer network with adequate mechanical rigidity is capable of efficiently and effectively inducing the activation of FVII, which in turn leads to the activation of the common pathway and subsequent fibrin formation. Furthermore, the material is able to induce the activation of

FVII irrespective of calcium or platelets which are typically vital cofactors of the process.

[0010] In one aspect, the present invention provides a cross-linked primary amine containing polymer hydrogel capable of inducing blood coagulation, and subsequent fibrin clot formation, while simultaneously delivering therapeutics in a controlled or regulated manner for wound care applications.

[0011] In another aspect the present invention is able to induce coagulation in Factor XII, XI, IX, VIII, and V deficient blood plasma.

[0012] In another aspect the present invention is capable of inducing the activation of FVII irrespective of calcium and platelets.

[0013] In another aspect, the present invention provides a method of forming the specific type of cross-linked primary amine containing polymer hydrogel in order to effectively induce blood coagulation: (a) adding either a primary amine containing monomer or primary amine containing polymer with a pKa greater than 7.4 thereby being positively charged within a plasma or blood environment (pH 7.4); (b) addition of additional monomers different from the initial primary amine containing monomer; (c) forming a polymer matrix by initiating polymerization of monomer units into polymer strand; (d) cross-linking the polymer strands to produce a polymeric mesh network.

[0014] In other aspects, the present invention provides various uses for a polymer hydrogel capable of inducing blood coagulation and delivering therapeutics in a controlled manner, in the health care field.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **Figure 1: Coagulate complex formed by optimal hydrogel after immersion in citrated plasma.** Typical coagulate complex (fibrin-hydrogel complex) formed after rotating the optimal hydrogel in human plasma (4 % w/v sodium citrate) for 18 hours.

[0016] **Figure 2: Characterization images (H&E, IHC, ESEM) of coagulate complex formed by optimal hydrogel after immersion in citrated plasma.** (**A**) H&E stained micrograph image of coagulate complex. Polymer hydrogel appears as lighter, smoother material on right side of the micrograph while fibrin appears as the darker, rougher material on the left side of them micrograph. (**B**) IHC stained micrograph image of coagulate complex. (**C**) ESEM surface image of the coagulate complex.

[0017] **Figure 3: Optimization experiment.** Experiment aimed to investigate the dependence of fibrin formation on various compositional factors including total monomer

concentration (acrylamide + APM + BIS), positive electrostatic charge (APM), and cross-linker ratio (acrylamide:APM:BIS). Acrylamide concentration is located on the horizontal axis while APM concentration is on the vertical axis. BIS concentration is also indicated on the horizontal axis and is kept constant for each respective acrylamide concentration. The amount of fibrin formation induced by each composition was visually scored from 0 (no fibrin formation) to 10 (substantial fibrin formation). All samples were run in triplicate.

[0018] Figure 4. Factor deficient and factor inhibited plasma experiment. Optimal hydrogel composition tested in various factor deficient and factor inhibited plasmas. The resulting fibrin formation was visually scored from 0 (no fibrin formation) to 10 (substantial fibrin formation) and graphed accordingly. All samples were run in triplicate.

[0019] Figure 5: Kinetic biological mechanism experiments. Factor VIIa concentration (**A**), calcium concentration (**B**) , and TFPI activity (**C**) was measured in human plasma containing various hydrogel compositions at 30, 90, and 180 minutes (left axis: bar graph). The amount of fibrin formation was also rated for each composition at each time point (right axis: line graph). Data is representative of an average and corresponding standard deviation (error bar) of three (n=3) separate sample trials. Asterisk (*) indicates duplicate sample point.

[0020] Figure 6: Dynamic mechanical analysis. Dynamic mechanical analysis of three compositions used in the kinetic biological mechanism experiments (FVIIa, calcium, TFPI) ranging from high APM, low acrylamide and BIS content (composition A) to low APM, high acrylamide and BIS content (composition F). Spectra for sample compositions C and F are shifted vertically to avoid overlapping of data.

[0021] Figure 7: Fresh sheep blood experiment. 250 mg of our hydrogel material (**A**) compared to a control (**B**). Clotting time of blood with material was dramatically decreased (~45 seconds) compared to control (~10 minutes).

[0022] Figure 8: Prototype images. (**A**) Computer generated graphic of prototype used in animal experiment. (**B**) Actual prototype used in animal trial.

[0023] Figure 9: Animal trial. (**A**) Image of lung at time of incision, before hydrogel was applied. (**B**) Image of the incision site after the hydrogel prototype bandage was applied for approximately 2 minutes.

[0024] Figure 10: Stained lung section of incision site. Micrograph of hematoxylin and eosin (H&E) stained section of incision site after hydrogel material was applied for two minutes.

DETAILED DESCRIPTION OF THE INVENTION

[0025] A reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present. Rather, the article "a" or "an" is intended to mean one or more (or at least one) unless the text expressly indicates otherwise. The terms "first," "second," and so on, when referring to an element, are not intended to suggest a location or ordering of the elements. Rather, the terms are used as labels to facilitate discussion and distinguish elements from one another.

[0026] The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting. Each of the disclosed aspects and embodiments of the present invention may be considered individually or in combination with other aspects, embodiments, and variations of the invention. Modifications of the disclosed embodiments incorporating the spirit and substance of the invention may occur to persons skilled in the art and such modifications are within the scope of the present invention.

[0027] The present invention provides the development of a primary amine containing polymer hydrogel capable of inducing blood coagulation and delivering therapeutics for hemostatic or wound care applications. Various therapeutics intended to be delivered include but are not limited to ester or amide based anesthetics such as Novocain or Lidocain, antibiotics such as erythromycin or bacitracin, vasoconstrictors such as adrenaline, and pain relievers or anti-inflammatory medicines such as topricin, acetaminophen, or ibuprofen. The hydrogel may be designed in order to deliver the drugs in various ways including based on a swelling change, a change in pH, or via the introduction of a magnetic or electric field.

[0028] The present invention provides the development of a primary amine containing polymer hydrogel capable of inducing blood coagulation and delivering other hemostatic agents for hemostatic or wound care applications, including biological-based hemostatic agents and non biological-based hemostatic agents.

[0029] Biological-based hemostatics contain, incorporate, or are derived from biological substrates, i.e. proteins, or cells. They can further be subdivided into the type of biological substrates incorporated into the system including collagen, thrombin, fibrin, albumin, and/or platelets.

[0030] Collagen is the main protein of connective tissue in mammals, including the skin, bones, ligaments, and tendons making up about 30% of the total protein in the body. In addition to providing structural integrity for the animal body, including all organs, collagen also activates the contact activation pathway of the coagulation cascade. Due to collagen's

ability to induce coagulation, along with the fact that is it naturally occurring, makes it an ideal choice for a hemostatic agent. Collagen is typically incorporated into the products via gelatin or microfibrillar form. Gelatin is an irreversibly hydrolyzed form of collagen and may be prepared as a powder, sponge, sheet, film or foam. Gelatin products are typically pliable, easy to handle, and relatively inert. When placed in soft tissue gelatin products typically absorb in 4 to 6 weeks, yet when applied to bleeding nasal, rectal or vaginal mucosa, will liquefy in approximately 2 to 5 days. The product Gelfoam (Pfizer, New York, NY), first introduced in 1945, is produced from purified pork skin gelatin granules. The foam swells up to 45 times its original dry weight and 200% of its initial volume.

[0031] Microfibrillar collagen is the predominant form used in modern hemostatic products. The collagen network acts as a framework which aggregates clotting factors, platelets, along with various coagulative and adhesive proteins to facilitate clot formation. Furthermore, the collagen fibrils are able to efficiently activate the contact activation coagulation pathway. The product is typically formed into various products including powder (shredded fibrils), sheets, and sponges. Market examples include Ultrafoam and Avitene (Davol Inc., Cranston, RI), Instat (Johnson & Johnson, Langhorne, PA), Helistat and Helitene (Integra LifeSciences, Plainsboro, NJ), Collatape/CollaCote/CollaPlug (Integra Lifesciences Corporation, Plainsboro, NJ), Collastat and Collatene (Xemax, Napa, CA).

[0032] Collagen-based hemostatic products are easily removable, cause little aggravation to the wound site, and can be very effective hemostats (especially relative to cellulose or gelatin hemostats). Disadvantages of collagen products include their prohibitive high price (around $150 per dressing), poor biodegradability, inherent risk of antigenicity, low solubility (difficult to make concentrated solutions), and handling difficulties since the products will irreversibly adhere to any hydrated surface.

[0033] Thrombin is the central activating enzyme of the common coagulation pathway. Thrombin circulates within the blood in its precursor, or zymogen form, prothrombin. Prothrombin is specifically cleaved to produce the enzyme thrombin. The main role of thrombin in the coagulation pathway is to convert fibrinogen into fibrin, which in turn is covalently cross-linked to produce a hemostatic plug. Thrombin-based products are typically sold in liquid or powder form and include Thrombostat (ParkeDavis, Ann Arbor, MI), Thrombin-JMI (King Pharmaceuticals, Briston, TN), and Quixil (Omrix Biopharmaceuticals Ltd, Tel Hashomer, Israel). There are also several combination products which include Evicel

(Johnson & Johnson, Langhorne, PA) which is a combination of thrombin and fibrin used mainly as a tissue sealant, along with FloSeal (Baxter Healthcare Corporation, Westlake Village, CA) and SurgiFlow which are both hybrid products composed of bovine or porcine gelatin and thrombin.

[0034] Thrombin-based products take advantage of the natural physiologic coagulation response by augmenting, amplifying, and assisting the process. Advantages of these products include low risk of foreign body or inflammatory reactions, firm attachment to wound bed, and its excellent hemostatic effect, specifically with patients that have platelet dysfunctions. Another advantage of thrombin is the versatility that the product may be applied, in powder or liquid (spray on) form. Disadvantages of these products include their often prohibitive high price ($75-$300 per application), difficulty of use including the inconvenience of premixing preparation, along with the risk of intravenous introduction which may result in intravascular clotting.

[0035] Fibrin is a fibrillar protein which is polymerized and cross-linked to form a mesh network, typically at the site of an injury after the induction of the coagulation cascade. The mesh network, incorporative of other various proteins and platelets, forms a hemostatic plug to prevent continuous or further blood loss. Fibrin is activated from its inert zymogen, fibrinogen, by thrombin. Fibrin is in turn polymerized and covalently cross-linked by another coagulation factor, known as Factor XIIIa. Due to its natural mechanical hemostatic role fibrin has been commercially used to control blood flow since the early 1900s. Most fibrin glues or fibrin sealants are derived from human and bovine proteins. The product is typically sold in the form of a dual syringe. The first syringe compartment contains the matrix and matrix stabilizing components including fibrinogen, factor XIII, fibronectin, and fibrinolysis inhibitors. The second syringe compartment contains the activating agent, typically thrombin and calcium chloride. At the time of application, the contents of both syringes are ejected, combining to activate fibrin matrix formation which typically takes a matter of seconds to set and approximately 5 to 10 days to degrade or absorb into the body. Various fibrin sealants on the market include Tiseel (Baxter HealthCare Corporation, Westlake Village, CA), FibRx (CryoLife Inc., Kennesaw, GA), Crosseel (Johnson & Johnson, Langhorne, PA), Hemaseel (Haemacure Corporation, Montreal, Quebec), Beriplast P (Aventis Behring, King of Prussia, PA), and Bolheal (Kaketsuken, Kumamoto, Japan).

[0036] Fibrin-based hemostatics or tissue sealants are fast-acting, composed of native coagulative factors, are biodegradable, do not promote inflammation or tissue necrosis, have diverse applications, and are particularly useful in patients with coagulation deficiencies such as hemophilia or von Willebrand's disease. Major disadvantages of fibrin-based hemostatics include their often prohibitive price ($100- $300/mL), their fragile nature, and difficulty of handling and application.

[0037] Other prominent biological-based hemostatic products include those composed of covalently cross-linked protein networks such as BioGlue (Cryolife, Kennewsaw, GA), along with products which incorporate platelets such as Costasis, marketed as Vitagel (Orthovita, Malvern, PA). BioGlue is comprised of bovine serum albumin, and various other proteins, cross-linked with glutaraldehyde to form a rigid, insoluble matrix. The reaction occurs spontaneously upon the introduction of glutaraldehyde to the protein mixture, and requires no external factors such as coagulation factors. Disadvantages of the product include the high price ($300-$425/5 ml application), mediocre hemostatic effect, necessity of a dry environment for application, the toxic effects associated with tissue exposure to glutaraldehyde, and risk of immune reactions associated with glutaraldehyde-based products.

[0038] Costasis is a combination product combining bovine collagen and the patient's own platelets. The collagen within the product promotes the initiation of the contact activation pathway of the coagulation cascade. The presence of platelets in such a product improves overall clot strength and supplies various growth factors which facilitate tissue regeneration. Disadvantages include high price ($100- $150/mL) and difficultly of application.

[0039] Non biological-based, or synthetic, hemostatic agents are defined as any products which do not incorporate biological materials, or more specifically animal derived components. Synthetic hemostatics are typically cheaper, easier to use, and easier to apply relative to their biological counterparts. Furthermore, synthetic hemostatics have no innate antigenicity, rarely induce immune responses or inflammatory reactions, and are inherently free of disease vectors." The main classes of synthetic hemostatics include cyanoacrylates, polysaccharides (e.g. oxidized cellulose, N-acetyl glucosamine), synthetic polymers, and mineral/metal based.

[0040] Cyanoacrylates are liquids that rapidly polymerize. These products create a tight seal between tissues, obstructing blood flow. Cyanoacrylates are categorized upon their

length. Shorter chain cyanoacrylates (ethyl cyanoacrylates) are typically quicker to absorb yet more toxic relative to intermediate (butyl cyanoacrylates) or longer chain cyanoacrylates (octyl cyanoacrylates). Due to their inherent high toxicity few hemostatic products composed of short chain cyanoacrylates have reached the market. There is however some research supporting the efficacy of Krazy Glue (ethyl-2-cyanoacrylate, Elmer's, Columbus, OH) for cutaneous wound closure. Cohera Medical Corporation is currently in the process of developing a butyl cyanoacrylate (isobutyl-2-cyanoacrylate), marketed as TissuGlu (Cohera Medical Inc., Pittsburgh, PA). Furthermore, there are currently several octyl acrylate-based hemostatic products that are FDA-approved for skin closure which include Dermabond (Ethicon, Somerville, NJ) and Band-Aid Liquid Bandage (Johnson & Johnson, Langhore, PA).

[0041] Cyanoacrylates are typically nonreactive, do not promote infection, are rapidly curing, and are only moderately expensive. Disadvantages of cyanoacrylates and cyanoacrylate-based hemostatics include difficulty of application due to their highly adhesive nature, and risk of tissue neurotoxicity, fibrosis and inflammatory reactions.

[0042] The two main polysaccharides used as hemostatics today are oxidized cellulose and poly-N-acetyl glucosamine. The hemostatic effects of certain polysaccharides, specifically oxidized cellulose and N-acetyl glucosamine, have been known since the early twentieth century. Oxidized cellulose is derived from plant fiber, which is in turn oxidized in the presence of nitrogen dioxide to form cellulosic acid. Oxidized cellulose activates the coagulation cascade (contact activation pathway) and accelerates thrombin generation within the body. Furthermore, the polysaccharide meshwork serves as a physical framework for coagulation to occur, with moderate absorbent properties. Oxidized cellulose products on the market today include Oxycel (Becton Dickinson, Franklin Lakes, NJ), Celox (Medtrade Products Ltd., Crewe, England), Surgicel (Ethicon Incorporation), and BloodStop (LifeScience PLUS, Inc., Santa Clara, CA).

[0043] Cellulose-based hemostatics are relatively easy to handle, fully absorbable and biodegradable (over 1 to 6 weeks), relatively inexpensive, and have antibacterial properties. The major drawback of these products is the risk of foreign body reactions. Furthermore, these products have only moderate coagulation-inducing capability and therefore are reserved as an adjunct to the natural response rather than a synthetic replacement.

[0044] Poly-N-acetyl glucosamine, also known as chitin or chitosan, is a complex polysaccharide produced by fermenting microalgal cultures. The hemostatic effects of poly-N-acetyl glucosamine are believed to be a result of the attraction and binding of circulating blood cells. The positive charges on the polymer attract the negatively charged erythrocytes, to help seal the clot. Poly-N-acetyl glucosamine also has vasospasm effects. Poly-N-acetyl glucosamine products include HemCon (HemCon Inc., Portland, OR), TraumaDex (Medafor, Minneapolis, MN), SyvekPatch (Marine Polymer Technologies Inc., Danvers, MA), Clo-Sur P.A.D. (Scion Cardio-Vascular, Miami, FL), and Chito-Seal (Abbott Vascular Devices, Redwood, City, CA).1

[0045] Advantages of poly-N-acetyl glucosamine dressings include their ease of application, robustness, and lack of toxicity. Disadvantages include the high cost ($100 per unit), and variability of efficacy between batches.

[0046] Most polymer-based hemostatics are designed to provide a mechanical tissue sealant. The majority of products on the market today are composed of polyethylene glycol (PEG) which are applied and polymerized at the wound site. The polymer is typically cross-linked with itself or with a primer to yield a robust framework stopping blow flow and sealing tissue. Most PEG products undergo biodegradation in approximately 30 days. PEG products include Coseal (Baxter Healthcare Corporation, Westlake Village, CA) and AdvaSeal-S (Genzyme Corporation, Cambridge, MA). PEG-based hemostatics or tissue sealants are typically non inflammatory, do not induce immune response, and are biodegradable. Drawbacks include difficulty of application and high price ($400/application).

[0047] Pro QR Powder (Biolife, Sarasota, FL) is another polymer-based hemostatic on the market today. Pro QR is a combination product of a hydrophilic polymer and a potassium iron oxyacid salt. The polymer is absorptive of blood flow, promoting the formation of a natural blood clot while the potassium salt component releases iron which complexes with proteins and activates hemostatic channels. The product is inexpensive, nontoxic, easily stored, flexible, stops bleeding rapidly, and is available over the counter. The main drawback of the product is its awkward application.

[0048] The final class of non-biological, or synthetic, hemostatics includes those which incorporate metal salts or minerals such as zinc, iron, silver nitrate, or aluminum chloride. Although this class of hemostatics are typically easy to use, cost-effective, and provide adequate hemostatic effects their toxic side effects limit their appeal.

[0049] Zinc paste was first used to fix tissue after surgery in the early 1940s. Zinc paste solutions have impressive hemostatic abilities but are rarely used do to their harmful side effects including pain and toxicity of the site. Monsel's solution is a 20% ferric subsulfate solution, which is believed to occlude vessels via protein precipitation. Monsel's solution is easy to obtain, cost-effective, and resistant to bacterial contamination. Major disadvantages include its caustic and toxic nature which may promote melanocyte activity, increased erythema, dermal fibrosis, and reepithelialization. Silver nitrate is typically used as a 10% solution and coagulates blood through protein precipitation. Silver nitrate is cost-effective, easy to use, and has potent antibacterial properties. Disadvantages include its severe tissue toxicity, risk of permanent skin discoloration, and the painful burning sensation experienced upon application. Aluminum chloride has modest hemostatic properties and is prepared in concentrations of 20% to 40% in water, alcohol, ether, or glycerol. Its mechanism of action is thought to be caused by the hydrolysis of the salt, resulting in the generation of hydrogen chloride which causes vasoconstriction, and can assist in the activation of the extrinsic coagulation pathway. Aluminum chloride is cost effective, easy to use, and may be stored at room temperature. Side effects of its use include painful paresthesias, tissue irritation, and reepithelialization. Aluminum chloride solutions are marketed as Drysol and Xerac AC (person-Covey, Dallas, TX).I

[0050] A small subclass of hemostatics is based upon various mixtures of minerals. Zeolite is a granular mixture of silicon, aluminum, sodium, and magnesium derived from lava rock. When coming into contact with blood the mixture absorbs water, concentrating platelets and coagulation factors within the wound, accelerating the clotting process. QuikClot (Z-Medica, Wallingford, CT) and WoundStat (TraumaCure, Bethesda, MD) are two main products based upon a zeolite mixture. Zeolite is inexpensive, easy to manufacture, clots fairly quickly, robust under various conditions, and is fairly immunological inert. The main drawback of the formulation is the risk of thermal injury associated with use.

[0051] A hydrogel is generically defined as an insoluble, cross-linked network of polymer chains which swells in an aqueous environment. A hydrogel may be chemically cross-linked through covalent bonds or physically cross-linked through entanglements or non-covalent interactions. Due to their unique properties hydrogels have been used in various pharmaceutical and biomedical applications. Since it is possible to create hydrogel constructs with specific degradative and swelling characteristics their potential for tissue engineering

and artificial implantation is immense. Furthermore, because hydrogels can be engineered with "smart" swelling behavior based on time, pH, ionic concentration, electrical, or magnetic stimuli they have been used with incredible success as drug delivery systems.

[0052] A cationic, acrylamide-based hydrogel has been developed which exhibits unique and potent coagulation-inducing effects upon the interaction with blood or acellular plasma. The hydrogel is composed of acrylamide, N-(3-Aminopropy)methacrylamide hydrochloride, and cross-linked with N-N'- methylenebisacrylamide. Upon interaction with acellular plasma the hydrogel initiates the coagulation cascade which results in the formation of a natural, fibrin-based hemostatic matrix (Figure 1). The stained microscopic images clearly show two distinct materials; the polymer hydrogel, which appears smooth and glassy on the right side of each image and a fibrin layer, which surrounds the polymer hydrogel located on the left side of each image.

[0053] In one aspect, the present invention provides a specific method of forming such a primary amine containing polymer hydrogel capable of inducing the blood coagulation process. In one embodiment, the primary amine monomer may be a strong base (wherein its ability to exhibit a positive charge is largely pH independent). In another embodiment, the primary amine monomer may be a weak base (wherein its ability to exhibit a positive charge is largely pH dependent). In yet another embodiment, the primary amine monomer is a weak base with a pKa above 7.4 and is able to exhibit a strong positive charge at the pH of blood and plasma (~7.4).

[0054] The method involves mixing at least one monomer with a primary amine group, along with desired other monomers, different from the initial primary amine containing monomer in a solvent, specifically an aqueous solvent. The polymer hydrogel is formed by polymerizing the monomers and cross-linking either after or during the polymerization process. Preferably, the polymer hydrogel is cross-linked in such a way so as to ensure the creation of pockets within the hydrogel which are incredibly dense with primary amine functionality. These dense pockets of positive electrostatic charge are able to induce coagulation through a Factor VII dependent mechanism. Without being bound to any specific theory, it is believed that that hydrogel acts as a catalyst activating and enhancing the functioning of Factor VII along with the Factor VII-tissue factor complex. Research has shown that this phenomenon is dependent on positive electrostatic charge and the mechanical rigidity of the hydrogel formed. That is to say, the primary amine monomer, within the hydrogel, should be positively charged at the pH of blood and/or plasma, 7.4. Therefore, if

the monomer is a weak base it preferably has a pKa of at least 7.4, more preferably at least 8, and even more preferably, at least 8.5, to ensure the predominant majority of the monomers are hydrogenated bearing a positive charge. Furthermore, as stated previously the amine monomer containing polymer strand must be sufficiently cross-linked to create an appropriately rigid material.

[0055] In certain embodiments, the monomer units are capable of exhibiting an electrostatic charge in an aqueous solution. In particular the primary amine containing monomer is able to exhibit a positive electrostatic in a salt buffered, aqueous environment of pH 7.4 (blood/plasma). In some cases, the contributing monomer units may be acidic or basic, which under the appropriate pH conditions, exhibit a negative or positive electrostatic charge, respectively. The acid/base monomer units may have varying levels of acidity/basicity, which will determine the extent to which the monomer units will be present in the anionic/cationic form at the pH level of the aqueous solution. With respect to acidic monomer units, the monomer unit may be a strong acid (in which its ability to exhibit a negative charge is largely pH independent) or a weak acid (in which its ability to exhibit a negative charge is pH dependent respect to basic monomer units), the monomer unit may be a strong base (in which its ability to exhibit a positive charge is largely pH independent) or a weak base (in which its ability to exhibit a positive charge is pH dependent).

[0056] In certain embodiments, the monomer units used are able to exhibit marked morphological or structural changes based on certain stimuli such as pH, electric field, magnetic field, or temperature for regulated drug delivery applications. In some cases the contributing monomer units may be basic, which under the appropriate pH conditions, exhibit a positive electrostatic charge. The base monomer units may have varying levels of basicity, which will determine the extent to which the monomer units will be present in the cationic form at the pH level of the aqueous solution. The monomer unit may be a strong base (in which its ability to exhibit a positive charge is largely pH independent) or a weak base (in which its ability to exhibit a positive charge is pH dependent).

[0057] In some cases the contributing monomers may be electrically sensitive, that is, the monomer is able to exhibit a structural phase change upon introduction to an electrical field. Examples of such monomers include vinyl alcohol, diallyldimethylammonium chloride, and acrylic acid.

[0058] In some cases the contributing monomers may able to exhibit a marked morphological or structural change based upon temperature. An example of such a

temperature sensitive monomer is N-isopropylacrylamide. The monomer may be used to produce a temperature-sensitive hydrogel for regulated release or rather for a hydrogel capable of inducing coagulation in a temperature dependent manner.

[0059] Examples of primary amine containing monomers include but are not limited to allylamine, N-3-aminopropyl methacrylamide (APM), and N-2-aminoethyl methacrylamide (AEMA). Examples of monomer units that are strong bases include those having ammonium groups, such as 3-acrylamidopropyl trimethylammonium chloride (AMPTAC). The monomer units may also be neutral monomers exhibiting no electrostatic charge in the solution. Examples of such monomers include acrylamide (Am), N-tertbutylacrylamide (NTBAAm), N-isopropylacrylamide (NIPAAm), and N,N'-dimethylacrylamide (DMAAm).

[0060] Polymerization of the monomer units can be achieved using any of various techniques known in the art, including chemical processes (e.g., using free-radical initiators and/or catalysts), photochemical processes (e.g., exposure to UV-irradiation), or electrochemical processes. Likewise, cross-linking can be achieved using any of various techniques known in the art, including the addition of a cross-linking agent to the solution. In some cases, polymerization may be effected by the addition of ammonium persulfate (APS) as the polymerization initiator and N,N,N',N'-tetramethylethylenediamene (TEMED) as the catalyst. In some cases, the cross-linking agent is a difunctional monomer, N,N'-methylenebisacrylamide (BIS), epichlorohydrin (EPI), genipin, glutaraldehyde, or ethylene glycol diglycidyl ether (EDGE). Biodegradable cross-linkers such as ethylene glycol dimethacrylate and ethylene glycol diacrylate may also be used as the cross-linking agent. The biodegradable polymers are capable of undergoing hydrolytic cleavage in vivo. Polymerization and cross-linking may take place simultaneously or sequentially in any order. As such, the polymerization initiator, catalyst, and/or cross-linking agent may be added to the solution simultaneously or sequentially in any order.

[0061] Upon polymerization (and cross-linking, in some cases) of the monomer units, a polymer matrix is formed. The amount of cross-linker used (ratio of cross-linker monomer:total remaining functional monomers) determines the mesh size of the gel network. If a polymer hydrogel composed of a primary amine containing monomer is cross-linked appropriately the material, is capable of inducing the blood coagulation pathway, in a factor VII-tissue factor dependent manner. The ability of the polymer hydrogel to induce coagulation is dependent mainly on mechanical rigidity, i.e. cross-link density, and the primary amine functionality on the main chain polymer backbone. It should be noted that

experiments were conducted using the non-cross-linked amine containing polymers, and they were unable to induce coagulation.

[0062] In certain embodiments, the polymer hydrogel is able to induce clotting in platelet deficient plasma. In other embodiments, the polymer hydrogel is able to induce clotting in Factor XII, XI, Factor IX, or Factor VIII-deficient plasma.

[0063] In a specific aspect the invention details the production of a multi-component material consisting of two different compositions of polymeric hydrogels – one for use in any internal hemostatic application, and one for use in any external hemostatic application.

[0064] In another aspect, an embodiment of the present invention provides a polymeric material comprising a cross-linked polymer matrix having a cavity, highly dense in primary amine functionality capable of inducing the blood coagulation pathway. This polymeric hydrogel may be synthesized using any of various techniques, including those described above.

[0065] The cavity may have a geometry (including its size and shape) which is capable of aiding in the activation process. Geometry of the cavity, along with density of electrostatic functional groups within the cavity, is determined, in part, by the amount of cross-linker used in the process.

[0066] The created polymeric hydrogel, depending on the specific concentration of primary amine monomers and corresponding cross-link density may have varying degrees of inducing the blood coagulation cascade, as shown in Figure 6 herein. In a specific embodiment, the optimum concentration for the APM, acrylamide, BIS hydrogel is between 1.5-2 M of APM and 1.5-2 M of acrylamide cross-linked at between 5:1 and 7:1 (acrylamide:BIS). In another specific embodiment (blood optimization) the optimum composition is approximately 2.73 M of APM, .27 M of acrylamide, and .056 M BIS.

[0067] The ability of the hydrogel to initiate blood coagulation in the absence of cells offers a potentially substantial advantage over other hemostatic approaches. In particular these polymers may offer treatment alternatives for patients experiencing platelet-related disorders for which there are no accepted treatment methods available. Another desirable characteristic of the materials, depicted in Figure 1 herein, is their ability to swell in plasma. In practice this would allow the polymers to apply pressure (tamponade) at the site of action, which also aids in reducing blood loss. Furthermore, because of this characteristic swelling in plasma, the hydrogel may be designed in order to administer therapeutics in a controlled and regulated manner.

EXAMPLES

[0068] In one experiment, a randomized copolymer composed of acrylamide and APM, initiated with a 7.5% weight percent solution of TEMED (20 μL/1 mL) and a 15% weight percent solution of APS (20 μL/1 mL), and cross-linked with BIS, was produced. Figure 3 depicts an optimization chart where 156 different polymer compositions, each cross-linked at three different ratios, were tested in citrated human plasma, and rated accordingly their ability to produce a clot. As shown the optimal concentration for inducing coagulation lies between 1.5-2 M of acrylamide and 1.5-2 M of APM, each at its highest cross-link density (maximal amount soluble). The primary amine-containing hydrogel is able to induce the blood coagulation cascade resulting in the formation of a fibrin clot. Figure 1 depicts the ability of the material to induce a fibrin based clot in human plasma (4% sodium citrate). The hydrogel shown is composed of 1.5 M acrylamide 1.5 M APM and cross-linked with .3 M BIS (acrylamide:BIS ratio = 5:1).

[0069] Figure 2 shows micrographs of the coagulate complex (fibrin-hydrogel complex) after hematoxlyin and eosin (H&E) staining, immunohistochemical (IHC) staining, along with an image of the complex obtained using an environmental scanning electron microscope.

[0070] Figure 4 shows the ability of the optimized hydrogel (1.5 M acrylamide, 1.5 M APM< and .3 M BIS) to induce fibrin formation in a variety of factor deficient and factor inhibited plasmas.

[0071] Figure 5 shows the ability of the optimized hydrogel to induce the activation of FVII (5C).

[0072] Figure 6 shows that the optimized hydrogel is not in fact a homogenous network but rather is made up of several mechanically distinct regions.

[0073] Experimentation in human and sheep blood produced an optimum composition consisting of .27 M of acrylamide and 2.73 M of APM and .056 M (acrylamide:BIS ratio= 5:1). [Composition 2]

[0074] The effectiveness of the primary amine-containing hydrogel in hemostatic clot formation was assessed. Blood was drawn from a live adult sheep and added immediately to a vial containing a small amount of the primary amine-containing hydrogel (Figure 7A) and an empty vial (Figure 7B), used as a control. The material was able to induce the formation of a robust clot within seconds of blood contact, compared to the control which took

approximately 10 minutes. Furthermore, the mechanical integrity of the clot produced was dramatically superior to that of the control.

[0075] The primary amine-containing hydrogel was also effective in inducing hemostatic clot formation in vivo. A primary amine-containing hydrogel, consisting of 0.27 M acrylamide, 2.73 M N-3-aminopropyl methacrylamide (APM), and 0.054 M N-N'-methylene bisacrylamide (BIS), placed on a 4x4 inch gauze bandage (a prototype of the presently claimed invention, shown in Figure 8), was administered to inhibit bleeding from an incision introduced into a live sheep lung. The hydrogel was able to successfully stop bleeding from the induced lung incision in approximately 2 minutes. Figure 9 shows an image of the site immediately after the surgeon made the incision (Figure 9A) along with an image of the incision site after the hydrogel based prototype was applied for 2 minutes (Figure 9B). Initial post operative analysis showed that the material was able to induce fibrin formation at the incision causing a natural suturing process, and thus sealing the tissue preventing blood loss. Hematoxylin and eosin stained sections of the incision site confirmed that the material was able to induce the rapid formation of a natural, fibrous-based hemostatic suture, as shown in Figure 10.

INDUSTRIAL APPLICABILITY

[0076] The polymer hydrogel created of the present invention may have various uses. Such uses include a bandage for trauma related injuries or a surgical gauze for use in the operating rooms. In terms of the bandage the hydrogel would be incorporated into a filtered bandage, similar to that of a Band-Aid®, which would then be applied to the wound in order to prevent blood loss and deliver necessary therapeutics. In terms of the surgical gauze the hydrogel would be incorporated into a filtered gauze-like material for use by surgeons to control blood loss during surgery.

[0077] Notably, the bandage application of the hydrogel is novel in the sense that there is no other synthetic polymer, hydrogel material capable of inducing blood clotting while simultaneously delivering therapeutics. Furthermore, the hydrogel functions in Factor VIII and Factor IX deficient plasma, a functionality which should revolutionize wound care for people suffering from hemophilia.

CLAIMS

We claim:

1. A cross-linked polymer, comprising cross-links between at least two monomer backbones, wherein at least one monomer comprises a primary, secondary, tertiary or quaternary amine with a pKa of at least 7.4, and capable of displaying a positive electrostatic charge at the pH of blood or plasma (7.4), and wherein the polymer is capable of activating the blood coagulation cascade by inducing fibrin formation.

2. The polymer of claim 1, wherein said at least one monomer is selected from the group consisting of N-3-aminopropyl methacrylamide, allylamine, and a primary-amine containing monomer capable of displaying a positive electrostatic charge at the pH of blood or plasma (7.4).

3. The polymer of claim 1, wherein at least one of the monomer backbones is acrylamide, or a derivative thereof.

4. A hydrogel comprising the polymer of claim 1, wherein the monomer backbones are cross-linked with cross-linkers selected from the group consisting of N-N'-methylene bisacrylamide, N-N'-bisacrylylcystamine, bisacrylyl piperazine, ethylene glycol diglycidyl ether, epichlorohydrin, N-N'-diallyltartardiamide, ethylene glycol dimethacrylate and ethylene glycol diacrylate.

5. The hydrogel of claim 4, wherein the primary amine is allylamine and the cross-linker is either ethylene glycol diglycidyl ether or epichlorohydrin.

6. The hydrogel of claim 4, therein the monomer backbones are cross-linked with cross-linkers selected from the group consisting of ethylene glycol dimethacrylate and ethylene glycol diacrylate.

7. The polymer of claim 1, wherein the primary amine containing monomer is N-3-aminopropyl methacrylamide (APM), the co-monomer is acrylamide, and the cross-linker is N-N'-methylene bisacrylamide (BIS).

8. The hydrogel of claim 4, wherein said hydrogel consists of 1.5 M acrylamide, 1.5 M N-3-aminopropyl methacrylamide (APM), and 0.3 M N-N'-methylene bisacrylamide (BIS).

9. The polymer of claim 7, wherein said hydrogel consists of 0.27 M acrylamide, 2.73 M N-3-aminopropyl methacrylamide (APM), and 0.054 M N-N'-methylene bisacrylamide (BIS).

10. The hydrogel of claim 4, wherein said hydrogel consists of 1.5 M acrylamide, 1.5 M N-3-aminopropyl methacrylamide (APM), and 0.3 M N-N'-methylene bisacrylamide (BIS).

11. The hydrogel of claim 4, further comprising one or more pharmaceutical active ingredients selected from the group consisting of Novocain, Lidocain, erythromycin, bacitracin, adrenaline, topricin, acetaminophen, ibuprofen, and a hemostatic agent.

12. A method of forming the hydrogel of claim 4, comprising:

adding the monomer backbone comprising a primary amine to the aqueous solution, wherein the first monomer unit exhibits an electrostatic positive charge in the aqueous solution at pH of 7.4 (pH of blood or plasma);

adding a second monomer backbone to the aqueous solution, wherein the second monomer backbone is different from the first monomer unit;

forming the cross-linked polymer using a cross-linking agent, wherein the step of forming polymer comprises polymerizing the monomer backbone.

13. The method of claim 12, wherein the second monomer backbone is neutral or exhibits an electrostatic charge opposite to that of the first monomer backbone.

14. The method of claim 12, wherein the first monomer backbone is added before the second monomer backbone is added.

15. The method of claim 12, wherein the second monomer backbone is added before the first monomer backbone.

16. The method of claim 12, wherein the first and second monomer backbone are added simultaneously to the aqueous solution.

17. A kit for inducing hemostatic clot formation, comprising the polymeric hydrogel of claim 4.

18. A kit for inducing hemostatic clot formation, comprising the polymeric hydrogel of claim 5.

19. A kit for inducing hemostatic clot formation, comprising the polymeric hydrogel of claim 6.

20. A kit for inducing hemostatic clot formation, comprising the polymeric hydrogel of claim 8.

21. A kit for inducing hemostatic clot formation, comprising the polymeric hydrogel of claim 10.

22. A method of treating trauma-induced hemorrhage, comprising administering the hydrogel of any of Claims 4-6, 8, 10 and 11 to a subject in need thereof.

23. A method of treating internal hemorrhaging, comprising administering the hydrogel of any of Claims 4-6, 8, 10 and 11 to a subject in need thereof.

24. A method of treating hemorrhaging during surgical operations, comprising administering the hydrogel of any of Claims 4-6, 8, 10 and 11 to a subject in need thereof.

25. The method of any one of Claims 22-24, wherein said hydrogel is administered on a material selected from the group consisting of a bandage, gauze, tape and adhesive wound dressing.

FIG. 1

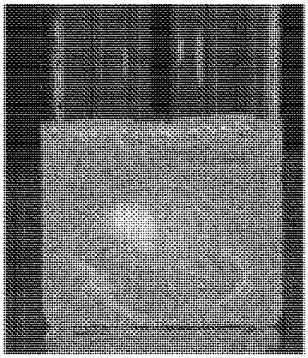
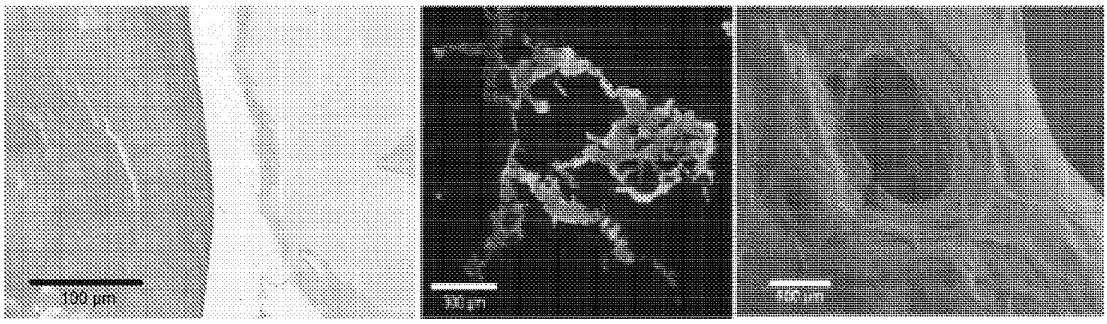


FIG. 2



a b c

FIG. 3

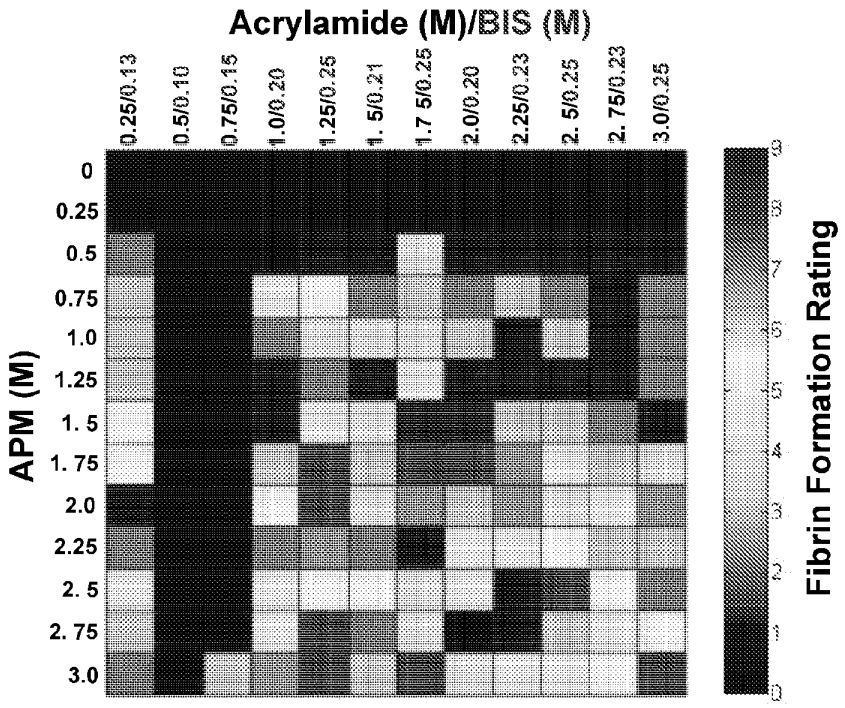

Acrylamide (M)/BIS (M)
0.25/0.13
0.5/0.10
0.75/0.15
1.0/0.20
1.25/0.25
1. 5/0.21
1.7 5/0.25
2.0/0.20
2.25/0.23
2. 5/0.25
2. 75/0.23
3.0/0.25
APM (M)
0
0.25
0.5
0.75
1.0
1.25
1. 5
1. 75
2.0
2.25
2. 5
2. 75
3.0
Fibrin Formation Rating

FIG. 4

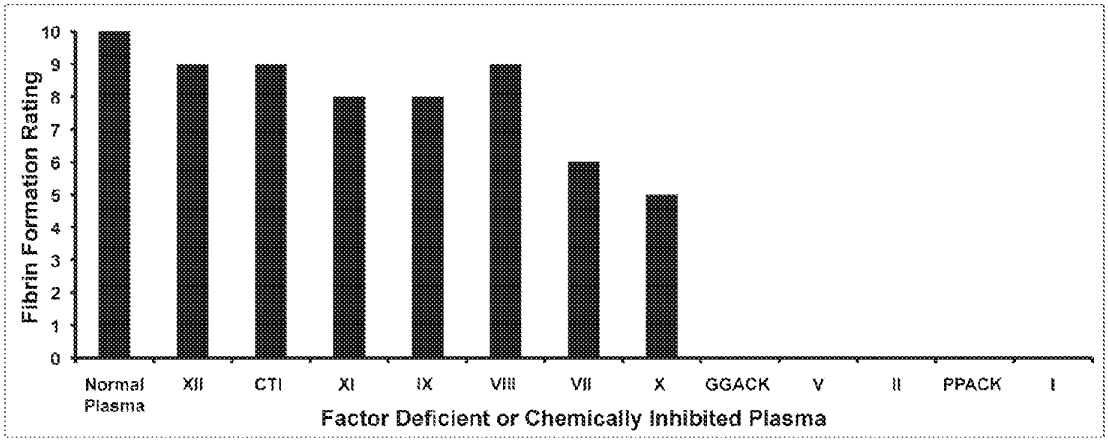

Fibrin Formation Rating
10
9
8
7
6
5
4
3
2
1
0
Normal Plasma
XII
CTI
XI
IX
VIII
VII
X
GGACK
V
II
PPACK
I
Factor Deficient or Chemically Inhibited Plasma

FIG. 5

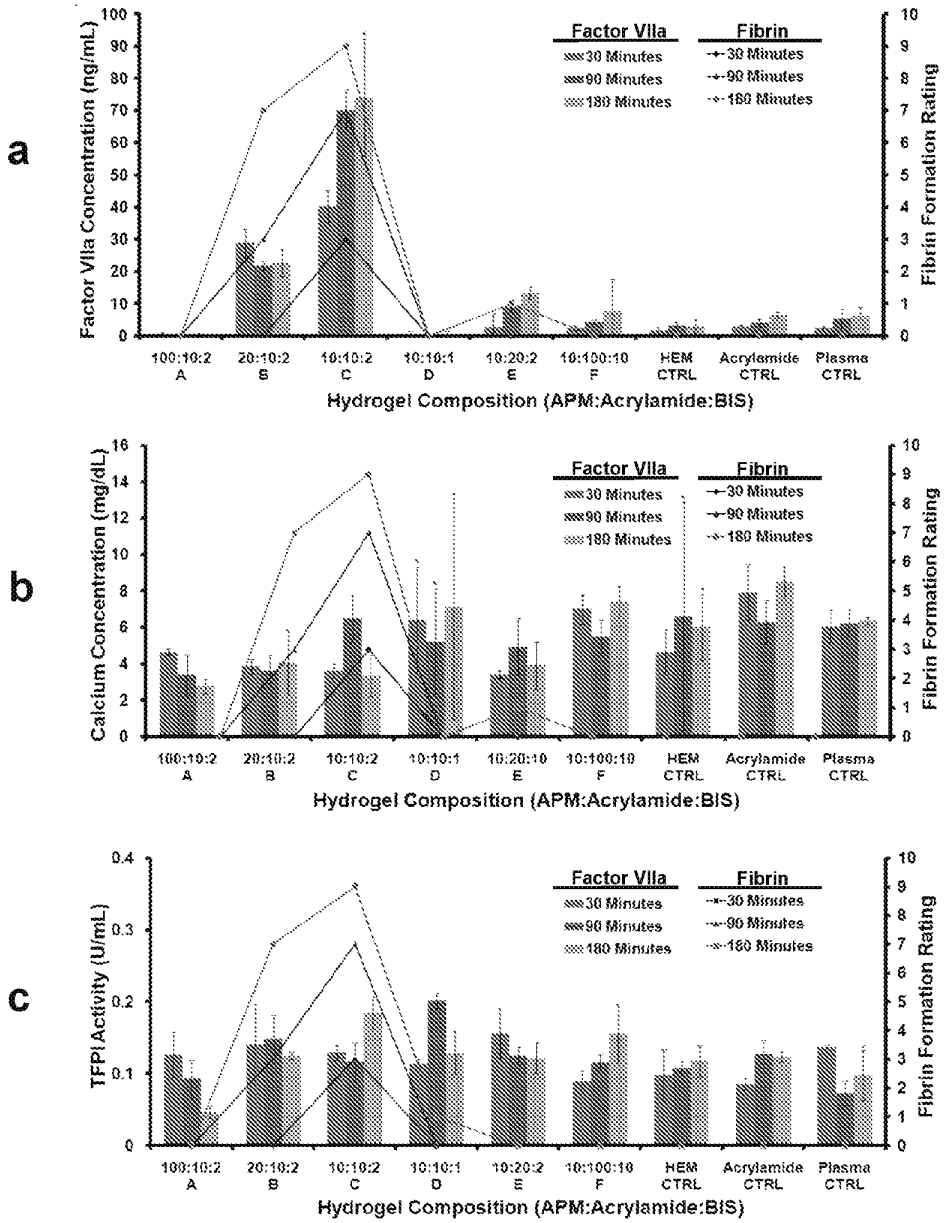

a
Factor VIIa Concentration (ng/mL)
Fibrin Formation Rating
Factor VIIa
30 Minutes
90 Minutes
180 Minutes
Fibrin
30 Minutes
90 Minutes
180 Minutes
100:10:2 A
20:10:2 B
10:10:2 C
10:10:1 D
10:20:2 E
10:100:10 F
HEM CTRL
Acrylamide CTRL
Plasma CTRL
Hydrogel Composition (APM:Acrylamide:BIS)
b
Calcium Concentration (mg/dL)
Fibrin Formation Rating
Factor VIIa
30 Minutes
90 Minutes
180 Minutes
Fibrin
30 Minutes
90 Minutes
180 Minutes
100:10:2 A
20:10:2 B
10:10:2 C
10:10:1 D
10:20:10 E
10:100:10 F
HEM CTRL
Acrylamide CTRL
Plasma CTRL
Hydrogel Composition (APM:Acrylamide:BIS)
c
TFPI Activity (U/mL)
Fibrin Formation Rating
Factor VIIa
30 Minutes
90 Minutes
180 Minutes
Fibrin
30 Minutes
90 Minutes
180 Minutes
100:10:2 A
20:10:2 B
10:10:2 C
10:10:1 D
10:20:2 E
10:100:10 F
HEM CTRL
Acrylamide CTRL
Plasma CTRL
Hydrogel Composition (APM:Acrylamide:BIS)

FIG. 6

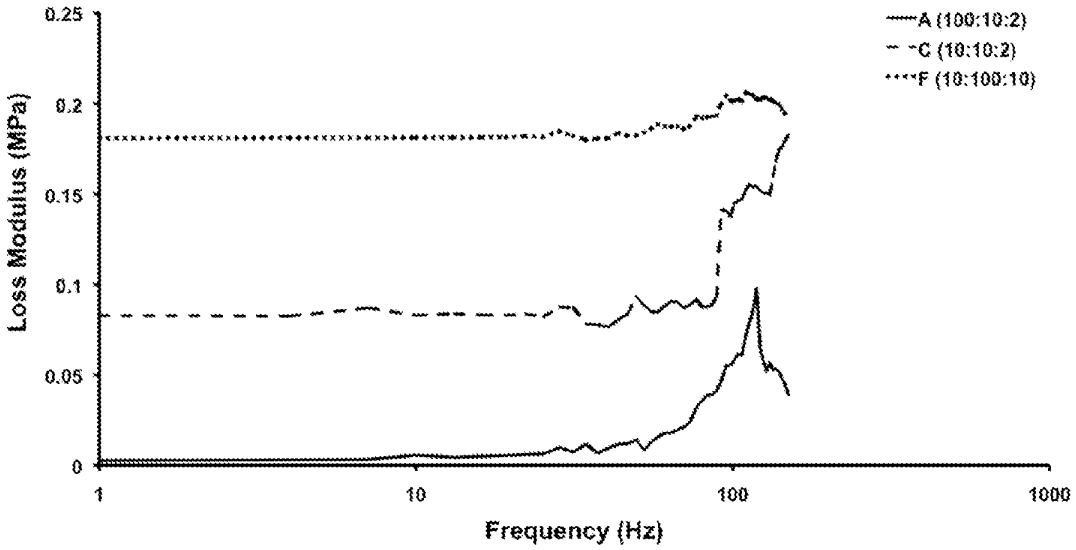

A (100:10:2)
C (10:10:2)
F (10:100:10)
Loss Modulus (MPa)
0.25
0.2
0.15
0.1
0.05
0
1
10
100
1000
Frequency (Hz)

FIG. 7

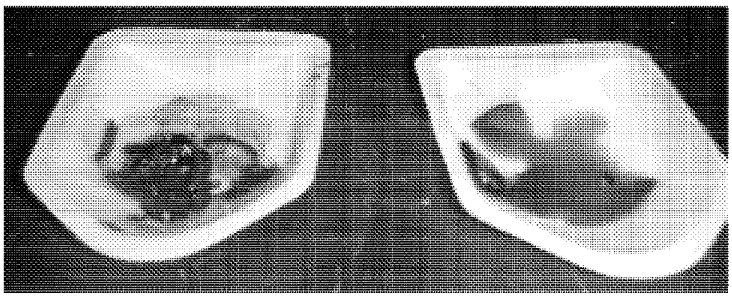
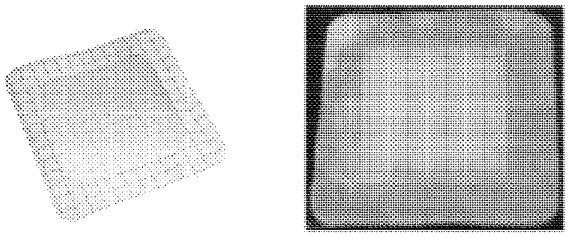
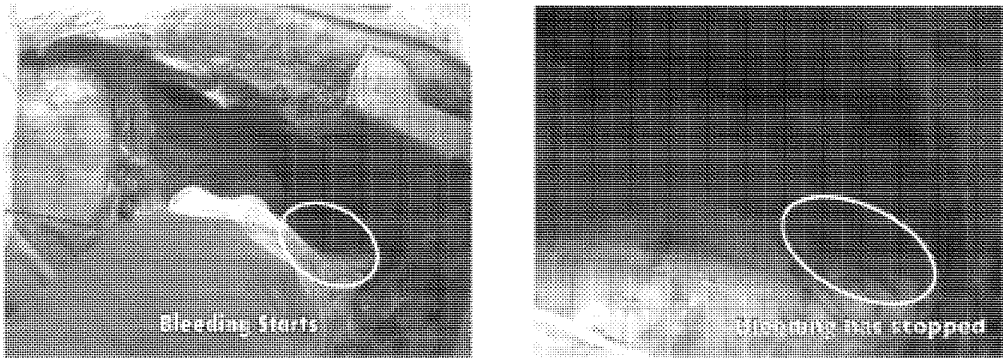

A
B

FIG. 8



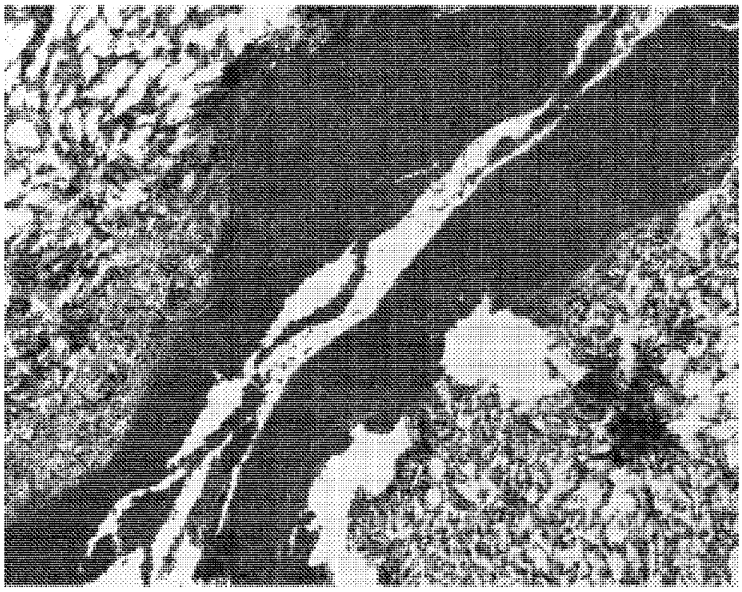
A B

FIG. 9



A B

FIG. 10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/063049

A. CLASSIFICATION OF SUBJECT MATTER

A61F 13/02(2006.01)i, A61L 15/44(2006.01)i, A61P 7/04(2006.01)i

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)
A61F 13/02; A61K 31/785; A61K 9/14; A61K 9/16; A61K 9/50; B01D 21/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models
(Chinese Patents and application for patent)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: coagulation, polymer, crosslink, hydrogel

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007-0237742 A1 (GARRET FIGULY et al.) 11 October 2007 See whole pages.	1-21
A	US 2003-0215519 A1 (ALEXANDER SCHWARZ et al.) 20 November 2003 See whole pages.	1-21
A	US 5648100 A1 (BOSCHETTI; EGISTO et al.) 15 July 1997 See whole pages.	1-21
A	US 4994192 A1 (CORIN; ALAN F. et al.) 19 February 1991 See whole pages.	1-21

☐ 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 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 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
31 MARCH 2010 (31.03.2010)	**01 APRIL 2010 (01.04.2010)**

Name and mailing address of the ISA/KR	Authorized officer
Korean Intellectual Property Office Government Complex-Daejeon, 139 Seonsa-ro, Seo-gu, Daejeon 302-701, Republic of Korea	LEE, Dong Won
Facsimile No. 82-42-472-7140	Telephone No. 82-42-481-5549

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2009/063049

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.: 22-25
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 22-25 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

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 addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest 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/US2009/063049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007-0237742 A1	11.10.2007	None	
US 2003-0215519 A1	20.11.2003	AU 2003-239374 A1	11.11.2003
		WO 03-094930 A1	20.11.2003
US 5648100 A1	15.07.1997	CA 2110290 C	05.02.2002
		EP 0588875 A1	30.03.1994
		EP 0588875 A4	03.08.1994
		EP 0588875 B1	09.04.1997
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		KR 10-1994-0700869 A	22.04.1994
		US 5635215 A1	03.06.1997
		WO 92-21327 A1	10.12.1992
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		JP 06-249849 A	09.09.1994
		KR 10-1991-0014707 A	31.08.1991

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
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		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)

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
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Journal of Clinical Microbiology®

J Clin Microbiol. 2010 Dec; 48(12): 4501–4503. PMCID: PMC3008433
Published online 2010 Oct 13. doi: 10.1128/JCM.00910-10 PMID: 20943670

Innovation for Reducing Blood Culture Contamination: Initial Specimen Diversion Technique

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Received 2010 May 5; Revised 2010 Jun 19; Accepted 2010 Oct 3.

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ABSTRACT

We hypothesized that diversion of the first milliliter of venipuncture blood—the initial specimen diversion technique (ISDT)—would eliminate incompletely sterilized fragments of skin from the culture specimen and significantly reduce our blood culture contamination rate (R). We studied our hypothesis prospectively beginning with our control culture (C) definition: one venipuncture with two sequentially obtained specimens, 10 ml each, the first specimen (M1) for aerobic and the second (M2) for anaerobic media. The test ISDT culture (D) was identical, with the exception that each was preceded by diverting a 1-ml sample (D_S) from the same venipuncture. During the first of two sequential 9-month periods, we captured D versus C data ($n = 3,733$), where $D_{MX}R$ and $C_{MX}R$ are R for D and C specimens. Our hypothesis predicted D_S would divert soiled skin fragments from D_{M1}, and therefore, $C_{M1}R$ would be significantly greater than $D_{M1}R$. This was confirmed by $C_{M1}R$ (30/1,061 [2.8%]) less $D_{M1}R$ (37/2,672 [1.4%]; $P = 0.005$), which equals 1.4%. For the second 9-month follow-up period, data were compiled for all cultures ($n = 4,143$), where $AD_{MX}R$ is R for all (A) diversion specimens, enabling comparison to test ISDT. Our hypothesis predicted no significant differences for test ISDT versus all ISDT. This was confirmed by $D_{M1}R$ (37/2,672 [1.4%]) versus $AD_{M1}R$ (42/4,143 [1.0%]; $P = 0.17$) and $D_{M2}R$ (21/2,672 [0.80%]) versus $AD_{M2}R$ (39/4,143 [0.94%]; $P = 0.50$). We conclude that our hypothesis is valid: venipuncture needles soil blood culture specimens with unsterilized skin fragments and increase R, and ISDT significantly reduces R from venipuncture-obtained blood culture specimens.

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As a clinical laboratory test, blood culture has played a major diagnostic role in medicine for decades. One limitation of this diagnostic role is false-positive results, which increase expenses and have an adverse patient safety impact (1, 2). Consequently, numerous interventions with blood culture processes have been employed by laboratories to reduce contamination (5, 6). The purpose of this report is to introduce a new blood culture technique that significantly reduced the blood culture contamination rate (*R*) in this study. This innovation, the initial specimen diversion technique (ISDT), omits the first approximately 1-ml portion of venipuncture blood from the culture specimen without compromising or diminishing the volume of blood optimum for culture. The basis for ISDT is the hypothesis that skin fragments incompletely sterilized by skin surface antisepsis and dislodged by venipuncture increase *R*. We evaluated our hypothesis prospectively first with test ISDT versus control cultures for a 9-month period (group 1; $n = 3,733$ cultures). Next, we collected data for a second 9-month period with an all-cultures ISDT (group 2; $n = 4,143$) for comparison to test ISDT.

MATERIALS AND METHODS

Patients and phlebotomists. The blood cultures in this study were from adults suspected of having sepsis who were hospitalized, evaluated in the emergency room, or seen as outpatients in a not-for-profit urban community hospital setting. Venipunctures (peripheral vein sites only) were performed by laboratory-trained and supervised phlebotomists who wore safety gloves during the procedure. No indwelling-catheter-obtained specimens were included in this study. Our standard procedure of monitoring needle puncture and other laboratory staff issues was continued during and after the study.

Skin preparation. Prior to venipuncture, the skin antisepsis agent 2% chlorhexidine-70% alcohol (Medi-Flex Hospital Products, Inc., Overland Park, KS) was applied with a sponge using vertical and horizontal strokes in a washboard manner for 30 s over a 5- by 5-cm area. The scrubbed area was allowed to dry and was not repalpated prior to venipuncture.

Blood culture definition and initial specimen diversion technique. A blood culture was defined as two separate 10-ml specimens obtained serially from one venipuncture for sequential inoculation of bottled media, M1 (aerobic) and M2 (anaerobic). Medium bottle stoppers were cleaned with a 70% isopropyl alcohol wipe, which was left in place prior to inoculation. The culture medium bottles were incubated in an automated computer-monitored system (BacT/Alert SN Microbial Detection System; bioMérieux S.A, Durham, NC) and in the event of growth were Gram stained and subcultured for identification. We used a pushbutton blood collection apparatus (Becton Dickinson and Company, Franklin Lakes, NJ) with a 21-gauge venipuncture needle for blood culture specimen collection and inoculation (Fig. 1). The apparatus included a venipuncture needle (1), wings (2) to aid insertion of the venipuncture needle, tubing (3) for blood transfer, and a protective adapter (4) that facilitated medium bottle inoculation. Inoculation was enabled within the adapter by a second needle (Fig. 1, inset). The venipuncture and inoculation needles had safety covers. The inoculation needle cover was rubberized and re-covered the needle between medium inoculations. Blood culture specimens (10 ml each) were collected sequentially directly to M1 and then to M2 (Fig. 2). The medium bottle volume in 5-ml increments was shown on the medium bottles, providing precision in measuring the culture specimen volume. The medium bottles were held vertically, and the desired 10-ml increment was marked with a pen or the phlebotomist's thumb nail. The procedure was the same for ISDT blood culture (D), with the exception that each was preceded by diverting the first milliliter (D_S) of the same venipuncture blood into a 3-ml sterile Vacutainer collection tube (Becton Dickinson and Company, Franklin Lakes, NJ) (Fig. 1). For patients with small veins, syringes and 23-gauge needles were used for blood collection as

follows. The collection needle/adapter attachment apparatus (Fig. 1, inset, 5) was removed, enabling a syringe connector (6) to be attached. Syringes (3 ml and 10 ml) collected the 1-ml D_S and culture samples, respectively. A separate safety needle was attached to the 10-ml syringes for transferring culture specimens to medium containers. The medium bottles were placed in racks for the syringe/safety needle inoculation; hand-held medium inoculation was not permitted.

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FIG. 1.

ISDT diversion step prior to culture. 1, venipuncture needle; 2, wings to aid insertion of the venipuncture needle; 3, tubing for blood transfer; 4, protective adapter to facilitate medium bottle inoculation; 5, collection needle/adapter attachment apparatus; 6, syringe connector; 7, diversion tube. (Inset) Diversion inoculation needle detail.

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FIG. 2.

ISDT direct-to-medium inoculation step.

Blood cultures were classified as false positive if one or more of the following organisms were isolated from only one of a series of blood culture specimens: coagulase-negative *Staphylococcus* spp., *Propionibacterium acnes*, *Micrococcus* spp., "viridans" group streptococci, *Corynebacterium* spp., or *Bacillus* spp. (2).

Data groups. For the first of two 9-month periods, June 2007 through February 2008, culture specimen collection was tracked for test ISDT versus C (group 1). Training for ISDT commenced prior to and continued at the beginning of the period, followed by randomization of test-ISDT versus C. Before randomization was fully implemented, significant reduction of *R* by ISDT became obvious; therefore, in the best interest of our patients and our institution, randomization was discontinued and all cultures were obtained with ISDT. For a second 9-month period, April through December 2008, blood culture specimens were obtained with all ISDT (group 2). Confirmation of receipt in the laboratory and the blood volume of D_S were also tracked. D_S was not cultured.

Statistical method. Pearson's chi-square test was used to evaluate the significance of the blood culture groups compared; significance was defined as a *P* value of ≤ 0.05.

RESULTS

During the first of two sequential 9-month periods, we captured test ISDT data, D versus C data (n = 3,733), which can be expressed as

$$D_T R = D_S R + D_{M1} R + D_{M2} R \quad (1)$$

and

$$C_T R = C_{M1} R + C_{M2} R \quad (2)$$

where $D_{MX}R$, $C_{MX}R$, and $D_S R$ are R for D, C, and D_S specimens and $D_T R$ and $C_T R$ are total R for D and C. Our ISDT hypothesis predicted that D_S would divert soiled skin fragments from D_{M1}, and therefore, $C_{M1}R$ would be significantly greater than $D_{M1}R$. This was confirmed by $C_{M1}R$ (30/1,061 [2.8%]) less $D_{M1}R$ (37/2,672 [1.4%]; $P = 0.005$) equaling 1.4%. Also predicted was that ISDT would show no significant difference between $C_{M2}R$ and $D_{M2}R$. Confirmation came as $C_{M2}R$ (11/1,061 [1.0%]) less $D_{M2}R$ (21/2,672 [0.8%]; $P = 0.31$) equaling 0.2%. Additionally, we assumed $D_T R$ was equal to $C_T R$, and therefore,

$$D_S R = C_{M1} R + C_{M2} R - D_{M1} R - D_{M2} R \quad (3)$$

Thus, $D_S R$ was discrete, could be calculated, and was 1.6%. Regarding the second 9-month follow-up period for comparison to test ISDT, ISDT data were compiled for all (A), $AD_T R$, and $AD_{MX}R$, cultures ($n = 4,143$),

$$AD_T R = AD_{M1} R + AD_{M2} R \quad (4)$$

Our hypothesis predicted no significant differences for test ISDT versus all ISDT. This was confirmed by $D_{M\,1}R$ (37/2,672 [1.4%]) versus $AD_{M\,1}R$ (42/4,143 [1.0%]; $P = 0.17$) and $D_{M2}R$ (21/2,672 [0.80%]) versus $AD_{M2}R$ (39/4,143 [0.94%]; $P = 0.50$). The data are shown in Table 1 for all cultured specimens, as are comparison contamination rates for control versus test ISDT and all ISDT versus test ISDT. The only significant comparison difference was test ISDT M_1 versus control M_1 (1.4%). This difference can be attributed to the diversion of unsterilized skin fragments from control M_1 by ISDT (formulas 1 and 2), and this difference in the study can be quantified (formula 3) as 1.6%. The lack of significant differences between test ISDT M_1 and M_2 and AD M_1 and M_2 rates are consistent with our hypothesis: ISDT significantly reduces contamination in venipuncture-obtained blood culture specimens.

TABLE 1.

Comparison of R for control versus test ISDT and all ISDT versus test ISDT culture groups

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[a]Test ISDT rate from first 9 months less all ISDT rate from second 9 months used for comparison.

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For one randomly chosen month (February 2008), the diversion volume distribution was 152 (40%) >0.5 ml and ≤1.0 ml, 256 (68%) ≤1.5 ml, 351 (93%) ≤2.0 ml, and ≤3.0 ml (100%) (n = 376).We conclude that ≥0.5 ml and ≤2.0 ml is adequate diversion volume to significantly reduce contamination.

The clinical service distribution of blood cultures during the study was inpatients 77.2%, emergency department 15.9%, and outpatients 6.9% (n = 11,330). None of these were ≤16 years of age.

Phlebotomists did not suffer needle sticks or other injuries as a result of this study.

DISCUSSION

Every pathologist who has examined numerous needle aspirations of bone marrow and other viscera has observed skin fragments (mini-biopsy specimens) contaminating these aspiration specimens. Based on this experience, we sought improvement in our blood culture contamination rate. We hypothesized that small fragments of skin dislodged by a venipuncture needle harbor bacteria not killed by skin surface antisepsis and that they are a discrete cause of contamination. Additionally, we hypothesized that diverting the first milliliter of venipuncture blood and subsequently obtaining a culture specimen from the same venipuncture would eliminate some of these fragments from the culture specimen and significantly reduce contamination and that it would do so without compromising blood culture sensitivity. We refer to this diversion method as ISDT.

Our results show that ISDT significantly reduces contamination of blood cultures by excluding contaminants from the first portion of venipuncture-obtained culture specimens. Given this, several questions arise. What other studies have been done that may corroborate our findings? What is the optimum volume of blood for diversion? What is the cost of ISDT, and are there laboratory worker safety issues? Finally, do we recommend ISDT to other laboratories?

Regarding other studies, to our knowledge, reduction of contamination by diversion has not been previously studied in detail or quantified for venipuncture-obtained blood culture specimens. In contrast, diversion has been extensively studied and quantified for donor blood components. Diversion of the first part of donor blood to reduce the risk of bacterial contamination in recipients is a worldwide standard. Diversion volumes ranging from 10 to 50 ml are credited with having reduced contamination of blood components by 40 to 90% between 1995 and 2007 (7). Similar reductions in contamination of blood cultures may be realized with less diversion volume, as a blood culture needle is commonly a smaller gauge than a donor needle. The usual 16-gauge donor needle (bore, 1.19 mm) captures numerous plugs of skin contaminants (3). One would expect less contamination from our 21-gauge culture needle (bore, 0.514 mm), which has a cross-sectional area less than 1/5 that of the donor needle.

As for the optimum diversion volume for blood cultures, this study showed significant improvement in contamination with a volume of ≥0.5 ml and ≤2 ml. More diversion volume is likely better. Our data show that all specimens subsequent to ≥2.0 ml of diversion (C_{M2}, D_{M1}, D_{M2}, AD_{M1}, and AD_{M2}) had an average R of 1%. Hence, 20 ml of diversion would very likely decrease contamination further. However, with meticulous oversight, increased experience with diversion, and both initial and remedial training using a video of our diversion technique, our phlebotomists have achieved an R of <1% in the first 6 months of 2010, an R which a short time ago we would have thought impossible. We are satisfied with our current diversion volume but are considering increasing the volume to 3 or possibly 5 ml. Another improvement tactic is drawing blood for other tests (blood counts, chemistry, etc.) prior to blood culture.

ISDT can be cost-effective by lowering patient care charges. Recently, in a large emergency department (ED), patient charges were increased by $8,720 for each contaminated blood culture (4). If our IDST procedure were implemented in this ED, with 5,432 blood cultures in 13 months, annual charges would decrease by $699,575 for an increase in supply costs of $3,510. Our costs for ISDT supplies are minimal (blood collection apparatus, $1.28, and diversion tube, $0.07), replacing a theoretical 20-ml syringe and two safety needles ($0.65). Reduced contamination is based on our calculated $D_S R$ of 1.6%, and these cost savings can accrue without employee safety issues. We had no needle sticks or other injuries to our phlebotomists or other laboratory workers during this study.

For venipuncture-obtained specimens, we believe ISDT significantly reduces blood culture contamination, has a high benefit/cost ratio, is practical and safe for laboratory personnel and patients, and does not compromise blood culture sensitivity. We recommend ISDT to other laboratories.

ACKNOWLEDGMENTS

This study was conducted with review and approval from the Quality Standards Committee at Northwest Hospital and Medical Center/UW Medicine.

Financial support for the study and the associated patent application submission was provided by Northwest Hospital and Medical Center/UW Medicine, as well as Magnolia Medical Technologies, LLC, an entity in which R.G.P. has an equity interest.

FOOTNOTES

▽Published ahead of print on 13 October 2010.

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Page et al. Annals of Intensive Care 2013, 3:14
http://www.annalsofintensivecare.com/content/3/1/14

Annals of Intensive Care
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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

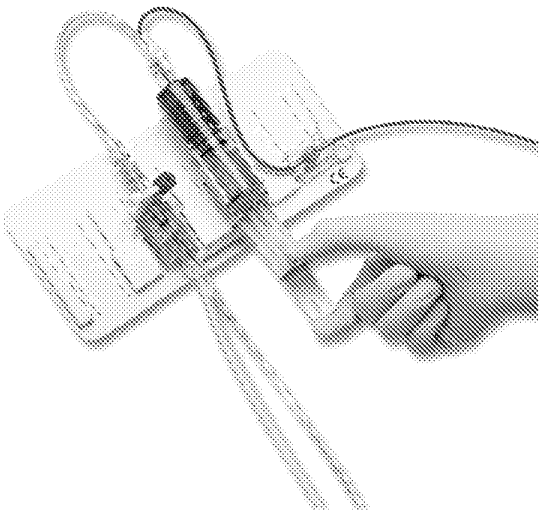


Figure 1 Edwards VAMP system. The port to the right of the image is the sampling port, which is accessed by a needless device. The middle syringe is the reservoir where the previous "discarded" blood is held before being reinfused back into the patient. Picture submitted with permission from Edwards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

Received: 15 February 2013 Accepted: 7 May 2013
Published: 28 May 2013

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doi:10.1186/2110-5820-3-14
Cite this article as: Page *et al.*: Blood conservation devices in critical care: a narrative review. *Annals of Intensive Care* 2013 **3**:14.

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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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Received 6.24.05 | Revisions Received 7.26.05 | Accepted 7.27.05

Bacterial Contamination of Platelets for Transfusion: Recent Advances and Issues

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DOI: 10.1309/16794BJY25TMY611

- Bacterial contamination of blood products has emerged as a serious problem in transfusion medicine in the past 20 years and is second only to ABO-mismatch in causing transfusion-associated death.
- Data from 1985 - 1999 showed that 11% (77/694) of transfusion-associated fatalities reported to the FDA were caused by bacterially contaminated products leading to sepsis.
- As platelets are stored at room temperature, and in a large volume of plasma and a bag that allows oxygen diffusion, it is platelet products that are the most frequently implicated in transfusion-associated fatalities due to bacterial contamination.

The transfusion medicine community has attempted to reduce the amount of bacterial contamination in the blood supply by several methods including improved skin disinfection prior to donation, removal of the skin plug with diversion of the first 10 cc of the collection, ongoing donor screening, and analysis/culture of the donated product. Even with these measures in place, several fatalities due to septic reactions associated with transfusion have occurred and been reported. At the time of this writing, the exact "residual risk" of bacterial contamination is not known.

While packed red blood cell units can be contaminated by bacteria, the fact that they are *not* stored at room temperature and are not in a medium containing a large amount of plasma, leads the incidence of sepsis following transfusion of these units to be much less frequent. For a discussion of pRBC bacterial contamination, the first 3 references are recommended to the reader.[1-3] Below, the authors focus on the risks, strategies, and regulations regarding bacterial contamination of platelet products and its mitigation.

Estimates of Prevalence and Incidence

Prior to routine culturing of platelet units, which became universal following implementation AABB Standard 5.1.5.1 (discussed in more detail below), the estimated numbers of bacterially contaminated units, transfusion-associated septic reactions and deaths were usually made retrospectively based on reported or published reactions and sequelae.

By 2000, it was generally held that between 1:1,000 and 1:4,000 units[3-8] were contaminated with bacteria; the estimate of 1:2,000 to 3,000 became commonly accepted. Sepsis due to bacterial contamination was less common and estimated to occur in 1:20,000 to 1:85,000 units.[8] Estimates at the number of deaths due to this transfusion related complication were more difficult to elucidate.

In 2001, Yomtovian and colleagues estimated that 500 to 750 "severe and possibly fatal" events occurred annually.[4] Other estimates of this figure are more on the order of 100 to 150 deaths per year.[9,10] (The estimated risk of bacterially contaminated red cell units was significantly lower (approximately 1:500,000)[11] and approximately 10 to 1,000 times greater than the combined risk of transfusing HIV, HBV, HCV, and HTLV.[11]

Sources of Bacterial Contamination

Occult donor bacteremia and contamination of the product during collection have been the main avenues for entry of bacteria and have been the focus of prevention efforts. Gram-positive skin flora, introduced to the unit during collection, are the most common contaminates identified in retrospective analysis of platelet units.[12] Three reporting systems have suggested that 70% of contaminates isolated were gram-positive bacteria, while 80% of fatalities due to transfusion-related sepsis were caused by gram-negative organisms.[13-15] This finding was also observed in a recent review of the American Red Cross (ARC) experience with pretransfusion culturing of apheresis-derived platelets (ADP) between March and December 2004 (discussed in detail below).[16] This data showed that gram-positive organisms are implicated in approximately 4/5 of the cases. Gram-negative bacteria comprise the other 20%; however, they account for 40% of deaths due to septic transfusion reactions. Burns and colleagues recently published an extensive list of primary reports of clinically significant sepsis attributed to platelet transfusion from a PubMed literature search of all published cases.[17]

Due to the clinical significance of bacterial contamination, much effort has been made over the years to improve disinfection of skin at the phlebotomy site including the discontinuation of "green soap." Additionally, diversion of the skin plug produced by the needle as it passes through the skin, away from the bag into a pouch used for other viral testing, has been instituted nationwide in the United States. Despite these efforts, bacterial contamination of products continued(s) to be observed and skin flora continued(s) to be the most frequently cultured organisms.

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Asymptomatic donor bacteremia is the reason seemingly healthy volunteers may be allowed to donate while infectious, leading to bacterial contamination of blood products. In this case, even stringent donor screening will not catch this potential source of bacterial contamination. There are many examples of donors who unknowingly donate blood while bacteremic. For example, a case of transfusion associated *Staphylococcus aureus* platelet contamination has been reported in a blood donor who had undergone a tooth extraction 3 hours prior to donation, and was likely the result of transient bacteremia.[12] Haimowitz and colleagues discovered *Streptococcus bovis* at 11.4 hours after incubation of a platelet product donated by an asymptomatic female. After being informed of the result and despite negative follow up blood cultures, she underwent colonoscopy and a 3 cm mass was noted and removed.[18] Jafari and colleagues reported a case of *Salmonella* sepsis transmitted via platelet transfusion to 2 recipients from an asymptomatic donor who upon retrospective questioning reported that he had fever, abdominal pain, diarrhea, and hematochezia 13 days *prior* to donation. The donor owned a pet boa constrictor. The snake was thought to have been colonized with *Salmonella* and the original source of the infection.[19] Finally, there have been several cases of pRBC transfusion-associated *Yersinia enterolitica* septicemia in which many of the donors retrospectively reported diarrhea in the days preceding donation.[20]

An Open Letter to the Blood Community and AABB Standard 5.1.5.1

Physicians concerned that the risk from infected units was too high and that there were technologies that could address the issue at least in part wrote an "open letter" to the transfusion medicine community urging implementation of a method to stem this complication.[21] In 2003, AABB Standard 5.1.5.1 was released after considerable discussion, debate, and a public comment period. To be implemented within 1 year, the Standard read, "The blood bank or transfusion service shall have methods to limit and detect bacterial contamination in all platelet components."

At that time and presently, there were no FDA-approved tests for unit-by-unit bacteria screening at the time and point of transfusion. In addition, it was known that more than 15 tests *could* be used but none met "optimal" criteria including sensitivity and specificity, cost:efficacy, and logistical considerations affecting product supply and outdating. Thus, AABB was in an unenviable position of introducing a standard without guidance (at that time) as to *how* to implement it. **Table 1** below (adapted from reference 22) lists the tests capable of detecting bacteria and some comments regarding each.

Clinical Relevance

Typically at the time of collection, the level of contamination is relatively low (between 1 to 10 colony forming units (CFU)/mL.[23] However, once the product is inoculated, the bacteria can proliferate to levels of 10^6/mL or greater.[3] This amount of bacteria transfused during a short period of time can cause bacteremia, fever, chills, hypotension, nausea, vomiting, diarrhea, and oliguria, which may progress to sepsis and ultimately multi-system organ failure and death. Alternatively, the transfusion of contaminated cellular blood products may produce no symptoms or long-term clinical consequences. The severity of the reaction depends on: 1) the species of bacteria present, 2) the inoculum, 3) the rate of bacterial propagation, and 4) underlying disease, leukocyte count, the status of the immune system, and receipt of concomitant antibiotics in the recipient.[3] Gram-negative bacteria tend to cause more severe reactions due to the presence of endotoxin produced by these organisms. While causing only one-fifth of the cases, gram-negative bacteria have been reported to account for 40% of deaths due to septic transfusion reactions.[12,16]

Table 1_Description of Tests Capable of Detecting Bacteria

Methodology	Comments
Culture-based methodology: BacT/ALERT 3D Automated Microbial Detection System (bioMérieux, Durham, NC)	Detects CO_2 production by bacteria; FDA approved for quality control; Semi-closed system; Detects 5-10 CFU/mL (12-26 hr incubation);4 mL required
Culture-based methodology: (Pall eBDS, Pall Corporation, East Hills, NY)	Measures O_2 consumption by bacteria; FDA approved for quality control; Completely closed system; Requires 5-6 mL (concentrated to 2-3 mL)
DNA/RNA-based amplification and non-amplification, Chemiluminescence systems	Highly sensitive and specific; Requires highly conserved target by all bacteria or multiple primers and large inoculum; In experimental use only
Tests detecting changes in metabolic parameters or physical elements (glucose concentration, pH, platelet swirling)	Low sensitivity and specificity; Platelet concentration of the sample can affect results; Can be used at point of issue; Validation and QC difficult
Flow or static cytometry: (Scansystem, Hemosystem, Marseilles, France [laser-based, solid-phase cytometry])	Recently approved in Europe; Rapid (30 hr incubation and 90 min test time); Acceptable sensitivity and specificity; Requires reagent antibody to highly conserved common antigen or multiple reagent antibodies; 3 mL required
Bacterial cell wall component detection systems: (Platelet PGD test, Verax Biomedical, Worcester, MA)	Rapid (20 minutes); Lateral flow format; Sensitivity (10^3 to 10^4) in preliminary trial; 0.5 mL required; In experimental use only
Dielectrophoretic method: (Cell Analysis, Slough, United Kingdom)	Recently approved in Europe; Rapid (30 min); Sensitivity (10^3 to 10^5) in preliminary trial; 1 mL required
Gram stain	Requires a high level of contamination; Low sensitivity at lower concentrations; Can be used at point of issue; Validation and QC difficult
Endotoxin detection	Requires a high level of contamination; Low sensitivity at lower concentrations

Adapted from Reference 22.

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Strategies for the Mitigation of Contaminated Blood Products

As previously stated, detection strategies show variable sensitivity and specificity. Measuring abnormal glucose concentrations, low pH, microscopic examination of gram-stained specimens, and platelet swirling characteristics have been less useful due to low sensitivity and specificity. However, these methods have the advantage of being able to be used at the time and point of transfusion, are less expensive and use equipment commonly available.

Automated culture-based systems used for years in the hospital setting for detection of bacteremia in blood cultures obtained from patients were implemented by many of the nation's blood collection systems. Principally, they detect CO_2 generation or O_2 consumption by bacteria. Some of the limitations of culture-based systems are relatively insensitive at low levels of bacterial contamination causing false negative results, long incubation times for slow-growing bacteria, false positive results, high cost and the need for capital investment.[24-26] Holme and colleagues have recently shown that modifications to the Pall eBDS system have attempted to minimize these limitations.[29] While feasible for apheresis-derived platelets (ADP), culture based methods are not considered feasible for each whole blood-derived platelet (WBP) unit at the time of collection because of the high cost. Thus, those centers and services that used ADP could comply more easily and effectively with the new standard than those who used WBP, and converting entire systems from ADP to WBP was in-and-of-itself costly and met with resistance due to standard of care, cost, and availability concerns.

Apheresis Derived (ADP) Versus Whole Blood Derived Platelets (WBP)

Even before the implementation of Standard 5.1.5.1, the use of ADP had increased (52% to 99% of total transfused products per Ness and colleagues from 1987-1998) likely in part due to concern by some authorities about bacterial contamination.[8] Indeed, Ness and colleagues concluded that the rate of septic transfusion reactions due to WBP was 5.39 times higher than ADP (95% CI, 1.89, 12.9). Dykstra and colleagues found that the rate of bacterial contamination in ADP and WBP was identical (P=1.0); however, when platelet concentrates were pooled, the risk increased by 5 fold.[7]

Despite the apparent advantages of using ADP, maintaining adequate inventories and simultaneously providing adequate bacterial contamination testing is still a challenge due to the time it takes for the culture. Many experts have considered the effect and possibility of extending the expiration date to 7 days. In order to have a licensed 7 day ADP, clinical tests of the platelets, storage and medium will be required as will demonstration of bacteria detection and an acceptable rate of "residual risk." In order to allow the use of WBP with cost effective and optimal bacterial detection performance, 2 alternatives can be considered, but both are in clinical development and thus are not available. These include: 1) a 5 or 7 day "pooled and stored" WBP where a culture-based system could be used as a single test on a pre-storage pooled product, and 2) the approval of a effective test that could be used at the point and time of transfusion and which would be rapid enough for most clinical situations.

Residual Risk in "Tested" Components

Despite the strategies described above, bacterial contamination continues to be observed, although markedly reduced, and fatal consequences have been reported. As there was no standardized or required system in place to determine the true incidence of the morbidity and mortality caused by septic platelet units prior to the implementation of AABB Standard 5.1.5.1, it is impossible to determine with accuracy the effect of the standard in terms of percent improvement or reduction in adverse events. Some relevant data are available however.

From March 1, 2004 through December 31, 2004, approximately 350,000 units from 87,000 voluntary donors at 36 regional centers were cultured by the American Red Cross. Two hundred nineteen were initially positive, 67 were confirmed on re-sampling for an overall confirmed positive rate of 0.019% or 1:5,234 as compared to published reports of 1:2,000 to 3,000. Initially, 4 to 5 mL from each unit was transferred through a sterile docking device at least 24 hours after collection and used to inoculate BacT/ALERT BPA aerobic culture bottles. Confirmation of a positive blood culture bottle was performed by taking a new sample from product, inoculating a new BacT/ALERT aerobic culture bottle and if positive, performing bacterial isolation and identification. Eighty percent of the confirmed positive cases were gram-positive bacteria, mainly *Staphylococcus* (46.3%) and *Streptococcus* (26.9%) species. Serratia was the most commonly isolated gram-negative bacteria (n=4). Seventy-two percent of gram-negative organisms were identified within the first 12 hours of inoculation (personal communication; ARC). No patient transfused with an unconfirmed positive product had a septic transfusion reaction.

Three fatal cases and 2 non-fatal cases of transfusion-associated sepsis in platelet recipients have occurred since the standard was adopted. The first 2 cases were reported in MMWR.[27] The first case was that of a 74-year-old man who received 1 pool of 5 platelet concentrates. The pooled unit was tested by a pH method and found to be acceptable. After a hypotensive reaction, *S. aureus* was cultured from both the patient's blood and the platelet bag and by pulsed-field gel electrophoresis (PFGE) were identical. The second case was a 79-year-old man who was transfused a single platelet pheresis unit. The unit was tested by an automated culture system using a standard method. One hour after transfusion the patient had shortness of breath, chills, and fever. *S. lugdenensis* was cultured from both the patient's blood and the platelet bag and by PFGE were identical. The final case of fatality [presented to the Advisory Committee on Blood Safety (1/25/2005)] was a premature infant who received 2 doses of a single platelet pheresis. The unit was tested by a manual culture. The patient had symptoms consistent with sepsis. The platelet unit was then recultured and found to be growing *Serratia marcescens*. The patient's cultures were negative, but the cultures were taken after antibiotic therapy was initiated. One of the non-fatal cases was a BacT/ALERT failure of an apheresis platelet unit.[16]

Using numbers that are estimates only, and recognizing the limitations therein, a residual risk figure may be on the order of 3 to 6 fatal cases per year following the administration of approximately 2 million platelet doses per year (*The reader is asked to note that the true number of transfused platelet doses per year in the United States has not been established with certainty. While as many as 9 million units are given, the proportion of ADP vs. WBP is not known, nor is the number of WBP pooled into a dose*). Therefore, an incidence figure of approximately 1 fatality per approximately 500,000 tested doses may be posited. This is

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likely to be grossly inaccurate due to the lack of validated data, suboptimal test methods for WBP, and reporting and assumptions used. If one uses the figures given earlier in this report of 100 to 150 deaths annually (pre-standard implementation) and a residual as high as 6, then the improvement has been about 95%. Again, this number is a gross estimate, which will likely be revised with the collection of additional data. Though the "improvement rate" seems excellent, a residual risk of fatality incidence of 1:500,000 may be judged unacceptable by some, and thus other means of improving upon this complication may be warranted.

Pathogen Reduction (Inactivation)

Pathogen reduction is the term given to a number of technologies that prevent pathogens from replicating and thus prevent them from causing disease following transfusion. Methods under investigation (some are in use in Europe) use a variety of compounds including methylene blue, riboflavin and solvent-detergent treatment. In addition, a number of photodynamic processes use psoralen-based chemicals followed by ultraviolet light to inactivate bacteria and viruses by preventing replication and transcription of nucleic acids. This latter method has been extensively tested for bacterial reduction in platelet products. Gram-positive and gram-negative bacteria have been shown in three preclinical trials to be sensitive to pathogen inactivation (reviewed in reference 28). The main disadvantage of pathogen inactivation is that no method is equally effective for all organisms and these methods may be especially ineffective for spore-forming organisms.[28] The advantage is that this is a proactive method for bacterial reduction and has the potential to be as effective for known pathogens as it is for emerging pathogens.

Ongoing Issues

Bacterial contamination of blood products was, and may continue to be, a serious health risk to transfusion recipients. While we believe substantial improvement has been made, though difficult to accurately quantify, some level of residual risk appears to exist. Systems to help quantify this residual risk need to be implemented and/or strengthened. In addition, there is some evidence to suggest that the implementation of Standard 5.1.5.1 has caused a significant reduction in platelet availability, delay in their release to hospital transfusion services, and/or a declination in WBP use which may have added to the overall cost of platelet provision and transfusion. In order to address these issues, rapid and cost-effective tests need to be developed and approved for use at the time and point of transfusion. Alternatively, and with the use of a validated bacterial detection test, prestorage pooling may be "allowed" and thus lead to a state of equipoise between ADP and WBP safety and therefore use. An effective method or methods for bacterial detection and limitation will likely allow the extension of either ADP or pooled and stored WBP to 7 or perhaps even 8 days, thus likely improving the logistical and availability issues currently surrounding this valuable human resource. Finally, the adoption of pathogen reduction technologies in Europe and their approval in the United States may abrogate any residual or evolving risk.

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Bibliographic data: EP1665986 (A1) — 2006-06-07

Blood collection set with an expanded internal volume

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Classification: **- international:** ***A61B5/154; A61B5/155***
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150221 (EP, US); A61B5/150389 (EP, US); A61B5/150503 (EP, US); A61B5/150572 (EP, US); A61B5/15074 (EP, US); A61B5/150992 (EP, US); A61B5/1545 (EP, US)**

Application number: EP20050111371 20051128 Global Dossier

Priority number(s): US20040631515P 20041129 ; US20050280622 20051116

Also published as: EP1665986 (B1) BRPI0505336 (A) JP2006150083 (A) JP4914601 (B2) US2006129064 (A1)

Abstract of EP1665986 (A1)

The blood collection set includes an IV needle assembly, a length of flexible plastic tubing extending from the IV needle assembly and a non-patient needle assembly. The set is formed with an internal chamber that increases the internal volume of the blood collection set. Thus, the increase in internal volume allowing for greater flash visualization on venous entry.

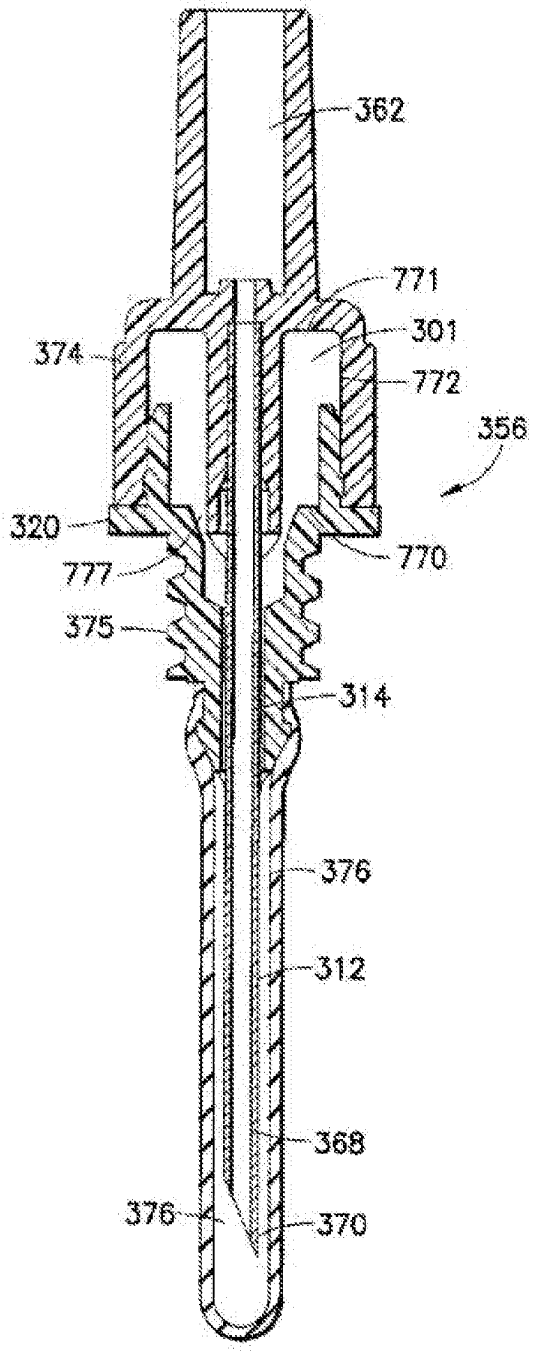


FIG.4

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

(11) EP 1 665 986 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
07.06.2006 Bulletin 2006/23

(51) Int Cl.:
A61B 5/154 *(2006.01)* ***A61B 5/155*** *(2006.01)*

(21) Application number: **05111371.0**

(22) Date of filing: **28.11.2005**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK YU

(30) Priority: **29.11.2004 US 631515 P**
16.11.2005 US 280622

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DE ES FR GB IT

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(54) Blood collection set with an expanded internal volume

(57) The blood collection set includes an IV needle assembly, a length of flexible plastic tubing extending from the IV needle assembly and a non-patient needle assembly. The set is formed with an internal chamber that increases the internal volume of the blood collection set. Thus, the increase in internal volume allowing for greater flash visualization on venous entry.

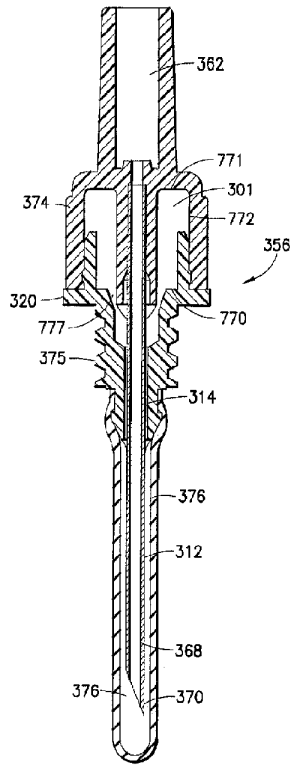


FIG.4

EP 1 665 986 A1

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Description

BACKGROUND OF THE INVENTION

[0001] This application claims priority to U.S. Provisional Application No. 60/631,515, which was filed on November 29, 2004.

1. Field of the Invention

[0002] The subject invention relates to a blood collection set with an internal chamber, which increases the internal volume of the blood collection set thereby improving flash.

2. Description of the Related Art

[0003] Phlebotomy procedures often are carried out using a blood collection set. A typical blood collection set includes an IV needle assembly with an IV cannula that has a proximal end, a sharply pointed distal end and a lumen extending between the ends. The needle assembly also includes a plastic IV hub with a proximal end, a distal end, and a passage extending between the ends. The proximal end of the IV cannula is mounted in the passage of the IV hub so that the lumen through the IV cannula communicates with the passage through the IV hub. The needle assembly may further include a shield for shielding the IV cannula after use (a so called safety blood collection set) and a packaging cover for safely covering the IV cannula prior to use. Packaging covers typically are rigid tubes with a proximal end that can be telescoped over the IV cannula and frictionally engaged with the distal end of the IV hub. Shields for shielding the IV cannula of blood collection sets have taken many forms. Some shields are telescoped over the IV hub and can be moved from a proximal position where the cannula is exposed to a distal position where the cannula is shielded. Other shields are hinged to the IV hub and can be rotated from an open position where the IV cannula is exposed to a closed position where the IV cannula is shielded. A needle assembly for a blood collection set also may include two flexible wings that project transversely from the IV hub or from the shield. The wings can be folded into face-to-face relationship with one another to effectively define a handle that facilitates manipulation of the needle assembly. The wings then can be rotated away from one another and held against the skin of the patient.

[0004] Blood collection sets also include a length of flexible plastic tubing. The tubing has a distal end that is connected to the proximal end of the IV hub, The tubing also has a proximal end that is connected to a plastic fitting. Thus, fluid communication is provided between the lumen of the IV cannula and the plastic fitting at the proximal end of the flexible tubing. The plastic fitting may be a female luer fitting that can be connected to a male luer fitting. The fitting then can be placed in communication with a reservoir or container for collecting a sample of blood.

[0005] Phlebotomy procedures often employ evacuated tubes, such as the VACUTAINER® brand of evacuated tubes sold by Becton Dickinson and Company. Evacuated tubes often are used with a tube holder that has a proximal end, a distal end, and a tubular side wall extending between the ends. The proximal end of the holder is widely open and is configured for slidably receiving the evacuated tube. The distal end of the holder typically includes an end wall with a mounting aperture. The mounting aperture includes internal threads or other mounting structures.

[0006] The tube holder may be used with a non-patient needle assembly that has a non-patient hub with external surface configurations for mounting in the mounting aperture of the holder. The non-patient needle assembly further includes a non-patient cannula extending proximally from the hub and a multiple sample sleeve telescoped over the non-patient cannula and mounted to the proximal end of the hub. The hub of the non-patient needle assembly can be threaded or otherwise engaged in the mounting aperture of the tube holder so that the non-patient needle and the multiple sample sleeve project into the tube receiving chamber of the holder.

[0007] The blood collection set may be used by mounting the fitting at the proximal end of the flexible plastic tubing to the distal end of the hub of the non-patient needle assembly. The packaging shield that covers the non-patient cannula then may be removed, and the hub of the non-patient needle assembly may be engaged with the tube holder. The medical practitioner then grips the IV needle assembly and removes the packaging cover from the IV cannula. The gripping of the IV needle assembly may include folding the flexible wings into face-to-face engagement and gripping the folded wings between a thumb and forefinger. The pointed distal end of the IV cannula then is urged into a targeted blood vessel. The wings then may be folded into engagement with the skin of the patient and may be taped in position. An evacuated tube then is urged into the open proximal end of the blood collection tube holder so that the non-patient needle pierces the stopper of the evacuated tube. As a result, the blood vessel of the patient is placed in communication with the interior of the evacuated tube, and the pressure differential between the blood vessel and the evacuated tube will generate a flow of blood through the IV cannula, through the passage of the IV hub, through the flexible tubing, through the non-patient hub and finally through the non-patient needle and into the evacuated tube.

[0008] The translucent or opaque plastic material of blood collection sets and IV cannula shields, combined with numerous cannula shield mechanism components and the length of the typical needle hub tends to inhibit a clear indication of venous or arterial access. Blood flow into the plastic tubing does provide an indication of venous or arterial access (known as "flash") as the plastic

tubing is often formed from a highly translucent or transparent plastic material. However, because of the existence of the elements associated with the IV needle assembly the length of flash obtained from a typical venous entry may not be sufficient for blood flow to be observed in the flexible tubing at a location proximal to the IV needle assembly itself. Thus, a medical practitioner may have a delayed indication of venous or arterial access and may incorrectly assume that the blood vessel was not accessed properly. In these situations, the medical practitioner may try to access the blood vessel again even though the initial access was successful. Accordingly, the patient may be subjected to unnecessary trauma during a repeated attempt to access the targeted blood vessel. Thus, improved techniques for increasing the length of flash such that initial blood flow will be observable in the flexible tubing proximal the IV needle assembly and associated shielding elements would be desirable.

SUMMARY OF THE INVENTION

[0009] The invention relates to a blood collection set with an internal chamber provided to increase the internal volume of the blood collection set when compared to a prior art blood collection set which does not have an internal chamber. In this manner, improved flash visualization, can be provided.

[0010] "Internal chamber" as used herein means an enclosed space or compartment, which is in communication with the fluid passage of the blood collection set. The "fluid passage" is defined as any part of the blood collection set in which blood flows and can include the lumen through the IV cannula, the passage through the IV hub, the passage through the flexible tubing, the passage through the non-patient hub and lumen through the non-patient cannula. "Flash" is defined as the initial blood flow into the fluid passage on venous entry, which provides an indication of venous or arterial access before an evacuated tube is urged into the open proximal end of the blood collection tube holder. "Flash length" is the linear distance that blood flows in a proximal direction along the fluid passage on venous entry. "Flash volume" is the volume of blood that flows into the fluid passage on venous entry expressed as a percentage of the total internal volume of the blood collection set.

[0011] In one embodiment, the blood collection set includes an IV needle assembly, a length of flexible plastic tubing extending from the IV needle assembly and a non-patient needle assembly. The internal chamber is advantageously disposed on or near the non-patient needle assembly to permit an increase in the internal volume of the blood collection set without being located directly in the blood flow path.

[0012] The IV needle assembly typically comprises an IV hub having a proximal end, a distal end and a passage extending between the ends. The IV needle assembly typically further comprises an IV cannula having a proximal end mounted in the passage of the IV hub, a pointed distal end projecting distally from the IV hub and a lumen that communicates with the passage through the IV hub. The flexible tubing is typically connected to the proximal end of the IV hub. The IV needle assembly typically includes a packaging cover that protectively encloses the IV needle cannula prior to use. The packaging cover is removed immediately prior to use to permit access to the IV cannula. The IV needle assembly may further include a protective shield that is moveable relative to the IV cannula from an open position where the IV cannula is exposed to a closed position where the IV cannula is substantially shielded. The shield protects against accidental sticks with the used IV cannula. A pair of flexible wings may be mounted to the IV hub or to the shield to facilitate manipulation of the IV needle assembly.

[0013] In this embodiment, the non-patient needle assembly includes a non-patient hub having a proximal end and a distal end. The non-patient needle assembly further includes a non-patient cannula having a distal end securely mounted in the hub, a proximal end projecting proximally from the non-patient hub and a lumen that communicates with the passage through the non-patient hub. A multiple sample sleeve is typically mounted over the non-patient cannula and secured to the proximal end of the non-patient hub. External portions of the non-patient hub near the proximal end thereof may be formed with an array of external threads or other mounting structure to enable the non-patient needle assembly to be mounted to a collection tube holder or other such medical device. Or, the holder may be pre-attached with the non-patient needle assembly. The blood collection set may further include a fitting mounted to the proximal end of the flexible plastic tubing and configured for mating with the distal end of the non-patient hub. For example, the fitting may be a female luer fitting that can be engaged with the male luer taper at the distal end of the non-patient hub.

[0014] In one embodiment, the internal chamber is located in the non-patient assembly beyond the non-patient cannula proximal end, which means that the air passes through the non-patient cannula proximal end from which blood is drawn, and then into the internal chamber. Specifically, on venous entry air is compressed and flows from the fluid passage and out of the non-patient cannula proximal end where it further flows through the space between needle exterior and multiple sample sleeve. The air then flows into the internal chamber, which may be at the non-patient barb, the non-patient hub thread, the non-patient hub body, or other location or combination of locations that are beyond the non-patient cannula proximal end. The collection tube, which is applied at the non-patient cannula proximal end, draws blood from only the fluid passage and not from the internal chamber.

[0015] In another embodiment, a one-way check valve is located within the internal chamber. The valve allows air and blood to enter the internal chamber but shuts closed both when vacuum is applied. Thus, when an

evacuated collection tube is applied at the non-patient needle tip, the tube draws blood from the fluid passage but not from the internal chamber, and upon removal of the IV needle from the targeted blood vessel, the check valve closes and inhibits blood from dripping from the IV needle tip.

[0016] In a further embodiment, the internal chamber utilizes a branch in the fluid passage, e.g., a "Y" or "T". The branching may be at any location or locations along the fluid passage, but is advantageously at the proximal end such as at the non-patient hub. The branching may be in the form of a separate component added into the fluid passage such as in between the female and male luer fittings or it may be integral within the hub. The branching includes some type of internal chamber as discussed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1A is a perspective view of a prior art blood collection set and collection tube holder.

[0018] FIG. 1B is a top plan view of the blood collection set and collection tube holder shown in FIG. 1A.

[0019] FIG. 2 is an exploded perspective view of a prior art blood collection set.

[0020] FIG. 3 is side elevation view of a prior art non-patient needle assembly, partly in section.

[0021] FIG. 4 is a cross-sectional side view of an embodiment of the non-patient needle assembly of the blood collection set.

[0022] FIG. 5 is a perspective view of the same embodiment shown in FIG. 4

[0023] FIG. 6 is a cross-sectional side view of an embodiment of the non-patient needle assembly of the blood collection set.

[0024] FIG. 7 is a perspective view of the same embodiment shown in FIG. 6

[0025] FIG. 8 is a cross-sectional side view of an embodiment of the non-patient needle assembly of the blood collection set.

[0026] FIG. 9 is an expanded view of the same embodiment shown in FIG. 8

[0027] FIG. 10 is a perspective view of one embodiment of a one way check valve.

[0028] FIG. 11 is a plan view of the same embodiment shown in FIG. 10

[0029] FIG. 12 is a cross-sectional side view of the same embodiment shown in FIG. 10

[0030] FIG. 13 is a perspective view of one embodiment of the blood collection set.

[0031] FIG. 14 is a perspective view of one embodiment of the blood collection set.

DETAILED DESCRIPTION

[0032] A prior art blood collection set that contains IV cannula shielding is identified generally by the numeral **10** in FIGS. 1A and 1B. Blood collection set **10** is employed in this embodiment with a collection tube holder **12.** Holder **12** has a proximal end **14,** a distal end **16** and a tubular sidewall **18** extending between the ends. Proximal end **14** of holder **12** is widely open and defines an entry to a tube receptacle within sidewall **18.** Thus, an evacuated collection tube can be slid in a proximal-to-distal direction through open proximal end **14** of holder **12** toward distal end **16.** Distal end **16** of holder **12** is characterized by an end wall **20.** End wall **20** is formed with an internally threaded mounting aperture **22,** as shown in FIG. 3.

[0033] Blood collection set **10** includes an IV needle assembly **24** that comprises an IV hub **26.** IV hub **26** includes a proximal end **28,** a distal end **30** and a passage (not shown) extending between the ends. IV needle assembly **24** further includes an IV cannula **32** with a proximal end **34,** a pointed distal end **36** and a lumen **38** extending between the ends. Proximal end **34** of IV cannula **32** is mounted securely in the passage of IV hub **26.** Thus, lumen **38** through IV cannula **32** communicates with the passage through IV hub **26.** Flexible wings **40** are mounted to IV hub **26** at a location near distal end **30.** Wings **40** can be folded into face-to-face relationship with one another for convenient gripping between a thumb and forefinger to enable manipulation of IV needle assembly **24.** Wings **40,** however, also can be rotated into a substantially coplanar disposition for taping to the skin of a patient.

[0034] IV needle assembly **24** further includes a tubular shield **42** that is telescoped over IV hub **26.** Shield **42** is formed with transverse slots **44** that slidably receive wings **40.** Thus, shield **42** can be slid from a proximal position, as shown in FIGS. 1A and 1B to a distal position. IV cannula **32** is exposed for use when shield **42** is in the proximal position shown in FIGS. 1A and 1B. However, IV cannula **32** is substantially surrounded by shield **42** when shield **42** is moved to the distal position. Additionally, slots **44** in shield **42** are configured to lockingly engage wings **40** when shield **42** is in the distal position to prevent or complicate a re-exposure of IV cannula **32.** In this case the presence of a shield does not inhibit flash visualization within the IV needle assembly. The shield illustrated in FIGS. 1A and 1B is one of many optional shield designs that can be incorporated into blood collection set **10.** Other designs may provide wings mounted directly to the shield. Still other designs may provide a hinged shield mounted to IV hub **26.** In still other designs, a shield may be entirely separate from IV needle assembly **24.**

[0035] Another prior art blood collection set is identified generally by the numeral **110** in FIG. 2. Fluid collection/infusion set **110** includes a length of flexible plastic tubing **112,** a proximal fitting **114,** a needle assembly **116,** a spring **118** and a barrel assembly that comprises a front barrel **120,** a rear barrel **122** and a wing **124.** Needle assembly **116** includes a needle cannula **134,** a needle hub **136** and a needle protector **138.** Needle cannula **134** has a proximal end **140,** a distal end **142** and a lumen

144 extending between the ends. Distal end 142 of needle cannula 134 is beveled to a sharp tip.

[0036] FIGS. 1 A and 1B also show that a blood collection set 10 further includes a length of flexible plastic tubing 46. Tubing 46 includes opposite proximal and distal ends 48 and 50 and a passage extending between the ends. Distal end 50 of tubing 46 is securely mounted to proximal end 28 of IV hub 26 so that the passage through IV hub 26 communicates with the passage through tubing 46. A female luer fitting 52 is securely mounted to proximal end 48 of tubing 46.

[0037] Blood collection set 10 further includes a non-patient needle assembly 54, as shown in FIG. 3. Non-patient needle assembly 54 includes a non-patient hub 56 with a proximal end 58, a distal end 60 and a fluid passage 62 extending between the ends. Exterior surface regions of non-patient hub 56 substantially adjacent proximal end 58 define an array of external threads 64 configured for threaded engagement with the internal threads formed in mounting aperture 22 of collection tube holder 12. External surface regions of non-patient hub 56 adjacent distal end define a male luer taper 66 configured for mating with female luer fitting 52. Non-patient needle assembly 54 further includes a non-patient cannula 68 having a pointed proximal end 70, a distal end 72 and a lumen 74 extending between the ends. Distal end 72 of non-patient cannula 68 is mounted securely in passage 62 through non-patient hub 56 and aligns substantially with external threads 64 on non-patient hub 56. Non-patient needle assembly 54 further includes a multiple sample sleeve 76 mounted over non-patient cannula 68 and securely engaged with proximal end 58 of non-patient hub 56. Multiple sample sleeve 76 effectively functions as a valve that prevents a flow of fluid from non-patient cannula 68. However, multiple sample sleeve 76 can be pierced by pointed proximal end 70 of non-patient cannula 68 in response to forces generated by a stopper on an evacuated collection tube.

[0038] It should be noted that flash visualization maybe acceptable in certain blood collection sets with safety features, such as the type shown in FIGS. 1A and 1B. The IV needle assembly and safety shield tend to be made from a translucent plastic material, and may only contain the IV cannula and flexible tubing, which may allow flash to be seen through the IV cannula hub walls. Therefore a minimum length of flash maybe sufficient, such that initial blood flow on venous entry maybe observed at the proximal end of the IV cannula. However in more advanced and complex IV cannula shielding mechanisms, such as the blood collection set shown in FIG. 2, the length of flash obtained from a typical venous entry may not be sufficient for blood flow to be observed in the flexible tubing at a location proximal to the IV needle assembly itself, therefore flash visualization tends to be inhibited within the IV needle assembly.

[0039] According to one embodiment of the invention, a blood collection set, for example of the type disclosed above, contains an internal chamber that increases the internal volume of the blood collection set. The increase in internal volume of the blood collection set provides a greater length of flash and therefore improved flash visualization, such that, advantageously, blood is observed in the flexible tubing proximal the IV needle assembly on the initial venous entry. While such improved or lengthened flash is particularly advantageous for such complex blood collection sets as shown in FIG 2, application in any blood collection set is contemplated.

[0040] According to this embodiment of the invention, a blood collection set includes a plurality of internal spaces that will initially be at ambient air pressure. These internal spaces include the lumen through the IV cannula, the passage through the IV hub, the passage through the flexible tubing, the passage through the non-patient hub and lumen through the non-patient cannula. The blood collection set is employed by folding wings into face-to-face engagement with one another and gripping the wings between a thumb and forefinger. Any packaging cover that may be mounted over IV cannula then is removed and discarded. The pointed distal end of the IV cannula then is urged into a targeted blood vessel. The healthcare practitioner then may release the grip on the wings, and if long term access to the blood vessel is required, the wings may be taped into face-to-face engagement with the skin of the patient. The venous or arterial access achieved with the IV cannula places the plurality of interior spaces of the blood collection set in communication with the pressure of the blood in the patient. Blood pressure exceeds the ambient air pressure. Accordingly, the pressure of air in the above-referenced internal spaces will increase, and blood will begin to flow into these internal spaces. The system will reach equilibrium as the air pressure within the blood collection set increases in response to a reduction of volume caused by the inflow of blood. Hence, a portion of the internal spaces in the system will remain filled with air at a pressure substantially equal to the venous or arterial pressure thereby preventing blood from flowing any further to or into the tubing. Stated differently, the system will include its original volume of air in the space between the proximal end of the non-patient needle and the blood that enters the blood collection set. This pressurized air will prevent any further flow of blood toward the non-patient assembly, thereby stopping flash. In prior art systems the total volume of the internal spaces maybe insufficient, such that flash maybe stopped before it can be observed. According to embodiments of the invention, however, the internal chamber which lacks direct communication to the exterior, provides more internal volume into which the air can be pushed, allowing blood to push further into the device before the pressure of the blood equals the pressure of the air. This increase in interior space thereby allows a greater length of flash to occur. Various embodiments of such internal chambers are described in detail below.

[0041] FIGS. 4 and 5 show an embodiment of the invention, where the internal chamber 301 is located be-

yond the proximal end **370** of the non-patient cannula in the non-patient hub **356** and lacks direct communication to the exterior. The internal chamber **301** is annular in cross-section and has opposite proximal **770** and distal ends **771** and a wall **772** extending therebetween; the proximal end **770** has an inlet **777** in communication with the passage. However all internal chamber geometries can be considered for the invention. The non-patient hub **356** is generally made from 2 separate parts; the male luer **374** and the non-patient thread assembly **375.** Other configurations are possible. On venous entry, air is compressed and flows from the fluid passage **362** and out of the non-patient cannula proximal end **370** where it further flows through the space **312** between needle exterior **368** and multiple sample sleeve interior **376,** then through a passage **314** through the non-patient barb and the male luer wall **320** into the internal chamber **301** through the inlet **777** in the male luer **374.**

[0042] FIGS 6 and 7 show another embodiment of the invention, with an elongated internal chamber to further increase the flash length. The internal chamber **301a** is annular in cross-section and has opposite proximal **770a** and distal ends **771a** and a wall **772a** extending therebetween, the proximal end **770a** has an inlet **777a** in communication with the passage. However all internal chamber geometries can be considered for the invention. The non-patient hub is made from 2 separate parts; the male luer **374a** and the non-patient thread assembly **375a.** The longer internal chamber **301a** is located beyond the proximal end **370a** of the non-patient cannula in the non-patient thread assembly **375a** and has no direct communication to the exterior. Other configurations are possible. On venous entry, air is compressed and flows from the fluid passage **362a** and out of the non-patient cannula proximal end **370a** where it further flows through the space **312a** between needle exterior **368a** and multiple sample sleeve interior **376a**, then through a passage **314a** through the non-patient barb into an internal chamber **301a** through an inlet **777a** in the non-patient thread assembly **375a.**

[0043] FIGS 8 to 12 show a further embodiment of the invention, in which a one-way valve **555** is located within an internal chamber similar to that shown in FIG. 6. The one way valve has a central core **550** surrounded by an annular flange **551** that has a sealing ring **552** around its outer diameter. The central core **550** is located around the non-patient needle exterior **368b** within the internal chamber **301b** and has a tapered base **553** which mates to the taper of inlet **777b.** Typically the one way valve **555** is formed from a resilient polymer such as an elastomer or thermoplastic.

[0044] As apparent to one skilled in the art, on venous entry, air flows from the fluid passage **362b** and out of the non-patient cannula proximal end **370b** where it further flows through the space **312b** between needle exterior **368b** and multiple sample sleeve interior **376b,** then through a passage **314b**, through the non-patient barb and the male luer wall **320b,** through the inlet **777b** where it moves the one-way valve **555,** flowing past the valve core base **553,** valve sealing ring **552** and into an internal chamber **301b** in the male luer **374b.** A vacuum is applied to the fluid passage, when an evacuated collection tube is applied at the non-patient needle tip. The resultant positive pressure differential between the internal chamber and the fluid passage causes the one way valve **555** to close, by the valve sealing ring **552** being pressed against the proximal end of the internal chamber **770b** and the valve core tapered base **553** being pressed into inlet 777b thereby preventing outflow of air or blood from the internal chamber,. It should be noted that the one way valve is not limited to the particular design described in this embodiment as all types of one way valves can be contemplated for this invention.

[0045] The one way valve **555** also inhibits blood from dripping from the IV needle tip upon removal of the IV needle from the targeted blood vessel after the blood collection has been completed. In prior art blood collection sets, at the instance of removal of the IV needle, the fluid passage of the blood collection set, will contain a reservoir of air and blood at venous pressure, which will be greater than the ambient atmospheric pressure. Thus a back pressure is created within the fluid passage which may cause a back-flow of blood to drip from the IV needle tip. In the embodiment of the invention shown in FIGS 8 to 12, the reservoir of air at venous pressure is within the internal chamber **301b**, therefore the back pressure causes the one way valve **555** to shut upon removal of the IV needle thereby preventing such a back-flow of blood in the fluid passage **362b.**

[0046] FIGS 13 and 14 show another embodiment of an internal chamber **401** which is branched from the fluid passage using a "Y" or "T" branched internal chamber in the fluid passage into which air is displaced. The branching may be at any location or locations along the fluid passage, but is typically near the proximal end such as at the non-patient hub. FIG 13 shows a "Y" branched internal chamber **454** in the form of a separate component added into the fluid passage **462** such as in between the female **455** and male luer **456** fittings. FIG 14 shows a "T" branched internal chamber **457,** which is an integral part of the non-patient hub, thus reducing the number of components. The use of a "Y" or "T" branched internal chamber may be accomplished with any convenient terminal shapes at the interfaces of each component. The embodiments exemplified previously are shown with luer tapered fittings but other interface designs such as direct connection to the flexible tubing may also be applied. Although typical applications use a three port "Y" or "T" branched internal chamber the use of a multiple port branched internal chamber system is also possible. The internal chamber **401**, can be a separate component which is affixed into a port **460** of the branch system as shown in FIG 13 or an integral part of the branched system as shown in FIG 14. All internal chamber geometries can also be contemplated.

Claims

1. A blood collection set comprising;
a first needle assembly comprising a first hub and a first cannula having a lumen therethrough, wherein said cannula is mounted to said first hub,
a length of flexible tubing having opposite first and second ends and a tubing passage extending between said ends, said first hub located proximate said first end for providing communication between said lumen of said first cannula and said tubing passage,
a second hub located proximate said second end and having a passage extending therethrough, said second hub passage being in fluid communication with said tubing passage,
a non-patient cannula having opposite proximal and distal ends and a lumen extending between said ends, said distal end of said non-patient cannula being mounted to said second hub such that said lumen through said non-patient cannula communicates with said second hub passage,
a multiple sample sleeve covering said non-patient cannula and mounted to said second hub, and
an internal chamber in communication with said second hub passage, wherein said internal chamber is located within said second hub or is branched from said second hub passage, and wherein said internal chamber lacks direct communication to the exterior.

2. The blood collection set of claim 1, wherein said second hub further comprises a male luer and a non-patient thread assembly, which form said internal chamber.

3. The blood collection set of claim 1, wherein said internal chamber communicates with said second hub passage beyond said proximal end of said non-patient cannula.

4. The blood collection set of claim 1, further comprising a one way valve, wherein said one way valve inhibits an outflow of air or fluid from said internal chamber.

5. The blood collection set of claim 4, wherein said one way valve is located within said internal chamber.

6. The blood collection set of claim 1, wherein upon venous access by said first needle cannula, venous pressure causes blood to flow into said tubing passage, such that the total internal volume of said internal chamber and tubing passage results in a flash length of at least approximately 0.25 inches in linear distance in a proximal direction along said tubular passage from said first end of said flexible tubing.

7. The blood collection set of claim 1, wherein upon venous access by said first needle cannula, venous pressure causes blood to flow into said tubing passage, such that the total internal volume of said internal chamber and tubing passage results in a flash length of at least approximately 0.50 inches in linear distance in a proximal direction along said tubular passage from said first end of said flexible tubing.

8. The blood collection set of claim 1, wherein said internal chamber is branched from said second hub passage.

9. The blood collection set of claim 8, wherein said internal chamber is a Y branched internal chamber or a T branched internal chamber.

10. The blood collection set of claim 1, wherein the volume of said internal chamber is at least approximately 1.0 ml.

11. The blood collection set of claim 10, wherein said volume of said internal chamber is approximately 1.0 ml to approximately 3.0 ml.

12. The blood collection set of claim 11, wherein said volume of said internal chamber is approximately 1.0 ml to approximately 2.0 ml.

13. A blood collection set comprising;
a first needle assembly comprising a first hub and a first cannula having a lumen therethrough, wherein said cannula is mounted to said first hub,
a length of flexible tubing having opposite first and second ends and a tubing passage extending between said ends, said first hub located proximate said first end for providing communication between said lumen of said first cannula and said tubing passage,
a second hub located proximate said second end and having a passage extending therethrough, said second hub passage being in fluid communication with said tubing passage,
a non-patient cannula having opposite proximal and distal ends and a lumen extending between said ends, said distal end of said non-patient cannula being mounted to said second hub such that said lumen through said non-patient cannula communicates with said second hub passage,
a multiple sample sleeve covering said non-patient cannula and mounted to said second hub, and
an internal chamber in communication with said second hub passage, wherein said internal chamber is located within said second hub or is branched from said second hub passage, and wherein said internal chamber lacks direct communication to the exterior,
wherein upon on venous access by said first needle cannula, venous pressure causes blood to flow into said tubing passage, such that the total internal volume of said internal chamber and tubing passage

results in flash being observed within said flexible tubing.

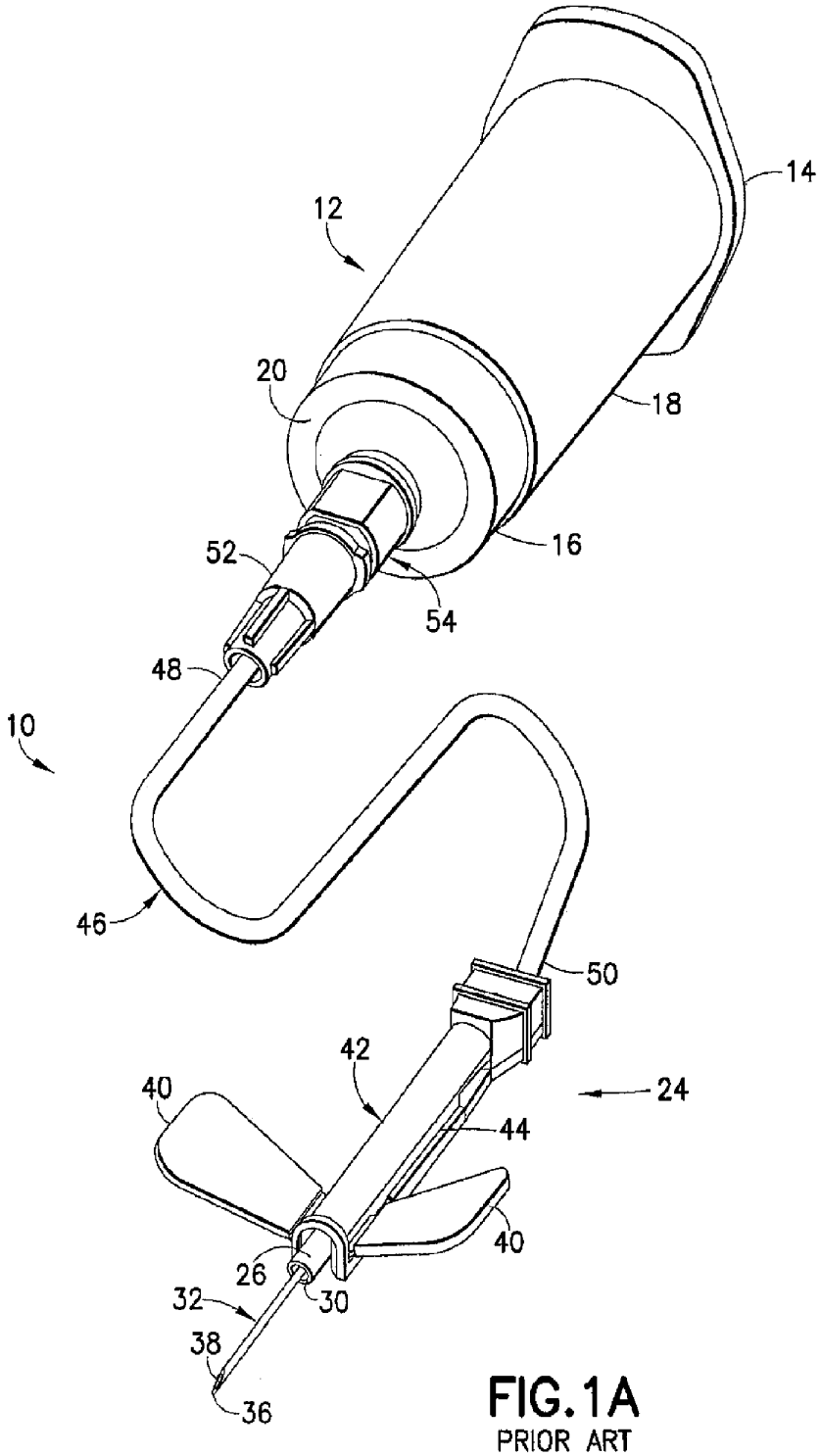


FIG. 1A
PRIOR ART

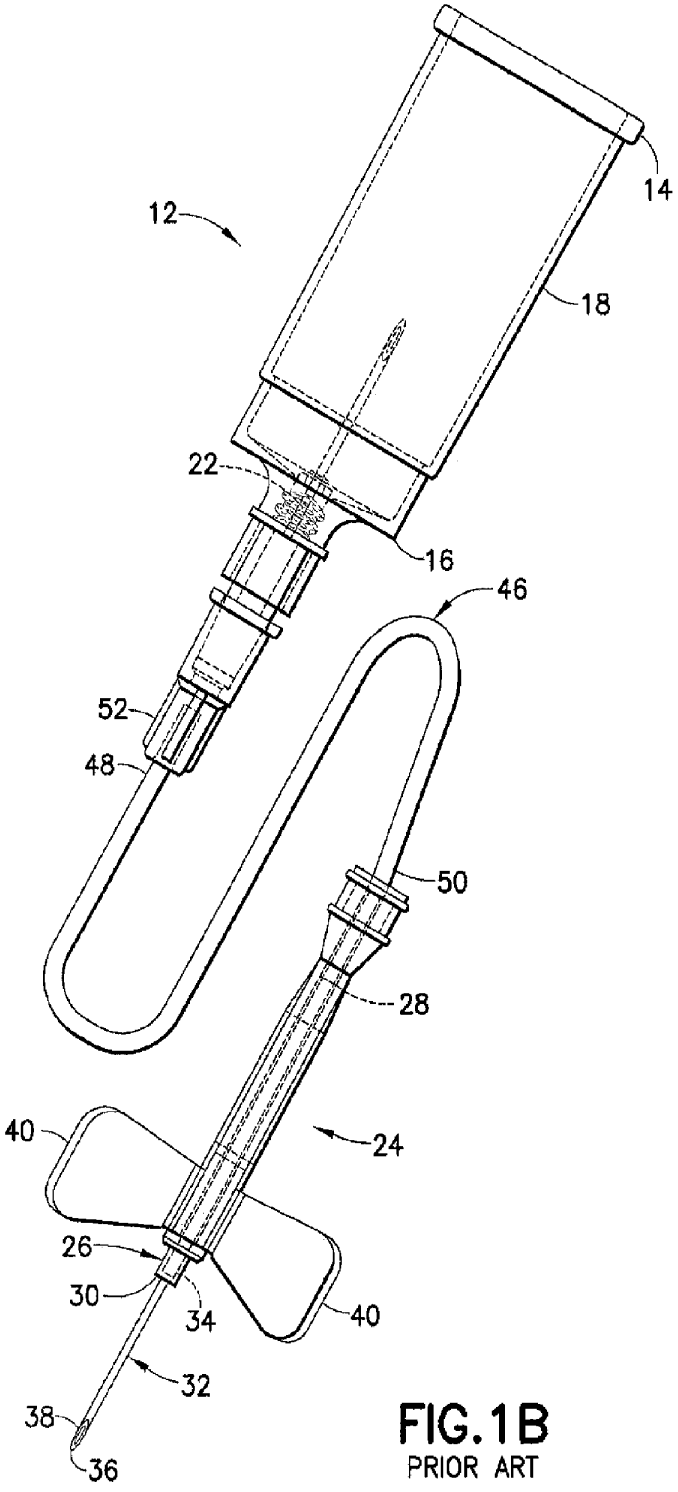


FIG.1B
PRIOR ART

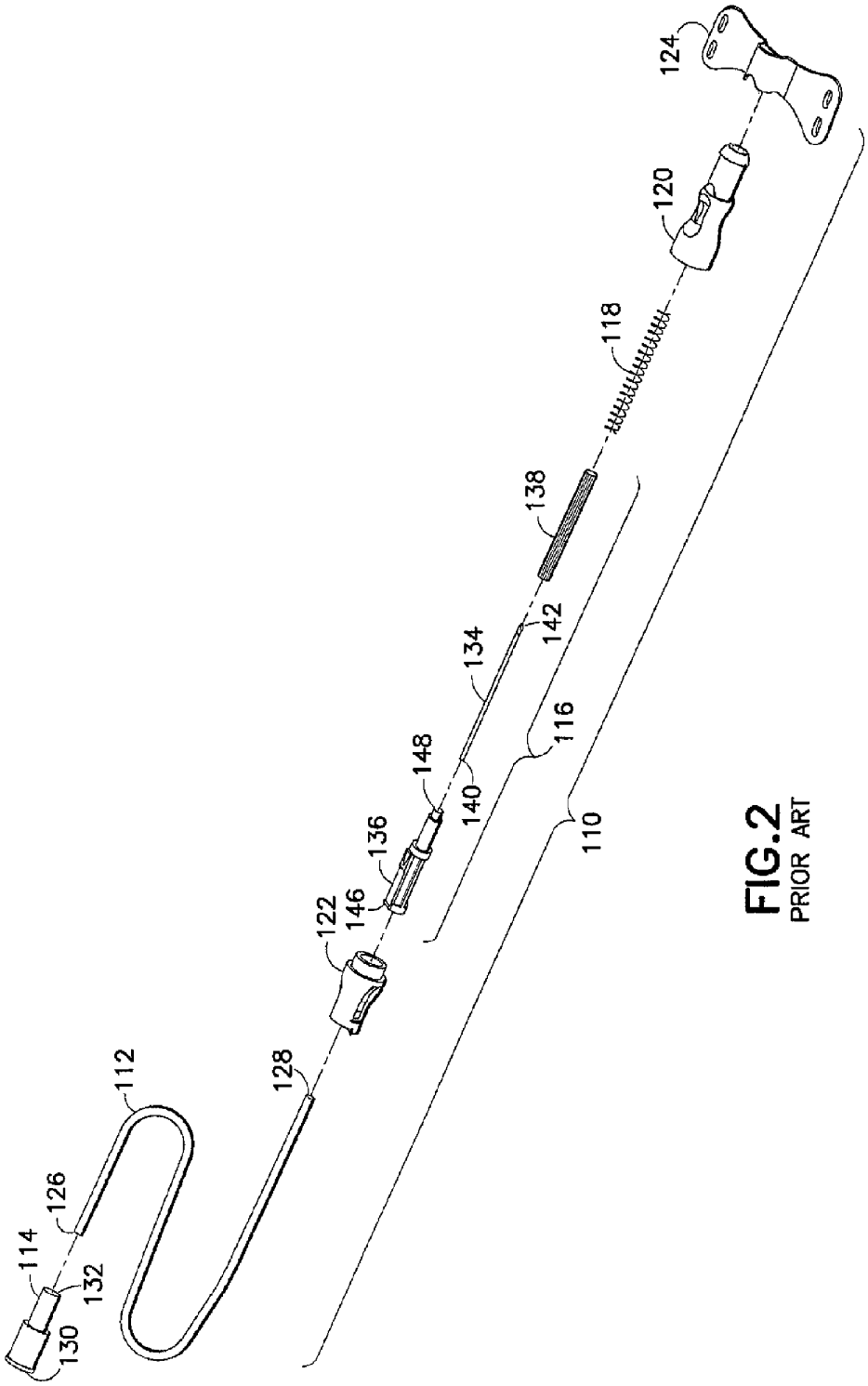


FIG.2
PRIOR ART

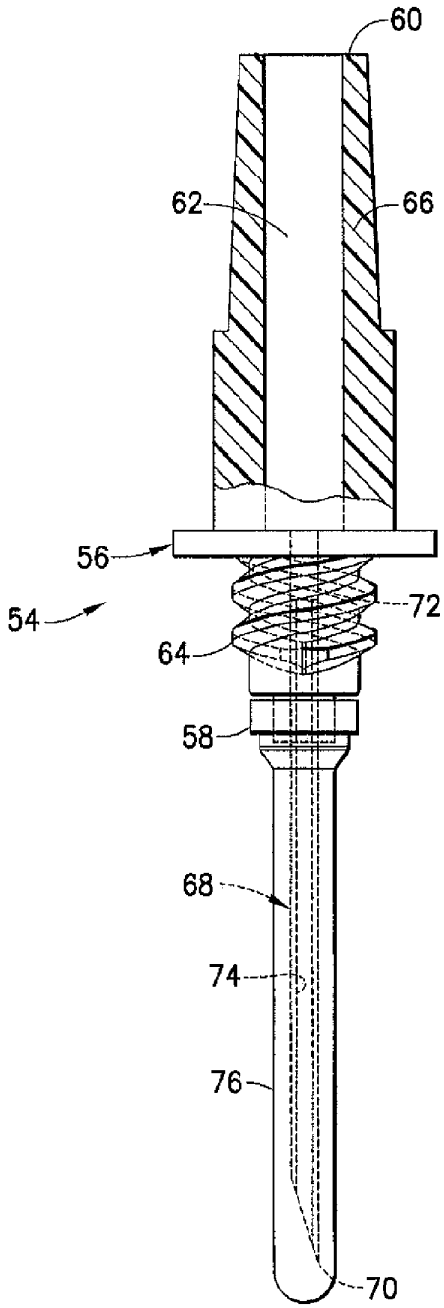


FIG.3
PRIOR ART

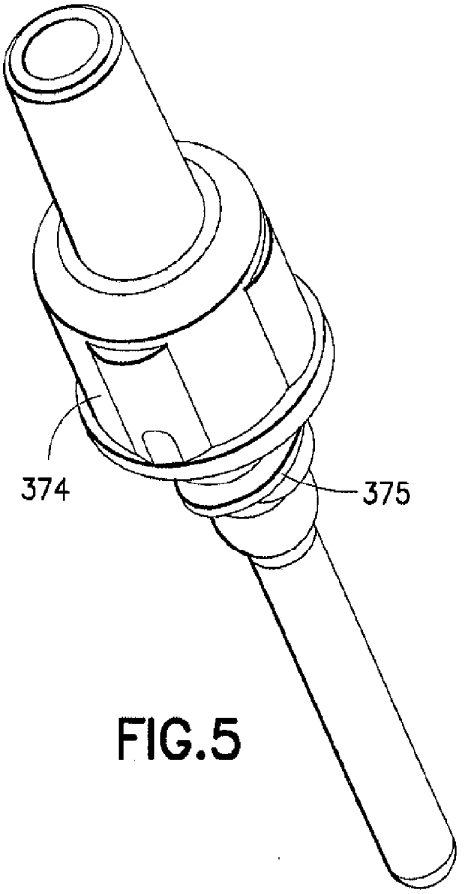

374
375

FIG.5

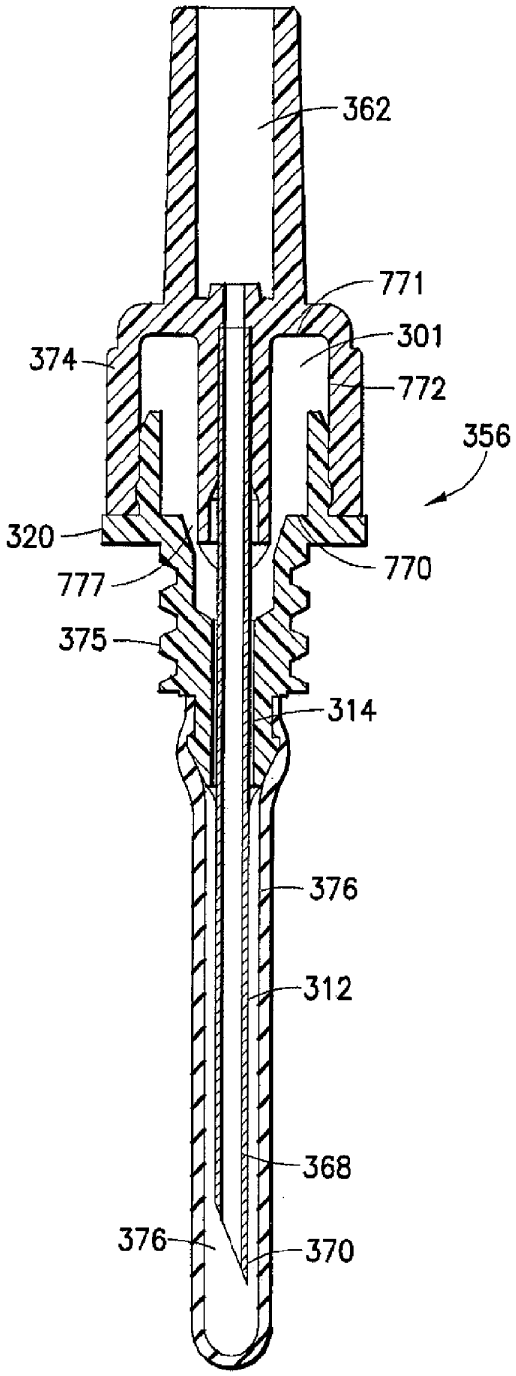

362
771
301
374
772
356
320
770
777
375
314
376
312
368
376
370

FIG.4

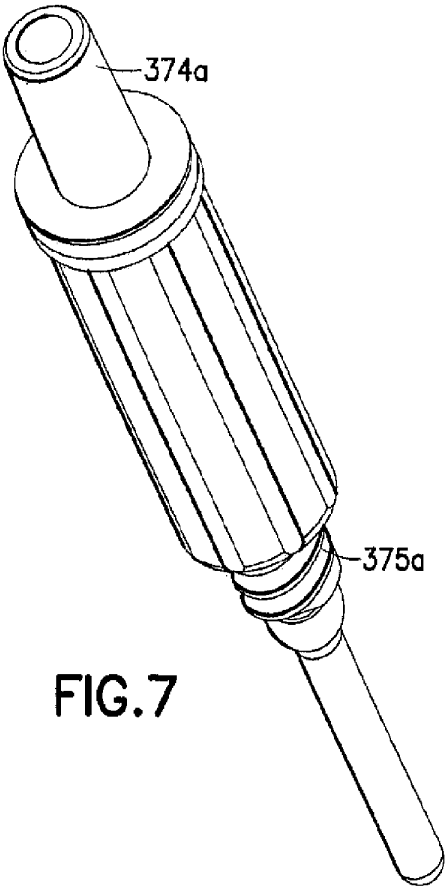

374a
375a

FIG.7

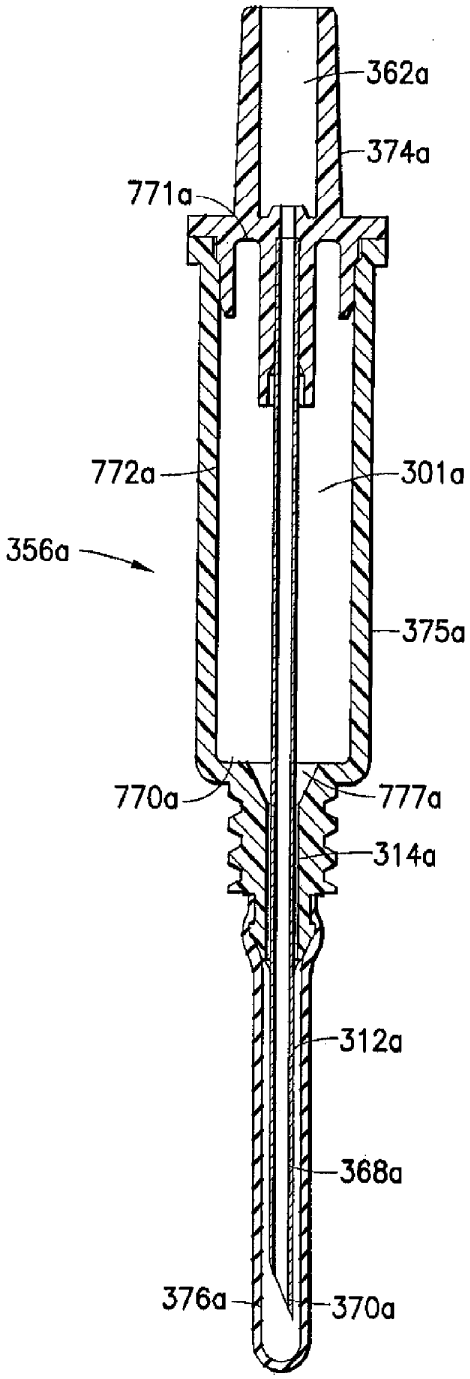

362a
374a
771a
772a
301a
356a
375a
770a
777a
314a
312a
368a
376a
370a

FIG.6

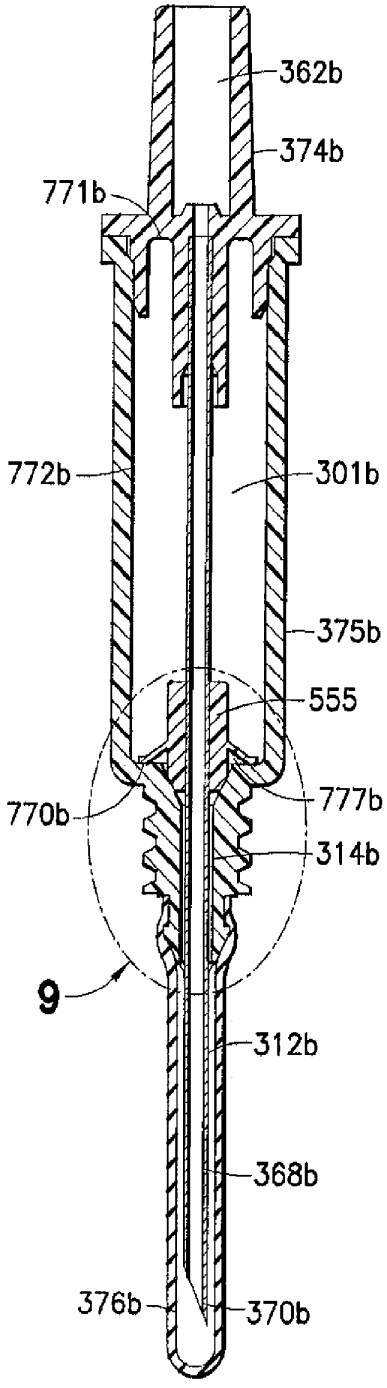

362b
374b
771b
772b
301b
375b
555
770b
777b
314b
9
312b
368b
376b
370b

FIG.8

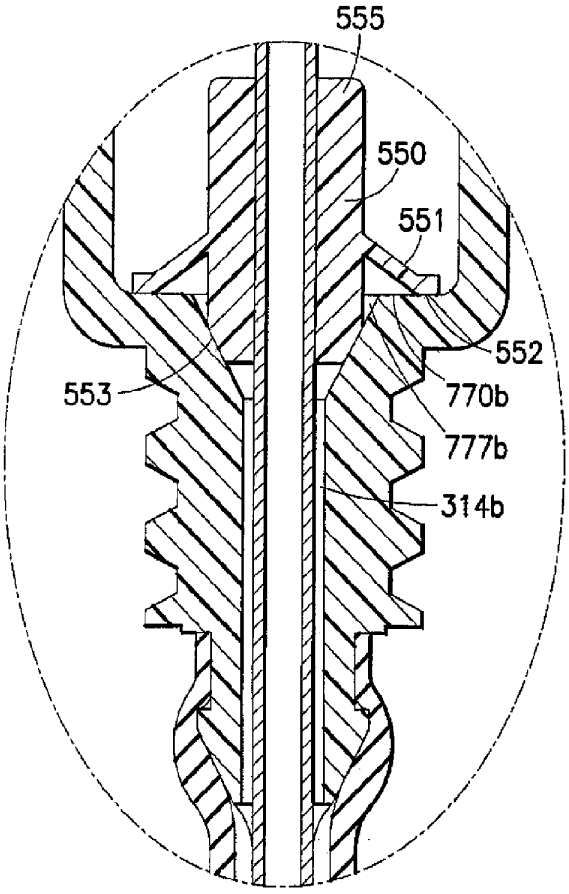

555
550
551
552
553
770b
777b
314b

FIG.9

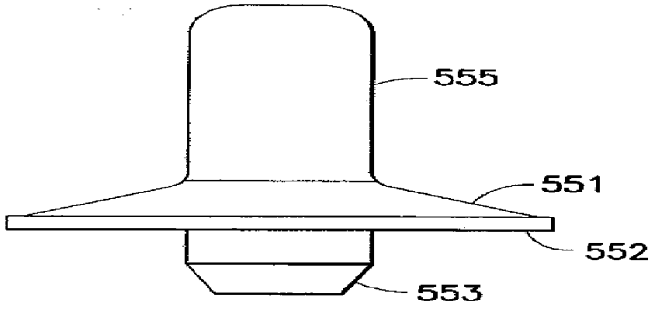


FIG. 10

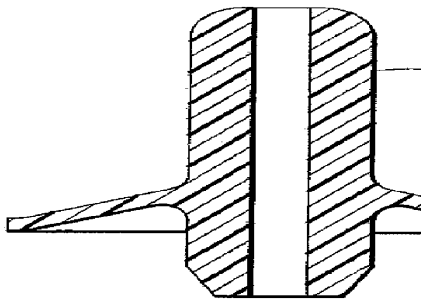


FIG. 12

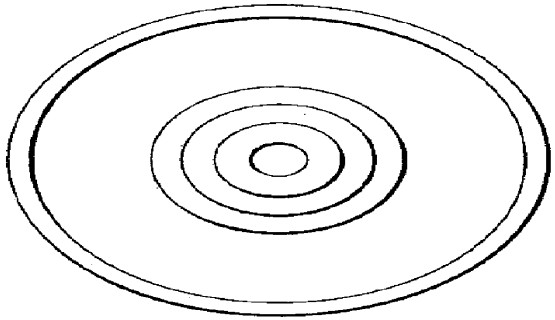


FIG. 11

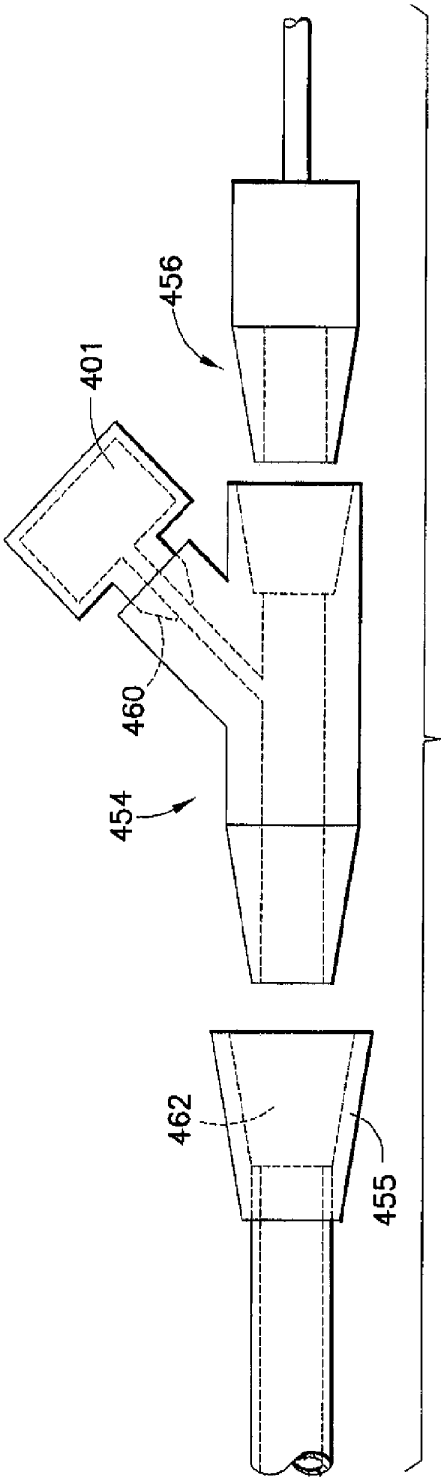


FIG.13

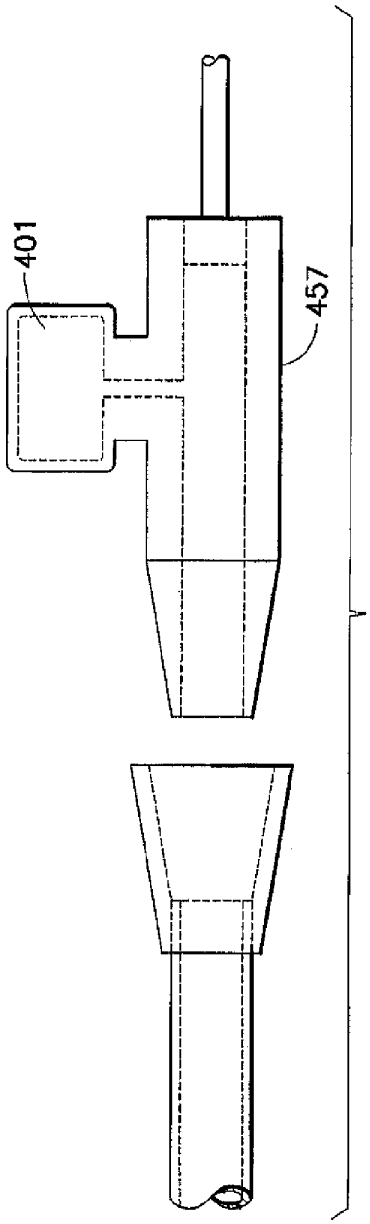


FIG.14

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 05 11 1371

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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TECHNICAL FIELDS SEARCHED (IPC)

A61B
A61M

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	16 March 2006	Ceccarelli, D

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
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D : document cited in the application
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EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 05 11 1371

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

Bibliographic data: CA2993646 (A1) — 2017-02-02

BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

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

Classification: **- international:** ***A61B5/15; A61B5/153; A61B5/154***
- cooperative: **A61B5/15003 (EP, IL, US); A61B5/150213 (EP, IL, US); A61B5/150221 (IL, US); A61B5/150389 (EP, IL, US); A61B5/150473 (EP, IL, US); A61B5/150572 (EP, IL, US); A61B5/150992 (IL, US); A61B5/153 (EP, IL, US); A61B5/154 (EP, IL, US); A61M39/04 (IL, US); A61M39/0693 (IL, US);** A61M2039/0202 (IL, US); A61M2039/0633 (IL, US); A61M2039/068 (IL, US)

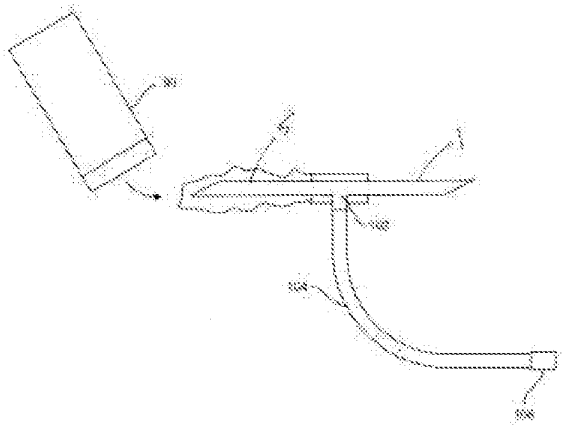
Application number: CA20162993646 20160722 Global Dossier

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

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

Abstract of CA2993646 (A1)

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



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Canadian Intellectual Property Office

CA 2993646 A1 2017/02/02

(21) 2 993 646

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2016/07/22
(87) Date publication PCT/PCT Publication Date: 2017/02/02
(85) Entrée phase nationale/National Entry: 2018/01/24
(86) N° demande PCT/PCT Application No.: US 2016/043709
(87) N° publication PCT/PCT Publication No.: 2017/019552
(30) Priorités/Priorities: 2015/07/24 (US62/196,797); 2015/10/07 (US62/238,636); 2016/04/04 (US62/318,194); 2016/04/27 (US15/140,443); 2016/04/27 (US15/140,448)

(51) Cl.Int./Int.Cl. *A61B 5/15* (2006.01), *A61B 5/153* (2006.01), *A61B 5/154* (2006.01)

(71) Demandeur/Applicant:
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(72) Inventeurs/Inventors:
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KANG, GINO, US;
DETLOFF, JOHN, US

(74) Agent: BRION RAFFOUL

(54) Titre : SYSTEME D'OPTIMISATION D'ECHANTILLON DE SANG ET DISPOSITIF ET PROCEDE DE SEQUESTRATION DE CONTAMINANTS DU SANG

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

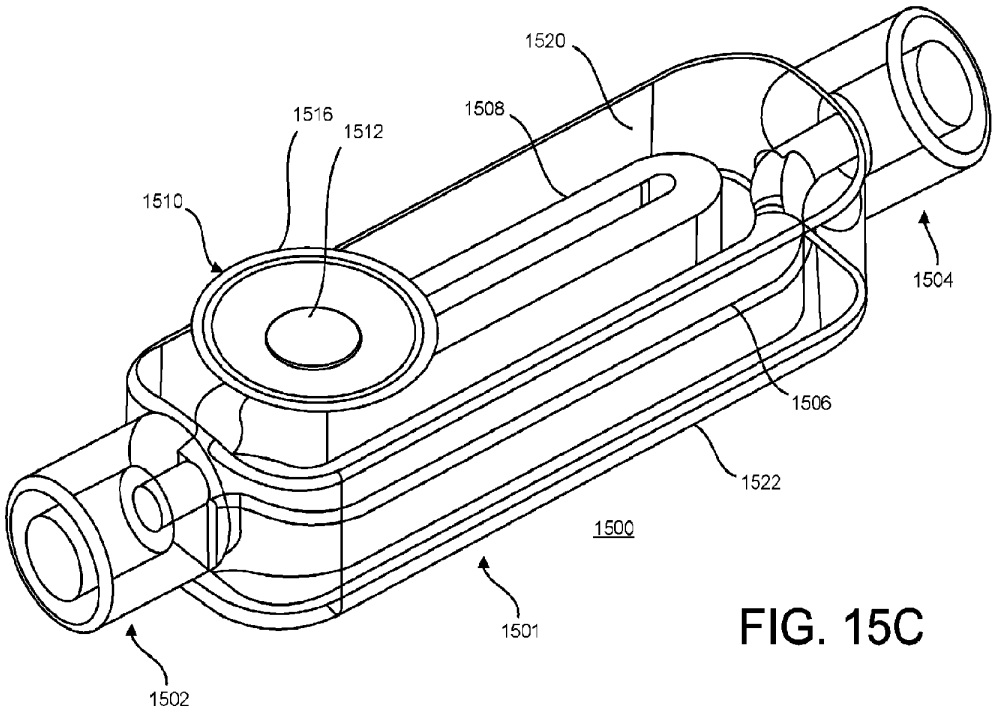


FIG. 15C

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

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

(19) World Intellectual Property Organization
International Bureau

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

WIPO | PCT

(10) International Publication Number
WO 2017/019552 A1

(51) International Patent Classification:
A61B 5/15 (2006.01) *A61B 5/154* (2006.01)
A61B 5/153 (2006.01)

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

(22) International Filing Date:
22 July 2016 (22.07.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/196,797	24 July 2015 (24.07.2015)	US
62/238,636	7 October 2015 (07.10.2015)	US
62/318,194	4 April 2016 (04.04.2016)	US
15/140,448	27 April 2016 (27.04.2016)	US
15/140,443	27 April 2016 (27.04.2016)	US

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(72) Inventors: **ROGERS, Bobby**; 10755 Scripps Poway Parkway No. 257, San Diego, CA 92131 (US). **KANG, Gino**; 10755 Scripps Poway Parkway No. 257, San Diego, CA 92131 (US). **DETLOFF, John**; 10755 Scripps Poway Parkway No. 257, San Diego, CA 92131 (US).

(74) Agents: **CLEARY, James, P.** et al.; Mintz Levin Cohn Ferris Glovsky And Popeo, P.C., 3580 Carmel Mountain Road, Suite 300, San Diego, CA 92130-6768 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

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

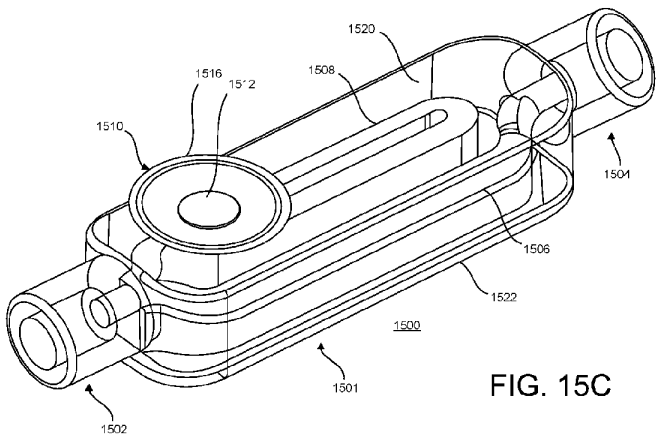


FIG. 15C

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

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BLOOD SAMPLE OPTIMIZATION SYSTEM AND BLOOD CONTAMINANT SEQUESTRATION DEVICE AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

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

BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

SUMMARY

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

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

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

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

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

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

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

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

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

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DETAILED DESCRIPTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS

1. A blood sequestration device comprising;

an inlet port;

an outlet port;

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

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

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

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

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

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

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

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

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

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

an inlet port connected with the patient needle;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

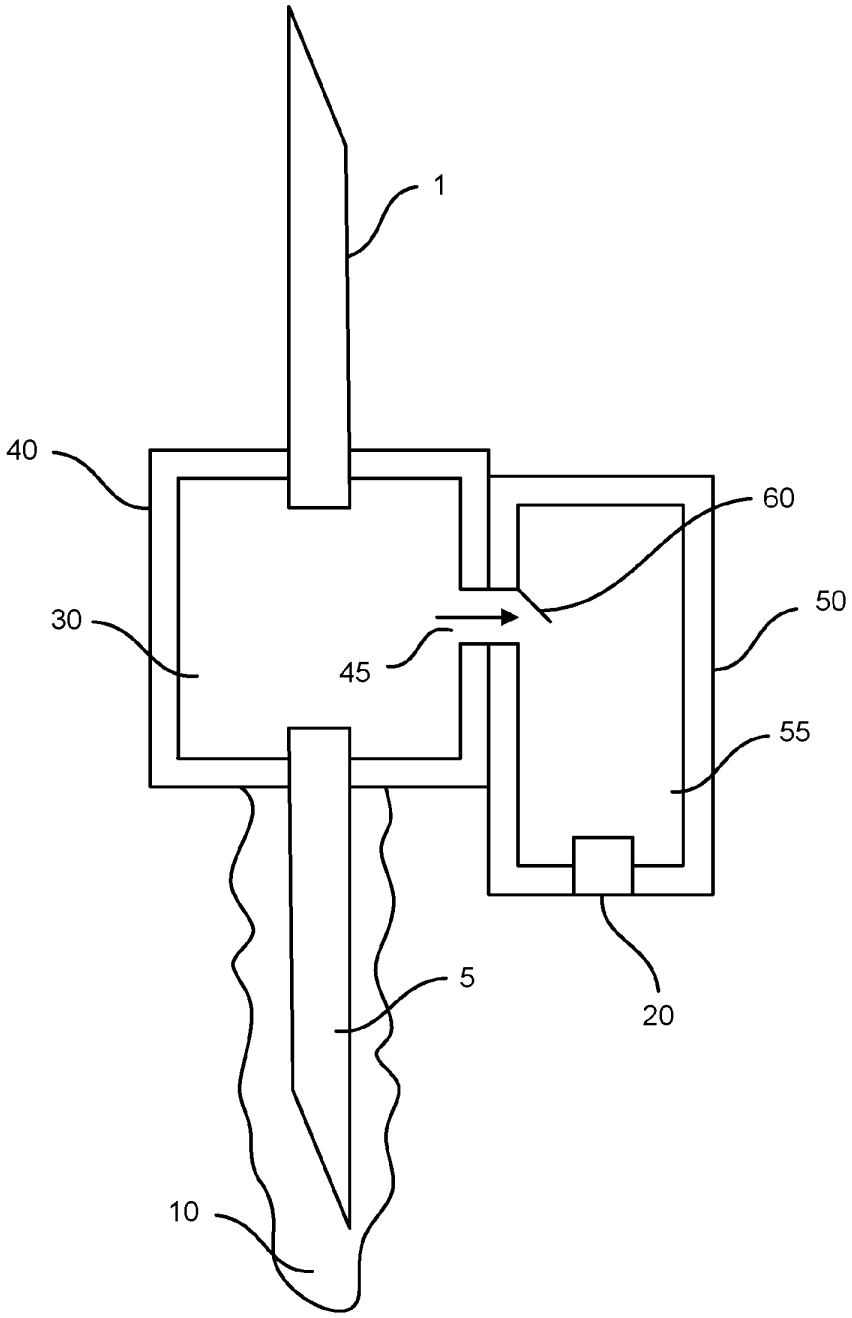


FIG. 1

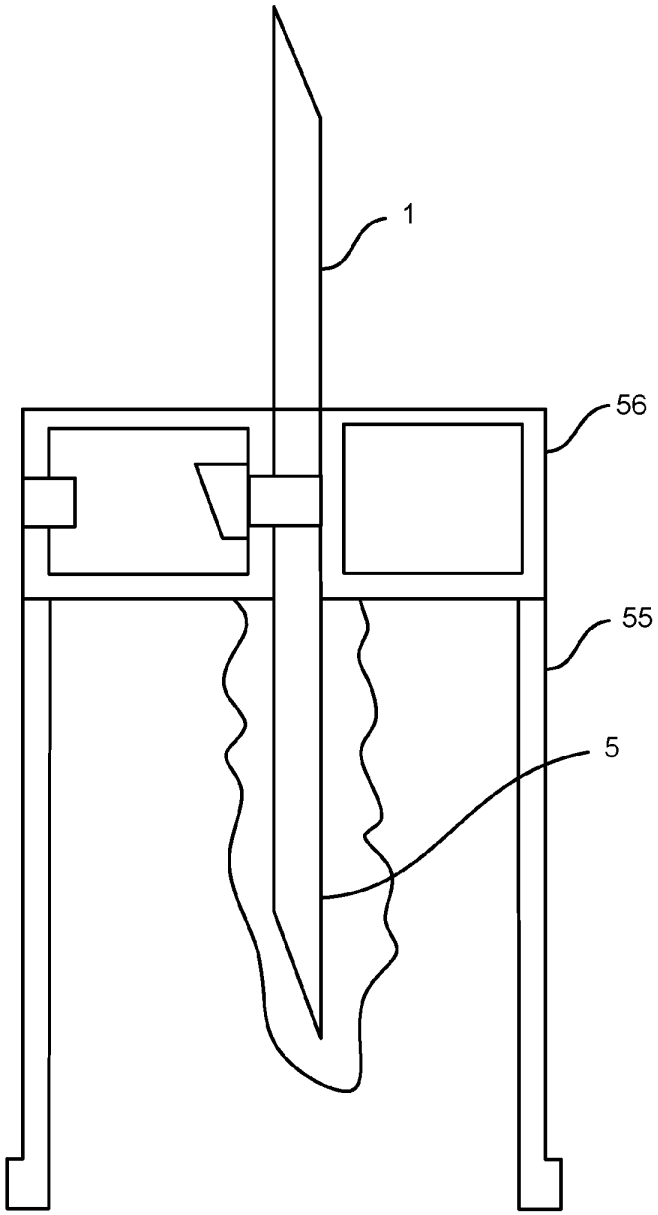


FIG. 2

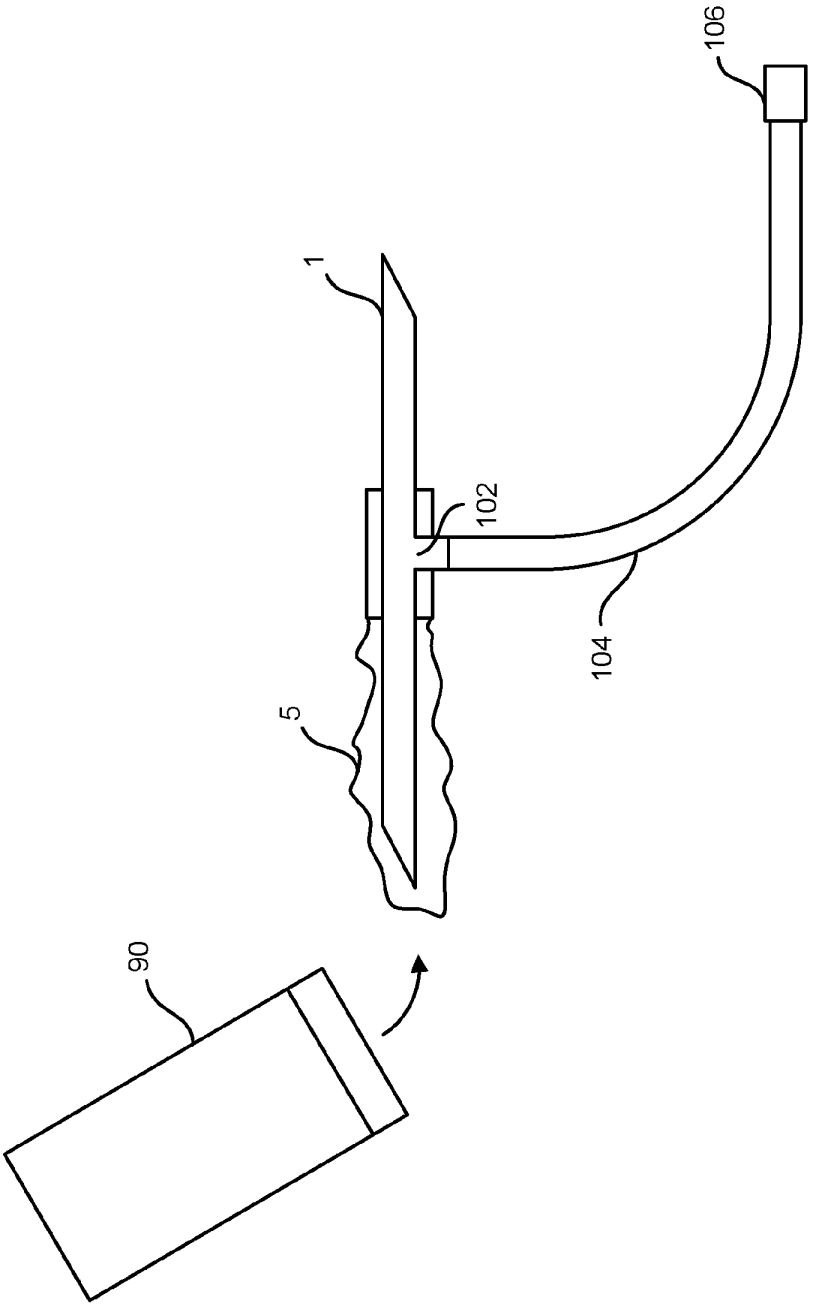


FIG. 3

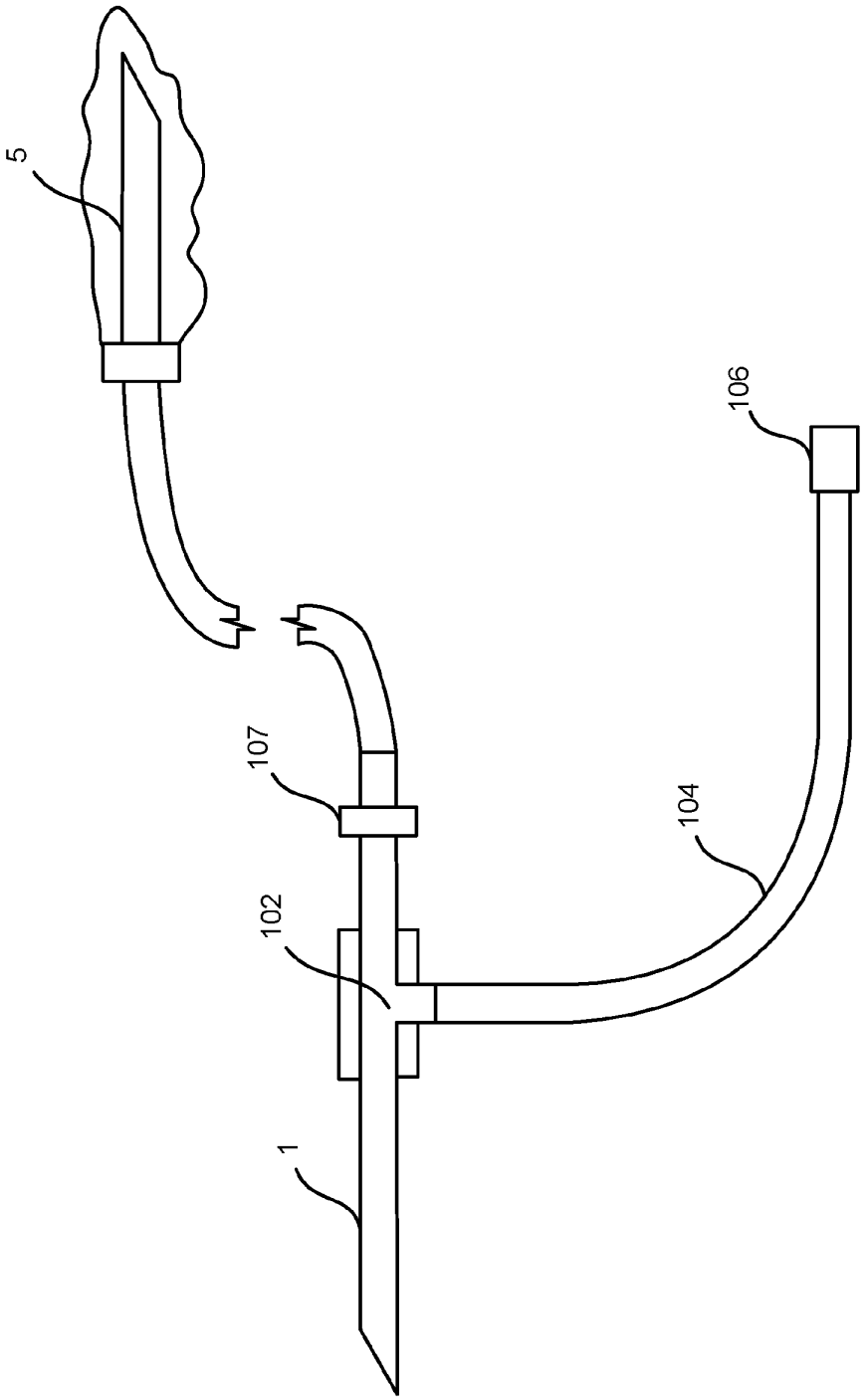


FIG. 4

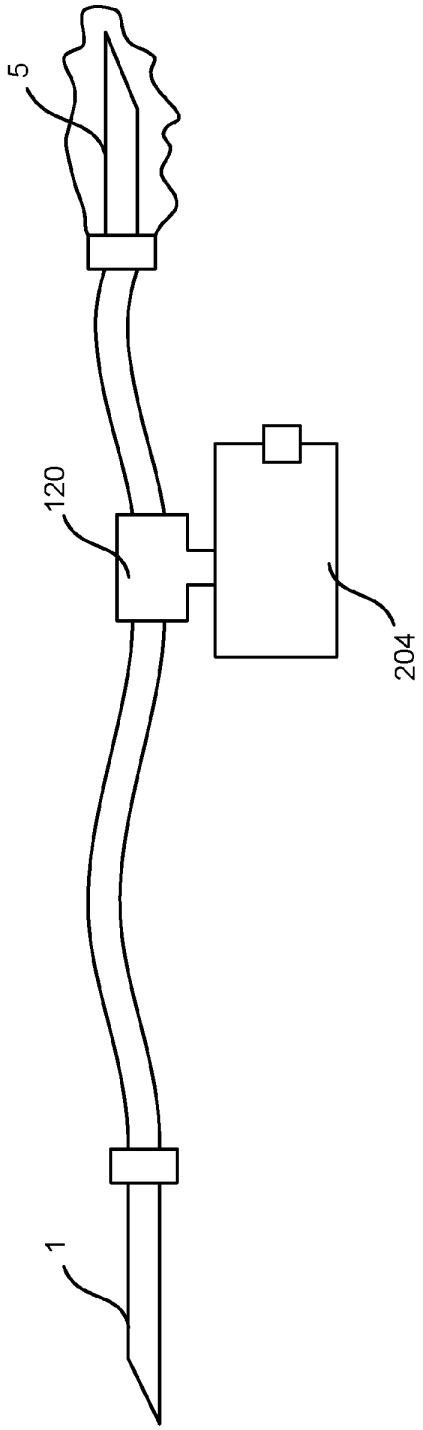


FIG. 5

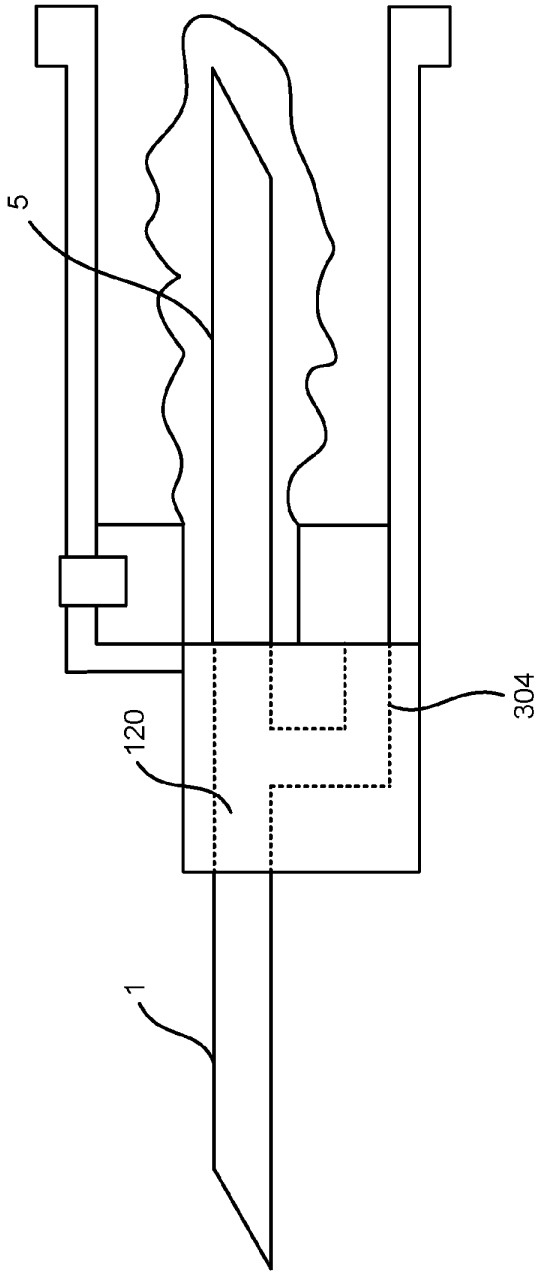


FIG. 6

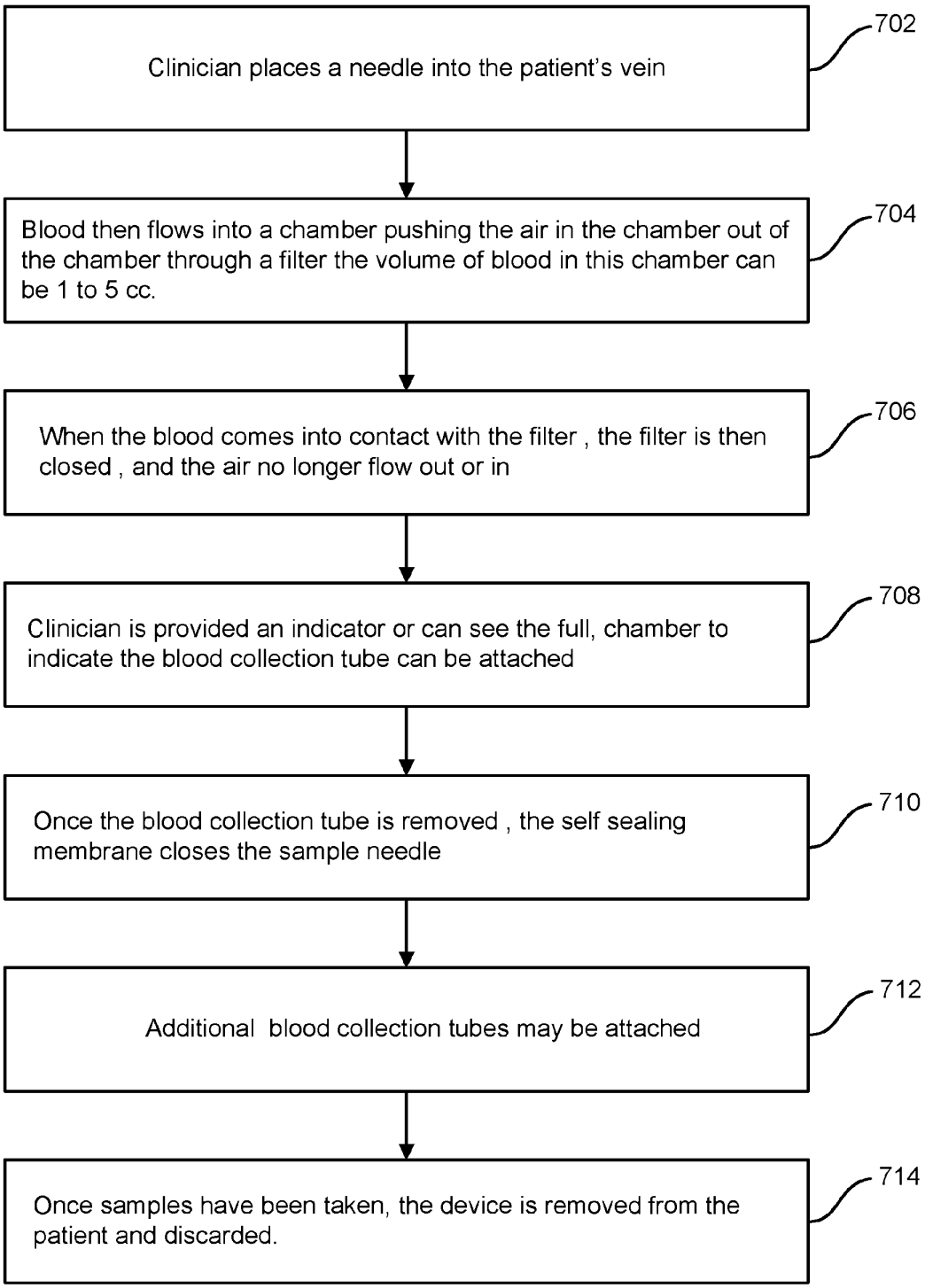

Clinician places a needle into the patient's vein
702
Blood then flows into a chamber pushing the air in the chamber out of the chamber through a filter the volume of blood in this chamber can be 1 to 5 cc.
704
When the blood comes into contact with the filter , the filter is then closed , and the air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

FIG. 7

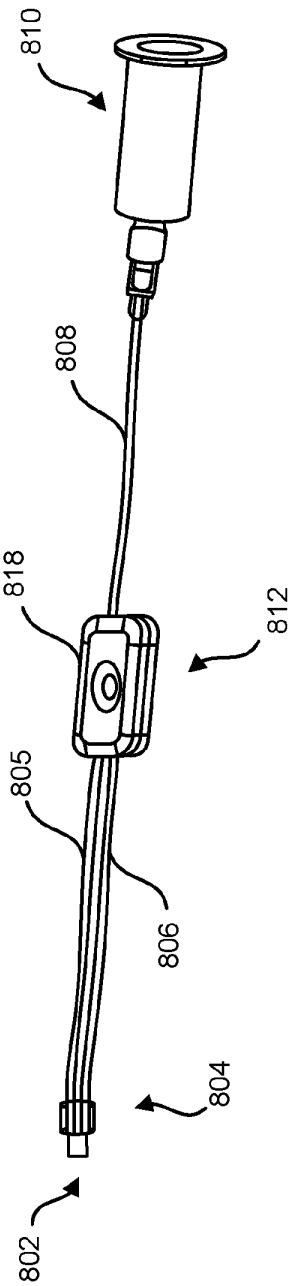


FIG. 8A

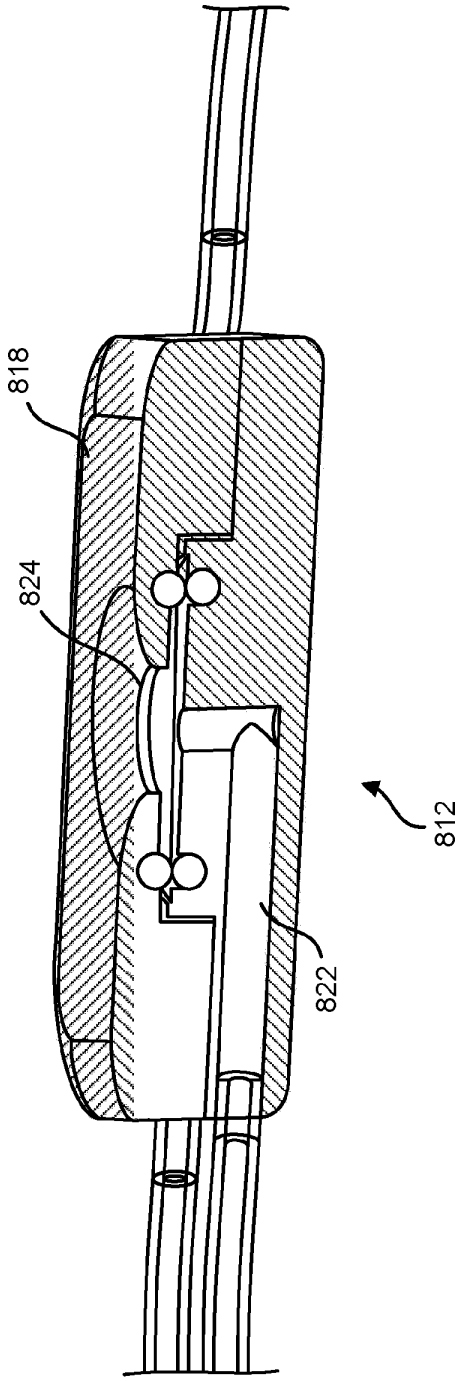


FIG. 8B

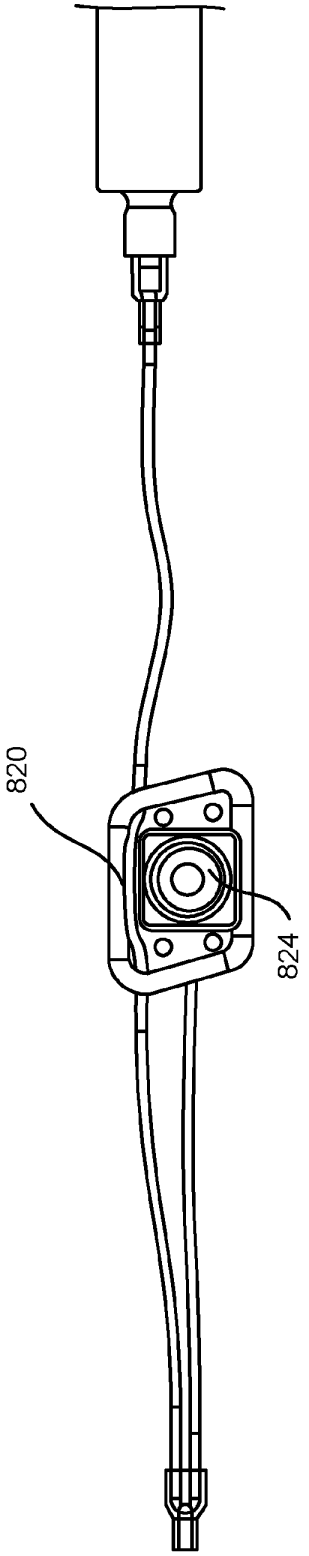


FIG. 8C

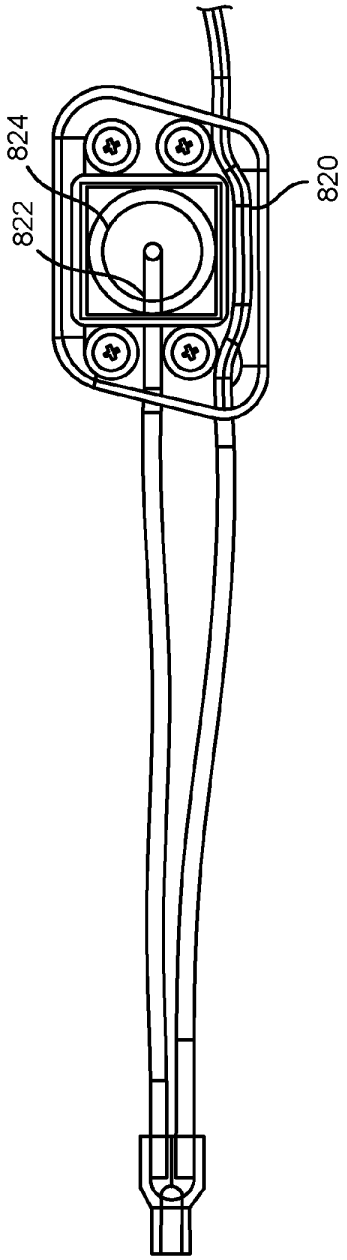


FIG. 8D

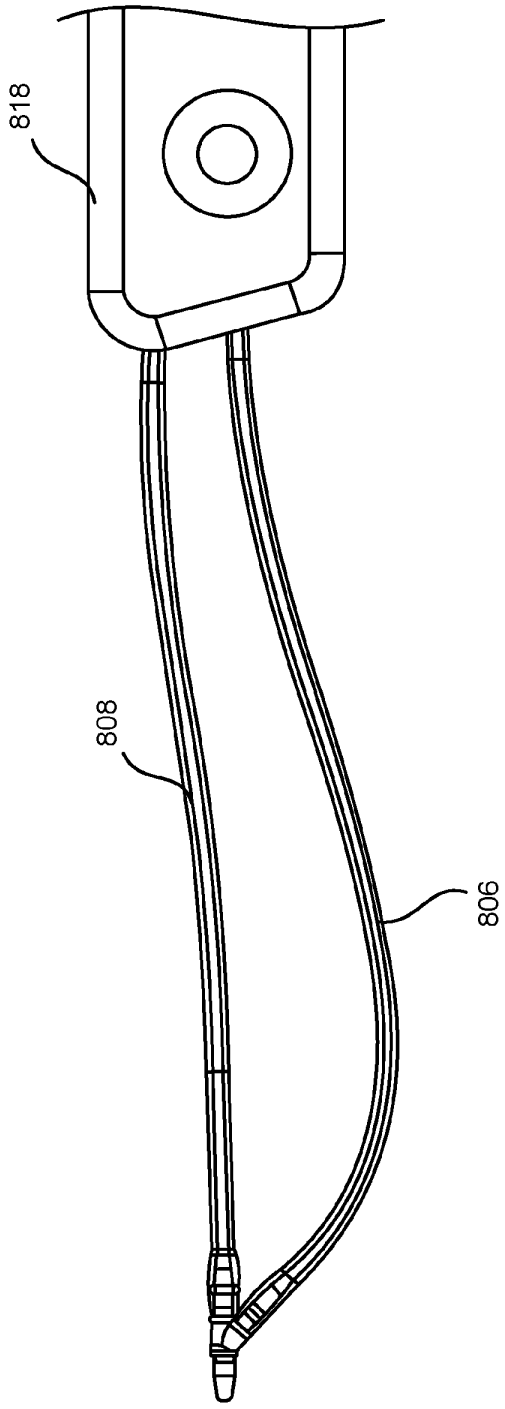


FIG. 8E

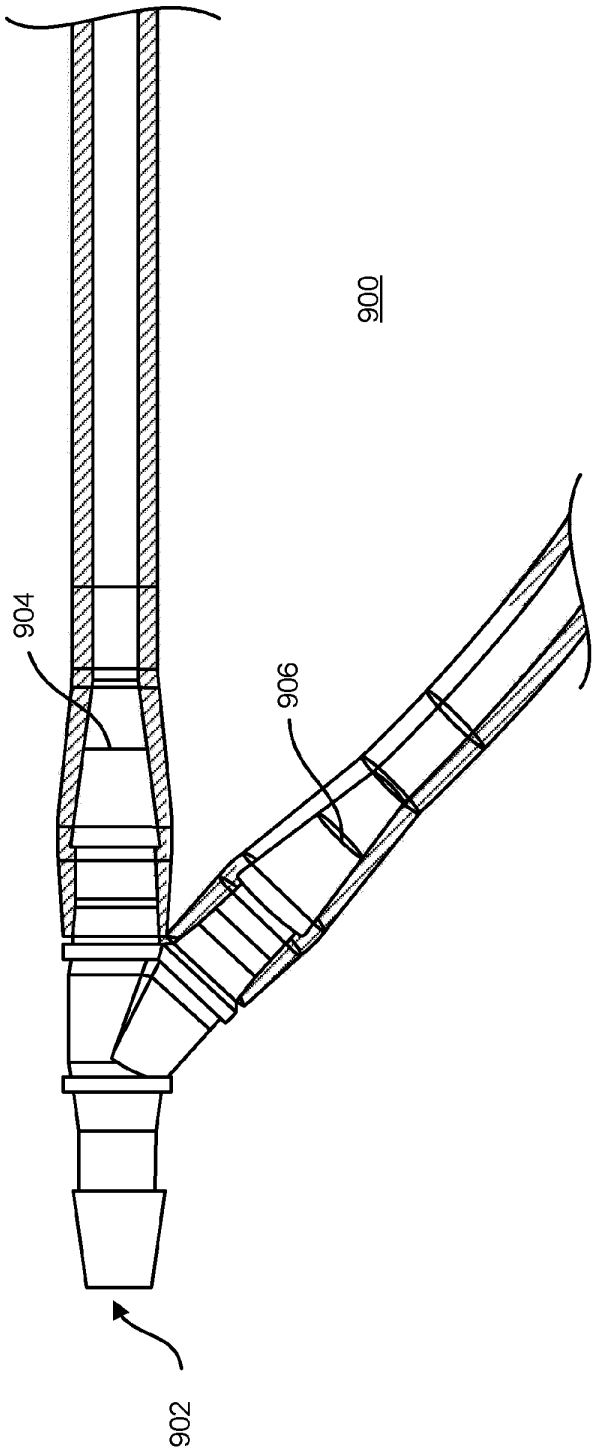


FIG. 9

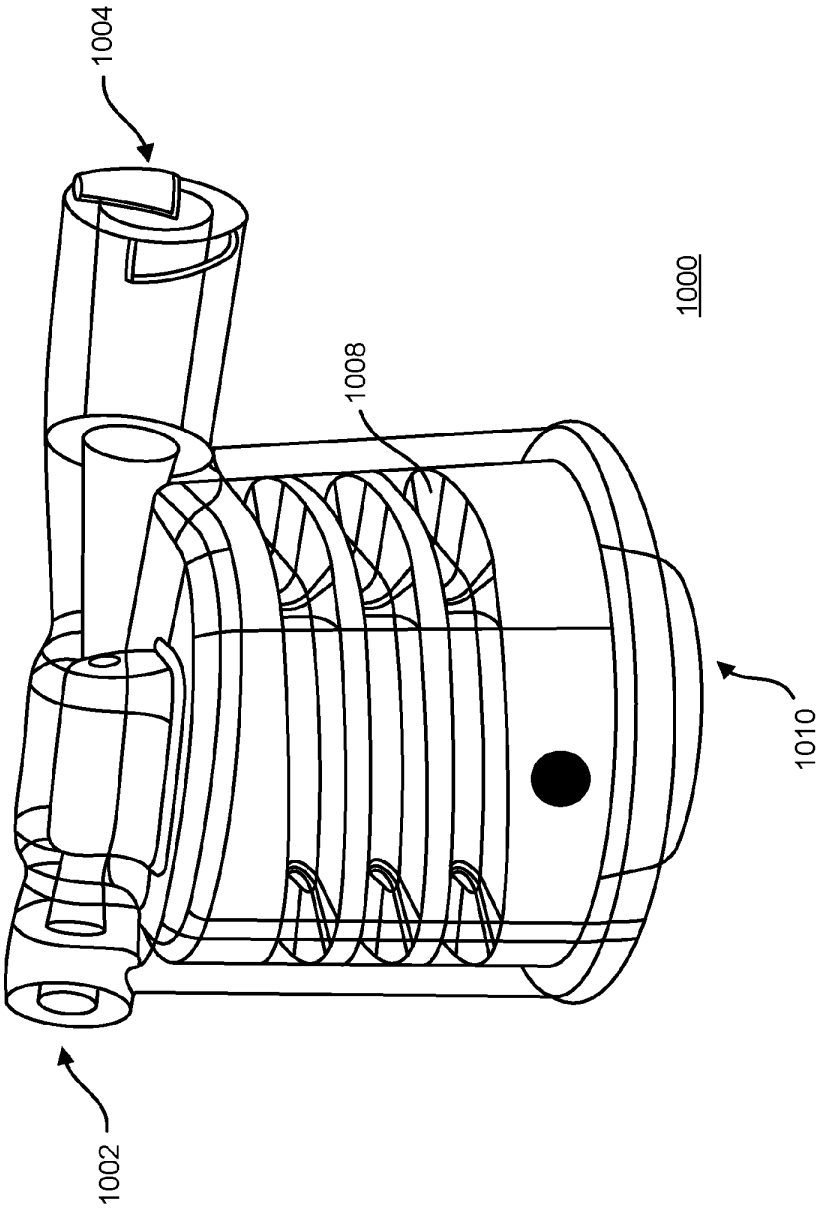


FIG. 10A

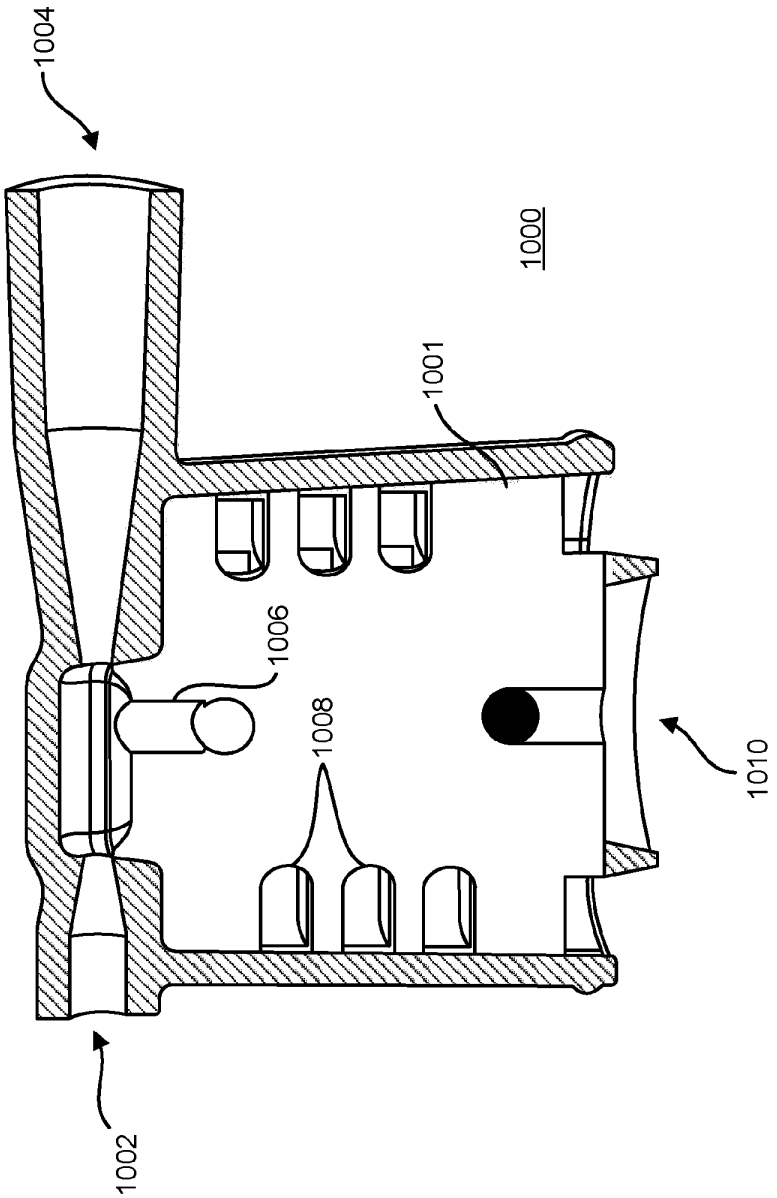


FIG. 10B

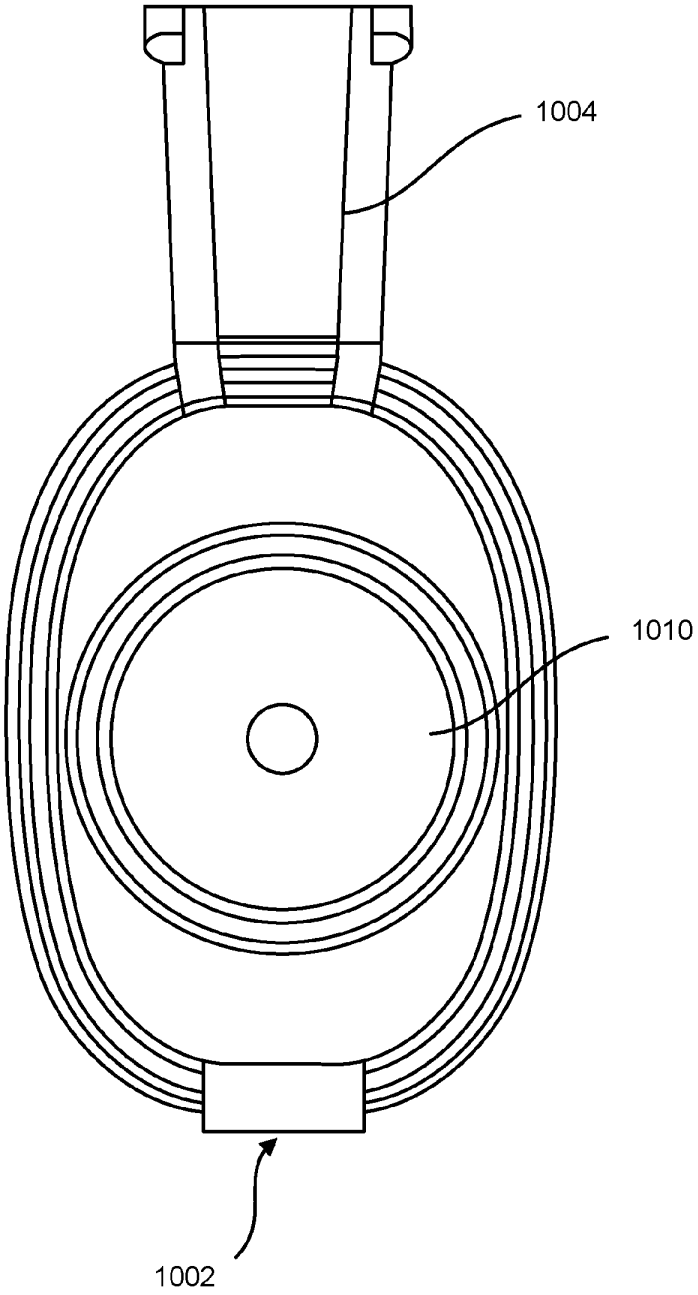


FIG. 10C

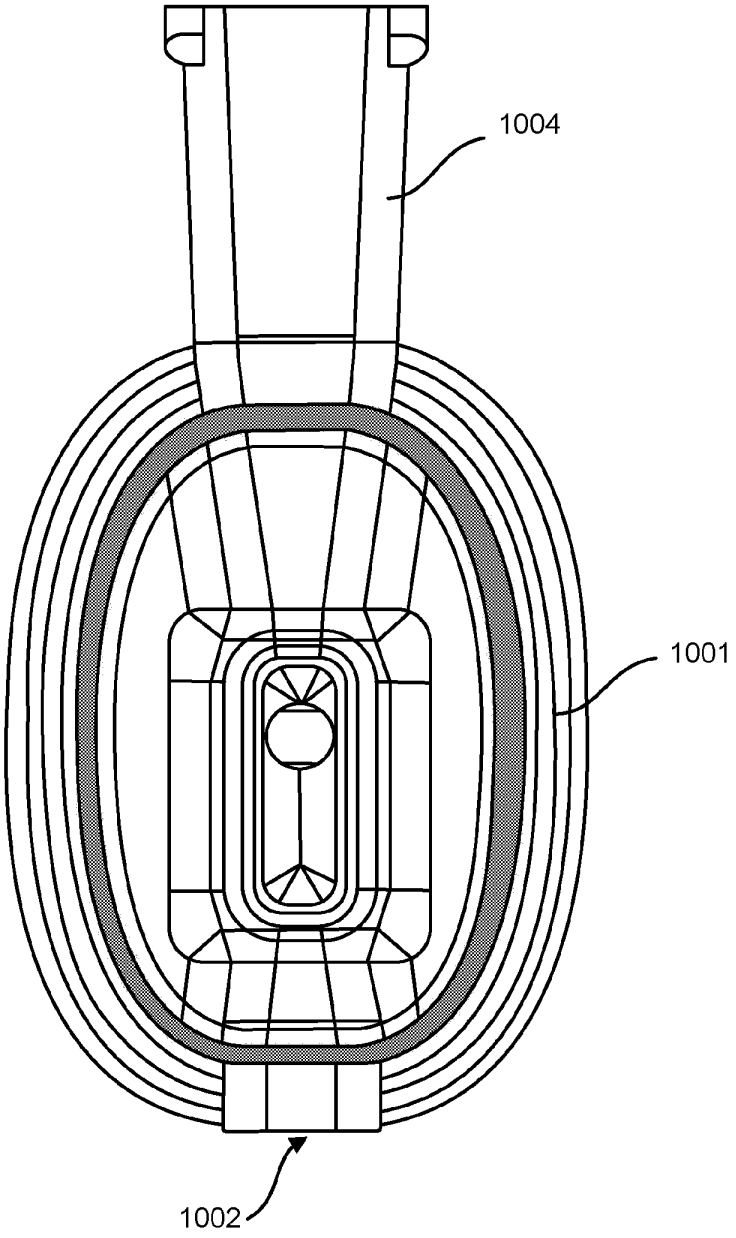


FIG. 10D

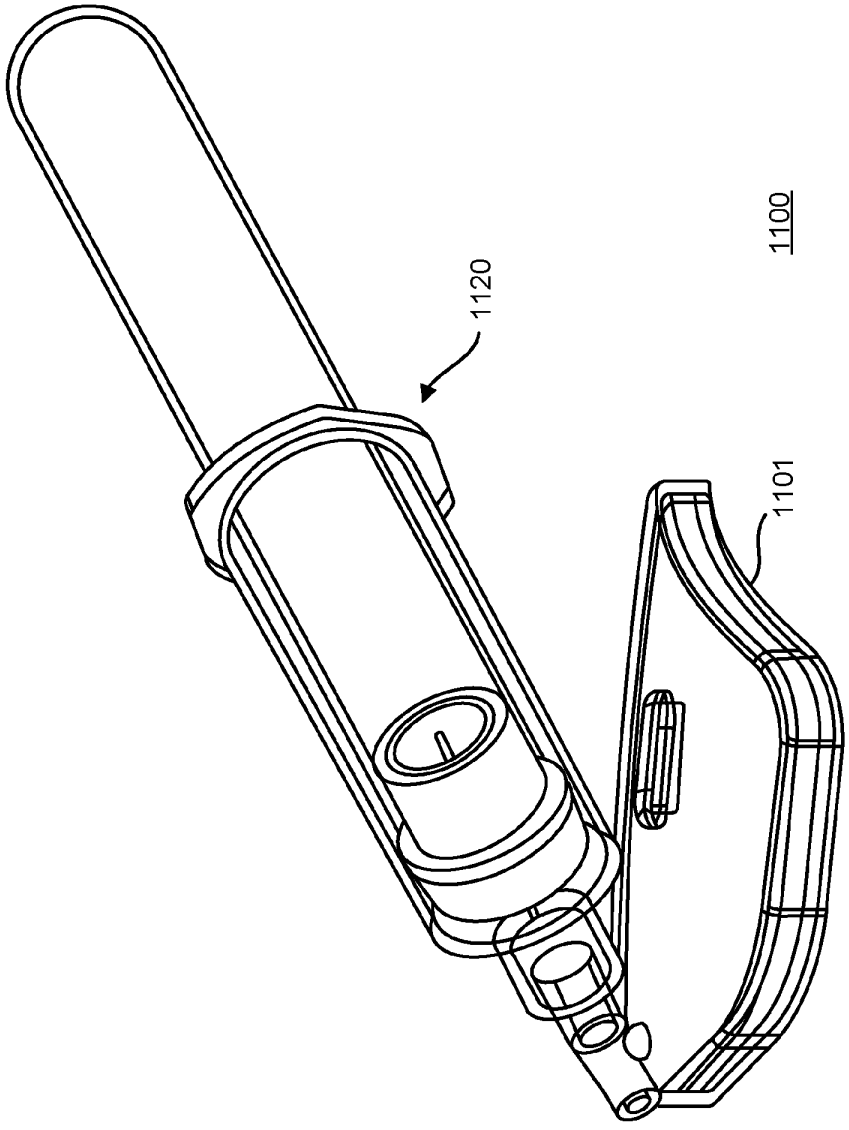


FIG. 11A

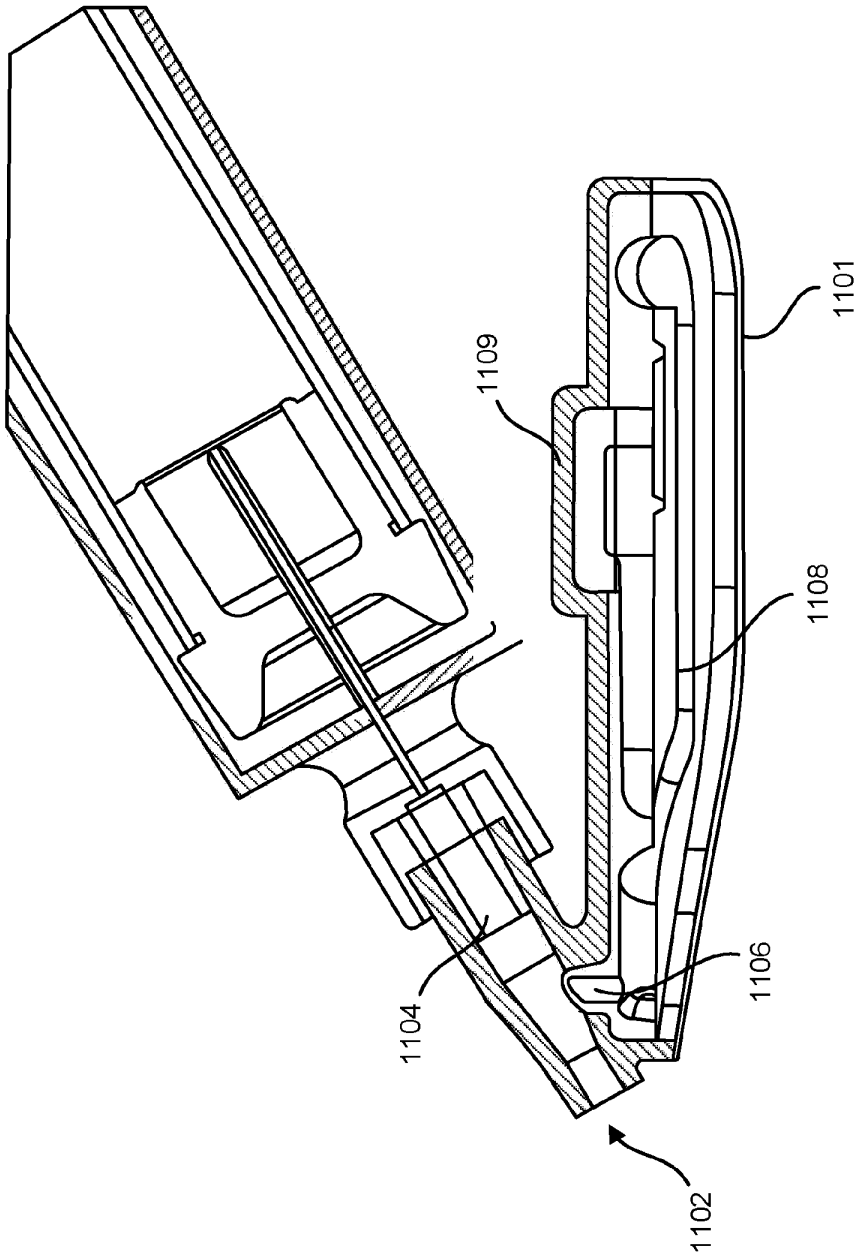


FIG. 11B

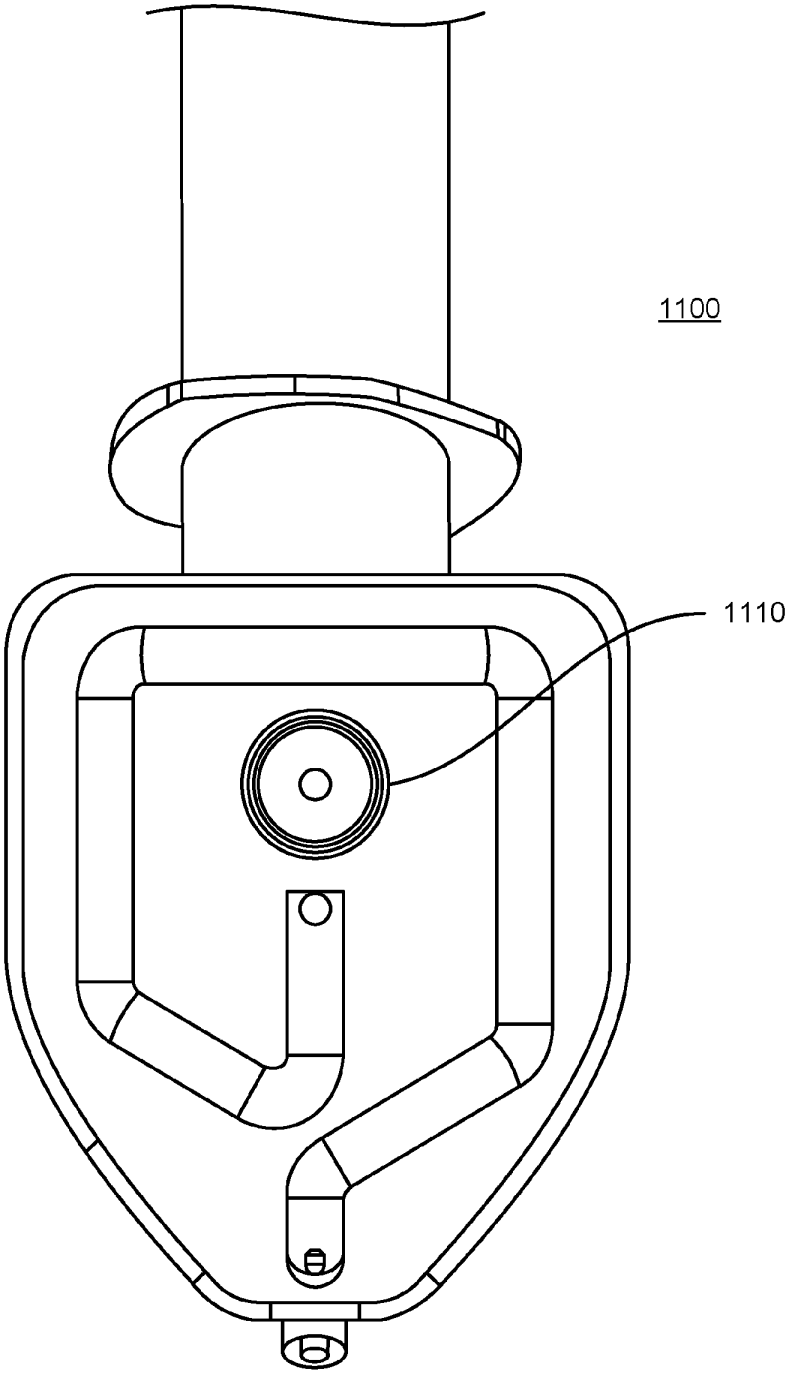


FIG. 11C

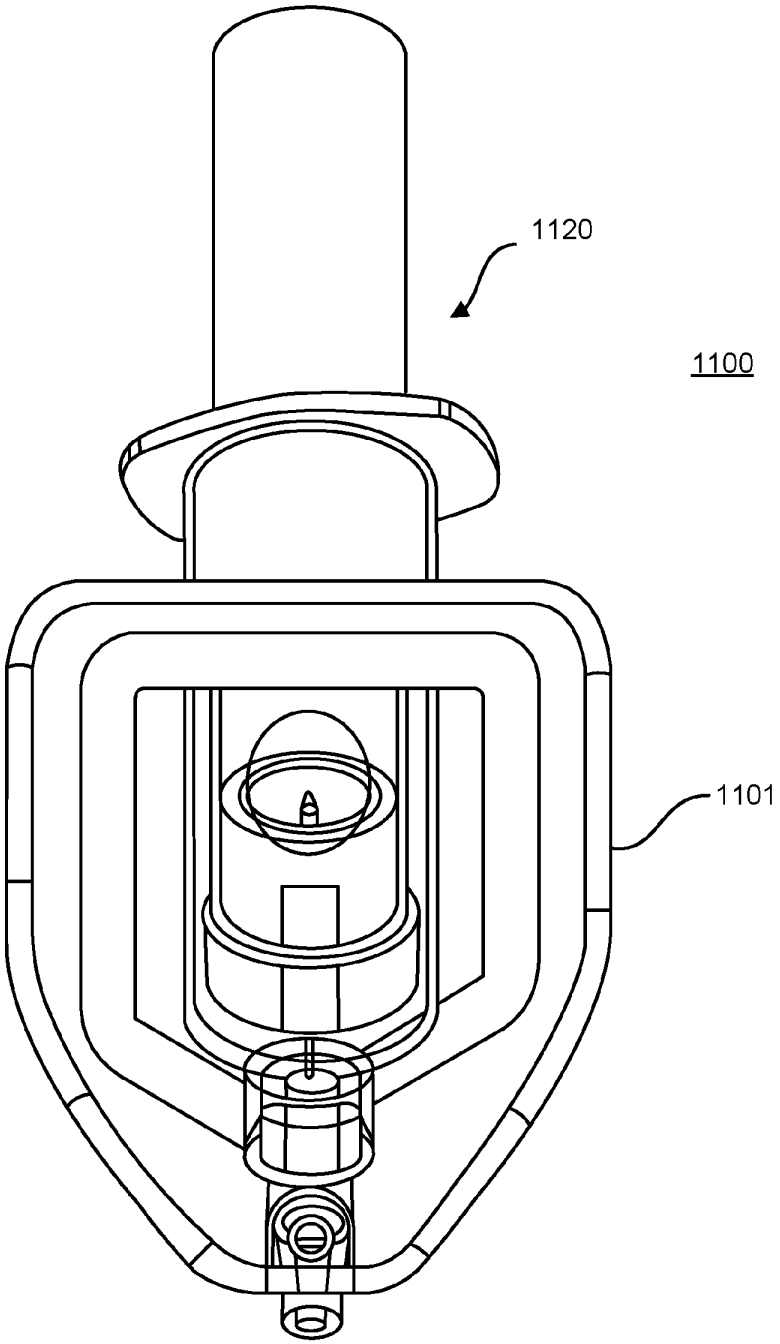


FIG. 11D

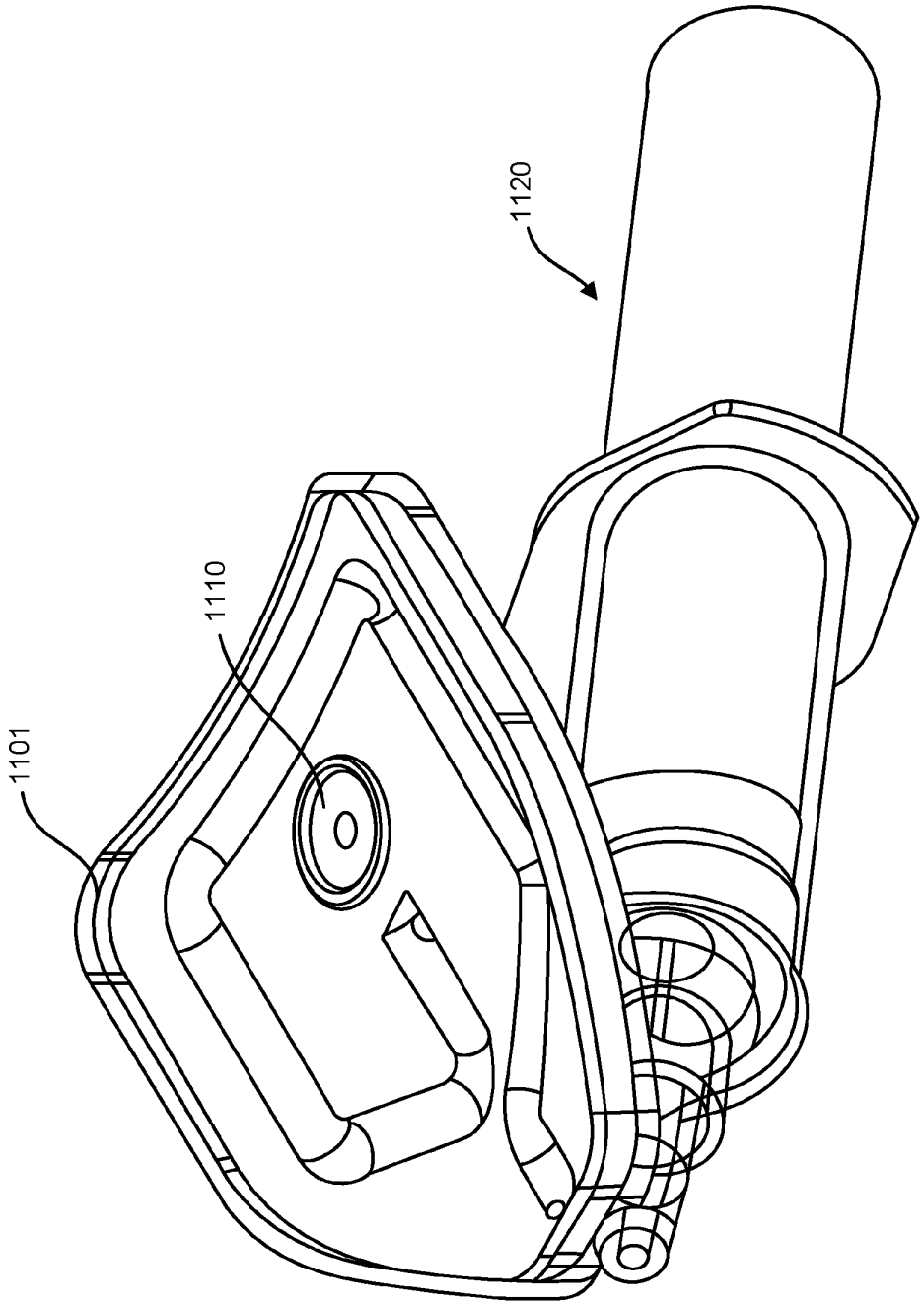


FIG. 11E

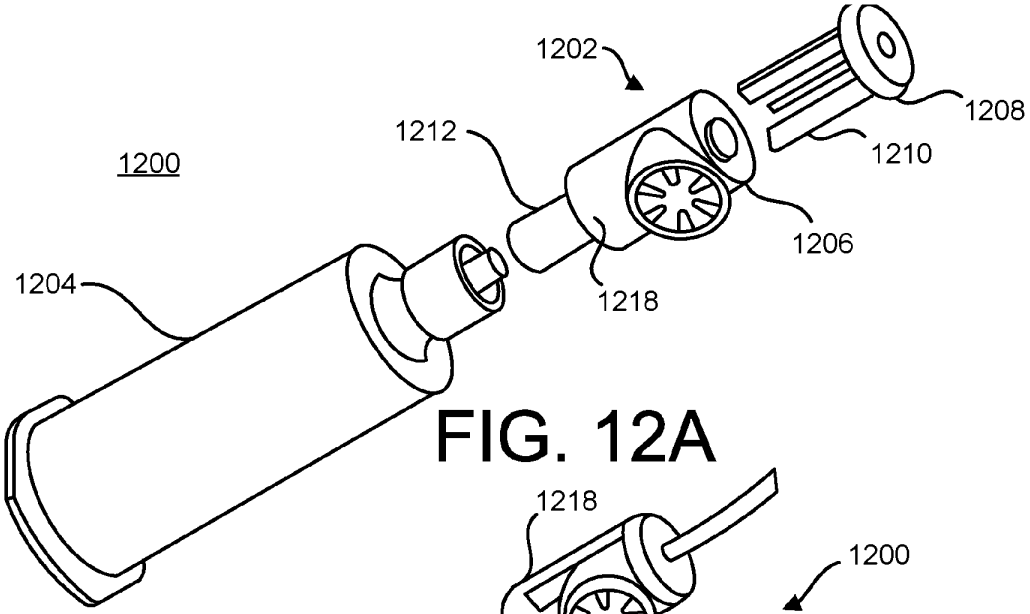


FIG. 12A

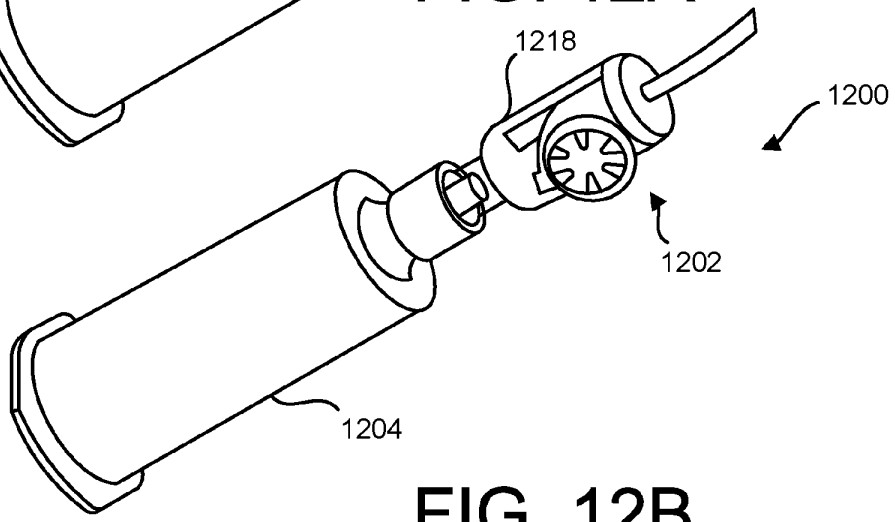


FIG. 12B

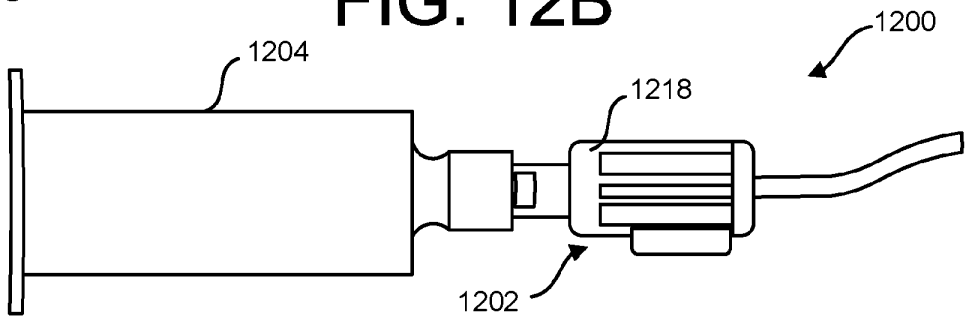


FIG. 12C

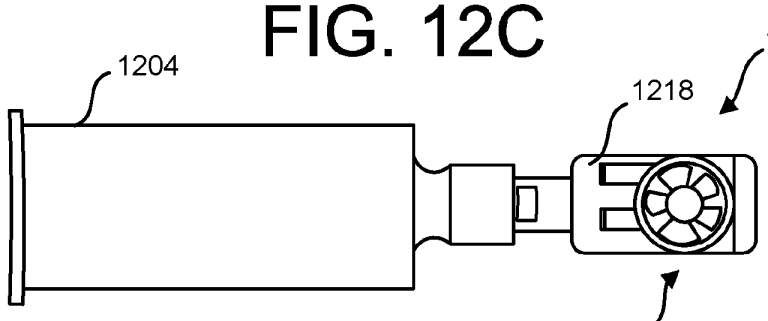


FIG. 12D

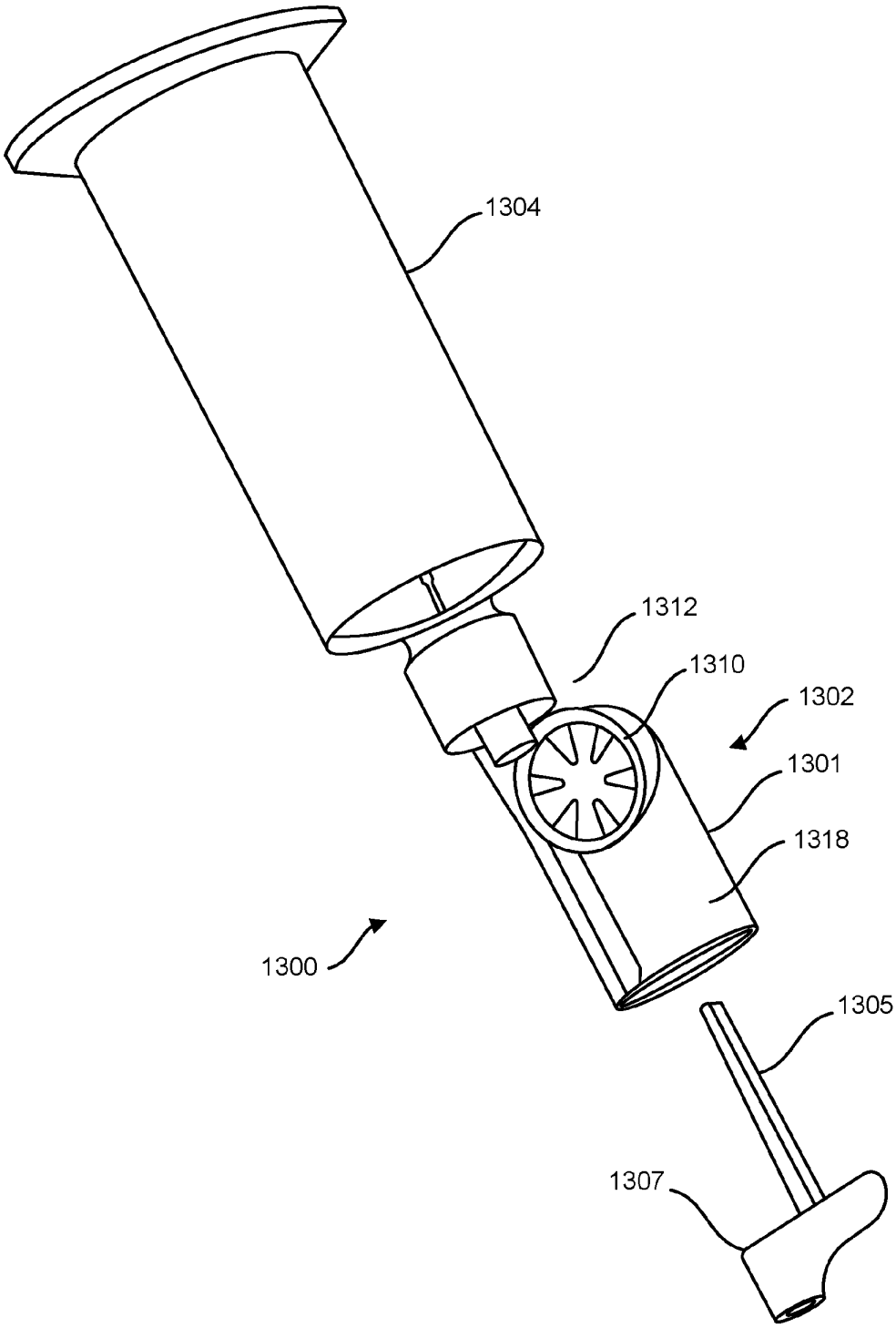


FIG. 13A

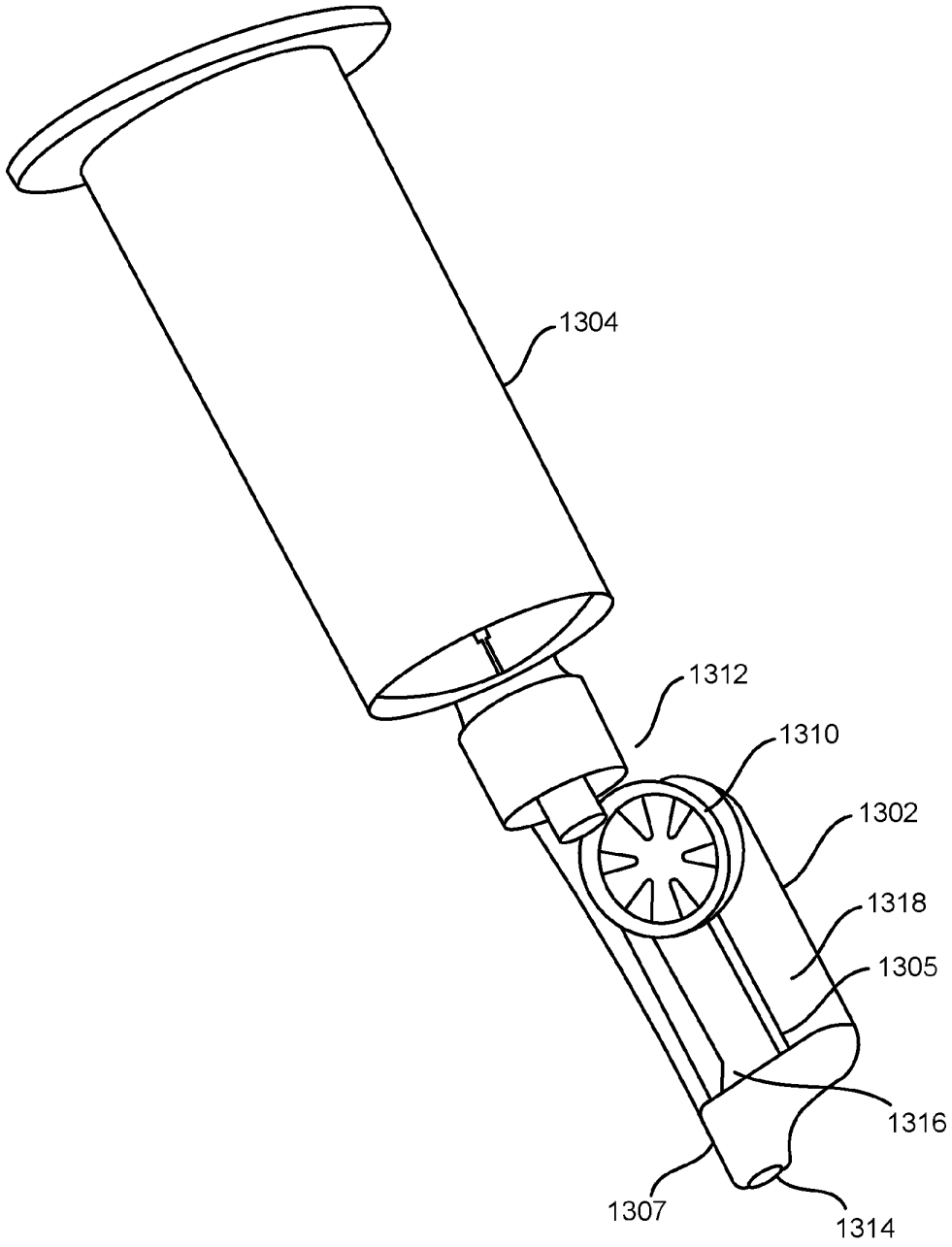


FIG. 13B

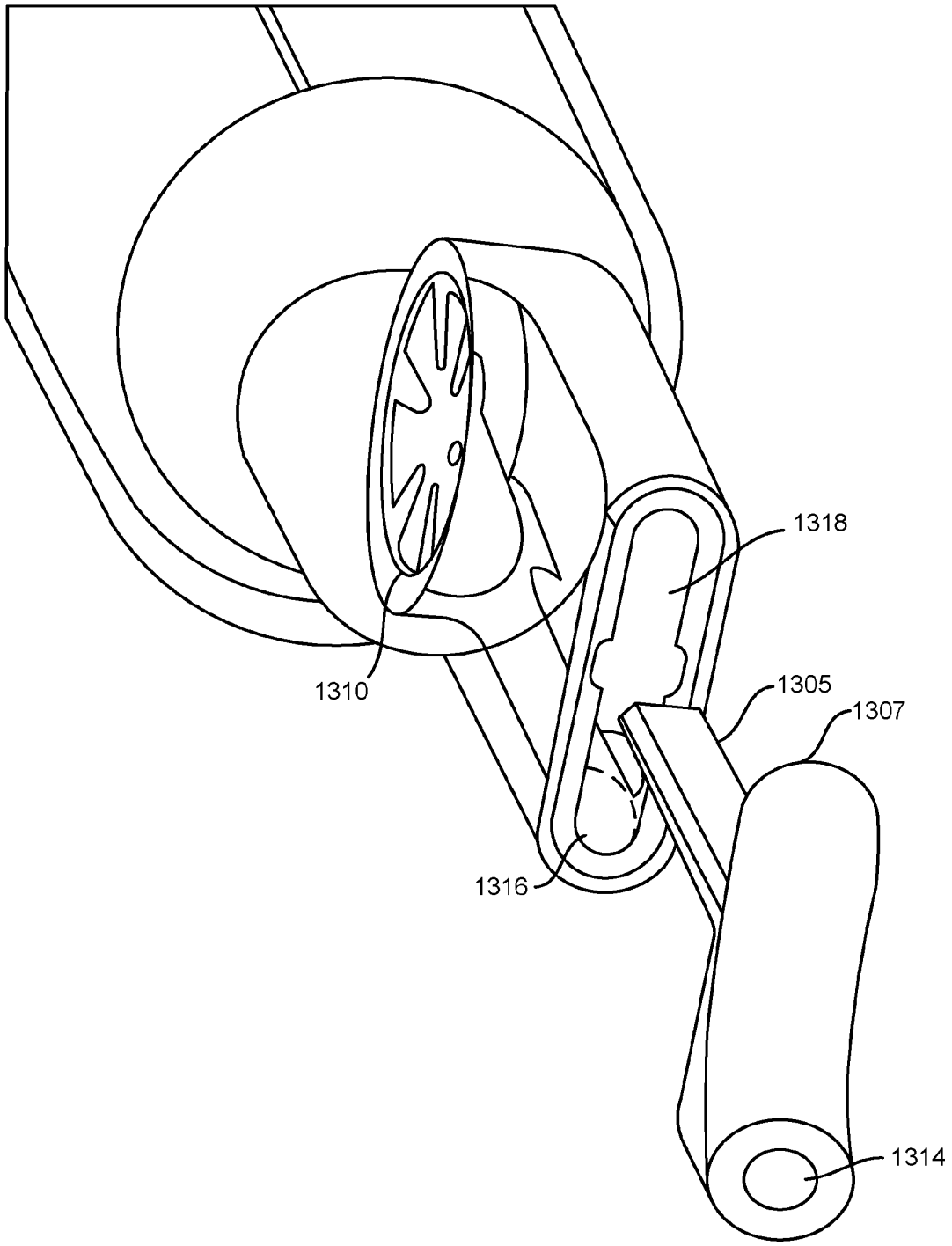


FIG. 13C

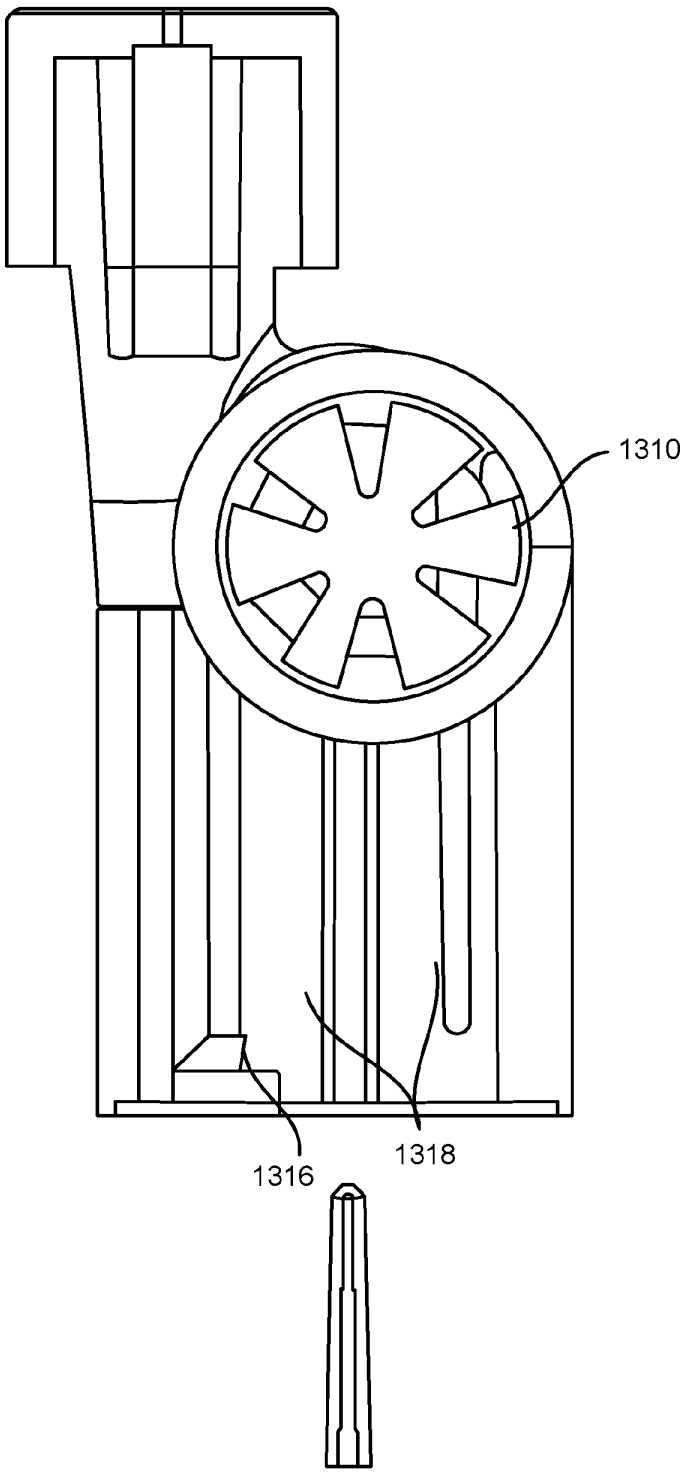


FIG. 13D

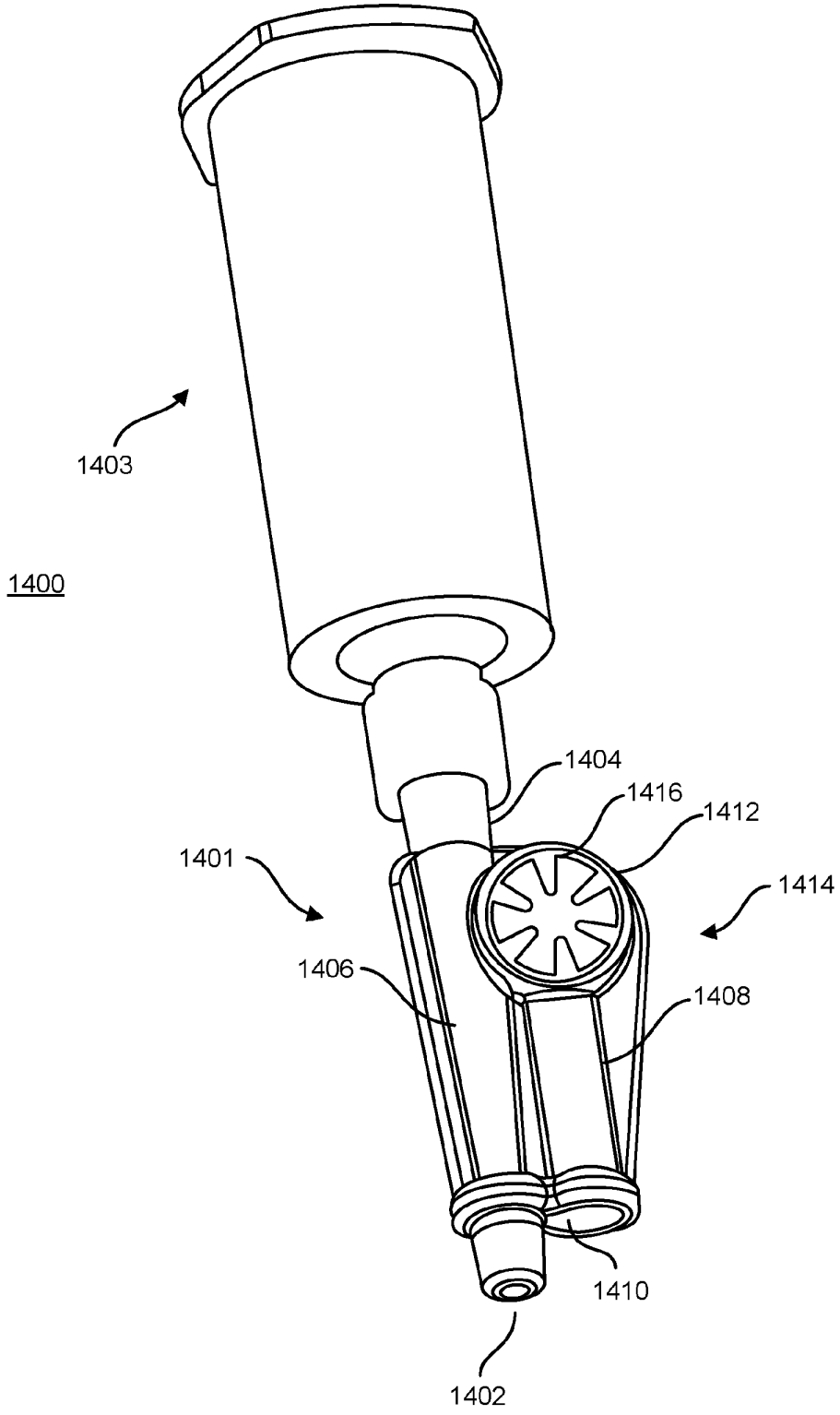


FIG. 14A

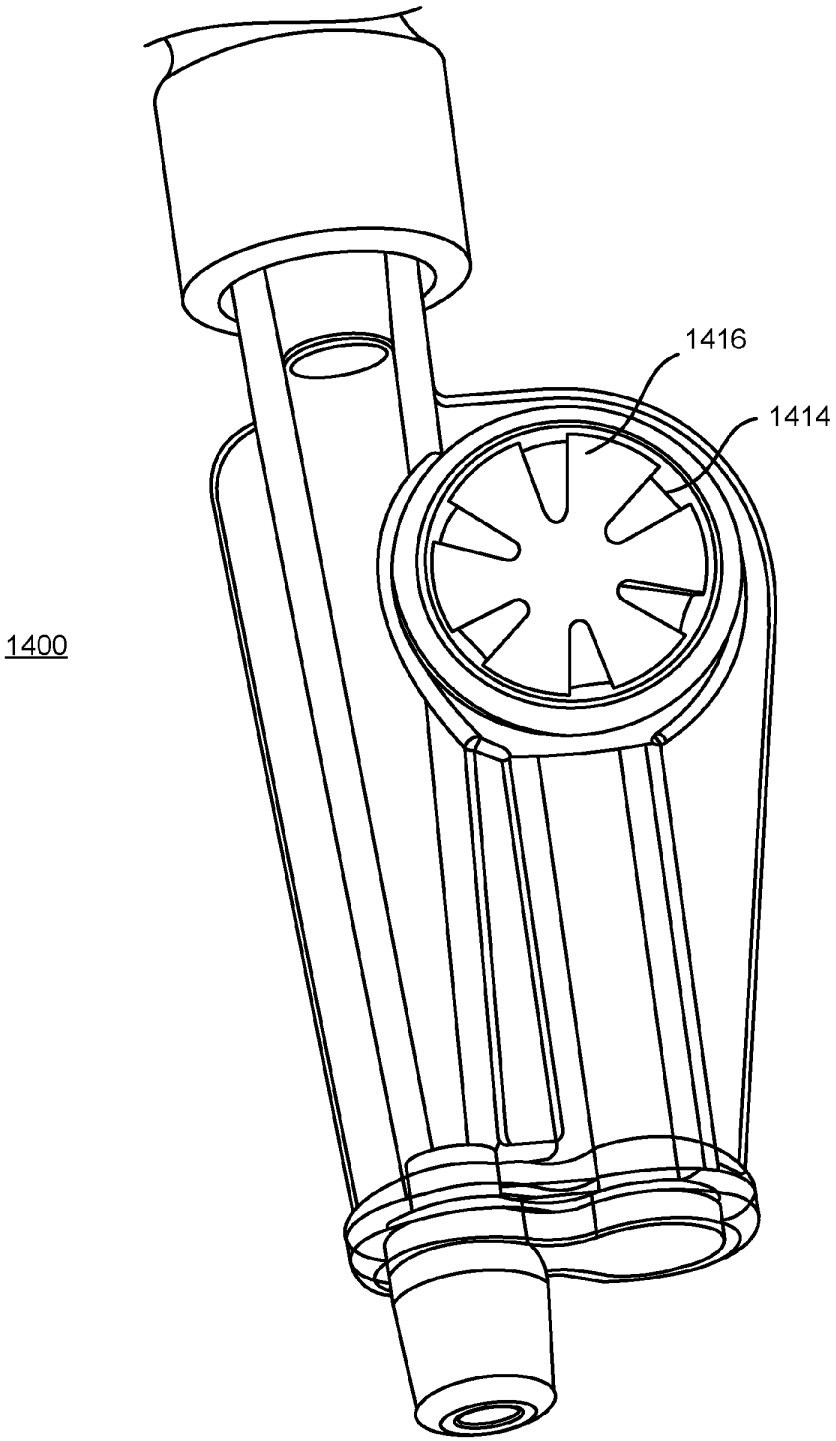


FIG. 14B

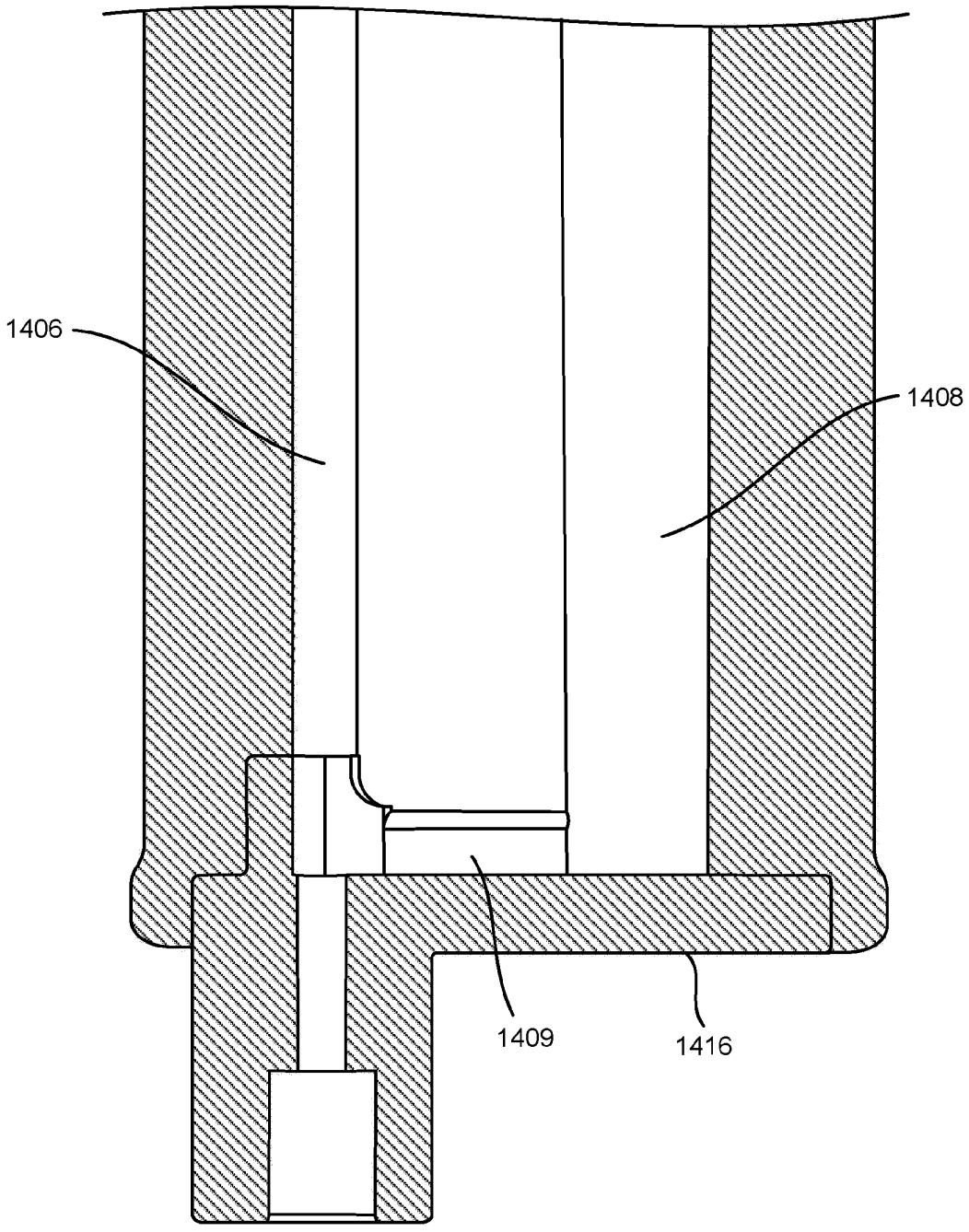


FIG. 14C

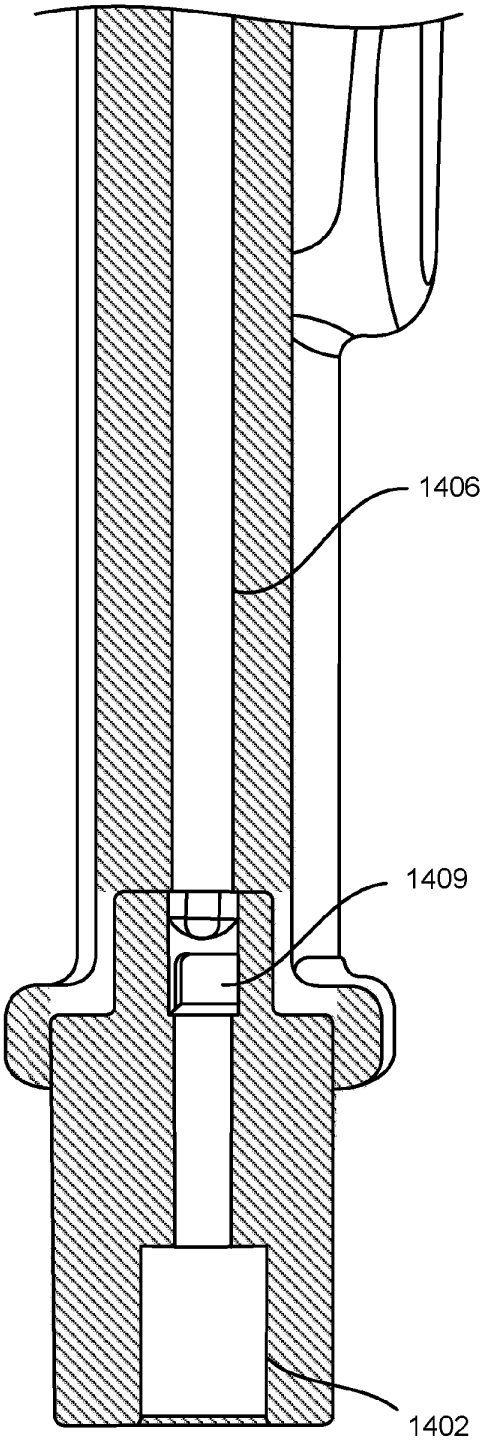


FIG. 14D

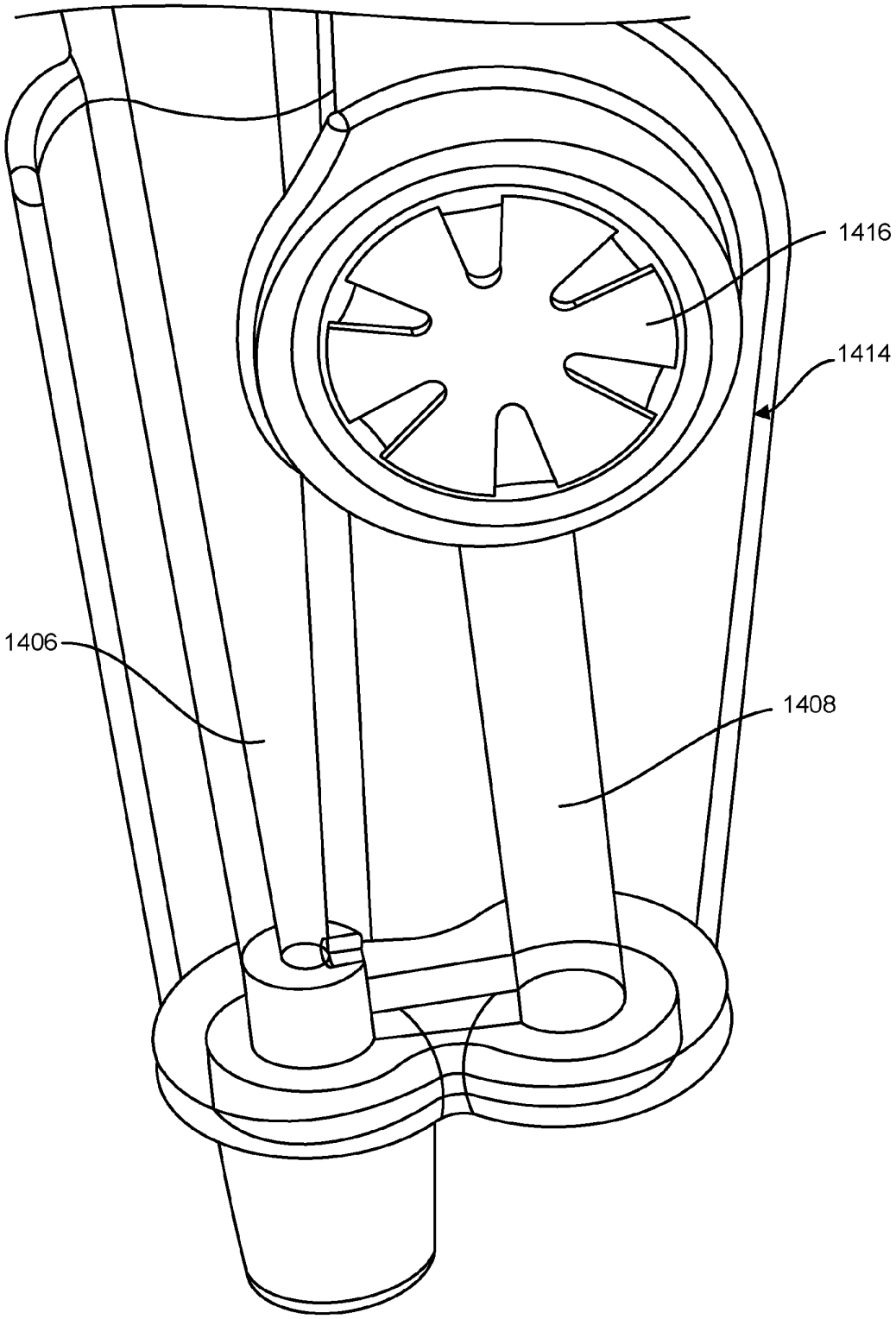


FIG. 14E

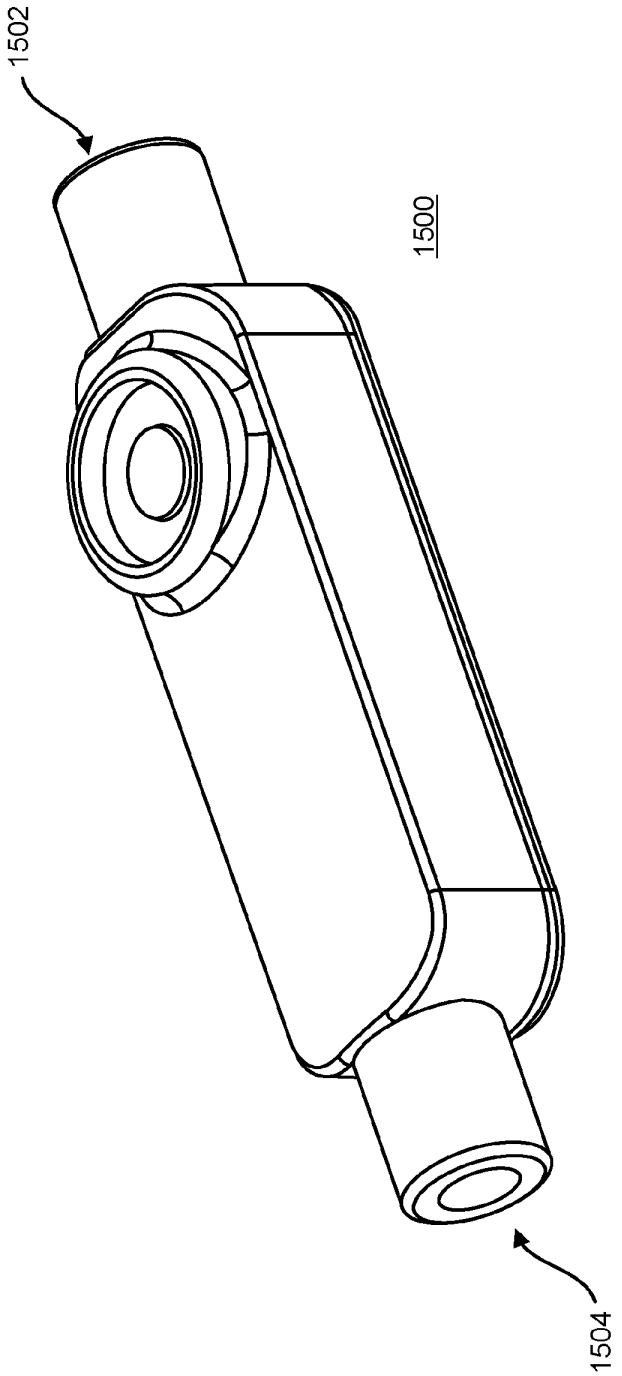


FIG. 15A

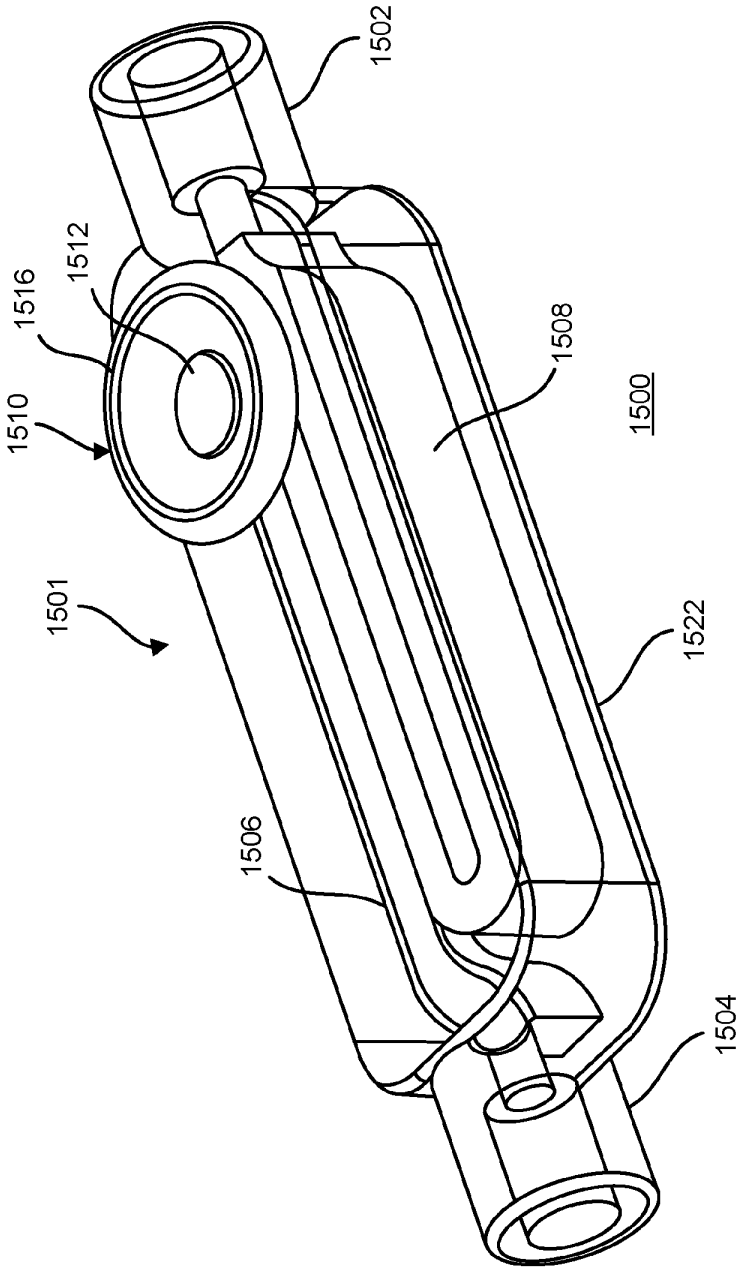


FIG. 15B

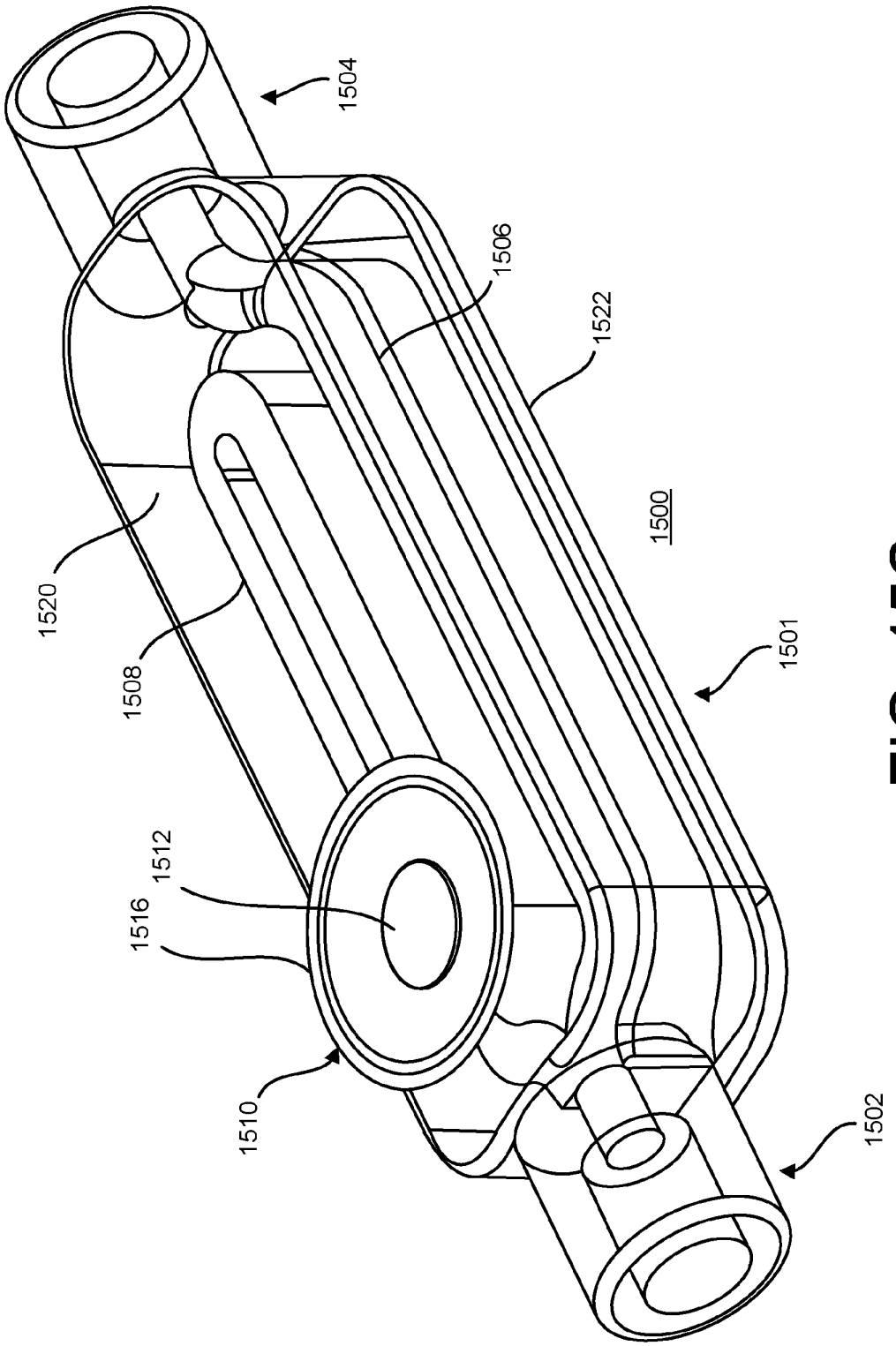


FIG. 15C

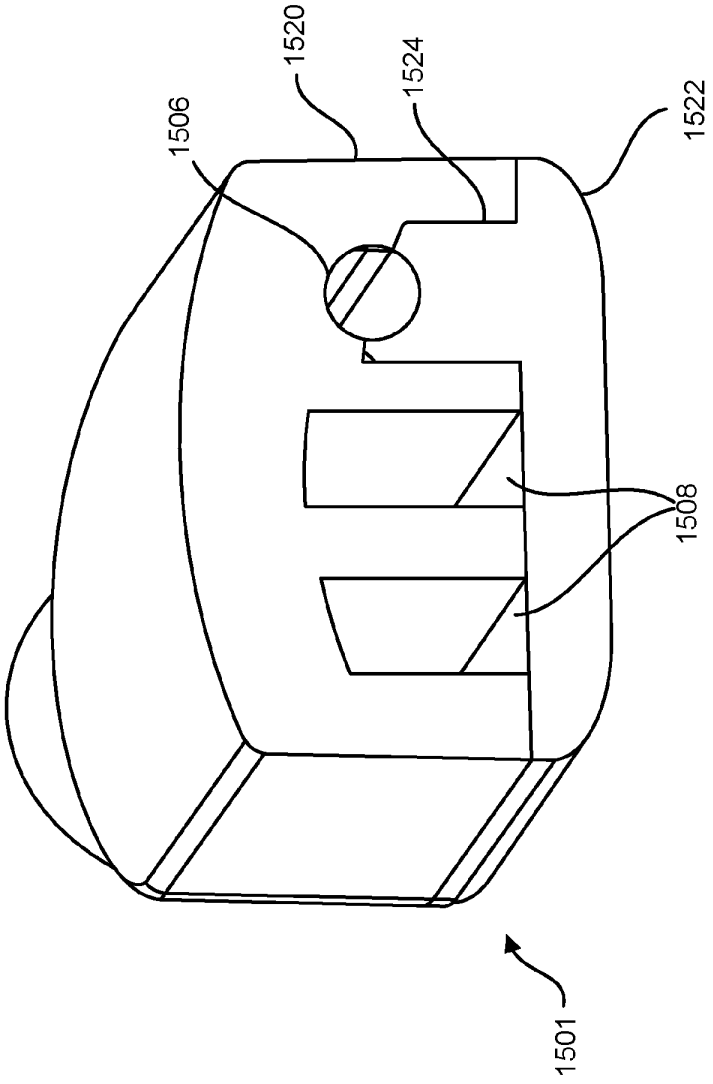


FIG. 15D

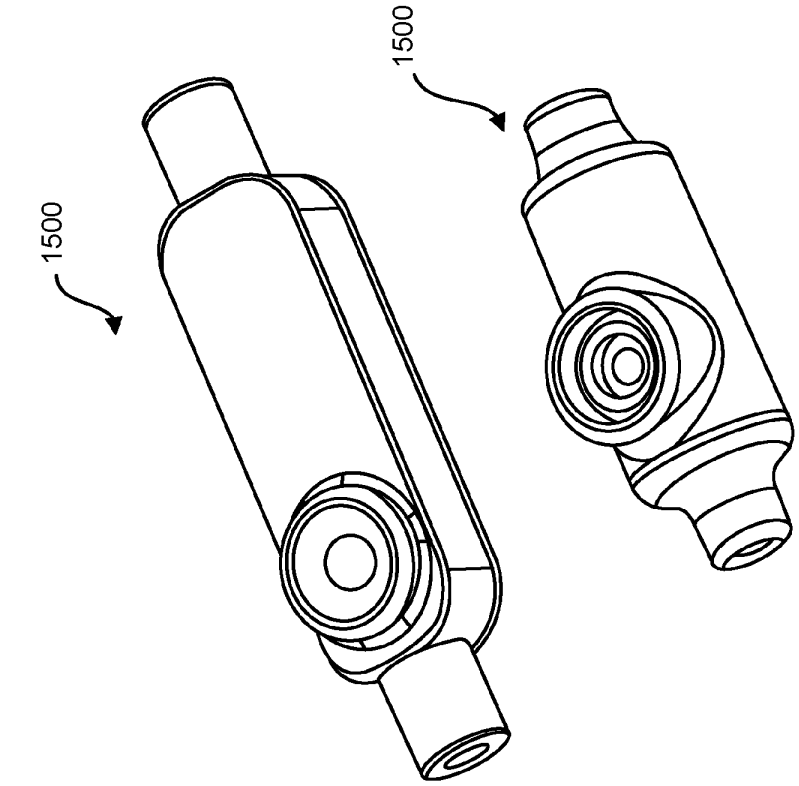


FIG. 15F

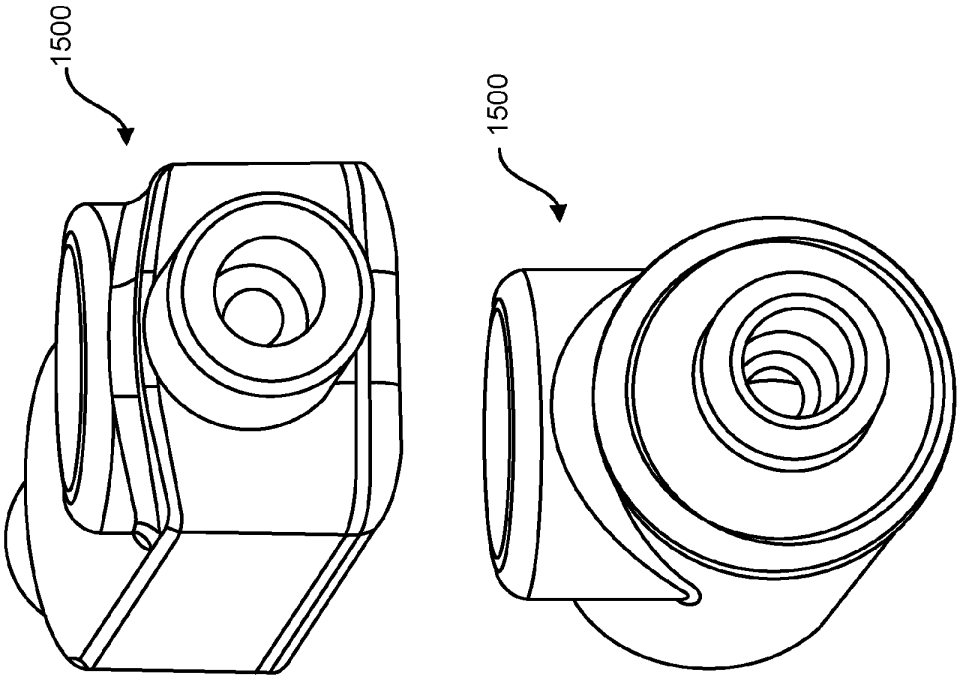


FIG. 15E

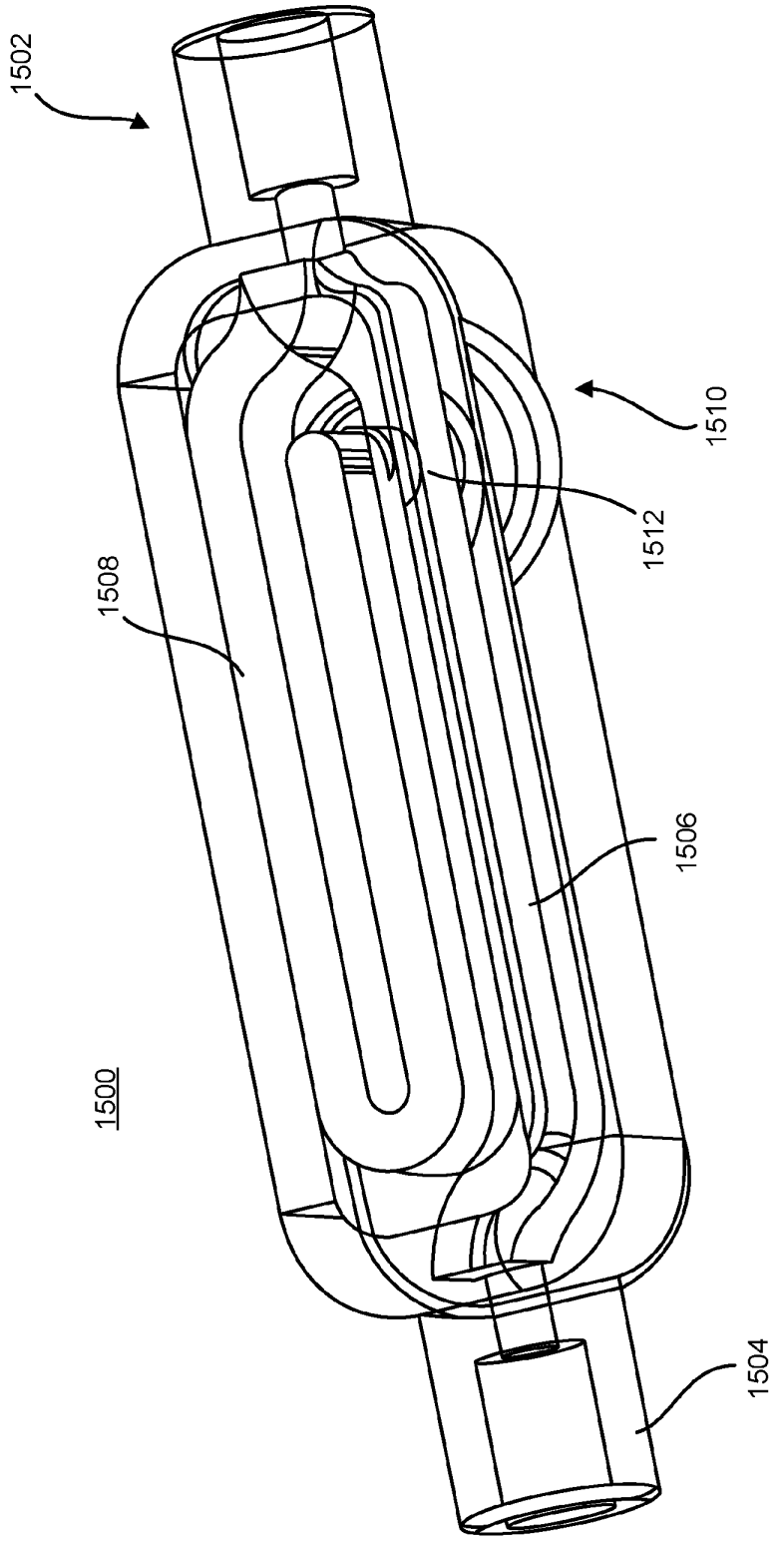


FIG. 15G

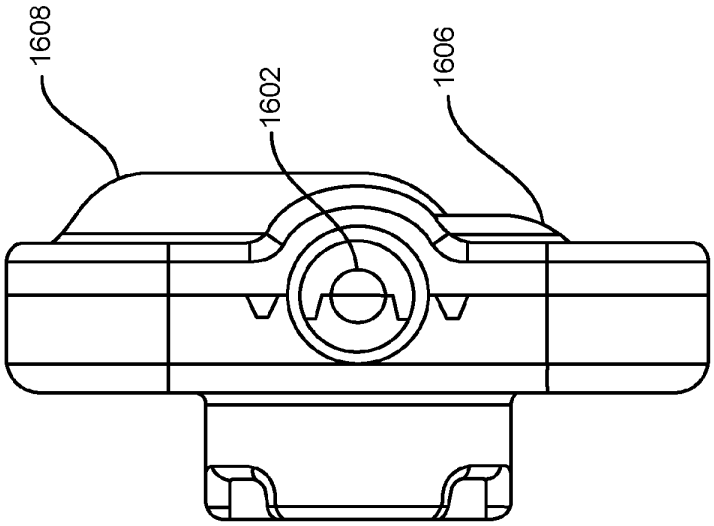


FIG. 16C

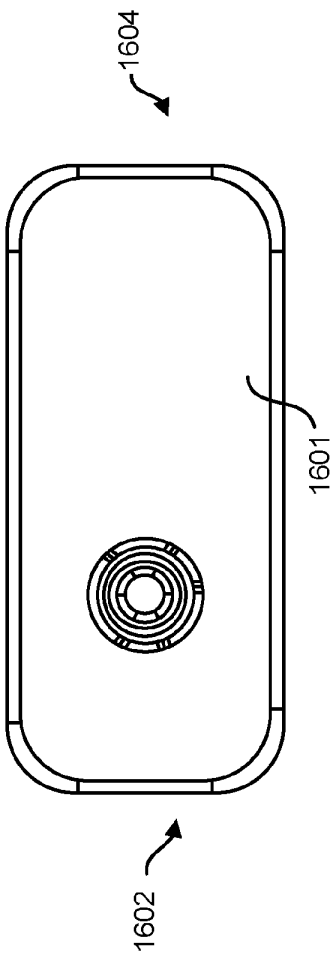


FIG. 16A

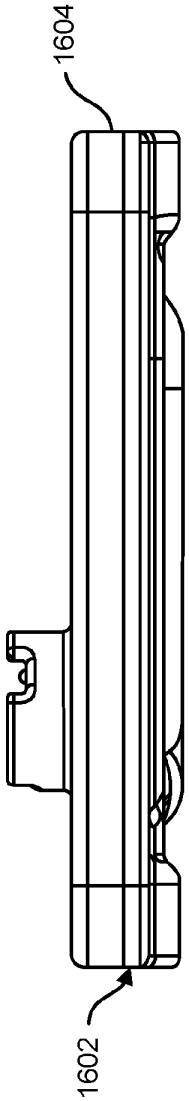


FIG. 16B

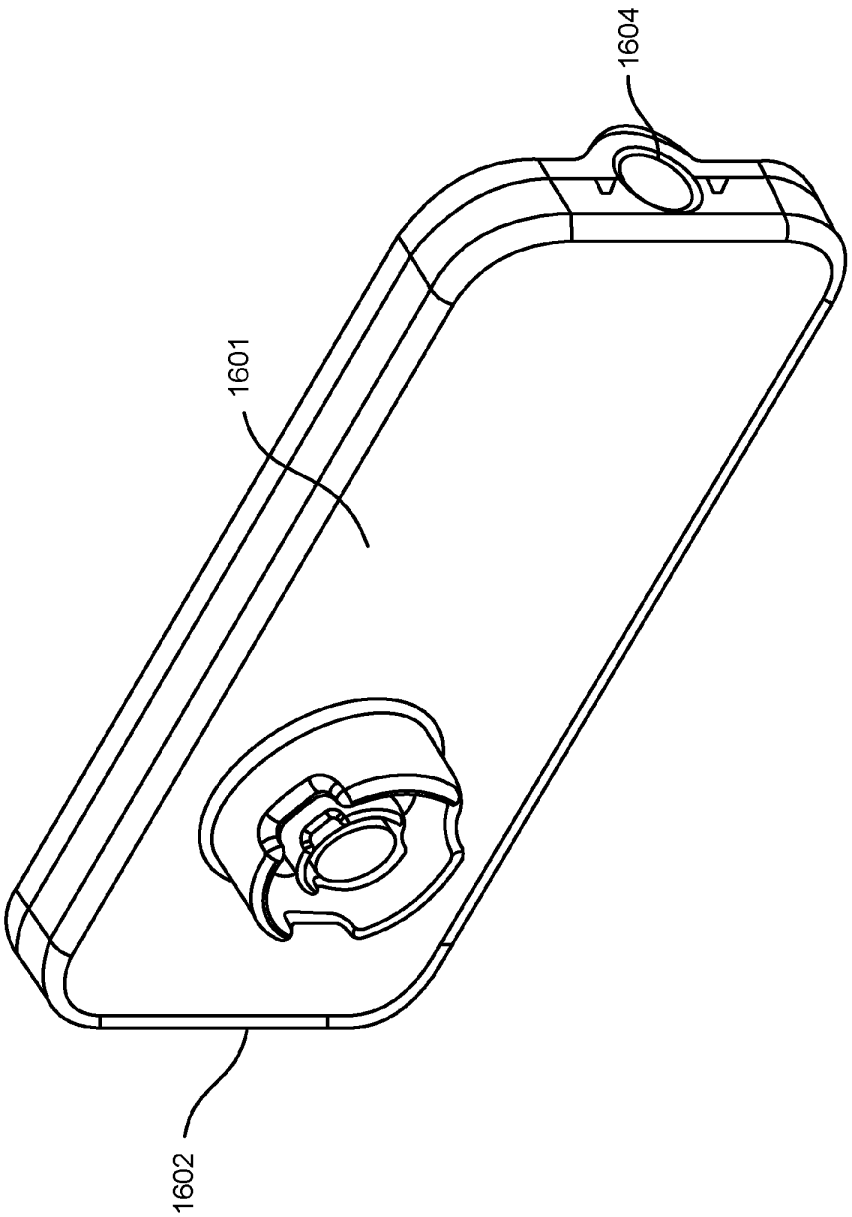


FIG. 16D

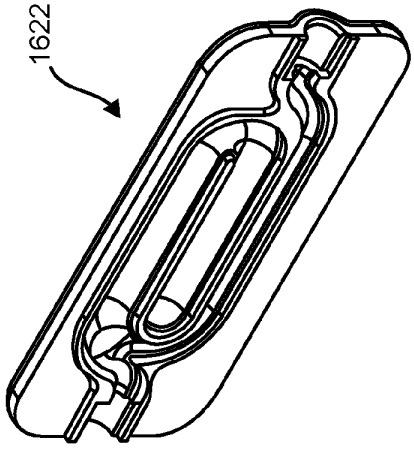


FIG. 17B



FIG. 17E

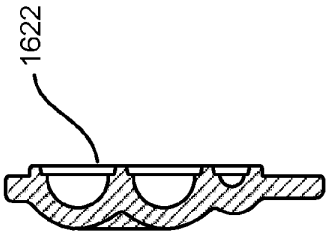


FIG. 17D

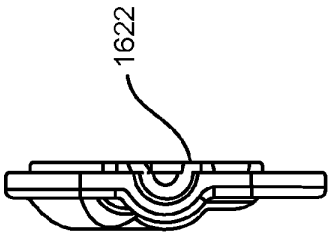


FIG. 17C

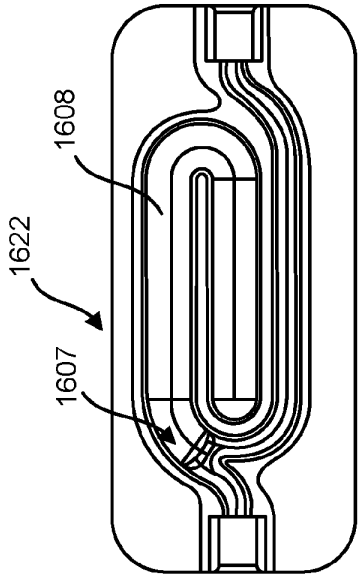


FIG. 17A

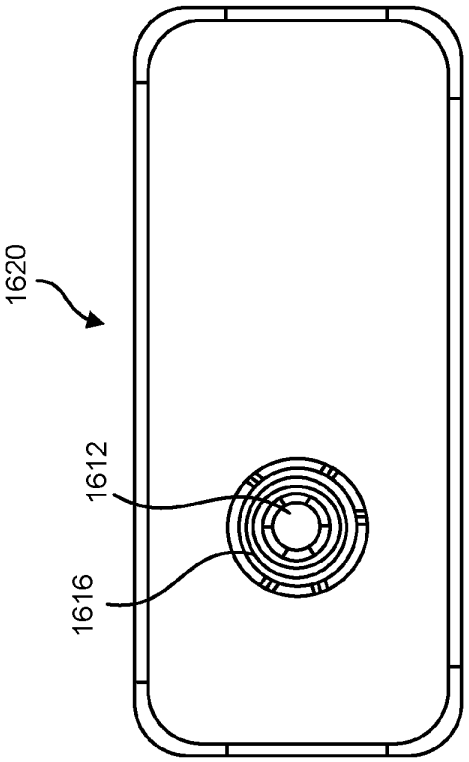


FIG. 18A

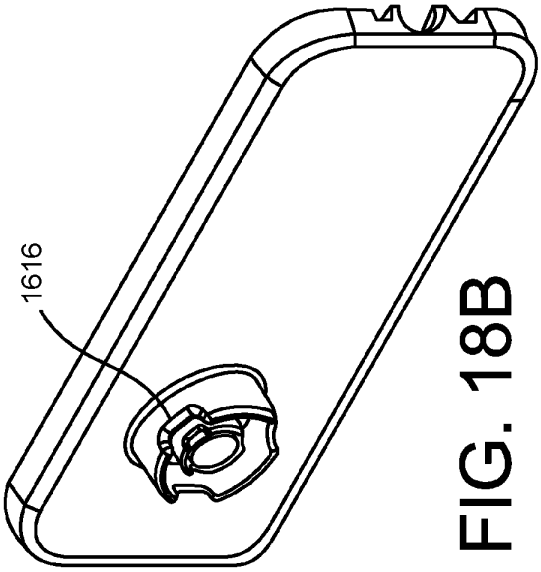


FIG. 18B



FIG. 18C

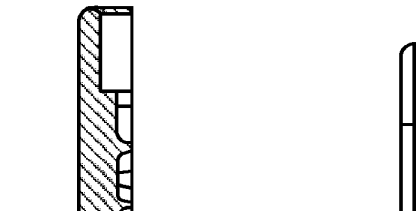


FIG. 18F

FIG. 18D

FIG. 18E

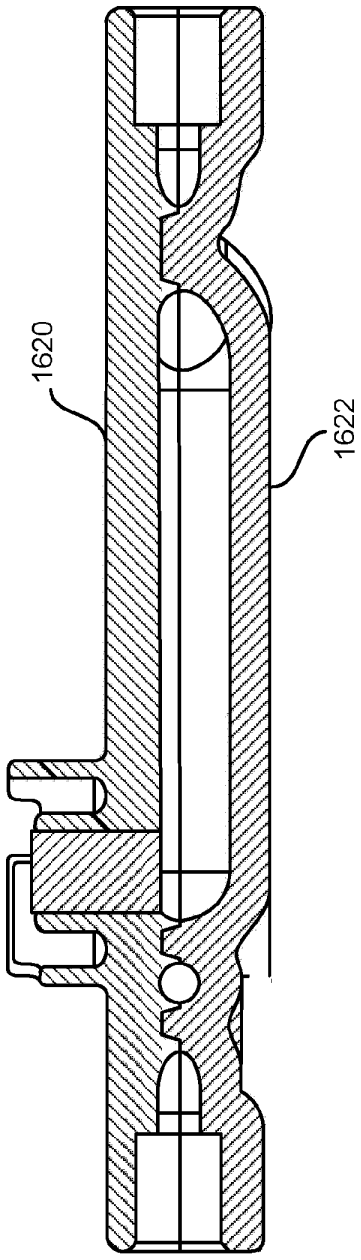


FIG. 19A

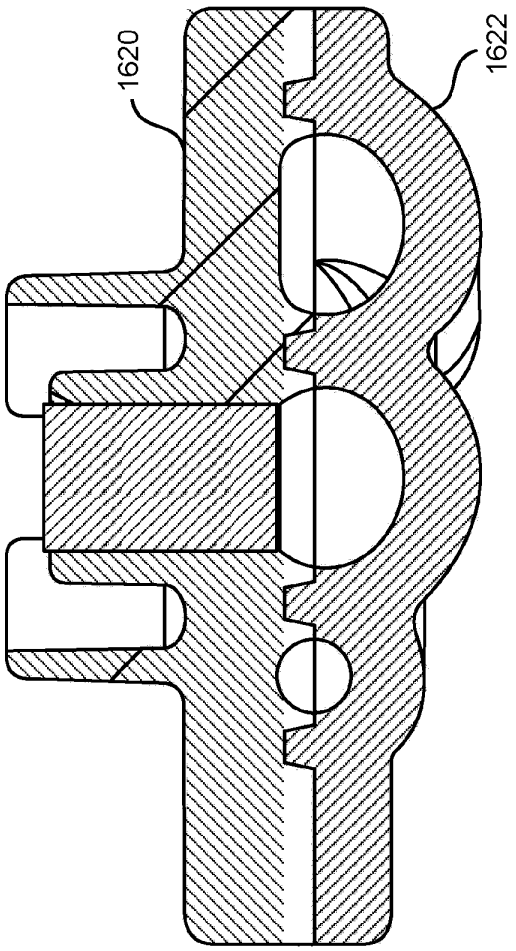


FIG. 19B

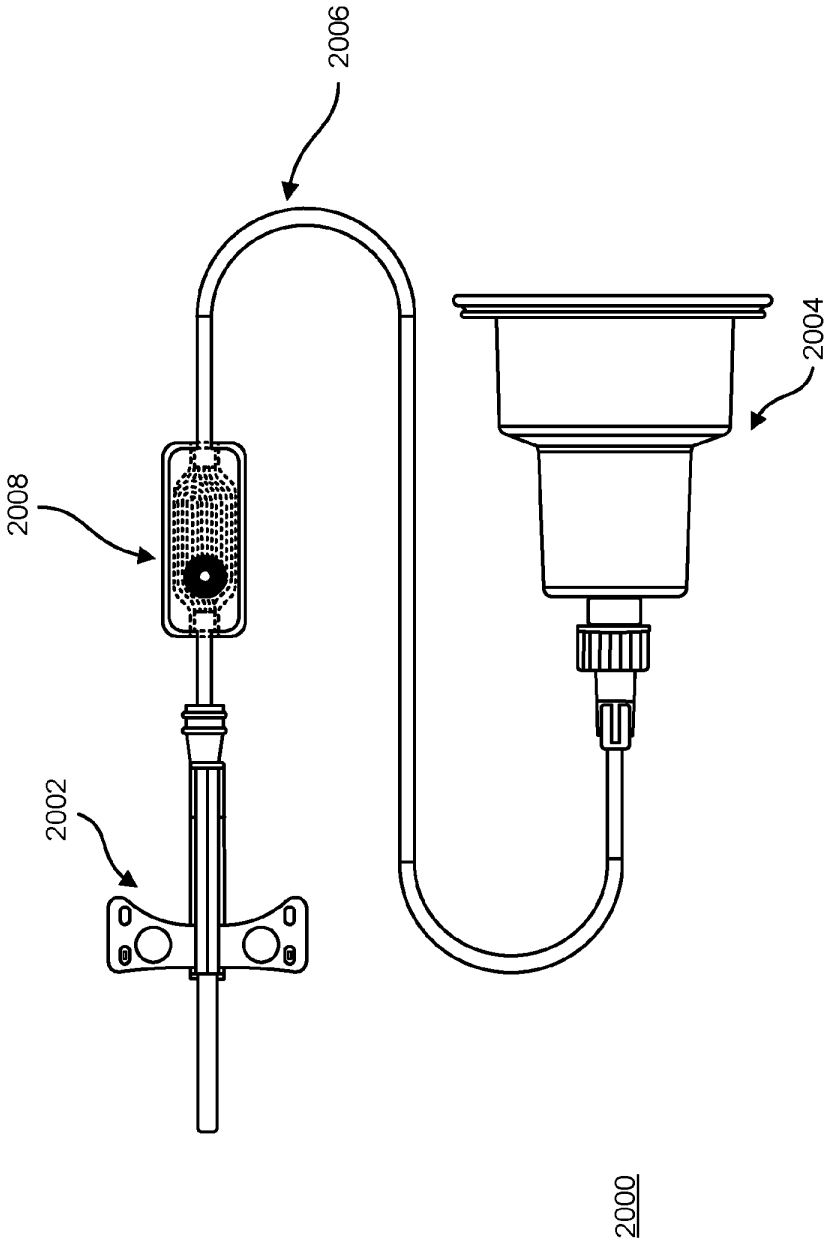


FIG. 20

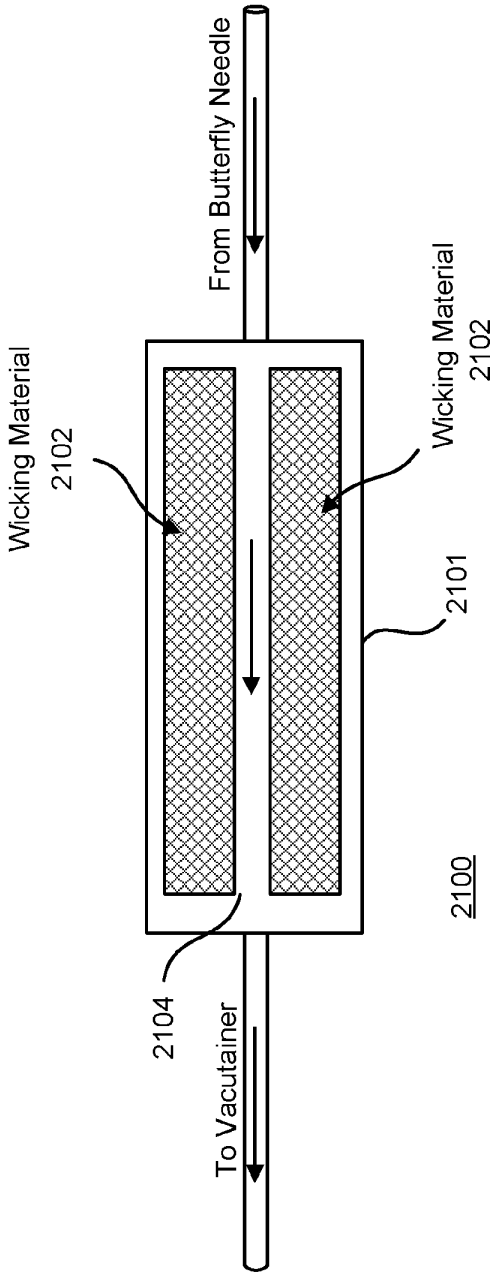

From Butterfly Needle
Wicking Material
2102
Wicking Material
2102
2101
2100
2104
To Vacutainer

FIG. 21

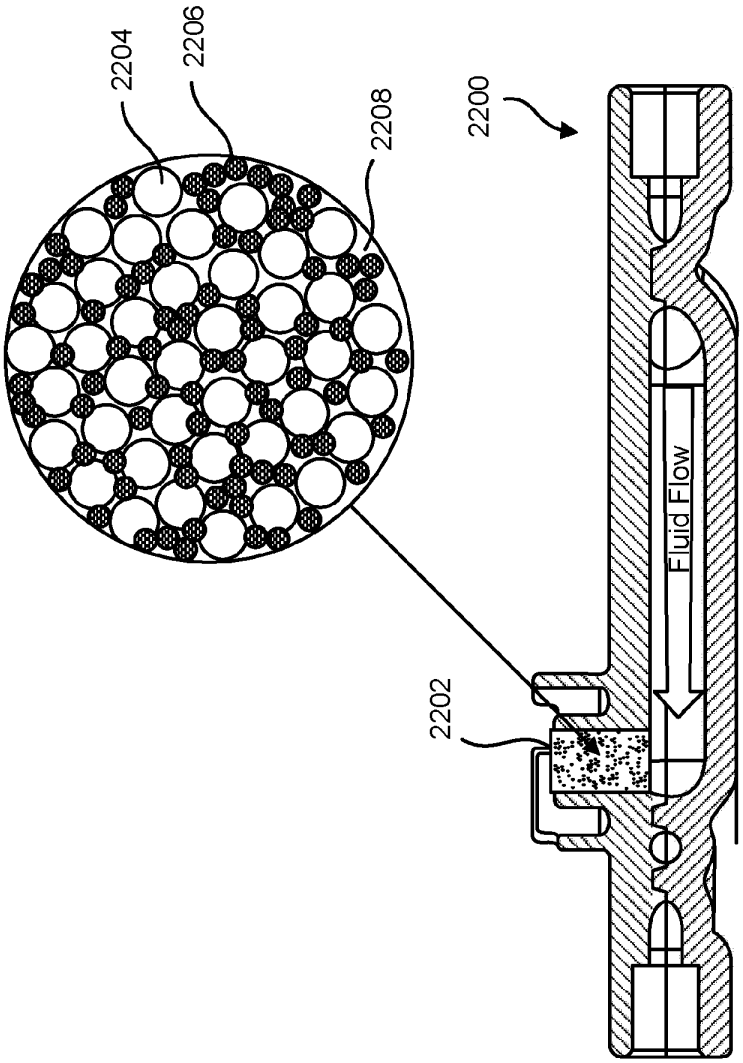


FIG. 22A

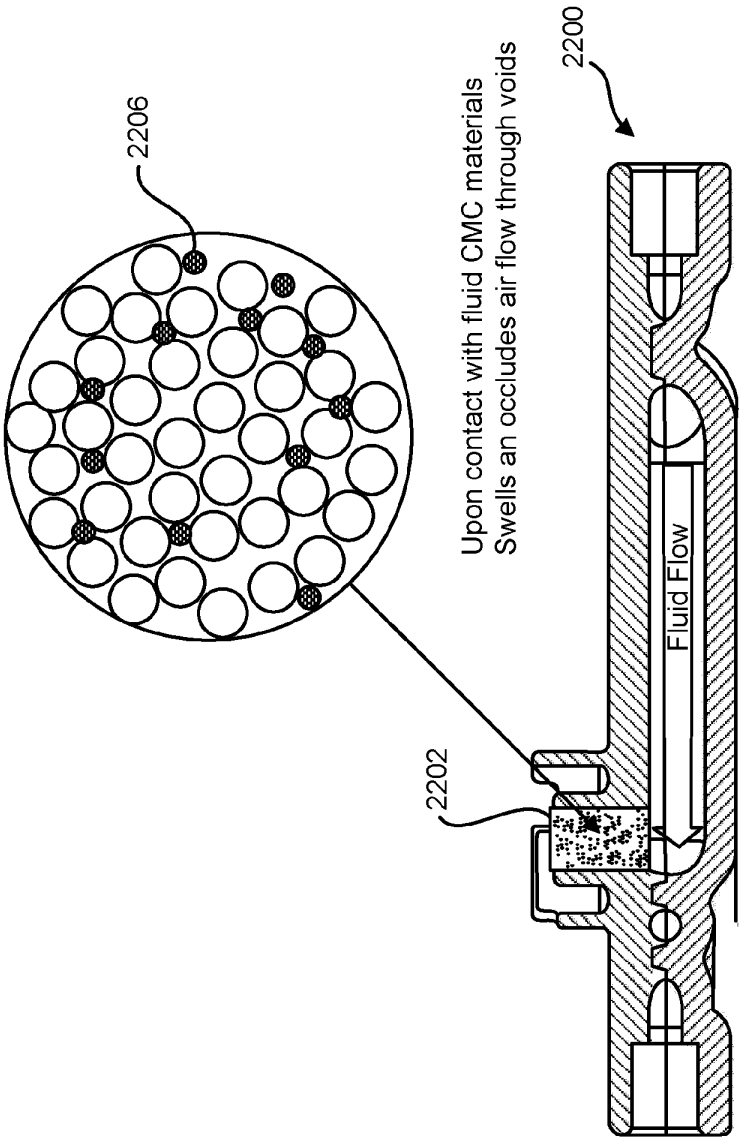

2206
2200
Upon contact with fluid CMC materials
Swells an occludes air flow through voids
Fluid Flow
2202

FIG. 22B

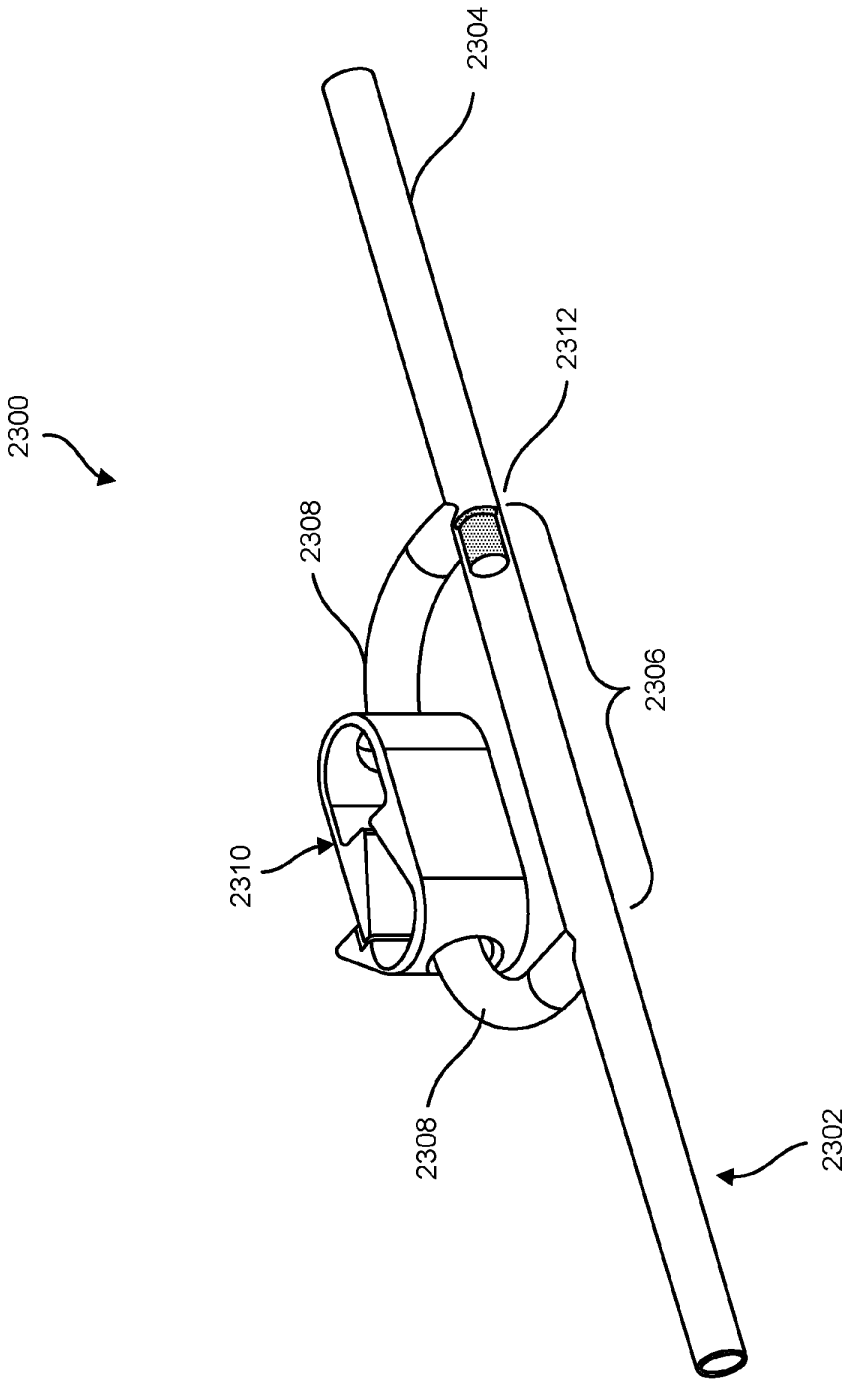


FIG. 23A

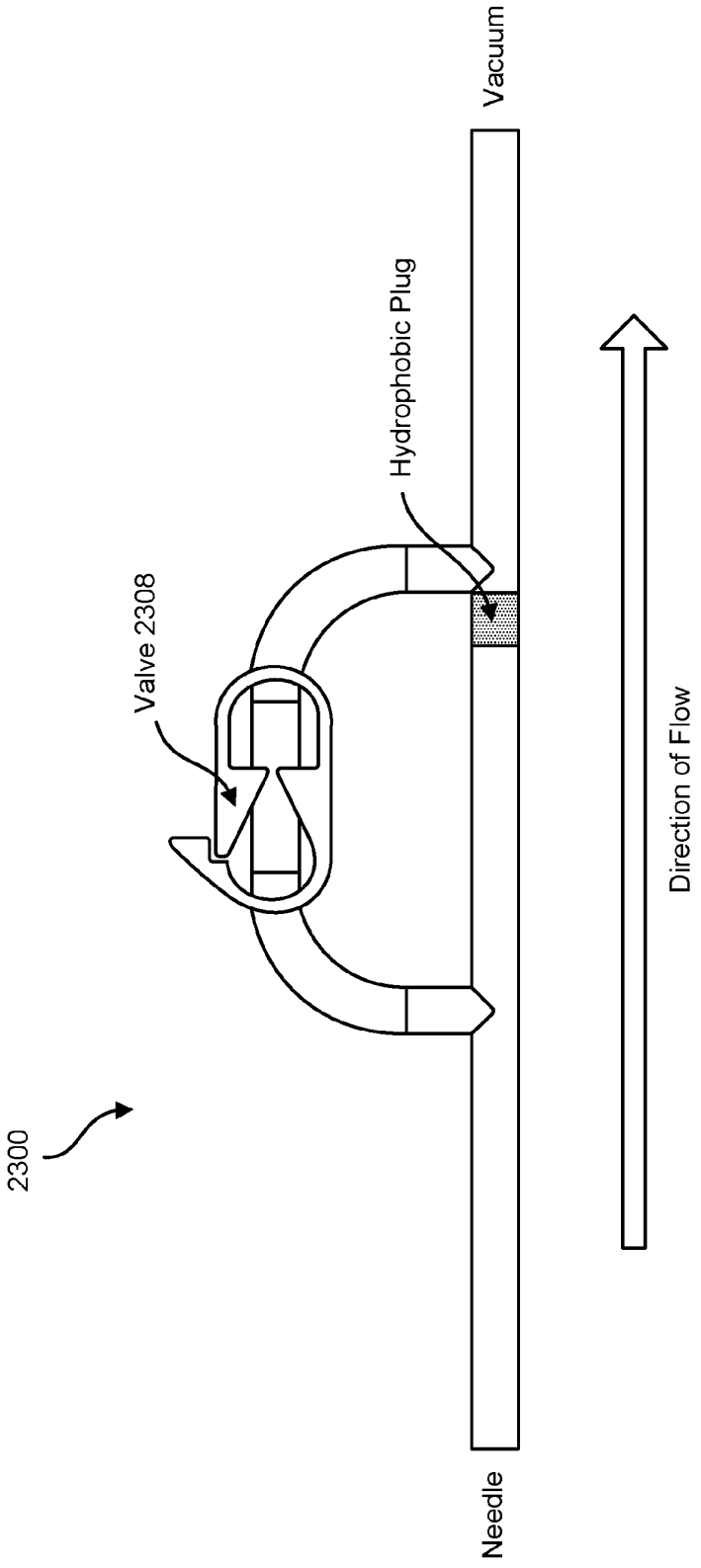

Vacuum
Hydrophobic Plug
Valve 2308
Direction of Flow
2300
Needle

FIG. 23B

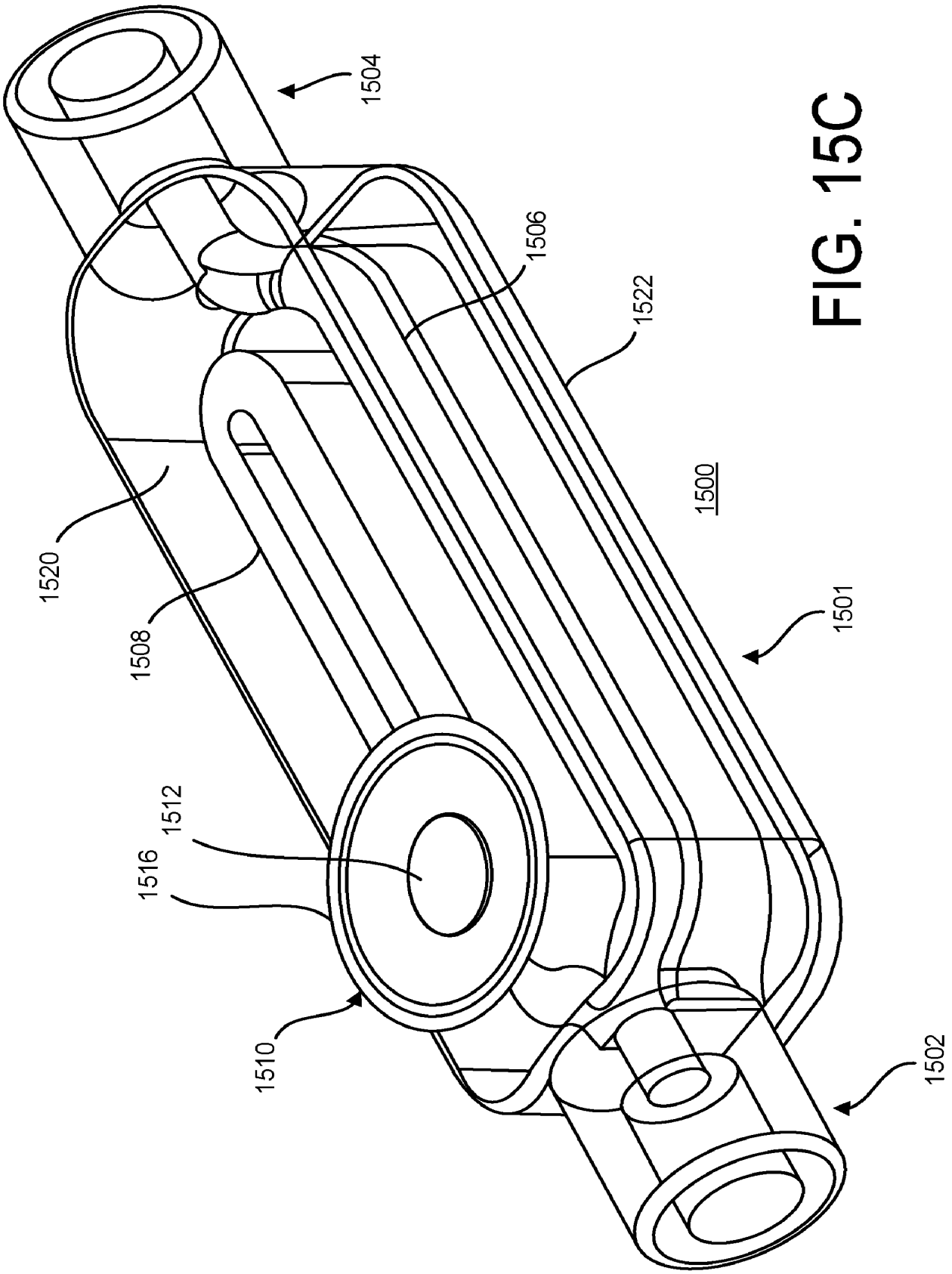


FIG. 15C

EXHIBIT H

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	

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.)

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Inventor 2 Remove

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Address 2			
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Postal Code	98199	Country	US

Inventor 3 Remove

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Prefix	Given Name	Middle Name	Family Name	Suffix
	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

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	Jay	M.	Miazga	

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Postal Code	98103	Country	US

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	Jed		McCann	

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

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Postal Code	98117	Country	US

Inventor 6 — Remove

Legal Name

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	Paul		Goldenbaum	

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	

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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)

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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).

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

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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.

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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.

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.

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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 Number	
Title of Invention	SYSTEMS AND METHODS FOR SAMPLE COLLECTION WITH REDUCED HEMOLYSIS	

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. ☒

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Address 2	Suite 1630		
City	Seattle	**State/Province**	WA
Country	US	Postal Code	98121
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:

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	Application Number	
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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. ☐

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

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

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

Signature	/Michael D. Wintemitz/			Date (YYYY-MM-DD)	2016-11-18
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	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

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

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

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

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

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

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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

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

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

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.

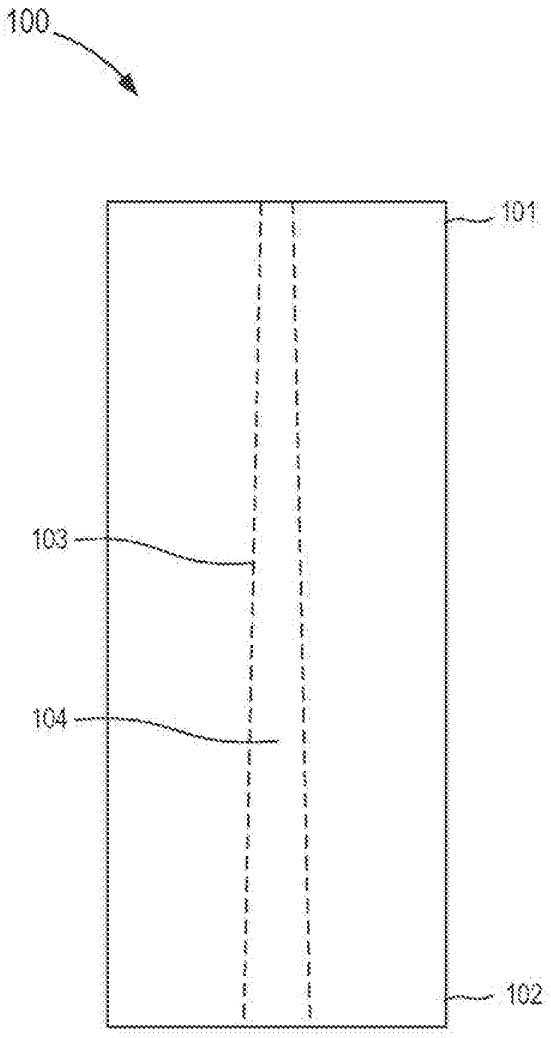


FIG. 1

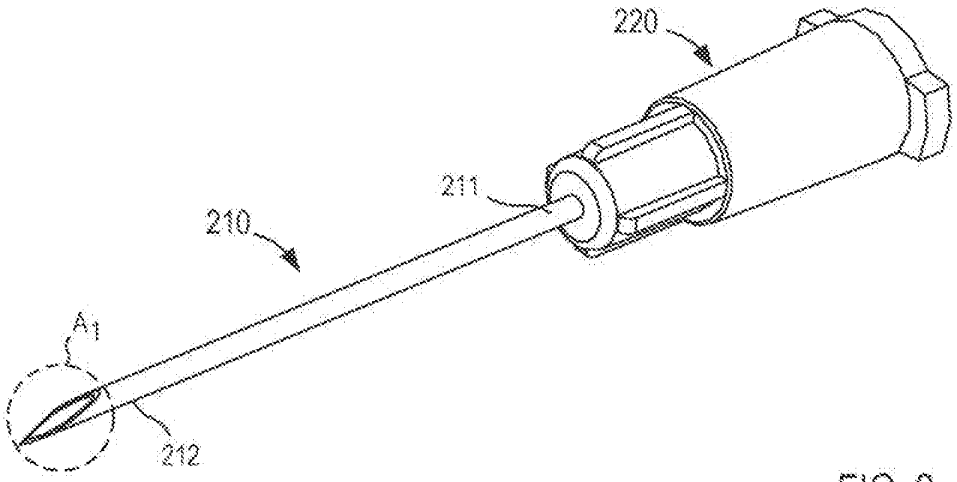


FIG. 2

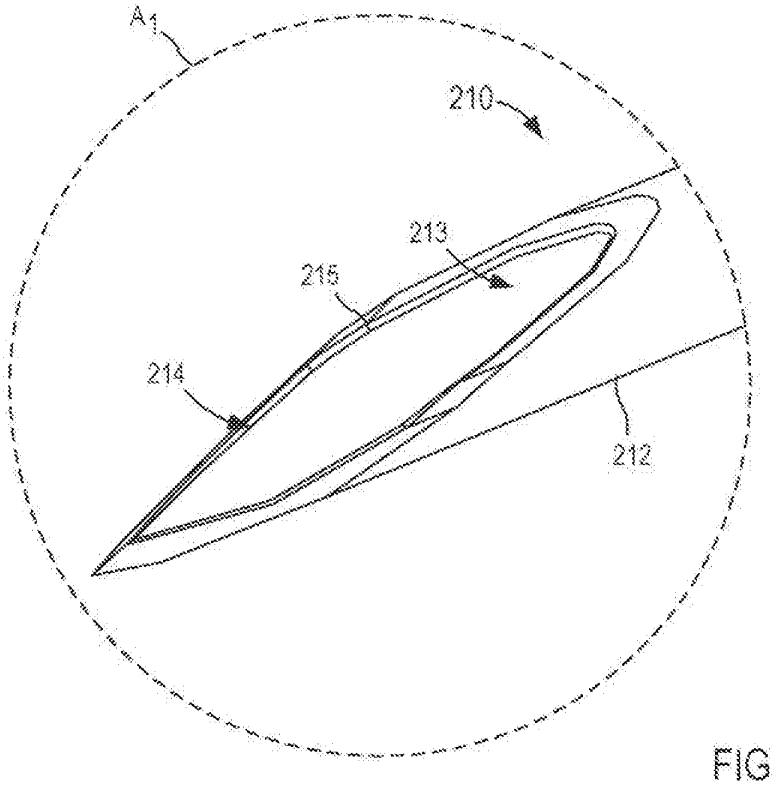


FIG. 3

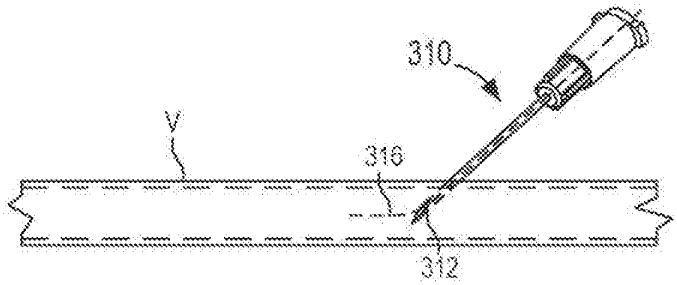


FIG. 4

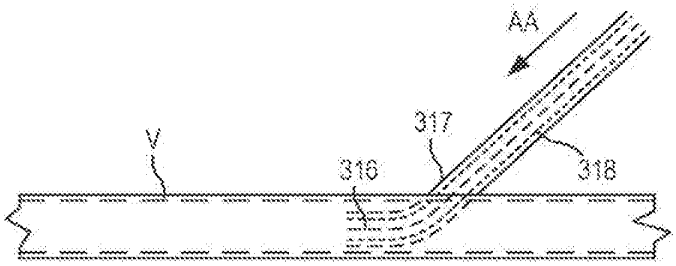


FIG. 5

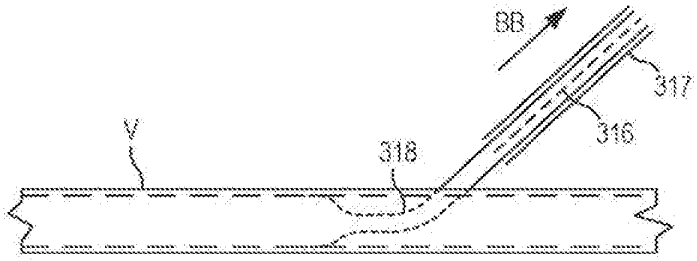


FIG. 6

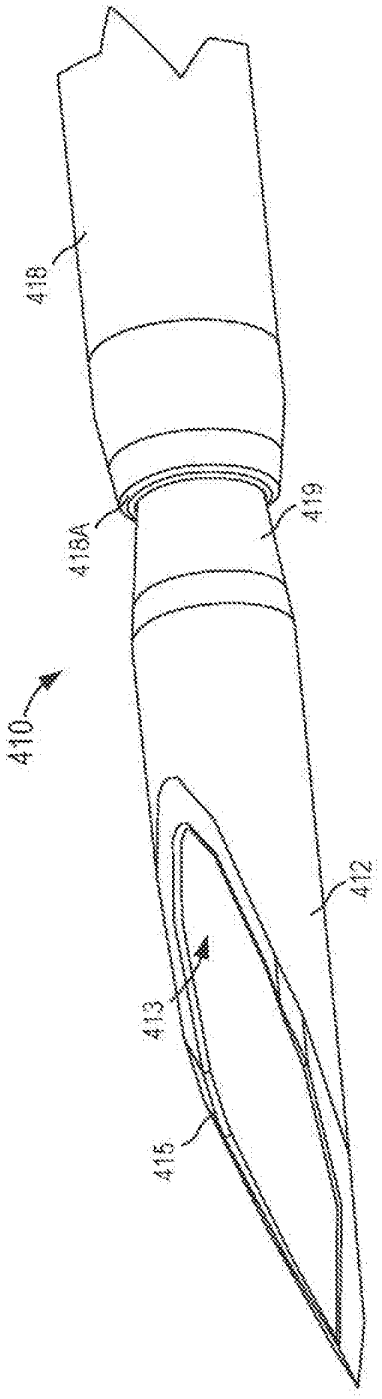


FIG. 7

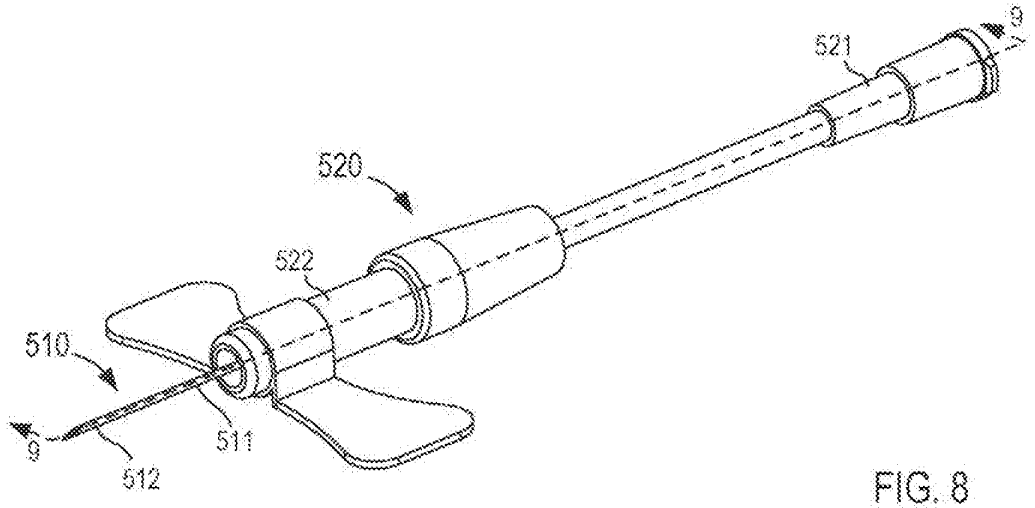


FIG. 8

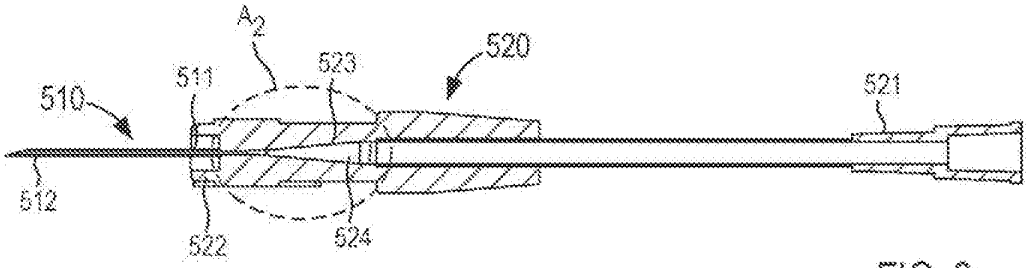


FIG. 9

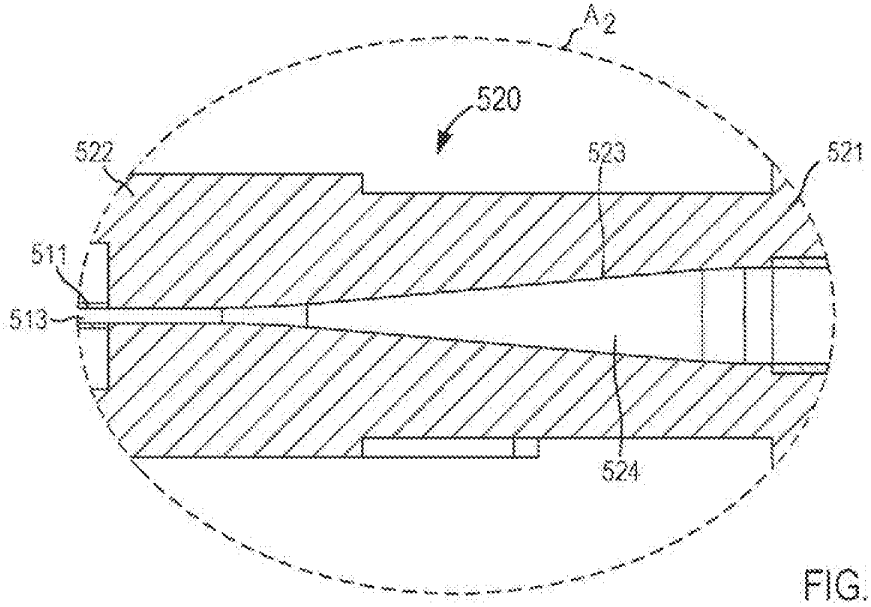


FIG. 10

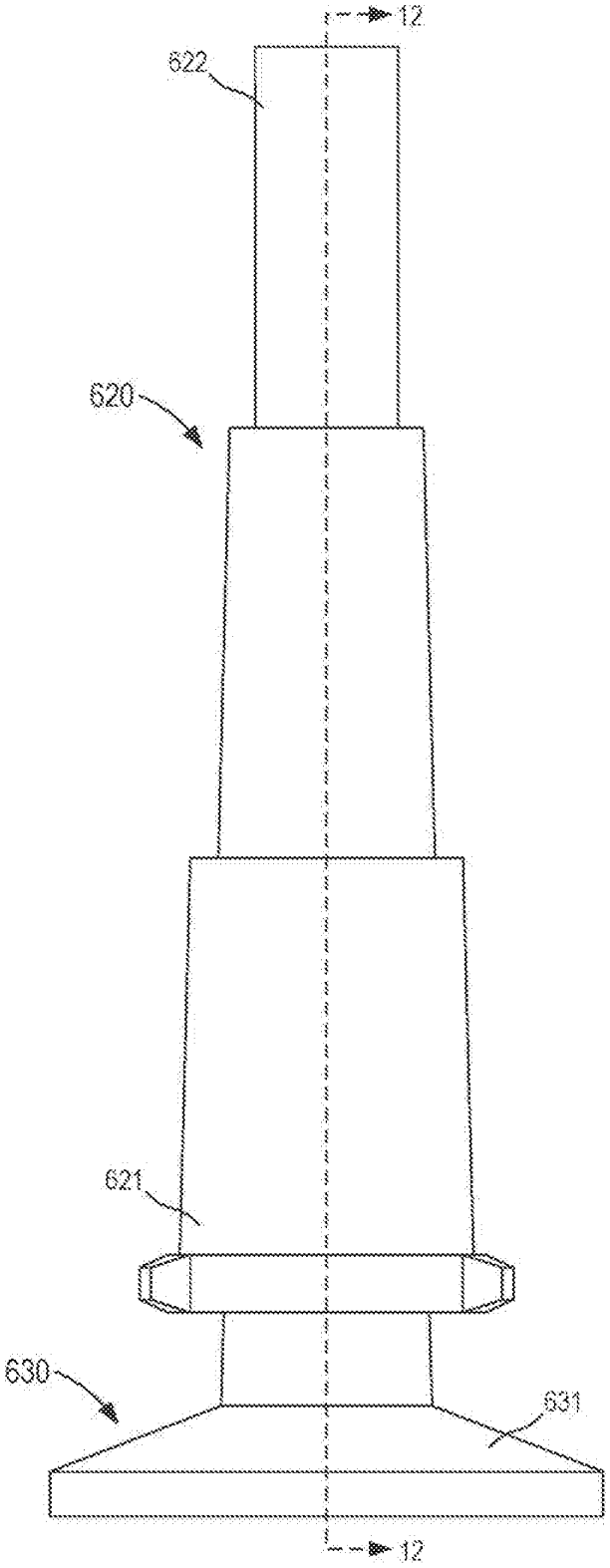


FIG. 11

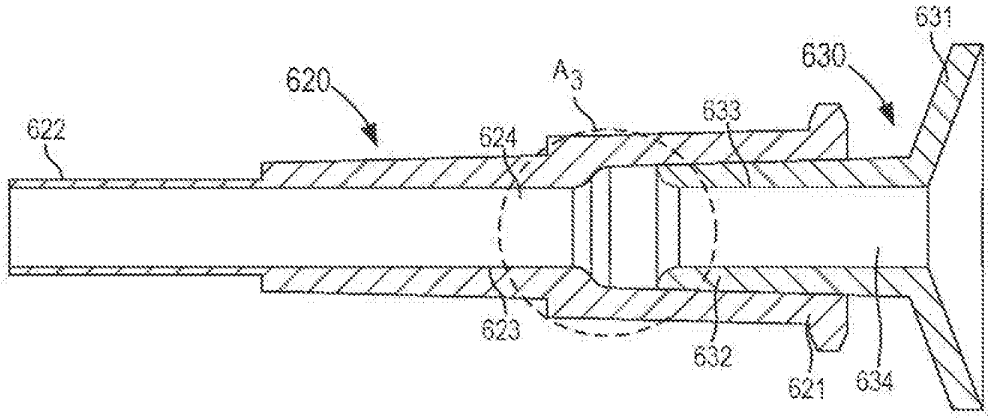

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FIG. 12

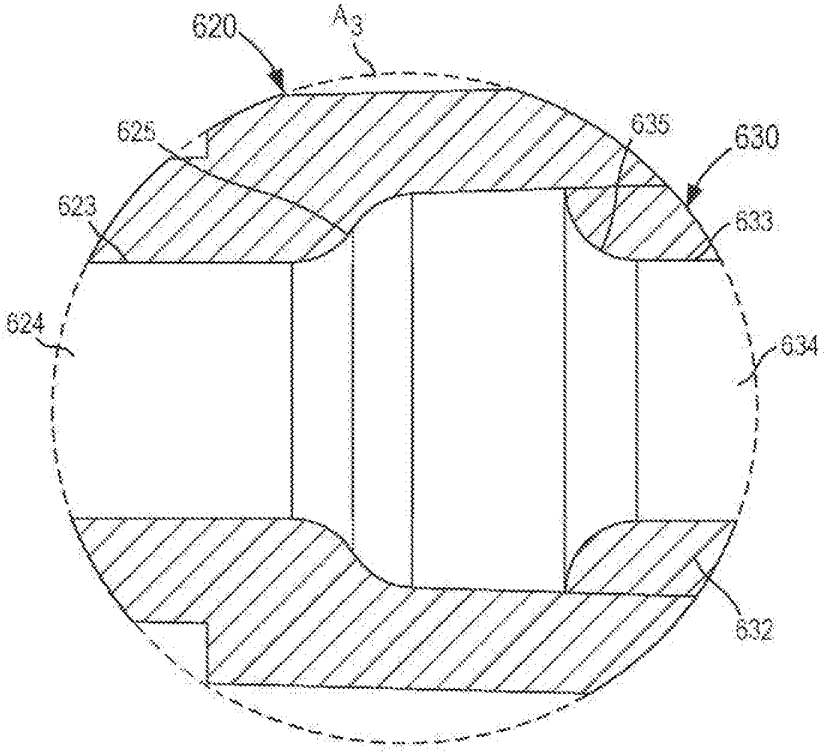

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FIG. 13

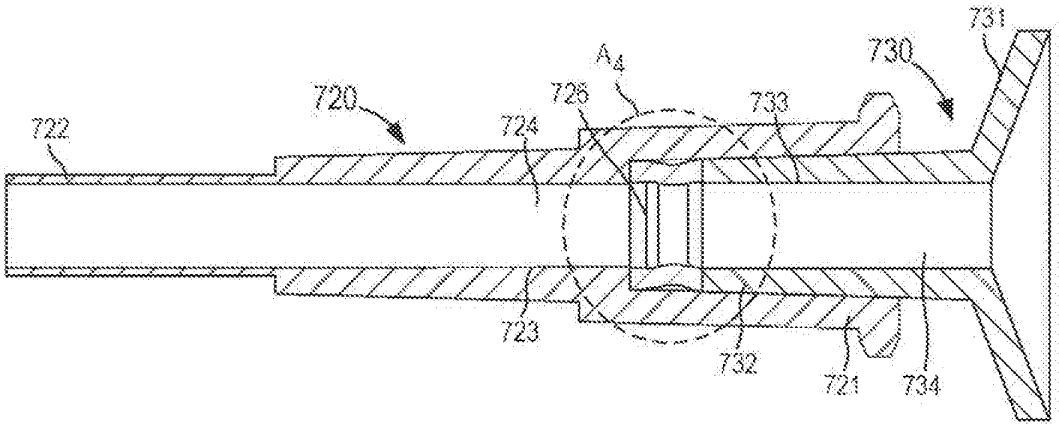

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FIG. 14

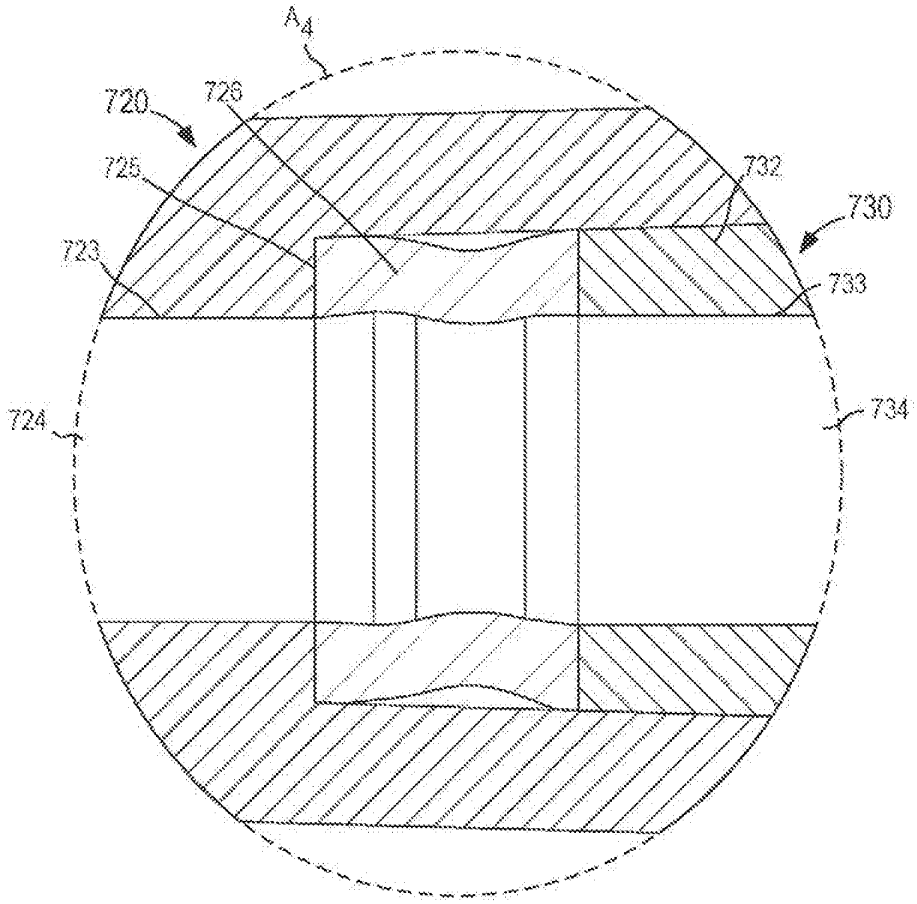

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FIG. 15

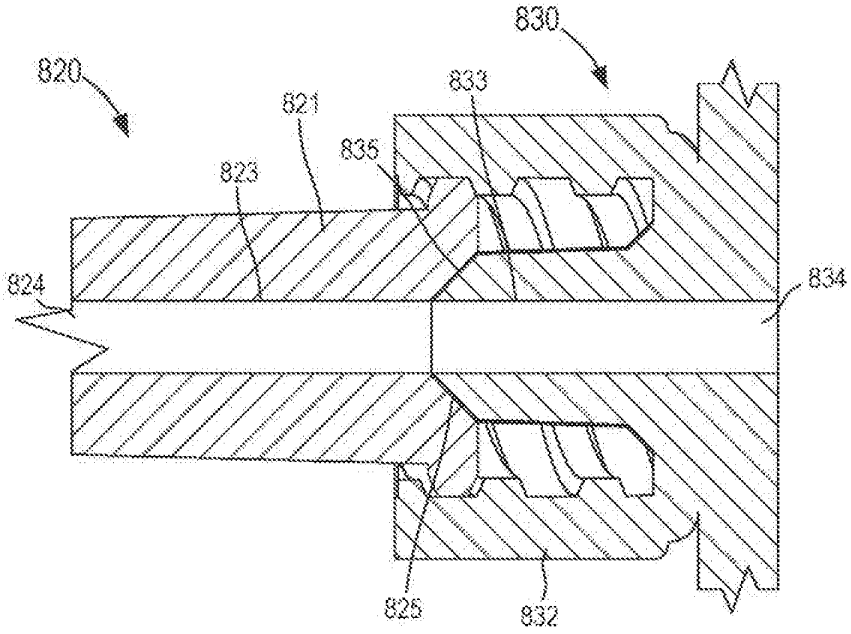

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FIG. 16

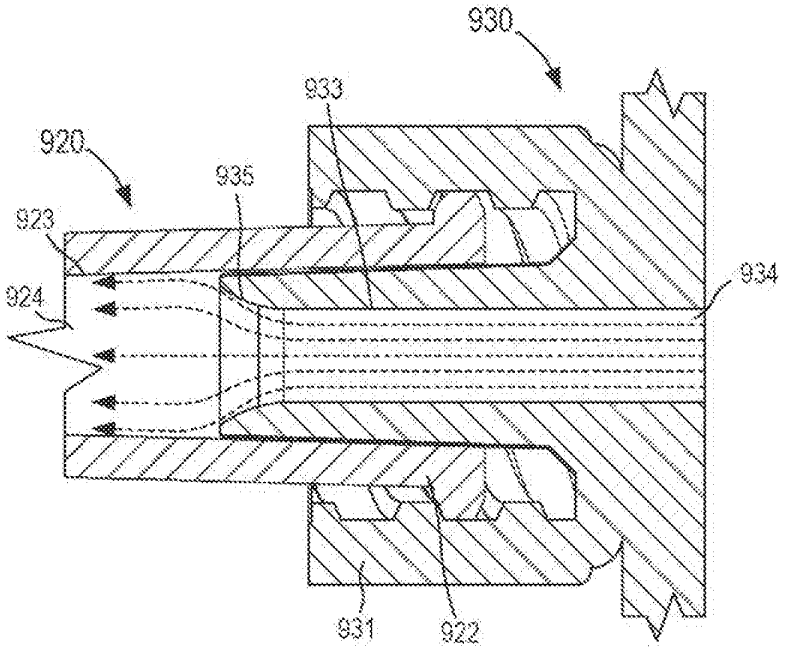

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FIG. 17

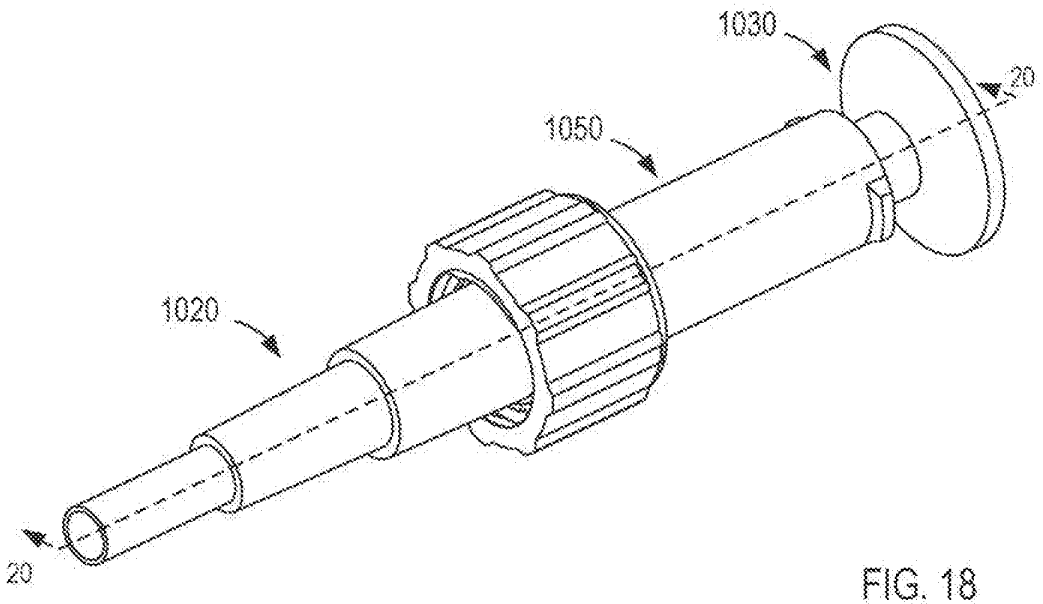

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FIG. 18

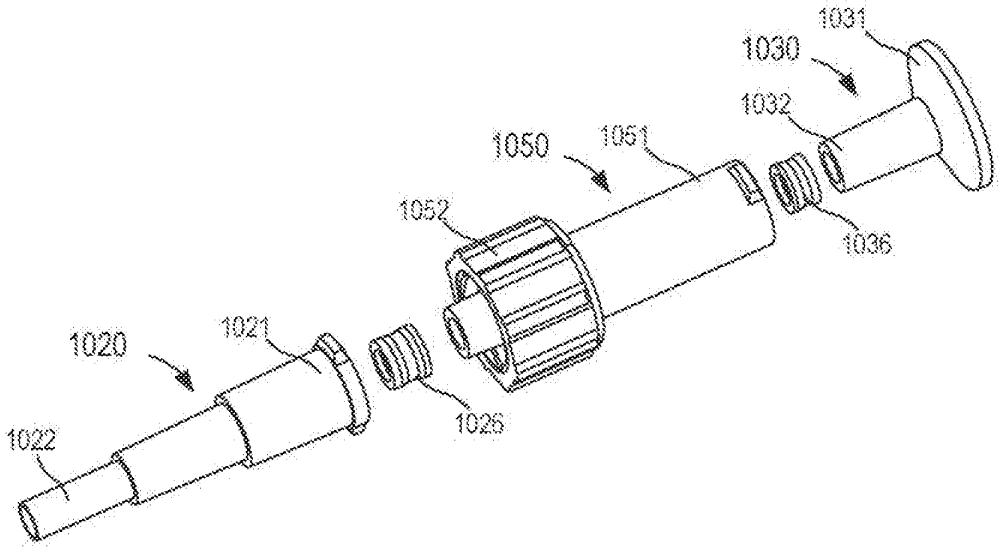

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FIG. 19

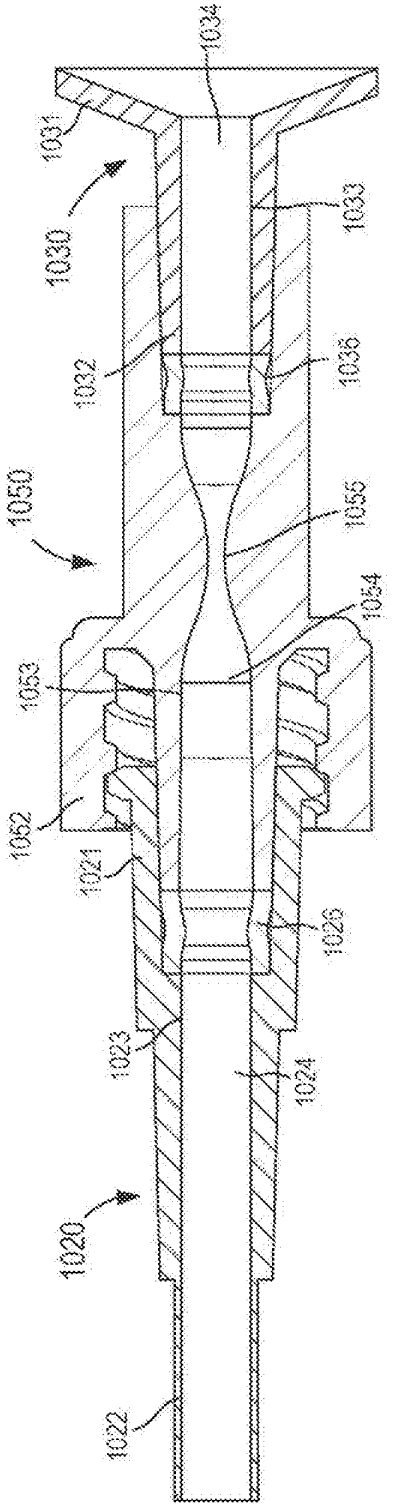

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FIG. 20

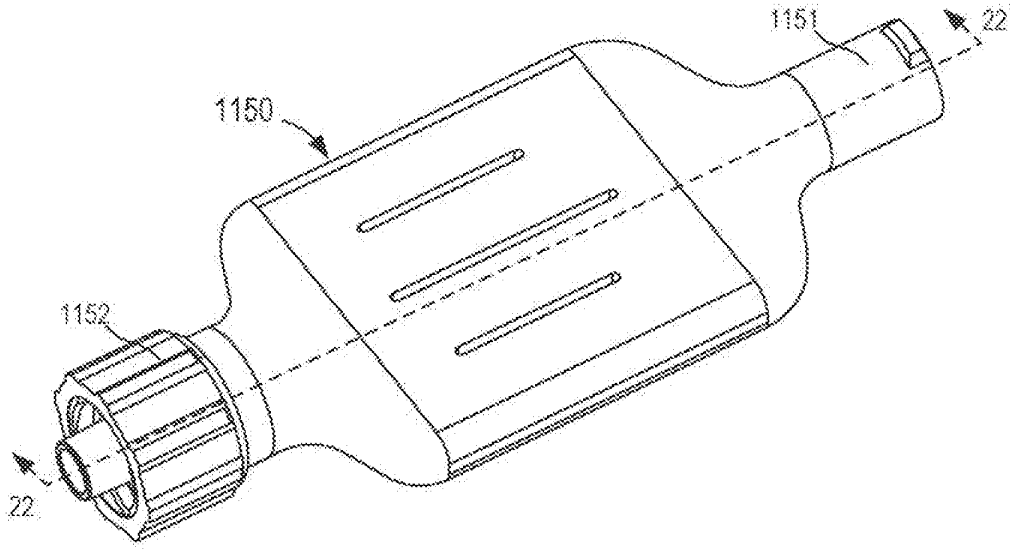


FIG. 21

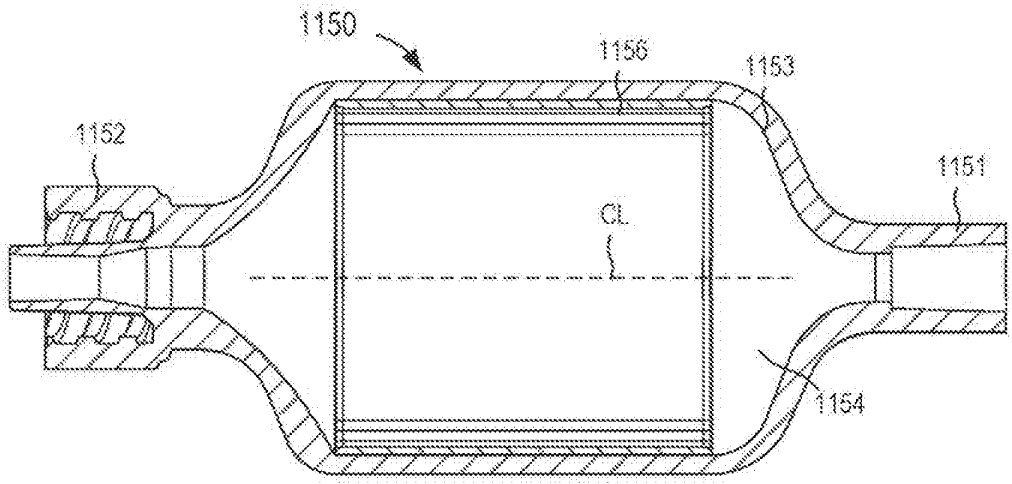


FIG. 22

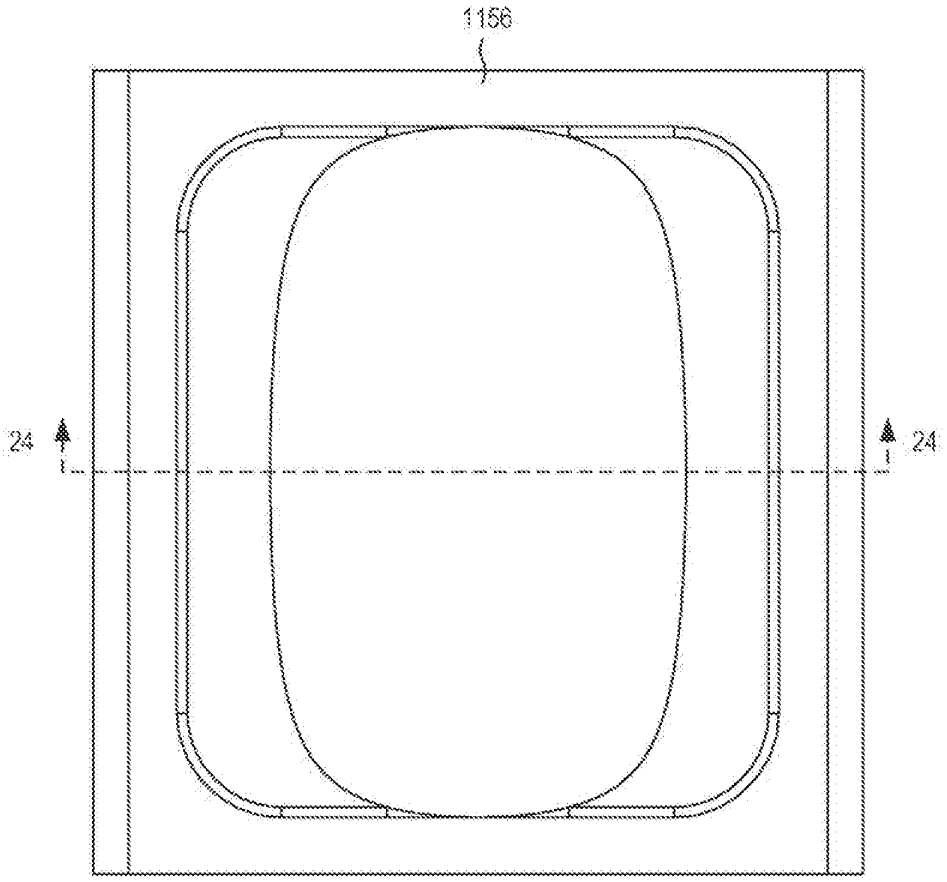


FIG. 23

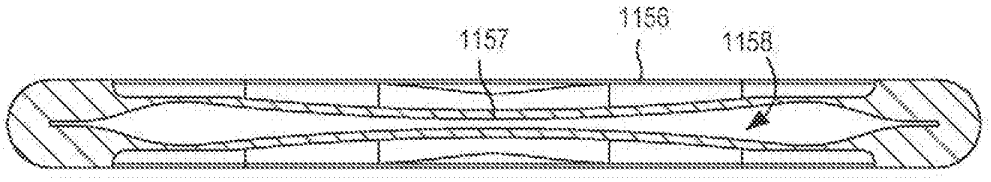


FIG. 24

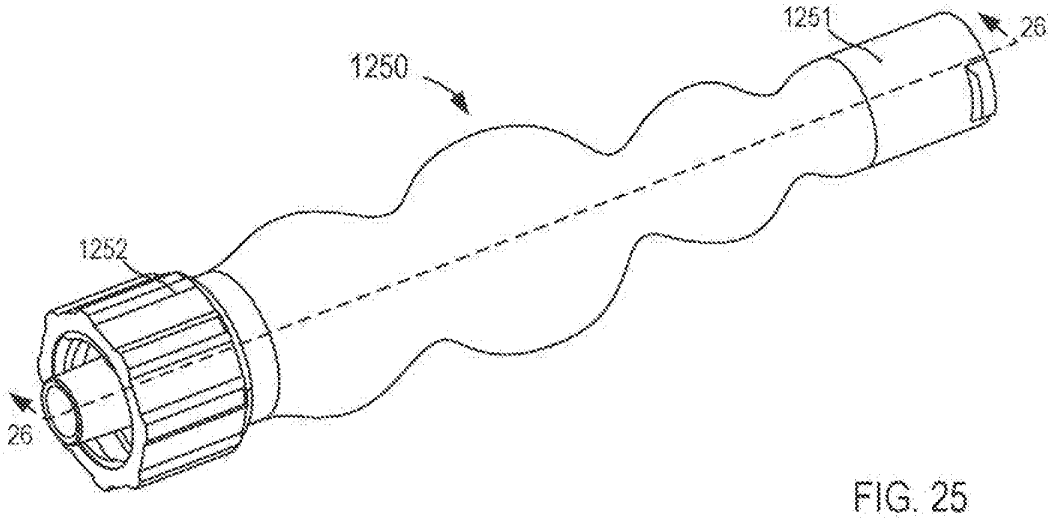

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FIG. 25

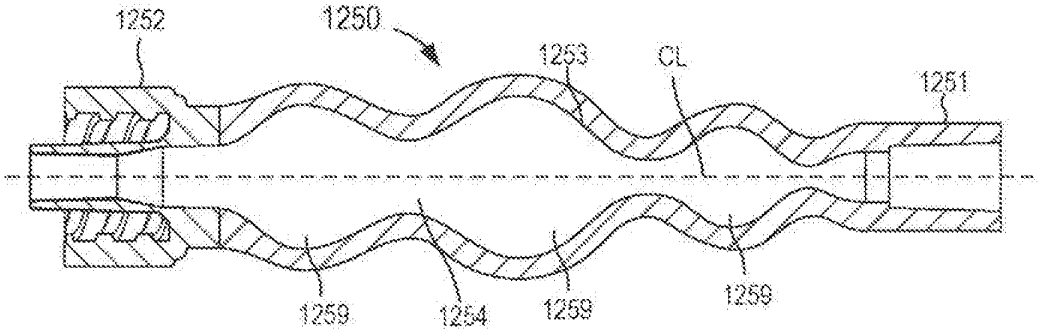

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FIG. 26

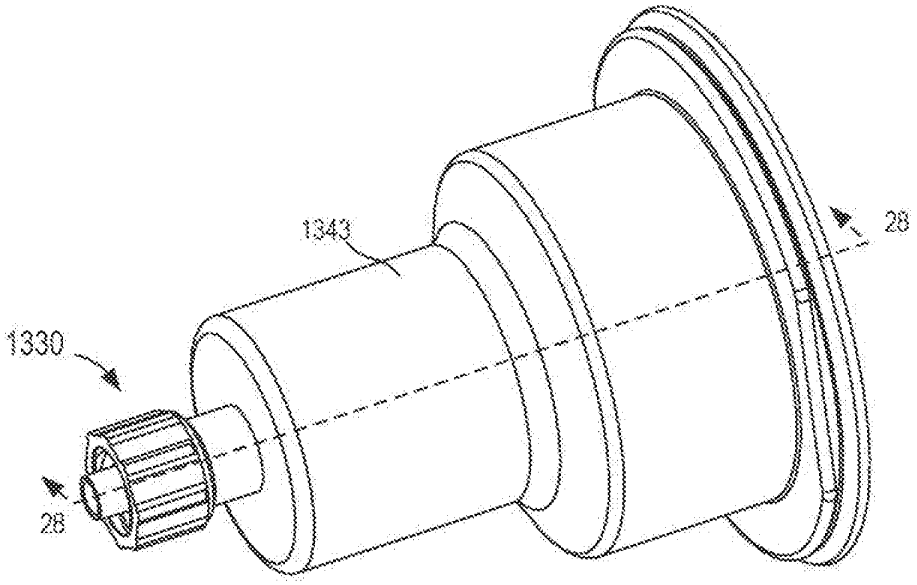


FIG. 27

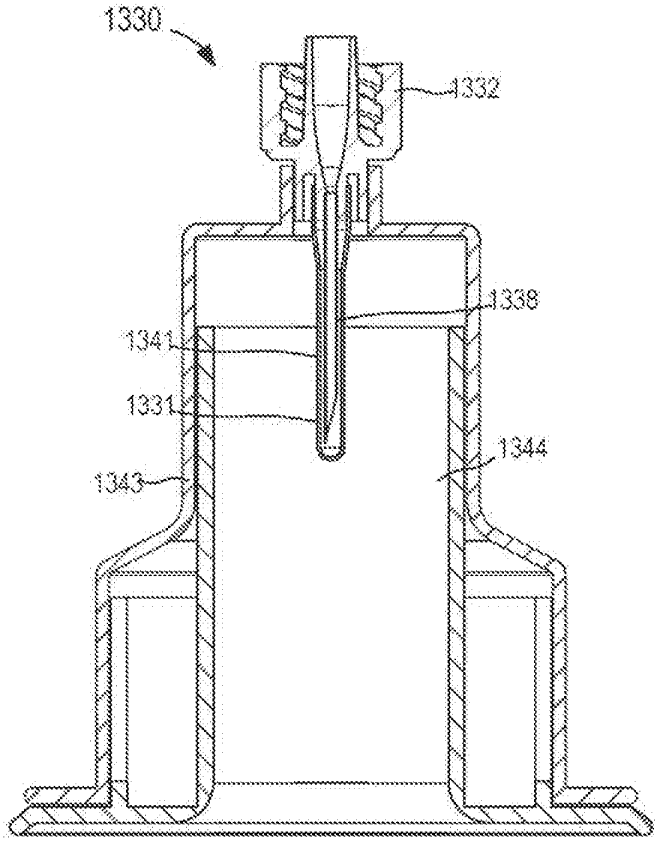


FIG. 28

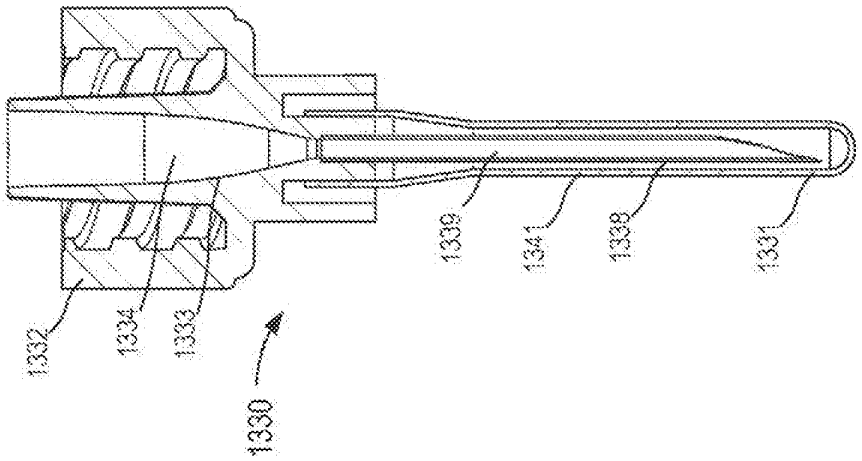


FIG. 30

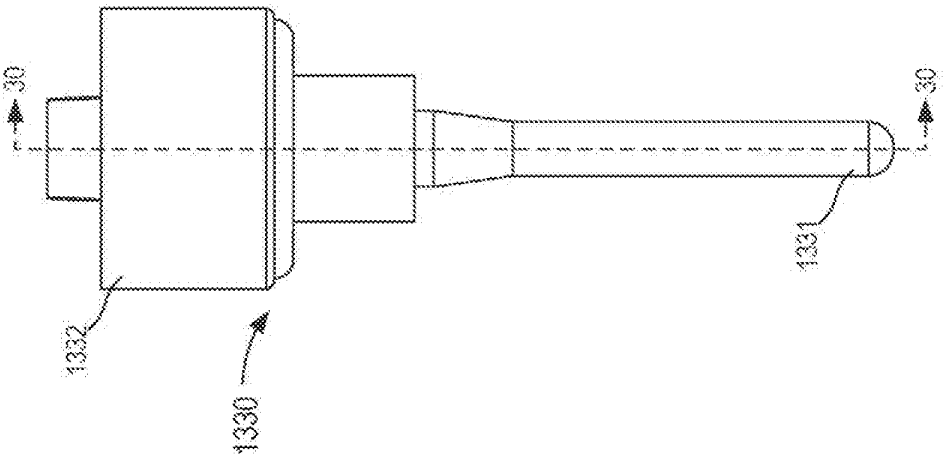


FIG. 29

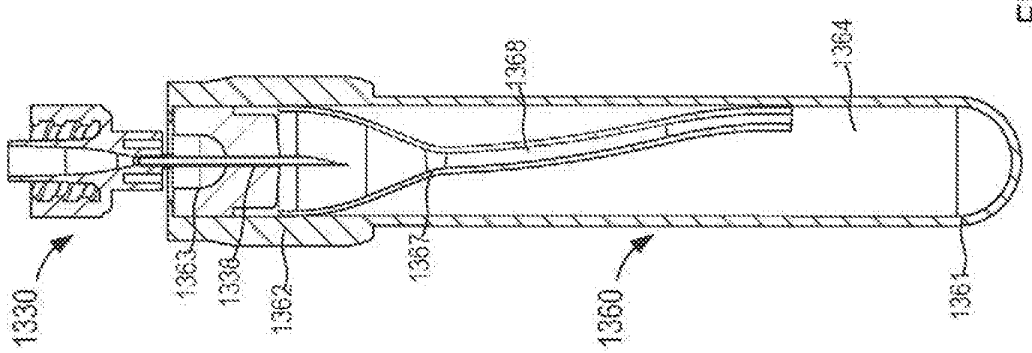


FIG. 33

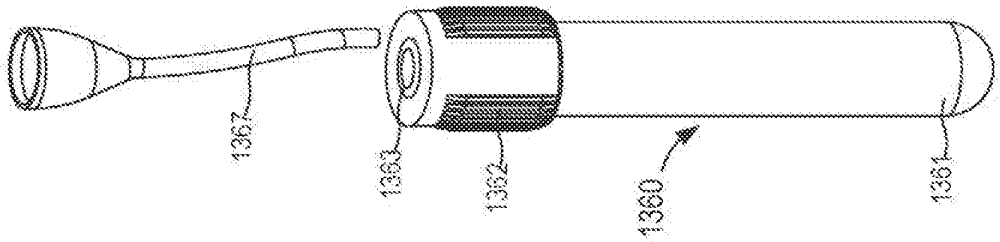


FIG. 32

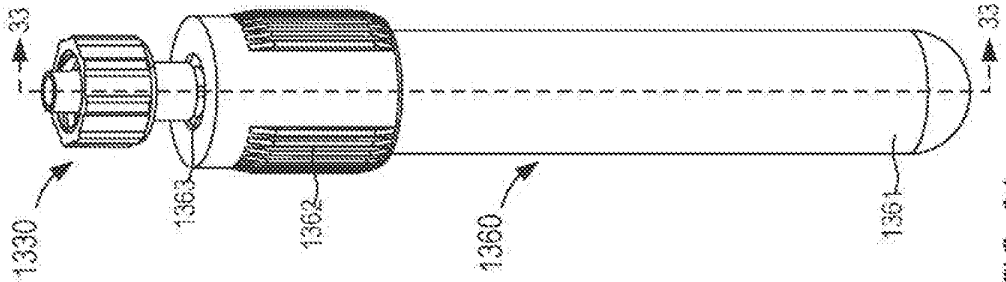


FIG. 31

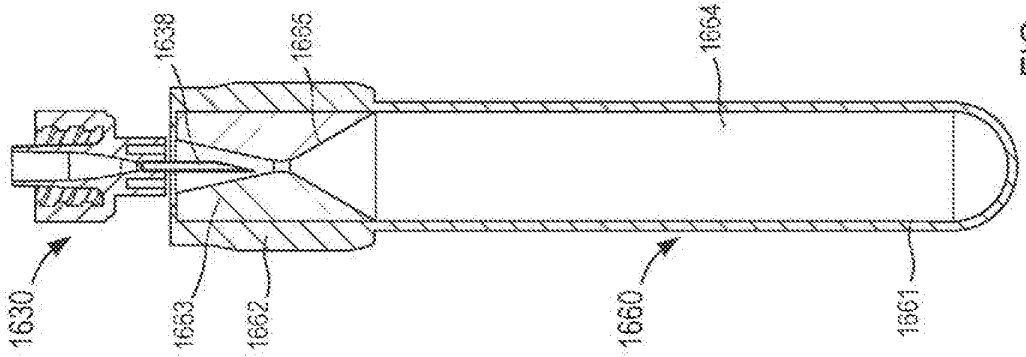


FIG. 36

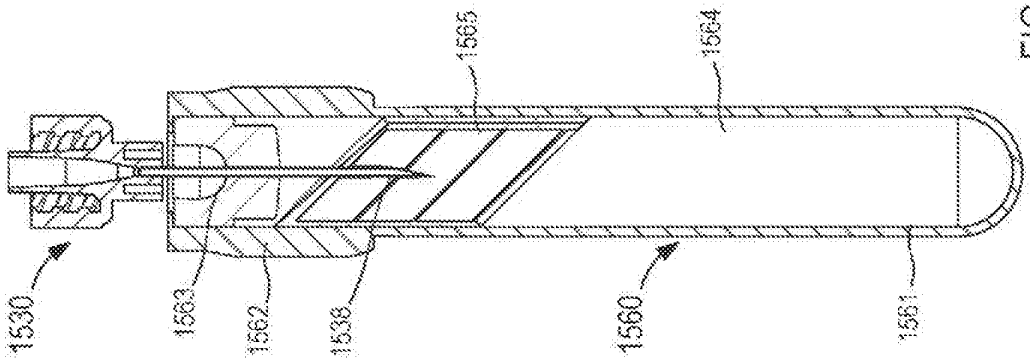


FIG. 35

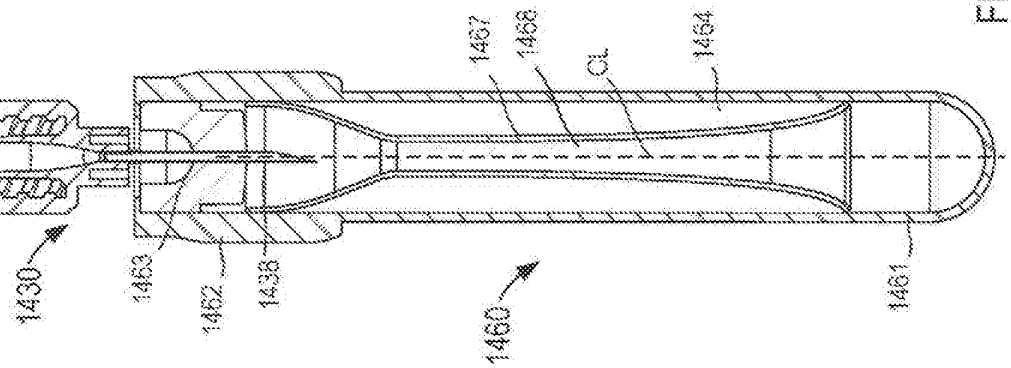


FIG. 34

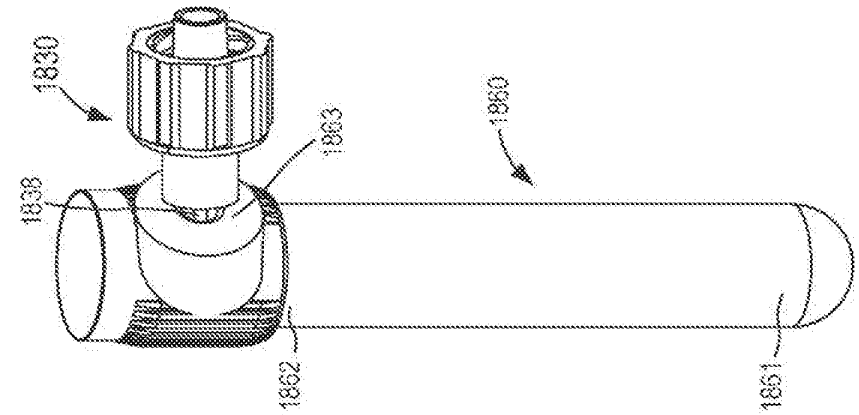


FIG. 39

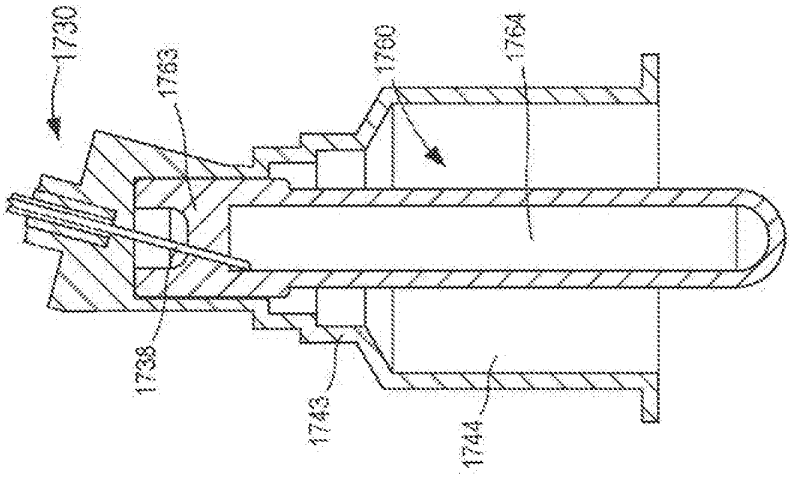


FIG. 38

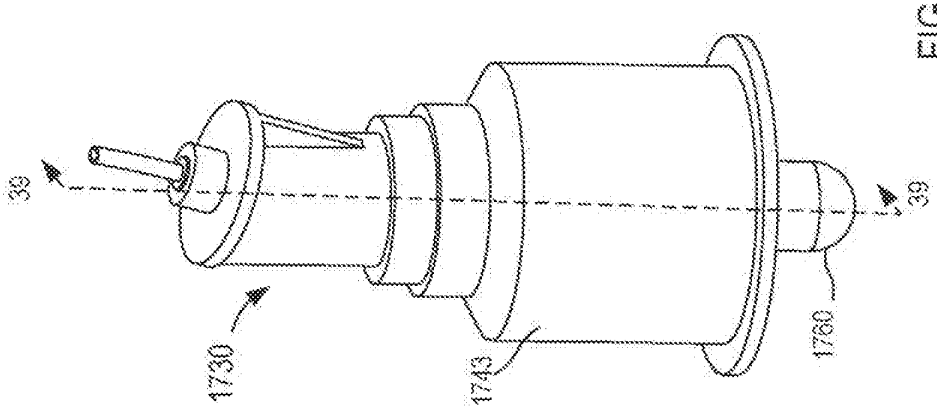


FIG. 37

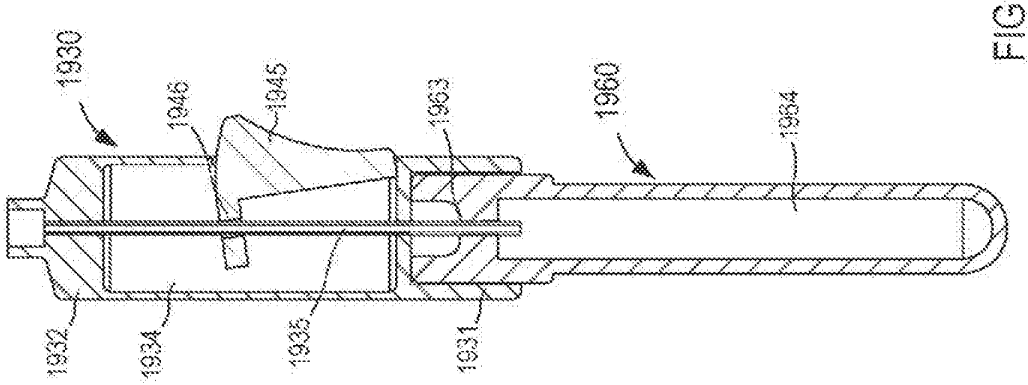


FIG. 42

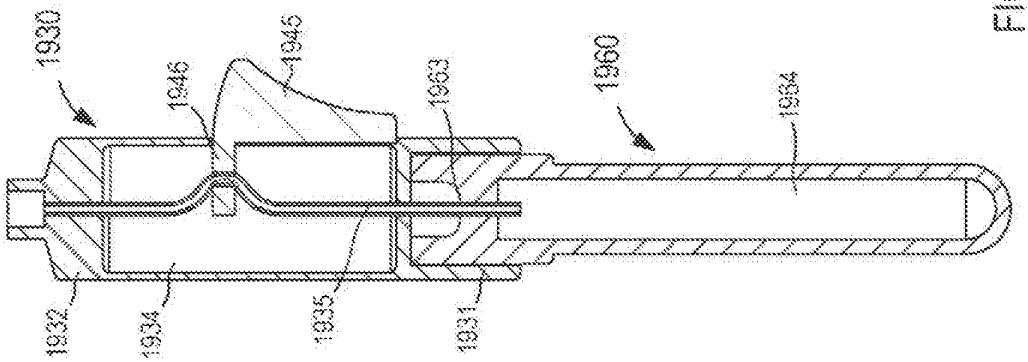


FIG. 41

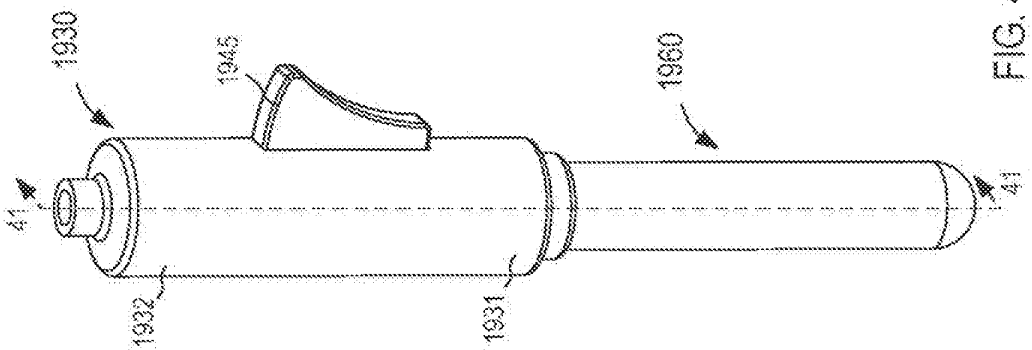


FIG. 40

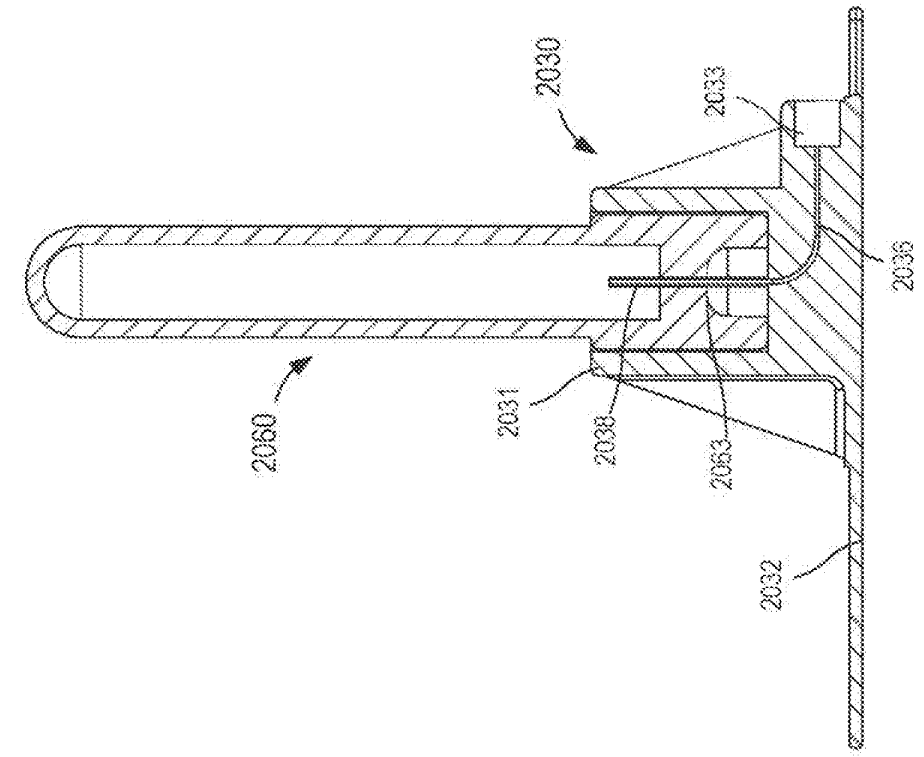

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FIG. 44

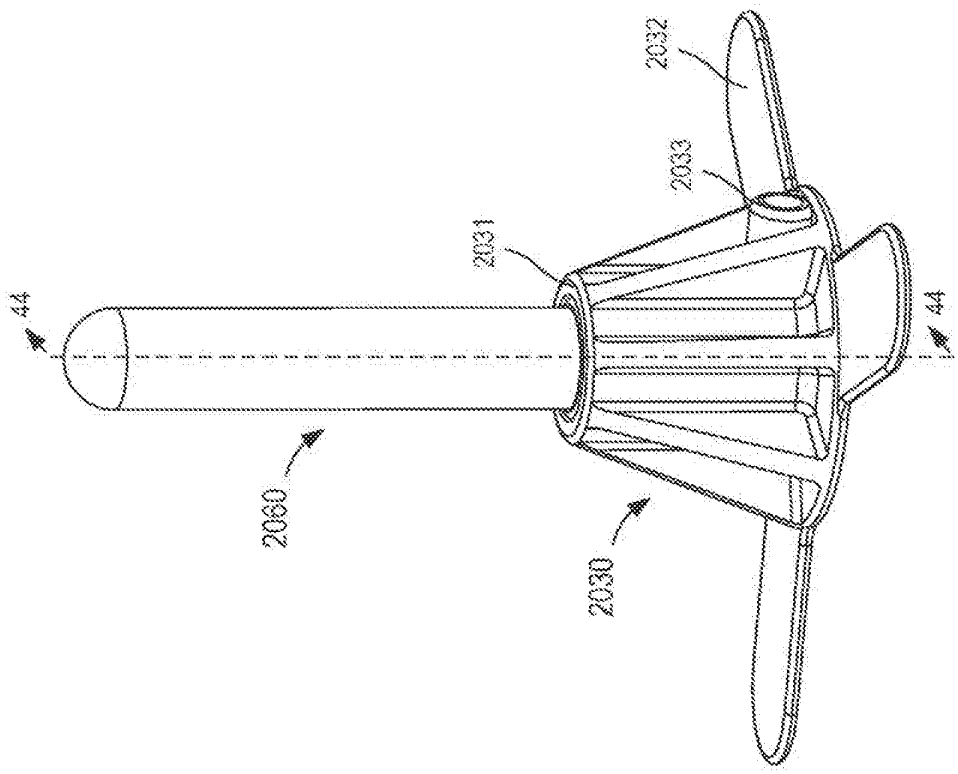

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FIG. 43

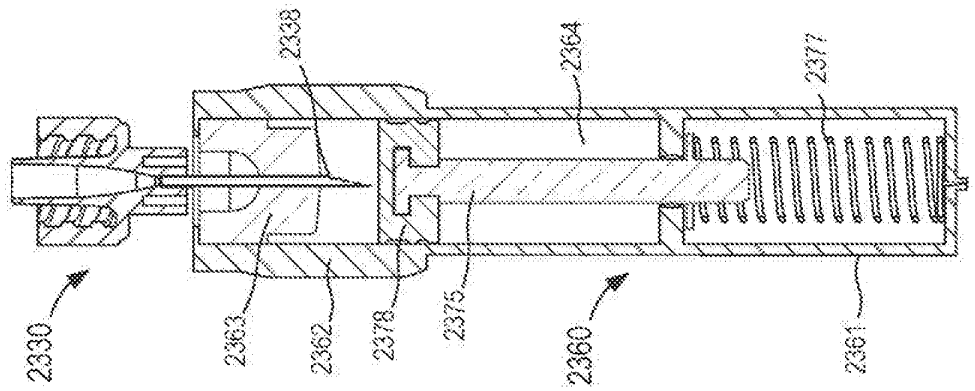


FIG. 47

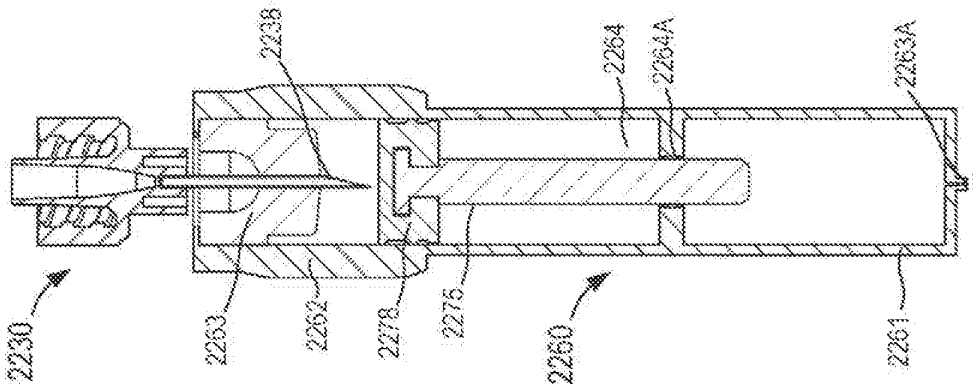


FIG. 46

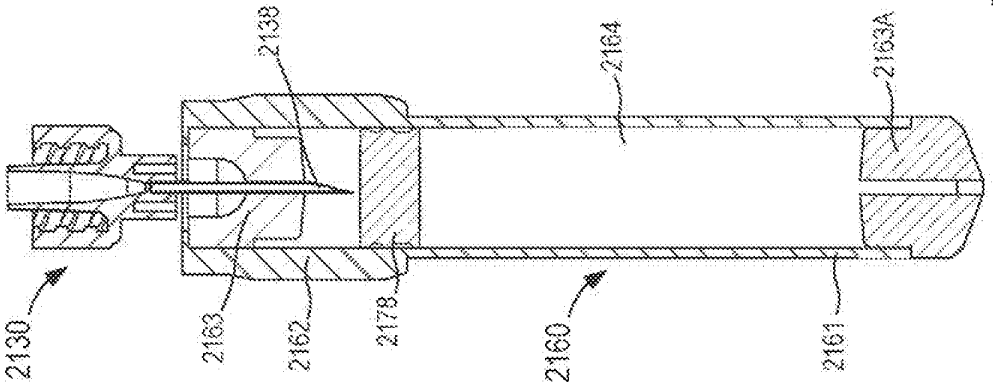


FIG. 45

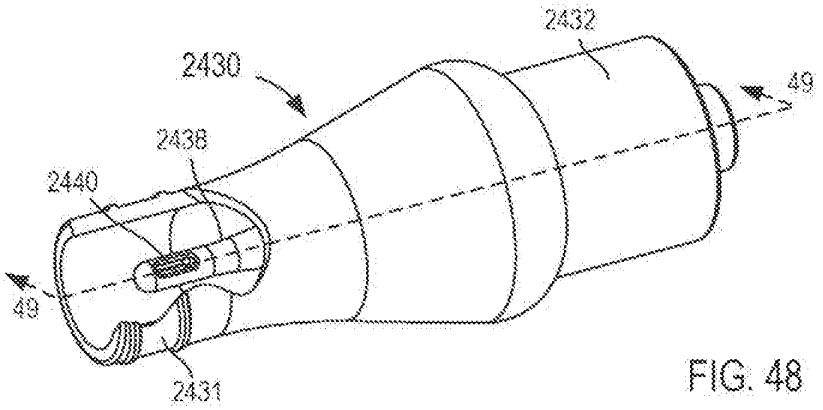


FIG. 48

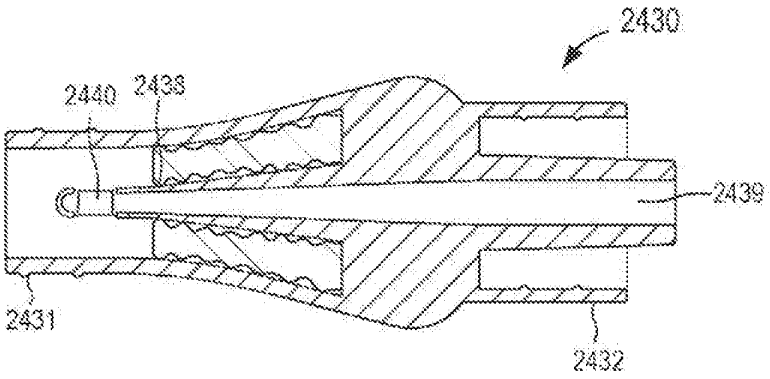


FIG. 49

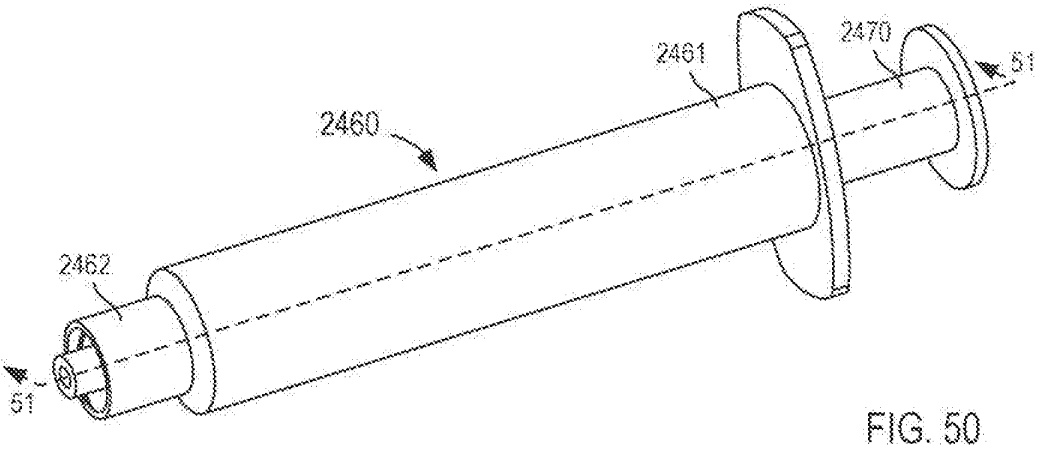


FIG. 50

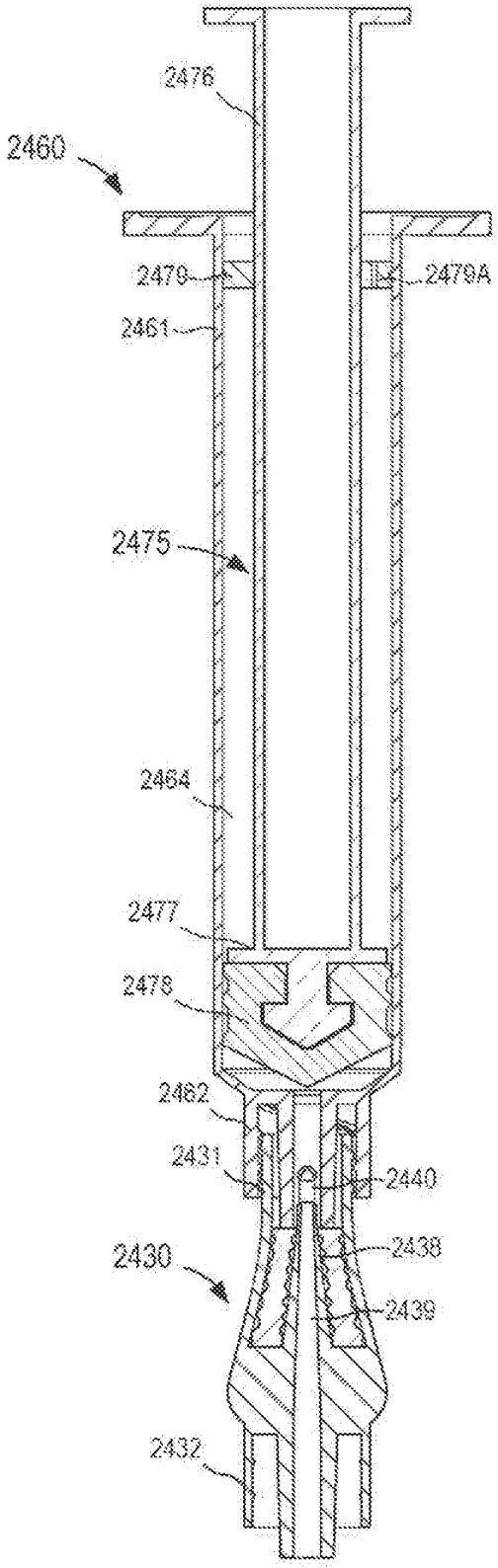

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FIG. 51

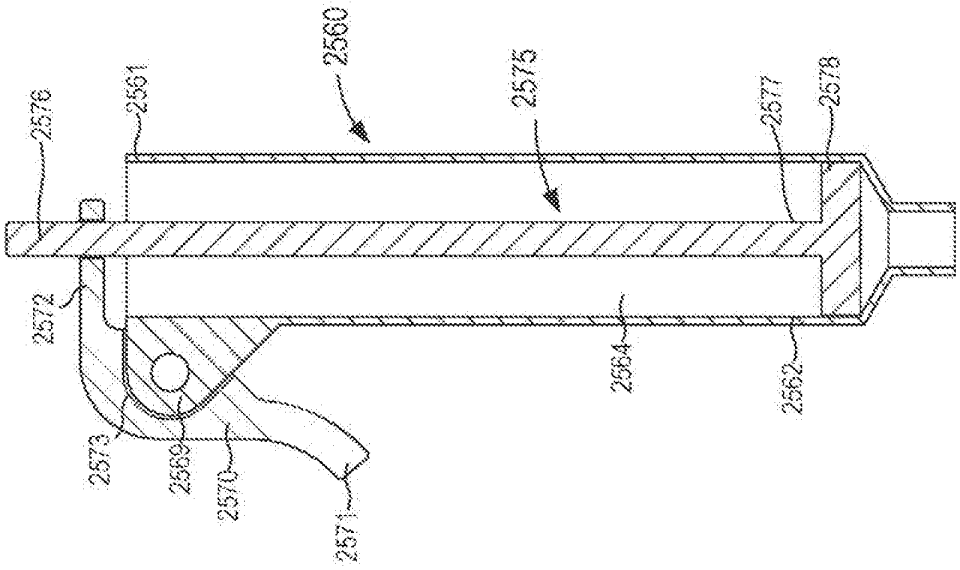

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FIG. 53

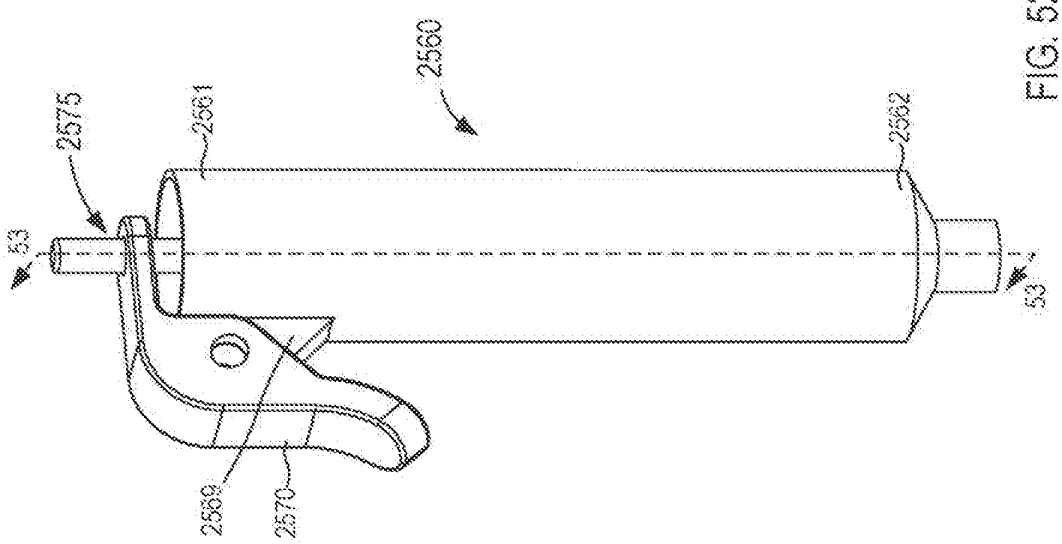

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FIG. 52

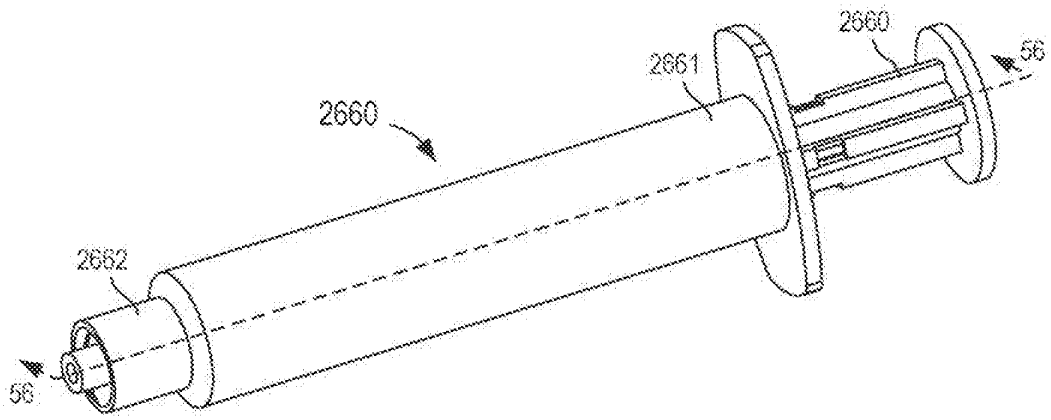

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FIG. 54

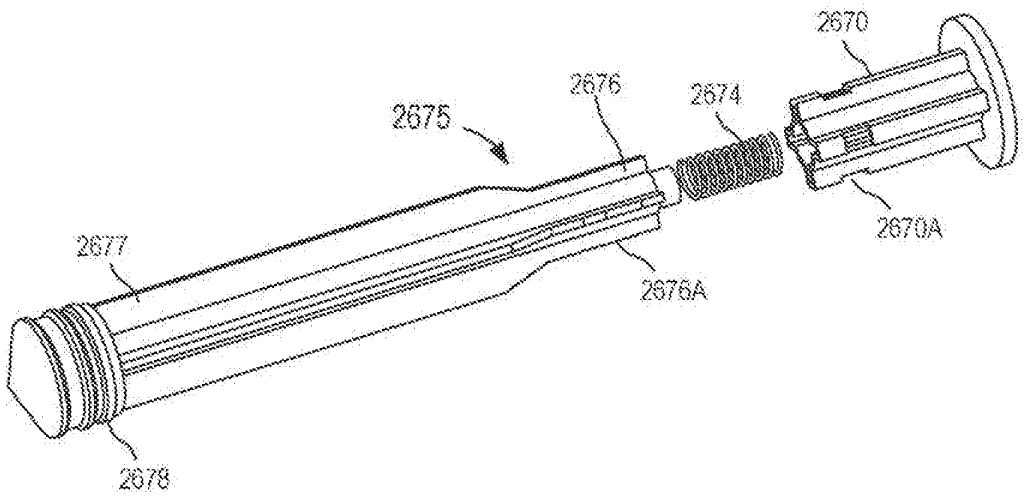

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FIG. 55

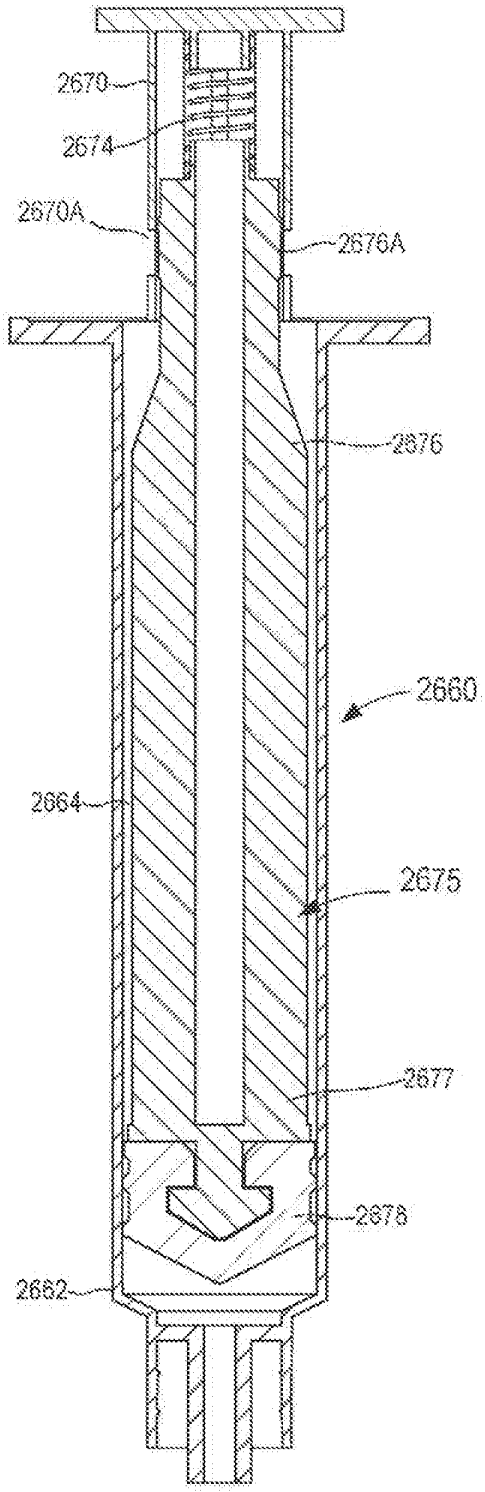


FIG. 56

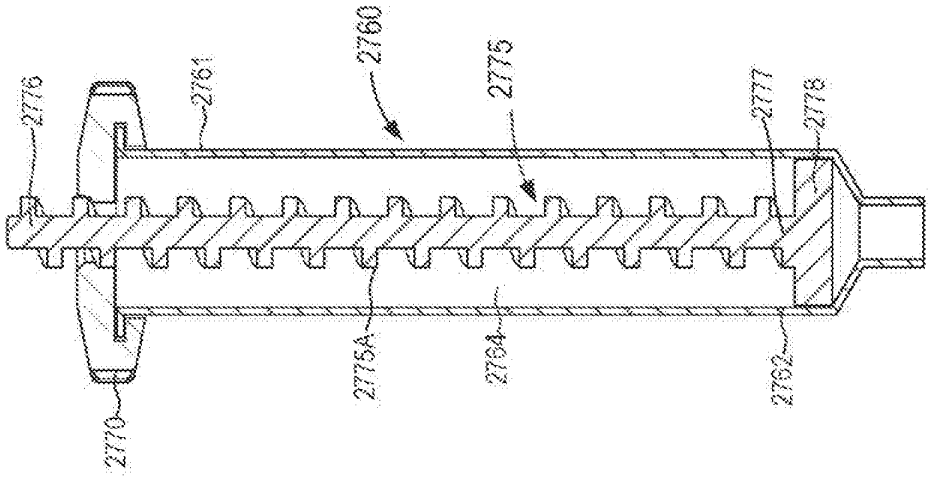

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FIG. 58

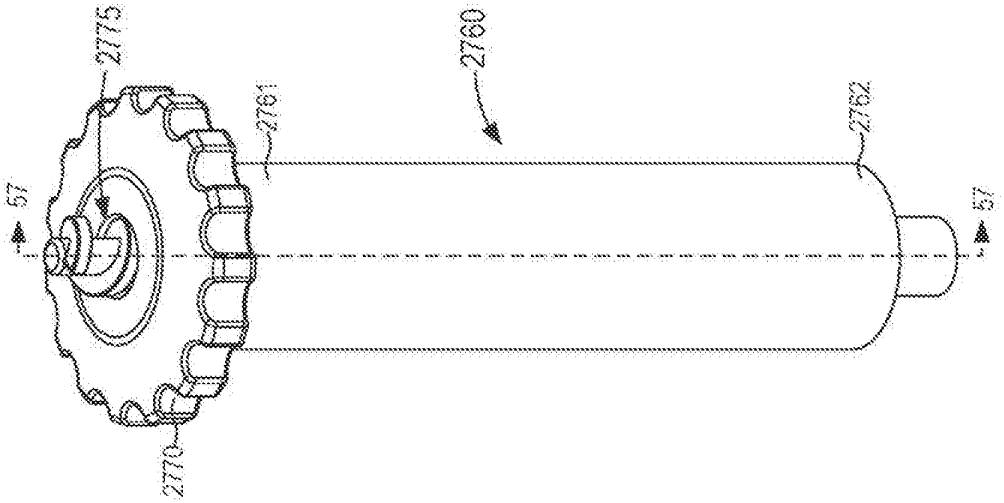

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FIG. 57

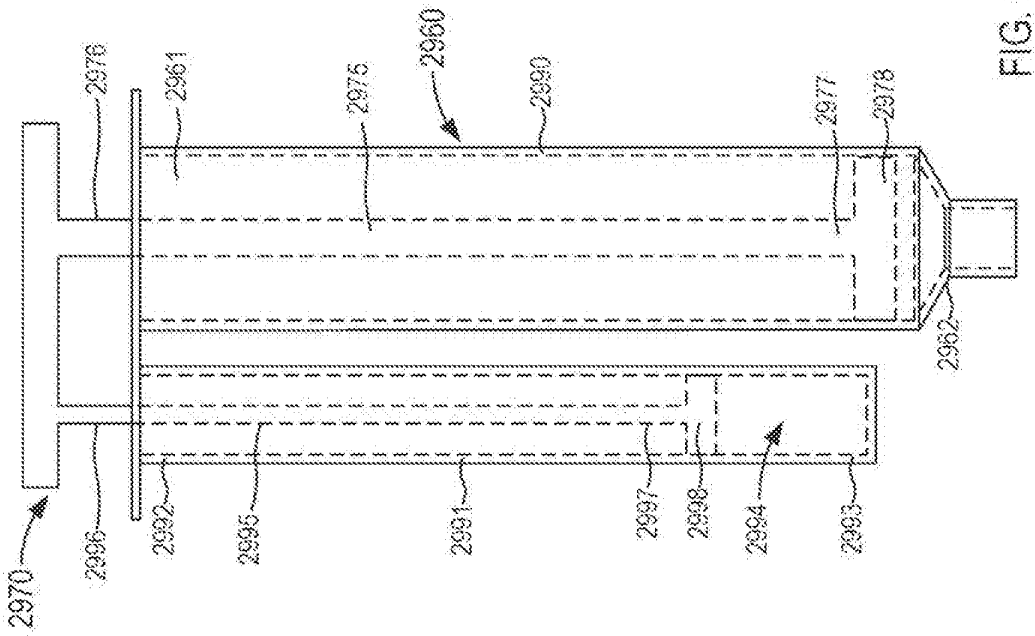

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FIG. 60

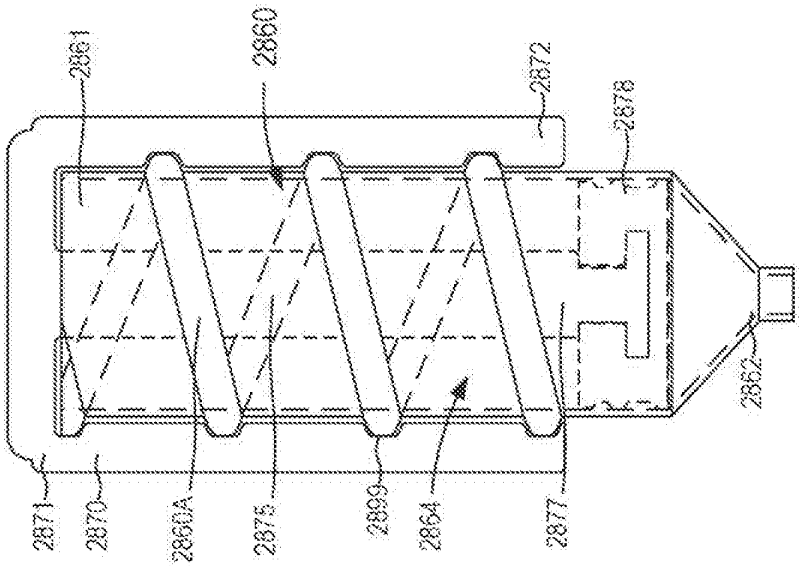

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FIG. 59

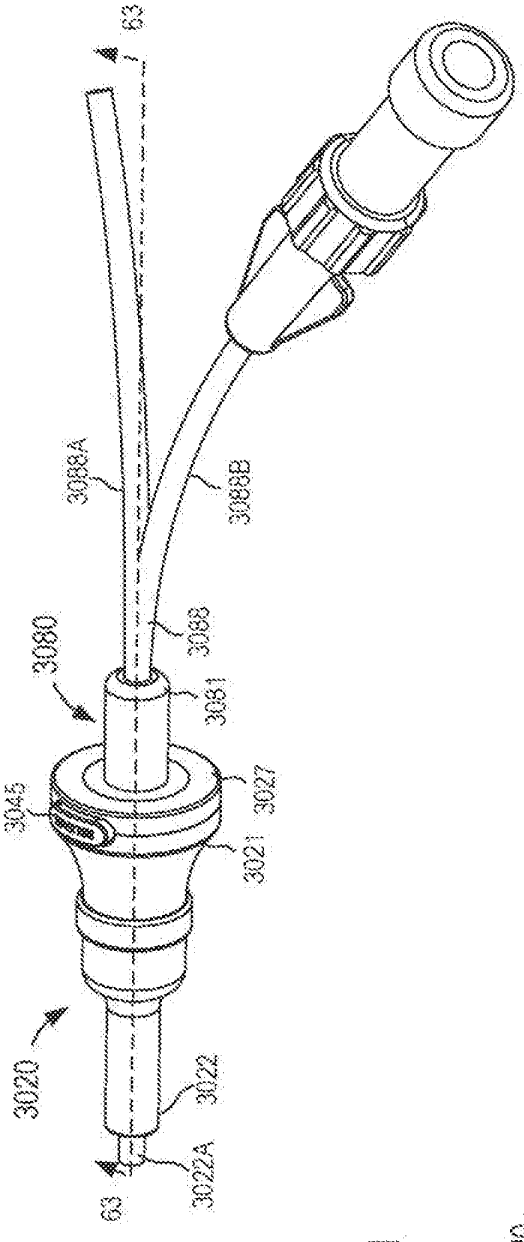

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FIG. 61

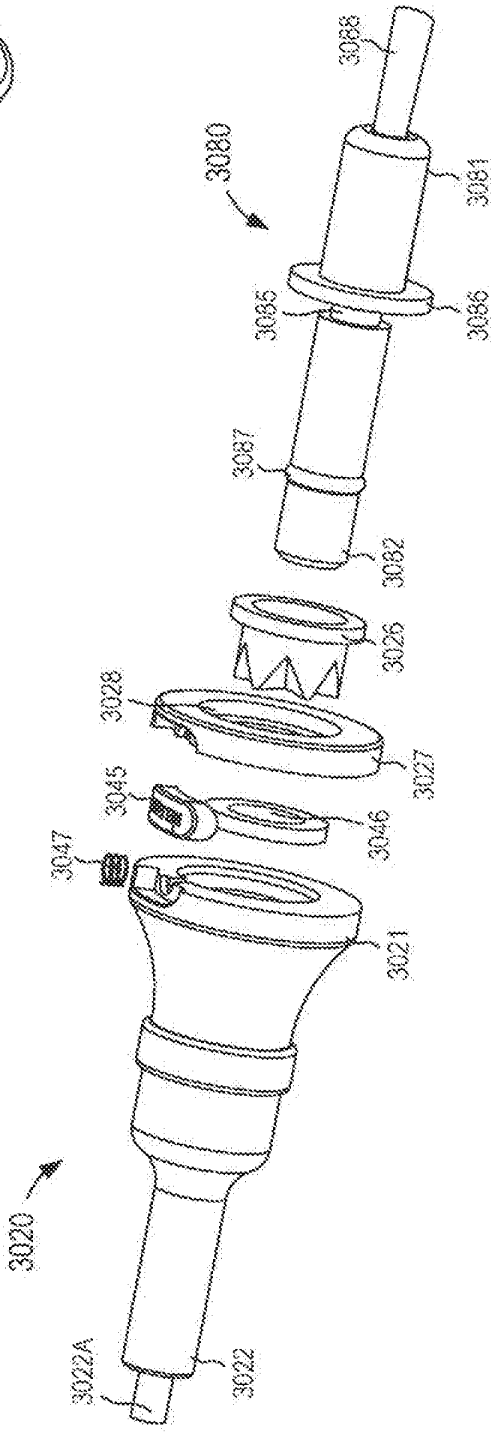

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FIG. 62

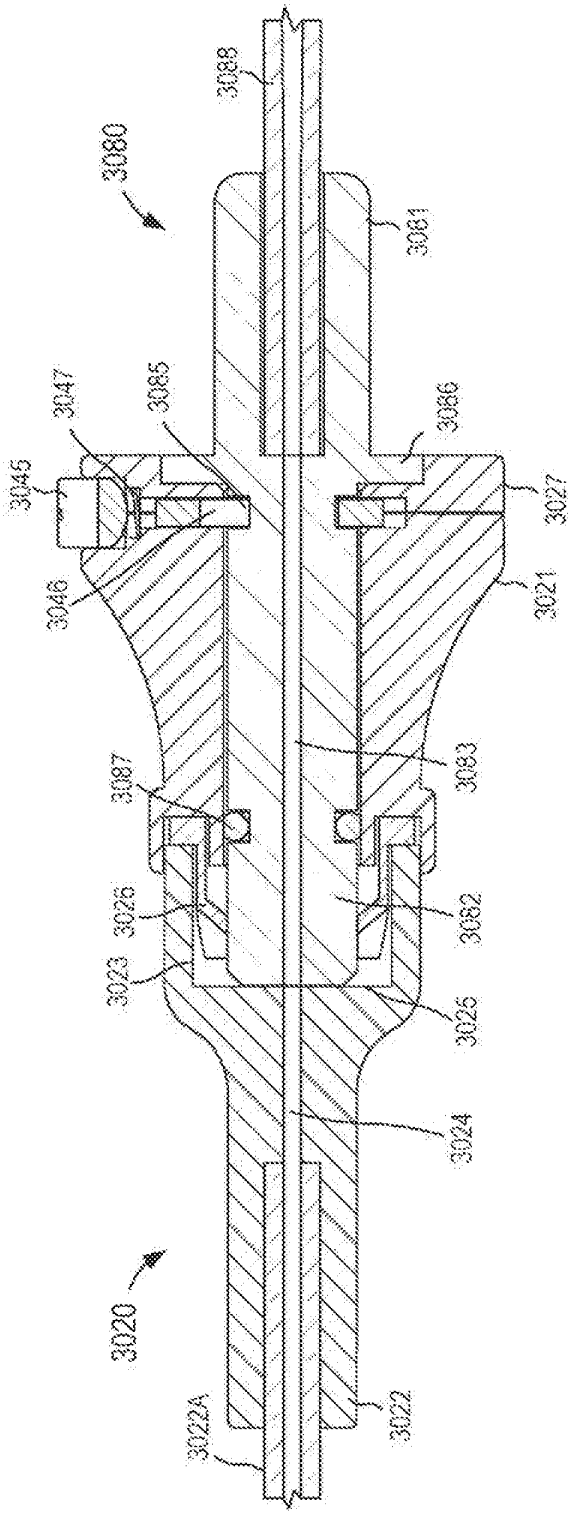

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FIG. 63

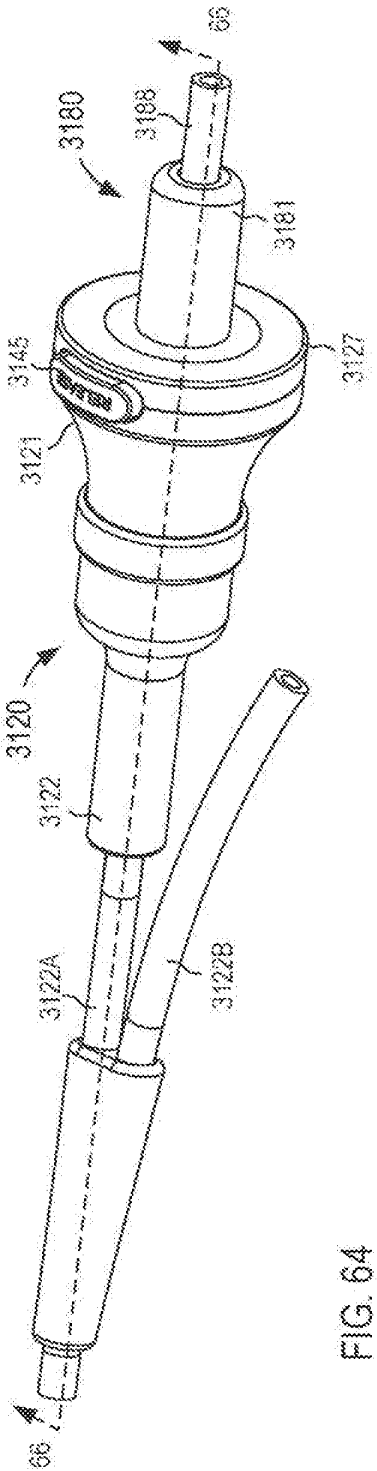

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FIG. 64

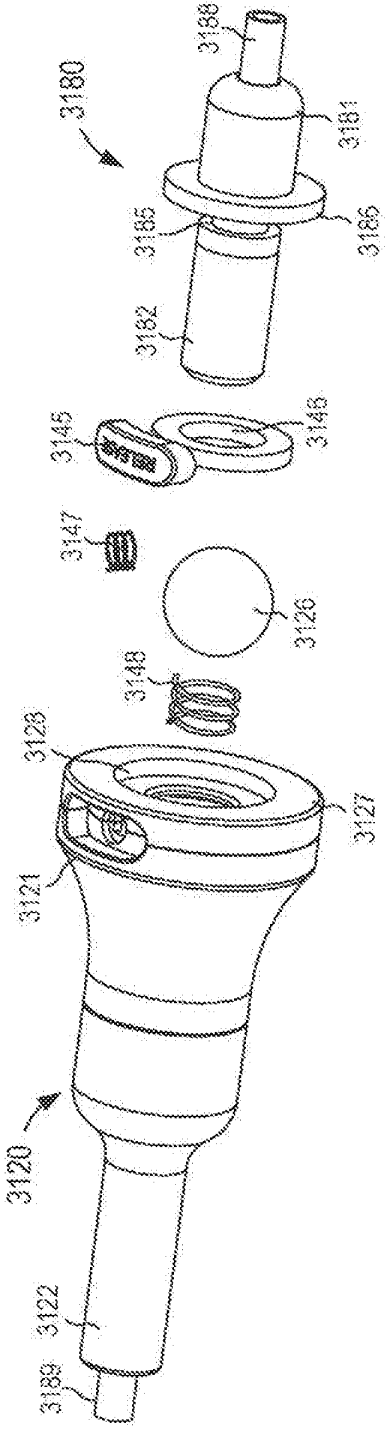

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FIG. 65

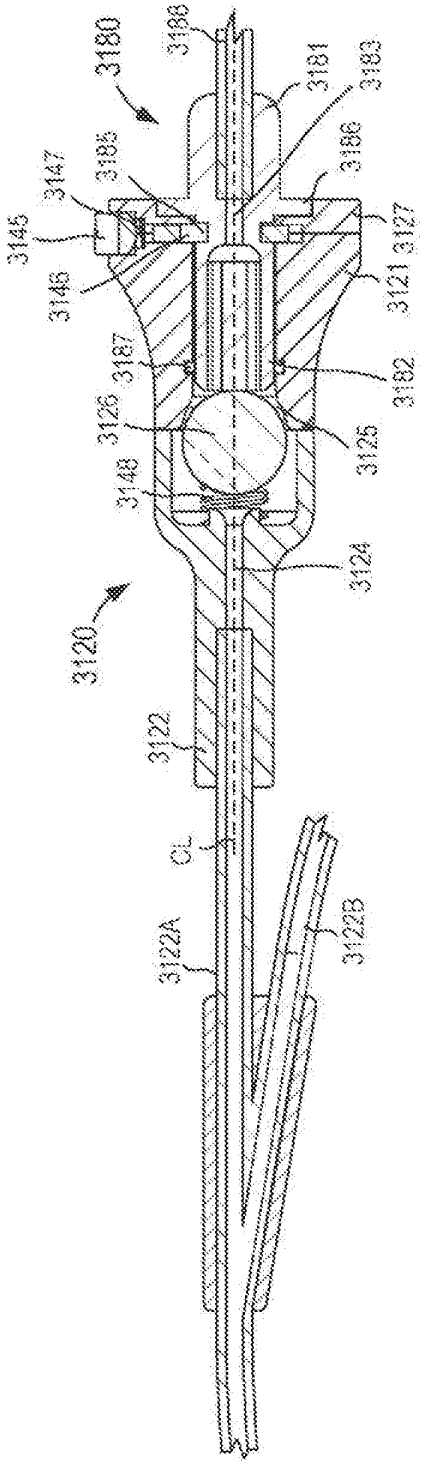

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FIG. 66

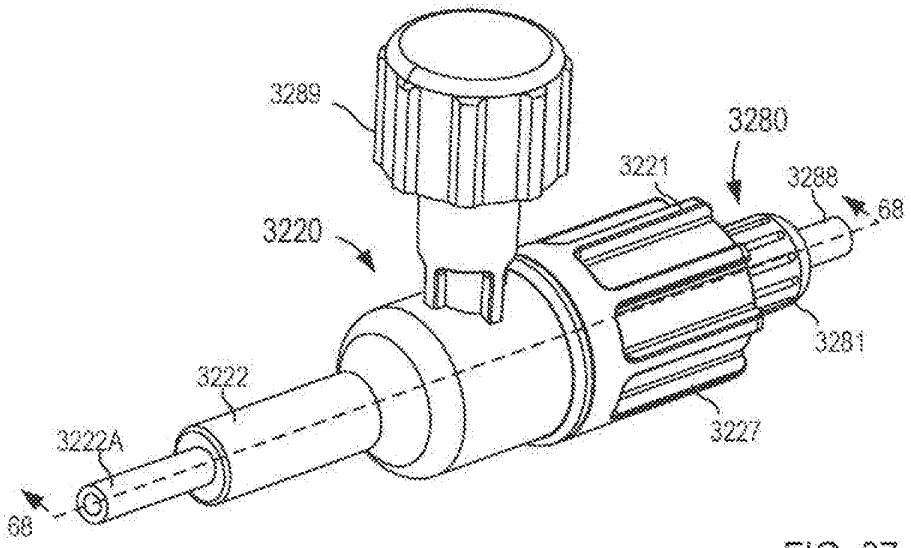

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FIG. 67

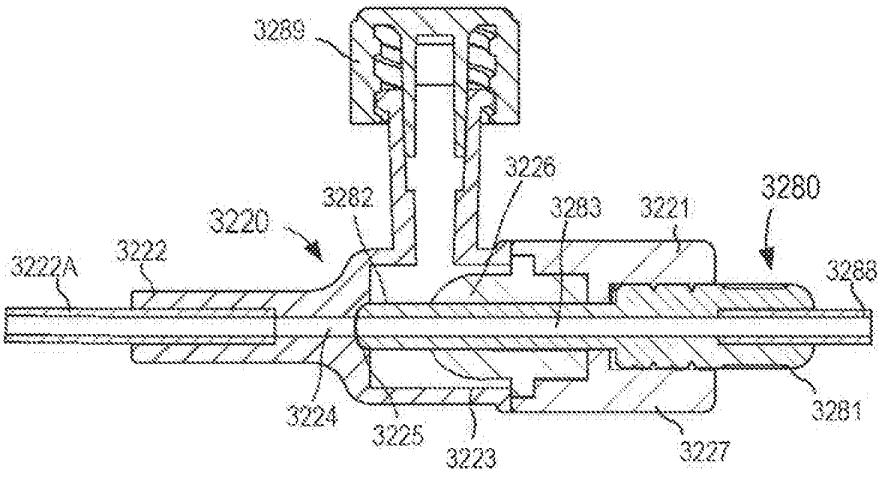

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FIG. 68

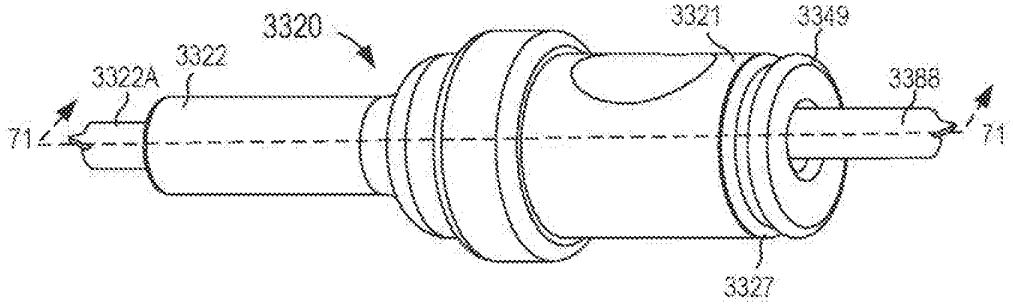

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FIG. 69

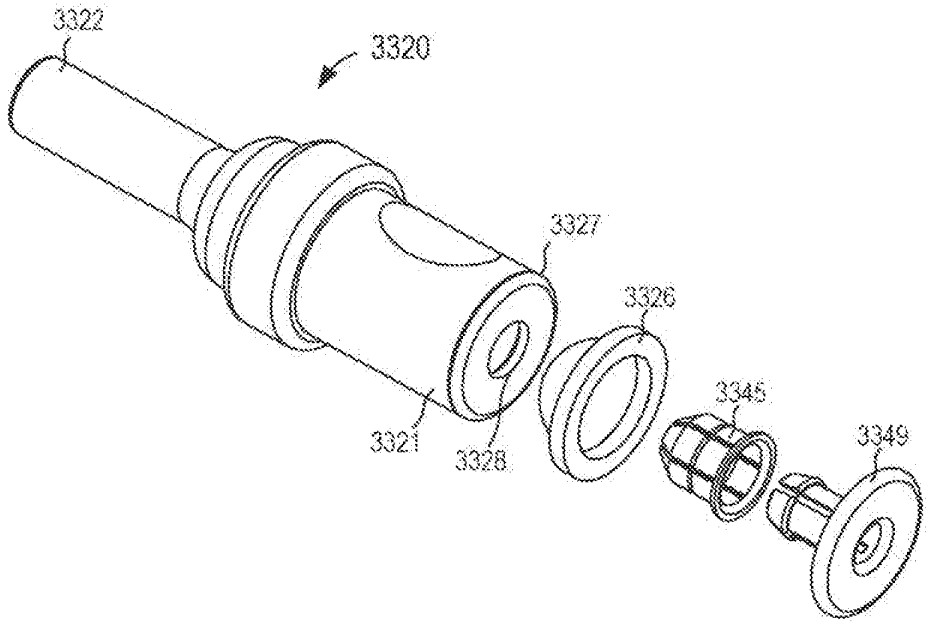

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FIG. 70

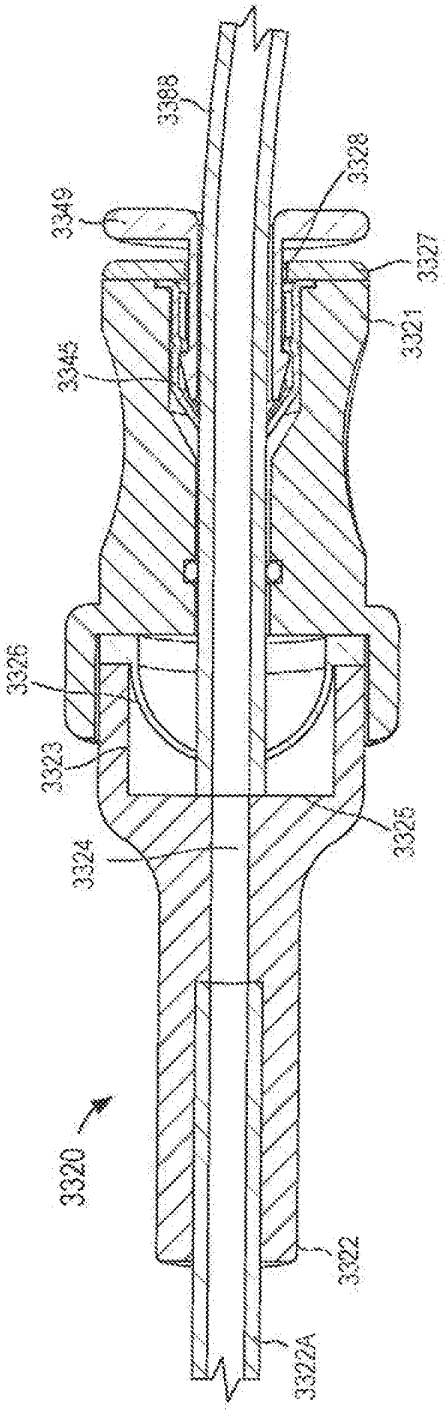

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FIG. 71

(1) Notify the designated first-aid trained personnel.

(2) Where practical, lay the patient flat or lower his/her head and arms, if the patient is sitting.

(3) Loosen tight clothing.

(4) The use of ammonia inhalants may be associated with untoward effects and is not recommended.

11.8.2 Nausea

The procedure for dealing with a patient who is experiencing nausea is to:

(1) Make the patient as comfortable as possible.

(2) Instruct the patient to breathe deeply and slowly.

(3) Apply cold compresses to the patient's forehead.

(4) Notify the designated first-aid trained personnel.

11.8.3 Vomiting

The procedure for dealing with a patient who vomits is to:

(1) Give the patient an emesis basin or carton, and have tissues ready.

(2) Give the patient water to rinse out his/her mouth.

(3) Notify the designated first-aid trained personnel.

11.8.4 Convulsions

The procedure for dealing with a patient who is having convulsions is to:

(1) Prevent the patient from injuring himself/herself. Do not restrain the movements of the patient's extremities completely, but try to prevent him/her from being injured.

(2) Notify the designated first-aid trained personnel.

11.8.5 Incident Reports

Incident reports should be filed according to institutional policy.

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NCCLS consensus procedures include an appeals process that is described in detail in Section 8 of the Administrative Procedures. For further information, contact the Executive Offices or visit our website at www.nccls.org.

Summary of Comments and Subcommittee Responses

H3-A4: *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fourth Edition*

General

1. NCCLS has inconsistencies in their own publications (H3 and H21) when it comes to the order of draw for coagulation testing relative to tissue thromboplastin contamination and procurement of a "discard tube." In performing intra-laboratory studies at our institution and sister institutions, results showed no significant clinical or statistical significance on any of the assays between each of the specimen tubes performed at each individual laboratory. Also, our results indicated that NCCLS guidelines for obtaining a second tube when performing coagulation testing should be eliminated when the revised document is published.

- **The text has been revised (see Section 8.10.2), including the order of draw, and several notes have been added to address the use of discard tubes for coagulation test collection. The next version of H21—*Collection, Transport, and Processing of Blood Specimens for Coagulation Testing and General Performance of Coagulation Assays* is due to be released by the end of 2003. The documents are now consistent.**

Section 7.9.3.4, Intravenous Therapy (Now Section 8.6.7.4)

2. The text of this section states, "Optimally, specimens should not be collected from an arm with an intravenous site. If this is impossible the attending physician should be consulted (see Section 10.3). Blood should never be collected from above any active intravenous site (see Section 10.6). We would like a clearer definition of what is considered to be "active." What defining factors are present that would classify an "active" intravenous site?

- **The term "active" has been removed from the text. The text in Sections 8.6.7.4 and 11.6 has been revised to describe the procedure for specimen collection in relation to intravenous fluids.**

Section 7.13.3.3, Coagulation Testing (Now Section 8.10.3)

3. The text of this section states, "if only a coagulation tube is drawn for routine coagulation testing (APTT and PT tests) the first tube drawn may be used for testing." This statement has raised some discussion regarding the definition of the phrase "routine coagulation testing." Does this include coumadin patient samples?

- **Specimens collected from patients on warfarin sodium (Coumadin™) are considered for routine coagulation testing.**

Section 10, Special Situations (Now Section 11)

4. H3-A4 does not list recommendations for obtaining venipuncture specimens during blood transfusions. Information on this topic would be greatly appreciated.

- **The directions outlined in Section 11.6 should be followed during transfusions as it is described for intravenous fluids.**

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Summary of Delegate Comments and Working Group Responses

H3-A5: *Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture; Approved Standard—Fifth Edition*

General

1. Nothing was included about pain management (EMLA, coldspray, etc.) or age-specific consideration on developmental stages of children. I can send you what we have if you like.

- **The working group recognizes the availability of pain reducing techniques. Topical sprays and treatments are available and are used at the discretion of each institution.**

  Age-specific considerations are outside the scope of this document. Please refer to the current edition of NCCLS document H4—*Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture.*

2. Add a Section 11.2.6, RNA Specimen. Since RNA is unstable, the whole blood should be transported to the laboratory at 2 to 25 °C within six hours of collection.

   References: de Gerbehaye A-I, et al. Stable hepatitis C virus RNA detection by RT-PCR during four days storage. *BMC Infectious Diseases.* 2002;2:22, and Halfon P, et al. Impact of various handling and storage conditions on quantitative defection of hepatitis C virus RNA. *J Hepatol.* 1996;25:307-311.

- **This comment is more related to specimen handling than collection and is beyond the scope of this document. This comment will be considered during the revision of NCCLS document H18-A2—*Procedures for the Handling and Processing of Blood Specimens; Approved Guideline.***

Foreword

3. Page vii should include hemolysis and clotting of samples, as these are common problems with hematology or coagulation samples. "The errors that can occur during the collection and handling of blood specimens are potentially numerous (e.g., inaccurate identification of specimens, the use of incorrect anticoagulant, the formation of hematomas, hemoconcentration)."

- **The text has been revised to include specimen hemolysis and improper handling of anticoagulants.**

Section 8, Venipuncture Procedure

4. Consider switching steps 14 and 15 so that bandaging occurs after specimens are labeled, not before. This helps assure that specimen labeling will occur before leaving the patient's side. It also accommodates situations in which the patient assists in applying pressure while the phlebotomist labels tubes.

- **The working group appreciates the comment; we believe, however, that the order is correct as written. The text in Section 8.15 emphasizes the need to label the tube before leaving the side of the patient.**

5. Between steps 5 and 6, add the following: "Inquire as to patient's sensitivity to latex products." Step 7, change as follows: "Put on appropriate gloves based on patient's response to Step 6."

- **The working group agrees with the comment. The text of step 3 has been revised as follows: "Verify patient's diet restrictions, as appropriate, and inquire if the patient has a latex sensitivity. Select appropriate gloves and tourniquet."**

6. Modify step 6 to new "step 6: Inquire on patient's allergy to latex products." Also add: "Due to the prevalence of latex sensitivity, the phlebotomist should inquire as the patient's sensitivity to latex products (tourniquet and gloves.)"

- **The text of Step 3 and Section 8.3 has been revised to include asking the patient if he/she has a latex sensitivity. The text in Section 8.6 has been revised to refer the reader to Section 7.7.**

7. The patient should be asked to open his/her hand just when entering the vein, therefore eliminating some of the pain a tense closed fist may cause. Also, recommend performing venipuncture using the correct order of draw.

- **In response to this comment, the text of step 9 has been revised as follows: "Perform venipuncture; once blood flow begins, request patient to open hand." Step 10 has been revised to recommend the use of the correct order of draw.**

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8. Following the removal of the needle, pressure should be applied to the venipuncture site (either by the patient or phlebotomist).

- **In response to this comment, the text of step 14 has been revised as follows: "Apply pressure to the site, making sure bleeding has stopped, and then bandage the arm."**

Section 8.1.1, Information for Test Request Form

9. "May include" should be utilized.

- **The working group believes that the test request form information listed should be included.**

Section 8.1.2, Accessioning Blood Bank Specimens

10. Neither AABB nor CAP requires "time of collection" on the specimen tube label.

- **Time of collection is important for some specimens (e.g., therapeutic drug monitoring). The subcommittee confirmed that AABB does not require "time of collection" on the specimen tube label. The text, "Blood bank specimens must be labeled according to the standards set by the American Association of Blood Banks (AABB)," has been incorporated into Section 8.15, Label Blood Collection Tubes and Record Time of Collection. The remainder of Section 8.1.2 has been deleted.**

11. This passage is more about patient identification and labeling specimens than accessioning. Passages are important, but seem out of place. Consider moving the passage on identifying blood bank patients to Section 8.2 ("Step 2: Approach and Identify the Patient.") and the passage about labeling to Section 8.15 ("Step 15: Label Blood Collection Tubes and Record Time of Collection").

- **See response to comment 10.**

Section 8.2.3, Patient Who Is Semiconscious, Comatose, or Sleeping

12. This passage does not address identification and is out of place. Consider moving to Section 8.5.4.

- **The location of this text is appropriate. Section 8.2 addresses both approaching and identifying the patient. The following has been added to the end of the paragraph: "If unable to identify the patient, then contact the nurse or physician."**

Section 8.2.4, Patient Who Is Unconscious, Too Young, Mentally Incompetent, or Does Not Speak the Language of the Phlebotomist

13. The first bullet states, "Ask the nurse, a relative, or a friend to identify the patient by name, address, and identification number and/or birth date." This is inconsistent with Section 8.2.2, re: asking for patient's address and identification number. Suggest changing "and" to "or" for consistency with step 1 of 8.2.2.

- **The text in Section 8.2.4 has been revised for consistency with Section 8.2.2.**

Section 8.4.1, Supplies

14. "Inspect all supplies for possible defects" should include inspection of expiration dates on blood collection tubes.

- **The text has been revised to include applicable expiration dates during inspection of supplies.**

15. Supplies, sharps, or other disposal container is missing from the list (as discussed in Section 8.13). This should be available at the bedside for safe disposal.

- **The following bullet point has been added to the list: "Sharps container, consistent with OSHA regulations."**

16. Supplies such as tubes and needles should be checked before use to ensure they are not outdated. Sterile conditions or tube vacuum could be lost in old supplies. NCCLS document H4-A discusses tube stability and dating; H1-A4 discusses expiration date. Therefore, this step should be added to the collection procedure.

- **See response to comment 13.**

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Section 8.6.3, Blood Pressure Cuff

17. In Section 7.7 the blood pressure cuff is said to be inflated to 40 mmHg. However, in Section 8.6.3 it is said that a blood pressure is taken first (an activity performed by NO phlebotomists I know) and maintained below the diastolic pressure of the patient. I would recommend using the specific 40 mm Hg found in Section 7.7 and replace the language in Section 8.6.3 with the same.

- **The text has been revised as recommended. The following text has been added to replace the previous text: "If a blood pressure cuff is used as a tourniquet, inflate it to 40 mm Hg."**

Section 8.6.5, Select Vein

18. "Brachial" is misspelled in Figure 1.

- **The spelling error in Figure 1 has been corrected.**

Section 8.7, Step 7: Put on Gloves

19. Step 7: Add the following after the existing sentence: "…is performed. The type of gloves (latex, vinyl or nitrile) used for venipuncture will depend on the patient's and/or phlebotomist's sensitivity to latex products." General note—As both a patient and laboratorian, I know the importance of covering the issue of latex sensitivity with both patients and the phlebotomists. I highly recommend that you incorporate the information presented here into the document.

- **The text has been revised as follows: "The phlebotomist must put gloves on before the venipuncture is performed, for each patient, with consideration for latex sensitivity as discussed in Section 7.3."**

Section 8.9.1, Venipuncture Procedure When Venous Blood Collection Tubes Are Used

20. The illustration on page 14 is very primitive and would be improved if the proper angle included a view of the needle bevel up just as the needle enters the skin.

- **The illustrations (Figures 2 and 3) have been replaced with comparable photographs.**

Section 8.9.3, Fill the Tubes If Syringe and Needle Are Used

21. The third bullet suggests a straight needle be applied to the syringe after removing the winged collection set. Consider substituting "attach a 19- to 21-gauge sterile needle" with "attach a safety transfer device."

- **The text of the third bullet has been revised as follows: "To transfer the blood from the syringe to a venous blood collection tube, activate the safety feature of the needle or winged blood collection set used to withdraw the specimen, remove and discard the needle or winged collection set, and apply a safety transfer device."**

22. The fourth bullet seems to define the third bullet. Consider combining the two.

- **The working group agrees with the comment and has deleted the fourth bullet.**

23. The fifth bullet is not necessary in light of the third bullet. If standards are being followed, a transfer device protects the user, and holding the tubes should be safe.

- **The fifth bullet has been deleted as suggested.**

Section 8.9.4, Blood Specimen That Cannot Be Obtained

24. Consider making the passage about trying another tube into a bullet. Consider differentiating between probing and a calculated needle relocation in an additional bullet so that the section is rewritten as follows:

    ► Try another tube to ensure the tube selected is not defective.
    ► Change the position of the needle. If the needle has penetrated too far into the vein, pull it back a bit. If it has not penetrated far enough, advance it farther into the vein. Rotate the needle half a turn.
    ► Lateral needle relocation should be attempted only if the phlebotomist has a high degree of confidence that so doing will access the vein successfully without risking injury to the patient. Lateral needle relocation should never be attempted in an effort to access the basilic vein, since nerves and the brachial artery are in close proximity.

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- ► Manipulation other than that recommended above is considered probing. Probing is not recommended. Probing is painful to the patient. In most cases, another puncture in a site below the first site (or use of another vein on the other arm) is advisable.
- ► It is not advisable to attempt a venipuncture more than twice. If possible, have another person attempt to draw the specimen or notify the physician.

- **The following text has been added to the first bullet point: "Lateral needle relocation should never be attempted in an effort to access the basilic vein, since nerves and the brachial artery are in close proximity."**

Section 8.10.2, Glass and Plastic Venous Blood Collection Tubes

25. Consider deleting tube 4: gel serum separator tube. Since gel does not carryover, its presence or absence should not affect the order of draw. It seems more fitting for the second italicized paragraph to immediately follow the order of draw than the first paragraph.

- **Gel serum separator tube has been deleted from the fourth position on the order of draw. The third position has been revised as follows: "Serum tube with or without clot activator, with or without gel (e.g., red closure)."**

  The italicized paragraphs have been reorganized as suggested; the note regarding the revised order of draw appears immediately following the order of draw.

Section 8.13, Step 13: Remove and Dispose of the Needle

26. Removal of a needle (after the safety feature is activated) is necessary and acceptable to OSHA if applying a safety transfer device. Consider modifying to read: "Needles should not be resheathed, bent, broken, or cut, nor should they be removed from disposable syringes unless attaching a safety transfer device…"

- **The text of the third sentence has been revised as follows: "Needles should not be resheathed, bent, broken, or cut, nor should they be removed from disposable syringes unless attaching a safety transfer device prior to disposal."**

Section 8.14.2, Continued Bleeding

27. "When a patient continues to bleed," indicates that it is inevitable. Consider revising to "If a patient continues to bleed or a hematoma develops, …"

- **The text has been revised as recommended. The first paragraph now reads as follows: "If a hematoma develops or bleeding persists longer than five minutes, a nurse should be alerted so that the attending physician can be notified."**

Section 8.15, Step 15: Label Blood Collection Tubes and Record Time of Collection

28. Step 15: Consider revising the paragraph after the bullet list to accommodate handwritten identification of tubes. Suggested revision: "The label must be attached to the tube or the tube inscribed with complete information before leaving the side of the patient …."

- **The text has been revised as recommended. The following text has been added to the second paragraph: "Alternatively, the manufacturer's tube label can be inscribed with the patient's complete information."**

29. Tubes should be labeled in accordance with the laboratory requirements. These may not meet all requirements for all laboratories.

- **The text in this section has been revised in response to comment 9.**

Section 9, Venipuncture in Children and Difficult Collections

30. Passage states, "If a venipuncture is done on a child younger than one year of age, the site should be limited to superficial veins." As opposed to what? This statement is unclear.

- **The first sentence has been revised for clarity. The revision is as follows: "If a venipuncture is requested on a child younger than one year of age, the phlebotomist should consult with the physician or follow institutional policy."**

Section 9.2, Equipment

31. Consider modifying the range of needles to be used on pediatrics from 20-23 to 22-23 for patient comfort unless platelet aggregation studies are required.

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- **The needle gauge range has been revised as suggested. The following text has also been added: "For pediatric patients, through the age of 16, larger gauge needles may be appropriate."**

Section 11.6, Intravenous Fluids

32. Add the following reference: Savage R, ed. Q&A column. *CAP Today*. 2002:16(4):102-103.

- **The recommended reference, regarding performance of venipunctures above intravenous sites, has been added as suggested.**

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The Quality System Approach

NCCLS subscribes to a quality system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1—*A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. The QSEs provide the framework for delivery of any type of product or service, serving as a manager's guide. The quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Service & Satisfaction
Personnel	Process Control	Assessment	Facilities & Safety

H3-A5 addresses the quality system essentials (QSEs) indicated by an "X." For a description of the other NCCLS documents listed in the grid, please refer to the Related NCCLS Publications section on the next page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
				X H1	X T/DM6						X M29

Adapted from NCCLS document HS1— *A Quality System Model for Health Care.*

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, GP26-A2 defines a clinical laboratory path of workflow which consists of three sequential processes: preanalytical, analytical, and postanalytical. All clinical laboratories follow these processes to deliver the laboratory's services, namely quality laboratory information.

H3-A5 addresses the clinical laboratory path of workflow steps indicated by an "X." For a description of the other NCCLS documents listed in the grid, please refer to the Related NCCLS Publications section on the next page.

Preanalytic					**Analytic**		**Postanalytic**	
Patient Assessment	Test Request	Specimen Collection	Specimen Transport	Specimen Receipt	Testing Review	Laboratory Interpretation	Results Report	Post-test Specimen Management
X	X	X C38 H4 H11 H21	X C38 H4 H11 H21	X H18	X T/DM6			

Adapted from NCCLS document HS1— *A Quality System Model for Health Care.*

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Related NCCLS Publications*

C38-A **Control of Analytic Variation in Trace Element Analysis; Approved Guideline (1997).** This document provides guidelines for patient preparation, specimen collection, transport, and processing for the analysis of trace metals in a variety of biological matrices.

H1-A4 **Evacuated Tubes and Additives for Blood Specimen Collection—Fourth Edition; Approved Standard (1996).** This document provides requirements for blood collection tubes and additives.

H4-A4 **Procedures and Devices for the Collection of Diagnostic Blood Specimens by Skin Puncture; Approved Standard—Fourth Edition (1999).** A consolidation of H4-A3 and H14-A2, this standard provides detailed descriptions and explanations of proper collection techniques, as well as hazards to patients from inappropriate specimen collection by skin puncture procedures.

H11-A3 **Procedure for the Collection of Arterial Blood Specimens; Approved Standard—Third Edition (1999).** *American National Standard.* This standard describes principles of collecting, handling, and transporting arterial blood specimens. The document is aimed at reducing collection hazards and ensuring integrity of the arterial specimen.

H18-A2 **Procedures for the Handling and Processing of Blood Specimens; Second Edition—Approved Guideline (1999).** This guideline addresses multiple factors associated with handling and processing specimens, as well as factors that can introduce imprecision of systematic bias into results.

H21-A3 **Collection, Transport, and Processing of Blood Specimen for Coagulation Testing and General Performance of Coagulation Assays; Approved Guideline—Third Edition (1998).** This guideline contains procedures for collecting, transporting, and storing blood; processing blood specimens; storing plasma for coagulation testing; and provides general recommendations for performing the tests.

M29-A2 **Protection of Laboratory Workers from Occupationally Acquired Infections; Approved Guideline—Second Edition (2001).** This document provides guidance on the risk of transmission of hepatitis viruses and human immunodeficiency viruses in any laboratory setting; specific precautions for preventing the laboratory transmission of blood-borne infection from laboratory instruments and materials; and recommendations for the management of blood-borne exposure.

T/DM6-A **Blood Alcohol Testing in the Clinical Laboratory; Approved Guideline (1997).** This document gives technical and administrative guidance on laboratory procedures related to blood alcohol testing.

* Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent edition.

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Published in final edited form as:
Nat Protoc. 2008 ; 3(11): 1703–1708. doi:10.1038/nprot.2008.172.

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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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.

Acknowledgments

We thank Dr George McNamara for critical reading of the manuscript. This work was supported by NIH grant EY12727, EY-015289, P30 EY14801, the Karl Kirchgessner Foundation and the Foundation Fighting Blindness.

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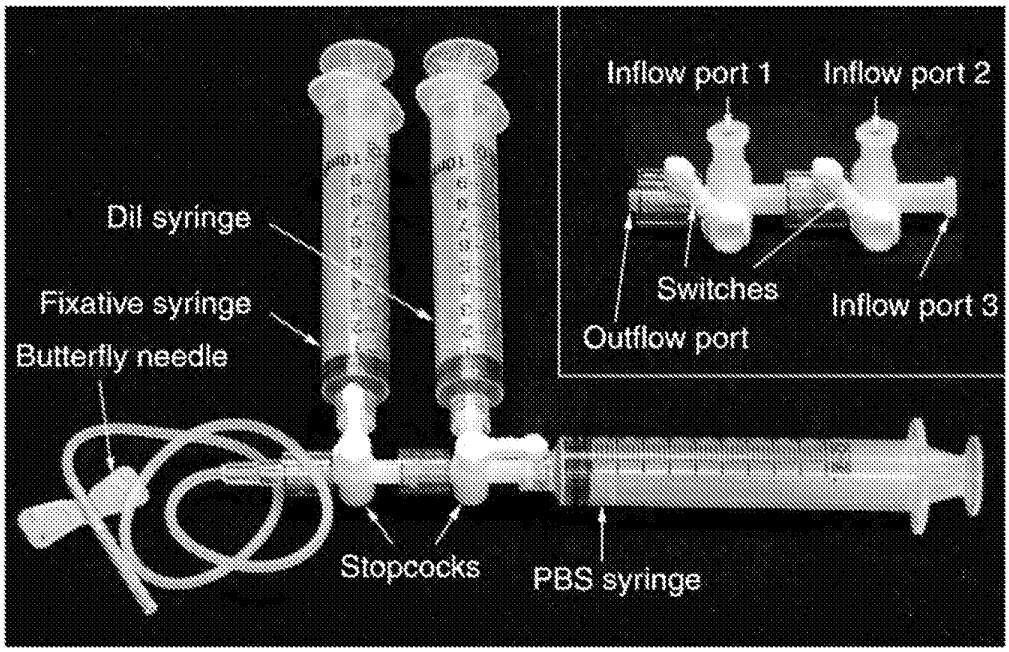


Figure 1.
Perfusion device. The main body of the perfusion device is two three-way stopcocks connected in series (inset). The output port of the stopcocks is connected to a butterfly needle. The inflow ports are connected to three 10-ml disposable syringes for PBS, DiI solution and fixative, respectively. 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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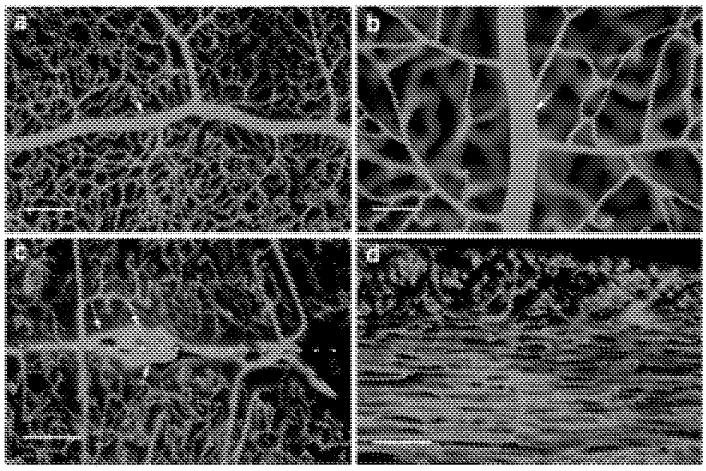


Figure 2.

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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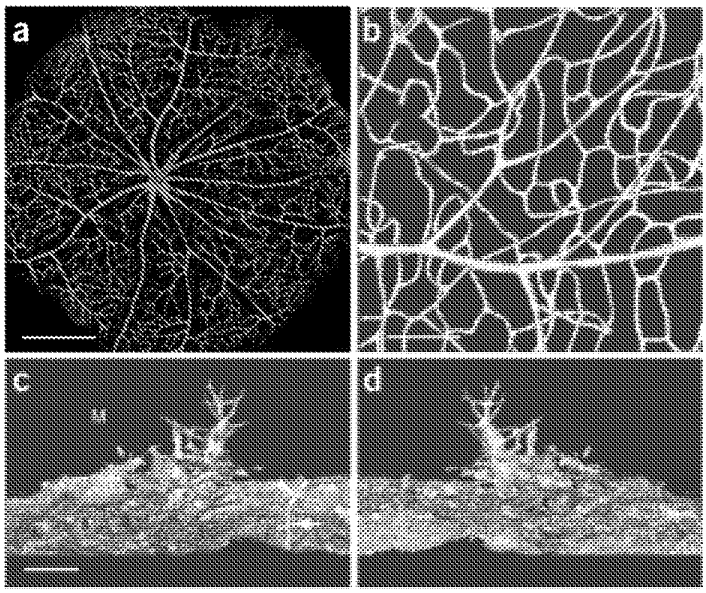


Figure 3.

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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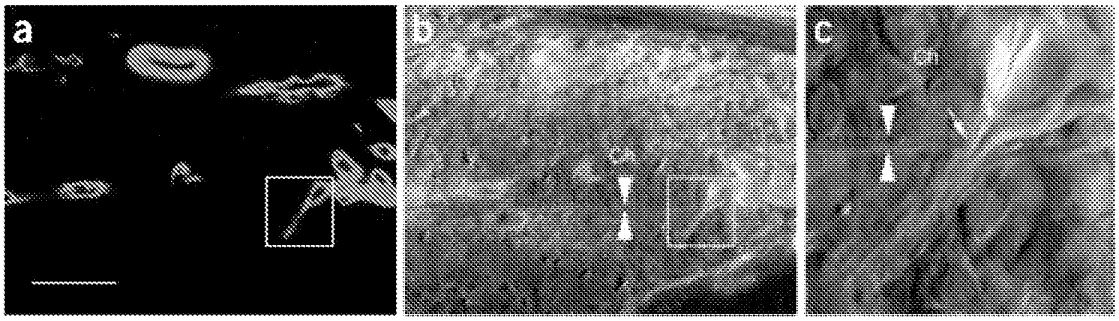


Figure 4.

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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(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Published patent publication (A)
(11) [Publication number] JP 2005-349196 (P2005-349196A)
(43) [Published date]] December 22, 2005 (2005.12.22)
(54) [Title of invention] Flashback type blood sampling needle
(51) [International Patent Classification 7th Edition]
A61B 5/15
A61M 5/158
A61M 5/32
[FI]
A61B 5/14 300H
A61M 5/32
A61M 5/14 369F
A61M 5/14 369H
[Request for examination] Unclaimed
[Number of claims] 45
[Application form] OL
[Foreign language application]

[Total number of pages] 22

(21) [Application number] Japanese Patent Application 2005-163169 (P2005-163169)

(22) [Application date] June 2, 2005 (2005.6.2)

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

(32) [Priority date] June 2, 2004 (2004.6.2)

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

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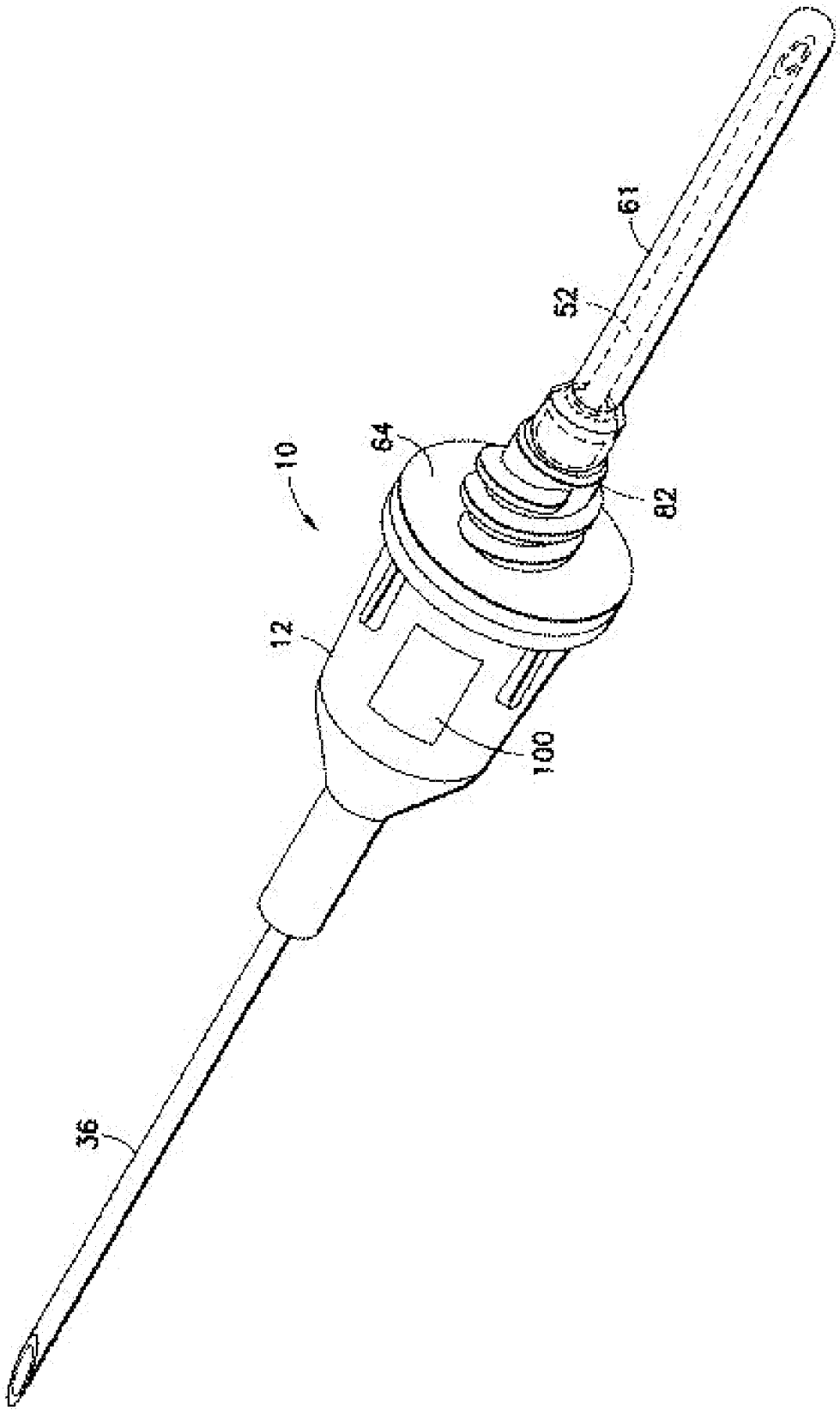
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4C038
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[F term (reference)]
4C038TA06
4C038UJ02
4C066AA09
4C066BB01
4C066CC01
4C066DD06
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wrap up close —

(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


61
52
64
10
82
12
100
36

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 venting 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 comprises a first passage through the non-patient thread assembly to th e reservoir, a second passage from the reservoir to the outside atmosphere, and a vent locate d 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-patient cannu la which allows air to pass through the proximal end of the non-patient cannula from which bl ood is aspirated and then through the vent. means to pass. A single cannula without a notch i s suitable in this case, but any cannula construction can be used. Specifically, air flows throug h the space between the outside of the needle and the multiple sample sleeve and exits the fl uid passageway out the proximal end of the non-patient cannula. The air is then directed to th e non-patient locking lug, non-patient hub threads, non-patient hub body, multiple specimen s leeves, or other location beyond the proximal end of the non-patient cannula. or through vent s in any combination of these locations. A collection tube attached to the proximal end of the non-patient cannula draws blood only from the fluid passageway and not from the vented spa ce. This embodiment thus allows blood to flow through the entire collection passageway. This also prevents contact of the blood sample with the vent, which could potentially lead to platel et activation or contamination or other undesirable consequences. This also prevents air from being drawn back into the fluid passageway when a vacuum tube is installed. It should also be noted that this embodiment requires a smaller ejection chamber than the previous embodime nt in which 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 stretch all the way through the receiving str ucture on the hub. When the vent media is placed on the support structure, it releases and us es its own elasticity 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 thi s embodiment may first compress the venting material, place the material in the opening, and then release the 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 for better flash viewing and/or part of the flashback chamber. Note that a flashback chamber or window can be placed in the air/blood passageway, especially for embo diments using a single cannula without a notch. In the embodiment of FIG. 5, air flows from the fluid passageway 306 to the proximal end 60 of the non-patient cannula and through the space 307 between the outside 308 of the needle and the inside of the multiple sample 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 which allows air to flow out but prevents blood or other fluids from fl owing out 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;

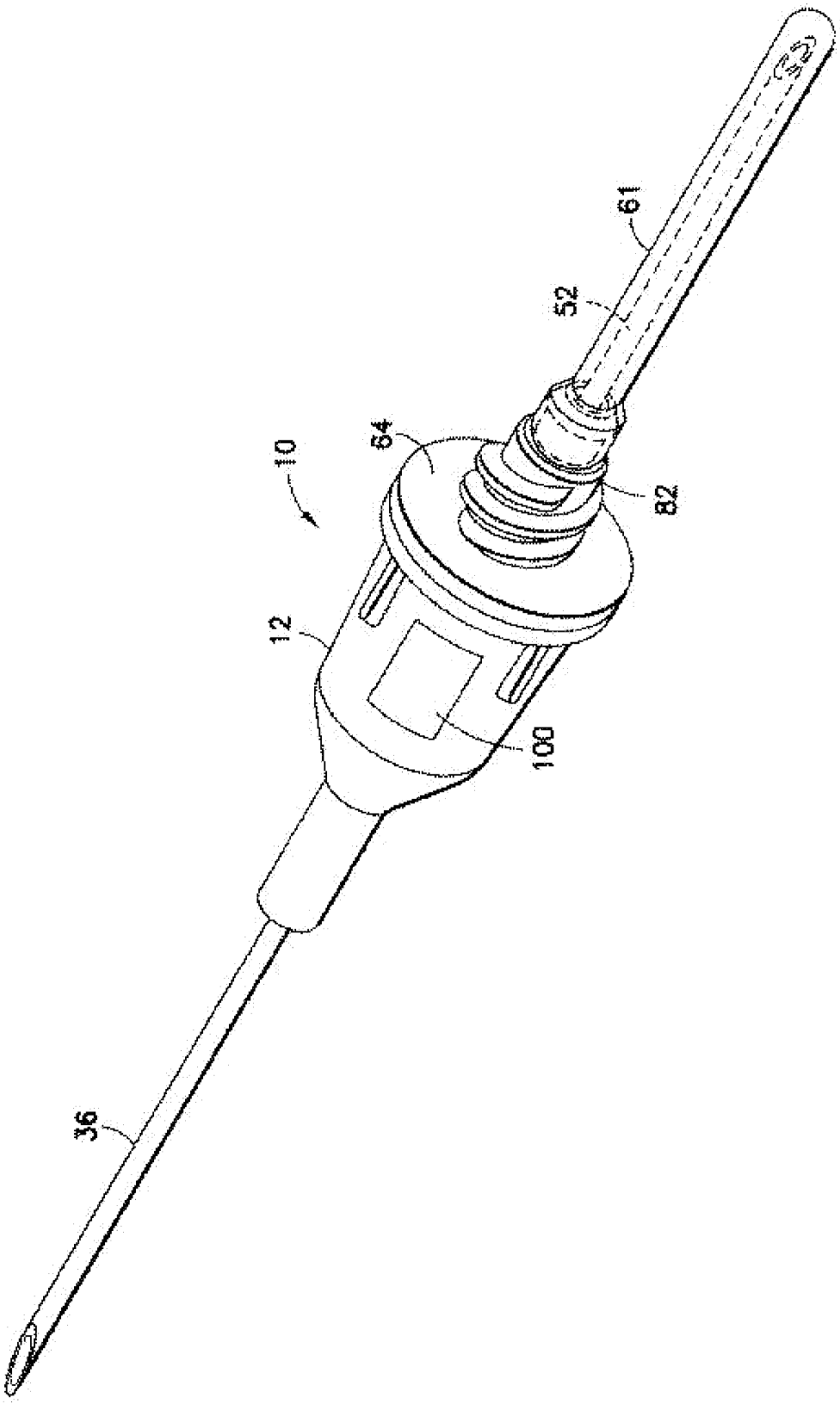
Figure 26 is a cross-sectional view similar to Figure 17 but showing another embodiment of th e invention;

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.

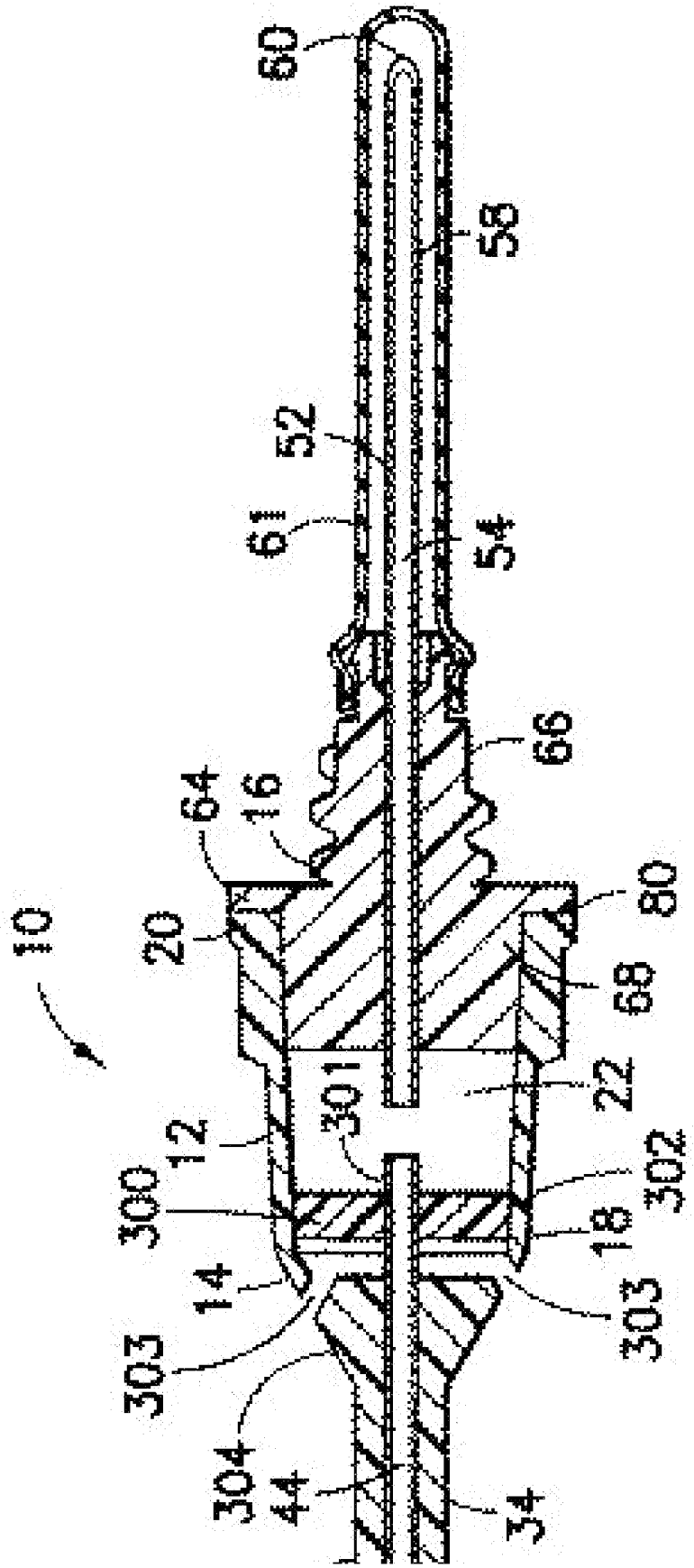
Figure 28 is a cross-sectional view of one embodiment of a blood collection needle assembly;

drawing	open ----

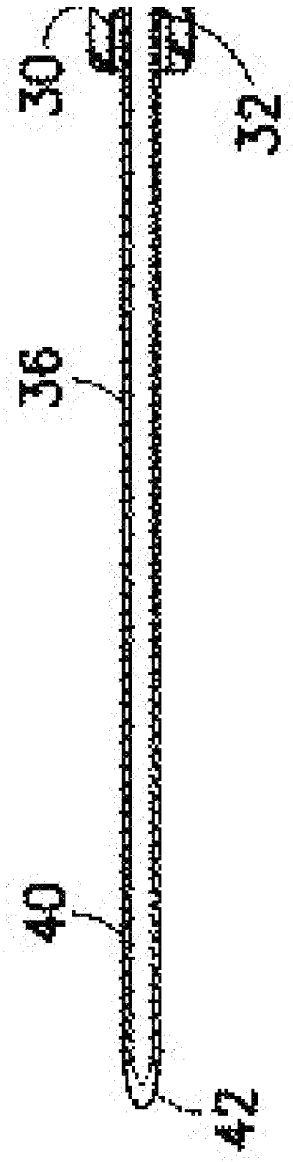
[Fig. 1]

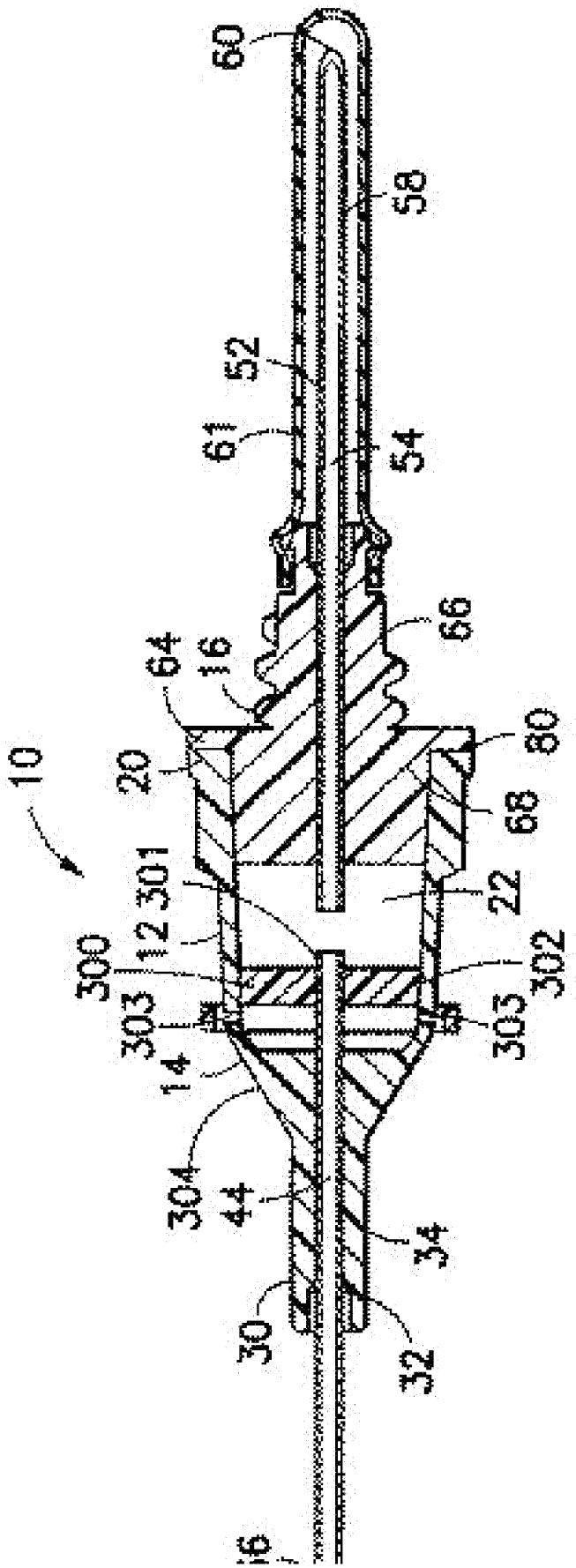


[Figure 2]

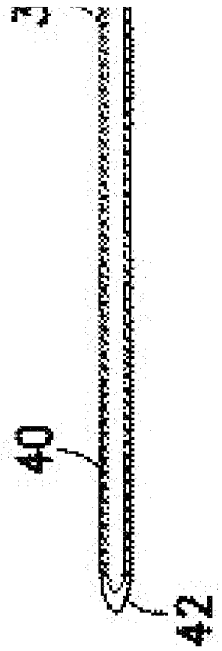

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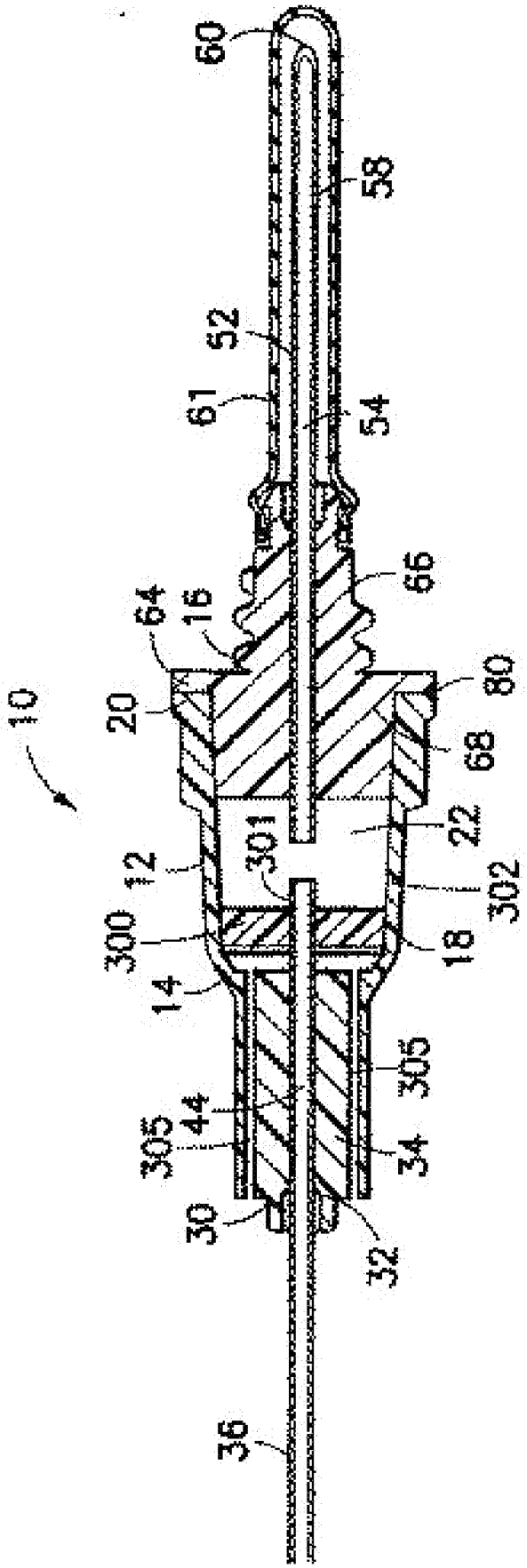
[Figure 3]



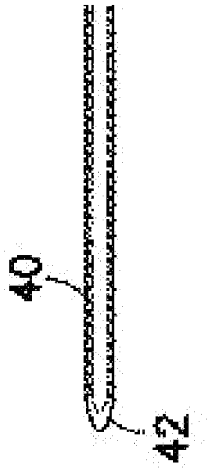

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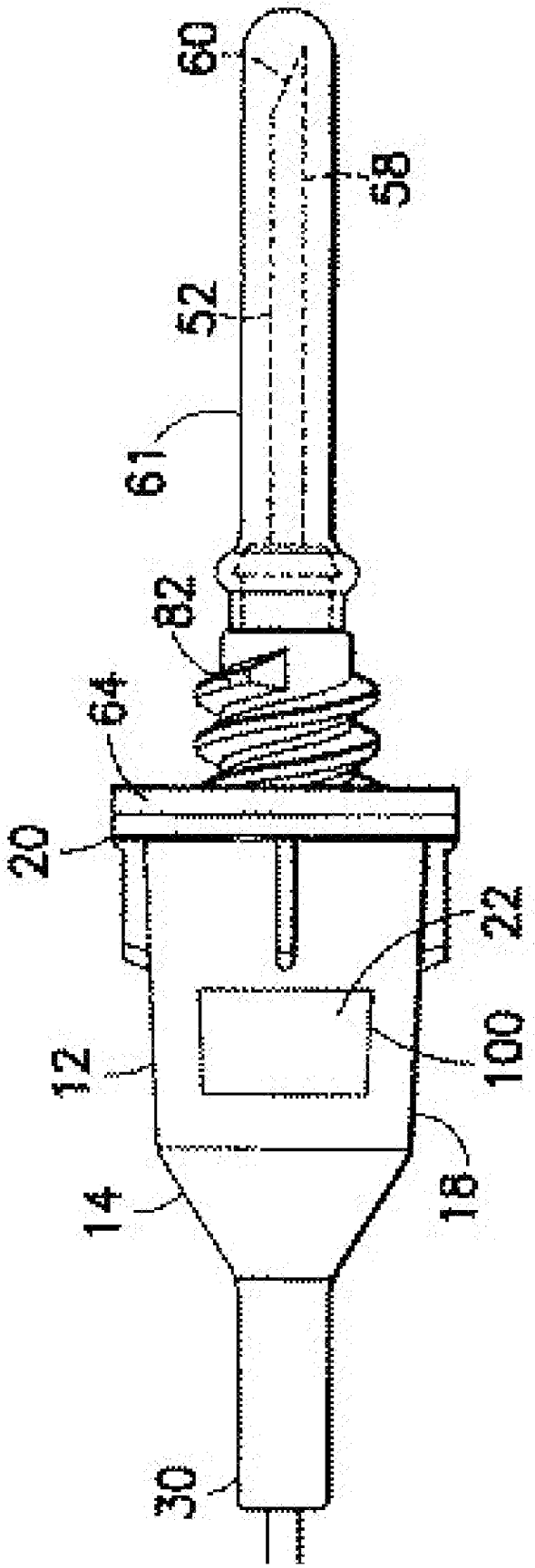
[Fig. 4A]



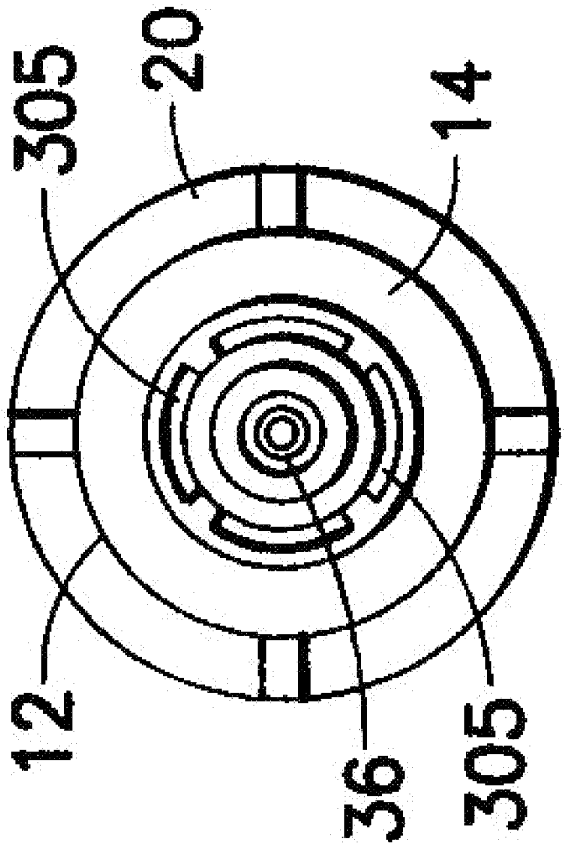

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[Fig. 4B]

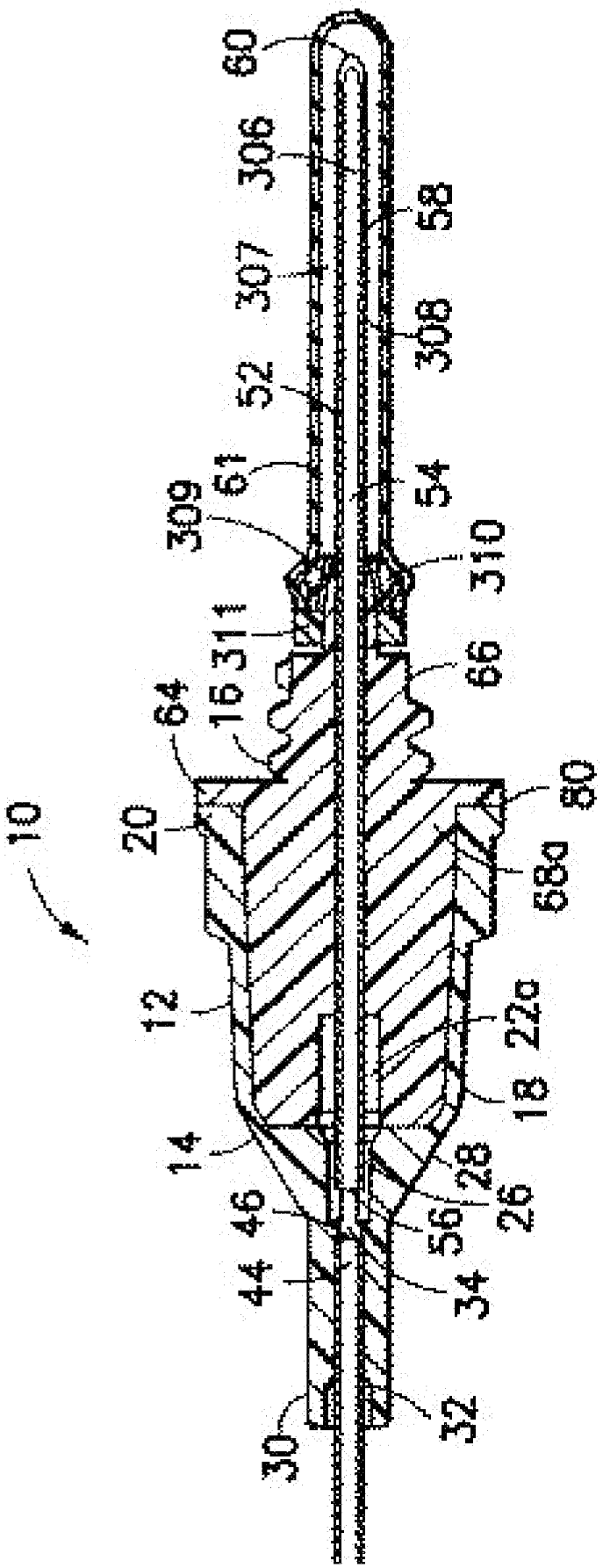



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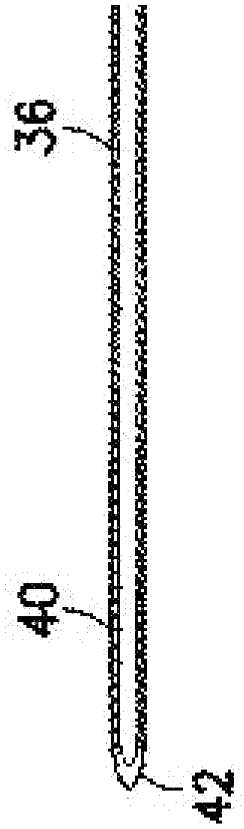
[Fig. 4C]

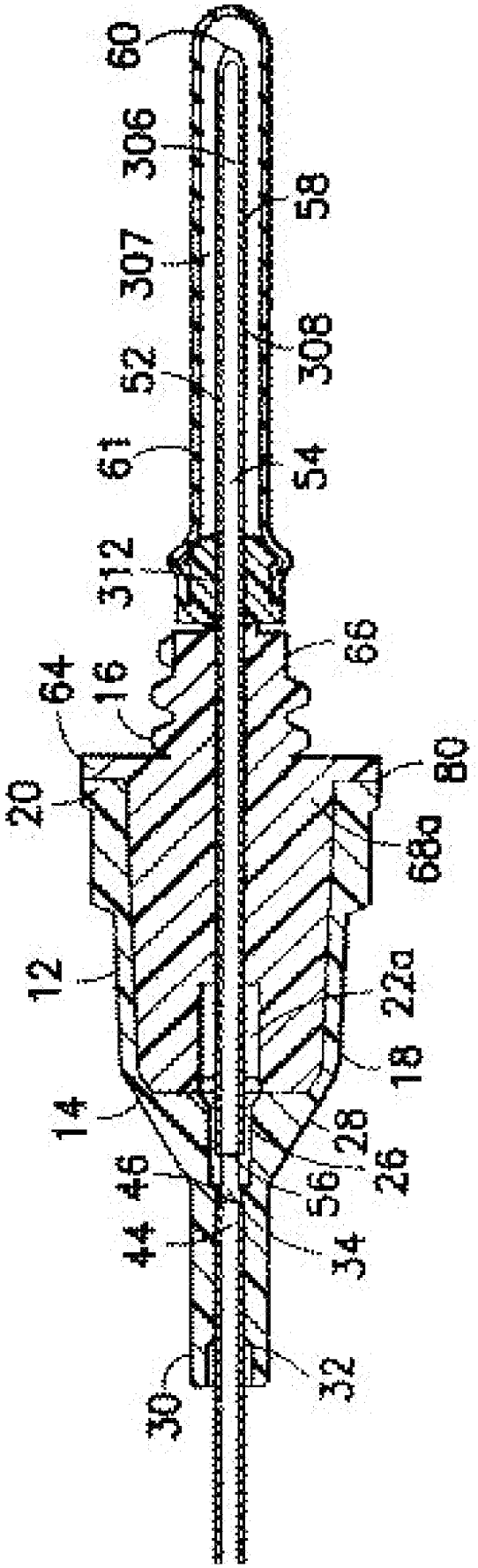


[Figure 5]

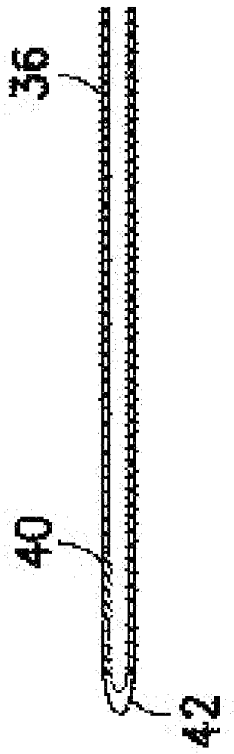

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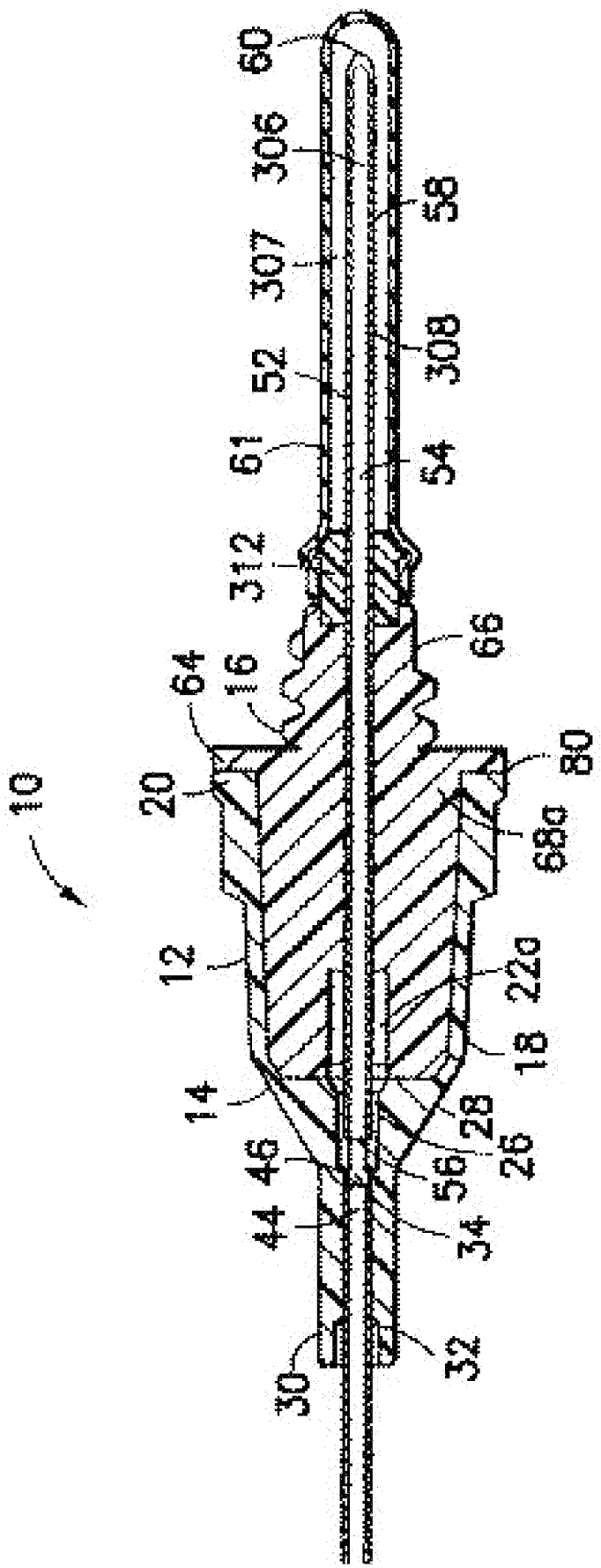
[Fig. 6]



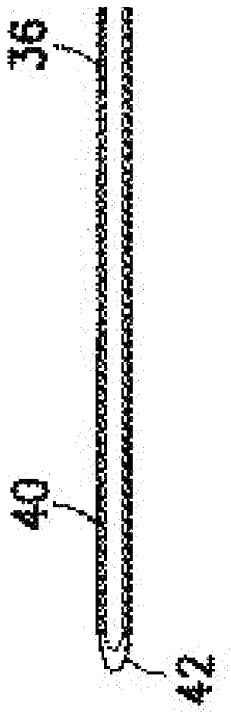

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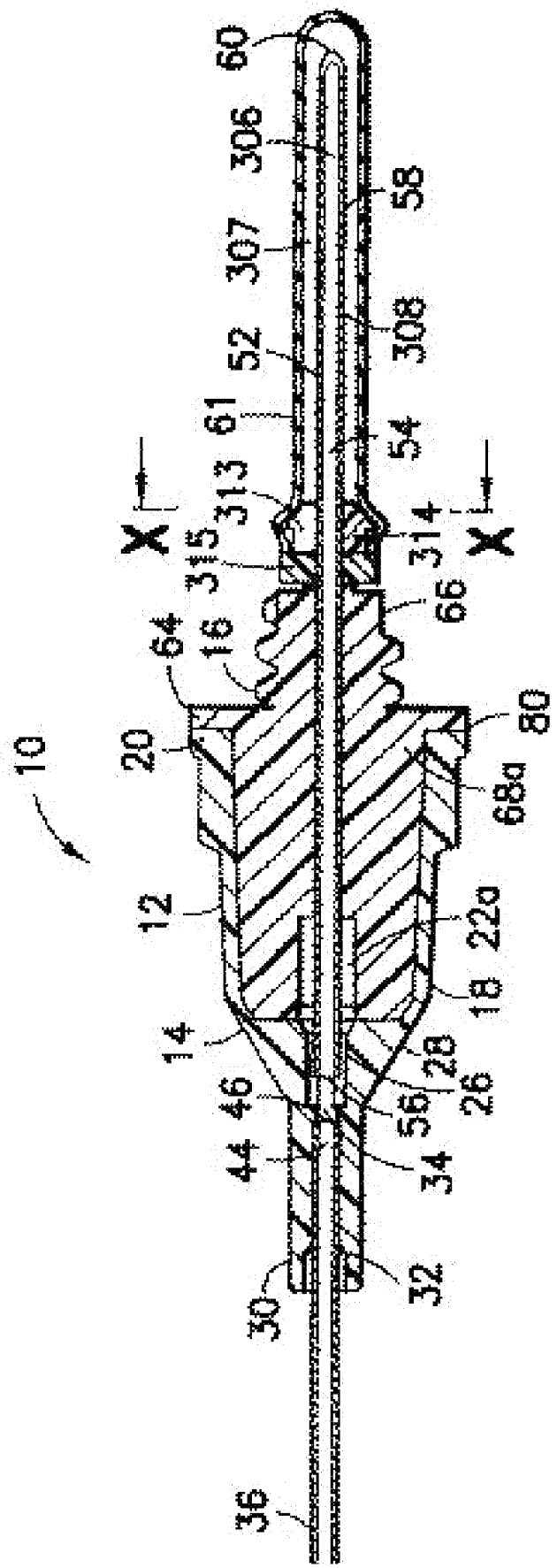
[Fig. 7]



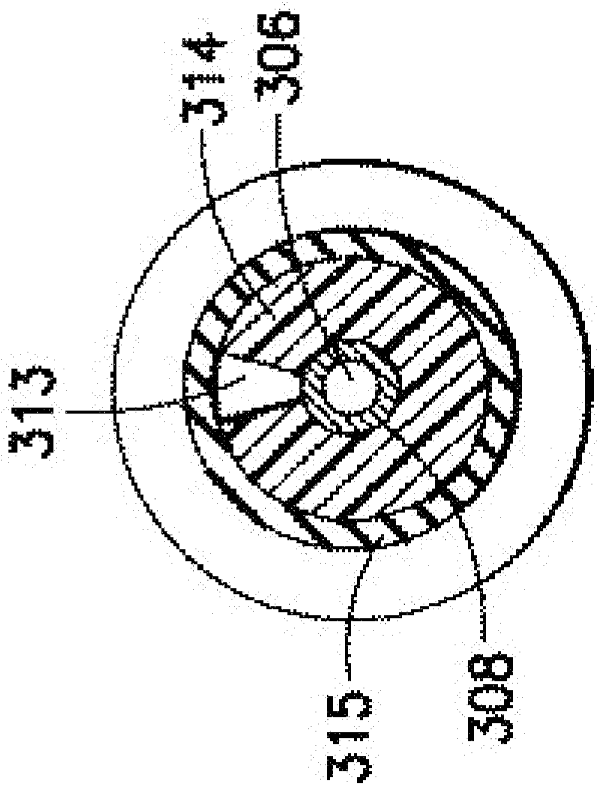

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[Fig. 8A]

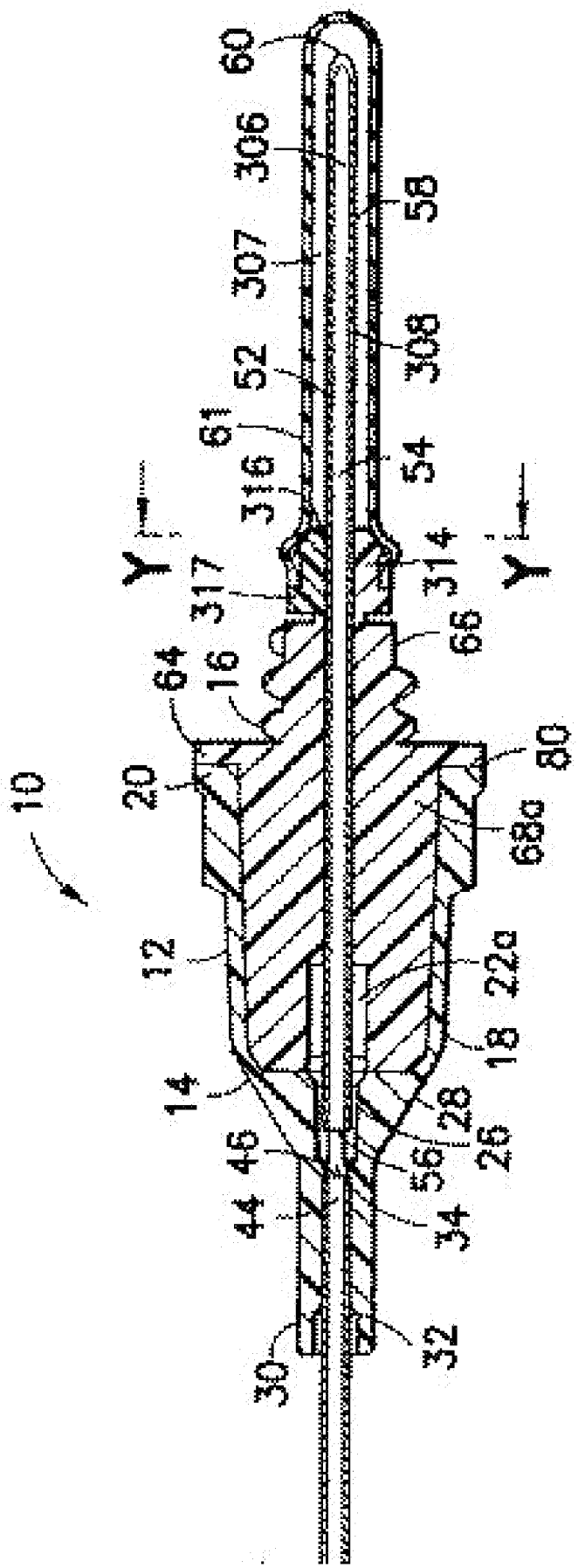



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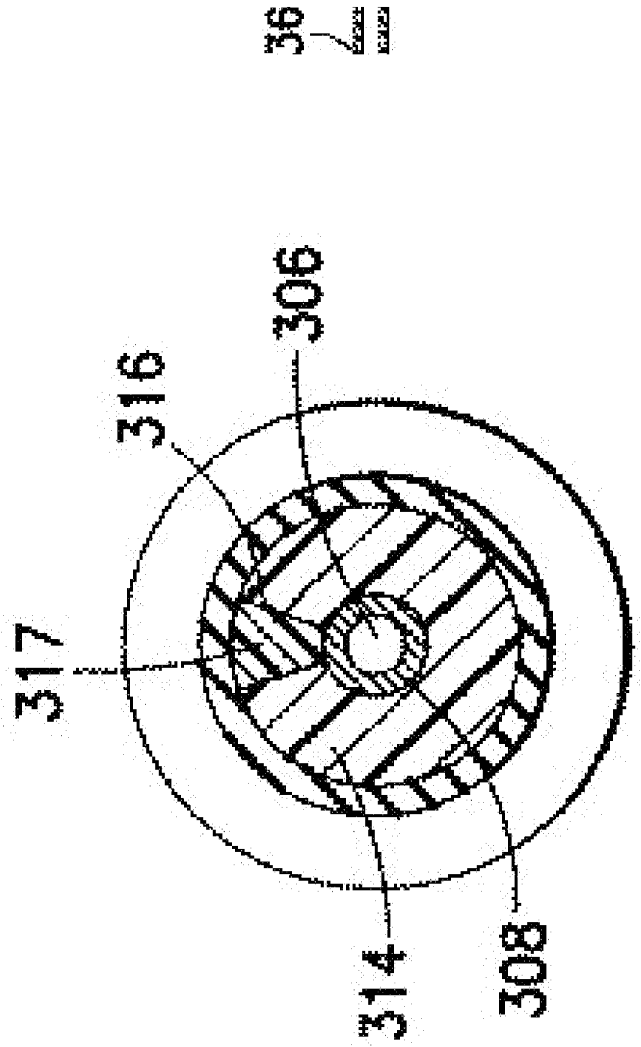
[Fig. 8B]



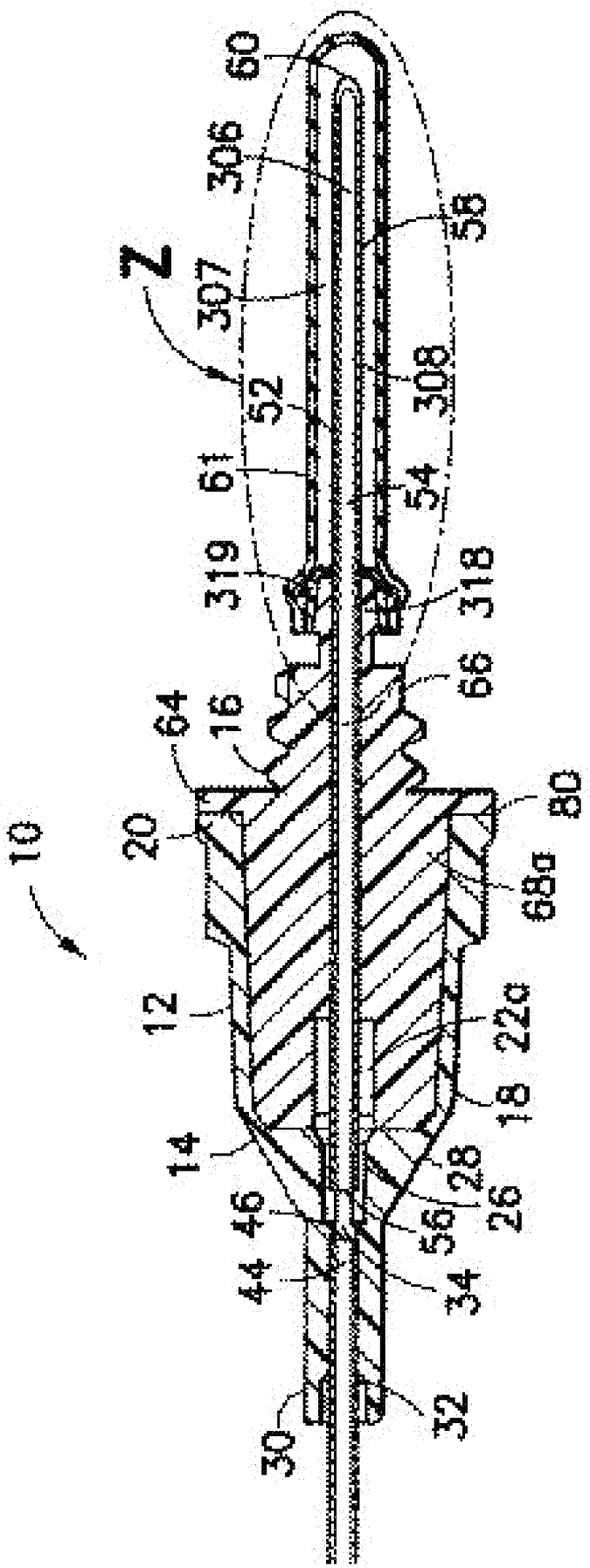
[Fig. 9A]


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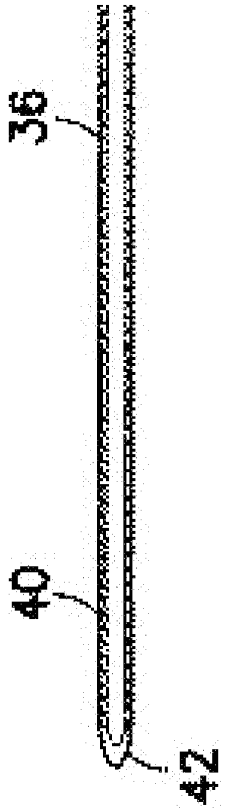
[Fig. 9B]

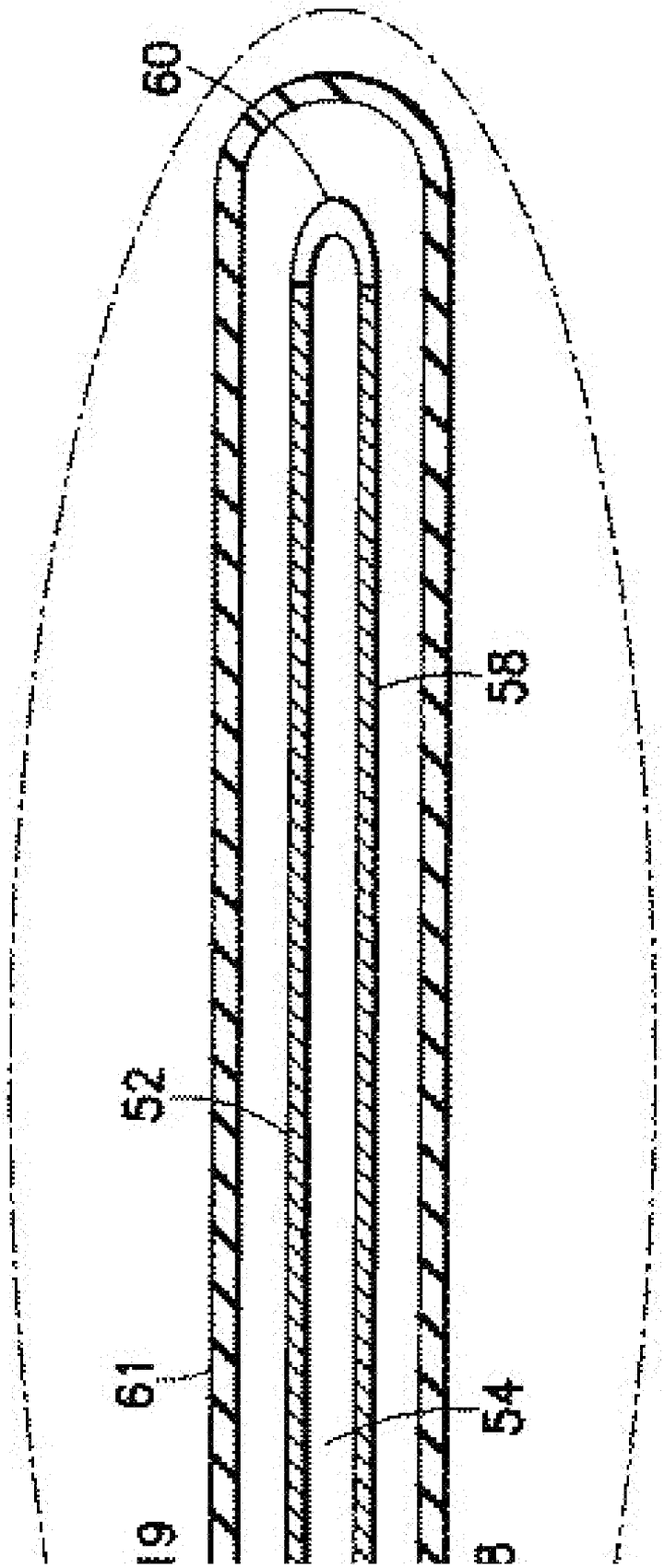


[Fig. 10A]

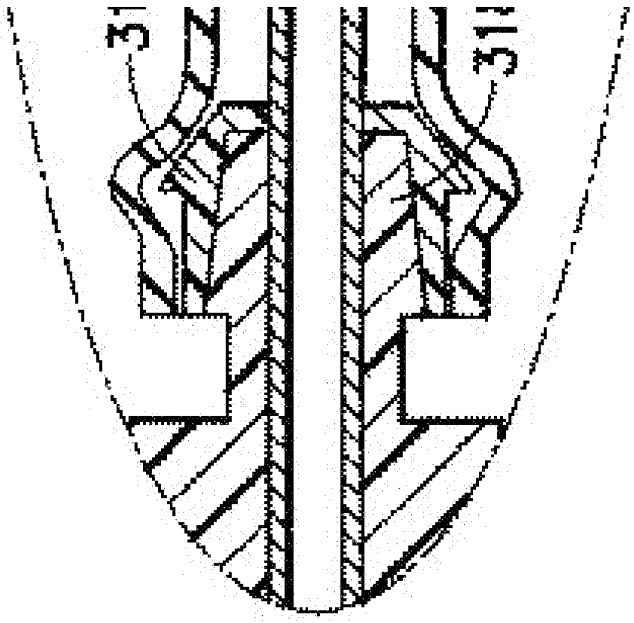

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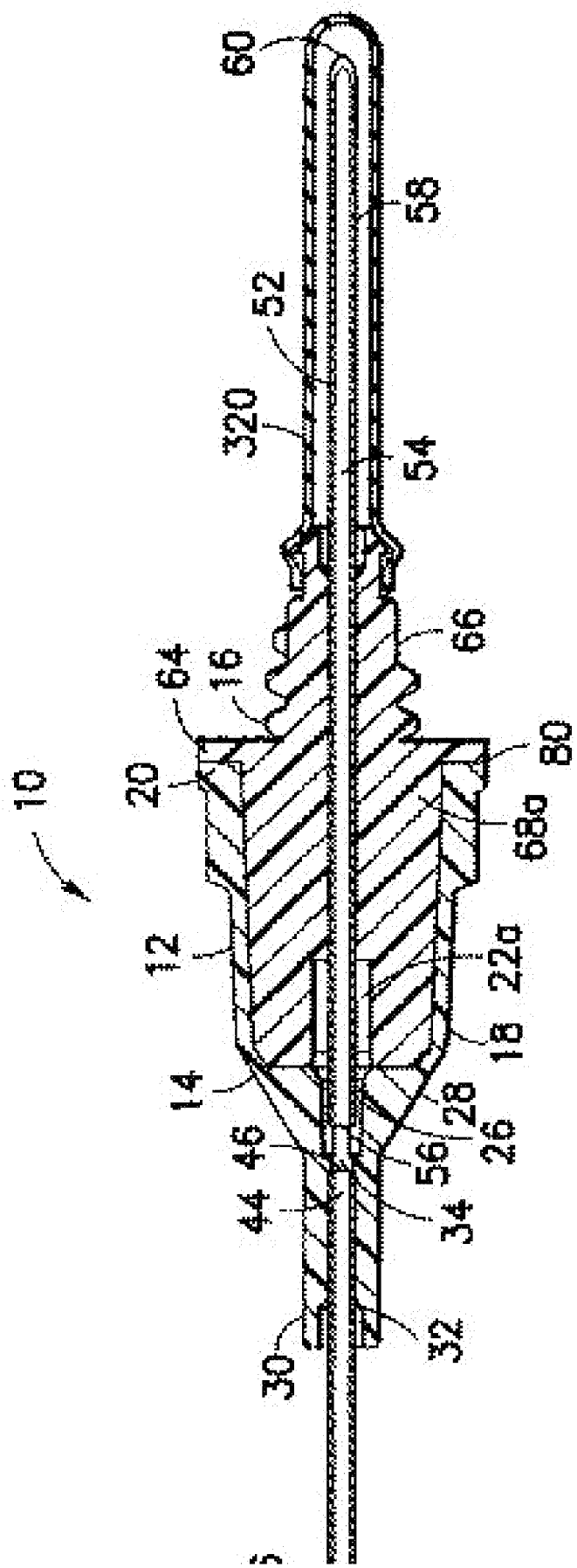
[Fig. 10B]



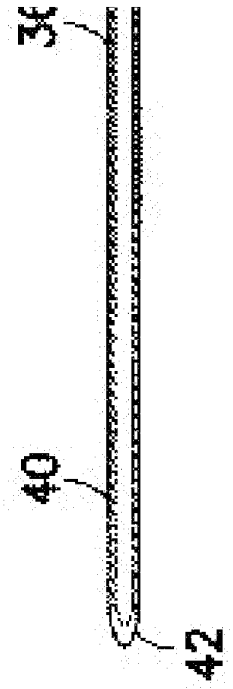

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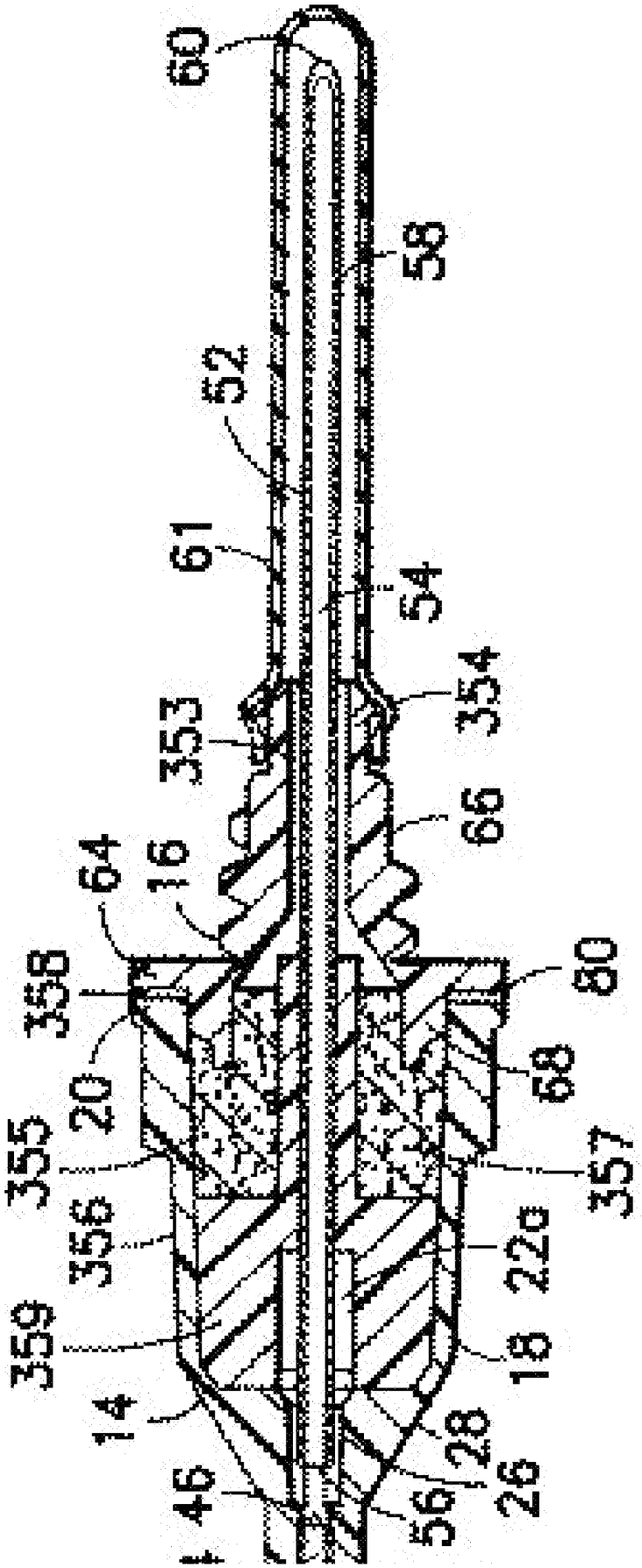
[Fig. 11]



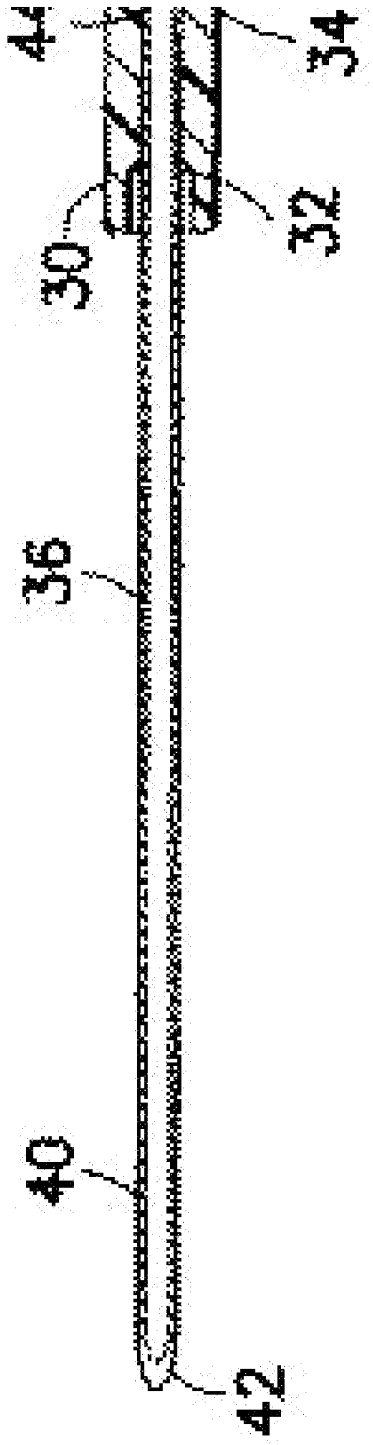

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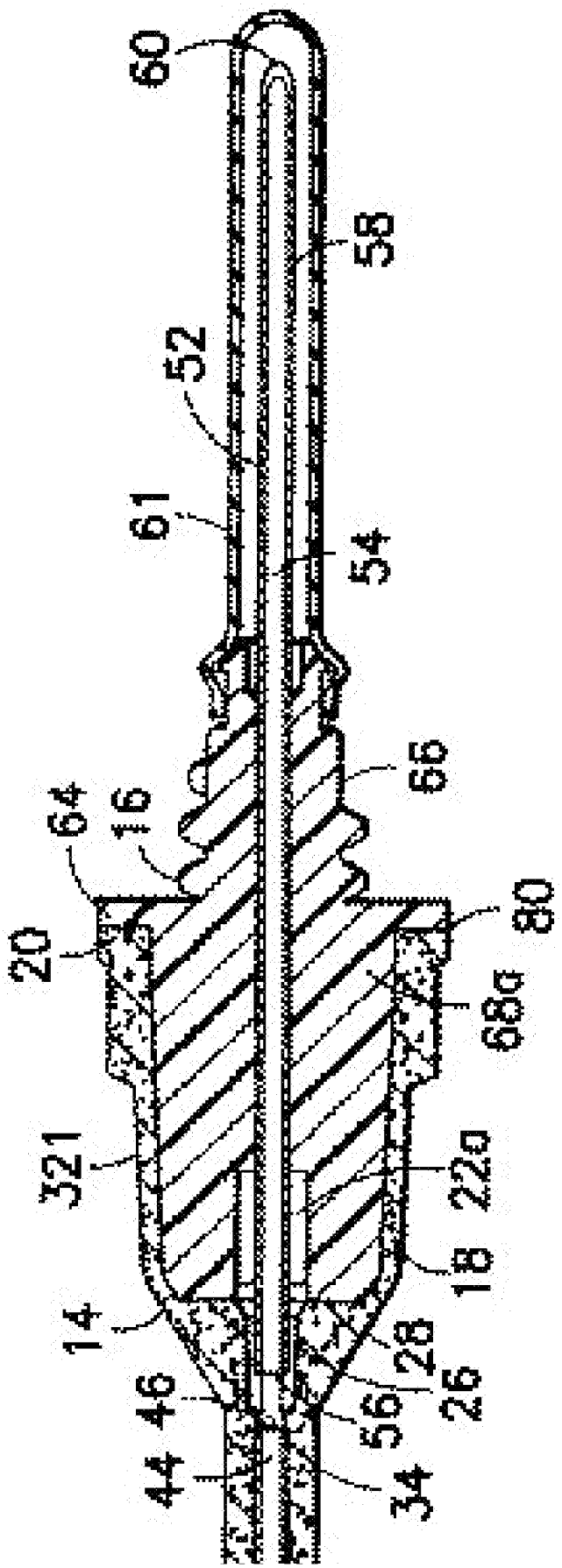
[Fig. 12]



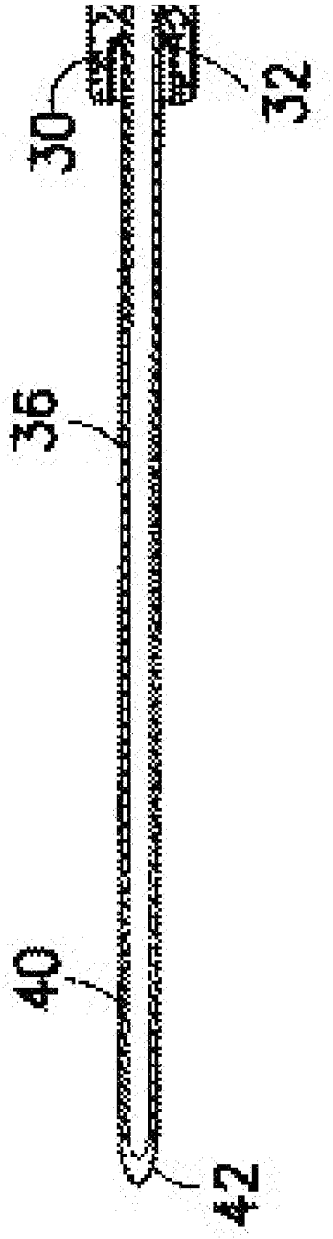

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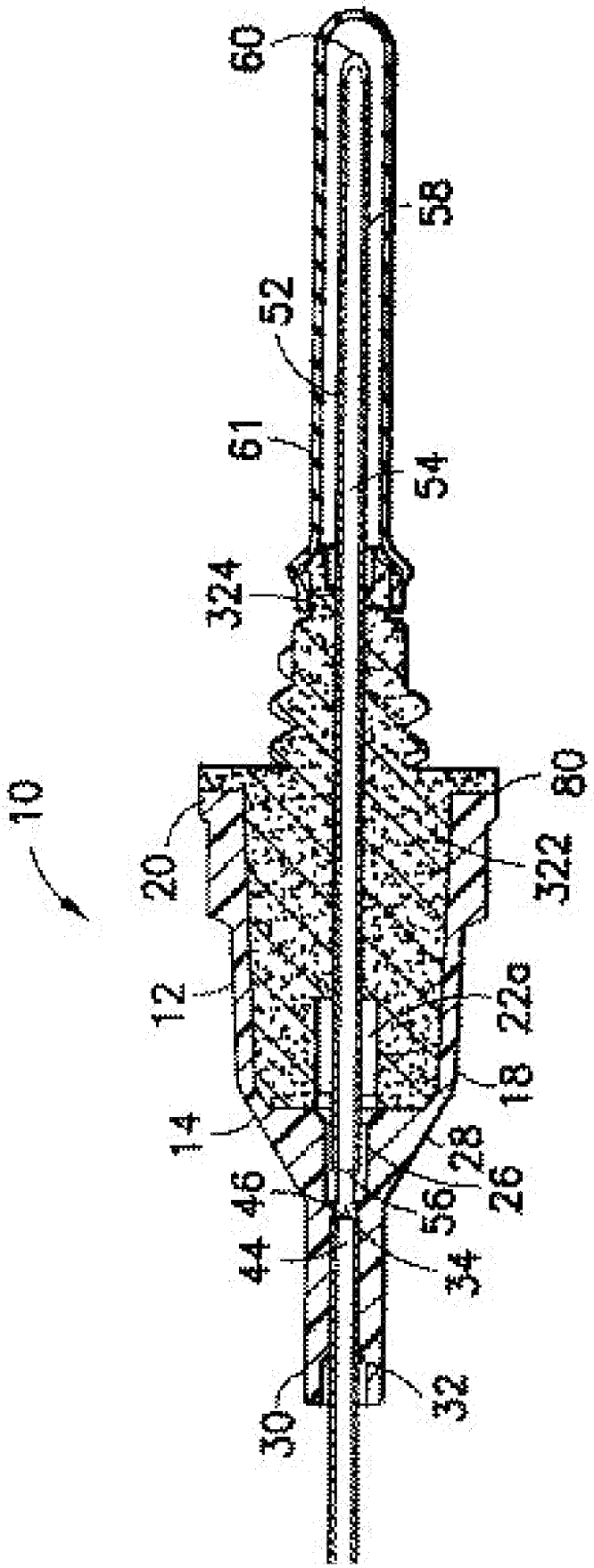
[Fig. 13]



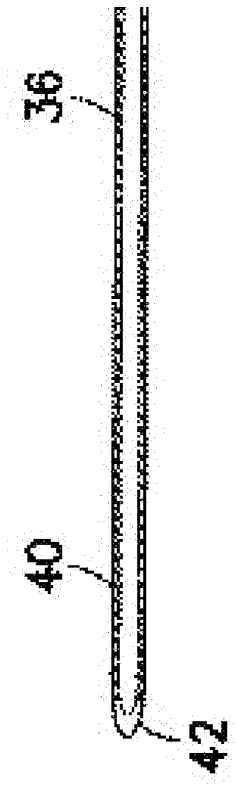

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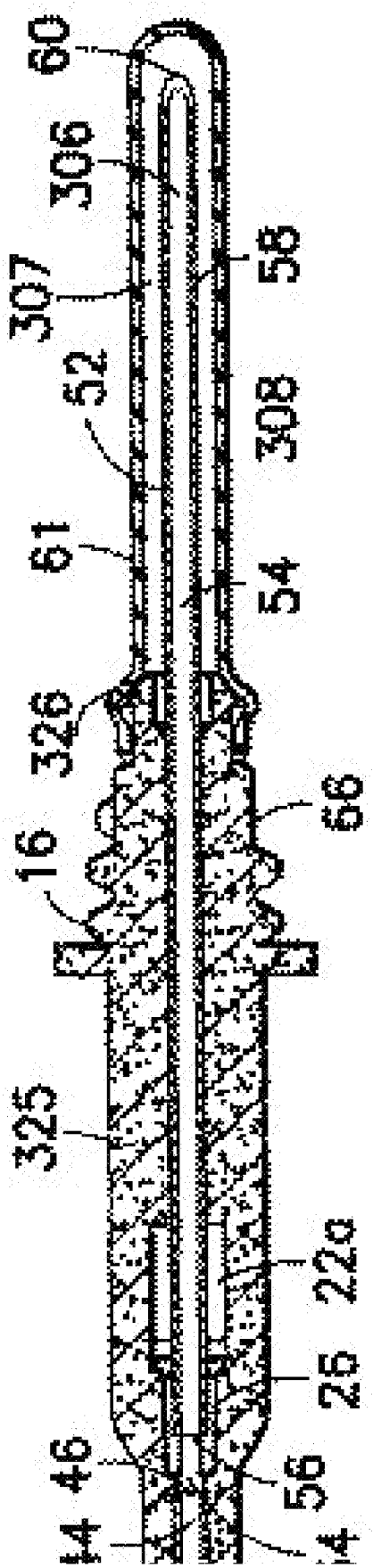
[Fig. 14]



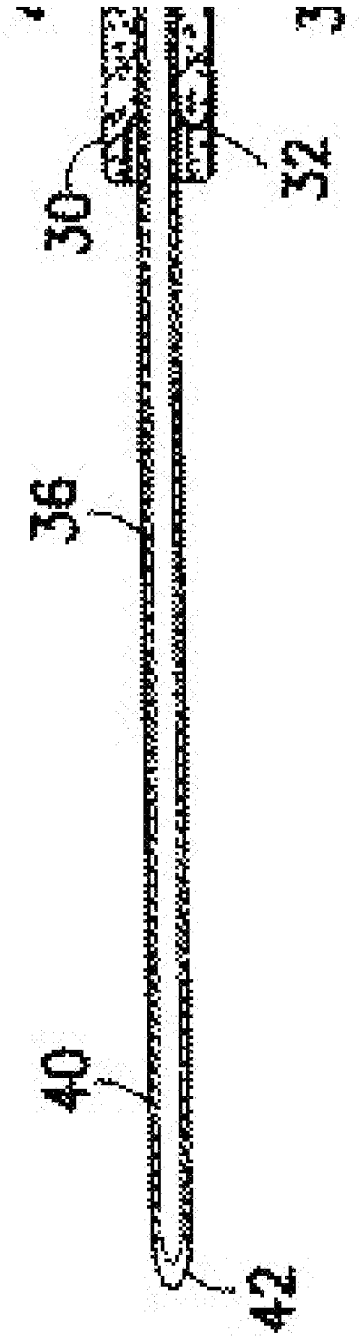

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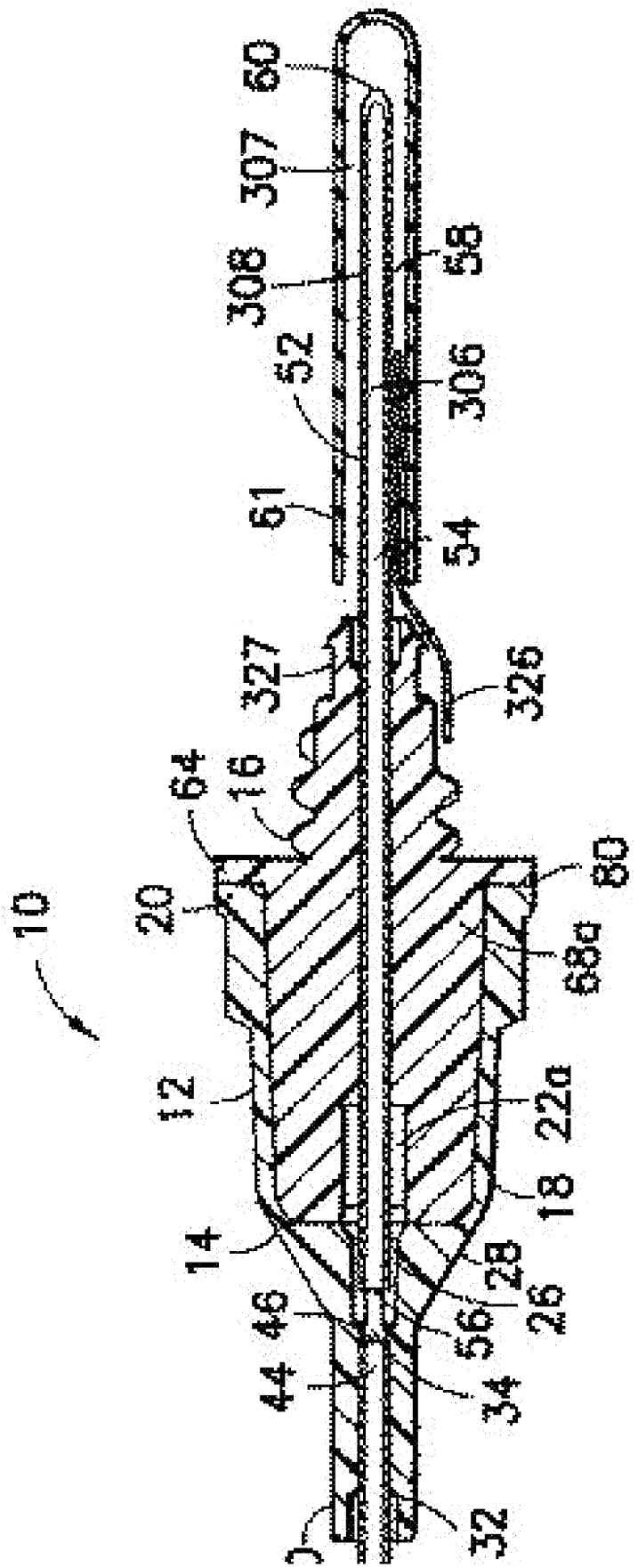
[Fig. 15]



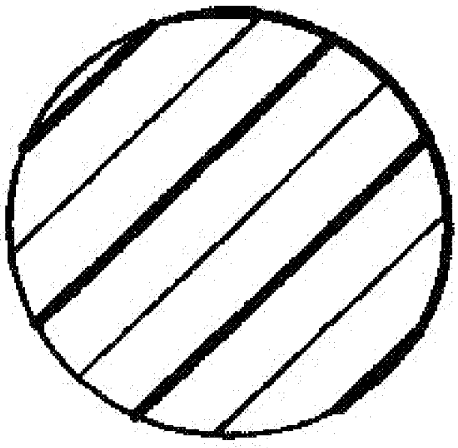

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[Fig. 16]

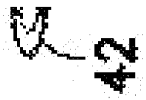


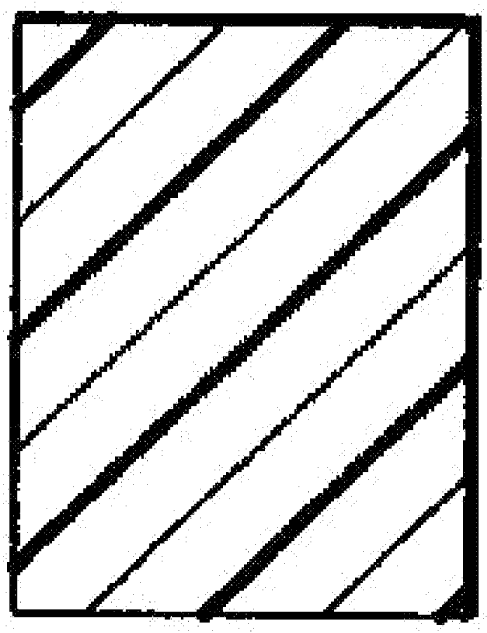

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[Fig. 17]

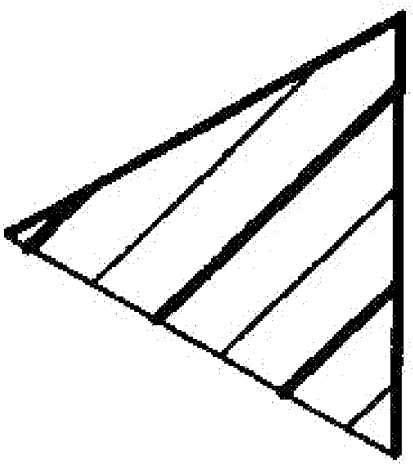


[Fig. 18]

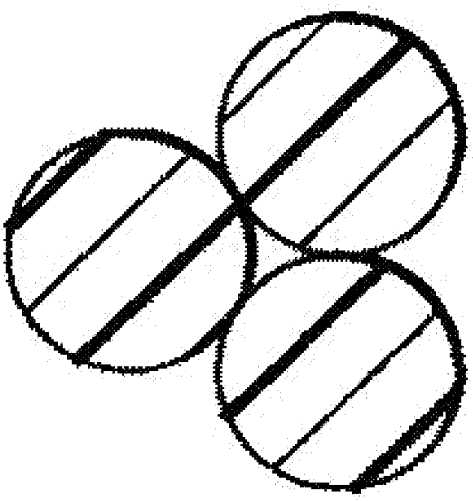




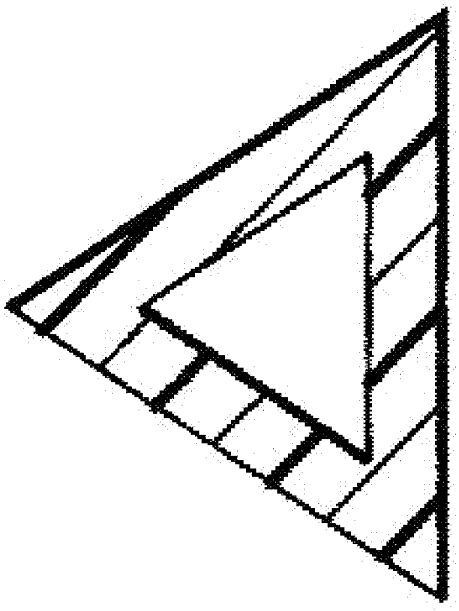
[Fig. 19]



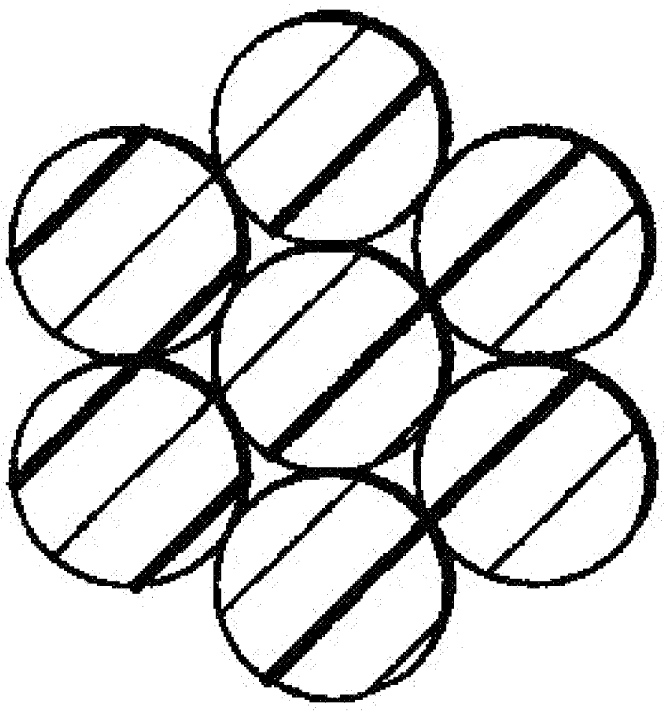
[Fig. 20]



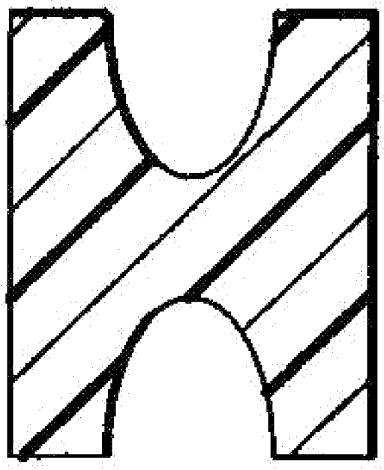
[Fig. 21]



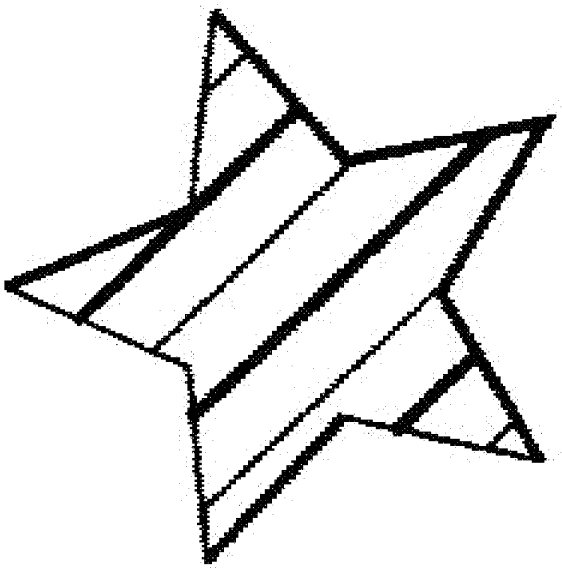
[Fig. 22]



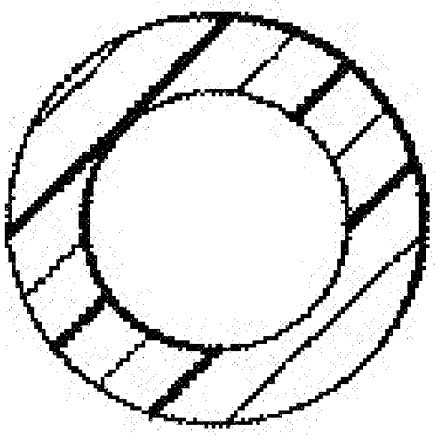
[Fig.23]



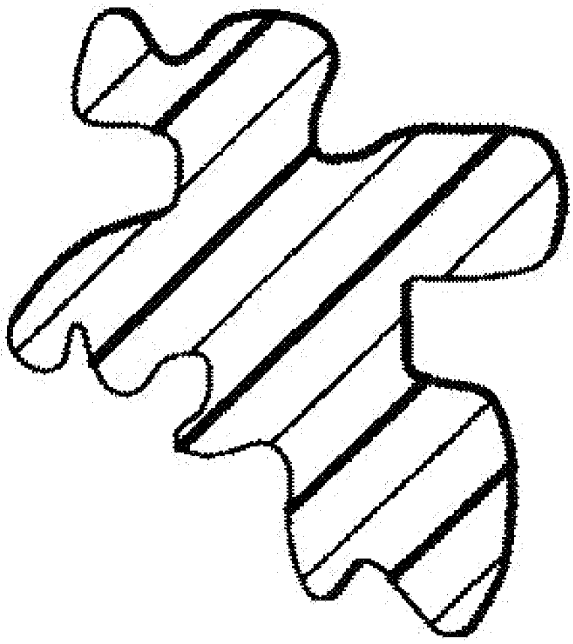
[Fig.24]



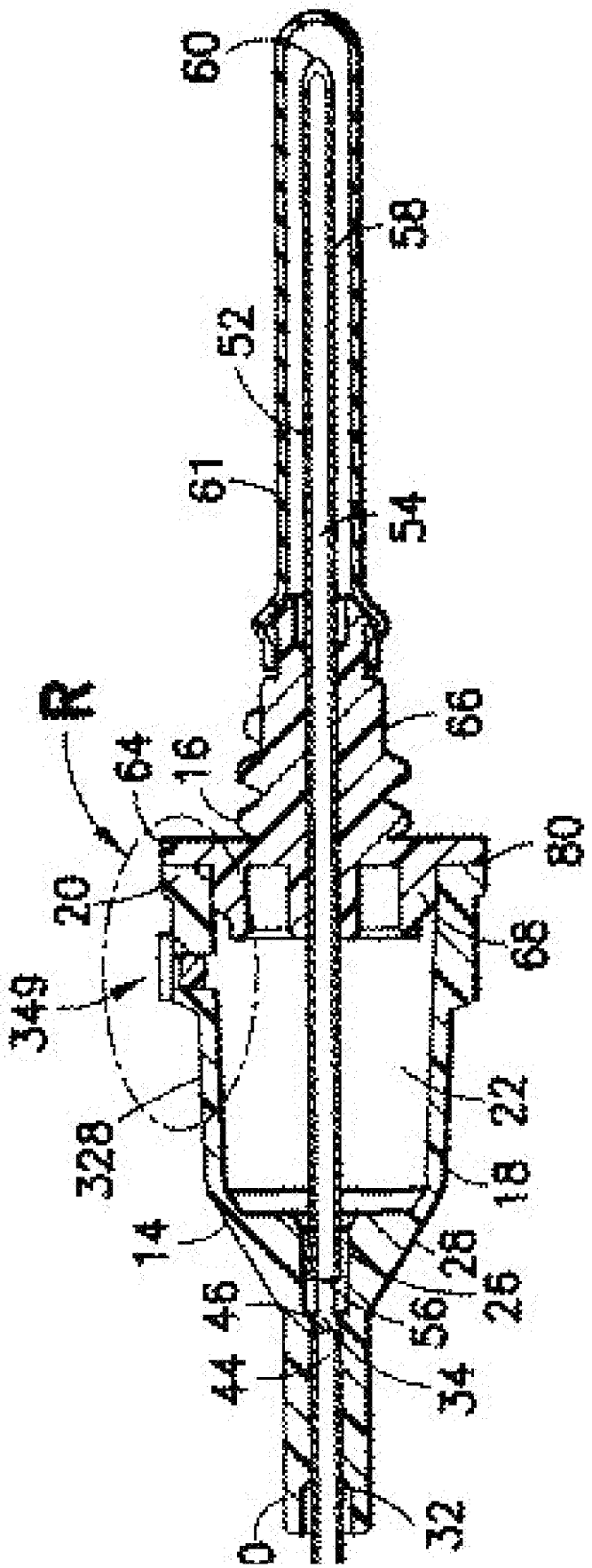
[Fig.25]



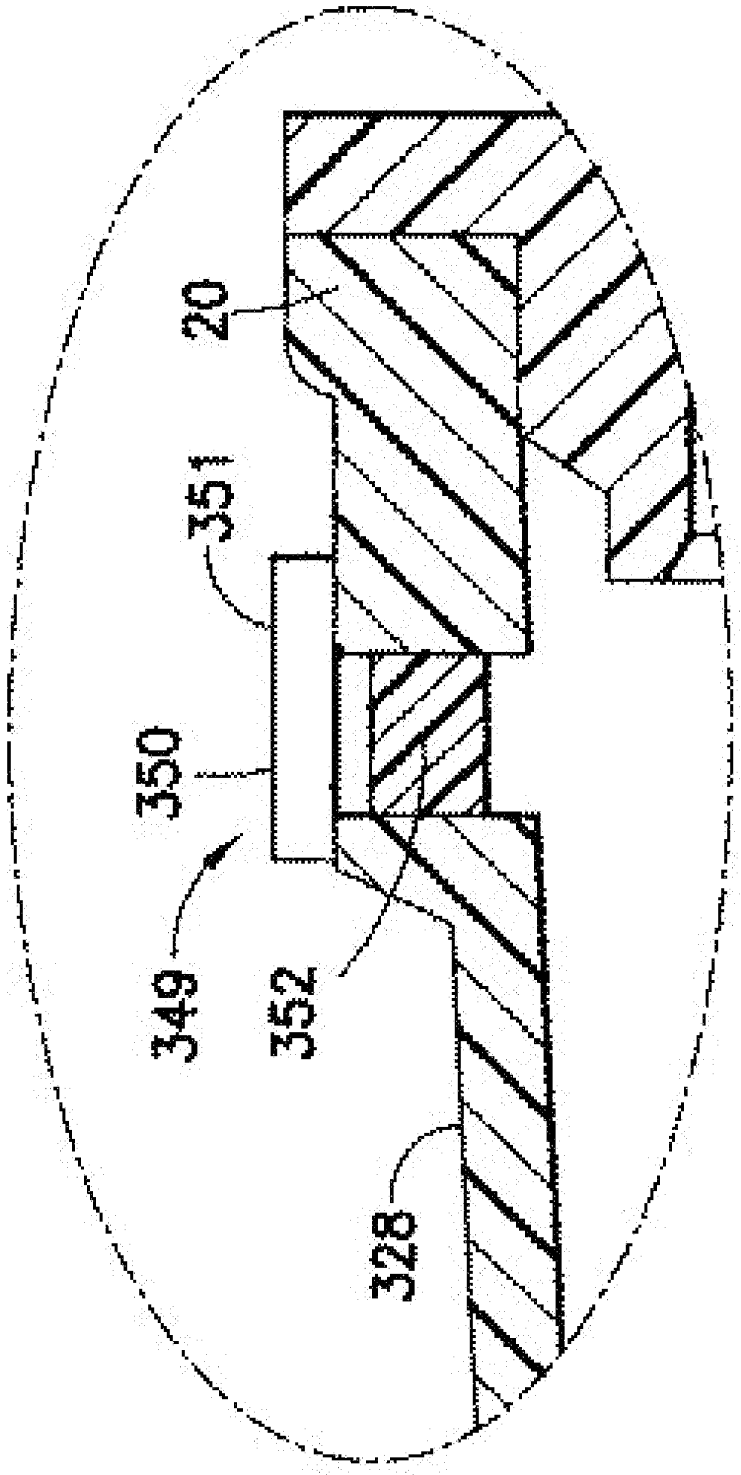
[Fig.26]



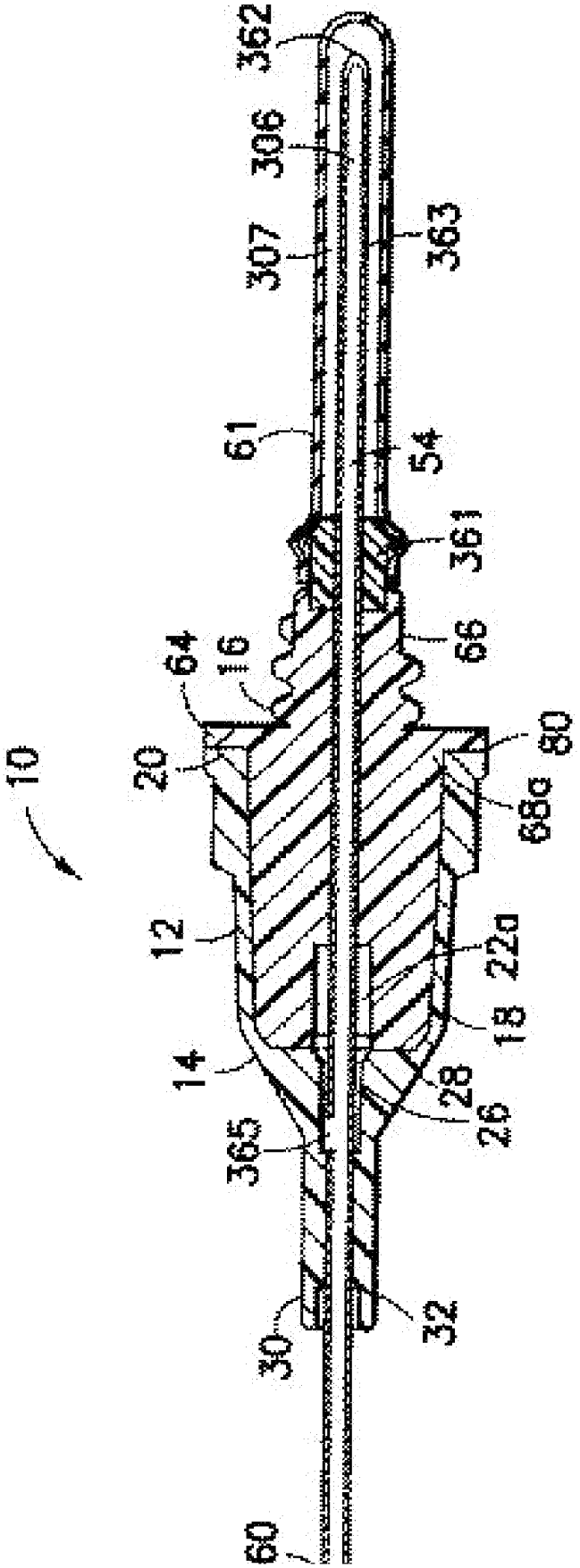
[Fig. 27A]


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[Fig. 27B]



[Fig.28]


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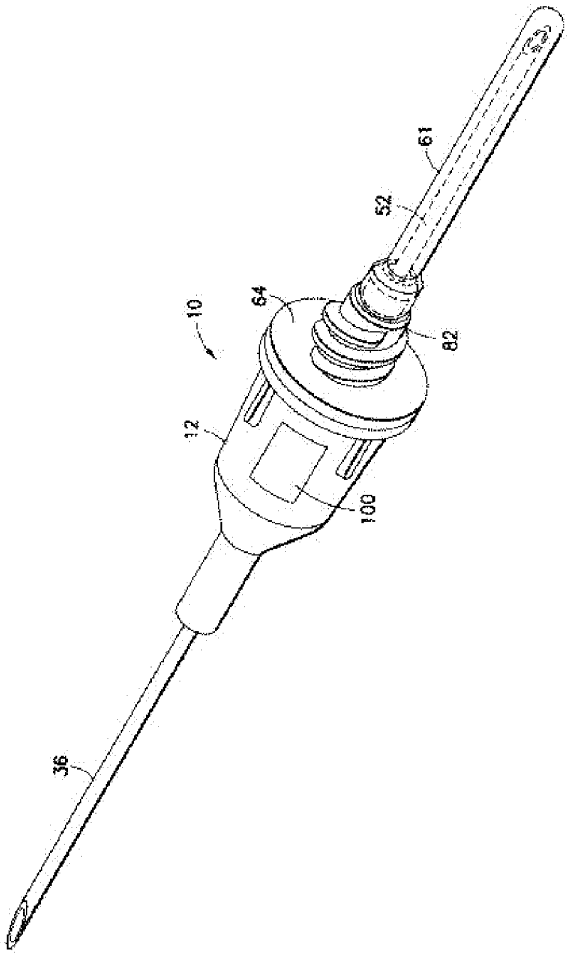
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Representative drawing

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

FLASHBACK BLOOD COLLECTION NEEDLE

Inventor(s): NAIR HAREESH; SWENSON KIRK D; CONWAY HUGH T; NEWBY C MARK; BLOCH CURTIS; LEVY RICHARD; WILKINSON BRADLEY; SCHNEIDER JAMES C; TOWNS BRYAN; ISKRA MICHAEL; ELLIS ROBERT; BENNETT MICHAEL; MARSDEN STEWART ± (NAIR HAREESH, ; SWENSON KIRK D, ; CONWAY HUGH T, ; NEWBY C MARK, ; BLOCH CURTIS, ; LEVY RICHARD, ; WILKINSON BRADLEY, ; SCHNEIDER JAMES C, ; TOWNS BRYAN, ; ISKRA MICHAEL, ; ELLIS ROBERT, ; BENNETT MICHAEL, ; MARSDEN STEWART)

Applicant(s): BECTON DICKINSON CO ± (BECTON DICKINSON & CO)

Classification: **- international:** ***A61B5/00; A61B5/15; A61M5/158; A61M5/32;*** (IPC1-7): A61B5/15; A61M5/158; A61M5/32
- cooperative: **A61B5/15003 (EP, US); A61B5/150213 (EP, US); A61B5/150389 (EP, US); A61B5/150488 (EP, US); A61B5/150496 (EP, US); A61B5/150572 (EP, US); A61B5/150732 (EP, US); A61B5/1545 (EP, US)**

Application number: JP20050163169 20050602 Global Dossier

Priority number(s): US20040576217P 20040602

Also published as: BRPI0502219 (A) CN1736332 (A) EP1602328 (A1) US2005283093 (A1) US2008275364 (A1) more

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

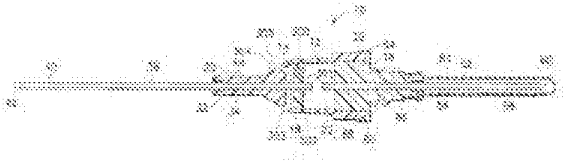


FIG.2

(19)日本国特許庁(JP)　(12)公開特許公報(A)　(11)特許出願公開番号
特開2005-349196
(P2005-349196A)
(43)公開日　平成17年12月22日(2005.12.22)

(51)Int.Cl.[7]	FI			テーマコード（参考）
A61B 5/15	A61B	5/14	300H	4C038
A61M 5/158	A61M	5/32		4C066
A61M 5/32	A61M	5/14	369F	
	A61M	5/14	369H	

審査請求 未請求　請求項の数 45　OL　外国語出願　（全 22 頁）

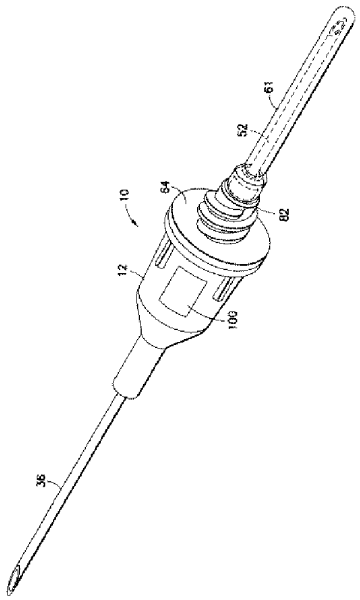
(21)出願番号　特願2005-163169 (P2005-163169)
(22)出願日　平成17年6月2日 (2005.6.2)
(31)優先権主張番号　60/576,217
(32)優先日　平成16年6月2日 (2004.6.2)
(33)優先権主張国　米国 (US)

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最終頁に続く

(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。

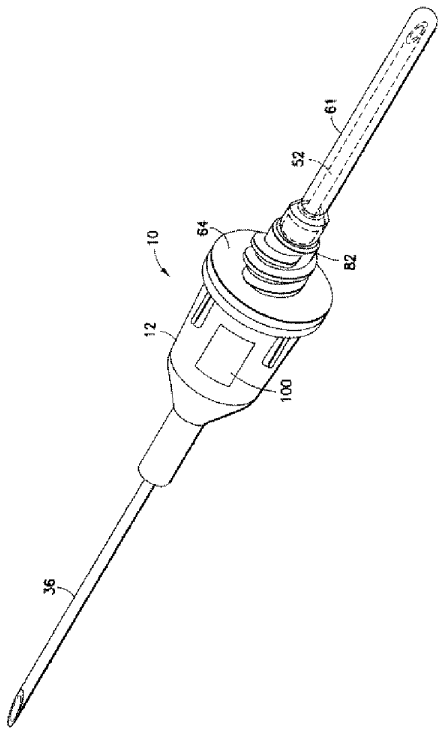
【図4A】図２と同様な側断面図であるが、本発明の別の実施形態を示している。

【図4B】図４Ｂの側面図である。

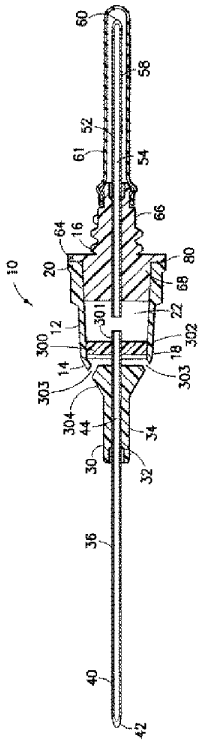
【図4C】Ｒ－Ｒの方向から見た図４ＢＡの正面図である。

【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。

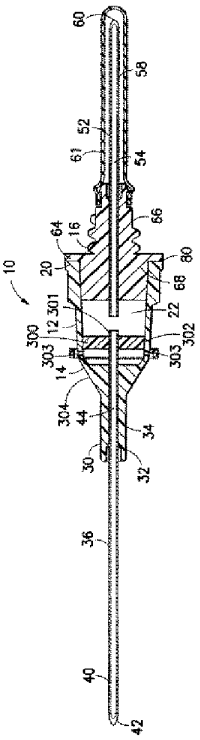
【図1】


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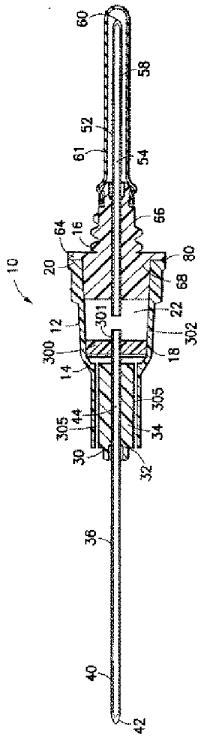
【図2】


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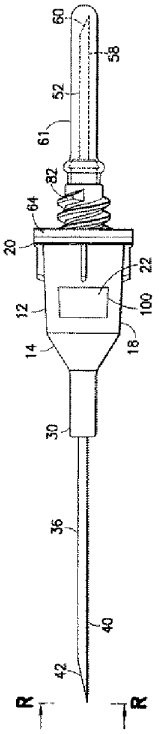
【図3】


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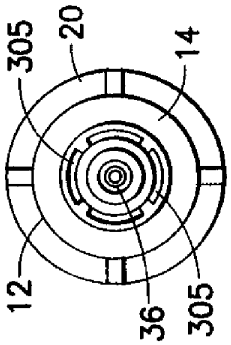
【図4A】


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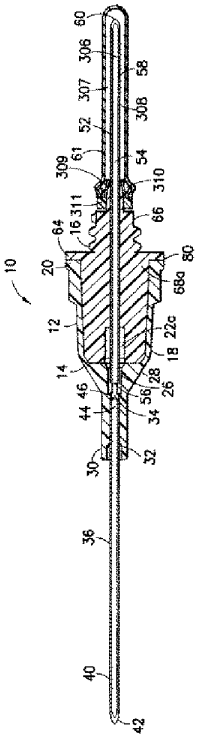
【図4B】


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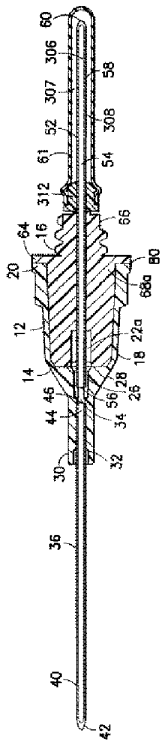
【図4C】


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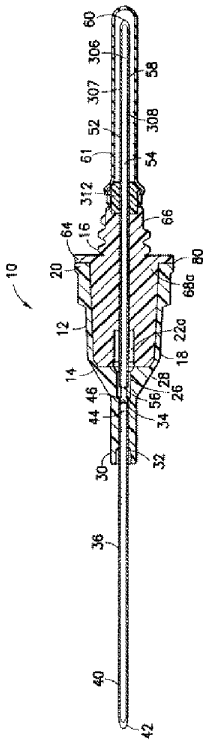
【図5】


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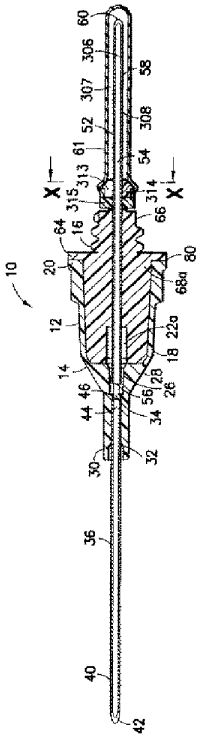
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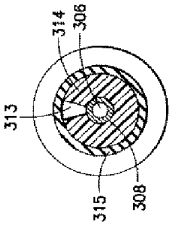
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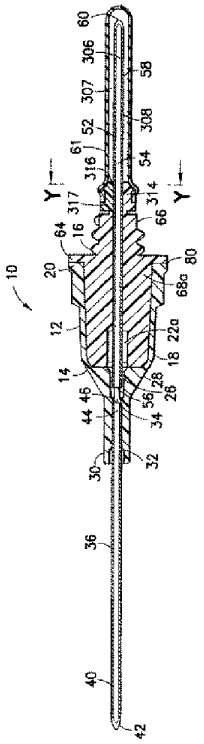
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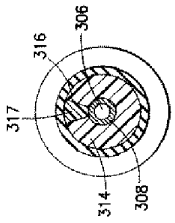
【図8B】



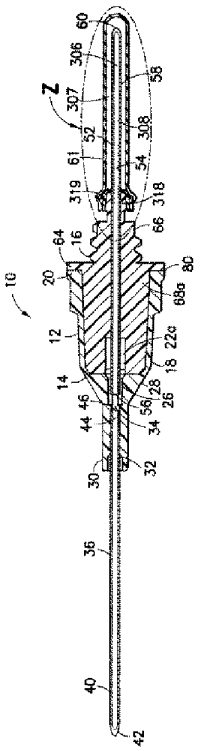
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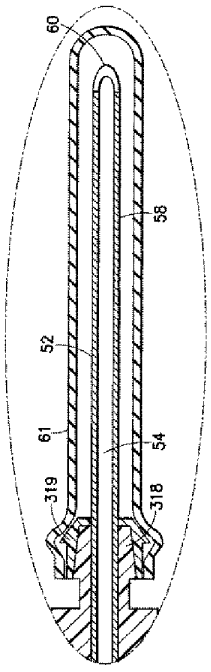
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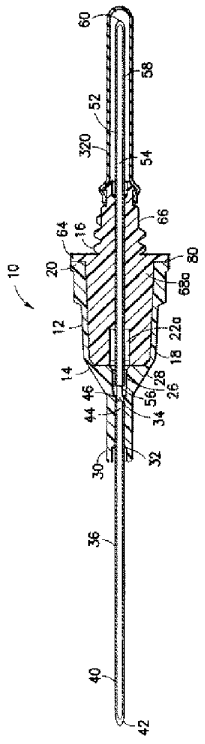
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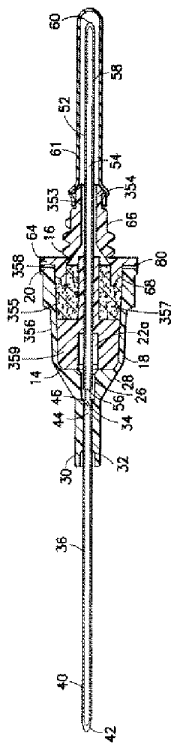
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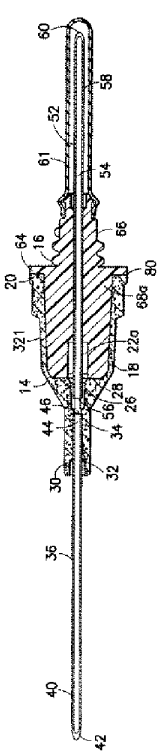
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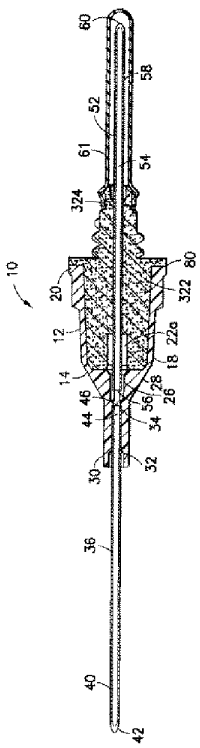
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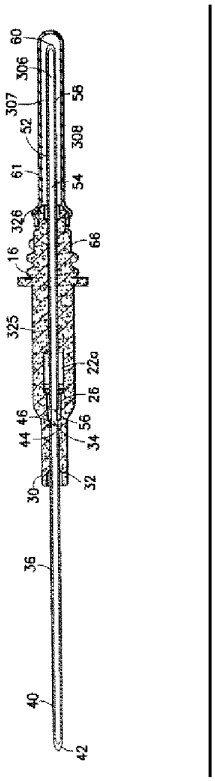
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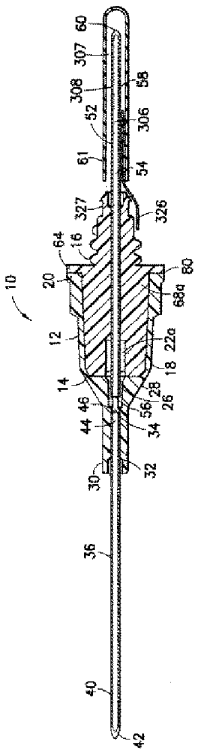
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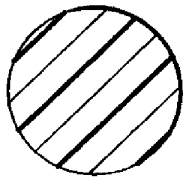
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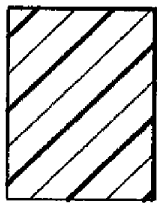
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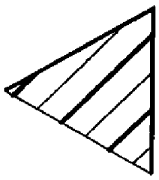
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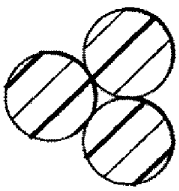
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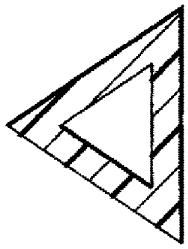
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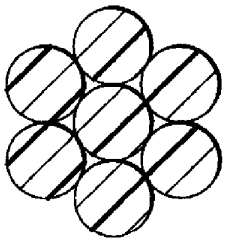
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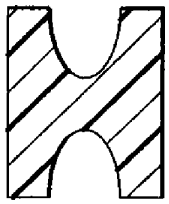
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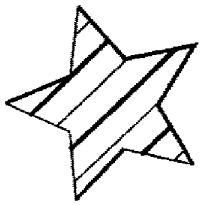
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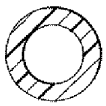
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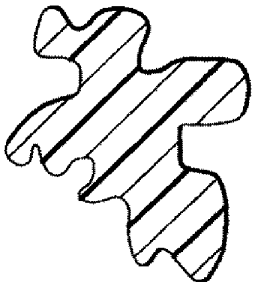
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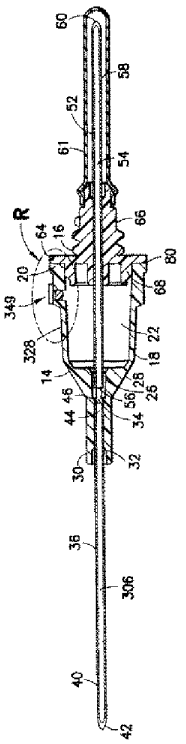
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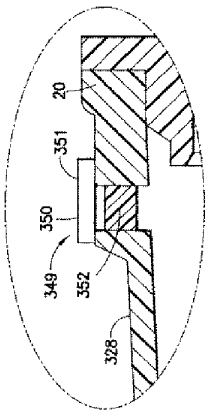
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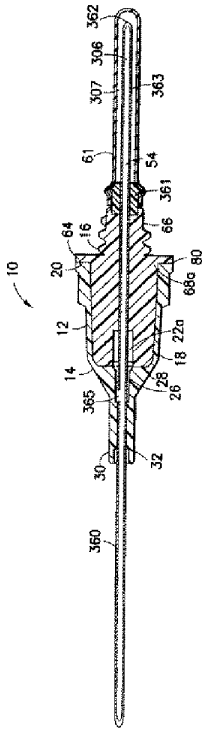
【図27A】



【図27B】



【図28】


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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

Espacenet

Bibliographic data: WO2007033319 (A1) — 2007-03-22

CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING

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Classification: **- international:** ***A61B5/15***
- cooperative: **A61B5/0215 (EP, US); A61B5/15003 (EP, US); A61B5/150221 (EP, US); A61B5/150816 (EP, US); A61B5/150824 (EP, US); A61B5/150992 (EP, US); A61B5/1535 (EP, US);** A61B5/150236 (EP, US); A61B5/150244 (EP, US)

Application number: WO2006US35832 20060913 Global Dossier

Priority number(s): US20050717119P 20050913 ; US20050720263P 20050921

Also published as: AT440541 (T) CA2623420 (A1) CA2623420 (C) CN101262818 (A) CN101262818 (B) more

Abstract of WO2007033319 (A1)

A closed blood sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The valve is a stopcock-like device that includes a rotating valve member and attached control handle with clear visible and tactile indicators for the mode of operation. The rotating valve member has a number of internal and circumferential channels for connecting or disconnecting select ports in the core of the valve. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room. The valve may also incorporate a blunt cannula sampling site therewithin.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 March 2007 (22.03.2007)

PCT

(10) International Publication Number
WO 2007/033319 A1

(51) International Patent Classification:
A61B 5/15 (2006.01)

(21) International Application Number:
PCT/US2006/035832

(22) International Filing Date:
13 September 2006 (13.09.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/717,119 13 September 2005 (13.09.2005) US
60/720,263 21 September 2005 (21.09.2005) US

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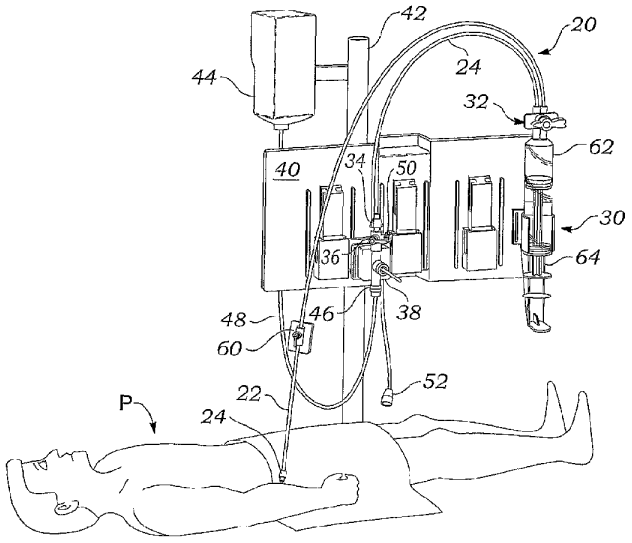
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) Title: CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING



(57) Abstract: A closed blood sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The valve is a stopcock-like device that includes a rotating valve member and attached control handle with clear visible and tactile indicators for the mode of operation. The rotating valve member has a number of internal and circumferential channels for connecting or disconnecting select ports in the core of the valve. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room. The valve may also incorporate a blunt cannula sampling site therewithin.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

CLOSED BLOOD SAMPLING SYSTEM WITH ISOLATED PRESSURE MONITORING

Field of the Invention

[0001] The present invention relates to blood sampling systems and, in particular, to closed blood sampling systems with a clearing reservoir and pressure monitoring.

Background of the Invention

[0002] In a hospital setting there is always the need to monitor patient health through the evaluation of blood chemistry profile. The simplest method employed in the hospital is to use a syringe carrying a sharpened cannula at one end and insert that cannula into a vein or artery to extract a blood sample from the patient. Patients that are in the critical care units or the operating room sometimes require as many as twelve samples a day. Such frequent sampling injections potentially expose the patient to airborne bacteria and viruses which can enter the bloodstream through the opening made by the sharpened cannula.

[0003] One way to obtain a blood sample is to draw the blood from a catheter that is already inserted in the patient, either in a central venous line, such as one placed in the right atrium, or in an arterial line. Typically, existing injection sites for arterial or venous drug infusion or pressure monitoring lines are used to take periodic blood samples from the patient. Conventional mechanisms for drawing blood from the lines used for infusion or pressure monitoring utilize a plurality of stopcock mechanisms that preclude flow from the infusion fluid supply or from the pressure column drip supply, while allowing blood to flow from the patient into a collecting syringe connected to a proximal port formed in one of the stopcocks. Typically, a blunt cannula through a slit septum is used to remove the danger of sticking the nurse or clinician, in a so-called "needle-less" system.

[0004] Most early systems required a two-step operation where a first sample of fluid, generally about 5ml in volume for intensive care environments was withdrawn into the sampling syringe and discarded. This first sample potentially included some of the infusion fluid and thus would be an unreliable blood chemistry measurement sample. After the initial sample had been discharged, the second sample was pure blood from the artery or vein and was typically re-infused to the patient.

[0005] In response to the drawbacks associated with earlier two-step sampling systems, closed systems were developed as described in U.S. Patent No. 4,673,386 to Gordon, and more recently in U.S. Patent No. 5,961,472 to Swendson, which are expressly incorporated by reference herein. Commercial closed systems such as the Edwards VAMP® and VAMP Plus® Venous Arterial blood Management Protection systems of Edwards Lifesciences in Irvine, CA feature a reservoir in the tubing line from the patient that can draw fluid past a sampling port. The clearing volume is held in the in-line reservoir, and not set-aside in a syringe for re-infusion later. The sampling systems are often used in conjunction with a pressure monitor having a transducer continually or periodically sensing pressure within the sampling line except during the draw of a blood sample.

[0006] The VAMP Plus® system conveniently utilizes a reservoir with one-handed operability, and includes a line from the patient into and out of the reservoir and to a proximal source of flushing fluid and a pressure transducer. (The standard directional nomenclature is that proximal is toward the clinician, or away from the patient, and distal is toward the patient). A stopcock valve at the reservoir controls the mode of operation. Prior to drawing a blood sample, the reservoir plunger is latched closed, though a reservoir gap allows a continuous drip of IV flushing fluid through an inlet port to an outlet port. A pressure transducer in the line proximal to the reservoir senses fluid pressure within the line and conveys the signal to a monitor. One exemplary pressure transducer used with both the VAMP® and

VAMP Plus® systems is the Edwards TruWave® Disposable Pressure Transducer.

[0007] When a blood sample is to be taken, the flow of flushing or infusion fluid is halted by turning the handle of the reservoir stopcock valve. The nurse or clinician then withdraws an amount of fluid into the reservoir chamber and distal line sufficient to pull pure blood past one or more fluid sampling sites. After full retraction of the plunger, the stopcock valve closes off the reservoir from the patient and a sample of blood is taken at one or the other sampling sites. Subsequently, the clinician manipulates the stopcock valve so that the volume within the reservoir can be reinfused back into the patient by depressing the plunger, and the flushing drip and pressure monitoring resumes.

[0008] In the closed blood sampling/pressure monitoring systems described above, the pressure transducer typically includes a diaphragm exposed to the in-line fluid on one side and has a device for measuring deflection of the diaphragm on the other. Such pressure lines typically make use of relatively stiff tubing primed with a suitable physiological fluid such as saline or 5% dextrose solution as a pressure column. For adults, a bag pressurized with air surrounds the fluid supply bag to maintain a constant pressure differential in the line urging fluid toward the patient through a restrictor orifice. The slow drip of physiological fluid flushes the line to prevent clotting. Some transducers such as the TruWave® Disposable Pressure Transducer include a flush device that also can be used for sending transient pressure waves through the line. A Snap-Tab™ device of the TruWave® is a rubber tab which when pulled and then released sends a square wave through the pressure column to check the inherent frequency response of the entire system, which includes the tubing and any components attached thereto, such as the sampling ports and reservoir. Proper system frequency response is necessary for reliable blood pressure measurements. In general, a more accurate signal may be obtained with a shorter sampling line and fewer

components so that the transducer is closer to the patient and there is less delay between the generation and receipt of the blood pressure signal, and less interference. However the limited amount of space available or the location of the anesthesiologist during a surgical procedure often necessitates a relatively long tubing line which degrades the signal. Furthermore, minimum functionality of the system requires various components such as sampling sites be included.

[0009] In view of the foregoing, there is a need for a blood sampling system used in conjunction with a pressure transducer that produces more accurate pressure readings.

Summary of the Invention

[0010] The present invention provides a fluid sampling system within a pressure monitoring line having a control valve that enables a clearance reservoir to be isolated from the pressure column when no samples are being taken. The control valve further permits complete flushing of the system with no dead spaces. Additionally, control valve desirably incorporates a sampling port therein capable of isolating the sampling port from the clearance reservoir. By isolating the clearance reservoir, the quality of the pressure signal is improved such that the sampling line can be lengthened for greater convenience in the intensive care or operating room.

[0011] In accordance with a first embodiment of the invention, a medical system for fluid sampling and pressure monitoring of a fluid system of a patient is provided. The system includes a conduit line with a proximal segment adapted to be supplied with a physiological fluid (e.g., saline) and a distal segment adapted to be in communication with a fluid system of a patient. A control valve has a manifold defining an interior chamber. The manifold has a proximal port fluidly connected to the proximal segment, a distal port fluidly connected to the distal segment, and a reservoir port,

wherein each of the manifold ports opens to the interior chamber. A system further includes a fluid sampling port and pressure transducer connected to the conduit line for sensing the pressure of the fluid therein. A reservoir fluidly communicates with the reservoir port of the control valve manifold. The control valve further includes a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports. The valve member is movable into at least two positions:

a first position that provides open fluid communication from the proximal segment to the patient through the control valve so as to eliminate any dead spaces therein, wherein reduced pressure within the reservoir pulls fluid from the distal segment through the control valve and into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port, and

a second position that provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member to the distal segment while bypassing the reservoir, such that the pressure of fluid within the conduit line exclusive of the reservoir can be sensed by the pressure transducer.

[0012] Desirably, the valve member also has a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

[0013] In a preferred embodiment the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, wherein mating features on the valve member core and manifold provide tactile feedback and positive positioning of the core in both first and second positions. Alternatively, or in addition, coordinated visible features on the control handle and manifold provide symbolic indicators of both first and second positions of the valve member.

[0014] The sampling port may be formed within the control valve or along the distal segment of the conduit line. If within the control valve, the sampling port may be formed within the valve member and communicates with a sampling cavity formed internally within the valve member open to at least one of the channels. Alternatively, the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the interior chamber of the manifold. Furthermore, the system may include a second sampling port having a sampling cavity positioned along the distal segment of the conduit line.

[0015] In accordance with one embodiment, the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold, the core having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core. The internal channel desirably opens to the exterior surface of the core at two separated locations spaced from the external channel.

[0016] System further may include means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position. Desirably, the reservoir has an inlet open to an outlet port of the control valve manifold and an outlet open to an inlet port of the control valve manifold. In this embodiment, the first position of the valve member provides open fluid communication between the control valve flow passages through the inlet and outlet of the reservoir to flush a chamber of the reservoir.

[0017] A second embodiment of the present invention comprises a medical system for fluid sampling of a fluid system of a patient. The system encompasses a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient. A control valve connects between the proximal segment and the distal segment of the conduit line. A

fluid sampling port defines a flow path therethrough whose opposite ends open to internal channels in the control valve. A reservoir fluidly communicates with a reservoir port of the control valve manifold. The control valve further includes a valve member movable into at least three positions:

a first position that provides open fluid communication from the proximal segment through the control valve to the distal segment,

a second position that provides open fluid communication from the proximal segment to the distal segment while bypassing the reservoir and sampling port, and

a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

[0018] Desirably, the control valve further includes a manifold defining an interior chamber. The manifold has a proximal port fluidly connected to the proximal segment of the conduit line, a distal port fluidly connected to the distal segment, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber. The valve member also comprises a core movable within the interior chamber of the manifold and having channels therein that selectively communicate with the manifold ports. The reservoir has an inlet open to the manifold outlet port and an outlet open to the manifold inlet port. In this embodiment:

the first position provides open fluid communication from the proximal segment to the proximal port and the outlet port of the control valve, through the inlet and outlet of the reservoir, to the inlet port and the distal port of the control valve to the distal segment,

the second position provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member core to the distal segment while bypassing the reservoir and sampling port, and

the third position provides open fluid communication from the distal segment to distal port and one of the channels of the valve member core, and to the sampling port.

[0019] The valve member core may have an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core. Desirably, the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

[0020] Another aspect of the invention is a method of taking samples and measuring the pressure of a fluid system of a patient. The method provides a fluid sampling system with a conduit line and a reservoir connected thereto between a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient. A control valve interposed between the reservoir and the conduit line has a movable valve member with a control handle, the valve member movable into at least a first position and a second position. A pressure transducer connects to the conduit line for sensing the pressure of the fluid therein, and a fluid sampling port is provided in the sampling system.

[0021] The method includes selecting the first position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve and the reservoir, and creating a reduced pressure within the reservoir such that fluid flows from the distal segment through the control valve into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port. The method further includes selecting the second position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve while bypassing the reservoir, and monitoring the pressure sensed by the pressure transducer. Desirably, the valve member has a third position, and the method includes selecting the third position of the valve

member to provide open fluid communication from the distal segment to the sampling port but prevent communication between the sampling port and both the reservoir and the proximal segment, and sampling fluid from the conduit line through the sampling port.

[0022] In a preferred embodiment, the fluid system of the patient is the blood system, and the method further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position. In this instance, the method including the steps of:

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient; then

creating a reduced pressure within reservoir and collecting sufficient fluid therein such that blood flows past the sampling port; then

selecting the third position of the valve member; then

sampling blood from the conduit line through the sampling port; then

creating an elevated pressure within the reservoir to expel blood therefrom into the distal segment of the conduit line; then

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient and flushes the reservoir of blood; and then

selecting the second position of the valve member and monitoring the pressure sensed by the pressure transducer.

[0023] Preferably, the control valve has a manifold defining an interior chamber within which the valve member rotates, and further including mating features on the valve member and manifold that provide tactile feedback and positive positioning of the core in both first and second positions, the method of selecting the first and second positions further including rotating the valve member until the tactile feedback is sensed. Or, the control valve includes

visible features that provide symbolic indicators of the first and second positions of the control handle, the method of selecting the first and second positions further includes interpreting the symbolic indicators to determine the placement of the control handle corresponding to the first and second positions.

[0024] Another useful aspect of the present invention is a medical system for fluid sampling of a fluid system of a patient. The sampling system includes a conduit line with a proximal end adapted to be supplied with a physiological fluid and a distal end adapted to be in communication with a fluid system of a patient. A pressure transducer connects to the conduit line for sensing the pressure of the fluid therein, and a fluid sampling port is provided having a sampling cavity. A control valve interposes between the conduit line and the sampling port and has a manifold defining an interior chamber. The manifold further includes a proximal port fluidly connected to the conduit line, a distal port fluidly connected to the conduit line, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber. The control valve also has a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least three positions:

a first position that provides open fluid communication from the conduit line to the proximal port and the outlet port of the control valve to the sampling cavity, and to the inlet port and the distal port of the control valve to the conduit line,

a second position that provides open fluid communication from the conduit line to the proximal port and through at least one channel in the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal end of the conduit line through the control valve to the sampling port but prevents communication between the sampling port and the proximal end of the conduit line.

[0025] A further understanding of the nature and advantages of the present invention are set forth in the following description and claims, particularly when considered in conjunction with the accompanying drawings in which like parts bear like reference numerals.

Brief Description of the Drawings

[0026] Features and advantages of the present invention will become appreciated as the same become better understood with reference to the specification, claims, and appended drawings wherein:

[0027] Fig. 1 illustrates a typical hospital room setup of a fluid sampling system of the present invention incorporating a reservoir, the sampling port, and a pressure transducer within a conduit line to a patient;

[0028] Figure 2 is a perspective view of a reservoir of the fluid sampling system in Figure 1 having an attached control valve of the present invention;

[0029] Figures 3A-3C are several orthogonal views of one end of the reservoir showing the control valve;

[0030] Figure 4 is a close-up perspective view of the control valve on the end of the reservoir having a central sampling port in a rotatable valve member;

[0031] Figure 5 is an exploded perspective view of the control valve;

[0032] Figures 6-11 are various external and sectional views of the rotatable valve member used in the control valve shown in Figures 4 and 5;

[0033] Figures 12-15 are various external and sectional views of a manifold of the control valve of Figures 4 and 5;

[0034] Figures 16 and 17 are axial sectional views of the control valve of the present invention taken along lines 16-16 and 17-17, respectively, of Figure 4;

[0035] Figures 18A-18C are axial sectional views of the control valve taken along line 18-18 of Figure 4 showing the positions of interior fluid flow channels for different positions of the valve member;

[0036] Figures 19A-19C are views similar to Figures 18A-18C of the interior fluid flow channels for the three different positions of the control valve showing selective interconnections between the various manifold ports;

[0037] Figures 20A-20E are various external and sectional views of an alternative control valve of the present invention with a different arrangement of internal flow paths and a central sampling port;

[0038] Figures 21A-21E are various external and sectional views of an alternative control valve with a different arrangement of internal flow paths and a luer-style central sampling port;

[0039] Figures 22A-22E are various external and sectional views of an alternative control valve with a sampling port extending from the side of a manifold;

[0040] Figures 23A-23E are various external views of a luer-style valved sampling port;

[0041] Figure 24 is an axial sectional view of the valved sampling port of Figures 23A-23E; and

[0042] Figures 25A-25E are various external and sectional views of a further alternative valved sampling port with the sampling port extending from the side of a manifold.

Detailed Description of the Preferred Embodiments

[0043] The present invention provides an improved closed blood sampling system in conjunction with pressure monitor. As mentioned above, continuous or periodic blood pressure monitoring is a common and extremely

useful tool in the intensive care or operating room. However, it should be mentioned that the apparatuses and methods described herein could be utilized in conjunction with any fluid system of a patient which would benefit from pressure monitoring. For instance, intracranial pressures could be monitored and cerebrospinal fluid samples taken by placing the system described herein in fluid communication with an intraventricular catheter. Therefore, the appended claims cover the sampling and monitoring of any fluid system within a patient unless otherwise specified.

[0044] The present invention comprises an improved, closed, one-handed fluid sampling system especially useful for sampling blood in the operating room or critical care unit (CCU). The overall functioning of the system is similar to those in the prior art, in particular the VAMP Plus® Venous Arterial blood Management Protection system available from Edwards Lifesciences of Irvine, CA. Furthermore, the blood sampling function is desirably combined with a pressure transducer and monitoring hardware. The term "closed fluid sampling system" should be understood to include both systems that have a dedicated reservoir (i.e., one that remains connected) and that utilize a removable reservoir (or syringe) that gains access to the fluid column through a port. As explained above, dedicated reservoirs are preferred because of their enhanced sterility, but the feature of the present invention that isolates the reservoir from the fluid pressure column may also be useful with removable reservoirs.

[0045] Figure 1 illustrates an exemplary blood sampling system 20 of the present invention in the environment of a typical set up in a hospital room and connected to a patient P. The blood sampling system 20 comprises a conduit line having a distal segment 22 toward the patient and a proximal segment 24. The conduit line is primarily medical grade pressure tubing. The distal segment 22 may terminate in a male luer connector 26 for attaching to a female luer connector (not shown) of an injection site, or other conduit leading to the patient. A reservoir 30 connects to the conduit line via a control valve

32 interposed between the distal segment 22 proximal segment 24. The control valve 32 externally resembles a stopcock and controls fluid flow between the conduit line and the reservoir 30.

[0046] The proximal segment 24 extends from the control valve 32 and terminates in a female luer connector 34 attached to a stopcock 36 of a pressure transducer 38. The reservoir 30 and pressure transducer 38 removably mount to a bracket 40 which, in turn, may be secured to a conventional pole support 42 with the reservoir in a vertical orientation.

[0047] As mentioned above, the blood sampling system 20 forms a portion of a pressure monitoring system, and the fluid pressure transducer 36 may be a TruWave™ Disposable Pressure Transducer available from Edwards Lifesciences of Irvine, CA. A supply of flush solution 44 connects to a flush port 46 of the transducer 38 via tubing 48. Typically for adults, the flush solution 44 comprises a bag of physiological fluid such as saline surrounded by a pressurized sleeve that squeezes the fluid and forces it through the tubing 48. In addition, an infusion fluid supply (not shown) may be provided in communication with an infusion port 50 of the stopcock 36. The pressure transducer 38 is thus placed in fluid communication with the arterial or venous system of the patient through the conduit line, and preferably includes a cable and plug 52 to connect to a suitable display monitor (not shown). Though the pressure transducer 38 is shown positioned within the proximal segment 24, it could also be located in the distal segment 22.

[0048] The sampling system 20 further comprises a fluid sampling site 60 that desirably defines a Z-shaped flow passage adjacent a pre-slit septum (not numbered). With this configuration, a minimal amount of flush volume is needed to clear the line after sampling. The septum preferably comprises an elastomeric disc which accepts a blunt cannula and reseals after each sample is drawn, reducing the potential for contamination and eliminating the danger of needle sticks. Such sampling site is described in U.S. Patent No. 5,135,489 to Jepson, et al., which is hereby expressly incorporated by reference.

[0049] Figure 2 better illustrates one embodiment of a blood sampling reservoir 30 of the present invention removed from the bracket 40. The reservoir 30 desirably includes a syringe-type variable volume chamber 62, though other reservoirs that have constant volume chambers or other receptacles for receiving fluid may be used. Preferably, the reservoir 30 is of a type that includes a constantly open flow channel through the variable volume chamber 62 for passage of flushing fluid therethrough. A particularly useful such reservoir 30 is the Edwards VAMP Plus® system mentioned above.

[0050] In one mode of operation of the system 20, a reduced pressure is created within the variable volume chamber 62 by withdrawing the plunger 64 such that a fluid sample from the distal segment 22 is drawn into the chamber. The chamber 62 has a sufficient volume, typically 12 ml, to draw blood from the patient P passed the sampling site 60. The clinician can then take a sample of undiluted blood from the site 60. Subsequently, the blood and other fluids drawn into the reservoir 30 during the sampling operation are re-infused by depressing the plunger 64. It should be noted that the pressure transducer 38 may include a flow restrictor or flow control means to prevent flushed solution from going proximally through the sensor rather than back to the patient. For instance, the stopcock 36 may be used to close off the fluid path through the pressure transducer 38 prior to re-infusing the reservoir clearance volume.

[0051] The entire sampling system 20 is thus closed as the "priming" volume that ensures a pure sample of blood reaches the sampling site 60 remains within the system 20 and is reinfused into the patient. It will be understood by those skilled in the art that the syringe-type reservoir 30 shown in Figures 1-2 is only exemplary and other configurations may be designed to adequately provide the variable volume chamber.

[0052] With reference now to Figures 3A-3C and 4-5, the proximate relationship between the reservoir 30 and the control valve 32 will be described. Desirably, the reservoir 30 and control valve 32 are molded plastic

pieces that are rigidly mounted together such as with adhesive or ultrasonic welding. However, the reservoir 30 simply needs to be in proximity with the control valve 32 such that they are connected by two fluid flow paths. For convention, the ordinary flow path of the whole system as seen in Figure 1 is from proximal to distal, or from the fluid bag 44 to the patient P. With reference back to Figure 2, the saline or other physiological fluid flows into the reservoir 30 and control valve 32 combination through the proximal segment 24 of the conduit line and flows out of the distal segment 22. In this regard, therefore, the reservoir 30 has an inlet that receives saline from an outlet port of the control valve 32, and also an outlet through which saline flows to an inlet port of the control valve. These internal flow paths and channels will become clearer below, and as mentioned are desirably molded into the mating sections of the reservoir 30 and control valve 32. It is entirely feasible, however, to separate these two components with short lengths of tubing.

[0053] The control valve 32 as best seen in Figures 4-5 comprises a manifold 70 that receives a movable valve member 72. In the exemplary embodiment, the manifold 70 defines a cylindrical interior chamber 74 sized to rotatably receive a generally cylindrical core 76 of the valve member 72. A control handle 78 extends externally from the chamber 74 and provides leverage for rotating the core 76 within the chamber. The interior chamber 74 is shown oriented 90° from the axis of the reservoir 30, although other arrangements are possible.

[0054] Figures 4 and 5 further illustrate an exemplary fluid sampling port 84 provided in an outer portion of the control handle 78. The fluid sampling 44 may take a variety of forms, but as illustrated includes an elastomeric slit septum 86 captured by a cap 88 over a sampling cavity 90 within the valve member 72. The assembly seen in Figure 4 provides access for a blunt cannula through the slit septum 86 to withdraw fluid from within the sampling cavity 90. The sampling site 84 is located along the center line

of the rotating valve member 72, although as will be explained below, other locations for a sampling site within the control valve are contemplated.

[0055] Figures 4 and 5 also illustrate exemplary indicators for the various rotational positions of the valve member 72 within the manifold 70. More specifically, the preferred form of the invention includes both tactile and visual indicators to help reduce clinician errors, speed up and clarify the process. The visual indicators include an arrow-shaped control handle 78 with a pointed end 92 that registers with one of three symbols 94a, 94b, 94c raised and/or printed on a faceplate 96 of the control valve 32. The valve member 72 may be rotated to one of the three positions with the pointed end 92 registering with one of the three symbols 94a, 94b, 94c. The indicator plate 96 shows the three position indicators 94 at the 0°, 90°, and 180° locations relative to a 0° horizontal reference line to the right (3:00). The 90° angular separation between the positions of the valve member 72 facilitates selection of one of three modes. An arc-shaped lip 98 projecting from an outer end of the interior chamber body desirably interferes with a small tooth 99 (see Fig. 6A) on the valve member 72 to prevent its rotation into the fourth, unmarked quadrant. The meaning of the symbols 94a, 94b, 94c will become apparent below. 91 psuedo inlet/outlet port, good flushing

[0056] In addition to visual indicators, the control valve 32 also desirably provides tactile feedback to the operator when the valve member 72 is in one of the three discrete positions. There are a number of ways to indicate tactilely the proper positioning of a rotating body within another, but the means used in the present context also preferably provide positive positioning of the valve member 72 within the interior chamber 74. For example, a small rib or bump 100 extending inward from the chamber 74 or lip 78 may be sized in position to register with small grooves or depressions 102 formed in the valve member core 76. These mating features are preferably sized large enough for the male portion to fit within the female portion and nominally restrain motion of the valve member 72, but small

enough to allow the user to relatively easily overcome their engagement and further rotate the valve member. As the engaging pieces are molded plastic, and the assembly is designed to be used once and disposed of, small rounded bumps engaging equal sized depressions are an effective short-term tactile indicator. It should be understood that the bumps and depressions could be provided on the parts as shown, or on the opposite elements in a reverse configuration. Moreover, these physical mating features desirably emit a small click when engaging, which provides a third, aural indicator.

[0057] Figures 6A-6E and 7-11 provide details of the exemplary valve member 72 having the central sampling port 84 therein. With reference to Figure 6A, the core 76 has a generally cylindrical exterior that slightly narrows away from the control handle 78 and is interrupted at a lower end by a trough 110 bordered by two shoulders 112. A pair of channels 114, 116 through the interior of the core 76 open to the core exterior at two locations separated circumferentially by almost 90° but in a common radial plane (as used herein, "radial" is relative to the rotational axis of the valve member 72). Looking at the reverse orientation of Figure 6E, the core 76 further features an arc-shaped groove or channel 120 that extends around the circumference of the core in a radial plane, preferably the same plane as that of the openings of the channels 114, 116. Figure 9 is a radial sectional view through that common plane and illustrates the relative positions and orientations of the channels 114, 116, 120.

[0058] The generally cylindrical portion of the core 76 is sized to closely fit within the interior chamber 74 of the manifold 70 (see Figure 5) such that the valve member 72 can rotate within the manifold but there is no unintended fluid leakage between the various ports and channels. The openings of the channels 14, 16 and the circumferential channel 120 lying in a common radial plane provide the only avenue for fluid passage around or through the valve member 72 when it is closely fit within the interior chamber 74. It should be understood that alternative configurations are possible with,

for example, the openings to the channels 114, 116 and circumferential channel 120 being spaced apart axially with respect to one or the others.

[0059] Figure 7 is an axial cross-sectional view through the valve member 72 that illustrates the inner components of the sampling port 84. Namely, the cap 88 restrains the elastomeric slit septum 86 over the sampling cavity 90. Figure 8 illustrates the sampling cavity 90 along a different axial plane that passes directly between a pair of axially-oriented channels 130, 132 seen in Figure 7 that communicate, respectively, with the radial channels 114, 116. Figure 8 further illustrates the generally semi-circular cross-section of the circumferential channel 120. With reference again to Figure 9, it should therefore be apparent that the radial channels 114, 116 are in constant fluid communication with each other via the respective connecting channels 130, 132 opening into the common sampling cavity 90. As will be explained below, these bifurcated channels through the valve member 72 function to permit blood or other body fluid into the sampling cavity 90, and also effectively flush the sampling cavity 90 in between samples. An axial extension 134 of the wall separating the connecting channels 130, 132 continues into close proximity with the slit septum 86. The extension 134 creates a pseudo inlet/outlet to the sampling cavity 90 such that a flow of flushing fluid therethrough is directed all the way to the slit septum 86 before turning the corner and continuing through the valve member 72. The extension 134 therefore enhances the efficacy of the flushing step and helps eliminate dead zones within the simply cavity 90 that might otherwise be a source of blood coagulation and contamination.

[0060] Structural details of the manifold 70 are seen in Figures 12-15. Specifically, the manifold 70 features a plurality of ports that opened into the interior chamber 74. A distal port 140 and a proximal port 142 extend upward from the chamber 74 in the orientation where the reservoir 30 plunger points downward. These ports 140, 142 are shown respectively connected to the distal segment 22 and proximal segment 24 of the conduit line in Figures 1

and 2. Therefore these ports 140, 142 represent the two diverging segments of the conduit line, the former extending toward the patient and the latter to the pressure transducer 38 and saline drip.

[0061] On the opposite side of the chamber 74, a manifold outlet port 144 leads to an inlet 146 to the reservoir variable volume chamber 62. An outlet 148 of the reservoir 30 leads directly into a manifold inlet port 150. The distal and proximal ports 140, 142 and outlet and inlet ports 144, 150 all open directly to the interior chamber 74 of the manifold 70. Note that one possible configuration is a reservoir connected through the control valve 32 using only a single reservoir port as opposed to inlet and outlet ports. For example, a syringe-type removable reservoir may be connected to a single port of the control valve 32. In such a system, the benefit of isolating the reservoir remains although the flush mode of operation will not pass through the reservoir. The term "reservoir port" therefore includes one or both of the outlet and inlet ports 144, 150.

[0062] Figures 13-14 show the manifold 70 having relatively long outlet and inlet ports 144, 150 leading to and from the reservoir 30 to provide some clearance for rotation of the valve member 72. Desirably, the manifold 70 is a single molded piece that is rigidly secured to the end of the reservoir 30. However, the manifold 70 could be a combination of more than one piece, and could be connected to the reservoir 30 through short tubes.

[0063] Figures 15A and 15B show the gradual taper of the interior chamber 74 at the narrow end of the chamber 74, a circular rib 160 projects inward for engaging and retaining the valve member 72, as will be explained next.

[0064] Figures 16 and 17 illustrate in cross-section the coupling of the valve member 72 within the manifold 70. Specifically, the gradual tapers of both closely match and provide an effective fluid seal at the point that the inward rib 160 of the manifold passes over the first shoulder 112 of the valve member 72 and resides within the trough 110. A cavity 162 in the narrow end

of the valve member 72 permits inward flexing of the shoulder 112 such that it can be forced passed the rib 160. Interference between the outwardly-sprung shoulder 112 and rib 160 effectively locks the valve member 72 within the manifold 70 and ensures good fluid sealing around the various ports and openings. Figure 16 shows the alignment of the proximal port 142 with the circumferential groove 120 two valve member 72. Likewise, the radial channel 114 also lies in the same plane. It is worth mentioning again at this stage that the coplanar nature of all of the ports and openings is an efficient and relatively straightforward design, but more complex fluid pathways between the rotating valve member 72 and manifold 70 could be designed to perform the same function. For example, one or more of the internal channels could be curvilinear, or there could be more than one circumferential surface channel.

[0065] Now with reference to Figures 18A-18C and 19A-1C, the fluid flow paths for the three positions of the valve member 72 will be explained.

[0066] The reader will recall from the description of the system of Figure 1 that there is a physiological fluid flush drip, preferably pressurized. When such flush is needed, the clinician rotates the valve member 72 to the downward position, as indicated by the arrow F/C in Figure 18A. This corresponds to a "Flush/Clear" mode of operation, and is symbolically indicated by the symbol 94a of three divergent flow paths in Figure 5, meaning all fluid communications are open. When pressure monitoring is desirable, the clinician rotates the valve member 72 to the left position, as indicated by the arrow M in Figure 18B. This corresponds to a "Monitoring" mode of operation, and is symbolically indicated by the symbol 94b of a pressure wave in Figure 5. Finally, when the clinician requires a fluid sample, he/she rotates the valve member 72 to the right position, as indicated by the arrow S in Figure 18C. This corresponds to a "Sampling" mode of operation, and is symbolically indicated by the symbol 94C of a drop of fluid in Figure 5. As mentioned above, the symbolic indicators 94a, 94b, and 94c are desirably

supplemented by the clear directional nature of the arrow-shaped control handle 78, and by tactile and audible feedback measures, to help avoid error.

[0067] Figures 18A-18C further illustrate the change in rotational orientation of the valve member 72 within the internal chamber of the manifold 70, in particular through the radial plane passing through the flow channels that open to the exterior of the valve member core 76. The same illustrations of the flow channels in the three positions are shown more clearly in Figures 19A-19C with relevant labels and fluid flows indicated. The two sets of diagrams further indicate the four manifold ports 140, 142, 144, and 150.

[0068] In the F/C position of the valve member 72 of Figures 18A and 19A, a slow drip of flushing fluid travels from the supply of flush solution 44 (Figure 1) through the proximal segment 24 (Figure 2) to the manifold proximal port 142, through the circumferential channel 120 and the outlet port 144. As indicated by the flow arrows in Figure 19A, the drip continues through the inlet 146 and outlet 148 of the reservoir 30 passing through the variable volume chamber 62. The fluid then passes through the inlet port 150 into the radial channel 114, and along the axial channel 130 into the sampling reservoir 90 (see Figure 7), and back through the parallel axial channel 132 into the other radial channel 132. Finally, the fluid exits the valve member 72 into the manifold distal port 140 and from there continues through the distal segment 22 of the conduit line to the patient.

[0069] In the F/C position of the valve member 72, all of the internal flow paths within the reservoir 30 and control valve 32 are open to form a single continuous flushing pathway. This desirably permits any blood or other bodily fluid to be completely flushed from within the system 20, leaving no dead spots for bubbles to form or blood to coagulate. This "pocket-less" fluid pathway through the system in conjunction with the ability to isolate components that degrade the pressure signal is extremely useful. Furthermore, the control valve 32 is desirably made of transparent or frosted plastic that

permits the user to visualize blood flow therethrough, thus insuring blood as been completely flushed out of the system after a sample is taken.

[0070] The F/C position also enables a clearing volume to be pulled into the reservoir 30. Specifically, a reduced pressure within the variable volume chamber 62 pulls fluid from the distal segment 22 into the reservoir 30 in a reverse flow from that shown in Fig. 19A. The volume of the chamber 62 is sufficient to draw blood from the patient past the sampling port 84 (sampling cavity 90), that is, through the internal channels of the valve member 72. A flow restrictor or control valve at the pressure transducer 38 toward the proximal segment 24 ensures that the reservoir 30 fills with fluid from the distal segment 22. That is, there is greater resistance to flow into the reservoir from the proximal segment 24 as compared to the distal segment 22.

[0071] Before a sample is taken, however, the control handle 78 must be rotated into the third S position shown in Figures 18C and 19C. In this position, the channels of the valve member 72 provide open fluid communication only from the distal port 140 to the radial channel 114 as shown, and from there to the sampling cavity 90 (Figure 7). A fluid sample is taken from the port 84 using a blunt cannula or other sampling device.

[0072] Pressure monitoring occurs with the valve member 72 in the second M position shown in Figures 18B and 19B. In that position, the pressure transducer 38 (or DPT, Disposable Pressure Transducer), is in fluid communication with the patient directly though the circumferential channel 120, bypassing the reservoir 30 and sampling port 84. This feature of the control valve 32 isolates the elastomeric elements of the reservoir 30 and sampling port 84, as well as the associated channels leading thereto, from the fluid pressure column. The fluid pressure column therefore extends directly from the patient through the distal segment 22, making a U-turn in the circumferential channel 120 to the proximal segment 24. Bypassing the reservoir 30, and in particular the elastomeric seal of the plunger 64, and the sampling port 84 (elastomeric septum 86), greatly improves the signals

received by the pressure transducer 38. A distal sampling port 60 in the distal segment 22 may be of a conventional type which includes an elastomeric septum that would affect the pressure signal, or that sampling port may also be isolated from the pressure column as will be described below. One benefit of improving the pressure response of the system by isolating the various functional elements is that the entire conduit line can be lengthened to move the reservoir 30 farther away from the patient. In conventional blood sampling systems, where the elastomeric components remain in contact with the pressure column, the maximum length of the conduit line from the reservoir to the patient is about __ cm. By isolating just the reservoir 30 as indicated above, the conduit line can be lengthened to about __cm. [Mark, please fill in these distances]

[0073] It is important to understand that the principles of the control valve 32 described above are applicable to other configurations of fluid sampling systems. In the exemplary system described above, a sampling port 84 is incorporated centrally in the rotating valve member 72 of the control valve 32, which is connected or adjacent to the reservoir 30. The control valve 32 isolates both the reservoir and the sampling port in the sampling mode. However, the sampling port in the control valve may connect through the manifold 70 instead of the valve member 72. Also, the exemplary valve member has three positions 90° apart from each other, but the arrangement of the channels within the valve member and manifold may be altered to change the amount of the valve member rotates in each position. Furthermore, the principles of isolating the elastomeric elements of the reservoir and sampling port can be transferred to a stand-along sampling port in the conduit line. Examples of each of these alternatives will be described below, and it should be clear that these are representative of numerous other alternatives.

[0074] Figures 20A-20E illustrate an alternative control valve 170 of the present invention adjacent a reservoir 30 with a modified arrangement of internal flow paths than the exemplary embodiment described above. The

control valve 170 is similar to the first embodiment in that a housing or manifold 172 connects to the reservoir 30 and rotatably receives therein a valve member 174. Furthermore, the valve member 174 carries a central sampling port 176, which is illustrated as a slit septum-type but could be any number of kinds of sampling ports. Figure 20B shows a control handle 178 of the valve member 174 oriented with its pointed and 180 down into the right at about a 45° angle. The indicator plate 182 shows the three position indicators at the 45°, 90°, and 180° locations relative to a horizontal reference line to the right at 0°. This is a departure from the 90° separation between the valve member positions in the first embodiment.

[0075] The control handle 178 in Figure 20B is in the "S" or sampling position. The internal flow channels defined within the valve member 174 in the radial plane of the ports of the manifold 172 are illustrated in Figure 20E. Comparing this view with a similar view shown in Figure 18C, the reader will discern the slightly different orientations of the internal channels within the valve member 174. By rotating the valve member 174 clockwise another 45°, the control valve 170 will be placed in the F/C mode wherein all of the internal flow paths are in series so that the system can be flushed. Rotating the valve member 174 a further 90° into the M position isolates both the reservoir 30 and the sampling port 176 from the attached conduit line for undegraded pressure monitoring. Although the relative spacing between the S position and the F/C position is only 45°, in contrast with 90° in the first embodiment, the flow channels are modified to prevent cross-talk or pressure perturbations transmitted to the proximal segment and pressure transducer when switching positions. Furthermore, the channels are arranged so that there is greater separation between the internal channels in the sampling mode.

[0076] Figures 21A-21E show another alternative control valve 190 similar to the valve 170 of Figure 20A-20E, but with a luer-style central sampling port. Specifically, the control valve 190 includes the modified internal flow paths such that the three operating positions of a control handle

192 seen in Figure 21B are other than 90° apart. More particularly, the cross-section of Figure 21E is the same as that of Figure 20E. Also, the control valve 190 includes a sampling port 194 provided in the center of a rotatable valve member 196. In contrast to the embodiments of Figures 20A-20E, however, the sampling port 194 includes a luer-style connector 198, best seen in Figure 21C. The male luer-style connector 198 mates with a female luer connector on a sampling syringe (not shown). Because of the typically larger sizes of the blunt cannulas in such sampling syringes, the septum 200 of the sampling port 194 is highly compliant, or at least more compliant than the slit septum 86 used in the sampling port 84 described above. The ability to isolate the luer-style sampling port 194 using the control valve 190 is therefore highly desirable as it greatly improves the quality of the pressure signal received by the pressure transducer by removing the compliance of the septum 200 from the pressure column.

[0077] Figures 22A-22E illustrates a control valve 210 that, as before, may be associated with or connected to a reservoir 30, but includes an alternative fluid sampling port 212. Specifically, the fluid sampling port 212 comprises a side port from a control valve manifold 214 rather than being formed centrally in a rotatable valve member 216. The sampling port 212 is shown in cross-section in Figure 22E which reveals an elastomeric septum 220 captured by a cap 222 over a sampling cavity 224. A pair of flow channels 226, 228 open into the sampling cavity 224. The opposite ends of the flow channels 226, 228 opened to an interior chamber of the control valve manifold 214. In this sense, the sampling port 212 communicates with internal channels in the control valve 210 via a through flow path defined by the channels 226, 228.

[0078] Figure 22E also shows six openings to the internal channel of the manifold 214, two of which lead to the sampling port channels 226, 228. Another two openings lead to proximal and distal ports 230, 232 that connect to the proximal and distal conduit line segments. Finally, two more openings

lead respectively to the inlet and outlet of the reservoir 30. The valve member 216 includes circumferential channels that selectively communicate with these 6 ports depending on the rotational position of a handle 234. As with the earlier embodiments, there are 3 positions of flush, monitor, and sample. In the monitor position, the control valve 210 isolates both the reservoir 30 and sampling port 212 from the conduit line for a more accurate pressure signal. Also, the valve 210 prevents flow from the proximal conduit line segment in the sampling mode. This embodiment illustrates the alternative of having the sampling port connected with the control valve manifold as opposed to the rotating valve member. ;

Figures 23A-23E are various views of a luer-style valved sampling station 250 which can be incorporated into a pressure monitoring line in conjunction with a reservoir or independently. The valved sampling station 250 includes a housing or manifold 252 that defines therewithin an internal chamber 254 as seen in Figure 24 with which a pair of ports 256, 258 communicate. The downstream port 256 may be connected to the patient, while an upstream port 258 is connected to a pressure transducer (not shown), in like manner as the manifold ports 140, 142 seen in Figure 12. Additionally, a loop-shaped channel 260 formed in the manifold 252 has opposite ends that open to the internal chamber 254. A valve member 262 rotates within the internal chamber 254. The valve member 262 has the same configuration has the valve member 196 shown in Figures 21A-21E. That is, the internal flow channels are the same and the valve member 262 carries a central luer-type sampling port 264.

[0079] With reference to Figure 23B, the manifold 252 includes an indicator plate 266 on which are provided the familiar three operational mode symbols of sampling, flush, and pressure monitoring. A control handle 268 is used to rotate the valve member 262 into the three operational positions. The reader will recognize that the three positions have the same spacing as the positions for the control valve 190 in Figures 21A-21E. Indeed, the valved

sampling station 250 functions analogously to the control valve 190 in that in the pressure monitoring position of the control handle 268, the central sampling port 264 is isolated from the ports 256, 258, and thus the attached conduit line and pressure column. The sole difference between the valved sampling station 250 and the control valve 190 is the substitution of the loop-shaped channel 260 for the clearance reservoir. The channel 260 is important in that a flow of fluid passes through it and through all of the internal channels of the valved sampling station 250 when the control handle 268 is in the flush position, seen in Figure 23B. Again, the valved sampling station 250 can be used in a conduit line of a pressure monitoring system where a clearance volume of fluid is pulled past the sampling port using a reservoir as described above, or other such clearing device.

[0080] Finally, Figures 25A-25E illustrate a further alternative valved sampling station 280 with a sampling port 282 extending from one side of a manifold 284. The manifold 284 is configured in a T-shape with a pair of ports 286, 288 that open to an internal chamber projecting outward at 90° with respect to one another, and with respect to the sampling port 282. The valve member 290 rotates within the internal chamber. As seen in Figure 25E, the valve member 290 includes two circumferential channels 292, 294 that selectively communicate with the ports 286, 288, and with two ports 296, 298 leading to and from the sampling port 282. As in the valved sampling station 250 of Figures 23-24, the valve member 290 rotates into three positions corresponding to flush, sampling, and pressure monitoring. The ports 286, 288 attach to proximal and distal segments of a conduit line in a manner described above. In the pressure monitoring mode, the sampling station 280 excludes the sampling port 282 from the conduit line. This embodiment is similar to the immediately preceding sampling station 250, but illustrates a sampling port 282 that connects directly to the manifold 284 rather than to the rotating valve member 290. Furthermore, the sampling port 282 has a slit

septum 299 for receiving a blunt cannula (not shown), but a luer-type sampling port could also be used.

[0081] While the invention has been described in its preferred embodiments, it is to be understood that the words which have been used are words of description and not of limitation. Therefore, changes may be made within the appended claims without departing from the true scope of the invention.

WHAT IS CLAIMED IS:

1. A medical system for fluid sampling and pressure monitoring of a fluid system of a patient, comprising:

a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

a control valve with a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the proximal segment, a distal port fluidly connected to the distal segment, and a reservoir port, wherein each of the manifold ports opens to the interior chamber,

a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

a fluid sampling port in the medical system;

a reservoir in fluid communication with the reservoir port of the control valve manifold;

the control valve further including a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least two positions:

a first position that provides open fluid communication from the proximal segment to the patient through the control valve so as to eliminate any dead spaces therein, wherein reduced pressure within the reservoir pulls fluid from the distal segment through the control valve and into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port, and

a second position that provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member to the

distal segment while bypassing the reservoir, such that the pressure of fluid within the conduit line exclusive of the reservoir can be sensed by the pressure transducer.

2. The system of claim 1, wherein the valve member has a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

3. The system of claim 1, wherein the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, and further including mating features on the valve member core and manifold that provide tactile feedback and positive positioning of the core in both first and second positions.

4. The system of claim 1, wherein the valve member comprises a core rotatable within the interior chamber of the manifold and a control handle external to the manifold, further including coordinated visible features on the control handle and manifold that provide symbolic indicators of both first and second positions of the valve member.

5. The system of claim 1, wherein the sampling port is formed within the control valve.

6. The system of claim 5, wherein the sampling port is formed within the valve member and communicates with a sampling cavity formed internally within the valve member open to at least one of the channels.

7. The system of claim 5, wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the interior chamber of the manifold.

8. The system of claim 5, further including a second sampling port having a sampling cavity positioned along the distal segment of the conduit line.

9. The system of claim 8, further including a second control valve interposed between the second sampling port and the distal segment and having a valve member movable into at least three positions:

a first position that provides open fluid communication from the conduit line through the control valve to the sampling cavity and back to the conduit line,

a second position that provides open fluid communication from the conduit line through the valve member and back to the conduit line while bypassing the second sampling port, such that the pressure of fluid within the conduit line exclusive of the second sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal segment through the control valve to the second sampling port but prevents communication between the second sampling port and the conduit line proximal from the second sampling port.

10. The system of claim 1, wherein the sampling port is positioned along the distal segment of the conduit line.

11. The system of claim 10, further including a second control valve interposed between the sampling port and the distal segment and having a valve member movable into at least three positions:

a first position that provides open fluid communication from the conduit line through the control valve to the sampling cavity and back to the conduit line,

a second position that provides open fluid communication from the conduit line through the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal segment through the control valve to the sampling port but prevents communication between the sampling port and the conduit line proximal from the sampling port.

12. The system of claim 1, wherein the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold, the core having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

13. The system of claim 12, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

14. The system of claim 1, further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position.

15. The system of claim 1, wherein the reservoir has an inlet open to an outlet port of the control valve manifold and an outlet open to an inlet port of the control valve manifold, and wherein the first position of the valve member provides open fluid communication between the control valve flow passages through the inlet and outlet of the reservoir to flush a chamber of the reservoir.

16. A medical system for fluid sampling of a fluid system of a patient, comprising:

a conduit line with a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

a control valve connected between the proximal segment and the distal segment of the conduit line;

a fluid sampling port having a flow path therethrough whose opposite ends open to internal channels in the control valve;

a reservoir in fluid communication with a reservoir port of the control valve manifold;

the control valve further including a valve member movable into at least three positions:

a first position that provides open fluid communication from the proximal segment through the control valve to the distal segment,

a second position that provides open fluid communication from the proximal segment to the distal segment while bypassing the reservoir and sampling port, and

a third position that provides open fluid communication from the distal segment to the sampling port but prevents communication between the sampling port and both the reservoir and the proximal segment.

17. The system of claim 16, wherein:

the control valve further includes a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the proximal segment of the conduit line, a distal port fluidly connected to the distal segment, an outlet port, and an inlet port, wherein each of the manifold ports opens to the interior chamber, and wherein the valve member comprises a core movable within the interior chamber of the manifold and having channels therein that selectively communicate with the manifold ports, and the reservoir has an inlet open to the manifold outlet port and an outlet open to the manifold inlet port, and wherein:

the first position provides open fluid communication from the proximal segment to the proximal port and the outlet port of the control valve, through the inlet and outlet of the reservoir, to the inlet port and the distal port of the control valve to the distal segment,

the second position provides open fluid communication from the proximal segment to the proximal port and through at least one channel in the valve member core to the distal segment while bypassing the reservoir and sampling port, and

the third position provides open fluid communication from the distal segment to distal port and one of the channels of the valve member core, and to the sampling port.

18. The system of claim 17, wherein the valve member core has an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

19. The system of claim 18, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

20. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber in which the valve member moves, and wherein the sampling port is formed within the valve member and includes a sampling cavity open to channels within the valve member that communicate with the manifold interior chamber.

21. The system of claim 20, wherein the valve member comprises a cylindrical core rotatable within the manifold interior chamber, and wherein the fluid sampling port opens in a control handle of the valve member and is centered along the axis of rotation of the valve member core.

22. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber in which the valve member moves, and wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the manifold interior chamber.

23. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber and the valve member comprises a core movable within the interior chamber of the manifold, and further including mating features on the valve member core and manifold that

provide tactile feedback and positive positioning of the core in all three positions of the valve member.

24. The system of claim 16, wherein the control valve further includes a manifold defining an interior chamber and the valve member comprises a movable within the interior chamber of the manifold and a control handle external to the manifold, and further including coordinated visible features on the control handle and manifold that provide symbolic indicators of all three positions of the valve member.

25. A method of taking samples and measuring the pressure of a fluid system of a patient, comprising:

providing a fluid sampling system with a conduit line and a reservoir connected thereto between a proximal segment adapted to be supplied with a physiological fluid and a distal segment adapted to be in communication with a fluid system of a patient;

interposing a control valve between the reservoir and the conduit line having a movable valve member with a control handle, the valve member movable into at least a first position and a second position;

providing a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

providing a fluid sampling port in the sampling system;

selecting the first position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve and the reservoir, and creating a reduced pressure within the reservoir such that fluid flows from the distal segment through the control valve into the reservoir sufficient to draw fluid from the fluid system of the patient past the sampling port; and

selecting the second position of the valve member to provide open fluid communication from the proximal segment to the distal segment via the control valve while bypassing the reservoir, and monitoring the pressure sensed by the pressure transducer.

26. The method of claim 25, wherein the valve member has a third position, and the method includes selecting the third position of the valve member to provide open fluid communication from the distal segment to the sampling port but prevent communication between the sampling port and both the reservoir and the proximal segment, and sampling fluid from the conduit line through the sampling port.

27. The method of claim 26, wherein the fluid system of the patient is the blood system, and further including means for pressurizing the physiological fluid such that at least some fluid continues to flow through the conduit line to the patient when the valve member is in the first position, the method including the steps of:

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient; then

creating a reduced pressure within reservoir and collecting sufficient fluid therein such that blood flows past the sampling port; then

selecting the third position of the valve member; then

sampling blood from the conduit line through the sampling port; then

creating an elevated pressure within the reservoir to expel blood therefrom into the distal segment of the conduit line; then

selecting the first position of the valve member such that the physiological fluid flows through the conduit line to the patient and flushes the reservoir of blood; and then

selecting the second position of the valve member and monitoring the pressure sensed by the pressure transducer.

28. The method of claim 25, wherein the control valve has a manifold defining an interior chamber within which the valve member rotates, and further including mating features on the valve member and manifold that provide tactile feedback and positive positioning of the core in both first and second positions, the method of selecting the first and second positions further including rotating the valve member until the tactile feedback is sensed.

29. The method of claim 25, wherein the control valve includes visible features that provide symbolic indicators of the first and second positions of the control handle, the method of selecting the first and second positions further includes interpreting the symbolic indicators to determine the placement of the control handle corresponding to the first and second positions.

30. A medical system for fluid sampling of a fluid system of a patient, comprising:

a conduit line with a proximal end adapted to be supplied with a physiological fluid and a distal end adapted to be in communication with a fluid system of a patient;

a pressure transducer connected to the conduit line for sensing the pressure of the fluid therein;

a fluid sampling port having a sampling cavity;

a control valve interposed between the conduit line and the sampling port and having a manifold defining an interior chamber, the manifold having a proximal port fluidly connected to the conduit line, a distal port fluidly connected to the conduit line, an outlet port, and an

inlet port, wherein each of the manifold ports opens to the interior chamber,

the control valve further including a valve member movable within the interior chamber and having channels therein that selectively communicate with the manifold ports, the valve member being movable into at least three positions:

a first position that provides open fluid communication from the conduit line to the proximal port and the outlet port of the control valve to the sampling cavity, and to the inlet port and the distal port of the control valve to the conduit line,

a second position that provides open fluid communication from the conduit line to the proximal port and through at least one channel in the valve member and back to the conduit line while bypassing the sampling port, such that the pressure of fluid within the conduit line exclusive of the sampling port can be sensed by the pressure transducer, and

a third position that provides open fluid communication from the distal end of the conduit line through the control valve to the sampling port but prevents communication between the sampling port and the proximal end of the conduit line.

31. The system of claim 30, wherein the valve member comprises a core movable within the interior chamber of the manifold and having an external channel formed along an exterior surface of the core and an internal channel formed along an interior bore of the core.

32. The system of claim 31, wherein the internal channel opens to the exterior surface of the core at two separated locations spaced from the external channel.

33. The system of claim 30, wherein the sampling port is formed within the valve member and includes a sampling cavity open to the valve member channels.

34. The system of claim 33, wherein the valve member comprises a cylindrical core rotatable within the manifold interior chamber, and wherein the fluid sampling port opens in a control handle of the valve member and is centered along the axis of rotation of the valve member core.

35. The system of claim 30, wherein the sampling port connects to the control valve manifold and defines a flow path therethrough whose opposite ends open to the manifold interior chamber.

36. The system of claim 30, wherein the valve member comprises a core movable within the interior chamber of the manifold and a control handle external to the manifold.

37. The system of claim 36, further including mating features on the valve member core and manifold that provide tactile feedback and positive positioning of the core in all three positions of the valve member.

38. The system of claim 36, further including coordinated visible features on the control handle and manifold that provide symbolic indicators of all three positions of the valve member.

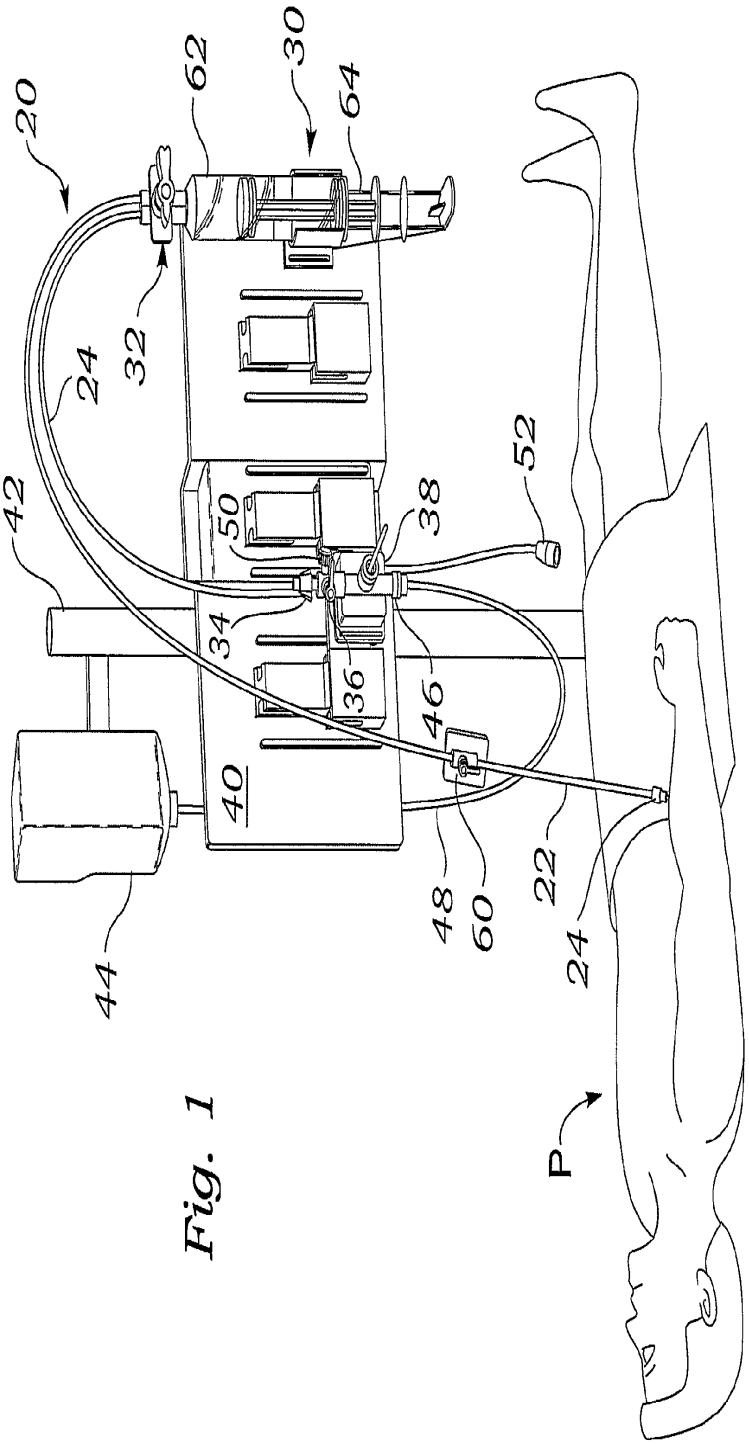


Fig. 1

Fig. 2

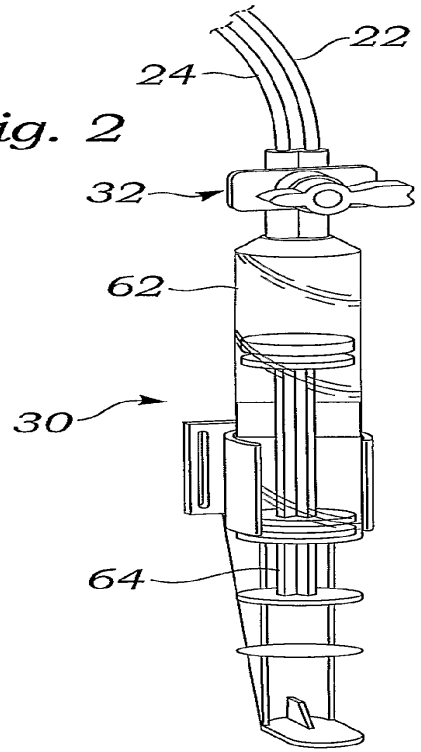


Fig. 3

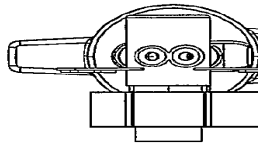


Fig. 3B

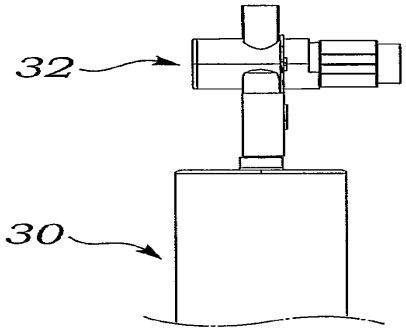


Fig. 3A

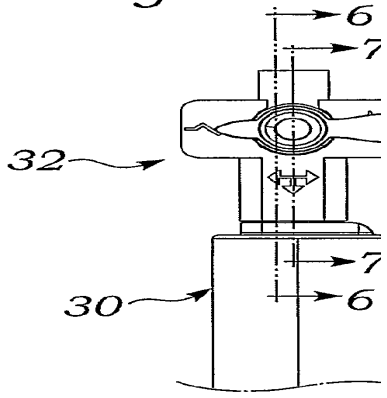


Fig. 4

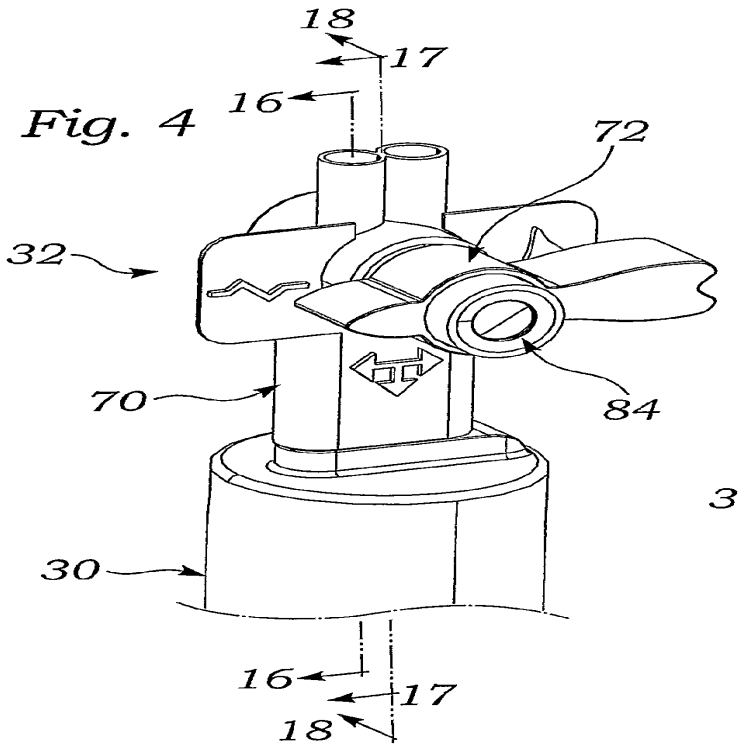

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Fig. 5

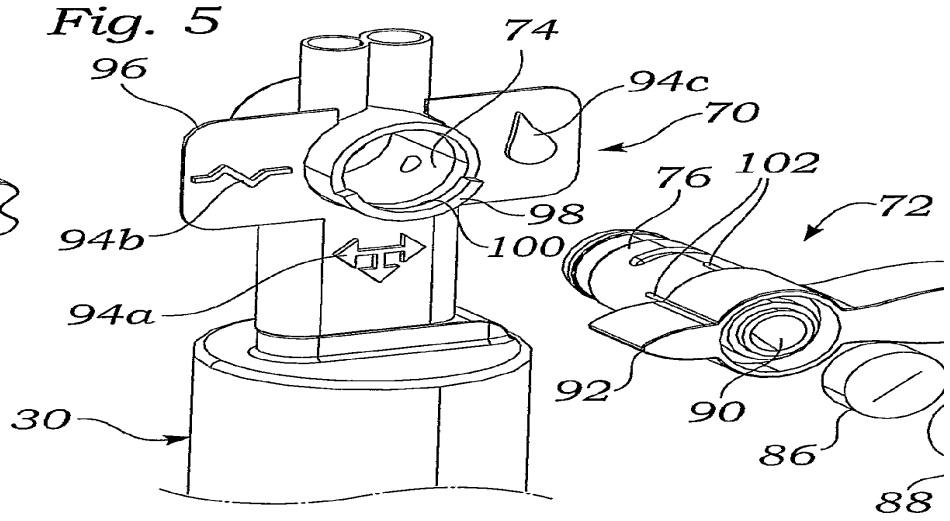

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Fig.6B

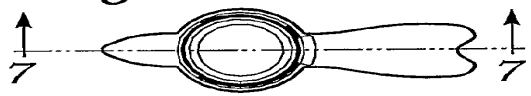


Fig.6D

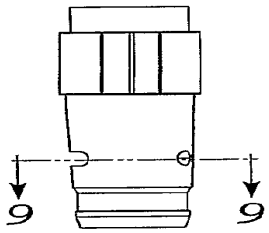


Fig.6A

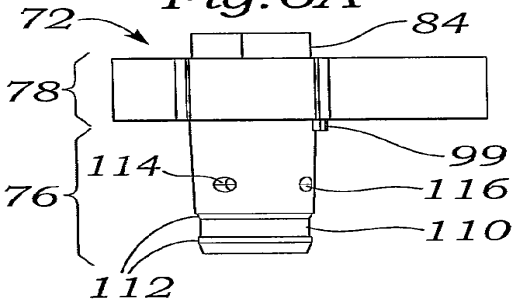


Fig.7

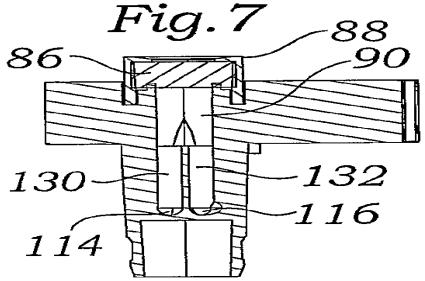


Fig.6

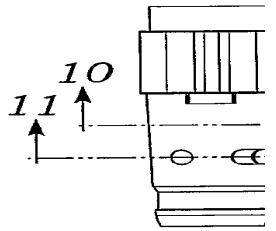


Fig.9



Fig.6E

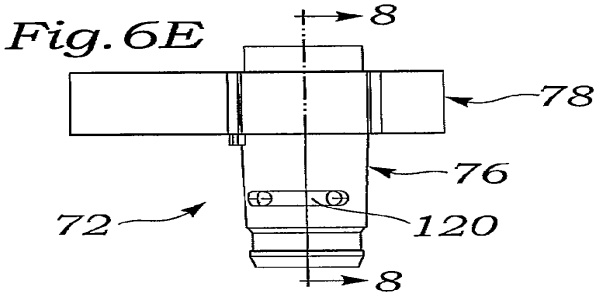


Fig.8

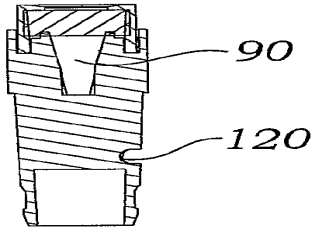


Fig.10

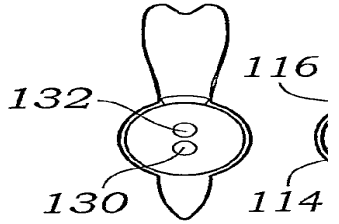


Fig. 12

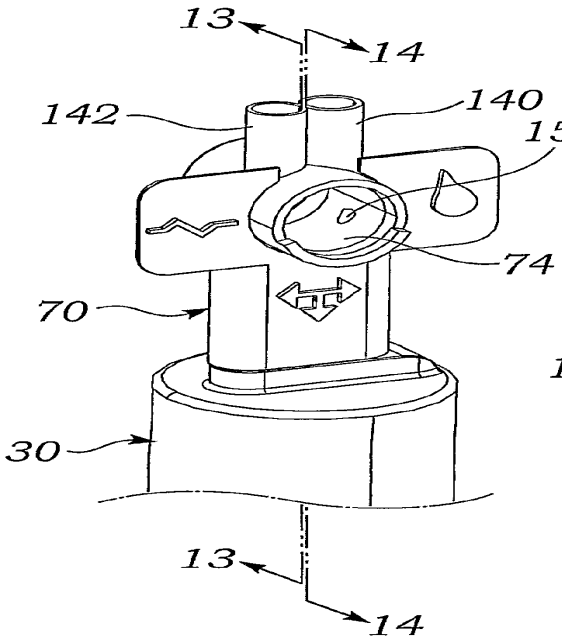


Fig. 13

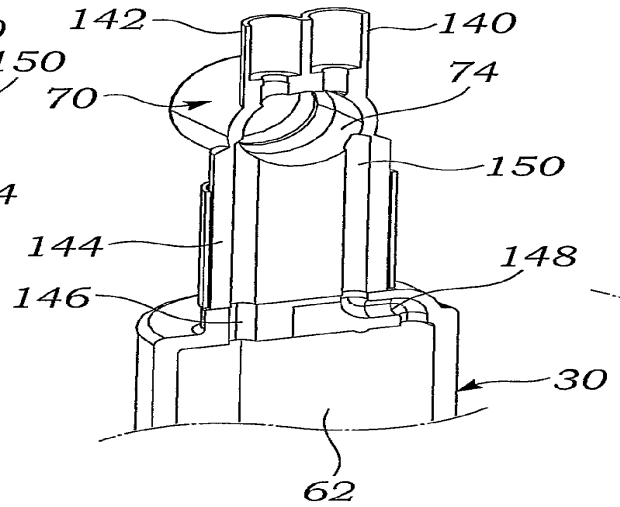


Fig. 14

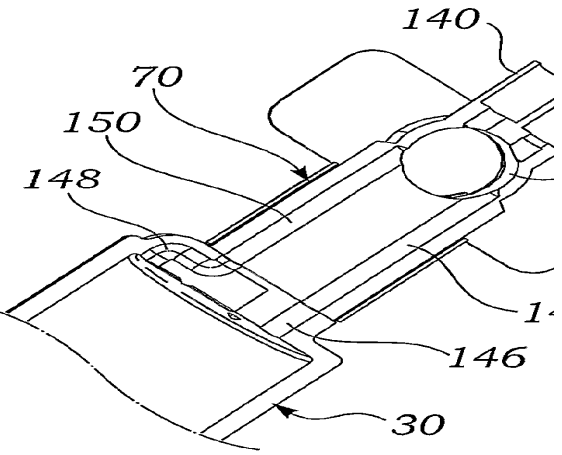


Fig. 15B

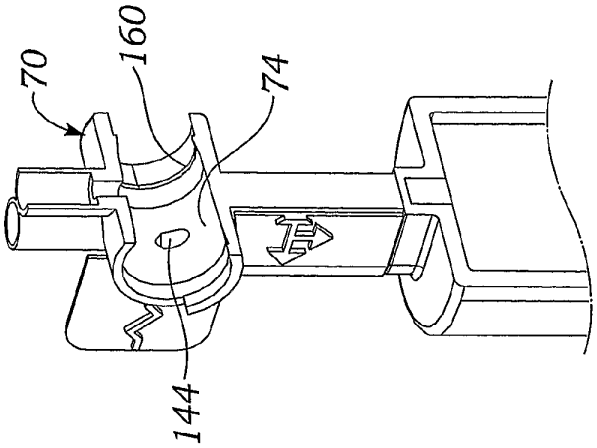


Fig. 15A

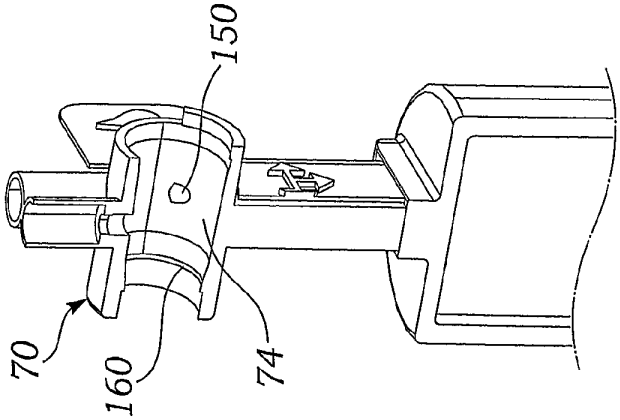


Fig. 17

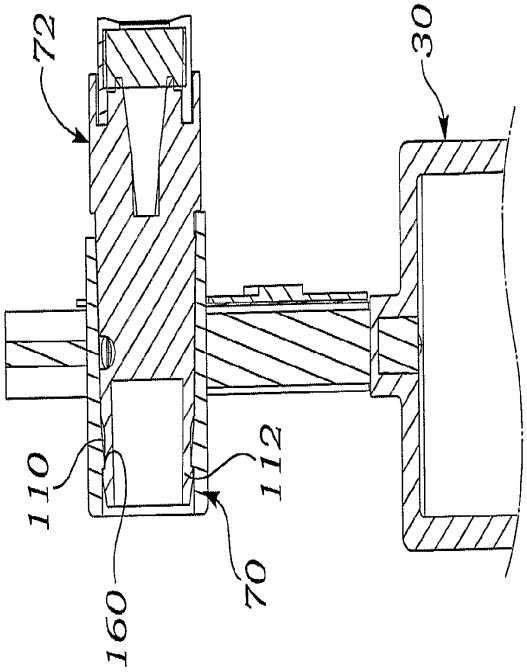


Fig. 16

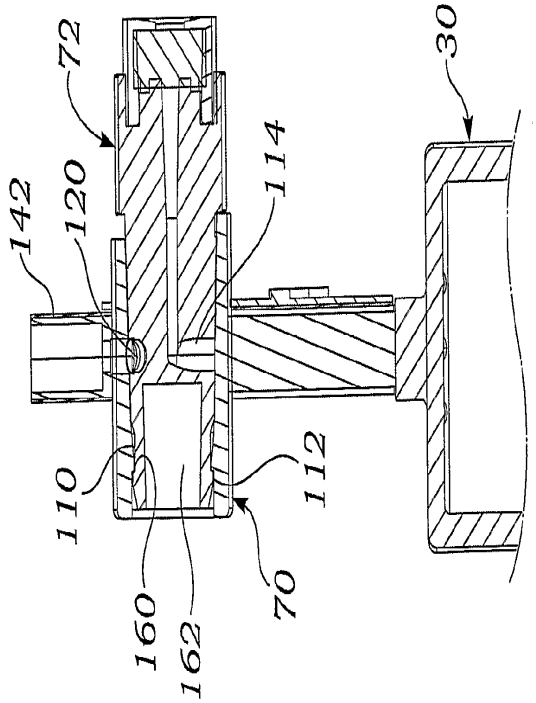


Fig. 18A

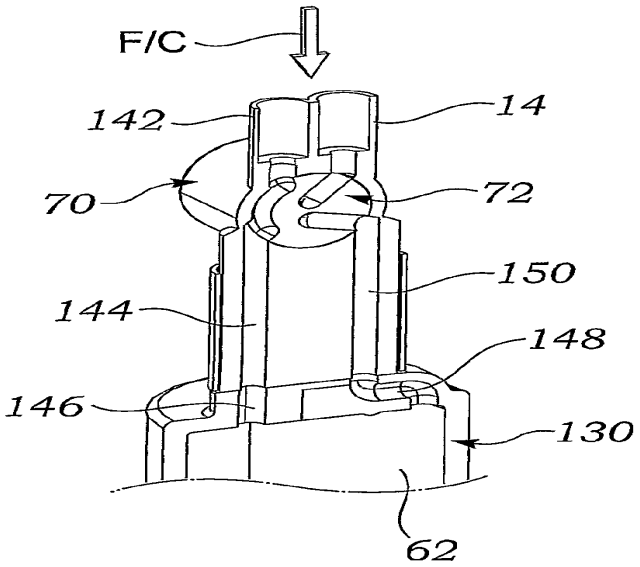


Fig. 18B

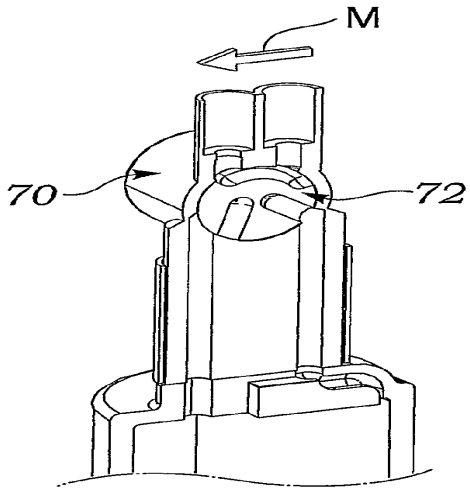


Fig. 18

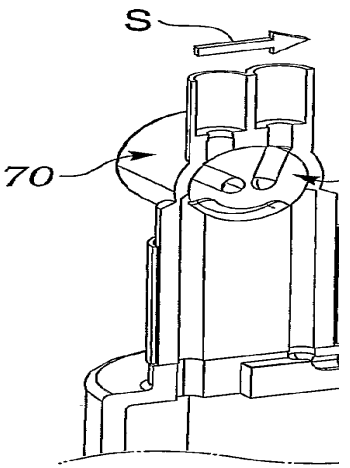


Fig. 19A

F/C POSITION

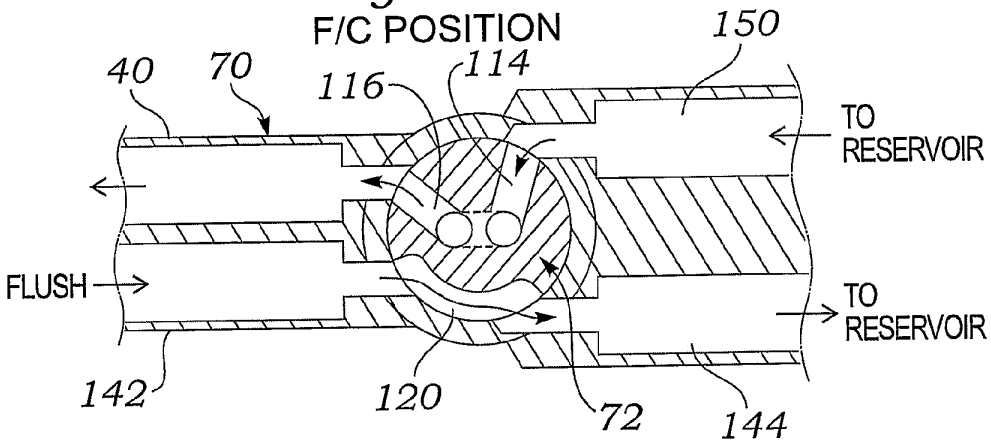


Fig. 19B

M POSITION

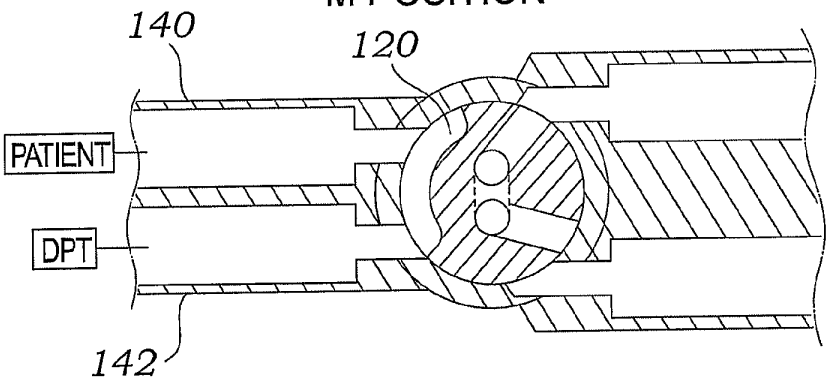


Fig. 19C

S POSITION

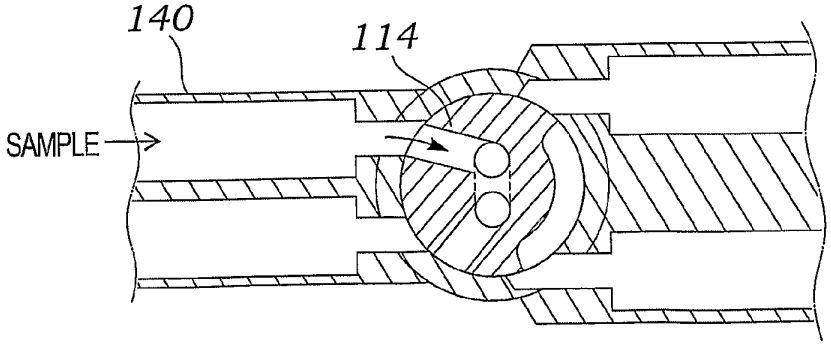


Fig.20A

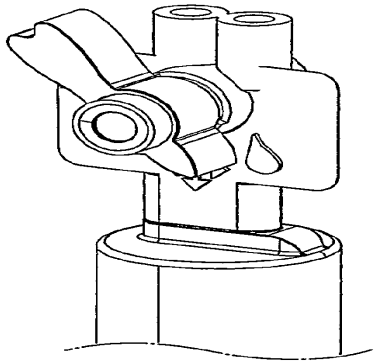


Fig.20D

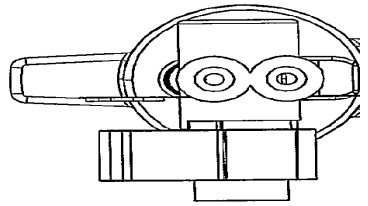


Fig.20C

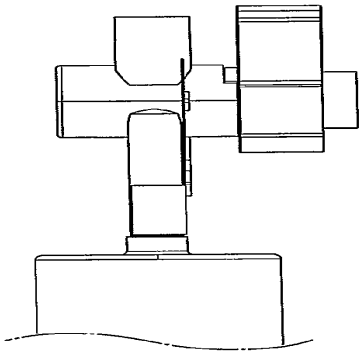


Fig.20B

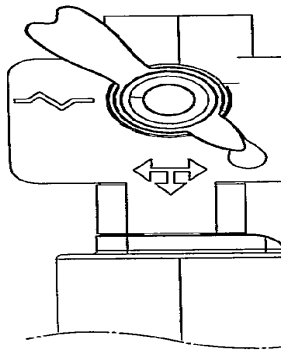


Fig.21A

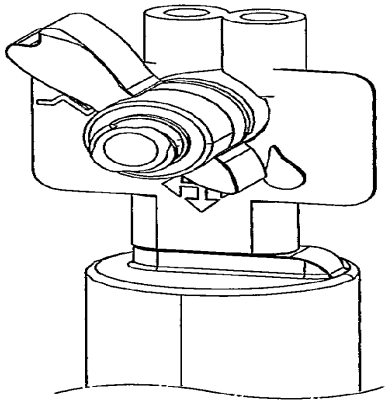


Fig.21L

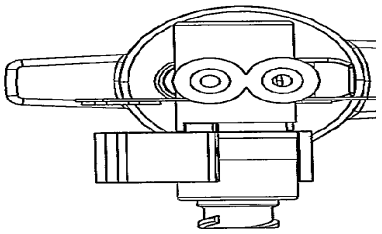


Fig.21C

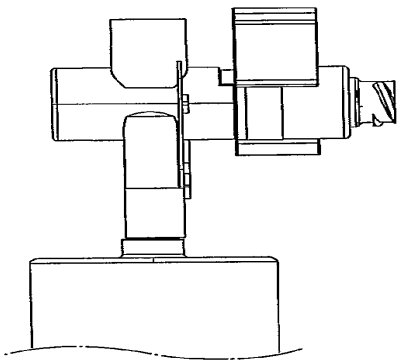


Fig.21B

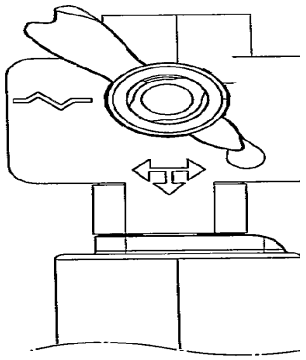


Fig.22A

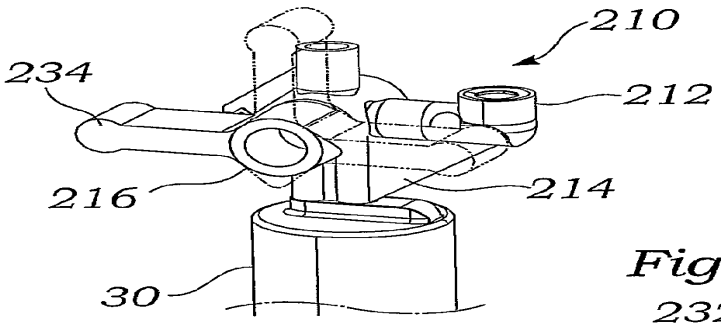


Fig.22

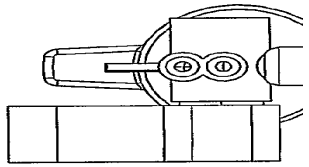


Fig.22E

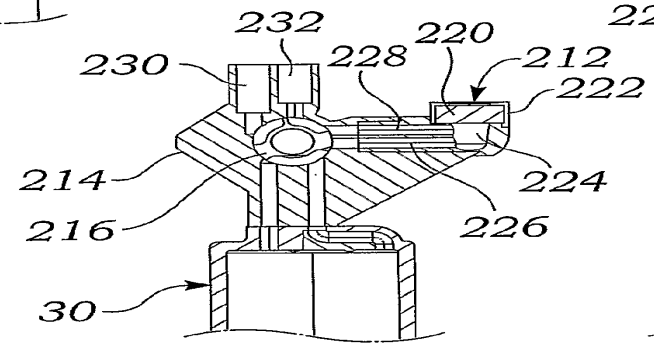


Fig.22C

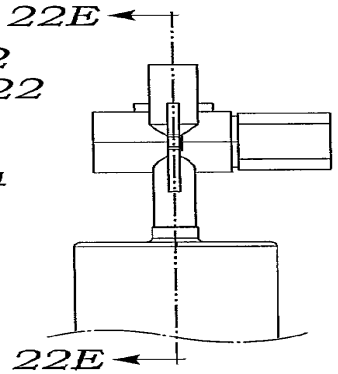


Fig.22

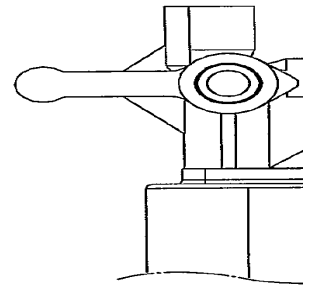


Fig.24D

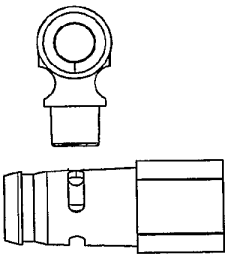


Fig.24B

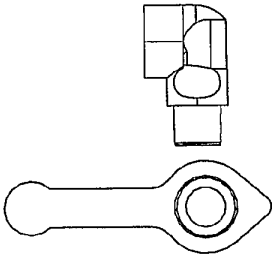


Fig.24A

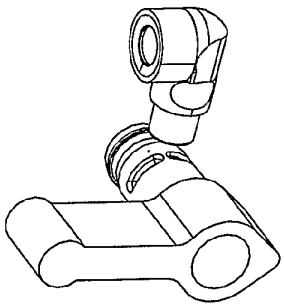


Fig.24C

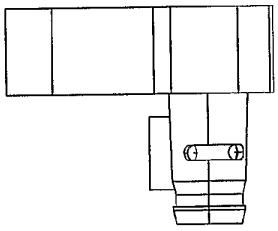


Fig.25D

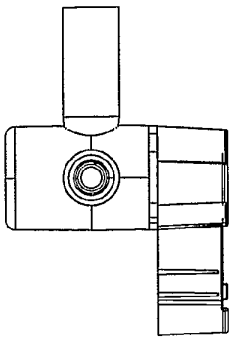


Fig.25B

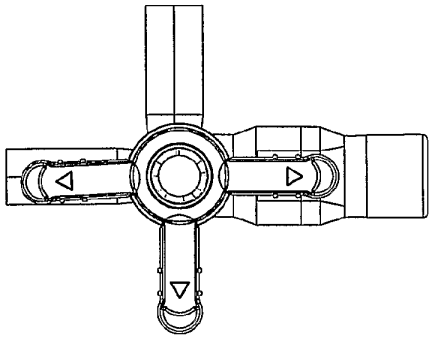


Fig.25C

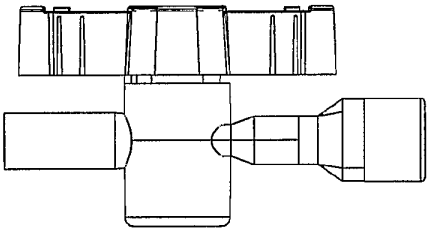
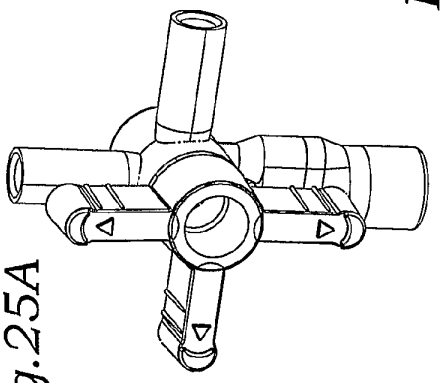


Fig.25A



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/035832

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/15

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 643 218 A (LYNN LAWRENCE A [US] ET AL) 1 July 1997 (1997-07-01) column 13, line 42 - column 14, line 57	1-24, 30-38
A	US 5 961 472 A (SWENDSON DAVID L [US] ET AL) 5 October 1999 (1999-10-05) cited in the application column 12, line 31 - column 14, line 64	1-24, 30-38
A	EP 0 376 603 A (MEDEX INC [US]) 4 July 1990 (1990-07-04) column 3, line 53 - column 4, line 58	1-24, 30-38

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 December 2006	27/12/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Manschot, Jan

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/035832

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25-29
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/035832

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5643218 A	01-07-1997	US 5743886 A	28-04-1998
US 5961472 A	05-10-1999	AT 309743 T	15-12-2005
		AU 732501 B2	26-04-2001
		AU 9508798 A	23-04-1999
		BR 9812532 A	25-07-2000
		CA 2304146 A1	08-04-1999
		CN 1278710 A	03-01-2001
		DE 69832399 D1	22-12-2005
		DE 69832399 T2	14-06-2006
		EP 1017317 A1	12-07-2000
		ES 2256960 T3	16-07-2006
		JP 3421320 B2	30-06-2003
		JP 2001517522 T	09-10-2001
		WO 9916354 A1	08-04-1999
		US 6224561 B1	01-05-2001
EP 0376603 A	04-07-1990	CA 2005042 A1	22-06-1990
		DK 653189 A	23-06-1990
		US 5002066 A	26-03-1991

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference KURIN7PCT		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US20/26276	International filing date *(day/month/year)* 01 April 2020 (01.04.2020)	(Earliest) Priority Date *(day/month/year)* 01 April 2019 (01.04.2019)
Applicant Bobby E. Rogers		

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. 1A

☒ 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/US20/26276

A. CLASSIFICATION OF SUBJECT MATTER

IPC - G01N 1/10, 1/02; A61B 5/15 (2020.01)

CPC - G01N 1/10, 1/02; B01L 3/0203

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 2018/0271425 A1 (KURIN, INC.) 27 September 2018; abstract; figures 24A-24D; paragraphs [0066], [0096], [0144]-[0148]	1-10, 14-18 -- 11-13, 19-20
Y	GB 1 3786 02 A (AYERS, WA) 02 May 1974; page 5, lines 34-95; figures 4, 6	11-12, 19-20
Y	US 2014/0112841 A1 (SCHOEN, C) 24 April 2014; abstract; paragraph [0035]	13
A	WO 2019/055487 A1 (MAGNOLIA MEDICAL TECHNOLOGIES, INC.) 21 March 2019; paragraphs [1071], [1080]; figures 2-5	13
P, X	WO 2019/232196 A1 (MAGNOLIA MEDICAL TECHNOLOGIES, INC.) 05 December 2019; entire document	1, 6, 14

Awaiting 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
25 June 2020 (25.06.2020)	16 JUL 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 Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: James Scott Nolan
P.O. Box 371710
San Diego, California 92110
United States of America

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	16 JUL 2020

Applicant's or agent's file reference	FOR FURTHER ACTION
KURIN7PCT	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US20/26276	01 April 2020 (01.04.2020)	01 April 2019 (01.04.2019)

International Patent Classification (IPC) or both national classification and IPC
IPC - G01N 1/10, 1/02; A61B 5/15 (2020.01)
CPC - G01N 1/10, 1/02; B01L 3/0203

Applicant
Bobby E. Rogers

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
- [x] 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.

International Processing

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	25 June 2020 (25.06.2020)	Shane Thomas PCT Help Desk Telephone No. 571-272-4300

Form PCT/ISA/237 (cover sheet) (revised January 2019)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US20/26276

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/US20/26276

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	4, 9, 11-13, 18-20	YES
	Claims	1-3, 5-8, 10, 14-17	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 1-3, 5-8, 10, and 14-17 lack novelty under PCT Article 33(2) as being anticipated by US 2018/0271425 Al to Kurin, Inc. (hereafter 'Kurin')

As per claim 1, Kurin discloses a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source, a first portion of the fluid sample potentially having contaminants (sample optimization systems that reduce or eliminate contaminates in collected blood samples by including a blood sequestration device; abstract), the fluid sample optimization device comprising: an inlet configured to connect with the fluid source (blood sequestration device 2408 includes an inlet port 2412; figure 24B; paragraph [0146]); an outlet configured to connect with the fluid collection device (blood sequestration device 2408 includes an outlet port 2414; figure 24B; paragraph [0146]); a sample path connected between the inlet and the outlet (a blood sample channel 2422; figure 24C; paragraph [0147]); and a contaminant containment reservoir connected between the inlet and the outlet (blood sequestration chamber 2418; figure 24B; paragraph [0147]), the contaminant containment reservoir having an air permeable fluid resistor proximate the outlet (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]), the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet, a first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet (upon drawing of blood by way of a syringe or Vacutainer (pressure differential is applied) initial aliquot of blood flows into the blood sequestration chamber 2418 displacing air through blood barrier 2420 (air permeable fluid) and the outlet; figures 24B-24C; paragraph [0148]), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir, subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (the blood in the sequestration chamber 2418 forces the inner chamber housing to the second position allowing one or more apertures 2424 to open 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 (still under pressure from a syringe or Vacutainer); figures 24B-24D; paragraph [0148]).

As per claim 2, Kurin discloses the fluid sample optimization device in accordance with claim 1, and Kurin further discloses comprising a housing that houses and/or defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (blood sequestration device 2408 houses the inlet, the outlet, the sample path, and the contaminant containment reservoir; figures 24B-24D; paragraph [0147]).

As per claim 3, Kurin discloses the fluid sample optimization device in accordance with claim 1, and Kurin further discloses wherein the air permeable fluid resistor (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]) includes a material that seals upon contact with the first portion of the fluid sample (the term "air permeable blood barrier" is 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; paragraph [0066]).

As per claim5, Kurin discloses the fluid sample optimization device in accordance with claim 1, and Kurin further discloses wherein each pressure differential is provided by a vacuum pressure provided by the fluid collection device (in a blood sample under vacuum pressure or force through the conduit 2006 [2406] from the patient needle 2402 using a syringe or Vacutainer; figure 24B; paragraphs [0144], [0148]).

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
WO 2019/232196 A1	05/12/2019	30/05/2019	31/05/2018

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

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Form PCT/ISA/237 (Box No. VI) (revised January 2019)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US20/26276

Supplemental Box

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-***-Continued from Box V: Citations and Explanations-***-

As per claim 6, Kurin discloses a fluid sample optimization device for optimizing a fluid sample collected by a fluid collection device from a fluid source, a first portion of the fluid sample potentially having contaminants (sample optimization systems that reduce or eliminate contaminates in collected blood samples by including a blood sequestration device; abstract), the fluid sample optimization device comprising: an inlet configured to connect with the fluid source (blood sequestration device 2408 includes an inlet port 2412, for blood sample; figure 24B; paragraph [0146]); an outlet configured to connect with the fluid collection device (blood sequestration device 2408 includes an outlet port 2414 for blood sample; figure 24B; paragraph [0146]); a sample path connected between the inlet and the outlet (a blood sample channel 2422; figure 24C; paragraph [0147]), the sample path further having a resistive plug that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path (in the first position one or more apertures 2424 are closed to flow blood into sequestration chamber 2418 (still under pressure from a syringe or Vacutainer); figures 24B-24D; paragraphs [0147]-[0148]); and a contaminant containment reservoir connected between the inlet and the outlet (blood sequestration chamber 2418; figure 24B; paragraph [0147]), the contaminant containment reservoir further having an air permeable fluid resistor proximate the outlet (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]), the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet, the first portion of the fluid sample from the fluid source to displace air therein through the air permeable fluid resistor and the outlet (upon drawing of blood by way of a syringe or Vacutainer (pressure differential is applied) initial aliquot of blood flows into the blood sequestration chamber 2418 displacing air through blood barrier 2420 (air permeable fluid) and the outlet; figures 24B-24C; paragraph [0148]), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir, subsequent portions of the fluid sample can be forced through the resistive plug and conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (the blood in the sequestration chamber 2418 forces the inner chamber housing to the second position allowing one or more apertures 2424 to open 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 (still under pressure from a syringe or Vacutainer); figures 24B-24D; paragraph [0148]).

As per claim 7, Kurin discloses the fluid sample optimization device in accordance with claim 6, and Kurin further discloses further comprising a housing that houses and/or defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (blood sequestration device 2408 houses the inlet, the outlet, the sample path, and the contaminant containment reservoir; figures 24B-24D; paragraph [0147]).

As per claim 8, Kurin discloses the fluid sample optimization device in accordance with claim 6, and Kurin further discloses wherein the air permeable fluid resistor (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]) includes a material that seals upon contact with the first portion of the fluid sample (the term "air permeable blood barrier" is 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; paragraph [0066]).

As per claim 10, Kurin discloses the fluid sample optimization device in accordance with claim 6, and Kurin further discloses wherein each pressure differential is provided by a vacuum pressure provided by the fluid collection device (in a blood sample under vacuum pressure or force through the conduit 2006 [2406] from the patient needle 2402 using a syringe or Vacutainer; figure 24B; paragraphs [0144], [0148]).

As per claim 14. A fluid sample optimization device for optimizing a fluid sample, a first portion of the fluid sample potentially having contaminants (sample optimization systems that reduce or eliminate contaminates in collected blood samples by including a blood sequestration device; abstract), the fluid sample optimization device comprising: an inlet (blood sequestration device 2408 includes an inlet port 2412; figure 24B; paragraph [0146]); an outlet (blood sequestration device 2408 includes an outlet port 2414; figure 24B; paragraph [0146]); a sample path connected between the inlet and the outlet (a blood sample channel 2422; figure 24C; paragraph [0147]); and a contaminant containment reservoir connected between the inlet and the outlet (blood sequestration chamber 2418; figure 24B; paragraph [0147]), the contaminant containment reservoir having an air permeable fluid resistor proximate the outlet (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]), the contaminant containment reservoir being arranged to receive, when a pressure differential is applied between the inlet and the outlet, a first portion of the fluid sample to displace air therein through the air permeable fluid resistor and the outlet (upon drawing of blood by way of a syringe or Vacutainer (pressure differential is applied) initial aliquot of blood flows into the blood sequestration chamber 2418 displacing air through blood barrier 2420 (air permeable fluid) and the outlet; figures 24B-24C; paragraph [0148]), such that upon receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir, subsequent portions of the fluid sample can be conveyed by the sample path from the inlet to the outlet when subsequent pressure differentials are applied between the inlet and the outlet (the blood in the sequestration chamber 2418 forces the inner chamber housing to the second position allowing one or more apertures 2424 to open 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 (still under pressure from a syringe or Vacutainer); figures 24B-24D; paragraph [0148]).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Supplemental Box

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As per claim 15, Kurin discloses the fluid sample optimization device in accordance with claim 14, and Kurin further discloses wherein the sample path further includes a resistive plug that is configured to inhibit at least a part of the first portion of the fluid sample and the contaminants from entering the sample path during receipt of the first portion of the fluid sample and containment of the contaminants in the contaminant containment reservoir (in the first position one or more apertures 2424 are closed to flow blood into sequestration chamber 2418 (still under pressure from a syringe or Vacutainer); figures 24B-24D; paragraphs [0147]-[0148]).

As per claim 16, Kurin discloses the fluid sample optimization device in accordance with claim 14, and Kurin further discloses further comprising a housing that houses and/or defines one or more of the inlet, the outlet, the sample path, and the contaminant containment reservoir (blood sequestration device 2408 houses the inlet, the outlet, the sample path, and the contaminant containment reservoir; figures 24B-24D; paragraph [0147]).

As per claim 17, Kurin discloses the fluid sample optimization device in accordance with claim 14, and Kurin further discloses wherein the air permeable fluid resistor (blood sequestration chamber 2418 includes an air permeable blood barrier 2420 at a distal end of the blood sequestration chamber 2418, near outlet 2414; figure 24B; paragraph [0147]) includes a material that seals upon contact with the first portion of the fluid sample (the term "air permeable blood barrier" is 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; paragraph [0066]).

Claims 4, 9, 18 lack an inventive step under PCT Article 33(3) as being obvious over Kurin,

As per claim 4, Kurin discloses the fluid sample optimization device in accordance with claim 1, but Kurin does not disclose, in the first embodiment, wherein the contaminant containment reservoir includes a tortuous path. In a different embodiment, Kurin further discloses wherein the contaminant containment reservoir includes a tortuous path (a blood sequestration chamber 2624, preferably a helical or corkscrew channel around the outer surface of im1er conduit 2620; figures 26C-26D; paragraph [0154]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of the first embodiment of Kurin to provide wherein the contaminant containment reservoir includes a tortuous path, as taught by the second embodiment of Kurin, in order to provide an associated amount of the sequestered fluid (paragraph [0096]).

As per claim 9, Kurin discloses the fluid sample optimization device in accordance with claim 6, and Kurin does not disclose, in the first embodiment, wherein the contaminant containment reservoir includes a tortuous path. In a different embodiment, Kurin further discloses wherein the contaminant containment reservoir includes a tortuous path (a blood sequestration chamber 2624, preferably a helical or corkscrew channel around the outer surface of im1er conduit 2620; figures 26C-26D; paragraph [0154]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of the first embodiment of Kurin to provide wherein the contaminant containment reservoir includes a tortuous path, as taught by the second embodiment of Kurin, in order to provide an associated amount of the sequestered fluid (paragraph [0096]).

As per claim 18, Kurin discloses the fluid sample optimization device in accordance with claim 14, but Kurin does not disclose, in the first embodiment, wherein the contaminant containment reservoir includes a tortuous path. In a different embodiment, Kurin further discloses wherein the contaminant containment reservoir includes a tortuous path (a blood sequestration chamber 2624, preferably a helical or corkscrew channel around the outer surface of im1er conduit 2620; figures 26C-26D; paragraph [0154]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of the first embodiment of Kurin to provide wherein the contaminant containment reservoir includes a tortuous path, as taught by the second embodiment of Kurin, in order to provide an associated amount of the sequestered fluid (paragraph [0096]).

Claims 11-12, 19-20 lack an inventive step under PCT Article 33(3) as being obvious over Kurin in view of GB 1378602 A (AYERS).

As per claim 11, Kurin discloses the fluid sample optimization device in accordance with claim 6, but Kurin does not disclose wherein the resistive plug includes a film that is pierceable by a first of the subsequent pressure differentials. Ayers discloses a resistive plug includes a film that is pierceable by a first of a subsequent pressure differentials (when blood fills chamber 26, the cannula is pushed (pressure differential) through stopper 41 to allow blood flow into tube 39; page 5, lines 34-60; figures 4, 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Kurin to provide wherein the resistive plug includes a film that is pierceable by a first of the subsequent pressure differentials, as taught by Ayers, in order to provide enable sealing until the sample is desired; (Ayers: page 5, lines 68-95).

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
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As per claim 12, Kurin and Ayers, in combination, disclose the fluid sample optimization device in accordance with claim 11, but Kurin does not disclose wherein the resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film. Ayers discloses a resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film (when blood fills chamber 26, the cannula is pushed (pressure differential) through stopper 41 to allow blood flow into tube 39; page 5, lines 34-60; figures 4, 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Kurin to provide wherein the resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film, as taught by Ayers, in order to provide enable sealing until the sample is desired; (Ayers: page 5, lines 68-95).

As per claim 19, Kurin discloses the fluid sample optimization device in accordance with claim 15, but Kurin does not disclose wherein the resistive plug includes a film that is pierceable by a first of the subsequent pressure differentials. Ayers discloses a resistive plug includes a film that is pierceable by a first of a subsequent pressure differentials (when blood fills chamber 26, the cannula is pushed (pressure differential) through stopper 41 to allow blood flow into tube 39; page 5, lines 34-60; figures 4, 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Kurin to provide wherein the resistive plug includes a film that is pierceable by a first of the subsequent pressure differentials, as taught by Ayers, in order to provide enable sealing until the sample is desired; (Ayers: page 5, lines 68-95).

As per claim 20, Kurin and Ayers, in combination, disclose the fluid sample optimization device in accordance with claim 19, but Kurin does not disclose wherein the resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film. Ayers discloses a resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film (when blood fills chamber 26, the cannula is pushed (pressure differential) through stopper 41 to allow blood flow into tube 39; page 5, lines 34-60; figures 4, 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Kurin to provide wherein the resistive plug further includes a piercing member configured to pierce the film when the first of the subsequent pressure differentials is exerted on an opposite side of the film, as taught by Ayers, in order to provide enable sealing until the sample is desired; (Ayers: page 5, lines 68-95).

Claim 13 lacks an inventive step under PCT Article 33(3) as being obvious over Kurin in view of US 2014/0112841 Al to Schoen, et al. (hereafter 'Schoen') as evidenced by WO 2019/055487 Al to Magnolia Medical Technologies (hereafter 'Magnolia').

As per claim 13, Kurin discloses the fluid sample optimization device in accordance with claim 6, and Kurin discloses the use of mesh for resistive plugs (barriers are made from mesh or filter material; paragraph [0066]), but Kurin does not disclose wherein the resistive plug includes a mesh with a dissolvable material that dissolves upon contact with a first of the subsequent portions of the fluid sample. Schoen discloses a resistive plug includes a mesh with a dissolvable material that dissolves upon contact with a first of the subsequent portions of the fluid sample (water-soluble membrane (mesh) used for temporarily retaining a liquid in a holding chamber, where the membrane dissolves after a certain amount of time; abstract; paragraph [0035]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the device of Kurin to provide wherein the resistive plug includes a mesh with a dissolvable material that dissolves upon contact with a first of the subsequent portions of the fluid sample, as taught by Schoen, as evidenced by Magnolia that discloses an actuator that changes a sample device from sequestration to flow through upon dissolving (Magnolia: actuator 250, used to change sample flow from sequestration to flow through, is transitioned by a change of configuration such as dissolving; paragraphs [1071], [1080]; figures 2-5).

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Pending Searching

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Literature display help

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(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Patent publication (B2)
(11) [Patent number] Patent No. 5643474 (P5643474)
(24) [Registration date] 2014 November 7 (2014.11.7)
(45) [Date of Issue] December 17, 2014 (2014.12.17)
(54) [Title of Invention] Multiphase Mixing Process Using Microchannel Process Technology
(51) [International Patent Classification]
B01F 3/04 (2006.01)
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

B01F 5/06

B01F 15/06 Z

[Number of claims] 35

[Total number of pages] 47

(21) [Application number] Patent application 2007-534825 (P2007-534825)

(86) (22) [Application date] September 30, 2005 (2005.9.30)

(65) [Publication number] Special table 2008-514428 (P2008-514428A)

(43) [Publication date] May 8, 2008 (2008.5.8)

(86) [International application number] PCT/US2005/035330

(87) [International publication number] WO2006/039568 (87)) [International publication date] April 13, 2006 (2006.4.13) [Examination request date] September 29, 2008 (2008.9.29) [Trial number] Appeal 2012-12061 (P2012-12061/J1) [Date of appeal] June 27, 2012 (2012.6.27) (31) [Priority claim number] 60/615,509 (32) [Priority date] October 1, 2004 (2004.10.1) (33)) [Country claiming priority] United States (US) (73) [Patent holder] [Identification number] 505056694 [Name] Verosys, Inc. (74) [Agent] [Identification number] 110000062 [Name] Daiichi International Patent Office (72) [Inventor] [Name] Tonkovic, Anna Lee (72) [Inventor] [Name: Silva, Laura, Jay. (72) [Inventor] [Name] Hesse, David John (72) [Inventor] [Name] Marchiando, Michael Allan

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(72) [Inventor]
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(72) [Inventor]
[Name] Sullivan, Tim
(72) [Inventor]
[Name] Jarosh, Kai Todd Paul
(72) [Inventor]
[Name] Yushak, Thomas
[Panel]
[Chief Judge: Shigeju Chiba
Judge: Toyohide Watanabe
Judge: Tsuyoshi Kumakura
(56) References: References
: Japanese Unexamined Patent Publication No. 2003-210957 (JP, A)
[Document] Japanese Unexamined Patent Publication No. 2003-1076 (JP, A) [Document] National Publication of International Patent Application No. 2000-509330 (JP, A) [Document] Japanese Unexamined Patent Publication No. 10-146523 (JP, A) (58) [Investigated field] (Int.Cl., DB name)B01F3/04

The scope of the claims — open

(57) [Claim]

[Claim 1]

A process for making a multiphase mixture, comprising

the step of flowing a first fluid stream through a process microchannel, wherein the first fluid stream is a liquid stream comprising , said process microchannel having an open section com prising a plurality of openings , said open section flowing through said process microchannel; a second fluid stream having a length along the flow path of a fluid stream and a thickness di mension perpendicular to the flow path of said first fluid stream flowing in said process microc hannel

; into the process microchannel and in contact with the first fluid stream to form the multiph ase mixture, wherein the second fluid stream is a gas stream comprising wherein the first flui d stream forms a continuous phase within the multiphase mixture and the second fluid stream forms a dispersed discontinuous phase within the continuous

phase ,

said second fluid stream flows through said open section from a second fluid stream channel adjacent said process microchannel, said heat exchange

channel being said process microchannel, said second fluid stream channel, or adjacent to b oth the process microchannel and the second fluid stream channel, between the process micr ochannel and the heat exchange channel, between the second fluid stream channel and the h eat exchange channel, or a process microchannel and said second fluid flow channel

A process in which heat is exchanged between both a cell and a heat exchange channel, and a heat exchange liquid is in the heat exchange channel.

2. The process of claim 1,

wherein said first fluid stream and said second fluid stream contact each other in a mixing zo ne within said process microchannel.

3.

The process of claim 1 or 2, wherein said process microchannel has a mixing zone with a nar rowed cross-section.

4.

The process microchannel has spaced apart walls and open sections in each of the spaced ap art walls, wherein the second fluid stream passes through each of the open sections to the pr ocess microchannel. 4. The process according to any one of claims 1 to 3, flowing into the

5. Said

process microchannel is a first process microchannel and is in a multiphase mixture forming unit, said multiphase mixture forming unit comprising a second process microchannel and sai d first process microchannel. a second fluid stream channel located between a process microc hannel and said second process microchannel, each process microchannel having a wall with a n open section, said first fluid stream comprising said flowing through a first process microcha nnel and said second process microchannel, said second fluid stream passing from said secon d fluid stream channel through said open section into said first process microchannel; 5. Any of claims 1-4, wherein the microchannel flows in and into contact with the first fluid stream an d through the open section into the second process microchannel and in contact with the first fluid stream. The process of paragraph 1.

6.

A process for making a multiphase mixture comprising:

flowing a first fluid stream through a process microchannel, said first fluid stream being a liq uid stream comprising ; a step having an open section , said open section being a length alon g a flow path of said first fluid stream flowing within said process microchannel and a flow pat h of said first fluid stream flowing within said process microchannel; and flowing a second flui d stream through a second fluid stream channel ,

said second fluid stream being a liquid stream comprising

at least one liquid. wherein said process microchannel has an apertured section comprising a plurality of apertures allowing said second fluid stream to enter said process microchannel, sai d apertured section receiving said second fluid stream having a length along the flow path of s aid second fluid stream flowing within said channel and a thickness dimension perpendicular t o the flow path of said second fluid stream flowing within said second fluid stream

channel ; flowing a fluid stream through a third fluid stream channel, said third fluid stream being a gas stream comprising said third fluid stream into a second fluid stream; having anot her open section comprising a plurality of openings to allow flow into two fluid flow channels, said separate open section flowing through said third fluid flow channel; having a length along a fluid flow path and a thickness dimension perpendicular to the flow path of said third fluid st ream flowing 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 seco nd fluid flow channel passing said second fluid flow channel through said second fluid flow cha nnel. 19. A process according to any one of the preceding claims, having internal dimensions of 100 centimeters or less perpendicular to said flow of fluid stream.

20.

A process according to any one of claims 1 to 19, wherein said heat exchange channels have internal dimensions of 50 millimeters or less perpendicular to said flow of heat exchange fluid through said heat exchange channels.

21. The process

microchannels, second fluid flow channels and heat exchange channels are made of steel, m onel, inconel, aluminum, titanium, nickel, copper, brass, alloys of any of these metals, polyme rs, ceramics. 21. The process of any one of claims 1 to 20, made of a material comprising: , g lass, a composite comprising polymer and glass fibers, quartz, silicon, or a combination of two or more thereof.

22.

A process according to any one of claims 1 to 21, wherein said heat exchange fluid undergoe s a phase change within said heat exchange channels.

23.

A process according to any one of claims 1 to 21, wherein endothermic or exothermic proces ses are carried out in said heat exchange channels.

[Claim 24]

the heat exchange fluid is air, water vapor, liquid water, carbon monoxide, carbon dioxide, ga seous nitrogen, liquid nitrogen, at least one gaseous hydrocarbon, at least one liquid hydrocar

bon, or a combination of two or more thereof; 24. The process of any one of claims 1-23, com prising the first fluid stream, the second fluid stream, or a mixture of the first and second fluid streams.

25.

The process of any one of claims 1 to 24, wherein said multiphase mixture comprises foam.

26. The

multiphase mixture comprises emulsifiers, surfactants, UV protection agents, waxes, consist ency agents, thickeners, superfatting agents, stabilizers, cationic, anionic, zwitterionic, ampho teric or Nonionic polymers, silicone compounds, fats, waxes, lecithins, phospholipids, biophar maceuticals, antioxidants, deodorants, antiperspirants, antidandruff agents, swelling agents, a nthelmintics, self-tanning agents, tyrosine inhibitors, 26. A process according to any precedin g claim, comprising one or more of solubilizers, preservatives, perfume oils or pigments, or mi xtures of two or more thereof.

27.

The process of any one of claims 1 to 26, wherein solids are dispersed in said multiphase mi xture. 28. A process according to any one of claims 1 to 27, wherein said first fluid stream c omprises a reaction medium for conducting a hydrogenation reaction and said second fluid str eam comprises hydrogen

. 29. The first fluid stream comprises a liquid stream, and the second fluid stream comprises one or more of air, oxygen, nitrogen, carbon dioxide, hydrogen, ammonia, chlorine gas, ozon e, and one or more of one or more. gaseous hydrocarbons, or a combination of two or more t hereof, or said first fluid stream comprises a liquid waste stream of

said second fluid stream comprises air; or said first fluid stream comprises a liquid hazardous waste stream; said second fluid stream comprises air; or said first fluid stream comprises liqui d salad dressing or mustard, said second fluid stream comprises nitrogen, or said first fluid str eam comprises liquid beverage or beer, said second fluid stream comprises carbon dioxide, or said first fluid stream comprises the fluid stream comprises liquid bleached pulp, said second f luid stream comprises chlorine, or said first fluid stream comprises coal dispersed in water, sai d second fluid stream comprises air, or said The first fluid stream comprises motor oil with ent rained water, the second fluid stream comprises nitrogen, or the first fluid stream comprises li quid-containing cells for a culture reaction, the second comprises oxygen or air, or said first fl uid stream comprises a liquid reaction medium and said second fluid stream comprises air or oxygen, or said first fluid stream comprises a mixture of oil and water said second fluid strea m comprising air or natural gas, or said first fluid stream comprising liquid bleached pulp, said second fluid stream comprising oxygen, or said first fluid the streams comprise edible oil, win e or juice, the second fluid stream comprises nitrogen, or the first fluid stream comprises wat

er used in fish farming, the second fluid stream comprises oxygen, or said first fluid stream co mprises water and said second fluid stream comprises ozone; or said first fluid stream compri ses a liquid waste or process stream and said second fluid stream comprises carbon dioxide or ammonia, or wherein the first fluid stream comprises a liquid waste stream comprising volatil e organic compounds and the second fluid stream comprises air. process.

30.

A process according to any one of claims 1 to 29, wherein the process produces at least 1 lit er of multiphase mixture per minute.

[Claim 31]

31. The process of any one of claims 1-30, wherein the process is performed in a microchan nel mixer, the microchannel mixer comprising at least two process microchannels.

32.

Said process is carried out in a microchannel mixer, said microchannel mixer comprising a pl urality of process microchannels and a plurality of second fluid flow channels, said process mic rochannels comprising at least one first fluid stream channel. connected to one fluid flow mani fold, wherein the first fluid flow flows through the at least one first fluid flow manifold to the p rocess microchannel; the second fluid flow channel is connected to the process microchannel; Adjacent to the microchannel, at least one second fluid flow manifold connects to said second fluid flow channel, said second fluid flow passing through said at least one second fluid flow m anifold to said first fluid flow manifold. 32. The process of any one of claims 1-31, wherein the process flows into two fluid flow channels.

33.

The microchannel mixer further comprises at least one heat exchange manifold connected to the heat exchange channels, wherein heat exchange fluid flows through the at least one heat exchange manifold into the heat exchange channels. 33. The process of claim 32.

34.

The process microchannel of claims 1 to 33, wherein the process microchannel includes surf ace features formed in and/or on one or more inner walls for altering flow within the process microchannel. A process according to any one of paragraphs.

[Claim 35]

The surface features are depressions in one or more of the inner microchannel walls oriented at an oblique angle to the direction of fluid flow through the process microchannel and/or the i nner microchannel walls. or said surface features are in the shape of at least two surface feat ure regions, and said mixing of said first and second fluids is in the form of a first carried out i n a flow through a surface feature region followed by a second surface feature region, said flo w pattern in said second surface feature region being formed by said first surface feature regi on; Different from said flow pattern in the region or said opening

A section includes an interior portion forming one or more portions of the inner wall of the pro cess microchannel and a surface feature sheet overlying the interior portion of the open sectio

n, wherein the surface feature sheet includes: or the multiphase mixture comprises solid parti cles dispersed in the first and/or second fluid streams and is in the form of the fluidized bed; i ncludes surface features formed in and/or on one or more of the inner walls thereof to alter fl ow within said process microchannel; or said surface features are stacked on top of each othe r; and or comprising two or more layers intertwined in a three-dimensional pattern, or wherei n said surface features are circular, elliptical, square, rectangular, checkerboard, V-shaped, co rrugated or combinations thereof; Alternatively, the surface features include sub-elements, an d the main wall of the surface features is notched, corrugated, jagged, perforated, burr-shape d, checkered, fan-shaped, or a combination thereof. 35. The process of Claim 34, further com prising small surface features.

detailed description open —

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to multiphase mixing processes using mi crochannel process technology. BACKGROUND OF THE INVENTION The dispersion of air bub bles in liquids, with or without chemical reaction, is useful for gas-liquid contact to promote ab sorption or stripping or for foam product production . can be Examples of these are air injectio n to meet the BOD (Biological Oxygen Demand) requirements of waste streams, air injection t o mix liquids in baths, stimulation of bacterial growth for hazardous waste treatment. Nitroge n blowing to extend salad dressings or mustards, CO2 blowing for carbonated drinks and beer, Chlorine blowing for bleaching pulp in the manufacture of paper, Coal flotation and other solids Blowing air for separation, blowing nitrogen to remove entrained water from motor oil, blowin g oxygen or air to enhance cell growth in culture reactions, reacting air, oxygen or other gases for improved performance hydrogen blowing for various types of chemical hydrogenation reac tions, air or natural gas blowing for oil removal from well spring water, for bleaching pulp in th e manufacture of paper Oxygen blowing, Nitrogen blowing to remove oxygen from edible oils, wine and juices, Oxygen blowing to stimulate fish growth in fish farming, Ozone blowing to st erilize ultrapure water systems in pharmaceutical plants, waste or process streams CO2 or NH 3 to adjust the pH in

Blowing, efficient heating, and direct steam injection to quell steam hammering, air blowing f or removal of VOCs (volatile organic compounds) from waste streams, and similar operations.

One problem with many of these operations is the inefficiency of gas distribution. SUMMARY OF THE INVENTION The present invention provides a solution to this problem. In one embodiment, the present invention provides dispersion of relatively small gas bubbles having a relatively large surface area into a liquid. As a result, a relatively large gas/liquid contact area is obtained. The bubbles are small and have a large surface area, so the gas can be efficiently dissolved in the liquid. This results in a reduced gas consumption. It also reduces the time required to dissolve the gas into the liquid, resulting in faster processing and higher productivity. The present invention is a process for making a multiphase mixture comprising flowing a first fluid stream through a process microchannel, the first fluid stream comprising at least one liquid and a /or a step comprising at least one gas and the process microchannel having an open section, flowing a second fluid stream into the process microchannel through the open section;

contacting the streams to form a multi-phase mixture, the second fluid stream comprising at least one gas and/or at least one microbody-forming material, and the first fluid stream comprising a multi-phase mixture; Forming a continuous phase in the phase mixture, the second fluid stream comprising forming a discontinuous phase dispersed within the continuous phase.

[0005]

In one embodiment, the second fluid dissolves in the first fluid. This may occur within the process microchannels or after the multiphase mixture exits the process microchannels. One advantage of the process of the present invention is that, in at least one embodiment, the second fluid in the multiphase mixture has a higher density than the larger bubbles formed by conventional techniques that do not employ microchannel processing technology. The advantage is that it can contain relatively small air bubbles that dissolve more efficiently into the fluid.

[0006]

In one embodiment, the multiphase mixture further comprises solid particles dispersed in the first fluid stream.

[0007]

In one embodiment, heat is exchanged between the process microchannel and the heat source and/or heat sink. In one embodiment, the heat source and/or heat sink comprises at least one heat exchange channel.

[0008]

In one embodiment, the open section extends along at least part of the axial length of the process microchannel. In one embodiment, the open section is at least about 10% of the axial length of the process microchannel, in one embodiment at least about 20% of the axial length of the process microchannel, and in one embodiment at least about 20% of the axial length of

the process microchannel. At least about 35% of the directional length, in one embodiment at least about 50% of the axial length of the process microchannel, in one embodiment at least about 65% of the axial length of the process microchannel, in one embodiment the process It extends along at least about 80% of the axial length of the microchannel, and in one embodi ment at least about 95% of the axial length of the process microchannel.

In one

embodiment, the second fluid stream flows from the second fluid stream channel through th e open section.

[0010]

In one embodiment, between a process microchannel and a heat source and/or heat sink, be tween a second fluid stream channel and a heat source and/or heat sink, or between a proces s microchannel and a second fluid stream channel. and heat sources and/or heat sinks. Heat s ources and/or heat sinks may be used for heating, cooling, or both cooling and heating. The h eat source may include heat exchange channels and/or heating elements. The heat sink may i nclude heat exchange channels and/or cooling elements. In one embodiment, the heat source and/or heat sink can be adjacent to the process microchannel, the second fluid stream channe l, or both the process microchannel and the second fluid stream channel. In one embodiment, the heat source and/or heat sink may be remote from the process microchannel and/or the se cond fluid stream channel, but not into the process microchannel and/or the second fluid strea m channel or into the process microchannel. It should be sufficiently close to the process micr ochannel and/or the second fluid stream channel to transfer heat from the channel and/or the second fluid stream channel.

[0011]

In one embodiment, the process is performed in a polyphase mixer. Within the multi-phase mixer, one or more headers or manifolds are used to provide fluid flow into the process microc hannels, the second fluid stream channels and the heat exchange channels, the process micro channels and the heat exchange channels. One or more footers or manifolds are used to provi de fluid flow out of the exchange channels

.

In one embodiment, the first fluid stream and the second fluid stream contact each other in a mixing zone within the process microchannel. In one embodiment, heat is exchanged betwe en heat sources and/or heat sinks and at least a portion of the process microchannels in the mixing zone. In one embodiment, heat is exchanged between the heat source and/or heat sin k and at least a portion of the process microchannel upstream of the mixing zone. In one emb odiment, heat is exchanged between the heat source and/or heat sink and at least a portion o f the process microchannel downstream of the mixing zone.

[0013]

In one embodiment, the process microchannel has a restricted cross-section within the mixin g 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 sections into th e process microchannel. flow into. In one embodiment, the aperture section in each of the spa ced 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 opposite w all. be done. In one embodiment, the opening section in each of the spaced apart walls includ es a plurality of openings, and at least some of the openings in the opening section of one wal l are the openings in the opening section of the other wall. They are staggered so that they ar e 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 A second fluid stream enters two fluid stream channels 270 and t hen through open sections 240 and 240a into mixing zones 213 and 213a, respectively, as ind icated by arrows 274 and 274a. Within mixing zones 213 and 213a, the second fluid stream c ontacts and mixes with the first fluid stream to form a multiphase mixture. The second fluid st ream may form a discontinuous phase within the first fluid stream. The first fluid stream may form a continuous phase. The multiphase mixture flows through non-opened compartments 2 17 and 217a and out of process microchannels 210 and 210a, respectively, as indicated by arr ows 218 and 218a. Heating or cooling can be an option. When heating or cooling is desired, h eat 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 cooling may vary over the length of the channel. Heating or cooling may be negligible or nonexistent in so me sections of process microchannels 210 and 210a and second fluid stream channel 270, an d may be moderate or relatively large in other sections. Heats or cools the fluid in the cells 21 0, 210a and 270. The degree of heating or cooling may vary over the length of the channel. H eating or cooling may be negligible or nonexistent in some sections of process microchannels 210 and 210a and second fluid stream channel 270, and may be moderate or relatively large i n other sections. Heats or cools the fluid in the cells 210, 210a and 270. The degree of heatin g or cooling may vary over the length of the channel. Heating or cooling may be negligible or nonexistent 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.

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

. In one embodiment, the first fluid stream contains salad dressing or mustard and the seco nd fluid stream contains nitrogen . [0097] In one embodiment, the first fluid stream compris es a liquid beverage or beer and the second fluid stream comprises carbon dioxide. In one e mbodiment, the first fluid stream contains bleached pulp used in paper manufacture and the s econd fluid stream contains chlorine . [0099] In one embodiment, the first fluid stream com prises a dispersion of coal in water and the second fluid stream comprises air. In one embodi ment, the first fluid stream comprises motor oil with entrained water and the second fluid stre am comprises nitrogen . [0101] In one embodiment, the first fluid stream contains the cells for the culture reaction and the second fluid stream contains oxygen or air. In one embodime nt, the first fluid stream contains the liquid reaction medium and the second fluid stream cont ains air or oxygen . In one embodiment, the first fluid stream contains the reaction medium for carrying out the hydrogenation reaction and the second fluid stream contains hydrogen .

[0104]

In one embodiment, the first fluid stream comprises a mixture of oil and water and the seco nd fluid stream comprises air or natural gas. In one embodiment, the first fluid stream conta ins bleached pulp used in paper manufacture and the second fluid stream contains oxygen . In one embodiment, the first fluid stream contains edible oil, wine or juice and the second f luid stream contains nitrogen . In one embodiment, the first fluid stream contains water use d in fish farming and the second fluid stream contains oxygen . In one embodiment, the first fluid stream contains water and the second fluid stream contains ozone . [0109] In one emb odiment, the first fluid stream comprises a waste or process stream and the second fluid strea m comprises carbon dioxide or ammonia. In one embodiment, the first fluid stream contains air and the second fluid stream contains water vapor . In one embodiment, the first fluid stre am comprises a waste or process stream containing volatile organic compounds and the secon d fluid stream comprises air . [0112] In one embodiment, the first fluid stream comprises a gas or liquid and the second fluid stream comprises the microbody-forming material. In one embodiment, the first fluid stream contains the water-based composition and the second fluid stream contains hydrogen and/or oxygen . This may be used for direct combination for hydrog en peroxide production. [0114]

In one embodiment, the first fluid stream contains the 2-alkylanthraquinone and the second stream contains hydrogen. It may be used to generate hydrogen peroxide. The first fluid str eam material comprises about 0.1 to about 80 weight percent, in one embodiment about 1 to about 50 weight percent, in one embodiment about 0.1 to about 80 weight percent, in the mu ltiphase mixture made by the process of the present invention

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may be present in concentrations ranging from about 1 to about 20% by weight. The second f luid stream material comprises from about 1 to about 95 weight percent, in one embodiment f rom about 10 to about 50 weight percent, in one embodiment from about 10 to about It may be present at a concentration in the range of 25% by weight. The third fluid stream material c omprises up to about 0.01% to about 50% by weight, in one embodiment about 1 to about 1 5% by weight, in one embodiment It may be present in concentrations ranging from about 0. 1 to about 1% by weight.

[0116]

In one embodiment, the second fluid may dissolve in the first fluid. This may occur within th e process microchannel or after the multiphase mixture exits the process microchannel. In on e embodiment, the second fluid is mixed with the first fluid within a period of up to about 10 h ours, in one embodiment up to about 1 hour, into the first fluid. It should dissolve.

[0117]

The multiphase mixture of the present invention may contain more than one type of solid pa rticles. These may be premixed with the first, second and/or third liquid. Solid particles may b e organic, inorganic, or a combination thereof. The solid particles are catalysts (e.g. CeO2 / Ba Al12O19 , Pt / Al Combustion catalysts such as 2O3 , polymerization catalysts and the like) , pigments (e. g.

TiO 2 , carbon black, iron oxide, etc.), fillers (eg, mica, silica, talc, barium sulfate, polyethylen es, polytetrafluoroethylene, nylon powder, methyl methacrylate powder) and the like. Solid pa rticles may include nano-sized particles. The solid particles may have an average particle diam eter ranging from about 0.001 to about 10 microns, and in one embodiment from about 0.01 to about 1 micron. The concentration of solid particles in the multiphase mixture may range u p to about 70% by weight, and in one embodiment from about 0.1 to about 30% by weight, b ased on the weight of the multiphase mixture.

[0118]

In one embodiment, the multiphase mixture made by the process of the present invention c

omprises a discontinuous phase dispersed within a continuous phase. The discontinuous phas e is up to about 200 microns, in one embodiment about 0.01 to about 200 microns, in one em bodiment about 0.01 to about 100 microns, in one embodiment about 0.01 to about 50 micro ns, one In embodiments from about 0.01 to about 25 microns, in one embodiment from about 0.01 to about 10 microns, in one embodiment from about 0.01 to about 5 microns, in one em bodiment from about 0.01 to about 2 microns. , in one embodiment about 0.01 to about 1 mi cron, in one embodiment about 0.01 to about 0.5 micron, in one embodiment about 0.01 to a bout 0.2 micron, in one embodiment about 0 .01 to about 0.1 microns, in one embodiment ab out 0.01 to about 0.08 microns, in one embodiment about 0.01 to about 0.05 microns, in one embodiment about 0.01 to about 0 It may contain bubbles or microbodies having volume-bas ed average dimensions (eg, diameter, height, width, length) in the range of 0.03 microns. On e advantage of the process of the present invention is that, in at least one embodiment, the b ubbles or microbodies are characterized by having a relatively narrow average diameter (or h eight, width or length) distribution.

[0119]

A "relative span" is often referred to as a "span". Relative span is a dimensionless parameter calculated from the volume distribution. As with the volume median foam or microbody size (VMD), D[v, 0.1] and D[v, 0.9] correspond to 10% and 90% of the dispersed foam or microbo dy volume, respectively. A diameter (or height, width or length) representing a point within a smaller diameter bubble or microbody. The span may be defined as the quotient of D[v,0.9] m inus D[v,0.1] divided by VMD(D[v,0.5]). In one embodiment, the span of bubbles or microbod ies in the multiphase mixture made by the process of the present invention ranges from about 1.3 to about 5, in one embodiment from about 1.8 to about 2.5. Good to have. In one embodi ment, the process of the invention is carried out in a single process microchannel and the spa n may range from about 1.3 to about 2.5. In one embodiment, the process of the present inv ention is carried out in a scaled-up multiphase mixing process using multiple process microch annels and spans may range from about 1.3 to about 5. In one embodiment, the volume-ba sed average diameter (or height, width or length) of the bubbles or microbodies in the multip hase mixture made by the process of the present invention is from about 0.1 to about
100
It may be in the micron range and the span may be in the range of about 1 to about 25. In on e embodiment, the volumetric average diameter (or height, width or length) may range from about 1 to about 10 microns and the span may range from about 1.8 to about 2.5. Good to ha ve.

[0121]

In one embodiment, cells are formed, the cells having a volume-based average diameter in t he range of up to about 25 microns and a span in the range of about 1.9 to about 2.5.

[0122]

In one embodiment, microbodies are formed having a volumetric average diameter (or heigh

t, width or length) in the range of up to about 5 microns and a diameter in the range of about 1.8 to about 2.5. span. Microbodies formed by the process of the invention have numerous u ses

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these

includes glass microspheres for density-reducing cast filings, glass microspheres for selective species immobilization in fluid bed reactors, and the like. Other examples include microsphere polymer, gel or colloidal suspension generation used for immunoassays and treatments. Micro bodies (e.g. microspheres) are processed in secondary processes to form aggregates, catalyti c fluidized or packed beds, drug delivery systems (e.g. protein-enzymatic reactions), and mod ern separation and fluidized bed applications (e.g. magnetic vibration Encapsulated solids may be formed for some applications, including coated magnetic carriers that can be advantageous ly separated or excited by In at least one embodiment, one advantage of the process of the present invention is that whether the process is for laboratory, pilot plant scale, or commercial scale, the process microchannel,

first

The gap distance between the two fluid flow channels, optionally the third fluid flow channel, and/or the heat exchange channel may be the same. As a result, whether the microchannel m ixer is built at laboratory or pilot plant scale, or as a commercial scale plant unit, the particle s ize distribution of the multiphase mixture produced by the microchannel mixer used in the pro cess of the present invention is , can be substantially the same. The shear force in the direct ion of velocity u for a fluid control element (discrete) is given by the formula F

$X = mu^{*}$

It can be calculated by du/dy. where mu is the viscosity and du/dy is the velocity gradient of the liquid flow perpendicular to the aperture section. However, as with liquid position (represe nted by a control element), velocity generally has three components, and shear force also has three components. For near-surface and surface-channel flow, one-dimensional assumptions c an be made and the net shear force of the liquid at the element surface can be approximated by Fx . Computational fluid dynamics, including commercially available software packages such as Fluent or FEMLAB, can be used to solve the necessary transport equations and consequentl y to calculate surface shear forces. Surface shear forces parallel to the direction of flow along the channel length can be calculated. Shear forces between parallel channels can also be calc ulated, incorporating flow distribution effects to determine the mass flux into each parallel cha nnel as a function of detailed channel and manifold geometry. For example, "Fundamentals of Fluid Mechanics", 3rd Edition, BR Munson, D.F. Young and T.H. Okiishi (T. H. Okiishi), John Wil ey & Sons, Inc., Weinheim, 1998, for more detailed calculations.

In one embodiment, the shear force deviation

factor (SFDF) for a process using a single process microchannel is within about 50% of the S FDF for a scaled-up process containing multiple process microchannels. can do. The SFDF is c

alculated by the formula

SFDF=(F max −F min)/(2F mean)

. where F max is the maximum shear force in the process microchannel for a particular liquid, F min is the minimum shear force in the process microchannel for the same liquid, F mean is th e open section in the process microchannel (240, 240a, 311, 321, 331, 341, 415, 425, 435, 4 45, 550, 560, 570, 580) are the arithmetic mean shear forces for the same liquid at the surfa ce. Within a single process microchannel operated by the process of the present invention, the SFDF is less than about 2, in one embodiment less than about 1, in one embodiment less than about 0.5, in one embodiment about 0.5. Should be less than 2. In one embodiment, the pr ocess of the present invention can provide relatively uniform shear forces while using multiple process microchannels

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of multiple process microchannels

To measure the inter-channel shear force uniformity, the average shear force for each channel is calculated and compared. F max is the maximum average channel shear force and F min is t he minimum average shear force. F mean is the mean value of the mean shear force of all cha nnels. SFDF can be calculated from these values. Among the plurality of process microchannel s, in at least one embodiment of the process of the invention, the SFDF is less than about 2, i n one embodiment less than about 1, in one embodiment less than about 0.5, in one embodi ment In embodiments it can be less than about 0.2.

[0128]

The heat exchange fluid may comprise any fluid. These include air, steam, liquid water, gase ous nitrogen, liquid nitrogen, other gases including inert gases, carbon monoxide, carbon diox ide, molten salts, oils such as mineral oil, gaseous hydrocarbons, liquid hydrocarbons and Do w. - including heat exchange fluids such as Dowtherm A and Therminol available from Dow-Un ion Carbide.

Heat

exchange fluids may include first, second and/or third fluids used to create a multiphase mix ture. This can provide process preheating or precooling to increase the overall thermal efficien cy of the process.

[0130]

In one embodiment, the heat exchange channels include process channels in which endother mic or exothermic processes are performed. These heat exchange process channels may be m icrochannels. Examples of endothermic processes that can be carried out in heat exchange ch annels include steam reforming and dehydrogenation reactions. In one embodiment, the incor poration of simultaneous endothermic reactions that provide heat sink enhancement typically allows for heat fluxes approximately an order of magnitude greater than convective cooling he at fluxes. Examples of exothermic processes that can be carried out in heat exchange channel s include water gas shift reactions, methanol synthesis reactions and ammonia synthesis react

ions.

In one embodiment

, the heat exchange fluid undergoes a phase change within the heat exchange channels. This phase change provides additional heating or removal of heat from the process microchannels or liquid channels beyond the heat supplied by convective heating or cooling. In the case of a n evaporating liquid heat exchange fluid, this additional heat transferred from the process mic rochannels can come from the latent heat of vaporization required by the heat exchange fluid. Examples of such phase changes are nucleate boiling oil or water. In one embodiment, the va por mass fraction quality of boiling of the phase change fluid can be up to about 100%, in one embodiment up to about 75%, and in one embodiment up to about 50%. The use of phase c hange or chemical reaction enhancement heat transfer can be made even more advantageous when multiphase mixture generation occurs in concert with the chemical reaction in the proce ss channel

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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
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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

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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 when compared to classical laminar flow. Results from CF D simulations show that, unlike laminar flow in microchannels, the mixing surface features twi st and swirl the flow path in continuous channels, which is expected in the case of laminar flo w

.

push 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;

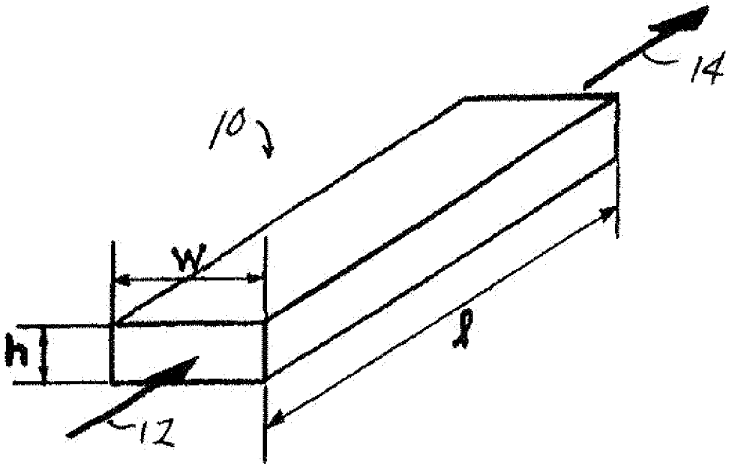
FIG. 18 is an illustration of a relatively thin apertured sheet overlying a relatively thick apertur ed sheet or plate useful in creating the apertured section of the process microchannels used in the process of the present invention;

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.

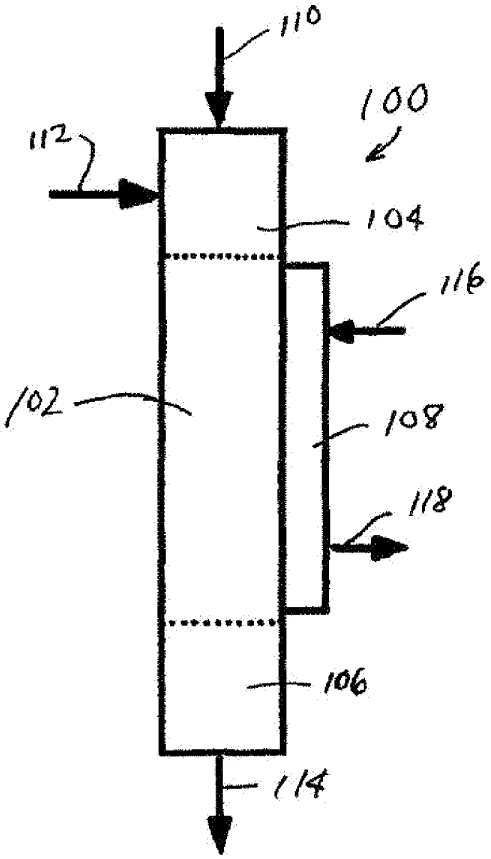
FIG. 20 shows examples of alternative embodiments of apertures that can be used in the aper tured section of process microchannels used in the process of the present invention; The aper ture has a coating partially filling the aperture and overlying the sidewalls of the aperture.
FIG. 21 is a schematic diagram showing the formation of gas bubbles or microbodies during o peration of the process of the invention;
FIG. 22 is a schematic representation of surface features that can be provided within a microc hannel used in the process of the invention;
FIG. 23 is a schematic representation of surface features that can be provided within a microc hannel used in the process of the invention;
FIG. 24 is a schematic representation of surface features that can be provided within a microc hannel used in the process of the invention;
FIG. 25 is a schematic representation of surface features that can be provided within a microc hannel used in the process of the invention;
FIG. 26 is a schematic representation of surface features that can be provided within a microc hannel used in the process of the invention;
FIG. 27 is a plan view of the surface feature geometry simulated by computational fluid dyna mics (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 cente rline 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 alon g 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 th e inlet face (drawn between arrows). Looking down the flow axis from the inlet face as describ ed in Example 5.

drawing open ----

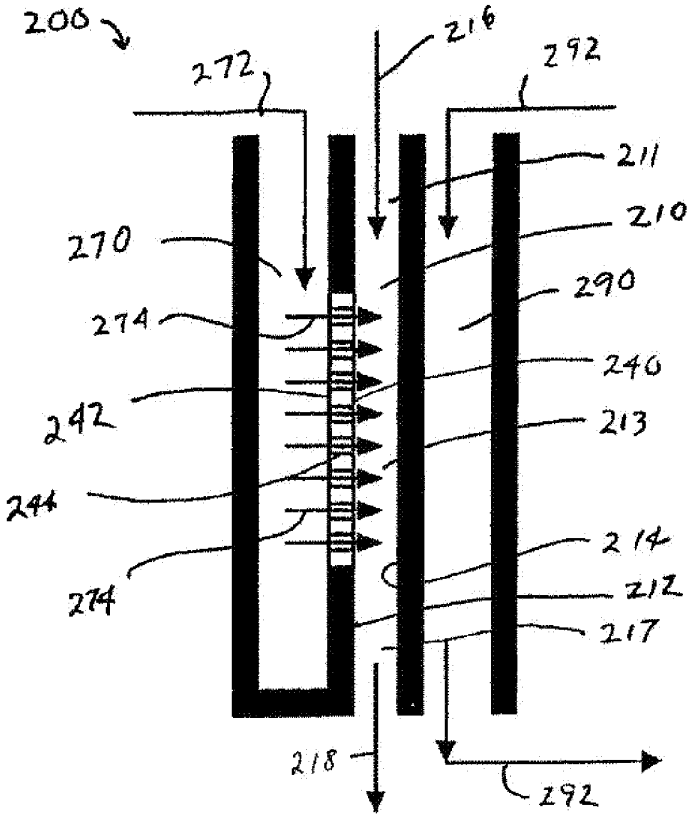
[Fig. 1]



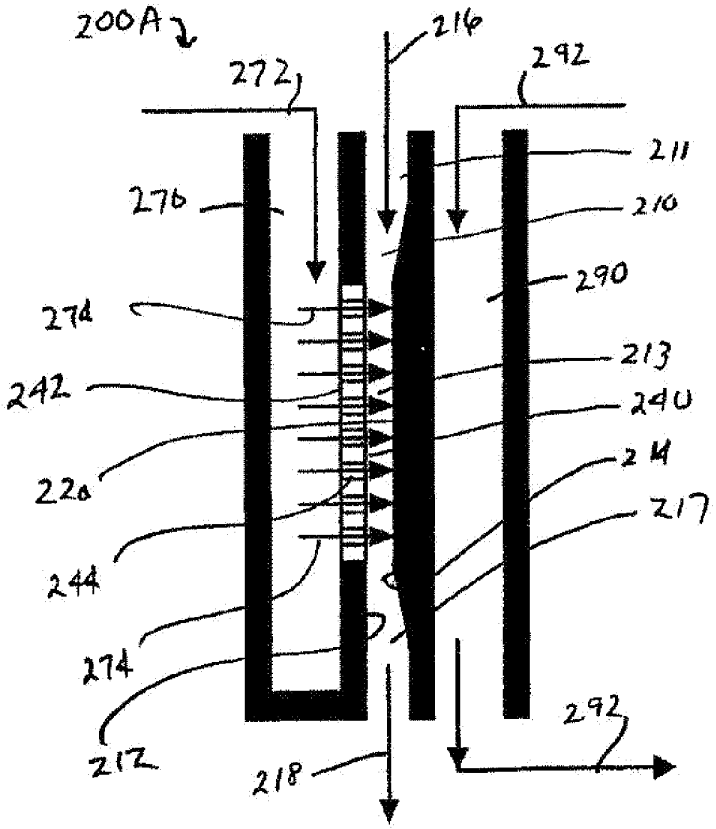
[Figure 2]



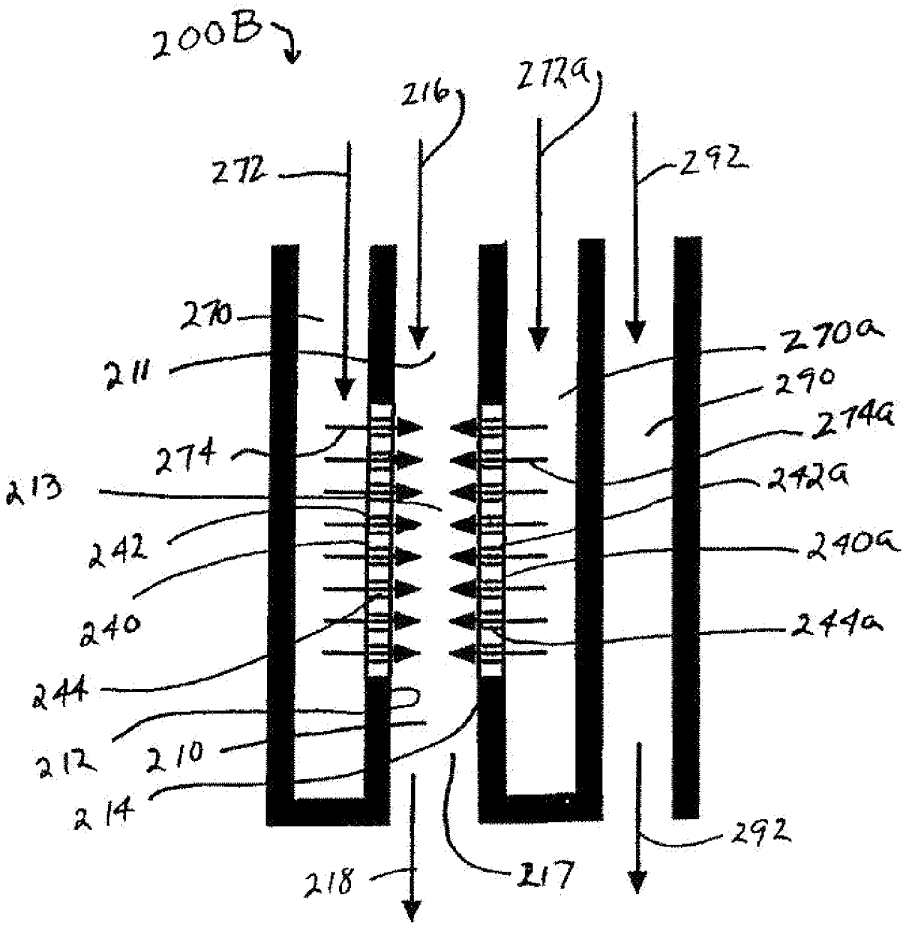
[Figure 3]


200
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274
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292

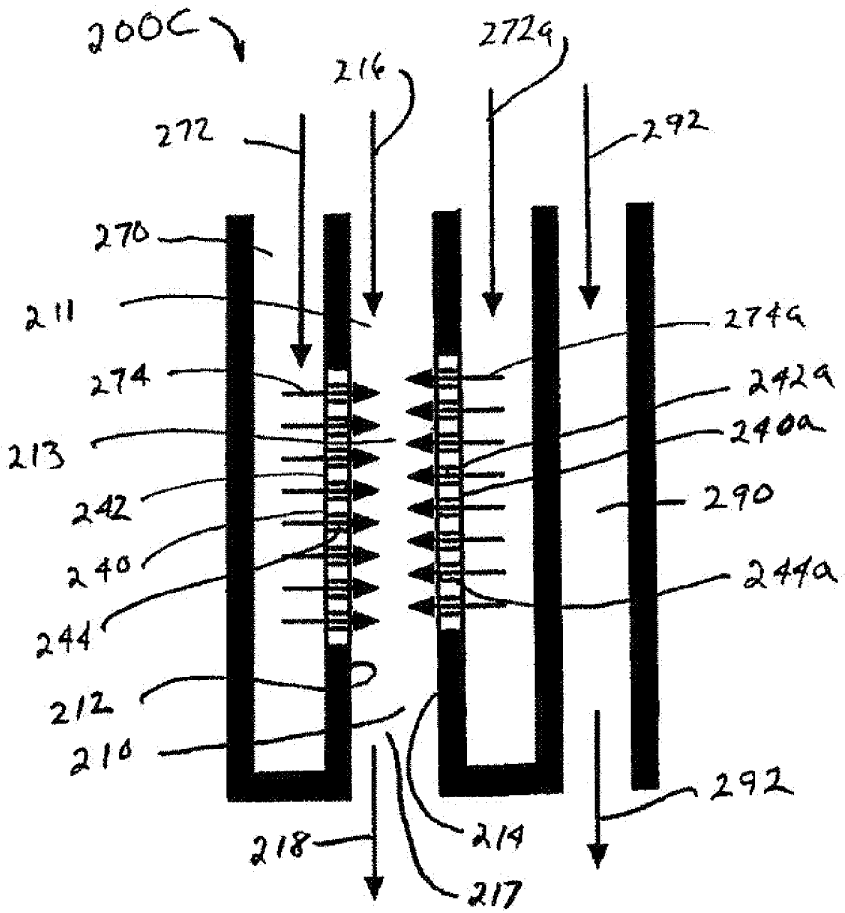
[Figure 4]


200A
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216
292
211
276
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242
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292

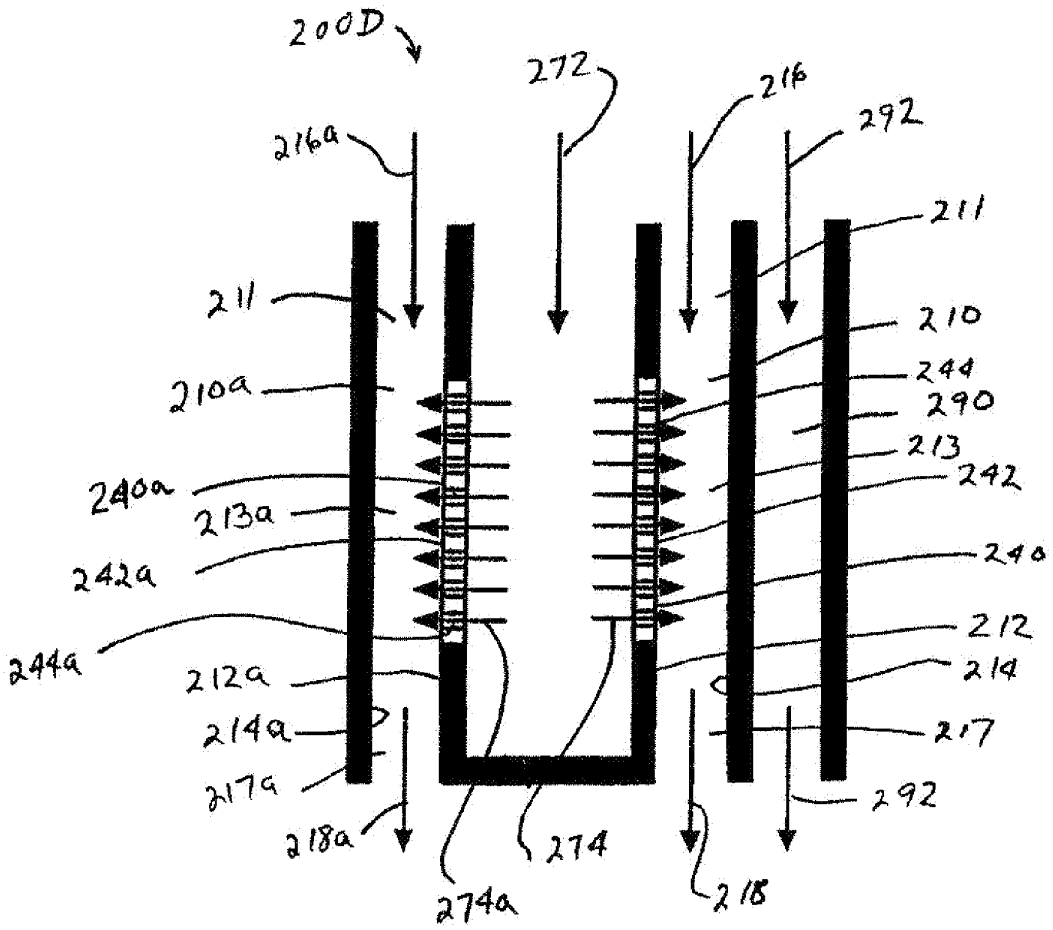
[Figure 5]


200B
216
272a
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242a
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240a
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244a
244
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214
292
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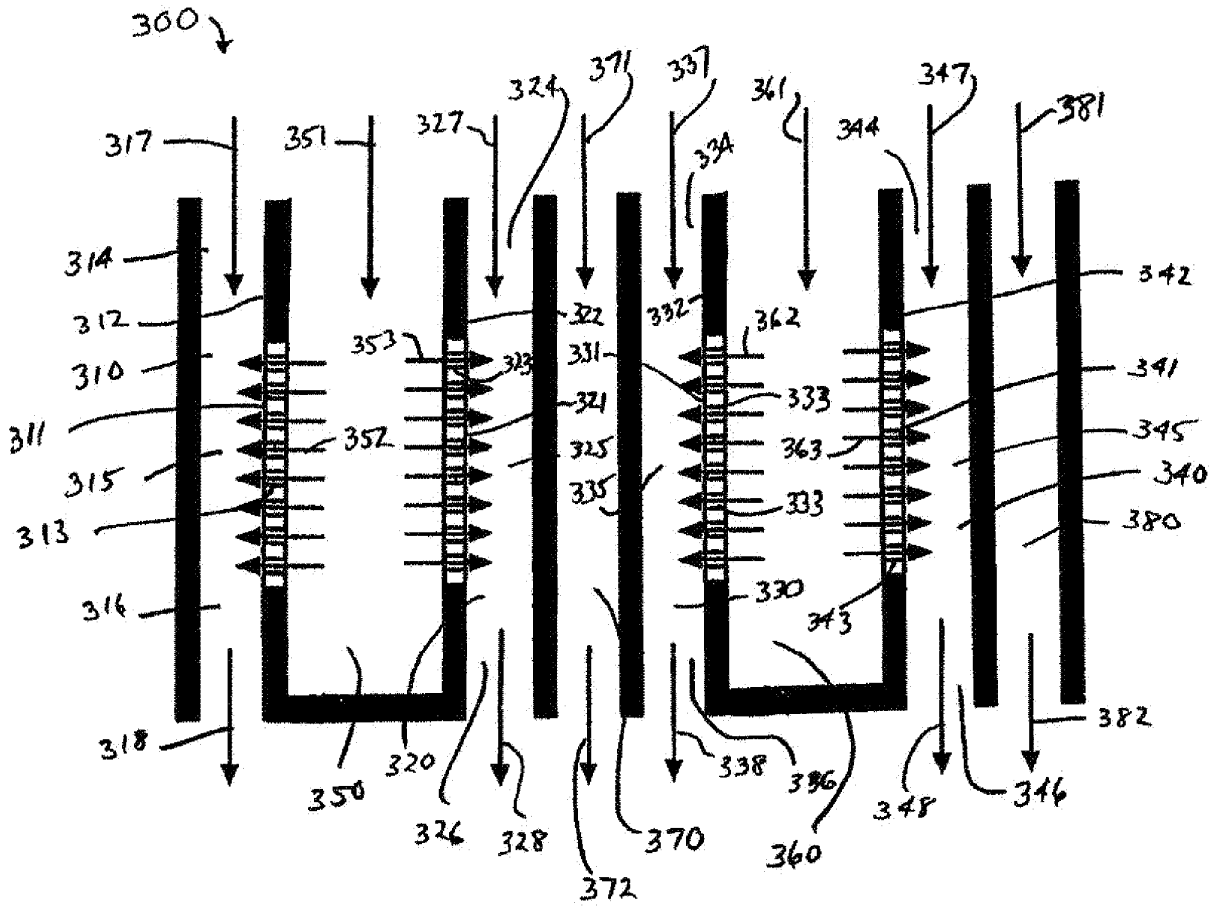
[Fig. 6]


200C
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272a
272
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274a
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244a
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292
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217

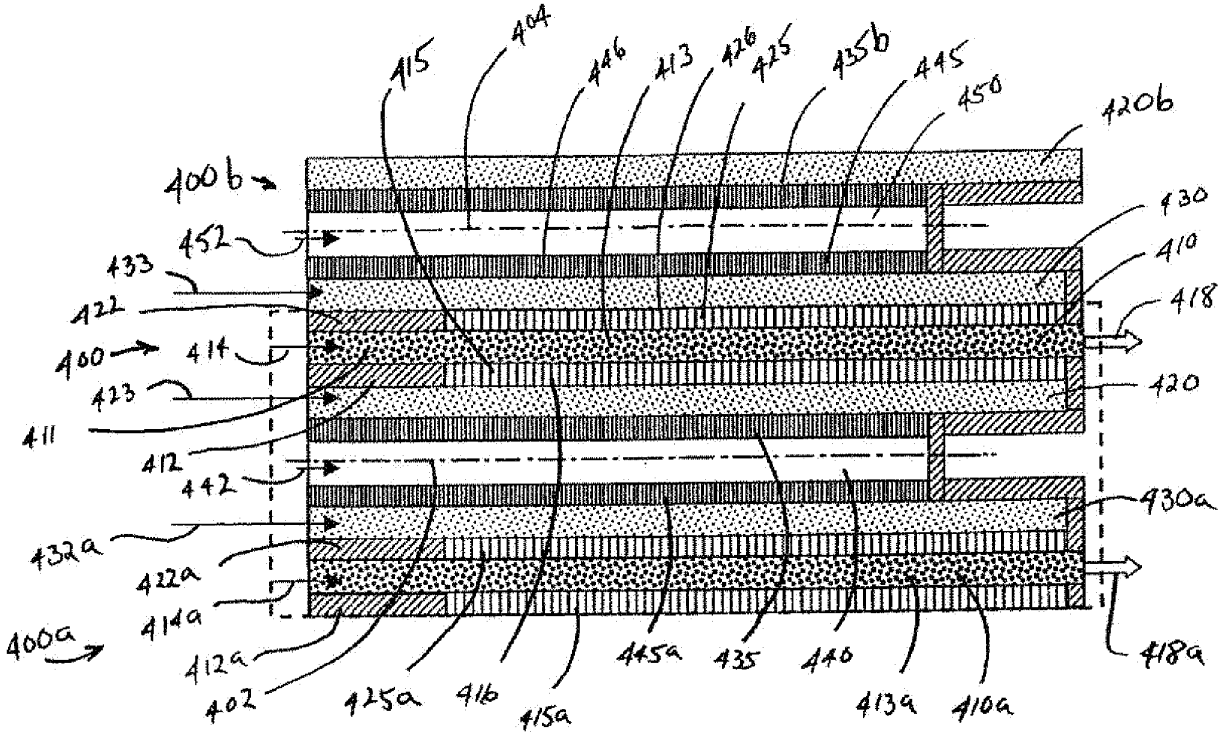
[Fig. 7]


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

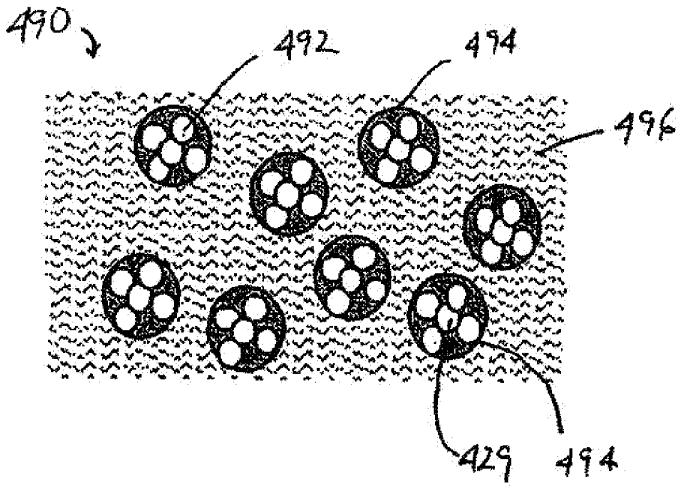
[Fig. 8]


300
317
351
327
324
371
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361
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381
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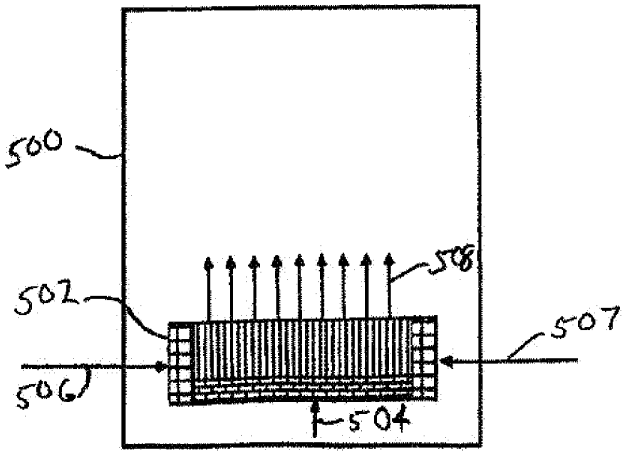
[Fig. 9]


415
404
446
413
426
425
435b
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420b
400b
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433
422
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411
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432a
422a
414a
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418
420
430a
418a

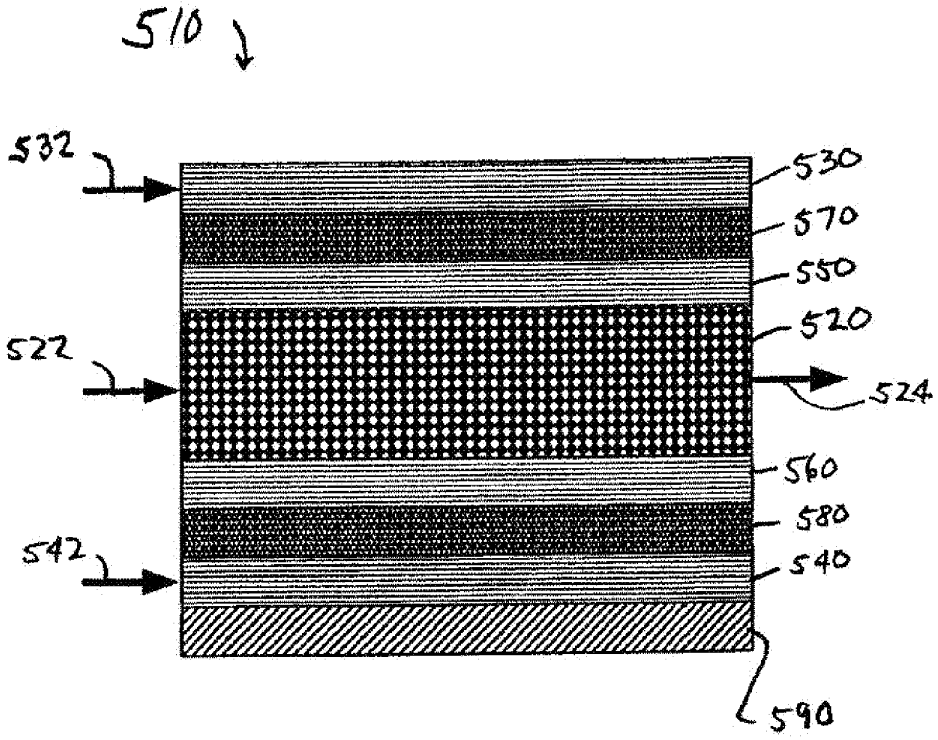
[Fig. 10]



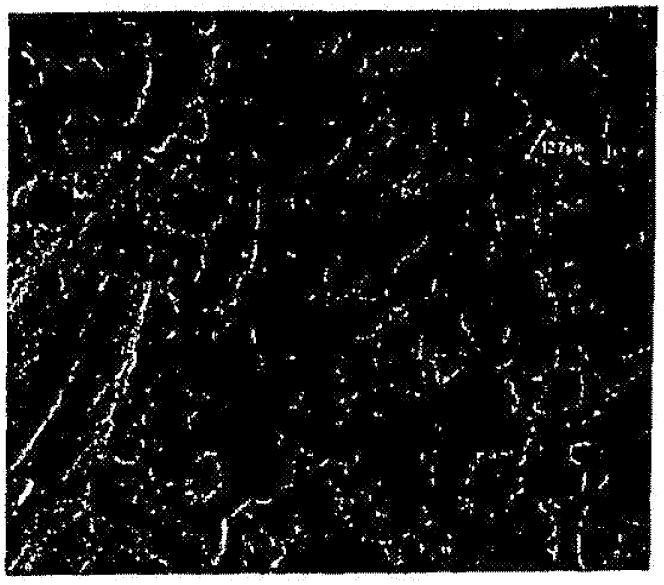
[Fig. 11]



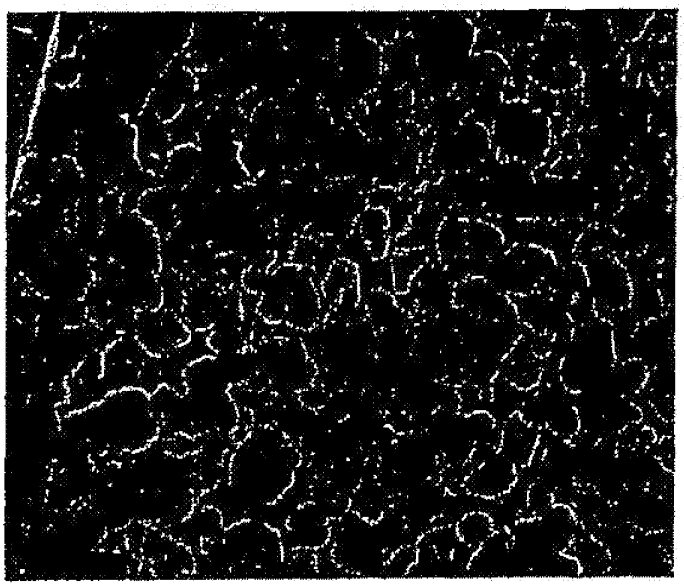
[Fig. 12]



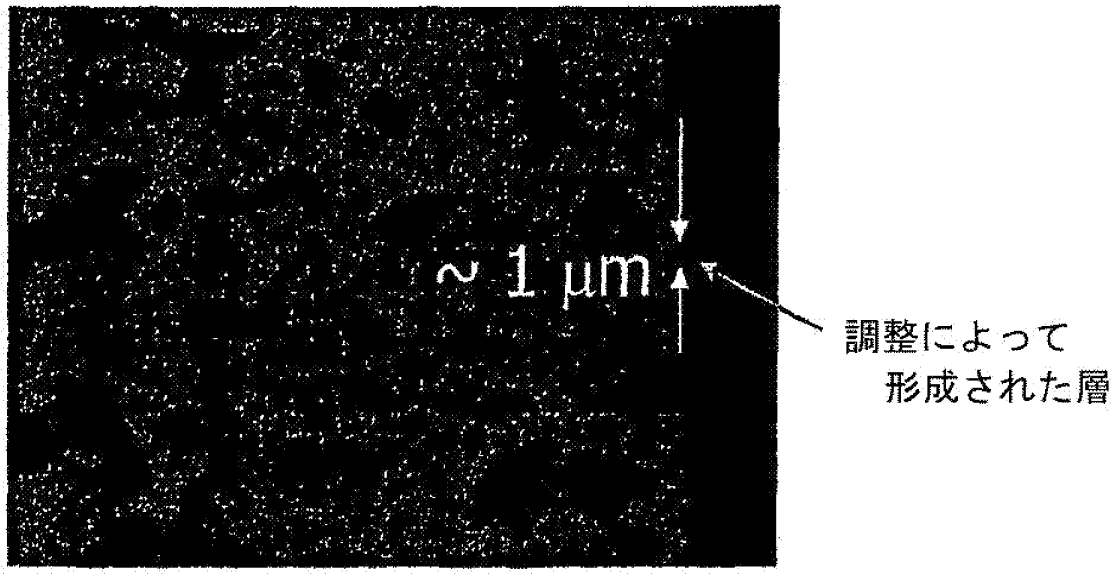
[Fig. 13]



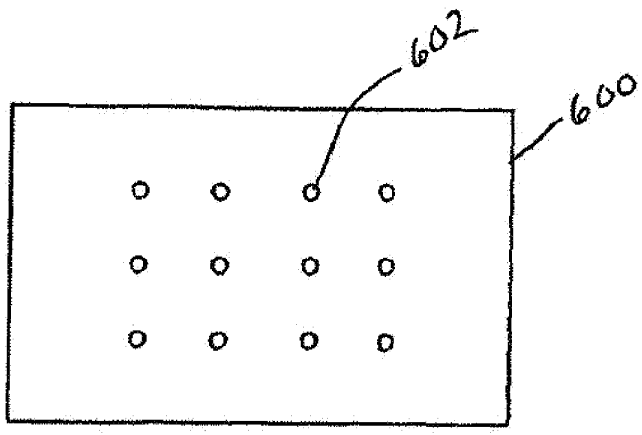
[Fig. 14]



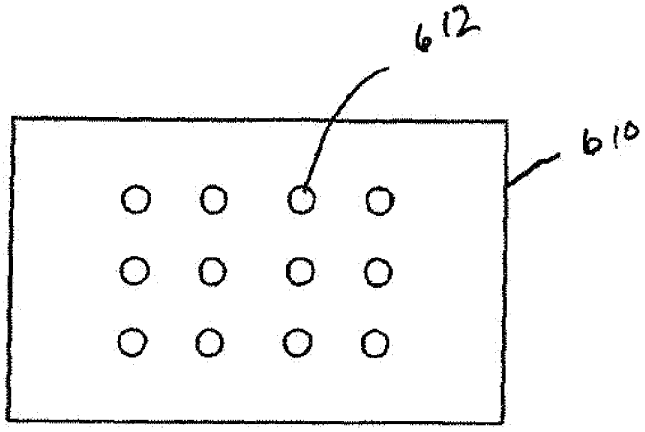
[Fig. 15]



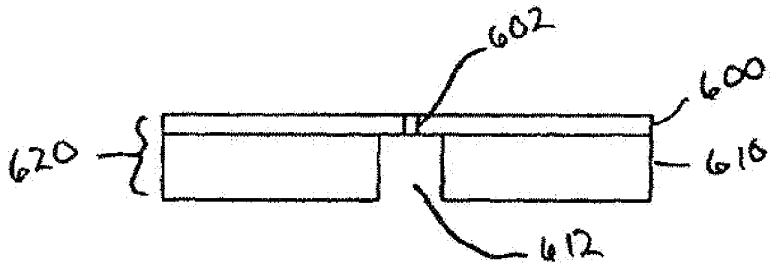
[Fig. 16]



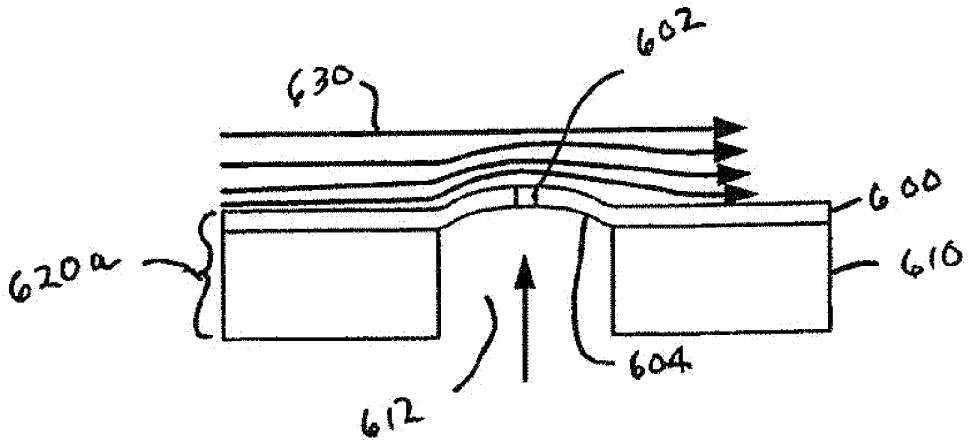
[Fig. 17]



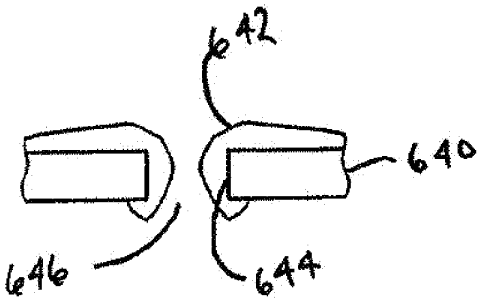
[Fig. 18]



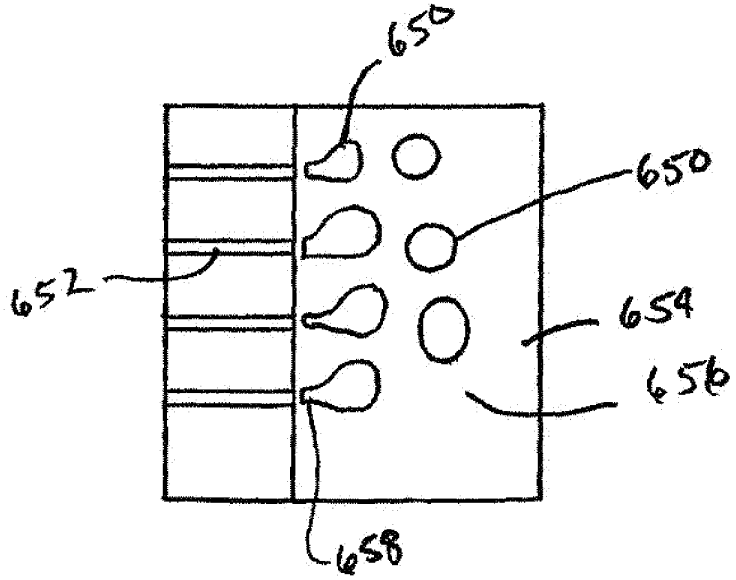
[Fig. 19]



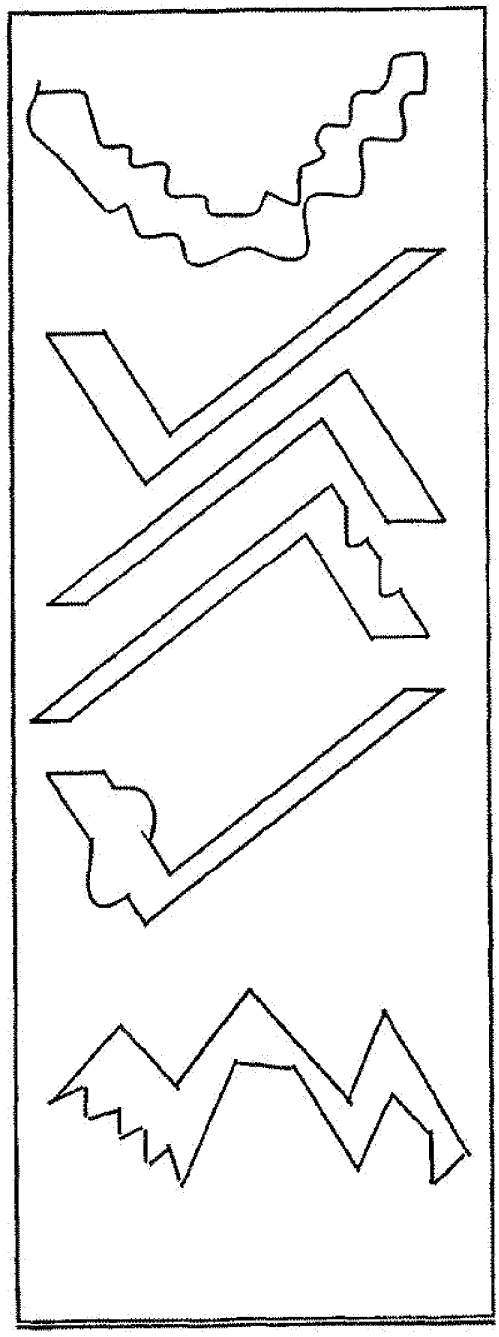
[Fig. 20]



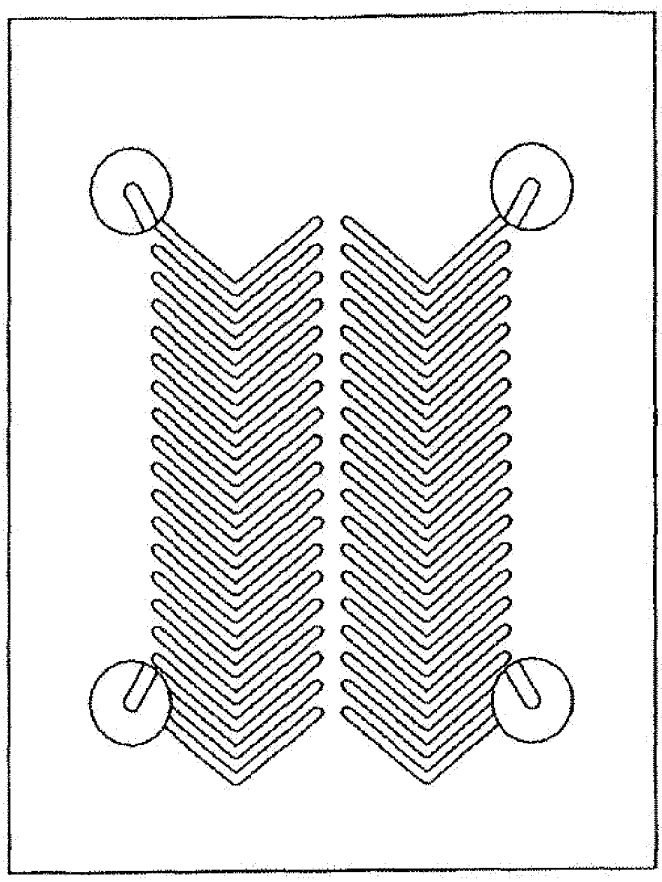
[Fig. 21]



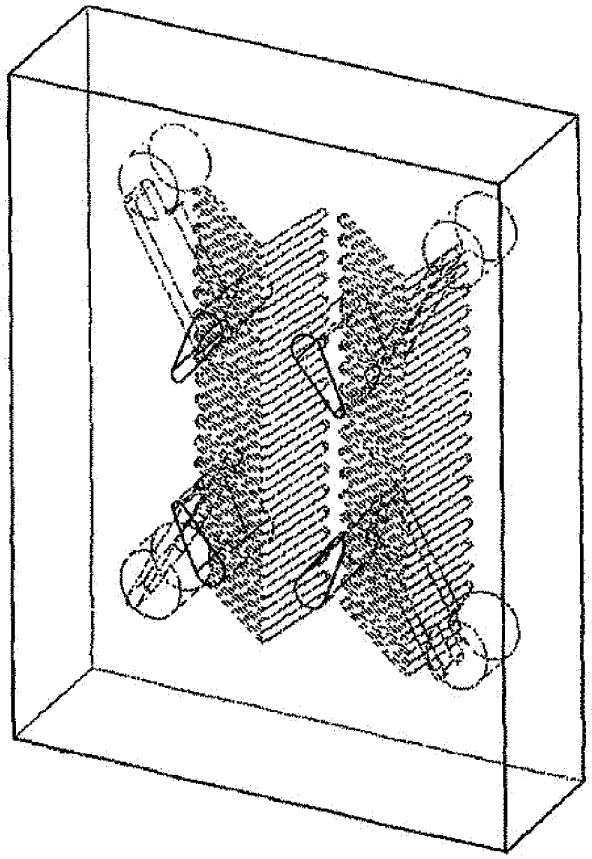
[Fig. 22]



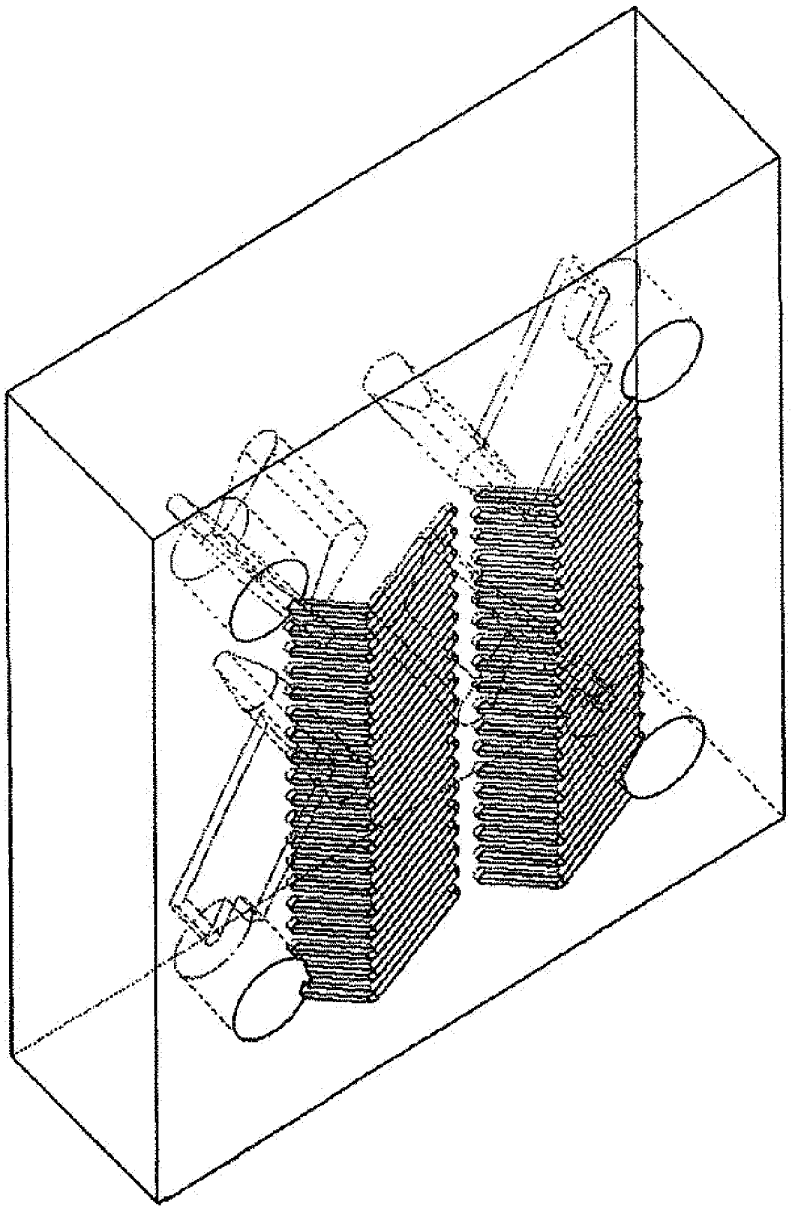
[Fig.23]



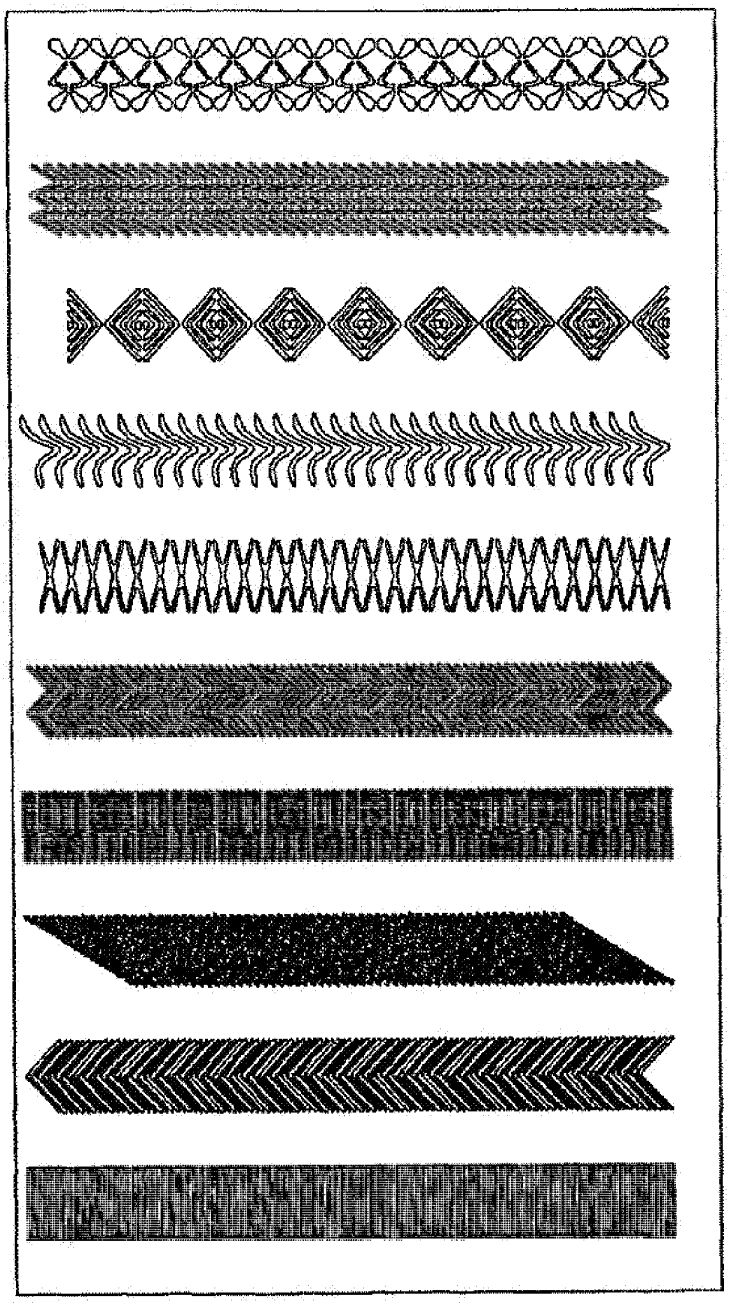
[Fig.24]



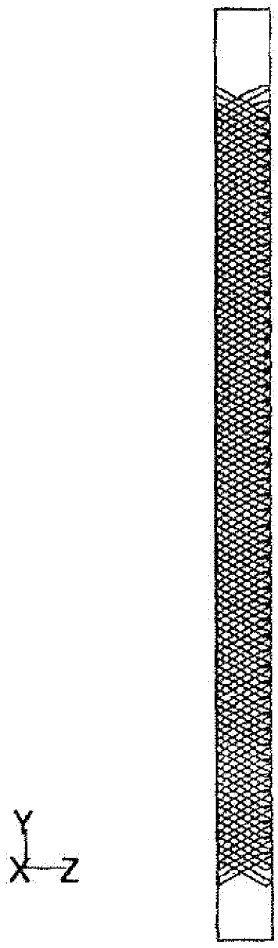
[Fig.25]



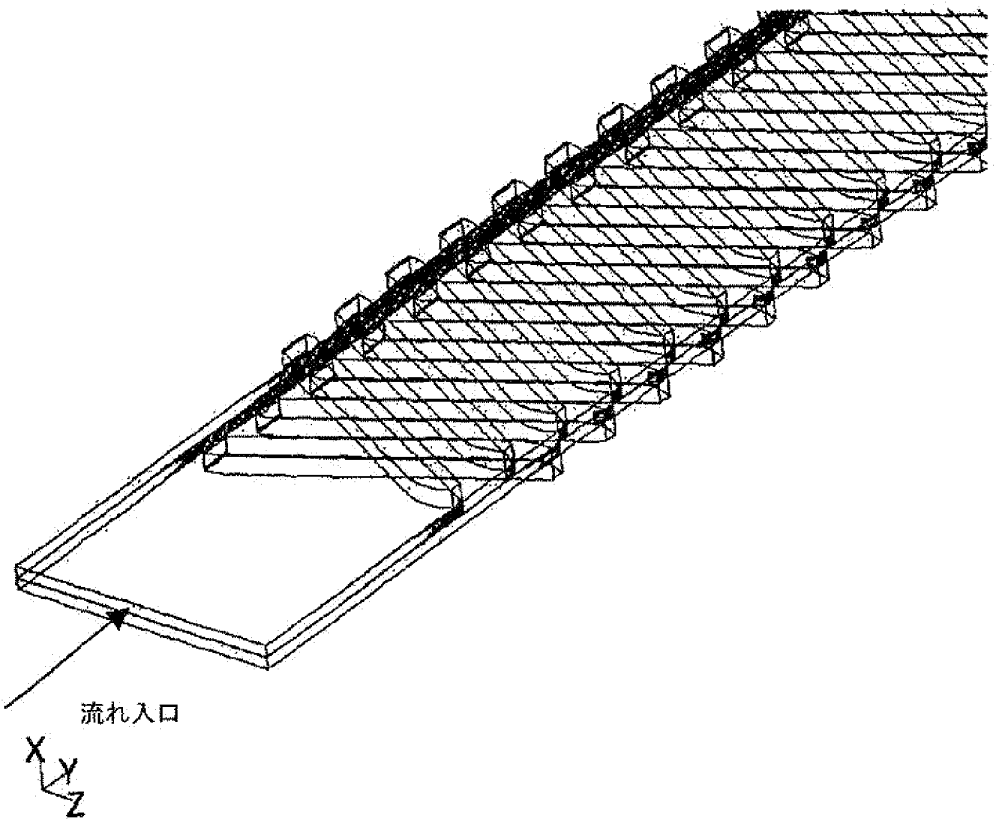
[Fig.26]



[Fig.27]



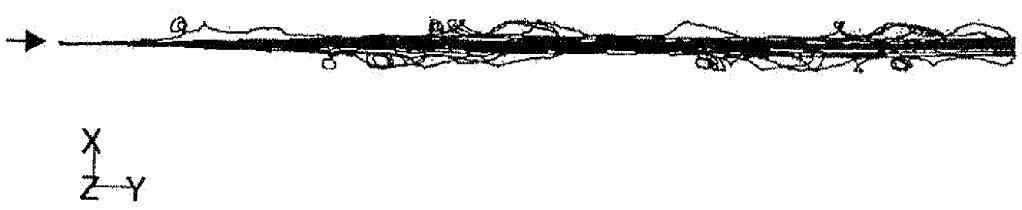
[Fig.28]



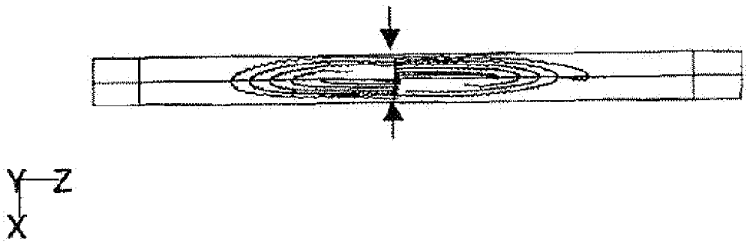
[Fig.29]



[Fig. 30]



[Fig. 31]



drawing open —

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

Magnify and Rotate

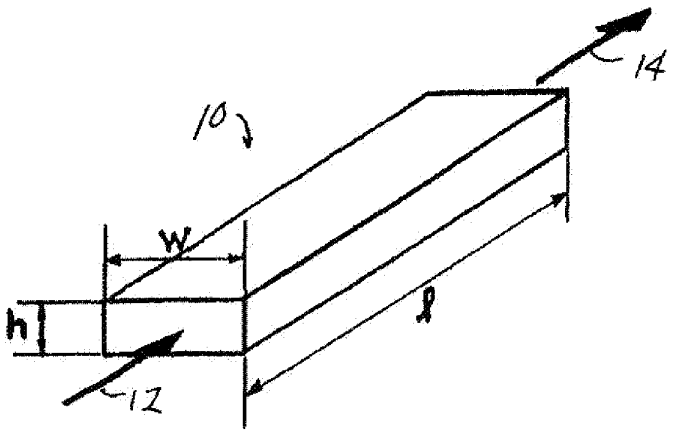


Figure 1

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Bibliographic data: JP5643474 (B2) — 2014-12-17

MULTIPHASE MIXING PROCESS USING MICROCHANNEL PROCESS TECHNOLOGY

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

- cooperative: **B01F23/232 (EP, US); B01F23/41 (EP, US); B01F23/4144 (EP); B01F23/4145 (EP); B01F25/3142 (EP, US); B01F25/31421 (EP, US); B01F25/31424 (EP, US); B01F33/30 (EP, US); B01F35/92 (EP, US); B01J19/0093 (EP, US); F28F3/12 (EP, US);** B01F2215/0431 (EP, US); B01F2215/045 (EP, US); B01F2215/0472 (EP, US); B01F23/4144 (US); B01F23/4145 (US); B01J2219/00783 (EP, US); B01J2219/00788 (EP, US); B01J2219/00822 (EP, US); B01J2219/00826 (EP, US); B01J2219/00828 (EP, US); B01J2219/00831 (EP, US); B01J2219/00833 (EP, US); B01J2219/00835 (EP, US); B01J2219/0086 (EP, US); B01J2219/00873 (EP, US); B01J2219/00889 (EP, US); F28D2021/0052 (EP, US); F28F2260/02 (EP, US); Y10S516/928 (EP, US); Y10S516/929 (EP, US); Y10T436/2575 (EP, US)

Application number: JP20070534825 20050930 Global Dossier

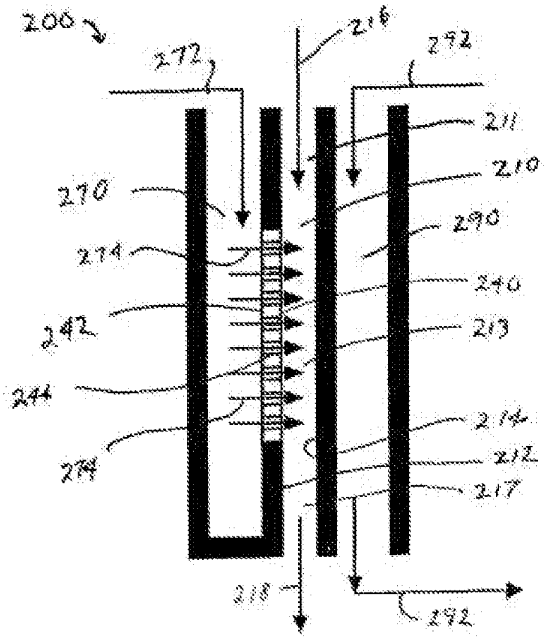
Priority number(s): US20040615509P 20041001 ; WO2005US35330 20050930

Also published as: CA2582378 (A1) CA2582378 (C) CN101084061 (A) CN101084061 (B) EP1804964 (A1) more

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

The disclosed invention relates to a process for making a multiphase mixture, comprising: flowing a first fluid stream (216) through a process microchannel (210), the first fluid stream (216) comprising at least one liquid and/or at least one gas, the process microchannel (210) having an apertured section (244); flowing a second fluid

stream (272) through the apertured section (244) into the process microchannel (210) in contact with the first fluid stream (216) to form the multiphase mixture (218), the second fluid stream (272) comprising at least one gas and/or at least one microbody-forming material, the first fluid stream (272) forming a discontinuous phase dispersed in the continuous phase. Heat exchange may also take place between the process microchannel (210) and a heat source or heat sink (290).



(19)日本国特許庁(JP)　(12)特　許　公　報(B2)　(11)特許番号
特許第5643474号
(P5643474)
(45)発行日　平成26年12月17日(2014.12.17)　(24)登録日　平成26年11月7日(2014.11.7)

(51)Int.Cl.			F I		
B01F	***3/04***	***(2006.01)***	B01F	3/04	A
B01F	***1/00***	***(2006.01)***	B01F	1/00	A
B01F	***5/06***	***(2006.01)***	B01F	1/00	B
B01F	***15/06***	***(2006.01)***	B01F	1/00	G
			B01F	5/06	

請求項の数 35　(全 47 頁)　最終頁に続く

(21)出願番号　特願2007-534825 (P2007-534825)
(86)(22)出願日　平成17年9月30日 (2005.9.30)
(65)公表番号　特表2008-514428 (P2008-514428A)
(43)公表日　平成20年5月8日 (2008.5.8)
(86)国際出願番号　PCT/US2005/035330
(87)国際公開番号　WO2006/039568
(87)国際公開日　平成18年4月13日 (2006.4.13)
審査請求日　平成20年9月29日 (2008.9.29)
審判番号　不服2012-12061 (P2012-12061/J1)
審判請求日　平成24年6月27日 (2012.6.27)
(31)優先権主張番号　60/615,509
(32)優先日　平成16年10月1日 (2004.10.1)
(33)優先権主張国　米国(US)

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(54)【発明の名称】マイクロチャネルプロセス技術を用いる多相混合プロセス

(57)【特許請求の範囲】
【請求項１】
多相混合物を作るためのプロセスであって、
第一の流体流をプロセスマイクロチャネルの中に流す工程であって、前記第一の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、複数の開口を含む開口区間を有する工程であって、前記開口区間は前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に沿った長さと前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に垂直な厚さ寸法を有し、
前記厚さを有する前記開口区間を通して第二の流体流を前記プロセスマイクロチャネルの中に流し、前記第一の流体流と接触させて前記多相混合物を形成させる工程であって、前記第二の流体流は、少なくとも一種類の気体を含む気体流であり、前記第一の流体流は、前記多相混合物の中の連続相を形成し、前記第二の流体流は、前記連続相の中の分散した不連続相を形成する工程、
を含み、
前記第二の流体流は、前記プロセスマイクロチャネルに隣接する第二の流体流チャネルから前記開口区間を通って流れ、
熱交換チャネルは、前記プロセスマイクロチャネル、前記第二の流体流チャネル、または前記プロセスマイクロチャネルと前記第二の流体流チャネルとの両方に隣接して、前記プロセスマイクロチャネルと前記熱交換チャネルとの間、前記第二の流体流チャネルと熱交換チャネルとの間、あるいは前記プロセスマイクロチャネルと前記第二の流体流チャネ

ルとの両方と熱交換チャネルとの間で熱が交換され、熱交換液体が熱交換チャネル内にある、プロセス。

【請求項２】

前記第一の流体流と前記第二の流体流とは、前記プロセスマイクロチャネルの中の混合ゾーンの中で互いに接触する、請求項１に記載のプロセス。

【請求項３】

前記プロセスマイクロチャネルは、狭くなった断面を有する混合ゾーンを有する、請求項１または２に記載のプロセス。

【請求項４】

前記プロセスマイクロチャネルは、離間した壁と、前記離間した壁のそれぞれの中に開口区間を有し、前記第二の流体流は、開口区間のそれぞれを通って前記プロセスマイクロチャネルに流入する、請求項１から３のいずれか一項に記載のプロセス。

【請求項５】

前記プロセスマイクロチャネルは、第一のプロセスマイクロチャネルであり、多相混合物形成ユニットの中にあり、該多相混合物形成ユニットは、第二のプロセスマイクロチャネル、および前記第一のプロセスマイクロチャネルと前記第二のプロセスマイクロチャネルとの間に位置する第二の流体流チャネルを含み、各プロセスマイクロチャネルは、開口区間を有する壁を有し、前記第一の流体流は、前記第一のプロセスマイクロチャネルおよび前記第二のプロセスマイクロチャネルを通って流れ、前記第二の流体流は、前記第二の流体流チャネルから、前記開口区間を通って前記第一のプロセスマイクロチャネルの中に流れて前記第一の流体流と接触し、前記開口区間を通って前記第二のプロセスマイクロチャネルの中に流れて前記第一の流体流と接触する、請求項１から４のいずれか一項に記載のプロセス。

【請求項６】

多相混合物を作るためのプロセスであって、

第一の流体流をプロセスマイクロチャネルの中に流す工程であって、前記第一の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、複数の開口を含む開口区間を有する工程であって、前記開口区間は前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に沿った長さと前記プロセスマイクロチャネル内を流れる前記第一の流体流の流路に垂直な厚さ寸法を有し、

第二の流体流を第二の流体流チャネルの中に流す工程であって、前記第二の流体流は、少なくとも一種類の液体を含む液体流であり、前記プロセスマイクロチャネルは、前記第二の流体流をプロセスマイクロチャネルに流入させることができるようにする複数の開口を含む開口区間を有する工程であって、前記開口区間は第二の流体流チャネル内を流れる前記第二の流体流の流路に沿った長さと前記第二の流体流チャネル内を流れる前記第二の流体流の流路に垂直な厚さ寸法を有し、

第三の流体流を第三の流体流チャネルの中に流す工程であって、前記第三の流体流は気体を含む気体流であり、第二の流体流チャネルは、前記第三の流体流を第二の流体流チャネルに流入させることができるようにする複数の開口を含む別の開口区間を有する工程であって、前記別の開口区間は前記第三の流体流チャネル内を流れる前記第三の流体流の流路に沿った長さと前記第三の流体流チャネル内を流れる前記第三の流体流の流路に垂直な厚さ寸法を有し、

前記第三の流体流を前記第三の流体流チャネルから前記厚さを有する前記別の開口区間を通して前記第二の流体流チャネルに流入させて、前記第二の流体流と接触させて別の多相混合物を形成させる工程、

前記別の多相混合物を前記厚さを有する前記開口区間を通して前記プロセスマイクロチャネルに流入させて、前記第一の流体流と接触させて前記多相混合物を形成させる工程、

熱交換チャネルは、前記プロセスマイクロチャネルおよび／または前記第二の流体流チャネルまたは前記第三の流体流チャネルのどちらかに隣接し、前記プロセスチャネルと前記熱交換チャネルとの間で熱が交換され、熱交換液体が熱交換チャネル内にある工程、

を含むプロセス。
【請求項７】
前記プロセスマイクロチャネルは、平行な離間したシートおよび／またはプレートから形成される、請求項１から６のいずれか一項に記載のプロセス。
【請求項８】
第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成される請求項７に記載のプロセス。
【請求項９】
前記熱交換チャネルは、平行な離間したシートおよび／またはプレートから形成される請求項８に記載のプロセス。
【請求項１０】
前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、複数の前記プロセスマイクロチャネルおよび第二の流体流チャネルを含み、各プロセスマイクロチャネルは、開口区間を有する壁および隣接する第二の流体流チャネルを有し、前記第二の流体流は、前記第二の流体流チャネルから前記開口区間を通って前記プロセスマイクロチャネルに流入して前記第一の流体流と接触し、前記プロセスマイクロチャネルおよび第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成され、前記プロセスマイクロチャネルおよび第二の流体流チャネルは、互いに隣接し、横に並べられた交互平面、または上下に積み重ねられた交互平面の中に配置される、請求項１から９のいずれか一項に記載のプロセス。
【請求項１１】
前記マイクロチャネルミキサは、平行な離間したシートおよび／またはプレートから形成される複数の熱交換チャネルをさらに備え、前記熱交換チャネルは、前記プロセスマイクロチャネル、前記第二の流体流チャネル、または前記プロセスマイクロチャネルと前記第二の流体流チャネルとの両方に隣接する、請求項１０に記載のプロセス。
【請求項１２】
前記プロセスマイクロチャネルおよび前記第二の流体流チャネルは、同心状に配置された円形の管を含む、請求項１から６のいずれか一項に記載のプロセス。
【請求項１３】
前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、複数の前記プロセスマイクロチャネルを含み、前記プロセスマイクロチャネルのそれぞれの中で別個の多相混合物が形成され、前記プロセスマイクロチャネルの少なくとも二つの中で形成された前記多相混合物は互いに異なる、請求項１から１２のいずれか一項に記載のプロセス。
【請求項１４】
前記開口区間は、シートおよび／またはプレートと、前記シートおよび／またはプレートの中にある複数の開口とを含む、請求項１から１３のいずれか一項に記載のプロセス。
【請求項１５】
前記シートおよび／またはプレートの少なくとも一部の上を覆っており、前記開口の一部に充填される、コーティングを有し、または、前記シートおよび／またはプレートは熱処理される、請求項１４に記載のプロセス。
【請求項１６】
前記開口区間は、多孔質材料から作られ、前記多孔質材料は、金属、非金属、酸化されている、またはアルミナ、ニッケルまたはそれらの組み合わせでコーティングされている、請求項１から１５のいずれか一項に記載のプロセス。
【請求項１７】
前記第一の流体流は、水または有機液体を含み、前記第二の流体流は、少なくとも一種類の気体を含み、または前記第二の流体流は、空気、水素、窒素、二酸化炭素またはそれらの二種類以上の混合物から選択される気体を含む、請求項１から１６のいずれか一項に記載のプロセス。

【請求項１８】
前記プロセスマイクロチャネルは、前記プロセスマイクロチャネルを通る前記第一の流体流の前記流れに垂直な、１０ミリメートル以下の内部寸法を有する、請求項１から１７のいずれか一項に記載のプロセス。
【請求項１９】
前記第二の流体流は、第二の流体流チャネルから前記開口区間を通って流れ、前記第二の流体流チャネルは、前記第二の流体流チャネルを通る前記第二の流体流の前記流れに垂直な、１００センチメートル以下の内部寸法を有する、請求項１から１８のいずれか一項に記載のプロセス。
【請求項２０】
前記熱交換チャネルは、前記熱交換チャネルを通る熱交換流体の前記流れに垂直な５０ミリメートル以下の内部寸法を有する、請求項１から１９のいずれか一項に記載のプロセス。
【請求項２１】
前記プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルは、鋼、モネル、インコネル、アルミニウム、チタン、ニッケル、銅、真鍮、これら金属の任意のものの合金、重合体、セラミック、ガラス、重合体とガラス繊維とを含むコンポジット、石英、ケイ素、またはそれらの二種類以上の組み合わせを含む材料で作られている、請求項１から２０のいずれか一項に記載のプロセス。
【請求項２２】
前記熱交換流体は、前記熱交換チャネル内で相変化を行う、請求項１から２１のいずれか一項に記載のプロセス。
【請求項２３】
前記熱交換チャネル中で吸熱プロセスまたは発熱プロセスが実行される、請求項１から２１のいずれか一項に記載のプロセス。
【請求項２４】
前記熱交換流体は、空気、水蒸気、液体水、一酸化炭素、二酸化炭素、気体窒素、液体窒素、少なくとも一種類の気体炭化水素、少なくとも一種類の液体炭化水素またはそれらの二つ以上の組み合わせ、前記第一の流体流、前記第二の流体流、または前記第一の流体流と前記第二の流体流との混合物を含む、請求項１から２３のいずれか一項に記載のプロセス。
【請求項２５】
前記多相混合物は、泡を含む、請求項１から２４のいずれか一項に記載のプロセス。
【請求項２６】
前記多相混合物は、乳化剤、界面活性剤、紫外線保護因子、ワックス、ちょう度因子、増粘剤、過脂肪剤、安定剤、カチオン性、アニオン性、双性イオン、両性または非イオン性重合体、シリコン化合物、脂肪、ワックス、レシチン、リン脂質、生体薬剤、酸化防止剤、脱臭剤、発汗抑制剤、フケ防止剤、膨潤剤、駆虫剤、自己なめし剤、チロシン阻害剤、可溶化剤、防腐剤、香油または色素、あるいはそれらの二種類以上の混合物、の一つ以上を含む、請求項１から２５のいずれか一項に記載のプロセス。
【請求項２７】
前記多相混合物の中に固体が分散される、請求項１から２６のいずれか一項に記載のプロセス。
【請求項２８】
前記第一の流体流は水素化反応を行うための反応媒質を含み、前記第二の流体流は水素を含む、請求項１から２７のいずれか一項に記載のプロセス。
【請求項２９】
前記第一の流体流は液体流を含み、前記第二の流体流は、空気、酸素、窒素、二酸化炭素、水素、アンモニア、塩素ガス、オゾンの一種類以上、一種類以上の気体炭化水素、またはそれらの二種類以上の組み合わせを含み、または前記第一の流体流は液体廃棄物流を

含み、前記第二の流体流は空気を含み、または前記第一の流体流は液体の有害廃棄物流を含み、前記第二の流体流は空気を含み、または前記第一の流体流は液体のサラダドレッシングまたはマスタードを含み、前記第二の流体流は窒素を含み、または前記第一の流体流は液体飲料またはビールを含み、前記第二の流体流は二酸化炭素を含み、または前記第一の流体流は液体の漂白パルプを含み、前記第二の流体流は塩素を含み、または前記第一の流体流は水中に分散した石炭を含み、前記第二の流体流は空気を含み、または前記第一の流体流は随伴水を含むモータ油を含み、前記第二の流体流は窒素を含み、または前記第一の流体流は培養反応用の、液体を含有する細胞を含み、前記第二の流体流は酸素または空気を含み、または前記第一の流体流は液体反応媒質を含み、前記第二の流体流は空気または酸素を含み、または前記第一の流体流は油と水との混合物を含み、前記第二の流体流は空気または天然ガスを含み、または前記第一の流体流は液体の漂白パルプを含み、前記第二の流体流は酸素を含み、または前記第一の流体流は食用油、ワインまたはジュースを含み、前記第二の流体流は窒素を含み、または前記第一の流体流は魚の養殖に用いられる水を含み、前記第二の流体流は酸素を含み、または前記第一の流体流は水を含み、前記第二の流体流はオゾンを含み、または前記第一の流体流は液体の廃棄物流またはプロセス流を含み、前記第二の流体流は二酸化炭素またはアンモニアを含み、または前記第一の流体流は揮発性有機化合物を含む液体の廃棄物流を含み、前記第二の流体流は空気を含む、請求項１から２７のいずれか一項に記載のプロセス。

【請求項３０】

前記プロセスは、毎分少なくとも１リットルの多相混合物を製造する、請求項１から２９のいずれか一項に記載のプロセス。

【請求項３１】

前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは、少なくとも二つのプロセスマイクロチャネルを含む、請求項１から３０のいずれか一項に記載のプロセス。

【請求項３２】

前記プロセスは、マイクロチャネルミキサの中で実行され、前記マイクロチャネルミキサは複数のプロセスマイクロチャネルと複数の第二の流体流チャネルを含み、前記プロセスマイクロチャネルは、少なくとも一つの第一の流体流マニホルドに接続されており、前記第一の流体流は、前記少なくとも一つの第一の流体流マニホルドを通って前記プロセスマイクロチャネルへ流れ、前記第二の流体流チャネルは、前記プロセスマイクロチャネルに隣接し、少なくとも一つの第二の流体流マニホルドは前記第二の流体流チャネルに接続し、前記第二の流体流は、前記少なくとも一つの第二の流体流マニホルドを通って前記第二の流体流チャネルへ流れる、請求項１から３１のいずれか一項に記載のプロセス。

【請求項３３】

前記マイクロチャネルミキサは、前記熱交換チャネルに接続された少なくとも一つの熱交換マニホルドをさらに含み、前記少なくとも一つの熱交換マニホルドを通って前記熱交換チャネルへと熱交換流体が流れる、請求項３２に記載のプロセス。

【請求項３４】

前記プロセスマイクロチャネルは、前記プロセスマイクロチャネル内の流れを変化させるために一つ以上の内壁の中および／または上に形成された表面構成要素を含む、請求項１から３３のいずれか一項に記載のプロセス。

【請求項３５】

前記表面構成要素は、前記プロセスマイクロチャネルを通る流体の流れの前記方向に対して斜めの角度に配向された前記マイクロチャネル内壁の一つ以上の中にあるくぼみ、および／または、前記マイクロチャネル内壁の一つ以上からの突起の形状であり、または前記表面構成要素は、少なくとも二つの表面構成要素領域の形状であって、前記第一の流体と第二の流体との混合は、第一の表面構成要素領域の中とそれに続く第二の表面構成要素領域の中の流れの中で実行され、前記第二の表面構成要素領域の中の前記流れのパターンは、前記第一の表面構成要素領域の中の前記流れのパターンとは異なり、または前記開口

区間は、前記プロセスマイクロチャネルの前記内壁の一つ以上の部分を形成する内部部分と、前記開口区間の前記内部部分の上を覆う表面構成要素シートとを含み、前記表面構成要素シートの中および／または上に表面構成要素があり、または前記多相混合物は、前記第一および／または第二の流体流の中に分散した固体粒子を含み、前記流動床の形であり、前記プロセスマイクロチャネルは、前記プロセスマイクロチャネル内の流れを変えるためにその内壁の一つ以上の中および／または上に形成された表面構成要素を含み、または前記表面構成要素は、互いに重ねられて積層され、および／または、三次元パターンにからみ合った二つ以上の層を含み、または前記表面構成要素は、円形、楕円形、正方形、長方形、市松模様、Ｖ字型、波型またはそれらを組み合わせた形であり、または前記表面構成要素は、副構成要素を含み、前記表面構成要素の主壁は、ノッチ形、波形、ギザギザ形、孔形、バリ形、市松模様、扇形またはそれらを組み合わせた形のさらに小さな表面構成要素をさらに含む、請求項３４に記載のプロセス。

【発明の詳細な説明】

【技術分野】

【０００１】

本発明は、マイクロチャネルプロセス技術を用いる多相混合プロセスに関する。

【背景技術】

【０００２】

液体の中の気泡の分散は、化学反応の有無にかかわらず、気‐液接触させて吸収またはストリッピングを促進するために、あるいは泡状製品生産のために有用なものとすることができる。これらのものの例は、廃液流のＢＯＤ（生物学的酸素要求量）要件を満たすための空気吹き込み、槽の中の液体を混合するための空気噴射、有害廃棄物処理用の細菌の成長を刺激するための空気吹き込み、サラダドレッシングまたはマスタードを増量するための窒素吹き込み、炭酸飲料およびビールのためのCO_2吹き込み、紙の製造においてパルプを漂白するための塩素吹き込み、石炭浮遊選鉱およびその他の固体の分離のための空気吹き込み、モータオイルから随伴水分を除去するための窒素吹き込み、培養反応において細胞発育を増強するための酸素または空気吹き込み、性能の改善のために空気、酸素またはその他の気体を反応器の中に吹き込むこと、多様な種類の化学的水素化反応のための水素吹き込み、油井からの湧水からのオイル除去のための空気または天然ガス吹き込み、紙の製造においてパルプを漂白するための酸素吹き込み、食用油、ワインおよびジュースから酸素を除去するための窒素吹き込み、魚の養殖における魚成長の刺激のための酸素吹き込み、医薬品プラントの超純水システムを滅菌するオゾン吹き込み、廃棄物またはプロセス流の中のｐＨを調節するためのCO_2またはNH_3吹き込み、効率的加熱、および蒸気ハンマリングを鎮めるための直接水蒸気噴射、廃液流からのＶＯＣ（揮発性有機化合物）の除去のための空気吹き込み、および類似の操作を含む。これらの操作の多くに伴う一問題は、気体の分散の効率がよくないことである。

【発明の開示】

【課題を解決するための手段】

【０００３】

本発明は、この問題に解決法を提供する。一実施態様では、本発明は、比較的大きな表面積を有する比較的小さな気泡の液体への分散を提供する。その結果、比較的大きな気／液接触面積が得られる。気泡が小さく、表面積が大きいので、液体の中に気体を効率的に溶解させることができる。これによって、気体消費量の低減が得られる。また、気体を液体の中に溶解するために必要な時間も短縮し、その結果、プロセス処理が迅速化し、生産性が高くなる。

【０００４】

本発明は、多相混合物を作るためのプロセスであって、プロセスマイクロチャネルの中に第一の流体流を流す工程であって、第一の流体流は、少なくとも一種類の液体および／または少なくとも一種類の気体を含み、プロセスマイクロチャネルは開口区間を有する工程、開口区間を通して第二の流体流をプロセスマイクロチャネルの中に流し、第一の流体

流と接触させて多相混合物を形成させる工程であって、第二の流体流は、少なくとも一種類の気体および／または少なくとも一種類のマイクロボディ形成材料を含み、第一の流体流は、多相混合物の中の連続相を形成し、第二の流体流は、連続相の中に分散した不連続相を形成する工程を含む。

【０００５】

一実施態様では、第二の流体は、第一の流体の中に溶解する。これは、プロセスマイクロチャネルの中で起こることもあり、多相混合物がプロセスマイクロチャネルから出た後で起こることもある。本発明のプロセスの一利点は、少なくとも一実施態様では、多相混合物の中の第二の流体が、マイクロチャネルプロセス技術を用いない従来の技法によって形成されたより大きな気泡と比較すると、第一の流体の中により効率的に溶解する、比較的小さな気泡を含むことができる点にある。

【０００６】

一実施態様では、多相混合物は、第一の流体流の中に分散した固体粒子をさらに含む。

【０００７】

一実施態様では、プロセスマイクロチャネルと発熱源および／または吸熱源との間で熱が交換される。一実施態様では、発熱源および／または吸熱源は、少なくとも一つの熱交換チャネルを含む。

【０００８】

一実施態様では、開口区間は、プロセスマイクロチャネルの軸方向長さの少なくとも一部に沿って延在する。一実施態様では、開口区間は、プロセスマイクロチャネルの軸方向長さの少なくとも約１０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約２０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約３５％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約５０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約６５％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約８０％、一実施態様ではプロセスマイクロチャネルの軸方向長さの少なくとも約９５％に沿って延在する。

【０００９】

一実施態様では、第二の流体流は、第二の流体流チャネルから開口区間を通って流れる。

【００１０】

一実施態様では、プロセスマイクロチャネルと発熱源および／または吸熱源との間、第二の流体流チャネルと発熱源および／または吸熱源との間、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方と、発熱源および／または吸熱源との間で、熱が交換される。発熱源および／または吸熱源は、加熱、冷却、または冷却と加熱との両方に用いてもよい。発熱源は、熱交換チャネルおよび／または加熱素子を含んでもよい。吸熱源は、熱交換チャネルおよび／または冷却素子を含んでもよい。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネル、第二の流体流チャネル、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方に隣接させることができる。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネルおよび／または第二の流体流チャネルから離してもよいが、プロセスマイクロチャネルおよび／または第二の流体流チャネルへ、またはプロセスマイクロチャネルおよび／または第二の流体流チャネルから熱を移動させるために、プロセスマイクロチャネルおよび／または第二の流体流チャネルに十分近くするとよい。

【００１１】

一実施態様では、本プロセスは、多相ミキサの中で実行される。多相ミキサの中では、プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルの中への流体の流れを提供するために、一つ以上のヘッダまたはマニホルドが使用され、プロセスマイクロチャネルおよび熱交換チャネルから出る流体の流れを提供するために、一つ以上のフッタまたはマニホルドが使用される

【００１２】

一実施態様では、第一の流体流と第二の流体流とは、プロセスマイクロチャネルの中の混合区域の中で互いと接触する。一実施態様では、発熱源および／または吸熱源と、混合区域の中のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。一実施態様では、発熱源および／または吸熱源と、混合区域の上流のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。一実施態様では、発熱源および／または吸熱源と、混合区域の下流のプロセスマイクロチャネルの少なくとも一部との間で、熱が交換される。

【００１３】

一実施態様では、プロセスマイクロチャネルは、混合区域の中で制限された断面を有する。

【００１４】

一実施態様では、プロセスマイクロチャネルは、離間した壁と、離間した壁のそれぞれの中の開口区間とを有し、第二の液体は、開口区間のそれぞれを通って、プロセスマイクロチャネルの中に流入する。一実施態様では、離間した壁のそれぞれの中の開口区間は、複数の開口を含み、一方の壁の開口区間の中の開口は、反対側の壁の開口区間の中の開口の真向かいに配置される。一実施態様では、離間した壁のそれぞれの中の開口区間は、複数の開口を含み、一方の壁の開口区間の中の開口の少なくともいくつかは、他方の壁の開口区間の中の開口の真向かいにならないようにずらして配置される。

【００１５】

一実施態様では、プロセスマイクロチャネルは、多相混合物形成ユニットの中にある。多相混合物形成ユニットは、第一のプロセスマイクロチャネル、第二のプロセスマイクロチャネル、および第一のプロセスマイクロチャネルと第二のプロセスマイクロチャネルとの間に位置する第二の流体チャネルを含み、各プロセスマイクロチャネルは、開口区間を含む壁を有し、第一の流体流は、第一のプロセスマイクロチャネルと第二のプロセスマイクロチャネルとを通って流れ、第二の流体流は、第二の流体流チャネルから、第一のプロセスマイクロチャネルの中の開口区間を通って流れて第一の流体流と接触し、第二のプロセスマイクロチャネルの中の開口区間を通って流れて第一の流体流と接触する。

【００１６】

一実施態様では、第三の流体流チャネルの中に第三の流体流が流れ、第三の流体流チャネルは、別の開口区間を有する別の壁を有し、本プロセスは、別の開口区間を通して第二の流体流を流し、第三の流体流と接触させて別の多相混合物を形成させる工程、および開口区間を通して別の多相混合物をプロセスマイクロチャネルの中に流し、第一の流体流と接触させる工程、をさらに含む。

【００１７】

一実施態様では、プロセスマイクロチャネルは、平行な離間したシートおよび／またはプレートから形成される。一実施態様では、第二の流体流チャネルは、平行な離間したシートおよび／またはプレートから形成され、第二の流体流チャネルは、プロセスマイクロチャネルに隣接する。一実施態様では、熱交換チャネルは、平行な離間したシートおよび／またはプレートから形成され、熱交換チャネルは、プロセスマイクロチャネル、第二の流体流チャネル、またはプロセスマイクロチャネルと第二の流体流チャネルとの両方に隣接する。

【００１８】

一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、複数のプロセスマイクロチャネルと第二の流体流チャネルとを含み、各プロセスマイクロチャネルは、開口区間を有する壁と隣接する第二の流体流チャネルとを有し、第二の流体流は、第二の流体流チャネルから開口区間を通ってプロセスマイクロチャネルの中に流れて第一の流体流と接触し、プロセスマイクロチャネルと第二の流体流チャネルとは、平行な離間したシートおよび／またはプレートから形成され、プロセスマイクロチャネルと第二の流体流チャネルとは、互いに隣接し、交互に横に並べられた面または交互に上下に重ねられた面の形で配置される。

【００１９】
一実施態様では、プロセスマイクロチャネルは、二つ以上の開口区間を含み、開口区間のそれぞれを通って、別々の第二の流体流が流れる。一実施態様では、開口区間のそれぞれを通って流れる別々の第二の流体流は、異なる組成を有する。一実施態様では、開口区間のそれぞれを通って流れる別々の第二の流体流は、異なる性質を有する。
【００２０】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、少なくとも二つのプロセスマイクロチャネル、一実施態様では少なくとも約１０のプロセスマイクロチャネル、一実施態様では少なくとも約１００のプロセスマイクロチャネル、一実施態様では少なくとも約１０００のプロセスマイクロチャネルを含む。
【００２１】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、少なくとも一つの第一の流体流マニホルドに接続された複数のプロセスマイクロチャネルを含み、第一の流体流は、少なくとも一つの第一の流体流マニホルドを通ってプロセスマイクロチャネルへ流れる。一実施態様では、プロセスマイクロチャネルに第二の流体流チャネルが隣接し、マイクロチャネルミキサは、第二の流体流チャネルに接続された少なくとも一つの第二の流体流マニホルドをさらに含み、第二の流体流は、少なくとも一つの第二の流体流マニホルドを通って第二の流体流チャネルへ流れる。一実施態様では、プロセスマイクロチャネルおよび／または液体チャネルに熱交換チャネルが隣接し、マイクロチャネルミキサは、熱交換チャネルに接続された少なくとも一つの熱交換マニホルドをさらに含み、少なくとも一つの熱交換マニホルドを通って熱交換チャネルへ熱交換流体が流れる。
【００２２】
一実施態様では、第二の流体流は、第二の流体流チャネルから開口区間を通ってプロセスマイクロチャネルの中に流れ、プロセスマイクロチャネルおよび液体チャネルは、同心状の環状管を含む。
【００２３】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、複数のプロセスマイクロチャネルを含み、プロセスマイクロチャネルのそれぞれの中で別々の多相混合物が形成され、プロセスマイクロチャネルの少なくとも二つの中で形成される多相混合物は、互いに異なっている。これらの多相混合物は、異なる組成および／または異なる性質を有してもよい。このマイクロチャネルミキサは、コンビナトリアル合成およびスクリーニングデバイスと呼ぶことができる。本発明のこの実施態様の一利点は、同じ装置を用いて同時に、複数の多相混合物製品の形成および評価を提供する点である。これは、新製品の候補として、複数の製剤をスクリーニングすることが望まれるとき、利点とすることができる。
【００２４】
一実施態様では、本プロセスは、マイクロチャネルミキサの中で実行され、マイクロチャネルミキサは、横に並べられるか、または上下に重ねられた、複数の多相混合物形成ユニットを含み、各多相混合物形成ユニットは、プロセスマイクロチャネルおよび隣接する第二の流体流チャネルを含み、プロセスマイクロチャネルおよび隣接する第二の流体流チャネルは、共通の壁と、共通の壁の中の開口区間とを有し、開口区間は、第二の流体流を第二の流体流チャネルから開口区間を通してプロセスマイクロチャネルの中に流すのに適し、各プロセスマイクロチャネルと第二の流体流チャネルとは、平行な離間したシート、プレート、またはそのようなシートおよびプレートの組み合わせから形成され、本プロセスは、プロセスマイクロチャネルの中に第一の流体流を流す工程、第二の流体流チャネルから開口区間を通してプロセスマイクロチャネルの中に第二の流体流を流す工程、および第一の流体流と第二の流体流とをプロセスマイクロチャネルの中で混合して多相混合物を形成させる工程を含む。

【００２５】
一実施態様では、本発明のプロセスは、プロセスマイクロチャネルを通る第一の流体流の流れの圧力降下を比較的低くして、動作させることができる。一実施態様では、本発明のプロセスは、開口区間を通るプロセスマイクロチャネルへの第二の流体流の流れの圧力降下を比較的低くして、動作させることができる。
【００２６】
一実施態様では、プロセスマイクロチャネル内の混合は、プロセスマイクロチャネルの一つ以上の内壁の上に形成された表面構成要素の使用によって改善することができる。一実施態様では、第二の流体は、プロセスマイクロチャネル内で第一の流体と接触し、次に、プロセスマイクロチャネルの一つ、二つまたは三つ以上の内壁の上に表面構成要素が形成されたプロセスマイクロチャネル内の領域を通って流れてもよい。表面構成要素は、プロセスマイクロチャネルを通る流体の流れの方向に対して斜めの角度で配向した、マイクロチャネル内壁の一つ以上の中にあるくぼみ、および／または、マイクロチャネル内壁からの突起物の形状であるとよい。角度のある構成要素は、流れの方向と同じに、または流れの方向と逆に配置してもよい。表面構成要素は、流れの方向に対して、ある角度（例えば、約１°から約８９°、一実施態様では約３０°から約７５°）で、配置するとよい。表面構成要素と接触する流体の流れによって、流体流の一部がくぼみまたは表面構成要素の中へ流れることを強いられるが、一方、流体流の一部は表面構成要素の上をそのまま流れる。表面構成要素内の流れは、表面構成要素と同じ形になり、バルクの流れに対して角度ができる。流体は、表面構成要素から出るとき、バルク流体がｚ方向に流れるｘ、ｙ、ｚ座標系で、ｘおよびｙ方向に運動量を及ぼすことができる。この効果によって、流体流を撹拌または回転させることができる。このパターンは、付与された速度勾配が流体せん断を発生させ、第二の流体を小さな良く分散した気泡または微粒子に細分化するので、二相の流れを混合するために特に有用なものとすることができる。
【００２７】
一実施態様では、第一の表面構成要素領域とそれに続く、別の流れのパターンを作り出す少なくとも一つの第二の構成要素領域とを用いて、第一の流体と第二の流体との混合が実現できるように、プロセスマイクロチャネル内の表面構成要素領域を直列に配置してもよい。第二の流れのパターンは、第一の流体と第二の流体とを分けるか、または引き離すために用いてもよい。この工程は、気体または液体回収を支援するために用いてもよい。本発明のこの実施態様は、液体の中に気体が導入された後、その結果得られた混合物が不均一触媒または均一触媒を含むか、あるいは触媒を含まない第一の表面構成要素領域を通って流れる、気液反応の場合に特に有用なものとすることができる。混合物は、次に、オプションとして、流れパターンが遠心力を発生させ、液体を環状流れパターンでプロセスマイクロチャネルの内壁の方へ押しやる一方、気体は流体コアの中に残る第二の表面構成要素領域を通って流れてもよい。この後者のプロフィルによって、未反応気体を反応体混合物から分けるか、または引き離すのを支援してもよい。流体の中に強い中心渦を作り出すことができる表面構成要素の一パターンは、プロセスマイクロチャネルの上部と底部との角度のある一対のスロットのことがある。中心渦流れパターンを作り出すことができる。一実施態様では、泡の多い混合物によって、液体をプロセスマイクロチャネルの壁の方へ流し、気体をプロセスマイクロチャネルの中心へ押しやるとよい。
【００２８】
一実施態様では、開口区間は、プロセスマイクロチャネルの内壁の一つ以上の一部を形成する内部部分を含んでもよい。開口区間のこの内部部分の上に表面構成要素シートがあってもよい。表面構成要素シートの中および／または上に、表面構成要素を形成してもよい。第二の流体は、開口区間と表面構成要素シートとを通って流れてもよい。開口区間を通って入って来る流体の流束は、表面構成要素シートの表面構成要素の中にある間は、表面構成要素シートの表面から離すことができる。表面構成要素シートは、流れの長さ全体と比較すると、比較的小さな幅またはスパンを有する角度のある構成要素を含んでもよい。表面構成要素シートは、開口区間に機械的支持を提供してもよい。さらに、表面構成要

素によって作り出される流れの渦または角度のある流れは、開口区間を通って流れる第二の流体にせん断をさらに付与し、ひいてはバルク流路の中の第二の流体の粒子または泡のサイズを減らす上で好ましいものとすることができる。

【００２９】

一実施態様では、多相混合物は、液体－固体の流れ、または気体－液体－固体の流れを含んでもよい。第二の流体流は、気体または液体どちらかの中の固体の分散を含んでもよい。第一の流体流は、気体、液体、あるいは気体または液体の中に分散した固体を含んでもよい。プロセスマイクロチャネルの中の表面構成要素区間を通る多相混合物の流れは、付与された流れの方向と異なる運動量が混合物を良く混合された、または分散された状態に保つように作用することができるので、有利なものとすることができる。この利用は、液体反応体の中の固体触媒の分散に有用なものとすることができる。

【００３０】

一実施態様では、多相混合物は、第一および／または第二の流体流の中に分散した固体粒子を含んでもよく、流動床の形であり、プロセスマイクロチャネルは、プロセスマイクロチャネル内の流れを変更するためにその内壁の一つ以上の中および／または上に形成された表面構成要素を含む。これは、固体粒子含有流体流の中に気体流を混合することを含んでもよい。固体は、キャリア流体の中に吹き込んでもよく、またはキャリア流体によって取り込んでもよい。表面構成要素は、多相混合物の混合を促進することがある。

【００３１】

一実施態様では、化学反応および／または沈殿の結果として、多相混合物の中に固体が形成されてもよい。

【００３２】

一実施態様では、多相混合物は泡の形である。一実施態様では、多相混合物は、オプションとして、一種類以上の界面活性剤を含んでもよい。気泡によっては、界面活性剤の存在は必要ではないが、気泡を形成させるために、これらを含んでもよい。

【００３３】

添付の図面では、同様な部品および構成要素は、同様な参照符号を有する。

【発明を実施するための最良の形態】

【００３４】

用語「マイクロチャネル」は、最大約１０ミリメートル（ｍｍ）、一実施態様では最大約５ｍｍ、一実施態様では最大約２ｍｍ、一実施態様では最大約１ｍｍの高さまたは幅のうちの少なくとも一方の内部寸法を有するチャネルを指す。マイクロチャネルを通る流体の流れは、マイクロチャネルの高さおよび幅に垂直なマイクロチャネルの長さ方向に進むことができる。本発明のプロセスでプロセスマイクロチャネル、オプションとして、第二の流体流チャネル、第三の流体流チャネルおよび／または熱交換チャネルとして用いることができるマイクロチャネルの例が図１に示される。図１に例が示されるマイクロチャネル１０は、高さ（ｈ）、幅（ｗ）および軸方向長さ（ｌ）を有する。矢印１２および１４によって示される方向のマイクロチャネルの長さに沿って、マイクロチャネル１０を通って流体が流れる。マイクロチャネルの高さ（ｈ）または幅（ｗ）は、約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．０５から約１．５ｍｍ、一実施態様では約０．０５から約１ｍｍ、一実施態様では約０．０５から約０．７５ｍｍ、一実施態様では約０．０５から約０．５ｍｍの範囲にあるとよい。高さまたは幅のうち、他方の寸法は、任意の寸法、例えば最大約３メートル、一実施態様では約０．０１から約３メートル、一実施態様では約０．１から約３メートルであるとよい。マイクロチャネルの軸方向長さ（ｌ）は、任意の寸法、例えば最大約１０メートル、一実施態様では約０．１から約１０メートル、一実施態様では約０．２から約６メートル、一実施態様では約０．２から約３メートルであるとよい。図１に例が示されるマイクロチャネル１０は、長方形の断面を有するが、マイクロチャネルは、任意の形状、例えば正方形、円形、半円形、台形等の断面を有してもよいと理解すべきである。マイクロチャネルの断面の形状および／またはサイズは、その長さにわた

って変化してよい。例えば、高さまたは幅は、マイクロチャネルの長さにわたって、比較的大きな寸法から比較的小さな寸法へ、またはその逆に、テーパを有してもよい。

【００３５】

用語「隣接する」は、別のチャネルに対する一つのチャネルの相対的な位置を指すとき、直接隣接し、その結果、これらの二つのチャネルを一枚の壁が分断することを意味する。この壁は、厚さが変化してもよい。しかし、「隣接する」チャネル同士は、チャネル間の伝熱に干渉する介在チャネルで分断されることはない。

【００３６】

用語「表面構成要素」は、マイクロチャネル内の流れを変更する、マイクロチャネル壁の中のくぼみおよび／またはマイクロチャネル壁からの突起を指す。表面構成要素は、円形、楕円形、正方形、長方形、市松模様、Ｖ字形、波形および類似の形状であってもよい。表面構成要素は、副構成要素を含んでもよい。この場合、表面構成要素の主壁は、より小さな表面構成要素をさらに含み、これらの表面構成要素は、ノッチ形、波形、ギザギザ形、孔形、バリ形、チェック形、扇形および類似の形であってもよい。表面構成要素は、深さ、幅を有し、非円形表面構成要素なら長さを有する。図２２～２６に例が示される。表面構成要素は、本発明のプロセスで用いられるプロセスマイクロチャネルの内部側壁の一つ以上の上または中に形成することができる。表面構成要素は、本発明のプロセスで用いられる第二の流体流チャネルおよび／または熱交換チャネルの内部側壁の一つ以上の上または中に形成することができる。表面構成要素は、受動表面構成要素または受動混合構成要素と呼ぶことができる。

【００３７】

用語「上流」および「下流」は、マイクロチャネルを含む本発明のプロセスで用いられるチャネルの中の位置を指し、チャネルを通る流体の流れの方向に対するものである。例えば、チャネルを通って流れてその位置に向かって来る流体の一部分がまだ到着していないチャネル内の位置は、流体のその一部分の下流にある。チャネルを通って流れてその位置から遠ざかる流体の一部分が既に通り過ぎたチャネル内の位置は、流体のその一部分の上流にある。本発明のプロセスで用いられるプロセスチャネルは、水平、垂直、あるいはある角度に配向させてもよいので、用語「上流」および「下流」は、必ずしも垂直位置を指すものではない。

【００３８】

用語「マイクロボディ」は、最大約２００ミクロン、一実施態様では約０．０１から約２００ミクロン、一実施態様では約０．０１から約１００ミクロン、一実施態様では約０．０１から約５０ミクロン、一実施態様では約０．０１から約２５ミクロン、一実施態様では約０．０１から約１０ミクロン、一実施態様では約０．０１から約５ミクロン、一実施態様では約０．０１から約２ミクロン、一実施態様では約０．０１から約１ミクロン、一実施態様では約０．０１から約０．５ミクロン、一実施態様では約０．０１から約０．２ミクロン、一実施態様では約０．０１から約０．１ミクロン、一実施態様では約０．０１から約０．０８ミクロン、一実施態様では約０．０１から約０．０５ミクロン、一実施態様では約０．０１から約０．０３ミクロンの範囲の平均寸法（例えば直径、高さ、幅、長さ）を有する三次元ボディを指す。これらのマイクロボディは、円および／または楕円の形状の断面を有するボディを含む。マイクロボディは、球体、楕円球体、卵形体および類似の形であってもよい。マイクロボディは、針状の形を有してもよい。マイクロボディは、中空であってもよく、あるいは中空でなくてもよい。マイクロボディは、マイクロスフェアであってもよい。マイクロボディは、主寸法（例えば直径、長さ）と副寸法（例えば直径、高さ、幅）とを有してもよく、副寸法に対する主寸法の比は、約１０：１から約１：１、一実施態様では約５：１から約１：１、一実施態様では約２：１から約１：１の範囲にある。

【００３９】

用語「流体」は、気体、液体、分散固体を含む気体または液体、液滴を含む気体、気泡を含む液体、液滴および分散固体を含む気体、あるいは気泡および分散固体を含む液体、

および類似物を指す。

【００４０】

用語「発熱源」は、熱を放出し、別の物体またはデバイスを加熱するために用いることができる物体またはデバイスを指す。発熱源は、熱交換流体を内部に有し、別の物体またはデバイスへ熱を伝える熱交換チャネルの形であってもよく、別の物体またはデバイスは、例えば、熱交換チャネルに隣接するか、または熱交換チャネルから伝えられる熱を受け取るのに十分に近いチャネルである。熱交換流体は、熱交換チャネルの中に収容されてもよく、および／または、熱交換チャネルを通って流れてもよい。発熱源は、加熱素子、例えば、電熱素子または抵抗加熱器の形であってもよい。用語「吸熱源」は、熱を吸収し、別の物体またはデバイスを冷却するために用いることができる物体またはデバイスを指す。吸熱源は、熱交換流体を内部に有し、別の物体またはデバイスから伝えられる熱を受け取る熱交換チャネルの形であってもよい。別の物体またはデバイスは、例えば、熱交換チャネルに隣接するか、または熱交換チャネルへ熱を伝えるのに十分に近いチャネルである。熱交換流体は、熱交換チャネルの中に収容されてもよく、および／または、熱交換チャネルを通って流れてもよい。吸熱源は、冷却素子、例えば、非流体冷却素子の形であってもよい。

【００４１】

用語「発熱源および／または吸熱源」は、熱を放出するか、または熱を吸収することができる物体またはデバイスを指す。発熱源および／または吸熱源は、熱交換流体を内部に有し、熱交換チャネルに隣接するかまたは近くにある別の物体またはデバイスが加熱されるとき、それらの別の物体またはデバイスに熱を伝えるか、あるいは、熱交換チャネルに隣接するかまたは近くにある別の物体またはデバイスが冷却されるとき、それらの別の物体またはデバイスから伝えられる熱を受け取る、熱交換チャネルの形であってもよい。発熱源および／または吸熱源として機能する熱交換チャネルは、あるときは加熱チャネル、他のときは冷却チャネルとして機能してもよい。熱交換チャネルの一部分（単数または複数）が加熱チャネルとして機能し、一方、熱交換チャネルの別の一部分（単数または複数）が冷却チャネルとして機能してもよい。

【００４２】

用語「熱交換チャネル」は、熱交換流体を内部に有し、熱を放出し、および／または熱を吸収することができるチャネルを指す。

【００４３】

用語「熱交換流体」は、熱を発生し、および／または熱を吸収することができる流体を指す。

【００４４】

図２を参照すると、本プロセスは、マイクロチャネルミキサ１００を用いて実行することができ、マイクロチャネルミキサ１００は、マイクロチャネルミキサコア１０２、プロセス流体ヘッダ１０４、生成物フッタ１０６および熱交換マニホルド１０８を含む。マイクロチャネルミキサコア１０２は、複数のプロセスマイクロチャネル、隣接する第二の流体流チャネルおよび熱交換チャネルを含む。第二の流体流チャネルおよび／または熱交換チャネルは、マイクロチャネルであってもよい。プロセスマイクロチャネル、第二の流体流チャネルおよび熱交換チャネルは、上下に重ねられるか、または横に並べられて、層状に配置してもよい。プロセスヘッダ１０４は、第一の流体流がプロセスマイクロチャネルに流入し、第二の流体流が第二の流体流チャネルに流入し、これらのチャネルの流れの分布を一様にまたは実質的に一様にするための通路を提供する。生成物フッタ１０６は、多相混合物生成物がプロセスマイクロチャネルから迅速に流れ、比較的高い流速を有するための通路を提供する。第一の流体流は、矢印１１０で示されるように、ヘッダ１０４を通ってマイクロチャネルミキサ１００に流入する。第二の流体流は、矢印１１２で示されるように、ヘッダ１０４を通ってマイクロチャネルミキサ１００の中に流入する。第一の流体流と第二の流体流とは、マイクロチャネルミキサコア１０２の中に流入し、混合されて多相混合物を形成する。多相混合物は、マイクロチャネル混合コア１０２から生成物フッ

タ１０６を通り、矢印１１４で示されるように、生成物フッタ１０６から流出する。一実施態様では、多相混合物は、任意の回数、例えば、１回、２回、３回、４回等、マイクロチャネルミキサコア１０２を通って戻り、リサイクルしてもよい。矢印１１６で示されるように、熱交換マニホルド１０８の中に熱交換流体が流入し、熱交換マニホルド１０８からマイクロチャネルミキサコア１０２の中の熱交換チャネルを通ってから熱交換マニホルド１０８に戻り、矢印１１８で示されるように、熱交換マニホルド１０８から流出する。マイクロチャネルミキサ１００は、貯槽、ポンプ、バルブ、流量制御デバイスおよび類似デバイスとともに使用してもよい。これらは、図面に示していないが、当業者には自明である。

【００４５】

マイクロチャネルミキサコアは、複数の多相混合物形成ユニットを含んでもよい。図３～９および１２に、多相混合物形成ユニットの有用な実施態様の例が示される。図３を参照すると、本発明のプロセスは、対向する側壁２１２および２１４と、側壁２１２の中の開口区間２４０とを有するプロセスマイクロチャネル２１０を含む多相混合物形成ユニット２００を用いて実行することができる。開口区間２４０は、多孔質区間または多孔質基板と呼んでもよい。開口区間２４０は、開口区間全体に広がる開口のアレイ２４４を有するシートまたはプレート２４２を含んでもよい。側壁２１２に隣接して第二の流体流２７０があり、開口区間２４０の中の開口２４４を通ってプロセスマイクロチャネル２１０に開放される。プロセスマイクロチャネル２１０は、非開口領域または非多孔質領域２１１および２１７と、混合区域２１３とを有する。非開口領域２１１は、プロセスマイクロチャネルへの入口から混合区域３１３への入口へ延在する。非開口領域２１１は、混合区域２１３の上流である。混合区域２１３は、開口区間２４０に隣接する。非開口領域２１７は、混合区域２１３の終りからプロセスマイクロチャネル２１０の出口へ延在する。非開口領域２１７は、混合区域２１３の下流である。側壁２１４に隣接して、熱交換チャネル２９０がある。動作時、第一の流体流は、矢印２１６で示されるように、プロセスマイクロチャネル２１０に流入し、非開口領域２１１を通って混合区域２１３に流入する。矢印２７２で示されるように、第二の流体流が第二の流体流チャネル２７０に流入し、次に、矢印２７４で示されるように、開口区間２４０を通って混合区域２１３に流入する。混合区域２１３の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の流体流の中の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、混合区域２１３から非開口領域２１７を通り、矢印２１８で示されるように、プロセスマイクロチャネル２１０から流出する。加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネルおよび液体チャネルのある区間では無視できるか、または存在しなくてもよく、他の区間では中程度または比較的大きくてもよい。あるいは、加熱または冷却は、熱交換チャネル以外を用いて実現してもよい。例えば、加熱は、電熱素子または抵抗加熱器を用いて実現してもよい。電熱素子または抵抗加熱器は、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の一つ以上の壁を形成するために用いてもよい。電熱素子または抵抗加熱器は、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の一つ以上の壁の中にあってもよい。冷却は、非流体冷却素子を用いて実現してもよい。プロセスマイクロチャネル２１０の長さに沿って、複数の加熱または冷却区域が使用されてもよい。同様に、プロセスマイクロチャネル２１０および／または第二の流体流チャネル２７０の長さに沿って、一つ以上の熱交換チャネルの中でさまざまな温度の熱交換流体を使用してもよい。

【００４６】

図４に例が示される多相混合物形成ユニット２００Ａは、プロセスマイクロチャネル２

１０の側壁２１０が開口区間２４０に対向して配置されたテーパを有する区間２２０を含む点を除けば、図３に例が示される多相混合物形成ユニット２００と同一である。テーパを有する区間２２０は、混合区域２１３の中のプロセスマイクロチャネル２１０の幅または高さを小さくし、従って、混合区域２１３の中のプロセスマイクロチャネル２１０に狭くなった断面を提供する。この幅または高さは、約０．００１から約５ｍｍ、一実施態様では約０．０１から約２ｍｍの範囲にあるとよい。テーパを有する区間２２０が存在すると、混合区域２１３を通って流れる流体の速度の増加がもたらされる。混合区域２１３を通って流れる液体の速度が増加すると、開口２４４を通って混合区域２１３に流入する第二の流体に作用するせん断力が増加する。これは、開口２４４を通る第二の流体流の流れを容易にする。プロセスマイクロチャネル２１０の狭くなった断面を通って流れる流体が混合区域２１３を通る速度は、１秒あたり約０．００５から約１００メートル（ｍ／ｓ）、一実施態様では約０．０１から約５０ｍ／ｓの範囲にあるとよい。

【００４７】

図５に例が示される多相混合物形成ユニット２００Ｂは、多相混合物形成ユニット２００Ｂが第二の流体流チャネル２７０ａおよび開口区間２４０ａも含む点を除けば、図３に例を示した多相混合物形成ユニット２００と類似している。第二の流体流チャネル２７０ａは、プロセスマイクロチャネル２１０と熱交換チャネル２９０との間に位置する。側壁２１４の中に開口区間２４０ａが形成される。開口区間２４０ａを通って第二の流体流チャネル２７０ａがプロセスマイクロチャネル２１０に開放される。開口区間２４０ａは、全体に広がる開口のアレイ２４４ａを有するシートまたはプレート２４２ａを含んでもよい。プロセスマイクロチャネル２１０は、非開口領域または非多孔質領域２１１および２１７と、混合区域２１３とを有する。非開口領域２１１は、プロセスマイクロチャネルへの入口から混合区域２１３への入口へ延在し、混合区域２１３の上流である。混合区域２１３は、開口区間２４０と２４０ａとの間に位置する。非開口領域２１７は、混合区域２１３の終わりからプロセスマイクロチャネル２１０の出口へ延在する。非開口領域２１７は、混合区域２１３の下流である。動作時、矢印２１６で示されるように、プロセスマイクロチャネル２１０に第一の液体流が流入し、非開口領域２１１を通って混合区域２１３に流入する。矢印２７２および２７２ａでそれぞれ示されるように、第二の流体流チャネル２７０および２７０ａの中に第二の流体流が流入する。第二の流体流は、矢印２７４および２７４ａでそれぞれ示されるように、開口区間２４０および２４０ａを通って混合区域２１３に流入する。混合区域２１３の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の液体内の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、非開口領域２１７を通り、矢印２１８で示されるように、プロセスマイクロチャネル２１０から流出する。加熱または冷却は、選択肢としてもよい。加熱または冷却が望まれるとき、方向矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、プロセスマイクロチャネル２１０および第二の流体流チャネル２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、プロセスマイクロチャネルおよび第二の流体流チャネルの長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネルおよび液体チャネルの中のある区間では無視できるかまたは存在しなくてもよく、他の区間では中程度または比較的大きくてもよい。

【００４８】

図６に例が示される多相混合物形成ユニット２００Ｃは、図５に例が示される開口２４４と２４４ａとは互いに真向かいに配置されていたが、一方、図６に例が示される開口２４４と２４４ａとはそのような直接配置からずらされている点を除けば、図５に例が示される多相混合物形成ユニット２００Ｂと同一である。図５では、開口２４４と２４４ａとを通って流れる第二の流体流の流れは、互いと直接衝突し、それによって、第一の流体流の中への第二の流体流の拡散を促進する。一方、図６では、開口２４４と２４４ａとを通って流れる第二の流体流の流れは、互いにずらされ、それによって、混合区域２１３内の渦巻き効果を提供することによって拡散を促進する。

【００４９】
図７に例が示される多相混合物形成ユニット２００Ｄは、プロセスマイクロチャネル２１０および２１０ａ、開口区間２４０および２４０ａ、第二の流体流チャネル２７０および熱交換チャネル２９０を含む。側壁２１２の中に開口区間２４０が形成され、側壁２１２ａの中に開口区間２４０ａが形成される。開口区間２４０および２４０ａは、多孔質区画または多孔質基板と呼んでもよい。開口区間２４０および２４０ａを通って、第二の流体流チャネル２７０がプロセスマイクロチャネル２１０および２１０ａにそれぞれ開放される。開口区間２４０は、全体に広がる開口のアレイ２４４を有するシートまたはプレート２４２を含んでもよい。同様に、開口区間２４０ａは、全体に広がる開口のアレイ２４４ａを有するシートまたはプレート２４２ａを含んでもよい。プロセスマイクロチャネル２１０および２１０ａは、非開口領域または非多孔領域２１１および２１７、ならびに２１１ａおよび２１７ａ、混合区域２１３および２１３ａをそれぞれ有する。非開口領域２１１および２１１ａは、プロセスマイクロチャネル２１０および２１０ａへの入口から、混合区域２１３および２１３ａへの入口へそれぞれ延在する。非開口領域２１１および２１１ａは、混合区域２１３および２１３ａのそれぞれ上流である。混合区域２１３および２１３ａは、開口区間２４０および２４０ａにそれぞれ隣接する。非開口領域２１７および２１７ａは、混合区域２１３および２１３ａの終わりから、プロセスマイクロチャネル２１０および２１０ａの出口へそれぞれ延在する。非開口領域２１７および２１７ａは、混合区域２１３および２１３ａのそれぞれ下流である。プロセスマイクロチャネル２１０に隣接して、熱交換チャネル２９０がある。動作時、矢印２１６および２１６ａで示されるように、プロセスマイクロチャネル２１０および２１０ａの中に、それぞれ第一の流体流が流れ、非開口領域２１１および２１１ａを通って混合区域２１３および２１３ａに流入する。矢印２７２で示されるように、第二の流体流チャネル２７０に第二の流体流が流入し、次に、矢印２７４および２７４ａで示されるように、開口区間２４０および２４０ａを通って混合区域２１３および２１３ａにそれぞれ流入する。混合区域２１３および２１３ａの中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。第二の流体流は、第一の流体流内の不連続相を形成してもよい。第一の流体流は、連続相を形成してもよい。多相混合物は、非開口区画２１７および２１７ａを通り、矢印２１８および２１８ａで示されるように、プロセスマイクロチャネル２１０および２１０ａからそれぞれ流出する。加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印２９２で示されるように、熱交換チャネル２９０を通って熱交換流体が流れ、チャネル２１０、２１０ａおよび２７０の中の流体を加熱または冷却する。加熱または冷却の度合いは、チャネルの長さにわたって変化してもよい。加熱または冷却は、プロセスマイクロチャネル２１０および２１０ａ、ならびに第二の流体流チャネル２７０のある区画では無視できるかまたは存在しなくてもよく、他の区画では中程度または比較的大きくてもよい。

【００５０】
一実施態様では、単一のマイクロチャネルミキサ内で、多重の多相混合調合物および／またはプロセス処理条件の組を用いて、別個の多相混合物を発生させることができる。例えば、単一のマイクロチャネルミキサが、二つ以上のプロセスマイクロチャネル、関連する第二の流体流チャネル、および熱交換チャネルを使用して、単一のマイクロチャネルミキサ内で、２、３、４、５、６、７、８、９、１０、数１０、数１００、数１０００、数万、数１０万等の別個の多相混合物を作ることができる。この種類のミキサは、コンビナトリアル合成デバイスと呼んでもよい。多相混合物形成ユニット３００の例が示される図８に、これが示される。多相混合物形成ユニット３００は、４つのプロセスマイクロチャネルを使用し、その結果、最大４つの別個の多相混合物を発生することができる。多相混合物形成ユニット３００は、任意の所望の回数、例えば２回、３回、４回、５回、６回、７回、８回、９回、１０回、数１０回、数１００回、数１０００回、数万回等繰り返し、上記で示した多重の別個の多相混合物の可能性を提供することができる。多相混合物形成ユニット３００は、プロセスマイクロチャネル３１０、３２０、３３０および３４０、第

二の流体流チャネル３５０および３６０、ならびに熱交換チャネル３７０および３８０を含む。側壁３１２の中に開口区間３１１が形成される。側壁３２２の中に開口区間３２１が形成される。側壁３３２の中に開口区間３３１が形成される。側壁３４２の中に開口区間３４１が形成される。開口３１３、３２３、３３３および３４３が開口区間３１１、３２１、３３１および３４１の中に位置し、それぞれ全体に広がる。プロセスマイクロチャネル３１０、３２０、３３０および３４０は、混合区域３１５、３２５、３３５および３４５の上流にそれぞれ位置する非開口区画３１４、３２４、３３４および３４４を含む。混合区域３１５、３２５、３３５および３４５が、開口区間３１１、３２１、３３１および３４１にそれぞれ隣接して位置する。プロセスマイクロチャネル３１０、３２０、３３０および３４０は、混合区域３１５、３２５、３３５および３４５のそれぞれ下流に位置する非開口区画３１６、３２６、３３６および３４６も含む。動作時、矢印３１７、３２７、３３７および３４７でそれぞれ示されるように、プロセスマイクロチャネル３１０、３２０、３３０および３４０の中に第一の流体流が流入する。プロセスマイクロチャネル３１０、３２０、３３０および３４０に入る第一の流体流は、互いに同じ組成を有してもよく、あるいは互いに異なる組成を有してもよい。第一の流体流は、非開口区画３１４、３２４、３３４および３４４を通って、混合区域３１５、３２５、３３５および３４５にそれぞれ流入する。第二の流体流は、矢印３５１および３６１で示されるように、第二の流体流チャネル３５０および３６０に流入する。第二の流体流チャネル３５０に入る第二の流体流は、第二の流体流チャネル３６０に入る第二の流体流と同じであってもよく、あるいは異なっていてもよい。第二の流体流チャネル３５０に入る第二の流体流と、液体チャネル３６０に入る第二の液体との間の差は、組成、プロセス処理条件、物理的性質（例えば粘度、密度、表面張力等）および／または操作パラメータにもとづくものでもよい。矢印３５１で示されるように、第二の流体流チャネル３５０に入る第二の流体流は、矢印３５２および３５３で示されるように、開口区間３１１および３２１を通って流れ、混合区域３１５および３２５にそれぞれ流入する。混合区域３１５および３２５の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。同様に、第二の流体流は、矢印３６１示されるように、第二の流体流チャネル３６０に流れ、次に、矢印３６２および３６３で示されるように、開口区間３３１および３４１を通って混合区域３３５および３４５それぞれ流入する。混合区域３１５、３２５、３３５および３４５の中で、第二の流体流は、第一の流体流と接触し、混合されて多相混合物を形成する。混合区域３１５、３２５、３３５および３４５の中で形成される多相混合物は、同じであってもよく、あるいは異なっていてもよい。異なる場合、多相混合物は、組成および／または物理的性質、あるいは操作パラメータ（例えば分散相および／または連続相の組成、粒子サイズ、粒子サイズ分布、粘度、密度、表面張力、温度、圧力、流量等）が互いに異なっていてもよい。多相混合物は、混合区域３１５、３２５、３３５および３４５から非開口区画３１６、３２６、３３６および３４６を通り、矢印３１８、３２８、３３８および３４８でそれぞれ示されるように、プロセスマイクロチャネル３１０、３２０、３３０および３４０から流出する。熱交換チャネル３７０および３８０を用いる加熱または冷却は、選択肢とすることができる。加熱または冷却が望まれるとき、矢印３７１および３７２、ならびに３８１および３８２で示されるように、熱交換チャネル３７０および３８０を通って熱交換流体が流れ、チャネル３１０、３２０、３３０、３４０、３６０および３６０の中の流体を加熱または冷却する。加熱または冷却の度合いは、チャネルのそれぞれの長さにわたって変化してもよい。プロセスチャネルおよび／または液体チャネルのある区間では、加熱または冷却は無視できるかまたは存在しなくてもよく、他の区間では中程度または比較的大きくもよい。本発明のこの実施態様の一利点は、同時に同じ装置を用いて、複数の多相混合物製品の形成および評価を提供できる点である。これは、新製品の候補として複数の製剤をスクリーニングすることが望まれるとき、利点とすることができる。

【００５１】

一実施態様では、本発明のプロセスは、二重多相混合物をつくるのに適する。これらの二重多相混合物は、図９に例が示される多相混合物形成ユニット４００を用いて作ること

ができる。図９では、多相混合物形成ユニット４００は、中心線４０２と４０４との間に配置される。多相混合物形成ユニット４００は、プロセスマイクロチャネル４１０と、液体チャネル４２０、４３０、４４０および４５０とを含む。流体流チャネル４２０および４３０が、プロセスマイクロチャネル４１０に隣接する。流体流チャネル４４０が、流体流チャネル４２０に隣接し、流体流チャネル４５０が流体流チャネル４３０に隣接する。粗い開口区間４１５を含む共通壁４１２が、プロセスマイクロチャネル４１０と流体チャネル４２０とを分ける。粗い開口区間４２５を含む共通壁４２２が、プロセスマイクロチャネル４１０と流体チャネル４３０とを分ける。開口区間４１５および４２５は、開口４１６および４２６をそれぞれ含む。流体流チャネル４４０と流体流チャネル４２０との間に、開口４３６を含む微開口区間４３５が位置し、流体流チャネル４４０と流体流チャネル４２０とを分ける。流体流チャネル４５０と流体流チャネル４３０との間に、開口４４６を含む微開口区間４４５が位置し、流体流チャネル４５０と流体流チャネル４３０とを分ける。粗開口区間４１５および４２５の開口４１６および４２６は、微開口区間４３５および４４５の開口４３６および４４６より大きい。プロセスマイクロチャネル４１０は、非開口領域または非多孔領域４１１および混合区域４１３を有する。非開口領域４１１は、プロセスへの入口から混合区域４１３への入口へ延在する。混合区域４１３は、開口区間４１５および４２５に隣接する。選択肢として、中心線４０２および／または４０４で示される位置に熱交換チャネルを挿入し、所望の加熱または冷却を流体に提供してもよい。

【００５２】

中心線４０２の下に、同じく図９に例が示される隣接する多相混合物形成ユニット４００ａの一部が位置する。多相混合物形成ユニット４００ａは、プロセスマイクロチャネル４１０ａ、粗開口区間４１５ａおよび４２５ａ、流体流チャネル４３０ａおよび微開口区間４４５ａを含む。これらは、上記で考察したプロセスマイクロチャネル４１０、粗開口区間４１５および４２５、流体流チャネル４３０および微開口区間４４５と同じである。図９の中心線４０４の上に、別の隣接する多相混合物形成ユニット４００ｂの一部も位置する。多相混合物形成４００ｂは、微開口区間４３５ｂおよび流体流チャネル４２０ｂを含む。これらは、上記で考察した微開口区間４３５および流体流チャネル４２０と同じである。図９に多相混合物形成ユニット４００ａと４００ｂとの一部を含むことによって、本発明のプロセスを希求してマイクロチャネルミキサの中で使用されるときの多相混合物形成ユニット４００の反復する性質の例が示される。

【００５３】

動作時、図９を参照すると、矢印４１４で示されるように、第一の流体流がプロセスマイクロチャネル４１０に入り、非開口領域４１１を通って混合区域４１３に流入する。矢印４２３および４３３で示されるように、第二の流体流が流体流チャネル４２０および４３０にそれぞれ入る。矢印４４２および４５２で示されるように、第三の流体流が液体チャネル４４０および４５０にそれぞれ入る。第三の流体流は、流体流チャネル４４０から開口区間４３５を通って流体流チャネル４２０に流入し、第二の流体流と混合されて別の多相混合物を形成する。第三の流体流は、流体流チャネル４５０から開口区間４４５を通って流体流チャネル４３０にも流入し、第二の流体流と混合されて別の多相混合物を形成する。流体流チャネル４２０および４３０の中で形成される別の多相混合物の中で、第三の流体流は不連続相を形成し、第二の流体流は連続相を形成する。流体流チャネル４２０および４３０の中で形成された別の多相混合物は、開口区間４１５および４２５をそれぞれ通って混合区域４１３に流入し、第一の流体流と混合される。混合区域４１３の中で、別の多相混合物は、第一の流体流の中に不連続相として分散し、第一の流体流は連続相の形になる。混合区域４１３の中で形成される多相混合物は、二重多相混合物と呼んでもよい。二重多相混合物の中で、第三の流体流の少なくとも一部は、第二の流体流の泡またはマイクロボディ（例えばマイクロスフェア）の中にカプセル化することができる。カプセル化された泡またはマイクロボディは、連続相の形であってもよい第一の流体流の中の不連続相として分散させることができる。二重多相混合物は、矢印４１８で示されるように

、プロセスマイクロチャネル４１０から出る。多相混合物４９０として図１０に概略が示される形であってもよい二重多相混合物は、一実施態様では、第一の流体流４９６（例えば気体または液体）の中に分散した第二の流体流４９４（例えば液体またはマイクロボディ）の中にカプセル化された第三の流体流４９２（すなわち気体）を含む。

【００５４】

一実施態様では、本発明のプロセスは空気吹き込みプロセスの中で用いることができる。図１１および１２に、これの例が示される。この実施態様では、本プロセスは、マイクロチャネルミキサ５０２を含む空気吹き込みタンク５００を用いて実行される。動作時、空気吹き込みされる流体は、タンク５００内に収容され、矢印５０４で示されるように、第一の流体流としてマイクロチャネルミキサ５０２に入る。空気吹き込みすることができる流体の例は、細胞培養液である。矢印５０６で示されるように、マイクロチャネルミキサ５０２の中に、第二の流体流が入る。第二の流体流は、空気または酸素を含んでもよい。マイクロチャネルミキサの中で、第一の流体流（例えば細胞培養液）と第二の流体流（例えば空気または酸素）と混合され、その結果、多相混合物（例えば空気吹き込みされた細胞培養液）が形成される。マイクロチャネルミキサ５０２は、複数の多相混合物形成ユニットを含んでもよい。多相混合物形成ユニット５１０は、プロセスマイクロチャネル５２０、第二の流体流チャネル５３０および５４０、微細セラミック膜の形であってもよい開口区間５５０および５６０、マクロ多孔質担体の形であってもよい開口区間５７０および５８０、ならびに熱交換チャネル５９０を含む。動作時、第一の流体流は、矢印５２２で示されるように、プロセスマイクロチャネル５２０に入る。第二の流体流は、矢印５３２および５４２でそれぞれ示されるように、第二の流体流チャネル５３０および５４０に入る。第二の流体流は、第二の流体流チャネル５３２から開口区間５７０を通った後、開口区間５５０を通ってプロセスマイクロチャネル５２０に流入する。同様に、矢印５４２で示されるように、別の第二の流体流が、第二の流体流チャネル５４０に入り、開口区間５８０を通った後、開口区間５６０を通り、プロセスマイクロチャネル５２０に流入する。第一の流体流と第二の流体流とは、プロセスマイクロチャネル５２０の中で混合され、その結果、多相混合物が形成される。多相混合物は、矢印５２４で示されるように、プロセスマイクロチャネル５２０から出る。多相混合物の中で、第一の流体流は連続相を形成してもよく、第二の流体流は不連続相を形成してもよい。一実施態様では、多相混合物は、細胞培養液全体に分散した高められたレベルの酸素または空気を有する細胞培養液を含むことができる。流体は、矢印５０７で示されるように、熱交換流体をマイクロチャネルミキサ５０２の中に流し、熱交換チャネル５９０を通した後、マイクロチャネルミキサ５０２から流出させることによって、加熱または冷却することができる。

【００５５】

図３～９および１２のそれぞれでは、一つの多相混合物形成ユニットしか完全に例が示されていないが、本発明のプロセスを実行するためにマイクロチャネルミキサの中で用いてもよい多相混合物形成ユニットの数に、事実上、上限はない。例えば、１、２、３、４、５、６、８、１０、２０、５０、１００、数１００、１０００、数１０００、一万、数万、１０万、数１０万、数１００万等の上記で説明した多相混合物形成ユニットを用いてもよい。一実施態様では、各多相混合物形成ユニットは、マニホルド接続してもよい。マニホルド接続は、各ユニットにマクロ配管、パイプ配管またはダクト配管を接続することによって実現してもよい。あるいは、各ユニットの間に比較的等しい圧力降下回路を創り出すことによって、多相混合物形成ユニットを含むマイクロチャネルミキサ内で、多相混合物形成ユニットの多数を内部マニホルド化してもよい。一方、幾分かの流れ不均衡があっても、製品の品質に影響を及ぼさないことがあるので、圧力降下は、各ユニットの間で等しくなくてもよい。一実施態様では、本発明のプロセスを用いる多相混合物を形成させるに際して、最大約５０％の流れ不均衡は許容できる。プロセスマイクロチャネル、関連する第二および第三の流体流チャネル、および熱交換チャネルは、横に並べるか、または上下に重ねて配置するとよい。例えば、多相混合物形成ユニット２００および２００Ａでは、プロセスマイクロチャネル２１０は、一平面内に平行に配置するとよく、第二の流体

流チャネル２７０は、プロセスマイクロチャネル２１０の一方の側の隣接平面内に平行に配置するとよく、熱交換チャネル２９０は、プロセスマイクロチャネル２１０の反対側の別の平面内に平行に配置するとよい。例えば、多相混合物形成ユニット２００Ｂおよび２００Ｃでは、プロセスマイクロチャネル２１０は、一平面内に平行に配置するとよく、第二の流体流チャネル２７０および２７０ａは、プロセスマイクロチャネル２１０のそれぞれの側の隣接平面内に平行に配置するとよく、熱交換チャネル２９０は、第二の流体流チャネル２７０ａに隣接する平面内に平行に配置するとよい。多相混合物形成ユニット２００Ｄでは、第二の流体流チャネル２７０は、一平面内に平行に配置するとよく、プロセスマイクロチャネル２１０および２１０ａは、液体チャネル２７０のそれぞれの側の隣接する平面内に平行に配置するとよく、熱交換チャネル２９０は、プロセスマイクロチャネル２１０に隣接する平面内に平行に配置するとよい。これらの多相混合物形成ユニットは、図３～９および１２には示していないが、当業者なら提供することができる、プロセス液体および熱交換流体の入出力を制御するために、適切なヘッダ、フッタ、マニホルド、バルブ、導路、配管、制御機構等を有してもよい。例えば、多相混合物形成ユニットを含むマイクロチャネルミキサへの入口および出口で、導路または配管を接続するために傾斜したヘッダおよびフッタを用いて、プロセスマイクロチャネルのサイズに伴う不必要な圧力降下を回避してもよい。

【００５６】

一実施態様では、複数の多相混合物形成ユニット（２００、２００Ａ、２００Ｂ、２００Ｃ、２００Ｄ、３００、４００、５１０）を上下に積み重ねて、オンデマンドの大きな生産能力用のスケールアップしたユニットのコアを形成してもよい。スケールアップしたユニットは、多相混合物製品のためだけでなく、多相混合物を形成させるために用いられる液体のためのマニホルドとしても、傾斜したヘッダおよびフッタを有してもよい。プロセスチャネル、分散相チャネルまたは熱交換チャネルの入口にオリフィスプレートまたはその他の開口区間を加えることによって、より一様な流れの分布を容易にしてもよい。フレーム区間を用いて、多相混合物形成ユニットを保持し、封止してもよい。

【００５７】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）のそれぞれは、任意の構成、例えば正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。プロセスマイクロチャネルは、管状であってもよい。プロセスマイクロチャネルは、横に並べられるか、または上下に重ねられた平行な離間したシートおよび／またはプレートから形成してもよい。用語「シート」は、最大約５ｍｍの壁の厚さを指す。用語「プレート」は、約５ｍｍ以上の壁の厚さを指す。シートは、ロールの形でユーザに供給されてもよく、一方、プレートは、平らな材料の片の形でユーザに供給されてもよい。プロセスマイクロチャネルのそれぞれは、プロセスマイクロチャネルを通る流体の流れに垂直な、最大約５０ｍｍ、一実施態様では最大約１０ｍｍ、一実施態様では最大約２ｍｍの範囲の内部寸法（例えば、高さ、幅または直径）を有するとよい。この寸法は、約０．０５から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．０５から約１．５ｍｍ、一実施態様では約０．０５から約１ｍｍ、一実施態様では約０．０５から約０．５ｍｍの範囲にあるとよい。プロセスマイクロチャネルを通る液体の流れに垂直な別の内部寸法（例えば、高さまたは幅）は、任意の値であってもよく、例えば、約０．０１ｃｍから約１００ｃｍ、一実施態様では約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。

【００５８】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）は、プロセスマイクロチャネルの中の第一の液体の流れの均一な分布を提供するために、混合区域（２１３、２１３ａ、３１５、３２５、３３５、３４５、４１３）の上流の入口の中の非開口領域または非多孔質領域（２１１、２１１

ａ、３１４、３２４、３３４、３４４、４１１）を有してもよい。これは、複数のプロセスマイクロチャネルが横に並べられ、および／または上下に重ねられて配置され、複数のプロセスマイクロチャネルの中への第一の液体流が一様でないとき、有用になることがある。これらの非開口領域を設けると、混合区域に到達する前の第一の流体流の流れを安定化することがある。非開口領域または非多孔質領域を使用すると、プロセスマイクロチャネルが円形の断面（すなわち管状幾何構造）を有するとき、利点になることがある。一実施態様では、非開口領域または非多孔質領域の中のプロセスマイクロチャネルの最小内部寸法に対する、プロセスマイクロチャネルへの入口から混合区域への入口までの非開口領域の長さの比は、約０．０００１から約１００００、一実施態様では約０．００１から約１０００の範囲にあるとよい。

【００５９】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）の内部壁の一つ以上は、プロセスマイクロチャネルの中の流れを変更するための表面構成要素を有してもよい。図２２～２６に、これらの表面構成要素の例が示される。表面構成要素は、三次元パターンで互いの上に重ねられるか、または絡み合った二つ以上の層を有してもよい。各別個の層の中のパターンは、同じであってもよく、あるいは異なっていてもよい。各層の中で、または一つの層の中だけで、流れが回転するか、または平行移動してもよい。バルクの流れのチャネルに隣接していなくてもよい副層を用いて、追加の表面積を作り出してもよい。例えば、これらを用いて触媒を析出させてもよい。流れは、表面構成要素の第一のレベルの中で回転し、第二の副層以降の中に分子拡散して反応を促進してもよい。金属キャスティングまたはその他のプロセスによって三次元構成要素を作ってもよい。これらの方法では、互いの上に積層されているかのように変化するパターンも個別の平面に分解しなくてよい。バルクの流れのチャネルに隣接して、三次元的に変化する表面構成要素を置くことができる。これらの構成要素は、さまざまな深さ、形状および位置を有し、さまざまな深さ、形状および位置のパターンを有する副構成要素を伴う。表面構造物は、触媒析出のために追加の表面積を必要とする化学反応、または蒸留などの化学的分離の場合に利点となることがある。

【００６０】

図２３は、三次元表面構成要素構造物の平面概略図である。図２４には、三次元表面構成要素構造物の背面図の例が示され、バルクの流れのマイクロチャネルの隣接する界面にくぼんだＶ字形があり、Ｖ字形の下には、バルクの流れの通路に隣接する構成要素に接続されるが、多彩な形状、深さおよび位置の構造物から作られた一連の三次元構造がある。開いた表面構成要素の直下にはなく、バルクの流れのマイクロチャネルに隣接するが、一つ以上の曲がりくねった二次元または三次元の通路によって接続される、副層通路を作り出すとさらに有利になることがある。この手法は、狭い滞留時間分布ではなく、広い滞留時間分布を有することが望ましい反応器の中に調整された滞留時間分布を作り出すために利点となることがある。

【００６１】

図２５は、くぼんだＶ字形がバルク流れのマイクロチャネルに接し、Ｖ字形の後ろには変化する深さおよび位置にあるさまざまな形状の追加の構成要素がある、三次元表面構成要素の前面図である。

【００６２】

表面構成要素は、約２ｍｍより小さい、一実施態様では約１ｍｍより小さい、一実施態様では約０．０１ｍｍから約０．５ｍｍの範囲にある深さを有するとよい。表面構成要素の横幅は、マイクロチャネル幅にほぼ達する（魚骨設計で示されるように）のに十分であるとよいが、一実施態様（充填構成要素など）ではマイクロチャネル幅の約６０％以下、一実施態様では約４０％以下、一実施態様では約０．１％から約６０％、一実施態様では約０．１％から約５０％の幅であるとよい。

【００６３】

表面構成要素の横幅は、約０．０５ｍｍから約１００ｃｍの範囲、一実施態様では約０

．５ｍｍから約５ｃｍの範囲、一実施態様では約１から約２ｃｍの範囲にあるとよい。

【００６４】

表面構成要素の長さおよび幅は、マイクロチャネルの長さおよび幅と同様に定めるとよい。深さは、表面構成要素がマイクロチャネル表面の中に沈む距離であってもよく、この場合は、マイクロチャネル高さまたはマイクロチャネルギャップと同じ方向である。これは、シート表面の上または中に形成された表面構成要素を有し、積層され、ボンディングされたマイクロチャネルデバイスを積層する方向に対応してもよい。表面構成要素のこれらの寸法は、表面構成要素の最大寸法を指す。例えば、角を丸めた溝の深さは、最大の深さ、すなわち、溝の底での深さを指すことがある。

【００６５】

マイクロチャネルの中に、一つ以上のマイクロチャネル壁の中にさまざまな深さでくぼむ構成要素を含む、複数の表面構成要素または表面構成要素の領域を含んでもよい。くぼみの間の間隔は、約０．０１から約１０ｍｍの範囲、一実施態様では約０．１から約１ｍｍの範囲にあるとよい。表面構成要素は、マイクロチャネルの長さ全体に存在してもよく、またはマイクロチャネルの部分または領域に存在してもよい。表面構成要素を有する部分または領域は、専用に調整された区域の中で所望の反応または単位操作を促進するように断続的であってもよい。例えば、マイクロチャネルの１インチの区間は密集した表面構成要素のアレイを有し、続く４インチは構成要素のない平坦なチャネルとし、続く２インチは疎な表面構成要素の区間としてもよい。疎に離間した表面構成要素とは、表面構成要素の長さの５倍より大きなピッチまたは構成要素間距離を有する表面構成要素を指す。

【００６６】

一実施態様では、表面構成要素は、実質的にマイクロチャネルの軸方向長さ全体にわたって延在してもよい。一実施態様では、マイクロチャネルは、その軸方向長さの約５０％以下にわたって、一実施態様ではその軸方向長さの約２０％以下にわたって表面構成要素を有するとよい。一実施態様では、表面構成要素は、マイクロチャネルの軸方向長さの約１０％から約１００％にわたって延在するとよい。

【００６７】

図２６は、表面構成要素のために用いることができる複数のさまざまなパターンを示す。これらのパターンは、本発明を限定するものではなく、複数の可能性の例を示すことだけとする。任意の表面構成要素の場合と同じく、パターンは、マイクロチャネルのさまざまな軸方向の区間または横の区間の中で用いてもよい。

【００６８】

第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）および第三の流体流チャネル（４４０、４５０）は、マイクロチャネルと特徴づけるには大きすぎる寸法を有することがあるが、マイクロチャネルであるとよい。これらのチャネルのそれぞれは、任意の構成、例えば、正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。これらのチャネルは、上記で説明したように、表面構成要素を含んでもよい。第二および第三の流体流チャネルは管状であってもよい。第二および第三の流体流チャネルは、横に並べられるか、または上下に重ねられて配置された平行な離間したシートおよび／またはプレートから形成してもよい。各第二および第三の流体流チャネルは、最大約１００ｃｍの範囲、一実施態様では約０．０５ｍｍから約１００ｃｍの範囲、一実施態様では約０．０５ｍｍから約５０ｃｍ、一実施態様では約０．０５ｍｍから約１０ｃｍ、一実施態様では約０．０５ｍｍから約５ｃｍ、一実施態様では約０．０５ｍｍから約１０ｍｍ、一実施態様では約０．０５ｍｍから約５ｍｍ、一実施態様では約０．０５ｍｍから約２ｍｍ、一実施態様では約０．０５ｍｍから約１ｍｍの、第二および第三の流体流チャネルを通る流体流に垂直な内部寸法（例えば高さ、幅または直径）を有するとよい。第二および第三の流体流チャネルを通る流体流に垂直な別の内部寸法（例えば高さまたは幅）は、約０．０１ｃｍから約１００ｃｍ、一実施態様では約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。第二および第三の流体流チャネルの長さは、

任意の値、例えば、約０．１ｃｍから約５００ｃｍ、一実施態様では約０．１ｃｍから約２５０ｃｍ、一実施態様では約１ｃｍから約１００ｃｍ、一実施態様では約１ｃｍから約５０ｃｍ、一実施態様では約２ｃｍから約２５ｃｍの範囲にあるとよい。各プロセスマイクロチャネルと次の隣接する第二の流体流チャネルまたは隣接する第二および第三の流体流チャネルとの間の距離は、約０．０５ｍｍから約５０ｍｍ、一実施態様では約０．１から約１０ｍｍ、一実施態様では約０．２ｍｍから約２ｍｍの範囲にあるとよい。

【００６９】

発熱源および／または吸熱源は、冷却、加熱、あるいは冷却と加熱との両方のために用いてもよい。発熱源および／または吸熱源は、一つ以上の熱交換チャネルを含んでもよい。発熱源は、一つ以上の電熱素子または抵抗加熱器を含んでもよい。吸熱源は、一つ以上の非流体冷却素子を含んでもよい。これらは、プロセスマイクロチャネルおよび／または第二または第三の流体流チャネルに隣接してもよい。一実施態様では、発熱源および／または吸熱源は、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルに接触も隣接もせず、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルのどちらかまたは両方から離れているが、発熱源および／または吸熱源とプロセスマイクロチャネルおよび／または第二および第三の流体流チャネルとの間で熱を移動させるために、プロセスマイクロチャネルおよび／または第二および第三の流体流チャネルに十分に近くすることができる。電熱素子、抵抗加熱器および／または非流体冷却素子を用いてプロセスマイクロチャネル（２１０、３１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）および／または第三の流体流チャネル（４４０、４５０）の一つ以上の壁を形成してもよい。電熱素子、抵抗加熱器および／または非流体冷却素子は、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの一つ以上の壁の中に構築してもよい。電熱素子および／または抵抗加熱器は、プロセスマイクロチャネルおよび／または液体チャネルの壁の中に埋め込まれた薄いシート、ロッド、ワイヤ、ディスクまたはその他の形状の構造物であってもよい。電熱素子および／または抵抗加熱器は、プロセスマイクロチャネル壁および／または液体チャネル壁に接着されたフォイルまたはワイヤの形状であってもよい。加熱および／または冷却は、ペルティエ型熱電冷却および／または加熱素子を用いて実現してもよい。プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの長さに沿って、複数の加熱および／または冷却区域を使用してもよい。同様に、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネルの長さに沿って、一つ以上の熱交換チャネルの中のさまざまな温度の伝熱流体を使用してもよい。発熱源および／または吸熱源は、プロセスマイクロチャネル、第二の流体流チャネルおよび／または第三の流体流チャネル内の精密な温度調節を提供するために用いてもよい。

【００７０】

熱交換チャネル（２９０、３７０、３８０、５９０）は、マイクロチャネルであってもよいが、典型的マイクロチャネルとは言えないような大きな寸法を有してもよい。これらのチャネルのそれぞれは、任意の構成、例えば、正方形、長方形、円形、環形、楕円形、台形等の断面を有してもよい。熱交換チャネルは、管状であってもよい。熱交換チャネルは、横に並べられるか、または上下に重ねられて配置された平行な離間したシートおよび／またはプレートから、隣接するプロセスマイクロチャネルまたは第二および第三の流体流チャネルと一緒に形成してもよい。これらのチャネルは、上記で説明された表面構成要素を含んでもよい。熱交換チャネルのそれぞれは、最大約５０ｍｍ、一実施態様では最大約１０ｍｍ、一実施態様では最大約２ｍｍの範囲の熱交換チャネルを通る熱交換流体流に垂直な内部寸法、例えば高さ、幅または直径を有するとよい。この寸法は、約０．０５から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．０５から約５ｍｍ、一実施態様では約０．０５から約２ｍｍ、一実施態様では約０．５から約１ｍｍの範囲にあるとよい。熱交換チャンルを通る熱交換流体流に垂直な別の内部寸法、例えば高さまたは幅は、任意の値、例えば約０．０１ｃｍから約１００ｃｍ、一実施態様で

は約０．０１ｃｍから約７５ｃｍ、一実施態様では約０．１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲にあるとよい。熱交換チャネルの長さは、例えば約０．１ｃｍから約５００ｃｍ、一実施態様では約０．１ｃｍから約２５０ｃｍ、一実施態様では約１ｃｍから約１００ｃｍ、一実施態様では約１ｃｍから約５０ｃｍ、一実施態様では約０．２ｃｍから約２５ｃｍの範囲の任意の値であるとよい。各プロセスマイクロチャネルあるいは第二または第三の流体流チャネルと次の隣接する熱交換チャネルとの間の距離は、約０．０５ｍｍから約５０ｍｍ、一実施態様では約０．１から約１０ｍｍ、一実施態様では約０．２ｍｍから約２ｍｍの範囲にあるとよい。

【００７１】

熱交換チャネル（２９０、３７０、３８０、５９０）は、チャネルを通って隣接するプロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体の流れと平行な、並流の方向に熱交換流体が流れるようにしてもよい。あるいは、熱交換流体は、熱交換チャネルを通って、プロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体流に対して向流となる方向に流れてもよい。あるいは、熱交換チャネルは、プロセスマイクロチャネルまたは第二および第三の流体流チャネルを通る流体流に対して交差流となる方向の熱交換流体流を提供するように、プロセスマイクロチャネルまたは第二および第三の流体流チャネルに対して配向してもよい。熱交換チャネルは、交差流と並流または向流との組み合わせを提供するために、蛇行する構成を有してもよい。

【００７２】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および／または熱交換チャネル（２９０、３７０、３８０、５９０）は、正方形または長方形の断面を有し、平行な離間したシートまたはプレートから形成される。これらのチャネルは、横に並べられた垂直配向の交互面、または上下に積層された水平配向の交互面に配列してもよい。平行プレート構成と呼んでもよいこれらの構成には、複数の利点がある。例えば、円形の管と比較すると、平行プレート構成は、同じ連続相物質流束での高さ、幅または直径に対して、同じせん断力を実現しながら、受ける圧力降下が小さい。例えば、長方形チャネルのアスペクト比が約１０に近づくと、すなわち平行シートまたはプレート構成に近づくと、その圧力降下は、同じ条件下の円形チャネルの中の圧力降下のわずか約５０％にすることができる。平行板構成を有するプロセスマイクロチャネル、第二の流体流チャネル、第三の流体流チャネルおよび熱伝達チャネルは、スケールアップのために、小型デバイスの中に容易に配置することができる。円形の管と比較すると、平行プレート構成を用いることによって、多相混合物形成プロセスのより高い単位体積あたり処理能力を実現することもできる。

【００７３】

平行プレート構成を用いる利点は、これらの構成が円形の管と比較してより大きな流体／壁材料比を有し、従ってより小型であり、より大きな製造能力または出力の可能性を有する点である。

【００７４】

一実施態様では、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および／または熱交換チャネル（２９０、３７０、３８０、５９０）は、同心状に配置された円形の管の形であるとよい。プロセスマイクロチャネルおよび第二の流体流チャネルは、互いに隣接し、一方のチャネルは環状の空間にあり、他方のチャネルは中心の空間または隣接する環状の空間にあるとよい。一実施態様では、本発明のプロセスで有用なマイクロチャネルミキサは、複数の交互に重ねられた同心円の管のプロセスマイクロチャネル、第二の流体流チャネル、および選択肢として第三の流体流チャネルを含み、マイクロチャネルミキサは円筒形の形状であるとよい。

【００７５】
開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）は、開口区間を通る示された流体の流れを可能にする十分なサイズであるとよい。開口は、細孔と呼んでもよい。開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、約０．０１から約５０ｍｍ、一実施態様では約０．０５から約１０ｍｍ、一実施態様では約０．１から約２ｍｍの範囲の厚さを有するとよい。開口は、最大約５０ミクロンの範囲、一実施態様では約０．００１から約５０ミクロンの範囲、一実施態様では約０．０５から約５０ミクロン、一実施態様では約０．１から約５０ミクロンの平均直径を有するとよい。一実施態様では、開口は、約０．５から約１０ナノメートル（ｎｍ）、一実施態様では約１から約１０ｎｍ、一実施態様では約５から約１０ｎｍの範囲の平均直径を有するとよい。開口区間の中の開口の数は、平方センチメートルあたり約１０から約５×１０^{8}開口、一つの実施態様では平方センチメートルあたり約１から約１×１０^{6}開口の範囲にあるとよい。開口は、互いに孤立していてもよく、孤立していなくてもよい。開口の一部またはすべては、開口区間内の他の開口と流体連通していてもよい。プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）を通って流れる流体の流れの経路に沿った開口区間の長さに対する、開口区間の厚さの比は、約０．００１から約１００、一実施態様では約０．０１から約５０、一実施態様では約０．０３から約２５、一実施態様では約０．０５から約１０、一実施態様では約０．０８から約５、一実施態様では約０．１から約１の範囲にあるとよい。開口区間は、本発明のプロセスの動作を可能にするのに十分な強度および寸法安定性を提供する任意の材料で構築するとよい。これらの材料は、鋼（例えばステンレス鋼、炭素鋼および類似物）、モネル、インコネル、アルミニウム、チタン、ニッケル、白金、ロジウム、銅、クロム、真鍮、上記金属の任意のものの合金、重合体（例えば熱硬化性樹脂）、セラミック、ガラス、一つ以上の重合体（例えば熱硬化樹脂）およびガラス繊維を含むコンポジット、石英、ケイ素、カーボンナノチューブまたはカーボンモレキュラーシーブを含む微多孔質炭素、ゼオライトまたはそれらの二つ以上の組み合わせを含む。開口は、レーザ穿孔、マイクロエレクトロマシニングシステム（ＭＥＭＳ）、リソグラフィー電着および成型（ＬＩＧＡ）、電気スパークリングまたは電気化学エッチングなどの既知の技法を用いて作製してもよい。開口は、押し出しなどの構造を有するプラスチックを作るために用いられる技法、または配列カーボンナノチューブ（ＣＮＴ）膜などの膜を作るために用いられる技法を用いて、作製してもよい。開口は、金属粉末または粒子を焼結または圧縮して曲がりくねって相互連絡した毛管チャネルを形成させるなどの技法、および膜作製の技法を用いて作製してもよい。開口は、これらの方法の任意のものによって提供されるサイズから、開口を部分的に埋める開口内部側壁へのコーティングの塗布によって大きさを小さくしてもよい。選択なコーティングによって、多孔質ボディの外に薄層を形成させ、連続する流れの経路に隣接して最小の細孔サイズを提供してもよい。最小平均細孔開口は、多相混合物用の所望の液滴サイズによって、約１ナノメートルから約数百ミクロンの範囲にあるとよい。開口は、熱処理によって、ならびに、開口内部側壁上に酸化物スケールまたはコーティングを形成させる方法によって、サイズを小さくしてもよい。これらの技法は、開口を部分的に閉塞して流れに当てられる開口のサイズを減らすために用いてもよい。図１３および１４は、熱処理の前後の、同じ倍率で、同じ位置のステンレス鋼多孔基板のＳＥＭ表面構造の比較を示す。図１３は熱処理前の表面を示し、図１４は熱処理後の表面を示す。熱処理後の多孔質材料の表面は、著しく小さなギャップおよび開口部サイズを有する。対応して、開口の間の平均距離は、増加する。

【００７６】
開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、約０．０１から約２００ミクロンの範囲の平均細孔サイズの相互連結チャネルまたは細孔を有する金属または非金属多孔質材料から作ってもよい。これらの細孔は、開口（２４４、２４４ａ、３１３、３２３、３

３３、３４３、４１６、４２６、４３６、４４６）として機能してもよい。多孔質材料は、平均細孔間距離が平均細孔径と同様になるように、粉末または微粒子から作ってもよい。非常に小さな細孔サイズが用いられると、細孔間距離も非常に小さくなることがあり、液滴は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、４１０、５２０）または第二の流体流チャネル（４２０、４３０）の側の表面で合体して望ましくない大きな液滴を形成することがある。多孔質材料は、約３００℃から約１０００℃の範囲の高温で、約１時間から約２０日間の長さの酸化によって、またはゾルコーティングによるアルミナまたは化学蒸着法を用いるニッケルなどの別の材料の薄層を表面の上および細孔の内部にコーティングして、小さな細孔をふさぎ、大きな細孔の細孔サイズを小さくし、その結果細孔間距離を増加させることによって、調整してもよい。そのようにして、液滴の合体を減らすか、またはなくし、より小さな液滴の生成を可能にしてもよい。図１５に、調整された基板または開口区間のＳＥＭ画像が示される。

【００７７】

開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）は、混合区域（２１３、２１３ａ、３１５、３２５、３３５、３４５、４１３）全体にわたって規則的に離間してもよい。開口は、小さな開口ほど、または大きな開口ほど、混合区域の前後のどちらかの近くで用いられるように、優先して離間してもよい。開口は、一緒に、混合区域の始めで互いに近く、混合区域の終わり近くで遠く離れて液滴融合を抑制する助けとしてもよい。約１ミクロンより小さな泡またはミクロスフェアサイズを有する多相混合物を提供するのに十分に小さなマイクロスケール開口または細孔（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）を有する開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）として用いられる基板の製作は、問題となることがある。これの理由の一つは、圧縮および／または焼結によって粉末／粒子から作られた金属多孔質基板などの未処理の通常の多孔質材料では、比較的大きな表面粗さが生じるという事実にある。一般に、これらの金属多孔質基板では、所定の名目細孔径が特定の値より低いとき、表面領域に必要な細孔サイズがない。多孔質材料のバルクは指定された名目細孔サイズを有するが、多くの場合、表面領域ははるかに大きなサイズの融合細孔および空洞を特徴とする。この問題は、これらの基板を調整して所望の細孔サイズおよび細孔間距離を表面領域の中に提供することによって、克服することができる。これは、多孔質基板から表面層を除去し、より小さな開口を有する滑らかな新しい表面を露出させるか、または加えることによって実施するとよい。これらの調整された基板を用いて形成される多相混合物の中の泡またはマイクロスフェアサイズは、基板にかかる圧力降下を増加させずに小さくすることができる。多孔質表面を直接研磨または機械加工すると、表面構造のスミアリングおよび細孔の閉塞の原因となることがあるので、多孔質構造を液体充填材で満たした後、固形化および機械研磨／磨き仕上げしてもよい。次に、充填材を除去して材料の多孔質構造を再び得る。充填材は、亜鉛またはスズなどの低い融点を有する金属またはエポキシなどの重合体の前駆体であってもよい。液体充填および除去工程は、真空の使用によって支援してもよい。研磨／磨き仕上げは、研削盤および研削粉を用いて実行してもよい。金属充填剤除去は、融解および真空吸引によって、または酸エッチングによって実現してもよい。エポキシまたはその他の重合体は、溶媒溶解によって、または空気中での燃焼除去によって除去してもよい。

【００７８】

図１６～１９を参照すると、一実施態様では、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、比較的小さな開口６０２を含む比較的薄いシート６００と、開口６００と同軸配置されるかまたは接続された比較的大きな開口６１２のアレイを含む比較的厚いシートまたはプレート６１０とで構築するとよい。比較的薄いシート６００は、比較的厚いシート６１０の上にあってボンディングされ、比較的薄いシート６００は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０）または第二

の流体流チャネル（４２０、４３０）の内部に対向し、比較的厚いシート６１０は、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）または第三の流体流チャネル（４４０、４５０）の内部に対向する。比較的薄いシート６００は、任意の適当な手順（例えば拡散結合）を用いて比較的厚いシート６１０にボンディングされ、機械的強度が大きくなったコンポジット構造６２０を提供することができる。比較的薄いシート６００は、約０．００１から約０．５ｍｍ、一実施態様では約０．０５から約０．２ｍｍの範囲の厚さを有するとよい。比較的小さな開口６０２は、任意の形状、例えば円形、三角形または長方形を有するとよい。比較的小さな開口６０２は、約０．０５から約５０ミクロン、一実施態様では約０．０５から約２０ミクロンの範囲の平均直径を有するとよい。比較的厚いシートまたはプレート６１０は、約０．１から約５ｍｍ、一実施態様では約０．１から約２ｍｍの範囲の厚さを有するとよい。比較的大きな開口６１２は、任意の形状、例えば円形、三角形または長方形を有するとよい。比較的大きな開口６１２は、約０．１から約４０００ミクロン、一実施態様では約１から約２０００ミクロン、一実施態様では約１０から約１０００ミクロンの範囲の平均直径を有するとよい。シート６００の中の開口６０２の数およびシートまたはプレート６１０の中の開口６１２の数は、それぞれ平方センチメートルあたり約２から約１００００開口、一実施態様では平方センチメートルあたり約２から約１０００開口の範囲にあるとよい。シート６００およびシートまたはプレート６１０は、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）を構築するために有用であるとして上記で説明した材料の任意のもので構築するとよい。開口６０２および６１２は、開口区間を通って流れる液体が最初に開口６１２を通り、次に開口６０２を通って流れるように同軸配置されるか、または接続されるとよい。液体が比較的小さな開口６０２を通って流れるための比較的短い通路は、開口の中の通路が開口６０２と６１２とを合わせた長さに等しい長さを有していたら起こると考えられる圧力降下と比べると比較的低い圧力降下で、液体が開口６０２を通って流れることを可能にする。

【００７９】

図１９に例が示される実施態様では、コンポジット構造物６２０ａは、開口６１２を覆う比較的薄いシート６００の凸部分６０４が提供される点を除けば、図１８に例が示されるものと同じ設計を有する。凸部分６０４は、隣接するチャネルの中の局所せん断力の増加をもたらす。図１９の方向矢印６３０は、開口６０２に隣接するチャネルの中の流体の流れを示す。せん断力がより大きいため、開口６０２を通って流れる流体の泡またはミクロスフェアサイズが小さくなる。

【００８０】

図２０に例が示される実施態様では、シートまたはプレート６４０の表面と、開口６４６の内部側壁６４４との上に表面コーティング６４２が析出される。このコーティングは、開口（２４４、２４４ａ、３１３、３２３、３３３、３４３、４１６、４２６、４３６、４４６）の直径を小さくする、より容易な方法を提供する。コーティング６４２を形成させるために用いられるコーティング材料は、アルミナ、ニッケル、金または重合材料（例えばテフロン（登録商標））を含んでもよい。コーティング６４２は、化学蒸着、金属スパッタリング、金属メッキ、焼結、ゾルコーティング、重合体コーティングおよび類似法を含む既知の技法を用いて、シートまたはプレート６４０に塗布してもよい。開口の直径は、コーティング６４２の厚さを調節することによって制御してもよい。

【００８１】

一実施態様では、開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）は、非対称多孔質材料、例えば、複数の焼結粒子の層を有する多孔質材料で形成してもよい。層の数は、２、３または４以上であってもよい。これらの多層基板の利点は、耐久性および接着強さの増加をもたらす点である。例は、一方の側に比較的大きな細孔、他方の側に比較的小さな細孔を有する焼結セラミックスを含む。比較的小さな細孔は、約２から約１０ｎｍの範囲の

直径を有するとよい。比較的小さな細孔は、多層基板の比較的薄い層に位置するとよい。比較的薄い層は、約１から約１０ミクロンの範囲の厚さを有するとよい。比較的小さな細孔を有する側は、プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）または第二の流体流チャネル（４２０、４３０）の内部に面して配置し、比較的高いせん断力を利用して比較的小さな多相混合物の泡またはミクロスフェアが形成されると除去するとよい。

【００８２】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）、第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）、第三の流体流チャネル（４４０、４５０）および熱交換チャネル（２９０、３７０、３８０、５９０）は、関連するヘッダ、フッタ、マニホルド等とともに、本発明のプロセスの動作を可能にするのに十分な強度、寸法安定性、耐食性および伝熱特性を提供する任意の材料で作ってもよい。これらの材料は、鋼（例えばステンレス鋼、炭素鋼および類似物）、モネル、インコネル、アルミニウム、チタン、ニッケル、白金、ロジウム、銅、クロム、真鍮、前述の金属の任意のものの合金、重合体（例えば熱硬化性樹脂）、セラミックス、ガラス、一つ以上の重合体（例えば熱硬化性樹脂）とガラス繊維を含むコンポジット、石英、ケイ素、またはそれらの二つ以上の組み合わせを含む。

【００８３】

第一の流体流は、気体または液体を含んでもよい。第二の流体流は、気体またはマイクロボディ形成材料を含んでもよい。第三の流体流は、気体を含んでもよい。

【００８４】

気体は、任意の気体を含んでもよい。一実施態様では、気体は、空気、酸素、窒素、二酸化炭素、水蒸気、アンモニア、オゾン、塩素ガス、水素および類似物の一種類以上を含んでもよい。気体は、一つ以上の気体炭化水素、例えば、１から約５個の炭素原子を含む炭化水素を含んでもよい。これらは、飽和および不飽和炭化水素を含む。炭化水素は、メタン、エタン、エチレン、プロパン、イソプロパン、プロピレン、ブタン類、ブチレン類、ペンタン類、シクロペンタン、ペンチレン類、シクロペンチレンおよび類似物を含む。

【００８５】

液体は、任意の液体を含んでもよい。液体は、水、有機液体またはそれらの組み合わせを含んでもよい。液体は、一つ以上の液体炭化水素を含んでもよい。これらは、１個から約２４個の炭素原子、一実施態様では約５個から約２４個の炭素原子、一実施態様では約６個から約１８個の炭素原子、一実施態様では約６個から約１２個の炭素原子を含む炭化水素化合物を含む。用語「炭化水素」は、炭化水素または主に炭化水素の性格を有する化合物を示す。これらの炭化水素化合物は、以下のものを含む。

（１）純炭化水素化合物、すなわち、脂肪族化合物（例えばアルカンまたはアルキレン）、脂環式化合物（例えばシクロアルカン、シクロアルキレン）、芳香族化合物、脂肪族および脂環式置換芳香族化合物、芳香族置換脂肪族化合物および芳香族置換脂環式化合物および類似物。例は、ヘキサン、１－ヘキセン、ドデカン、シクロヘキセン、シクロヘキサン、エチルシクロヘキサン、ベンゼン、トルエン、キシレン類、エチルベンゼン、スチレン等を含む。

（２）置換炭化水素化合物、すなわち、化合物の主に炭化水素の性格を変えない非炭化水素置換基を含む炭化水素化合物。非炭化水素置換基の例は、ヒドロキシ、アシル、ニトロ、ハロ等を含む。

（３）ヘテロ置換炭化水素化合物、すなわち性格としては主に炭化水素であるが、通常は炭素原子で構成される分子鎖または環の中に炭素以外の原子を含む炭化水素化合物。例えば、ヘテロ原子は、窒素、酸素および硫黄を含む。

【００８６】

液体は、天然オイル、合成オイルまたはそれらの混合物を含んでもよい。天然オイルは、動物オイルおよび植物オイル（例えばヒマシ油、ラード油）、ならびに液体石油系オイ

ル分およびパラフィン系、ナフテン系または混合パラフィン系－ナフテン系型の溶媒処理または酸処理鉱物オイルなどの鉱物オイルを含む。天然オイルは、石炭または頁岩から誘導されるオイルを含む。オイルは、トリグリセリドの仲間からのケン化可能なオイル、例えばダイズ油、ゴマ種子油、綿実油、サフラワー油および類似物であってよい。オイルは、シリコーンオイル（例えばシクロメチコーン、シリコンメチコーン類等）であってもよい。オイルは、ワセリン、スクアラン、スクアレンまたは一つ以上のジアルキルシクロヘキサン類、またはそれらの二つ以上の混合物などの脂肪族またはナフテン系炭化水素であってもよい。合成オイルは、重合および高分子間反応したオレフィン（例えばポリブチレン類、ポリプロピレン類、プロピレンイソブチレン共重合体等）、ポリ（１－ヘキセン類）、ポリ（１－オクテン類）、ポリ（１－デセン類）等およびそれの混合物などの炭化水素オイル、アルキルベンゼン類（例えばドデシルベンゼン類、テトラデシルベンゼン類、ジノニルベンゼン類、ジ－（２－エチルヘキシル）ベンゼン類等）、ポリフェニル類（例えばビフェニル類、テルフェニル類、アルキル化ポリフェニル類等）、アルキル化ジフェニルエーテル類およびアルキル化ジフェニルスルフィド類およびそれらの誘導体、類縁体および同族体ならびに類似物を含む。末端ヒドロキシル基がエステル化、エーテル化等によって修飾されたアルキレンオキシド重合体類およびそれらの共重合体および誘導体は、用いることができる合成オイルである。合成オイルは、ポリ－アルファ－オレフィンまたはフィッシャー－トロプシュ合成炭化水素を含んでもよい。

【００８７】

液体は、通常は液体の炭化水素燃料、例えば、ＡＳＴＭ規格Ｄ４３９で定められる自動車ガソリンなどの留出燃料、またはＡＳＴＭ規格Ｄ３９６で定められるディーゼル燃料または重油を含んでもよい。

【００８８】

液体は、脂肪族アルコール、脂肪酸エステルまたはそれらの混合物を含んでもよい。脂肪族アルコールは、ゲルベ（Ｇｕｅｒｂｅｔ）アルコールであってもよい。脂肪族アルコールは、約６個から約２２個の炭素原子、一実施態様では約６個から約１８個の炭素原子、一実施態様では約８個から約１２個の炭素原子を含むとよい。脂肪酸エステルは、約６個から約２２個の炭素原子の直鎖脂肪酸と約６個から約２２個の炭素原子の直鎖または分岐脂肪族アルコールとのエステル、約６個から約１３個の炭素原子の分岐カルボン酸と約６個から約２２個の炭素原子の直鎖または分岐脂肪族アルコールとのエステル、またはそれらの混合物であってもよい。例は、ミリスチン酸ミリスチル、パルミチン酸ミリスチル、ステアリン酸ミリスチル、イソステアリン酸ミリスチル、オレイン酸ミリスチル、ベヘン酸ミリスチル、エルシン酸ミリスチル、ミリスチン酸セチル、パルミチン酸セチル、ステアリン酸セチル、イソステアリン酸セチル、オレイン酸セチル、ベヘン酸セチル、エルシン酸セチル、ミリスチン酸ステアリル、パルミチン酸ステアリル、ステアリン酸ステアリル、イソステアリン酸ステアリル、オレイン酸ステアリル、ベヘン酸ステアリル、エルシン酸ステアリル、ミリスチン酸イソステアリル、パルミチン酸イソステアリル、ステアリン酸イソステアリル、イソステアリン酸イソステアリル、オレイン酸イソステアリル、ベヘン酸イソステアリル、オレイン酸イソステアリル、ミリスチン酸オレイル、パルミチン酸オレイル、ステアリン酸オレイル、イソステアリン酸オレイル、オレイン酸オレイル、ベヘン酸オレイル、エルシン酸オレイル、ミリスチン酸ベヘニル、パルミチン酸ベヘニル、ステアリン酸ベヘニル、イソステアリン酸ベヘニル、オレイン酸ベヘニル、ベヘン酸ベヘニル、エルシン酸ベヘニル、ミリスチン酸エルシル、パルミチン酸エルシル、ステアリン酸エルシル、イソステアリン酸エルシル、オレイン酸エルシル、ベヘン酸エルシルおよびエルシン酸エルシルを含む。脂肪酸エステルは、約１８個から約３８個の炭素原子のアルキルヒドロキシカルボン酸と、約６個から約２２個の炭素原子の直鎖または分枝脂肪族アルコールとのエステル（例えばりんご酸ジオクチル）、約６個から約２２個の炭素原子の直鎖または分枝脂肪酸と、多価アルコール（例えばプロピレングリコール、二量体ジオールまたは三量体トリオール）および／またはゲルベアルコールとのエステル、約６個から約１８個の炭素原子の一種類以上の脂肪酸から作られるトリグリセリド、約６個から

約１８個の炭素原子の一種類以上の脂肪酸から作られるモノ、ジおよび／またはトリグリセリドの混合物、約６個から約２２個の炭素原子の一種類以上の脂肪族アルコールおよび／またはゲルベアルコールと一種類以上の芳香族カルボン酸とのエステル（例えば安息香酸）、２個から約１２個の炭素原子の一種類以上のジカルボン酸と１個から約２２個の炭素原子を含む一種類以上の直鎖または分岐アルコール、２個から約１０個の炭素原子および２個から約６個のヒドロキシル基を含む一種類以上のポリオール、またはそのようなアルコールとポリオールとの混合物とのエステル、２個から約１２個の炭素原子の一種類以上のジカルボン酸（例えばフタル酸）と１個から２２個の炭素原子の一種類以上のアルコール（例えばブチルアルコール、ヘキシルアルコール）とのエステル、安息香酸と約６個から約２２個の炭素原子の直鎖および／または分岐アルコールとのエステル、またはそれらの二種類以上の混合物を含んでもよい。

【００８９】

液体は、約６個から約２２個の炭素原子の一種類以上の分岐第一アルコール、約６個から約２２個の炭素原子の一種類以上の直鎖および／または分岐脂肪族アルコール炭酸エステル、約６個から約２２個の炭素原子の一種類以上の脂肪族アルコールから作られる一種類以上のゲルベ炭酸エステル、各アルキル基が１個から約１２個の炭素原子を含む一種類以上のジアルキル（例えばジエチルヘキシル）ナフタレート、アルキル基あたり約６個から約２２個の炭素原子を含む一種類以上の直鎖または分岐、対称または非対称ジアルキルエーテル、約６個から約２２個の炭素原子のエポキシ化された脂肪酸エステルと、２個から１０個の炭素原子および２個から６個のヒドロキシル基を含むポリオールとの一種類以上の開環生成物、またはそれらの二種類以上の混合物を含んでもよい。

【００９０】

水は、任意の簡便な供給源から採取してもよい。水は、浸透法または蒸留法を用いて脱イオンまたは精製してもよい。

【００９１】

マイクロボディ形成材料は、任意のマイクロボディ形成材料を含んでもよい。マイクロボディ形成材料は、液体または固体メルトの形であってもよい。マイクロボディ形成材料は、ガラス、例えば、ガラスマイクロボディ（例えばマイクロスフェア）形成材料、重合体、例えば、重合体マイクロボディ（例えば重合体マイクロスフェア）形成材料を含んでもよい。重合体マイクロボディ形成材料は、一種類以上のアクリル樹脂、シリコン樹脂、ウレタン樹脂、酢酸ビニル樹脂、テフロン（登録商標）樹脂、ポリアミド樹脂、塩化ビニル樹脂、スチレン系樹脂、フェノール樹脂、エポキシ樹脂、スチレン－ブタジエン－スチレンブロック共重合体樹脂、スチレン－エチレン－ブチレン－スチレンブロック共重合体樹脂、スチレン－イソプレン－スチレンブロック共重合体樹脂、ｎ－ブチルゴム、クロロプレンゴム、天然ゴムまたはそれらの二種類以上の組み合わせを含んでもよい。一実施態様では、重合体マイクロボディ形成材料は、１個から約１４個の炭素原子のアルコールの（メタ）アクリル酸エステルを含んでもよい。一実施態様では、重合体マイクロボディ形成材料は、少なくとも一種類の（メタ）アクリル酸アルキルを含んでもよい。

【００９２】

本発明の一つ以上の実施態様では、乳化剤および／または界面活性剤は必要ないが、本発明のプロセスによって調製される多相混合物を形成する際に一つ以上の乳化剤および／または界面活性剤を用いてもよい。乳化剤および／または界面活性剤は、液体と予め混合してもよい。乳化剤および／または界面活性剤は、グリフィン（Ｇｒｉｆｆｉｎ）のシステムで０から約１８、一実施態様では約０．０１から約１８の範囲の親水性親油性バランス（ＨＬＢ）を有するイオン性または非イオン性化合物を含んでもよい。イオン化合物は、カチオン性または両性化合物のことがある。例は、「マッカチオンズ界面活性剤および洗剤（ＭｃＣｕｔｃｈｅｏｎｓ Ｓｕｒｆａｃｔａｎｔｓ ａｎｄ Ｄｅｔｅｒｇｅｎｔｓ）」、１９９８年版、北米版および国際版に開示されているものを含む。北米版の１～２３５頁および国際版の１～１９９頁は、そのような乳化剤の開示に関する部分が参照によって本明細書に組み込まれる。用いることができる乳化剤および／または界面活性剤は

、アルキレンオキシド繰り返し単位、カルボキシル化アルコールエトキシレート類、エトキシ化アルコール類、エトキシ化アルキルフェノール類、エトキシ化アミン類およびアミド類、エトキシ化脂肪酸、エトキシ化脂肪酸エステルおよびオイル、脂肪酸エステル、脂肪酸アミド、グリセロールエステル、グリコールエステル、ソルビタンエステル、イミダゾリン誘導体、レシチンおよび誘導体、リグニンおよび誘導体、モノグリセリドおよび誘導体、オレフィンスルホン酸エステル、リン酸エステルおよび誘導体、プロポキシル化およびエトキシル化脂肪酸またはアルコール類またはアルキルフェノール類、ソルビタン誘導体、ショ糖エステルおよび誘導体、硫酸エステルまたはアルコール類またはエトキシル化アルコール類または脂肪酸エステル類、ドデシルベンゼン類およびトリデシルベンゼン類または縮合ナフタレンまたは石油のスルホン酸エステル、スルホコハク酸エステルおよび誘導体、トリデシルベンゼンおよびドデシルベンゼンスルホン酸を含む。乳化剤および／または界面活性剤は、一種類以上のポリアルキレングリコール類、グリセロールまたはソルビタンと、約１２個から約２２個の炭素原子を含む脂肪酸との一種類以上の部分エステル、またはそれらの混合物を含んでもよい。乳化剤および／または界面活性剤は、レシチンなどの薬学上許容される材料を含んでもよい。本発明のプロセスによって作られる多相混合物の中のこれらの乳化剤および／または界面活性剤の濃度は、多相混合物の最大約２０重量％、一実施態様では約０．０１から約５重量％の範囲、一実施態様では約０．０１から約２重量％の範囲にあるとよい。一実施態様では、この濃度は、最大約２重量％、一実施態様では最大約１重量％、一実施態様では最大約０．５重量％であるとよい。

【００９３】

一実施態様では、第一の流体流は液体流を含み、第二の流体流は空気を含む。

【００９４】

一実施態様では、第一の流体流は液体廃棄流を含み、第二の流体流は空気を含む。

【００９５】

一実施態様では、第一の流体流は有害液体廃棄流を含み、第二の流体流は空気を含む。

【００９６】

一実施態様では、第一の流体流はサラダドレッシングまたはマスタードを含み、第二の流体流は窒素を含む。

【００９７】

一実施態様では、第一の流体流は液体飲料またはビールを含み、第二の流体流は二酸化炭素を含む。

【００９８】

一実施態様では、第一の流体流は紙の製造に用いられる漂白パルプを含み、第二の流体流は塩素を含む。

【００９９】

一実施態様では、第一の流体流は水の中の石炭の分散を含み、第二の流体流は空気を含む。

【０１００】

一実施態様では、第一の流体流は随伴水を含むモーター油を含み、第二の流体流は窒素を含む。

【０１０１】

一実施態様では、第一の流体流は培養反応用の細胞を含み、第二の流体流は酸素または空気を含む。

【０１０２】

一実施態様では、第一の流体流は液体反応媒質を含み、第二の流体流は空気または酸素を含む。

【０１０３】

一実施態様では、第一の流体流は水素化反応を実行するための反応媒質を含み、第二の流体流は水素を含む。

【０１０４】

一実施態様では、第一の流体流はオイルと水との混合物を含み、第二の流体流は空気または天然ガスを含む。

【０１０５】

一実施態様では、第一の流体流は紙の製造に用いられる漂白パルプを含み、第二の流体流は酸素を含む。

【０１０６】

一実施態様では、第一の流体流は食用油、ワインまたはジュースを含み、第二の流体流は窒素を含む。

【０１０７】

一実施態様では、第一の流体流は魚の養殖に用いられる水を含み、第二の流体流は酸素を含む。

【０１０８】

一実施態様では、第一の流体流は水を含み、第二の流体流はオゾンを含む。

【０１０９】

一実施態様では、第一の流体流は廃液流またはプロセス流を含み、第二の流体流は二酸化炭素またはアンモニアを含む。

【０１１０】

一実施態様では、第一の流体流は空気を含み、第二の流体流は水蒸気を含む。

【０１１１】

一実施態様では、第一の流体流は揮発性有機化合物を含む廃液流またはプロセス流を含み、第二の流体流は空気を含む。

【０１１２】

一実施態様では、第一の流体流は気体または液体を含み、第二の流体流はマイクロボディ形成材料を含む。

【０１１３】

一実施態様では、第一の流体流は水系組成物を含み、第二の流体流は水素および／または酸素を含む。これは、過酸化水素生成のための直接組み合わせのために用いてもよい。

【０１１４】

一実施態様では、第一の流体流は２‐アルキルアントラキノンを含み、第二の流は水素を含む。これは、過酸化水素の生成に用いてもよい。

【０１１５】

第一の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、約０．１から約８０重量％、一実施態様では約１から約５０重量％、一実施態様では約１から約２０重量％の範囲の濃度で存在するとよい。第二の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、約１から約９５重量％、一実施態様では約１０から約５０重量％、一実施態様では約１０から約２５重量％の範囲の濃度で存在するとよい。第三の流体流材料は、本発明のプロセスによって作られる多相混合物の中に、最大約０．０１％から約５０重量％、一実施態様では約１から約１５重量％、一実施態様では約０．１から約１重量％の範囲の濃度で存在するとよい。

【０１１６】

一実施態様では、第二の流体は第一の流体の中に溶解してもよい。これは、プロセスマイクロチャネルの中で起こってもよく、あるいは多相混合物がプロセスマイクロチャネルから出た後で起こってもよい。一実施態様では、第二の流体は、第一の流体と混合された後、最大約１０時間後の期間内に、一実施態様では最大約１時間の期間内に第一の流体の中に溶解するとよい。

【０１１７】

本発明の多相混合物は、一種類以上の固体粒子を含んでもよい。これらは、第一、第二および／または第三の液体と予め混合してもよい。固体粒子は、有機物、無機物またはそれらの組み合わせであってもよい。固体粒子は、触媒（例えば、CeO_2／$BaAl_{12}O_{19}$、Pt／Al_2O_3等などの燃焼触媒、重合触媒および類似物）、顔料（例えば、

TiO_2、カーボンブラック、酸化鉄等）、充填材（例えば、雲母、シリカ、滑石、硫酸バリウム、ポリエチレン類、ポリテトラフルオロエチレン、ナイロン粉、メタクリル酸メチル粉末）等を含んでもよい。固体粒子は、ナノサイズの粒子を含んでもよい。固体粒子は、約０．００１から約１０ミクロン、一実施態様では約０．０１から約１ミクロンの範囲の平均粒子直径を有するとよい。多相混合物の中の固体粒子の濃度は、多相混合物の重量を基準として最大約７０重量％、一実施態様では約０．１から約３０重量％の範囲にあるとよい。

【０１１８】

一実施態様では、本発明のプロセスによって作られる多相混合物は、連続相の中に分散した不連続相を含む。不連続相は、最大約２００ミクロン、一実施態様では約０．０１から約２００ミクロン、一実施態様では約０．０１から約１００ミクロン、一実施態様では約０．０１から約５０ミクロン、一実施態様では約０．０１から約２５ミクロン、一実施態様では約０．０１から約１０ミクロン、一実施態様では約０．０１から約５ミクロン、一実施態様では約０．０１から約２ミクロン、一実施態様では約０．０１から約１ミクロン、一実施態様では約０．０１から約０．５ミクロン、一実施態様では約０．０１から約０．２ミクロン、一実施態様では約０．０１から約０．１ミクロン、一実施態様では約０．０１から約０．０８ミクロン、一実施態様では約０．０１から約０．０５ミクロン、一実施態様では約０．０１から約０．０３ミクロンの範囲の体積基準平均寸法（例えば直径、高さ、幅、長さ）を有する泡またはマイクロボディを含むとよい。本発明のプロセスの一利点は、少なくとも一実施態様で、泡またはマイクロボディが比較的狭い平均直径（または高さ、幅または長さ）の分布を有することを特徴とする点である。

【０１１９】

「相対スパン」は、多くの場合「スパン」と呼ばれる。相対スパンは、体積分布から計算される無次元パラメータである。体積メジアン泡またはマイクロボディサイズ（ＶＭＤ）の場合と同じく、Ｄ［ｖ，０．１］およびＤ［ｖ，０．９］は、分散した泡またはマイクロボディの体積のそれぞれ１０％および９０％がそれより小さな直径の泡またはマイクロボディの中にある点を表す直径（または高さ、幅または長さ）である。スパンは、Ｄ［ｖ，０．９］からＤ［ｖ，０．１］を引いた後、ＶＭＤ（Ｄ［ｖ，０．５］）で除した商と定義してもよい。一実施態様では、本発明のプロセスによって作られる多相混合物の中の泡またはマイクロボディのスパンは、約１．３から約５、一実施態様では約１．８から約２．５の範囲にあるとよい。一実施態様では、本発明のプロセスは、単一のプロセスマイクロチャネルの中で実行され、スパンは約１．３から約２．５の範囲にあるとよい。一実施態様では、本発明のプロセスは複数のプロセスマイクロチャネルを使用するスケールアップされた多相混合プロセスの中で実行され、スパンは約１．３から約５の範囲にあるとよい。

【０１２０】

一実施態様では、本発明のプロセスによって作られる多相混合物の中の泡またはマイクロボディの体積基準の平均直径（または高さ、幅または長さ）は、約０．１から約１００ミクロンの範囲にあるとよく、スパンは、約１から約２５の範囲にあるとよい。一実施態様では、体積基準の平均直径（または高さ、幅または長さ）は、約１から約１０ミクロンの範囲にあるとよく、スパンは、約１．８から約２．５の範囲にあるとよい。

【０１２１】

一実施態様では、気泡が形成され、気泡は最大約２５ミクロンの範囲の体積基準の平均直径と、約１．９から約２．５の範囲のスパンとを有する。

【０１２２】

一実施態様では、マイクロボディが形成され、マイクロボディは最大約５ミクロンの範囲の体積基準の平均直径（または高さ、幅または長さ）と、約１．８から約２．５の範囲のスパンとを有する。

【０１２３】

本発明のプロセスによって形成されるマイクロボディは、多数の用途を有する。これら

は、密度を減らすキャストファイリング用のガラスミクロスフェア、流動床反応装置の中の選択化学種固定化用のガラスミクロスフェア、および類似物を含む。その他の例は、免疫試験および処理のために用いられるミクロスフェア重合体、ゲルまたはコロイド懸濁系発生を含む。マイクロボディ（例えばマイクロスフェア）は、第二のプロセスで処理して凝集体、触媒流動床または充填床、ドラッグデリバリシステム（例えば蛋白質酵素反応）、および最新の分離および流動床用途（例えば、磁気振動によって有利に分離または励起することができる被覆磁気担体）を含むいくつかの用途のためのカプセル化された固体を形成してもよい。

【０１２４】

少なくとも一つの実施態様では、本発明のプロセスの一利点は、プロセスが実験室用であろうと、パイロットプラント規模用であろうと、または実生産規模用であろうと、プロセスマイクロチャネル、第二の流体流チャネル、オプションとして、第三の流体流チャネル、および／または熱交換チャネルの間のギャップ距離が同じであってよいことである。その結果、マイクロチャネルミキサが実験室またはパイロットプラント規模で、または実生産規模のプラントユニットとして構築されても、本発明のプロセスで用いられるマイクロチャネルミキサによって製造される多相混合物の粒子サイズ分布は、実質的に同じにすることができる。

【０１２５】

液体制御素子（離散形）に対する速度ｕの方向のせん断力は、式　$F_X = mu * du / dy$　によって計算することができる。ここで、ｍｕは粘度、ｄｕ／ｄｙは開口区間に垂直な液体の流れの速度勾配である。しかし、液体の位置（制御素子によって表される）の場合と同じく、速度は、一般に、三つの成分を有し、せん断力も三つの成分を有する。表面近くおよび表面上のチャネルの流れの場合、一次元の仮定を置くことができ、F_Xによって素子表面での液体の正味のせん断力を近似できる。ＦｌｕｅｎｔまたはＦＥＭＬＡＢなどの市販のソフトウェアパッケージを含む計算機流体力学を用いて、必要な輸送方程式を解き、その結果、表面せん断力を計算することができる。チャネル長さ方向の流れの方向に平行な表面せん断力を計算することができる。平行なチャネルの間のせん断力も、計算することができ、流れ分布効果を取り込んでそれぞれの平行なチャネル中への物質流束を詳細なチャネルおよびマニホルドの幾何形状の関数として決定する。例えば、「流体力学の基礎（Ｆｕｎｄａｍｅｎｔａｌｓ　ｏｆ　Ｆｌｕｉｄ　Ｍｅｃｈａｎｉｃｓ）」、第３版、ビー・アール・マンソン（Ｂ．Ｒ．Ｍｕｎｓｏｎ）、ディー・エフ・ヤング（Ｄ．Ｆ．Ｙｏｕｎｇ）およびティー・エイチ・オキイシ（Ｔ．Ｈ．Ｏｋｉｉｓｈｉ）、ジョン・ワイリー・アンド・サンズ社（Ｊｏｈｎ　Ｗｉｌｅｙ　＆　Ｓｏｎｓ，Ｉｎｃ）、ヴァインハイム（Ｗｅｉｎｈｅｉｍ）、１９９８年、にさらに詳しい計算方法がある。

【０１２６】

一実施態様では、単一のプロセスマイクロチャネルを使用するプロセスのせん断力偏差因子（ＳＦＤＦ）は、複数のプロセスマイクロチャネルを含むスケールアップされたプロセスのＳＦＤＦの約５０％の範囲内にすることができる。ＳＦＤＦは、式

$SFDF = (F_{max} - F_{min}) / (2F_{mean})$

を用いて計算することができる。ここで、F_{max}は、特定の液体に対するプロセスマイクロチャネルの中の最大せん断力、F_{min}は同じ液体に対するプロセスマイクロチャネルの中の最小せん断力、F_{mean}はプロセスマイクロチャネル内の開口区間（２４０、２４０ａ、３１１、３２１、３３１、３４１、４１５、４２５、４３５、４４５、５５０、５６０、５７０、５８０）の表面における同じ液体に対する算術平均せん断力である。本発明のプロセスによって動作する単一のプロセスマイクロチャネル内では、ＳＦＤＦは約２より小さく、一実施態様では約１より小さく、一実施態様では約０．５より小さく、一実施態様では約０．２より小さいとよい。

【０１２７】

一実施態様では、本発明のプロセスは、複数のプロセスマイクロチャネルを使用しながら、比較的一様なせん断力を提供することができる。複数のプロセスマイクロチャネルの

間のせん断力一様性を測定するためには、各チャネルの平均せん断力を計算し、比較する。F_{max}は平均チャネルせん断力の最大値であり、F_{min}は平均せん断力の最小値である。F_{mean}は、すべてのチャネルの平均せん断力の平均値である。ＳＦＤＦは、これらの値から計算することができる。複数のプロセスマイクロチャネルの間で、本発明のプロセスの少なくとも一つの実施態様では、ＳＦＤＦは約２より小さく、一実施態様では約１より小さく、一実施態様では約０．５より小さく、一実施態様では約０．２より小さくすることができる。

【０１２８】

熱交換流体は、任意の流体を含んでもよい。これらは、空気、蒸気、液体の水、気体窒素、液体窒素、不活性気体を含むその他の気体、一酸化炭素、二酸化炭素、融解塩、鉱油などのオイル、気体炭化水素、液化炭化水素およびダウ・ユニオンカーバイド（Ｄｏｗ－Ｕｎｉｏｎ　Ｃａｒｂｉｄｅ）から入手できるダウサームＡ（Ｄｏｗｔｈｅｒｍ　Ａ）およびサーミノール（Ｔｈｅｒｍｉｎｏｌ）などの熱交換流体を含む。

【０１２９】

熱交換流体は、多相混合物を作るのに用いられる第一、第二および／または第三の流体を含んでもよい。これによって、プロセス予備加熱または予備冷却を提供し、プロセスの総合的な熱効率を高くすることができる。

【０１３０】

一実施態様では、熱交換チャネルは、吸熱または発熱プロセスが実行されるプロセスチャネルを含む。これらの熱交換プロセスチャネルは、マイクロチャネルであってもよい。熱交換チャネル中で実行することができる吸熱プロセスの例は、水蒸気改質および脱水素反応を含む。一実施態様では、吸熱源の増強を提供する同時吸熱反応の組み込みによって、通常、対流冷却熱流束よりほぼ一桁大きな熱流束が可能になる。熱交換チャネルの中で実行することができる発熱プロセスの例は、水性ガスシフト反応、メタノール合成反応およびアンモニア合成反応を含む。

【０１３１】

一実施態様では、熱交換流体は熱交換チャネルの中で相変化を行う。この相変化によって、対流加熱または冷却によって供給される熱の他に、プロセスマイクロチャネルまたは液体チャネルからの追加の加熱または除熱が提供される。蒸発する液体熱交換流体の場合、プロセスマイクロチャネルから移動するこの追加の熱は、その熱交換流体が必要とする蒸発潜熱から生じさせることが可能である。そのような相変化の例は、核沸騰するオイルまたは水である。一実施態様では、相変化流体の沸騰の蒸気質量分率品質は、最大約１００％、一実施態様では最大約７５％、一実施態様では最大約５０％にすることができる。

【０１３２】

相変化または化学反応による伝熱促進の使用は、多相混合物発生がプロセスチャネルの中の化学反応と協同して起ると、さらに有利なものにすることができる。一実施態様では、例えば、多相混合物は、重合反応用の反応性モノマーまたはその他の追加の熱交換を必要とするものであってもよい。

【０１３３】

マイクロチャネルミキサの中の対流加熱または冷却の熱流束は、マイクロチャネルミキサの中のプロセスマイクロチャネルの表面積の平方センチメートルあたり約０．０１から約１２５ワット（Ｗ／ｃｍ^2）、一実施態様では約０．１から約５０Ｗ／ｃｍ^2、一実施態様では約１から約２５ｃｍ^2、一実施態様では約１から約１０Ｗ／ｃｍ^{2}の範囲にあるとよい。加熱または冷却用の相の熱流束は、約１から約２５０Ｗ／ｃｍ^{2}の範囲、一実施態様では約１から約１００Ｗ／ｃｍ^2、一実施態様では約１から約５０Ｗ／ｃｍ^2、一実施態様では約１から約２５Ｗ／ｃｍ^2、一実施態様では約１から約１０Ｗ／ｃｍ^{2}であるとよい。

【０１３４】

熱交換チャネルを用いて、本発明のプロセスを用いる多相混合物の作製時に無菌状態を提供することができる。バッチミキサと異なって、本発明のプロセスは環境に対して閉じ

たものにすることができ、環境から切り離すために不活性気体で覆う必要がない。熱交換チャネルは、プロセスマイクロチャネルまたは液体チャネルに隣接するので、比較的短い熱輸送および拡散距離を提供して、マイクロチャネルミキサの中の液体を迅速に加熱および冷却して温度勾配を小さくすることができる。その結果、本発明のプロセスを用いると、長時間の加熱に適さないか、または大きな温度勾配の下では劣化する可能性のある多相混合物を調製することができる。一実施態様では、プロセスマイクロチャネルの中の同じ軸位置のプロセスマイクロチャネル壁とプロセスマイクロチャネルの内のバルクの流れとの間の温度勾配を、約５℃より小さく、一実施態様では約２℃より小さく、一実施態様では約１℃より小さくすることができる。

【０１３５】

制御された加熱および／または冷却を有するプロセスマイクロチャネルおよび／または第二または第三の流体流チャネルに密着する熱交換チャネルは、複数のプロセスマイクロチャネルの間に一様な温度プロフィルを提供することができる。これによって、混合タンクなどの従来の処理設備を用いて得ることができるよりも速い速度での一様な加熱および冷却が可能になる。多重チャネルマイクロチャネルミキサの中で、プロセス流れの長さに沿って少なくともいくつかの軸位置で、プロセスマイクロチャネルの間の温度差を約５℃より小さく、一実施態様では約２℃より小さく、一実施態様では約１℃より小さくすることができる。

【０１３６】

プロセスマイクロチャネルおよび／または第二または第三の流体流液体チャネルのどちらかに隣接する熱交換チャネルは、そのようなチャネルの長さに沿った温度区域を使用することができる。一実施態様では、プロセスマイクロチャネルへの入口に近い第一の区域の中の温度は、プロセスマイクロチャネルの終わりに近い第二の区域の中の第二の温度より高い温度に維持される。プロセスマイクロチャネルの中に冷却またはクエンチ区域を組み込んで多相混合物を急速に冷却し、安定化させてもよい。原料およびまたは多相混合物生成物を加熱および／または冷却するプロセスマイクロチャネルの中の混合区域の前および／または後ろの両方の区間の可能性を含めて、プロセスマイクロチャネルの長さに沿って最適な熱プロフィルを可能にする熱プロフィルの多数の組み合わせが可能である。

【０１３７】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）を通る流体の流速は、約０．０１から約５０１ｐｍ、一実施態様では約０．０１から約１０１ｐｍの範囲にあるとよい。プロセスマイクロチャネルを通って流れる流体の速度は、約０．１から約１００ｍ／ｓ、一実施態様では約０．１から約１０ｍ／ｓの範囲にあるとよい。プロセスマイクロチャネルを通って流れる流体のレイノルズ数は、約２５から約１０，０００、一実施態様では約２５０から約５０００の範囲にあるとよい。プロセスマイクロチャネルに入る流体の温度は、約１０℃から約５５０℃、一実施態様では約２５℃から約４００℃の範囲にあるとよい。プロセスマイクロチャネル内の絶対圧力は、約１から約２０気圧、一実施態様では約１から約５気圧の範囲にあるとよい。

【０１３８】

第二の流体流チャネル（２７０、２７０ａ、３５０、３６０、４２０、４３０、５３０、５４０）を通る第二の流体流および第三の流体流チャネル（４４０、４５０）を通る第三の流体流の流速は、約０．０１から約１０ｍｌ／ｓ、一実施態様では約０．１から約２ｍｌ／ｓの範囲にあるとよい。第二の流体流および第三の流体流の速度は、約０．１から約１００ｍ／ｓ、一実施態様では約０．１ｍ／ｓから約１０ｍ／ｓの範囲にあるとよい。第二の流体流および第三の流体流のレイノルズ数は、約５０から約５０００、一実施態様では約５０から約５００の範囲にあるとよい。第二の流体流チャネルに入る第二の流体流および第三の流体流チャネルに入る第三の流体流の温度は、約－１０℃から約６５０℃、一実施態様では約２５℃から約４５０℃の範囲にあるとよい。第二の流体流チャネルおよび第三の流体流チャネル内の絶対圧力は、約１から約２５気圧、一実施態様では約１から約５気圧の範囲にあるとよい。開口（２４４、２４４ａ、３１３、３２３、３３３、３４

３、４１６、４２６、４３６、４４６）を通って流れる流体の圧力降下は、約０．００５から約０．５気圧、一実施態様では約０．０５から約０．１気圧の範囲にあるとよい。

【０１３９】

本発明のプロセスによる気泡またはマイクロボディの形成の概略が図２１に示される。図２１を参照すると、気泡またはマイクロボディ６５０は、マイクロチャネル６５４の中の開口６５２から出現し、第一の流体流６５６の中に分散する。気泡またはマイクロボディは、開口６５２内の気体またはマイクロボディ形成材料基部６５８に付着している間、例えば、開口のサイズの約１０倍以上にサイズが成長してもよい。最終的には、気体またはマイクロボディ形成材料基部６５８の基部のせん断力によって泡またはマイクロボディは開口から分離され、泡またはマイクロボディは第一の流体流６５６の中に分散する。一実施態様では、比較的高い開口区間の圧力降下、または対応して、第二の流体流チャネルを通る高い第二の流体流の流速は、第一の流体流の中の第二の流体流の分散を実現するのに必要ないこともある。圧力降下が低いこと、または流速が低いことによって、開口区間を通って流れる第二の流体流のより慣性が低くなり、泡またはマイクロボディが開口から分離する前の泡またはマイクロボディ成長を減らすことがあるので、より小さな泡またはマイクロボディを生じさせることがある。

【０１４０】

プロセスマイクロチャネル（２１０、２１０ａ、３１０、３２０、３３０、３４０、４１０、５２０）から出る多相混合物は、約１０℃から約６００℃、一実施態様では約２５℃から約４５０℃の範囲の温度にあるとよい。

【０１４１】

熱交換チャネル（２９０、３７０、３８０、５９０）に入る熱交換流体は、約－４０℃から約３００℃、一実施態様では約２５℃から約１００℃の範囲の温度であるとよい。伝熱チャネルから出る熱交換流体は、約－３０℃から約５５０℃、一実施態様では約３０℃から約２００℃の範囲の温度を有するとよい。熱交換流体の圧力降下は、熱交換チャネルを通って流れるとき、約０．００５から約５気圧、一実施態様では約０．０５から約１気圧の範囲にあるとよい。熱交換チャネルを通って流れる熱交換流体流のレイノルズ数は、最大約１０，０００、一実施態様では最大約５０００、一実施態様では約１００から約５０００の範囲、一実施態様では約５００から約２０００の範囲にあるとよい。

【０１４２】

流体流は、マイクロチャネルミキサの中でまたはマイクロチャネルミキサに入る前にマイクロチャネルヒータまたはヒートパイプを含む任意の種類の伝熱デバイスを用いて予熱してもよい。一実施態様では、第一の流体流は、混合区域の上流のプロセスマイクロチャネルの非開口領域の中で予熱してもよい。マイクロチャネルミキサの中で作り出される多相混合物は、マイクロチャネルミキサの中で、またはマイクロチャネルミキサから出た後で、マイクロチャネル熱交換器を含む任意の種類の熱交換デバイスを用いて冷却してもよい。一実施態様では、多相混合物を安定化するために、または安定なままにしておくために、多相混合物をクエンチしてもよい。一実施態様では、多相混合物は、混合区域の下流のプロセスマイクロチャネルの非開口領域の中でクエンチしてもよい。一実施態様では、多相混合物は、室温に冷却してもよく、または約０．０１から約１００秒、一実施態様では約０．０１から約１０秒の範囲の時間内にクエンチしてもよい。

【０１４３】

本発明のプロセスを用いて、毎分少なくとも約０．０１リットル、一実施態様では毎分少なくとも約１リットルの速度で多相混合物を作ることができる。一実施態様では、本プロセスを用いて毎秒少なくとも約１０リットルの速度で多相混合物を作ることができる。

【０１４４】

一実施態様では、プロセスマイクロチャネルの中で、光学的または熱光学的特性を調節してもよい。これらの光学的または熱光学的特性を測定および／または調節するための技法の例は、平均液滴サイズおよびスパンを含む多相混合物品質管理および分析のためのインラインＬＳＤ（レーザ散乱回折）検出、製品粘度および固体含量を評価するための粘度

計、気泡またはマイクロスフェアサイズ測定のための写真を用いる光学測定、多相混合物の性質を調節することによる干渉計法を含むホログラフィー画像化および類似の方法を含む。

【実施例１】

【０１４５】

長方形の断面と、０．０４０×１．２５×３インチ（１．０２×３１．７５×７６．２ｍｍ）の内部寸法を有するアクリルのプロセスマイクロチャネルを含む多相混合装置が構築される。プロセスマイクロチャネルは、その側壁の一つの中に開口区間を有する。開口区間は、０．１ミクロンの名目開口または細孔サイズと、０．０１０×１×１．５インチ（０．２５４×２５．４×３８．１ｍｍ）の寸法とを有する。開口区間は、ステンレス鋼３１６Ｌで構築され、コネチカット州ファーミントン（Ｆａｒｍｉｎｇｔｏｎ，ＣＴ）のモット社（Ｍｏｔｔ　Ｃｏｒｐｏｒａｔｉｏｎ）によってカタログ番号１１１０－１２－１２－０１８－０１－Ａで供給される。開口区間は、開口区間を通ってプロセスマイクロチャネルの中に入る気体の流れを可能にするために、気体分配プレナムおよび配管に接続される。プロセスマイクロチャネルは、プロセスマイクロチャネルを通る液体の流れを可能にするために、配管に接続される。気体は、開口区間を通ってプロセスマイクロチャネルに流入し、プロセスマイクロチャネルを通って流れる液体と接触する。気体が開口区間の開口を通って流れるにつれ、プロセスマイクロチャネルの中で泡が形成される。プロセスは、空気を気体として、脱イオン水を液体として用いて実行される。空気の流速は毎分２から２０標準立方センチメートル（ＳＣＣＭ）との間で変化し、水の流速は毎分１０から８０ミリリットル（ｍｌ／分）との間で変化する。５から１５ミクロンの範囲にある直径を有する泡が形成される。

【実施例２】

【０１４６】

２ＳＣＣＭの気体流速と６０ｍｌ／分の液体流速とを用いて、実施例１に記載されたプロセスが実行される。

【実施例３】

【０１４７】

水素を気体として、１－ヘキセンを液体として用いて、実施例１に記載されたプロセスが実行される。

【実施例４】

【０１４８】

高速度の気体（１ＳＬＰＭより大きな流速）と液体（毎分０．１リットルより大きな流速）とが、プロセスマイクロチャネルの入口近くで混合されてから、表面構成要素領域を通って流れる。表面構成要素領域は、壁の片側の上に０．０１インチの深さと４５度の角度を有する構成要素を有する。表面構成要素内のバルク流路は、０．００６５インチである。平均直径が２５ミクロンより小さな一様な泡を有する発泡体が作り出される。流れの長さは１．５インチであり、チャネルの幅またはスパンは０．５インチである。プロセスマイクロチャネルは、室温および周囲圧力近くである。表面構成要素領域の上および全体に非常に小さな泡が観測される。

【実施例５】

【０１４９】

チャネルの中の層流から、チャネルの中の強い混合流れへの変化を誘起するマイクロチャネルの二つの側面への表面構成要素の追加を、Ｆｌｕｅｎｔ^{TM}を用いる計算機流体力学（ＣＦＤ）シミュレーションによって検討する。シミュレーションのために、流体の性質は一定と仮定し、密度５．０６７ｋｇ／ｍ^{3}、粘度３．６２ｅ$^{-5}$ｋｇ／ｍ・秒とした。境界条件として１２．１３ｍ／秒の一様な入口速度と、すべての壁で滑り流がないとした。３１５，１７４セルのグリッドサイズが用いられる。

【０１５０】

仮定された幾何構造は、４．０６ｍｍの幅、０．３１８ｍｍの高さおよび６３．５ｍｍ

の長さを有する連続チャネルの長方形の断面である。入口の０から３．５ｍｍ下流の区間と、出口の０から５．０ｍｍ上流の区間とは、混合用表面構成要素を含まない（簡単な長方形マイクロチャネル）。混合用表面構成要素（または溝）は、二つの対向する壁の中に切り込まれ、各構成要素は断面がほぼ長方形である。マイクロチャネルの中間区間（入口の３．５ｍｍから５８．５ｍｍ下流）は、混合用表面構成要素を含む。表面構成要素は、図２７および２８に示されるように、平均バルク層流の方向から６３°の角度でチャネル壁の一つに対角線状にまたがる。各表面構成要素は、深さ約０．２５ｍｍ、幅０．４８ｍｍ、長さ９ｍｍである。表面構成要素は、互いに平行に配置され、構成要素の間の間隔は０．４８ｍｍである。反対側の壁の上の表面構成要素は、第一の壁の上の表面構成要素と同じであり、チャネル中心線の周りに１８０°回転している（チャネル幾何構造は、入口面の中心点から出口面の中心点に延在する流れの軸の周りに対称である）。

【０１５１】

図２７は、ＣＦＤによってシミュレーションされた表面構成要素の幾何構造の平面図を示す。上部壁と下部壁との両方の混合用構成要素が重ね合わされている。図２８は、ＣＦＤによってシミュレーションされた、混合用構成要素を有するマイクロチャネルの等角投影図であり、チャネルに入る流れの方向を示す。図２９は、入口面の水平中心線（矢印の間に引かれている）に沿って開始される一般的な流れの経路線を示し、入口面から流れの軸を下に見ている。古典的な層流では、経路線は、入口面と出口面との間の直線を流れる（図２９に示される図では、古典的な層流の経路線は、矢印の間の中心線から逸脱しないと考えられる）。図３０で、入口面の水平中央線に沿って開始される流れの同じ経路線の側面図が示される（矢印は、流れの方向を示す）。図３０で、中心線からの流れ経路線の広がりと、表面構成要素の中の渦巻き運動とが、層流と比較すると改善された混合と、減少した熱および物質輸送抵抗を示す。図３１は、入口面の垂直中央線（矢印の間に引かれている）に沿って開始される流れの経路線を示し、入口面から流れの軸を下に見ている。図３１で、流れの渦巻き運動が、古典的な層流と比較すると改善された混合と、減少した熱および質量輸送抵抗を示唆する。

【０１５２】

ＣＦＤシミュレーションの結果によると、マイクロチャネルの中の層流と異なり、混合用表面構成要素は、連続チャネルの中の流れの経路線をねじれさせ、渦巻かせ、層流の場合に予想されるより速く壁に向かって押し広げる。計算された圧力降下は、５．２ｋＰａである。

【０１５３】

表面構成要素を含むマイクロチャネルに気体または第二の流体流を加えると、流れのパターンが作り出され、それによって、多相混合物は層流に近づき、泡は小さくなり、良く分散すると予測される。小さな泡とは、マイクロチャネルギャップの２５％より小さいと定義してもよい。

【０１５４】

特定の実施態様と関連させて本発明を説明してきたが、本明細書を読めば、これらの実施態様のさまざまな変更形は当業者にとって自明であると理解される。従って、本明細書に開示される本発明は、添付の請求項の範囲に属するものとしてそのような変更形を包含するものと理解される。

【図面の簡単な説明】

【０１５５】

【図１】本発明のプロセスで有用なものとすることができるマイクロチャネルの概略図である。

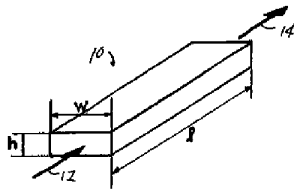
【図２】多相混合物を形成させるためにマイクロチャネルミキサが用いられる、特定の形の本発明のプロセスの例が示されるフローシートである。

【図３】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。第一の流体流がプロセスマイクロチャネルを通って流れ、隣接する第二の流体流チャネルからプロセスマイクロチャネルの中の開口区間を通ってプロセスマイクロチ

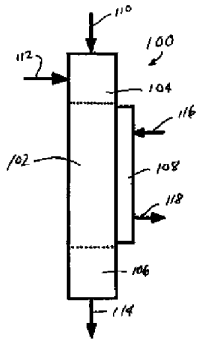
ャネルの中に流入する第二の流体流と混合される。
【図４】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図５】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図６】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図７】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図８】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図９】本発明のプロセスで用いられる多相混合物形成ユニットの例が示されるフローシートである。
【図１０】二重多相混合物の概略図である。
【図１１】本発明のプロセスに従って用いることができるマイクロチャネル空気吹き込みユニットの概略図である。
【図１２】図１１に例を示した空気吹き込みユニットの中で用いることができるマイクロチャネル多相混合物形成ユニットの概略図である。
【図１３】多孔質ステンレス鋼基板の熱処理される前のＳＥＭ画像である。
【図１４】図８に示した基板の熱処理された後のＳＥＭ画像である。
【図１５】本発明のプロセスで有用な専用の多孔質基板のＳＥＭ画像である。
【図１６】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な開口シートの平面図である。
【図１７】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な開口シートまたはプレートの平面図である。
【図１８】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な、比較的厚い開口シートまたはプレートの上にある比較的薄い開口シートの例示である。
【図１９】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間を作る際に有用な、比較的厚い開口シートまたはプレートの上にある比較的薄い開口シートの例が示される。
【図２０】本発明のプロセスで用いられるプロセスマイクロチャネルの開口区間の中で用いることができる開口の代替実施態様の例が示される。開口は、部分的に開口を満たし、開口の側壁の上にあるコーティングを有する。
【図２１】本発明のプロセスの動作の間の気泡またはマイクロボディの形成を示す概略図である。
【図２２】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２３】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２４】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２５】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２６】本発明のプロセスで用いられるマイクロチャネルの中に設けることができる表面構成要素の概略図である。
【図２７】実施例５で説明される計算機流体力学（ＣＦＤ）によってシミュレーションされた表面構成要素の幾何構造の平面図である。上部および下部壁の上の表面構成要素が見える。
【図２８】実施例５で説明されるＣＦＤによってシミュレーションされた表面構成要素を

有するマイクロチャネルの等角投影図である。
【図２９】入口面の水平中心線（矢印の間に引かれる）に沿って開始されるマイクロチャネルの中の流れの経路線の例が示される。実施例５で説明されるように、入口面から流れの軸を下に見ている。
【図３０】入口面の水平中心線に沿って開始されるマイクロチャネルの中の流れの経路線（矢印は流れの方向を示す）を示す。実施例５で説明されるように、側面から見ている。
【図３１】入口面の垂直中心線（矢印の間に引かれる）に沿って開始されるマイクロチャネルの中の流れの経路線を示す。実施例５で説明されるように、入口面から流れの軸を下に見ている。

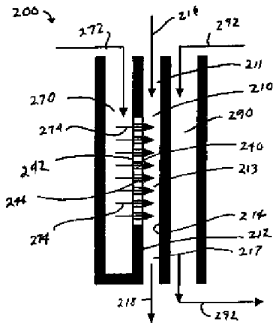
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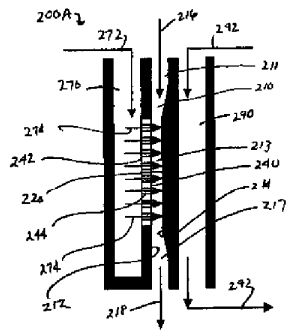
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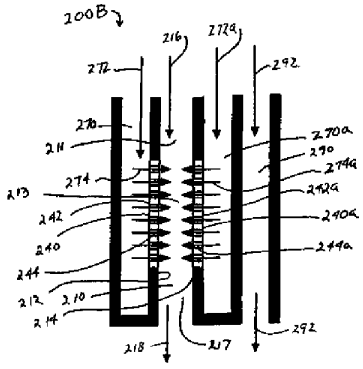
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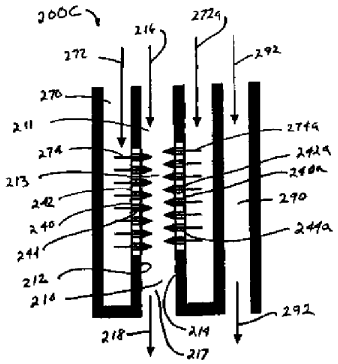
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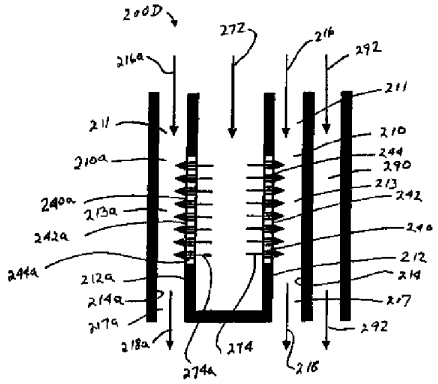
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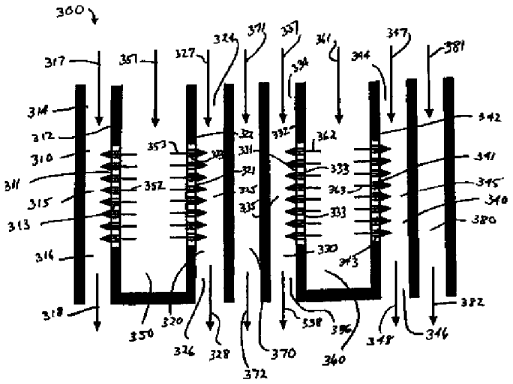
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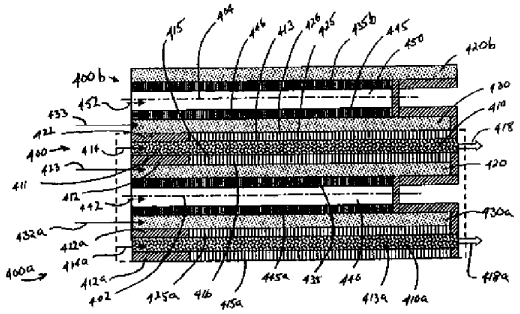
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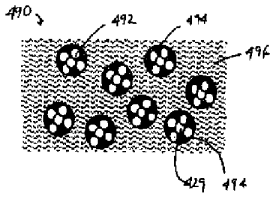
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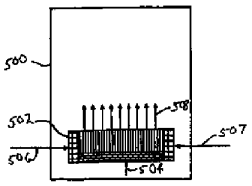
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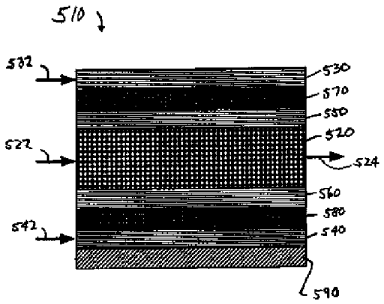
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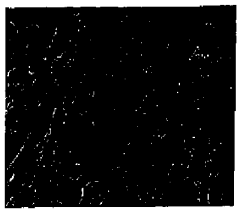
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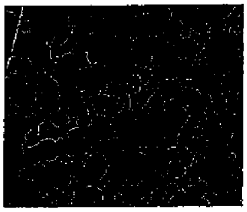
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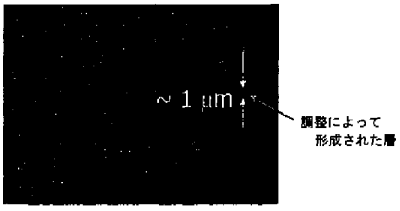
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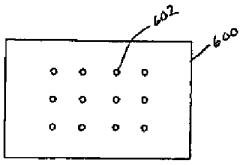
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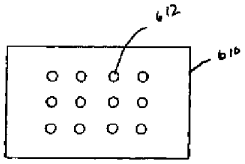
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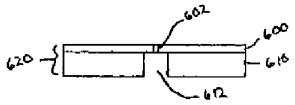
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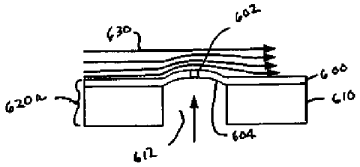
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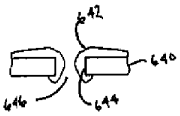
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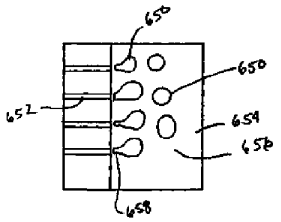
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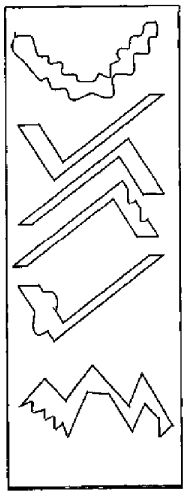
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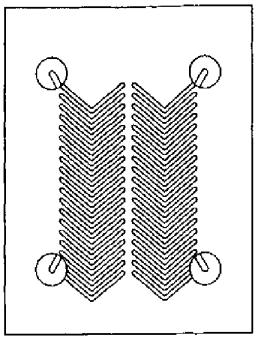
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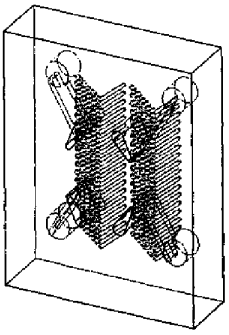
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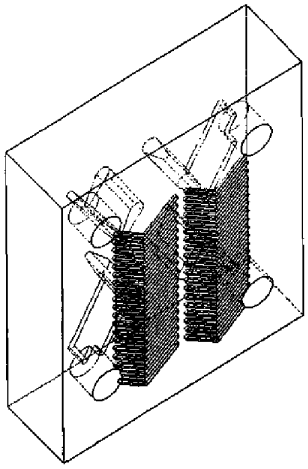
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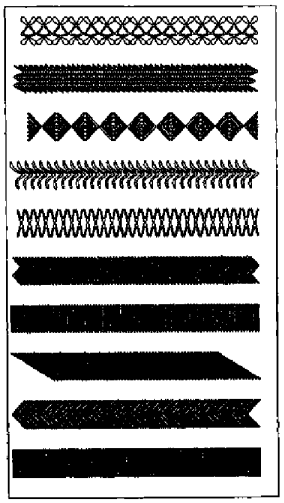
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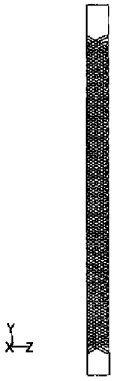
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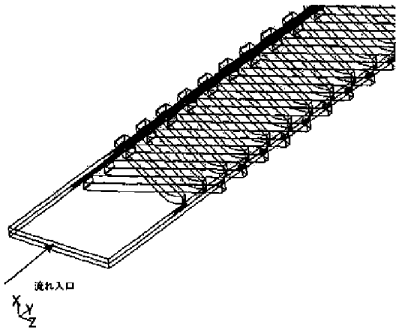
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【図２７】



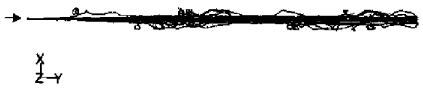
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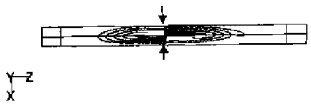
【図２９】



【図３０】



【図３１】



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(51)Int.Cl. F I
B01F 15/06 Z

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(56)参考文献 特開2003－210957（JP, A）
特開2003－1076（JP, A）
特表2000－509330（JP, A）

特開平１０－１４６５２３（ＪＰ，Ａ）

(58)調査した分野(Int.Cl.，ＤＢ名)
B01F3/04

Bibliographic data: DE10243129 (A1) — 2004-04-01

Multiple compartment blood collecting device for collecting blood from small animals such as dogs and cats comprises a cannula, blood receiving vessels and tubes connected to the rear end of the cannula

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Classification: **- international:** ***A61B5/155; A61D1/00;*** (IPC1-7): A61B5/15; A61J1/20

- cooperative: A61B5/15003 (EP); A61B5/150351 (EP); A61B5/150389 (EP); A61B5/150503 (EP); A61B5/15074 (EP); A61B5/154 (EP); A61D1/00 (EP)

Application number: DE20021043129 20020918

Priority number(s): DE20021043129 20020918

Abstract of DE10243129 (A1)

Multiple compartment blood collecting device comprises a cannula (1), blood receiving vessels (7, 8, 9), and tubes (2, 3, 4, 5, 6) connected to the rear end of the cannula with their branches connected to the blood receiving vessels. Preferred Features: Each blood receiving vessel is closed by a semi-permeable stopper (10) through which air can pass and the blood collected can not. The stopper are made from an air-permeable stopper body and a semi-permeable membrane formed on its inner side. Each branch of the tube has a hollow needle penetrating the stopper.

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DESCRIPTION DE10243129A1

[0001]

13 The invention relates to a multiple blood collection device for use in smaller animals such as cats, dogs and the like, or for similar applications where only limited amounts of blood are available, for example in small children.

[0002]

19 Multiple blood sampling, i.e. filling several tubes with blood, is required for various examination methods. For example, one tube of untreated blood is required for standard analyses. For blood count and cell tests as well as for HbA1 you need a collection tube coated with EDTA, for coagulation tests you need a tube that has been mixed with citrate, etc.

[0003]

26 Known multiple blood collection systems are designed for adult humans.

27 They consist of a cannula that is inserted into the vein once and then several blood collection tubes can be coupled to the cannula in order to be filled. In the case of animals, a simple cannula, open at the back, is usually used, to which the blood collection tubes, which are also open and to be filled, are simply held out until they are sufficiently filled.

[0004]

34 These known systems are not very suitable for smaller animals such as cats, for example, where only a limited amount of blood is available.

36 If the front leg of the cat is tied off to take blood, the blood accumulates and shoots out violently when a cannula is inserted due to the pressure that has built up. When using an open system,

blood is often splattered, which is then lost and can also occur when the tubes are changed blood are lost. In addition, the first tube fills up very quickly and possibly overflows, and there is then no longer enough blood for a second and possibly a third tube.

[0005]

44 The object of the invention is to create a multiple blood sampling device that is particularly suitable for applications where only a limited amount of blood is available.

[0006]

49 According to the invention, this object is achieved by the multiple blood sampling device specified in claim 1 .

51 Advantageous configurations of the invention are the subject matter of the dependent claims.

[0007]

55 The multiple blood collection device according to the invention embodies a closed or quasi-closed system which avoids the above-mentioned problems of the conventional systems which are unsuitable for the purposes under discussion here.

58 In the blood collection device according to the invention, a cannula is connected via a branching hose to a plurality of blood collection tubes, which are filled at the same time.

60 Even if blood rushes in heavily at the beginning, this is then distributed evenly over the connected tubes, so that the required number of tubes filled with sufficient blood is available without loss of blood.

[0008]

66 The device according to the invention can be realized in several versions, for example with two tubes or with three tubes, in order to take account of the cases in which only two tubes of blood or in which three tubes of blood are required.

69 It is also possible, for example with a device comprising three tubes, to take blood from only two tubes by pinching off the hose branch to the third tube.

[0009]

74 Further details and advantageous refinements of the invention are described in more detail below using an exemplary embodiment with reference to the attached drawing.

[0010]

79 The drawing shows a schematic representation of a multiple blood sampling device according to

the invention.

[0011]

84 The multiple blood sampling device according to the invention shown in the drawing has a cannula 1, which is shown only schematically.

86 Its rear end is connected to three blood collection vessels 7 , 8 , 9 via a hose 2 which branches at a junction 3 into three branch hoses 4 , 5 , 6 in the exemplary embodiment.

[0012]

91 The blood collection vessels 7 , 8 , 9 can each be closed by a semi-permeable stopper 10 .

92 Such plugs are known per se.

93 They are permeable to air, so if blood enters the tube, air can escape through the stopper, but they seal up on contact with liquid so that blood cannot escape.

95 Such plugs can also consist of an air-permeable plug body and a semi-permeable membrane formed on the inside thereof.

97 The ends of the branch hoses can be connected to hollow needles that are inserted into the respective stopper 10 .

99 Since such stoppers are also self-sealing, each blood withdrawal vessel can be removed from the hollow needle after it has been filled, with the stopper closing itself automatically.

[0013]

104 As an alternative to this, each blood collection vessel can also be provided with a cap which has an air outlet opening.

106 This can be closed, for example with a cap, or it can be designed as a small piece of tubing that can be closed with a clamp.

[0014]

111 During use, the three blood collection vessels fill evenly after the cannula has been inserted into the vein.

113 If, in individual cases, only two of the three blood collection vessels are to be filled, the branch hose of the third vessel can be pinched off with a clamp, or where caps with a closable ventilation opening are used for the blood collection vessels, the ventilation opening can be closed, with the result that vessel also no blood enters.

117 By closing the ventilation opening, the further inflow of blood can also be terminated when the desired filling quantity is reached in one vessel, while other vessels continue to be filled.

[0015]

122 It is also possible to design the branch in such a way that access to a blood collection vessel that is not required can be blocked there.

[0016]

127 For frequently occurring applications, for example for filling two vessels or for filling three vessels, versions of the device with branching of the tube 2 into only two vessels or, as in the exemplary embodiment, into three vessels can preferably be kept ready.

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CLAIMS DE10243129A1

1.

13 Multiple blood collection device, consisting of a cannula (1), at least two blood collection vessels (7 , 8 , 9), and a hose connection (2 , 3 , 4 , 5 , 6), the branches of which are each connected to one of the blood collection vessels (7 , 8 , 9).

16 Blood collection apparatus according to claim 1, wherein each blood collection vessel (7, 8, 9) is closed with a semi-permeable plug (10) which allows air to escape but blocks the escape of liquid and through which the respective branch of the tubing connection passes.

19 A blood collection device according to claim 2, wherein said semi-permeable plug consists of an air-permeable plug body and a semi-permeable membrane formed on the inside thereof

21 Blood collection device according to claim 2 or 3, wherein each branch of the hose connection has a hollow needle penetrating the stopper (10), and wherein the stopper is self-closing after the hollow needle has been withdrawn.

24 Blood collection device according to one of claims 1 to 4, wherein the hose connection has a branch piece (3) which is connected via a hose (2) to the cannula (1) and connected to three branch hoses (4, 5, 6) connected to the blood collection vessels .

27 A blood collection device according to claim 5, wherein the branch piece (3) has a mechanism for selectively shutting off one of the branch tubes.

2.

32 A sheet of drawings follows

(19) Bundesrepublik Deutschland
Deutsches Patent- und Markenamt

(10) **DE 102 43 129 A1** 2004.04.01

(12) # Offenlegungsschrift

(21) Aktenzeichen: **102 43 129.9**
(22) Anmeldetag: **18.09.2002**
(43) Offenlegungstag: **01.04.2004**

(51) Int Cl.[7]: **A61B 5/15**
A61J 1/20

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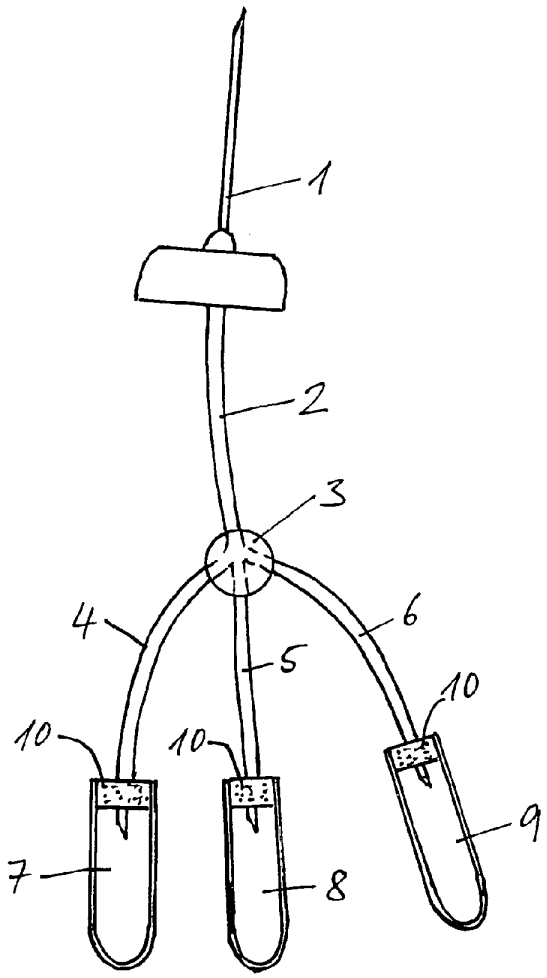
(56) Für die Beurteilung der Patentfähigkeit in Betracht zu ziehende Druckschriften:
DE 40 32 274 A1
US 58 82 318 A
US 55 07 299 A
WO 97/45 055 A1

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Rechercheantrag gemäß § 43 Abs. 1 Satz 1 PatG ist gestellt.

(54) Bezeichnung: **Mehrfachblutentnahmegerät für Kleintiere und ähnliche Anwendungen**

(57) Zusammenfassung: Mehrfachblutentnahmegerät mit einer Kanüle, die über eine sich verzweigende Schlauchverbindung (2, 3, 4, 5, 69 mit einer Mehrzahl von Blutentnahmegefäßen (7, 8, 9) verbunden ist.



Beschreibung

[0001] Die Erfindung betrifft ein Mehrfachblutentnahmegerät zur Verwendung bei kleineren Tieren wie Katzen, Hunden und dergleichen, oder auch für ähnliche Anwendungen, wo nur begrenzte Blutmengen zur Verfügung stehen, also zum Beispiel bei Kleinkindern.

Stand der Technik

[0002] Eine Mehrfachblutentnahme, das heißt das Füllen mehrerer Röhrchen mit Blut, ist bei verschiedenen Untersuchungsmethoden erforderlich. So benötigt man ein Röhrchen unbehandeltes Blut für Standardanalysen. Für Blutbild- und Zelluntersuchungen sowie für HbA1 benötigt man ein mit EDTA beschichtetes Entnahmeröhrchen, für Gerinnungsuntersuchungen benötigt man ein Röhrchen, das mit Zitrat versetzt ist, usw.

[0003] Bekannte Mehrfachblutentnahmesysteme sind für erwachsene Menschen ausgelegt. Sie bestehen aus einer Kanüle, die einmal in die Vene eingestochen wird, und dann können mehrere Blutentnahmeröhrchen nacheinander zum Füllen mit der Kanüle gekuppelt werden. Bei Tieren wird meist eine einfache, hinten offene Kanüle verwendet, an die einfach die ebenfalls offenen, zu füllenden Blutentnahmeröhrchen hingehalten werden, bis sie genügend gefüllt sind.

[0004] Bei kleineren Tieren wie beispielsweise Katzen, wo nur eine begrenzte Blutmenge zur Verfügung steht, sind diese bekannten Systeme wenig geeignet. Wird der Katze zur Blutentnahme der Vorderlauf abgebunden staut sich das Blut und schießt beim Einstechen einer Kanüle aufgrund des aufgebauten Drucks erst einmal heftig heraus, wobei bei Verwenden eines offenen Systems oftmals Blut verspritzt wird, das dann verloren ist, und auch beim Wechseln der Röhrchen kann Blut verloren gehen. Außerdem läuft dadurch das erste Röhrchen sehr schnell voll und womöglich über, und für ein zweites und eventuell ein drittes Röhrchen ist dann nicht mehr genügend Blut vorhanden.

Aufgabenstellung

[0005] Aufgabe der Erfindung ist es, ein Mehrfachblutentnahmegerät zu schaffen, das sich besonders bei Anwendungsfällen eignet, wo nur eine begrenzte Blutmenge zur Verfügung steht.

[0006] Diese Aufgabe wird gemäß der Erfindung durch das im Anspruch 1 angegebene Mehrfachblutentnahmegerät gelöst. Vorteilhafte Ausgestaltungen der Erfindung sind Gegenstand der Unteransprüche.

[0007] Das erfindungsgemäße Mehrfachblutentnahmegerät verkörpert ein geschlossenes oder quasi-geschlossenes System, das die oben erwähnten Probleme der herkömmlichen, für die hier in Rede stehenden Anwendungszwecke ungeeigneten Systeme vermeidet. Bei dem erfindungsgemäßen Blutentnahmegerät ist eine Kanüle über einen sich verzweigenden Schlauch mit einer Mehrzahl von Blutentnahmeröhrchen verbunden, die gleichzeitig befillt werden. Auch bei anfänglich stark hereinschießendem Blut verteilt sich dieses dann gleichmäßig auf die angeschlossenen Röhrchen, so daß ohne Verlust von entnommenem Blut ausreichend befiillte Röhrchen in der erforderlichen Anzahl zur Verfügung stehen.

[0008] Das erfindungsgemäße Gerät kann in mehreren Versionen, beispielsweise mit zwei Röhrchen oder mit drei Röhrchen realisiert werden, um den Fällen Rechnung zu tragen, in denen nur zwei Röhrchen Blut oder in denen drei Röhrchen Blut benötigt werden. Es ist auch möglich, beispielsweise mit einem drei Röhrchen umfassenden Gerät nur zwei Röhrchen Blut zu entnehmen, indem der Schlauchzweig zum dritten Röhrchen abgeklemmt wird.

[0009] Weitere Einzelheiten und vorteilhafte Ausgestaltungen der Erfindung werden nachstehend anhand eines Ausführungsbeispiels unter Bezugnahme auf die anliegende Zeichnung mehr im einzelnen beschrieben.

Ausführungsbeispiel

[0010] Die Zeichnung zeigt in schematischer Darstellung ein Mehrfachblutentnahmegerät nach der Erfindung.

[0011] Das in der Zeichnung dargestellte erfindungsgemäße Mehrfachblutentnahmegerät weist eine Kanüle **1** auf, die nur schematisch dargestellt ist. Ihr rückwärtiges Ende ist über einen Schlauch **2** der sich an einer Verzweigung **3** in beim Ausführungsbeispiel drei Zweigschläuche **4**, **5**, **6** verzweigt, mit drei Blutentnahmegefäßen **7**, **8**, **9** verbunden.

[0012] Die Blutentnahmegefäße **7**, **8**, **9** können jeweils durch einen halbdurchlässigen Stopfen **10** verschlossen sein. Solche Stopfen sind an sich bekannt. Sie sind luftdurchlässig, so daß beim Eintritt von Blut in das Röhrchen Luft durch den Stopfen entweichen kann, aber sie verschließen sich bei Kontakt mit Flüssigkeit, so daß kein Blut austreten kann. Solche Stopfen können auch aus einem luftdurchlässigen Stopfenkörper und einer an dessen Innenseite gebildeten halbdurchlässigen Membran bestehen. Die Enden der Zweigschläuche können dabei mit Hohlnadeln verbunden sein, die in den jeweiligen Stopfen **10** eingestochen sind. Da solche Stopfen auch selbstverschließend sind, kann jedes Blutentnahmegefäß nach dem Füllen von der Hohlnadel abgezogen werden, wobei der Stopfen sich selbsttätig verschließt.

[0013] Alternativ dazu kann jedes Blutentnahmegefäß auch mit einer Kappe versehen sein, die eine Luftaustrittsöffnung hat. Diese kann verschließbar sein, beispielsweise mit einem Hütchen, oder sie kann als kleines Schlauchstück ausgebildet sein, das mit einer Klemme verschließbar ist.

[0014] Im Gebrauch füllen sich die drei Blutentnahmegefäße nach dem Einstechen der Kanüle in die Vene gleichmäßig. Sollen im Einzelfall nur zwei von den drei Blutentnahmegefäßen befüllt werden, kann der Zweigschlauch des dritten Gefäßes mit einer Klemme abgequetscht werden, oder wo bei den Blutentnahmegefäßen Kappen mit verschließbarer Entlüfteöffnung verwendet werden, kann die Entlüfteöffnung geschlossen werden, mit der Folge, daß dann in dieses Gefäß ebenfalls kein Blut eintritt. Durch verschließen der Entlüfteöffnung kann auch bei Erreichen der gewünschten Füllmenge in einem Gefäß der weitere Blutzutritt beendet werden, während andere Gefäße noch weiter befüllt werden.

[0015] Es ist auch möglich, die Verzweigung so auszubilden, daß dort wahlweise der Zutritt zu einem nicht benötigten Blutentnahmegefäß gesperrt werden kann.

[0016] Für häufig auftretende Anwendungsfälle, beispielsweise zum Befüllen von zwei Gefäßen oder zum Befüllen von drei Gefäßen, können vorzugsweise Versionen des Geräts mit Verzweigung des Schlauchs **2** auf nur zwei Gefäße oder, wie beim Ausführungsbeispiel, auf drei Gefäße bereitgehalten werden.

Patentansprüche

1. Mehrfachblutentnahmegerät, bestehend aus einer Kanüle (**1**), mindestens zwei Blutentnahmegefäßen (**7**, **8**, **9**), und einer mit dem rückwärtigen Ende der Kanüle verbundenen und sich in eine der Anzahl der Blutentnahmegefäße entsprechenden Anzahl von Zweigen verzweigenden Schlauchverbindung (**2**, **3**, **4**, **5**, **6**), deren Zweige mit jeweils einem der Blutentnahmegefäße (**7**, **8**, **9**) verbunden sind.

2. Blutentnahmegerät nach Anspruch 1, wobei jedes Blutentnahmegefäß (**7**, **8**, **9**) mit einem halbdurchlässigen Stopfen (**10**) verschlossen ist, der Luft austreten läßt, aber den Austritt von Flüssigkeit sperrt und durch welchen der jeweilige Zweig der Schlauchverbindung hindurchverläuft.

3. Blutentnahmegerät nach Anspruch 2, wobei der halbdurchlässige Stopfen aus einem luftdurchlässigen Stopfenkörper und einer an dessen Innenseite gebildeten halbdurchlässigen Membran besteht

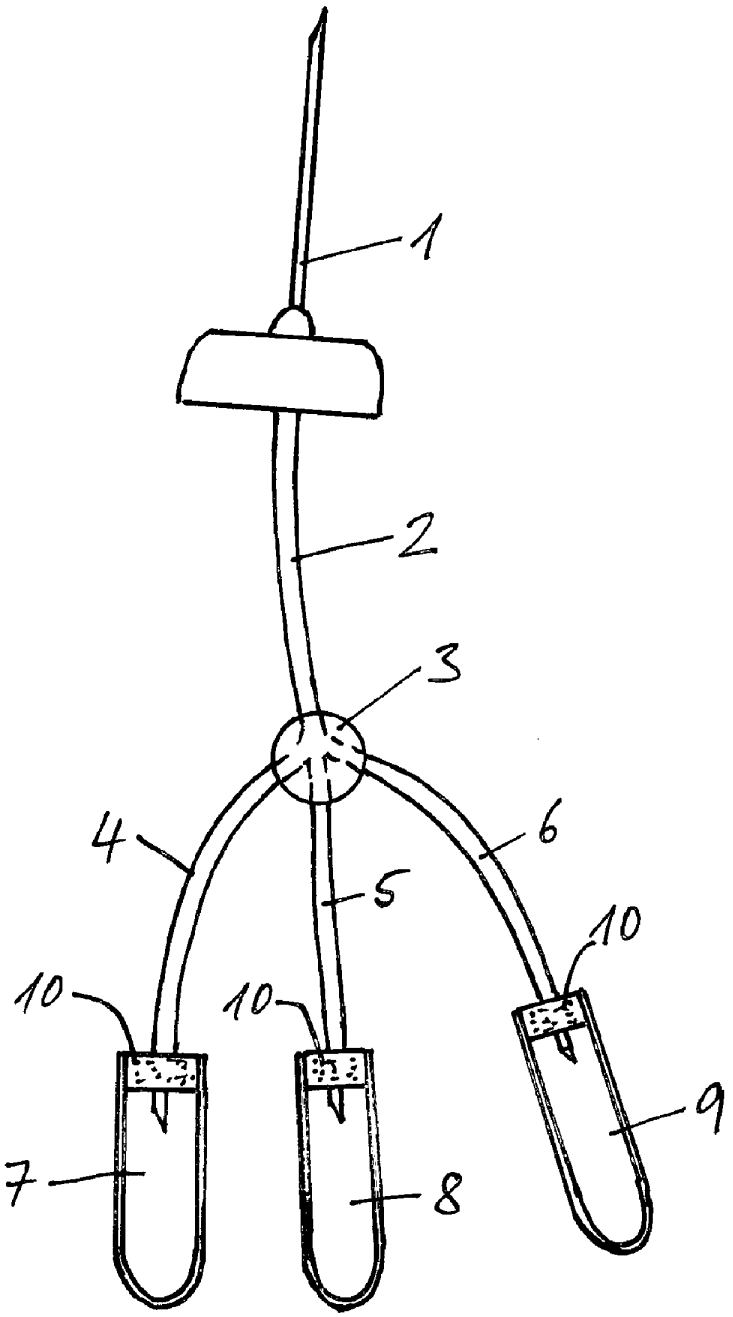
4. Blutentnahmegerät nach Anspruch 2 oder 3, wobei jeder Zweig der Schlauchverbindung eine den Stopfen (**10**) durchdringende Hohlnadel aufweist, und wobei der Stopfen nach Herausziehen der Hohlnadel selbstschließend ist.

5. Blutentnahmegerät nach einem der Ansprüche 1 bis 4, wobei die Schlauchverbindung ein Verzweigungsstück (**3**) aufweist, das über einen Schlauch (**2**) mit der Kanüle (**1**) verbunden und mit drei mit den Blutentnahmegefäßen verbundenen Zweigschläuchen (**4**, **5**, **6**) verbunden ist.

6. Blutentnahmegerät nach Anspruch 5, wobei das Verzweigungsstück (**3**) einen Mechanismus zum wahlweisen Absperren eines der Zweigschläuche aufweist.

Es folgt ein Blatt Zeichnungen

Anhängende Zeichnungen



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

(11) Veröffentlichungsnummer:
(11) Publication number: **EP 2 593 169 A0**
(11) Numéro de publication:

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

WO 2012/009459 (Art. 153(3) EPÜ).

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

WO 2012/009459 (Art. 153(3) EPC).

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

WO 2012/009459 (art. 153(3) CBE).

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 January 2012 (19.01.2012)

PCT

(10) International Publication Number
WO 2012/009459 A1

(51) International Patent Classification:
A61M 25/06 (2006.01) *A61B 5/153* (2006.01)

(21) International Application Number:
PCT/US2011/043892

(22) International Filing Date:
13 July 2011 (13.07.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/364,535 15 July 2010 (15.07.2010) US
13/181,265 12 July 2011 (12.07.2011) US

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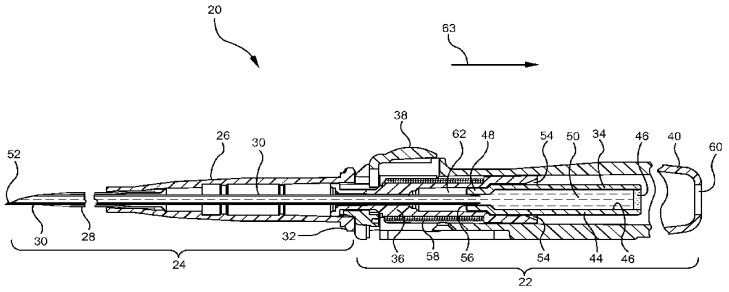
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: A REMOVABLE FLASH CHAMBER

FIG. 2



(57) **Abstract**: A needle hub (36) and catheter assembly are (20) disclosed herein. The needle hub includes an introducer needle (30) having a lumen extending therethrough. A needle hub is coupled to a proximal end of the introducer needle. A flash chamber (34) is removably coupled to the needle hub or the introducer needle. An interior of the flash chamber is in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub or the introducer needle. As such, the flash chamber can collect a sample of blood that can be accessed when the flash chamber is removed. In some instances, the blood can also be dispensed from the flash chamber into a test strip (70) or other testing device.

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A REMOVABLE FLASH CHAMBER

BACKGROUND

[0001] The present disclosure relates to venting air and blood sampling with vascular access devices. Blood sampling is a common health care procedure involving the withdrawal of at least a drop of blood from a patient. Blood samples are commonly taken from hospitalized, homecare, and emergency room patients either by finger stick, heel stick, or venipuncture. Once collected, blood samples are analyzed via one or more blood test levels.

[0002] Blood tests determine the physiological and biochemical states of the patient, such as disease, mineral content, drug effectiveness, and organ function. Blood tests may be performed in a laboratory, a distance away from the location of the patient, or performed at the point of care, near the location of the patient. One example of point of care blood testing is the routine testing of a patient's blood glucose levels. This involves the extraction of blood via a finger stick and the mechanical collection of blood into a diagnostic cartridge. Thereafter the diagnostic cartridge analyzes the blood sample and provides the clinician a reading of the patient's blood glucose level. Other devices are available which analyze blood gas electrolyte levels, lithium levels, ionized calcium levels. Furthermore, some point-of-care devices identify markers for acute coronary syndrome (ACS) and deep vein thrombosis/pulmonary embolism (DVT/PE).

[0003] Blood testing is frequently necessary prior to surgery or other medical procedures. For example, there are indications that diabetes contributes to an increase risk of Surgical Site Infection (SSI). Accordingly some guidelines suggest that diabetes is one characteristic that may influence the development of SSI. As such, preoperative blood glucose control is deemed a possible SSI risk reduction measure. Testing of creatine-based estimated glomerular filtration rate (GFR) can also be useful prior to some medical procedures. In February 2002, The National Kidney Foundation published that GFR is the best overall indicator of kidney function. The demonstration of normal kidney function may be important prior to a patient obtaining a contrast enhanced CT scan, which can have significant impact on the kidneys. Despite these needs, blood diagnosis is typically done at remote labs, which do not produce immediate results.

[0004] Furthermore, despite the rapid advancement in point of care testing and diagnostics, blood sampling techniques have remained relatively unchanged. Blood samples are frequently drawn using hypodermic needles or vacuum tubes coupled to a proximal end

of a needle or a catheter assembly. In some instances, clinicians collect blood from a catheter assembly using a needle and syringe that is inserted into the catheter to withdraw blood from a patient through the inserted catheter. These procedures utilize needles and vacuum tubes as intermediate devices from which the collected blood sample is typically withdrawn prior to testing. These processes are thus device intensive, utilizing multiple devices in the process of obtaining, preparing, and testing blood samples. Furthermore, each device required adds time and cost to the testing process. Accordingly, there is a need for more efficient blood sampling and testing devices and methods.

SUMMARY

[0005] The present invention has been developed in response to problems and needs in the art that have not yet been fully resolved by currently available blood sampling devices and methods. Thus, these devices and methods are developed to efficiently collect a blood sample from a flash chamber that is removably coupled to the proximal end of an introducer needle. Since blood is already collected in this chamber, the use of this blood can avoid the need for a separate blood sampling procedures and devices, which can decrease the cost and time of blood diagnosis. Once removed, blood can be dispensed from the flash chamber into a point-of-care diagnostic device, for prompt test results, which can enable time-sensitive health information, such as the risk of diabetes or impaired kidney function to be more quickly and easily acquired. Furthermore, the flash chamber can be sized to accommodate the desired blood sample. As such, the flash chamber can be enlarged, which increases the flashback visualization period.

[0006] In one aspect of the invention, a needle hub comprises: an introducer needle having a lumen extending therethrough; a needle hub coupled to a proximal end of the introducer needle; and a flash chamber removably coupled to the needle hub, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub.

[0007] Implementation may include one or more of the following features. A portion of the flash chamber can be compressible. The flash chamber can comprise: a chamber body defining an internal cavity; and an air permeable membrane coupled to the chamber body and in fluid communication with the internal cavity. The internal cavity of the chamber body of the flash chamber can have in an internal volume between about 0.1 mL to about 10 mL. The flash chamber can be press fit into the needle hub or introducer needle. The flash chamber can be screwed onto the needle hub. The flash chamber can be selectively coupled to the needle hub or the introducer needle via a keyed connection. The flash chamber can be

selectively coupled to the needle hub or the introducer needle via a breakable connection. The flash chamber can be a breakable ampoule.

[0008] In another aspect of the invention, a catheter assembly comprises: an introducer needle having a lumen extending therethrough; a needle hub coupled to a proximal end of the introducer needle; a flash chamber selectively coupled to the needle hub or the introducer needle, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub, the flash chamber having an air permeable membrane and a distal connector portion; the chamber body defining an internal cavity, the chamber body having at least a compressible portion that decreases the internal volume of the internal cavity when compressed; the air permeable membrane coupled to the chamber body and in fluid communication with the internal cavity; and the distal connector portion of the chamber body for selectively coupling to the needle hub.

[0009] Implementation may include one or more of the following features. At least a portion of the flash chamber can be compressible. The flash chamber can have an internal volume between about 0.1 mL to about 10 mL. The flash chamber can be press fit into the needle hub or introducer needle. The flash chamber can be screwed onto the needle hub. The flash chamber can be selectively coupled to the needle hub or the introducer needle via a breakable connection, the breakable connection including at least one scored line and a stress riser. The flash chamber is a breakable ampoule.

[0010] In another aspect of the invention, a method for providing a removable flash chamber of a catheter assembly, the method comprising: providing a catheter assembly having a needle hub, the needle hub having an introducer needle coupled thereto; providing an introducer needle coupled to the needle hub, the introducer needle having a lumen extending therethrough; and providing a flash chamber removably coupled to the needle hub, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub.

[0011] Implementation may include one or more of the following features. The method may further comprise providing at least a single compressible portion of the flash chamber for selectively ejecting blood within the flash chamber from therefrom. The method may further comprise providing an inner cavity within a body of the flash chamber having an internal volume about 0.1 mL to 10 mL. The flash chamber can have a distal connector portion, the distal connector portion having at least one of a press fit connector, screw threads, a keyed connection, and a breakable connection.

[0012] These and other features and advantages of the present invention may be incorporated into certain embodiments of the invention and will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter. The present invention does not require that all the advantageous features and all the advantages described herein be incorporated into every embodiment of the invention.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0013] In order that the manner in which the above-recited and other features and advantages of the invention are obtained will be readily understood, a more particular description of the invention briefly described above will be rendered by reference to specific embodiments thereof which are illustrated in the appended drawings. These drawings depict only typical embodiments of the invention and are not therefore to be considered to limit the scope of the invention.

[0014] Figure 1 illustrates a perspective view of a catheter assembly with a removable flash chamber, according to some embodiments.

[0015] Figure 2 illustrates a cross-section view of a catheter assembly of Figure 1 taken along line 2-2, according to some embodiments.

[0016] Figure 3 illustrates a cross-section view of a catheter assembly with a removable flash chamber after the introducer needle has been withdrawn from the catheter, according to some embodiments.

[0017] Figure 4 illustrates a perspective view of a catheter assembly with a removable flash chamber that has been removed therefrom, according to some embodiments.

[0018] Figure 5 illustrates a perspective view of a removable flash chamber dispensing a sample of blood on a blood test strip, according to some embodiments.

[0019] Figure 6 illustrates a cross-section view of a proximal portion of a catheter assembly with a removable flash chamber, according to some embodiments.

[0020] Figure 7 illustrates a cross-section view of a proximal portion of another catheter assembly with a removable flash chamber, according to some embodiments.

[0021] Figure 8 illustrates a perspective view of a keyed connection between a flash chamber and a needle hub or safety barrel, according to some embodiments.

[0022] Figure 9 illustrates a cross-section view of a removable flash chamber, according to some embodiments.

DETAILED DESCRIPTION OF THE INVENTION

[0023] Embodiments of the present invention can be understood by reference to the drawings, wherein like reference numbers indicate identical or functionally similar elements. It will be readily understood that the components of the present invention, as generally described and illustrated in the figures herein, could be arranged and designed in a wide variety of different configurations. Thus, the following more detailed description, as represented in the figures, is not intended to limit the scope of the invention as claimed, but is merely representative of presently preferred embodiments of the invention.

[0024] Reference will now be made to Figure 1, which illustrates a catheter assembly 20 that can be used to access the vascular system of a patient, such as the BD Insyte (TM) Autoguard (TM) from Beckton, Dickinson and Company, Inc. (as shown), the BD Protect IV (TM) also from Beckton, Dickinson and Company, Inc., and the Medikit Z5 from Medikit Company Inc. The catheter assembly 20 can include various other configurations. The catheter assembly 20 generally includes a catheter adapter 24 and a needle assembly 22. The catheter adapter 24 is inserted into a patient to establish fluid communication with the patient's vasculature, and may be used to infuse fluids therethrough. The needle assembly 22 includes an introducer needle 30 that is used to assist the catheter assembly 24 to be accurately placed into the vasculature of the patient. After the catheter assembly 24 is properly placed, the needle assembly 22 is removed and uncoupled from the catheter assembly 24.

[0025] The needle assembly 22 includes a generally rigid introducer needle 30 that provides structural support to the flexible or semi-flexible catheter 28 of the catheter assembly 24. In a pre-use position, the introducer needle 30 is inserted through the catheter 28, as shown. During infusion or other such procedures the introducer needle 30 and catheter 28 are inserted through the skin of a patient and advanced into the vasculature of a patient. Once the catheter 28 is properly placed, the introducer needle 30 is removed from the catheter 28.

[0026] As shown in Figure 1, the catheter adapter 24 includes a catheter hub 26 that is coupled to a catheter 28 that extends distally from the distal end of the catheter hub 26. The catheter hub 26 includes an inner lumen that extends therethrough and provides fluid communication to an inner lumen of the catheter 28. In some configurations, the catheter hub 26 also includes a proximal connector 32, such as a threaded luer connector, that can connect to a needle assembly 22 or other vascular access device.

[0027] The needle assembly 22 includes an introducer needle 30 that extends through the catheter assembly 20 in a pre-insertion state. The introducer needle 30 is coupled to a needle hub 36 at its proximal end. In some embodiments, as shown, the needle hub 36 is disposed within a safety barrel 40 that shields the introducer needle 30 after it is withdrawn from the patient and out of the catheter adapter 24. In the illustrated embodiment, the introducer needle 30 is withdrawn, via a spring force, from the catheter adapter 24 when a user presses a button 38 of the needle assembly 22. The button 38 releases a fastener that holds the introducer needle 30 in place, permitting it to be withdrawn proximally through the catheter 28 and catheter hub 26 into the safety barrel 40.

[0028] With continued reference to Figure 1, in some embodiments, a flash chamber (also known as "flashback chamber") 34 is coupled to the needle hub 36 or directly to the proximal end of the introducer needle 30. The flash chamber 34 can receive blood therein from the introducer needle 30. In some configurations, the flash chamber 34 is transparent or semi-transparent such that a user can view blood flowing into the flash chamber 34 from the introducer needle 30.

[0029] In some catheter placement procedures, flashback occurs when blood from within the vasculature of a patient enters into the catheter 28 and/or introducer needle 30 of the catheter assembly 20. In some instances, the catheter 28 is transparent or semi-transparent such that the clinician can recognize blood flowing through the catheter 28 after the introducer needle 30 has entered the patient's vascular. To provide an extended flashback period that may enable a clinician to verify that the catheter 28 has entered and remains properly placed. In some embodiments, the catheter hub 26 and/or the needle assembly 22 can include a flash chamber 34. A flash chamber 34 of the needle assembly 22 can be in fluid communication with the introducer needle 30 so that blood flowing through the introducer needle 30 enters into the flash chamber 34. The size of the flash chamber 34 can be varied so that the length of time required to fill the chamber provides the clinician adequate time to properly position the catheter 28. As mentioned, once the catheter 28 is properly placed, the introducer needle 30 can be withdrawn from the catheter 28.

[0030] After the needle assembly 22 is uncoupled from the catheter adapter 24, the sample of blood within the flash chamber 34 can be use for diagnosis. In some embodiments, the flash chamber 34 can be selectively uncoupled from the needle assembly 22 so that the blood therein can be accessed and tested. Thus, in some embodiments, there is a means for extracting the blood from the flash chamber 34. This means can include compressing at least a portion of the flash chamber 34 to dispense blood therefrom. This means can also include

breaking the flash chamber 34, sucking or wicking blood from the flash chamber 34, or otherwise removing the blood therefrom.

[0031] In some embodiments, the flash chamber 34 extends through a proximal opening 60 in the safety barrel 40 after the needle is withdrawn from the catheter adapter 24. Thus, the flash chamber 34 can be larger, with an increased internal volume, than it could be without a proximal opening 60. In some configurations, the flash chamber 34 has in an internal volume between about 0.1 mL to 10 mL. In other configurations, the flash chamber 34 has in an internal volume between about 0.5 mL to 7 mL. In other configurations, the flash chamber 34 has in an internal volume between about 1 mL to 3 mL. In other configurations, the flash chamber 34 has in an internal volume greater or less than the listed volumes. The larger internal volume of the flash chamber 34 can provide longer flashback indication periods. As such, a clinician can have more time to place and ensure proper placement of the catheter 28.

[0032] Reference will now be made to Figure 2, which depicts a cross section of the catheter assembly 20 of Figure 1 taken along line 2-2. This figure depicts at least some of the inner components of the catheter adapter 24 and needle assembly 22. For simplicity, the catheter hub 26 is depicted as having few features or components therein. However, it will be understood that the catheter hub 26 can include various known components and features, such as a valve, blood control valve, inner ridges, or other known elements.

[0033] As shown in Figure 2, in some embodiments, the needle assembly 22 includes a needle hub 36 coupled to an introducer needle 30, a spring 58, and a removable flash chamber 34. These components can be at least partially disposed within a safety barrel 40 that prevents blood and needle exposure after the introducer needle 30 is drawn into the safety barrel 40. A cross section of the button 38 and its related components shows how the button 38, when depressed, disengages the needle hub 36, which is then moved proximally 62 under the force of the spring 58. The spring 58 is positioned between the safety barrel 40 and the needle hub 36, so that when the button 38 is depressed it releases its mechanical energy, uncompresses, and forces the needle hub 36 proximally 62. In some instances, the spring 58 is a compression spring that stored energy when compressed. In some configurations, the flash chamber 34 is disposed on the proximal end of the needle hub 36, and the flash chamber 34 extends at least partially out of a proximal opening 60 in the safety barrel 40 as it moves to the proximal end of the safety barrel 40. The tip of the introducer needle 30 can be drawn into the safety barrel 40 as the needle hub 36 is forced proximally 63. This movement draws the introducer needle 30 and its tip into a shielded position, within the covering and the

containment of the safety barrel 40, which can serve as a shield between the introducer needle 30 and the clinician to prevent needle stick injuries and blood contamination.

[0034] In some instances, in the shielded position as shown in Figure 3, the introducer needle 30 is safely contained within the safety barrel 40 while the flash chamber 34 extends at least partly out of a proximal opening 60 of the safety barrel 40. In some embodiments, the proximal opening 60 is shaped and sized to conform quite closely to the outer geometry of the flash chamber 34 so as to minimize any spacing therebetween that might otherwise provide room for blood flow of blood within the safety barrel 40. In the shielded position, a proximal portion of the flash chamber 34 can be accessed by a clinician and selectively uncoupled from the needle hub 36. Depending on the type of coupling between the flash chamber 34 and the needle hub 36 or introducer needle 30, the clinician will pull and/or twist, or otherwise manipulate the flash chamber 34 to uncouple it from the needle hub 36. In some configurations, the flash chamber 34 is directly coupled to the needle hub 36 and the introducer needle 30, as shown in Figure 2. In some configurations, the flash chamber 34 is indirectly coupled to the needle hub 36 and directly coupled to the introducer needle 30, which is directly coupled to the needle hub 36. In other configurations, the flash chamber 34 is indirectly coupled to the needle 30 and directly coupled to the needle hub 36, which is directly coupled to the introducer needle 30, as shown in Figure 6.

[0035] Referring again to Figure 2, in some embodiments, the flash chamber 34 is removably or selectively coupled to the needle hub 36. This removable coupling can have various configurations, such as a press-fit coupling, a threaded screw-on coupling, a keyed connection, a breakable connection, and other various types of removable couplings. As shown, the flash chamber 34 is press fit within an inner bore 62 of the needle hub 36. Also shown, the introducer needle 30 is press fit within the flash chamber 34. In some embodiments, only one of these press-fit couplings is used, rather than both. In a press-fit coupling, the inner geometry of the inner bore 62 approximates and may be approximately equal to or slightly smaller than the outer geometry of the chamber body 44 of the flash chamber 34. Additionally or alternatively, the inner surface of the inner bore 62 can include one or more inward protrusions 54 that press against the outer surface of the chamber body 44 to provide pressure between these components. In other embodiments, the outer surface of the chamber body of the flash chamber 34 includes one or more outward protrusions that press against the inner surface of the inner bore 62 to provide pressure between these components.

[0036] In some embodiments, flash chamber 34 includes a distal connector portion 48 of the chamber body 44 for selectively coupling to the needle hub 36. As shown in Figure 2, this distal connector portion 48 includes the distal portion of the chamber body 44, which has an outer geometry that is press fit into the needle hub 36 and over the proximal end of the introducer needle 30. In other embodiments, the distal connector portion 48 includes a threaded member used to screw the flash chamber 34 into the needle hub 36. In some embodiments, the distal connector portion 48 includes a keyed connection that mates with a keyed portion of the needle hub 36, as shown in Figure 8. In some embodiments, the distal connector portion 48 includes a breakable connection having, for example, a scored line and/or a stress riser.

[0037] In some embodiments, the flash chamber 34 includes a membrane 46 that is air permeable, through which air from within the introducer needle 30 passes. In some embodiments, the membrane 46 is hydrophobic so that it does not permit blood to pass through it. In such embodiments, blood 50 entering the introducer needle 30 forces air out the membrane 46 as it enters the introducer needle 30 and fills the introducer needle 30 and the flash chamber 34 to the membrane 46. At this point, blood 50 ceases to flow into the introducer needle 30.

[0038] In some embodiments, the membrane 46 is both air permeable and hydrophobic, to permit air, but not blood 50 to pass therethrough. In other embodiments, the membrane 46 is hydrophilic. The membrane 46 can include various materials and components that provide these properties. For example, in some embodiments, the membrane 46 includes glass, polyethylene terephthalate (PET), a microfiber material, and/or other synthetic material made of high-density polyethylene fibers, such as TYVEK® material from DuPont. Other such materials and components can also be used as a layer of the membrane 46 or as the entire membrane 46 to enable the membrane 46 to be hydrophobic, hydrophilic, and/or air permeable, according to some configurations.

[0039] In some embodiments, the flash chamber 34 is configured to retain blood 50 as it is withdrawn from the needle hub 36 to prevent blood spills and blood contamination. Thus, in some configurations, a distal opening 56 of the flash chamber 34 is shaped and sized to retain blood 50. Blood retention within the internal cavity 66 is governed, at least in part, by the inner perimeter of the distal opening 56, the surface tension of blood 50, and the force on the blood 50 to flow out of the distal opening 56. Accordingly, the inner perimeter of the distal opening 56 can be designed so that blood 50 is retained within the internal cavity 66 when the

force of the blood 50 to flow out of the distal opening 56 is within a certain range, but permit at least some blood to flow out when the pressure on the blood 50 exceeds this range.

[0040] For example, in some embodiments, when the distal opening 56 is circular, an inner perimeter of less than or equal to approximately 2.0 mm, and a diameter of less than or equal to approximately 0.6 mm, permits the retention of blood 50 within the internal cavity 66 against approximately the force of gravity. When the force on the blood 50 is greater than the force of gravity some blood 50 can flow out of the distal opening 56. Similarly, a circular distal opening 56 with a diameter of about 0.3 mm may retain blood 50 therein against forces stronger than gravity, such as bumping, jarring, and movement of the filled flash chamber 34. When the distal opening 56 has a very small inner perimeter, the force required to expel blood 50 will be very large.

[0041] In some embodiments, the distal opening 56 has a inner perimeter greater than or equal to about 0.3 mm, which when the distal opening 56 is a circular opening, corresponds to a diameter of about 0.1 mm. Thus, in some configurations, the distal opening 56 has an inner perimeter between about 0.3 mm to about 2.0 mm. In some configurations, the distal opening 56 is approximately circular and has a diameter between about 0.1 mm to about 0.6 mm. In other embodiments, the distal lumen opening 58 is non-circular.

[0042] Reference will now be made to Figure 3, which depicts the needle assembly 22 in the shielded position, with the spring 58 released to a decompressed state, which has forced the needle hub 36 to the proximal end of the safety barrel 40 and the flash chamber 34 at least partially out of the proximal opening 60 of the safety barrel 40. The internal cavity 66 of the flash chamber 34 is filled at least partially with blood 50. In this shielded position, the proximal portion of the chamber body 44 can be gripped and selectively decoupled from the needle hub 36. In this manner, the blood 50 sample within the flash chamber 34 can be used for diagnosis.

[0043] As shown in Figure 4, flash chamber 34 is decoupled from the needle assembly 22. This flash chamber 34 can now be used as a storage vial of blood 50 as it is transported to a testing facility. Additionally, the blood 50 sample within the flash chamber 34 can be immediately used for point-of-care blood diagnostic testing.

[0044] Reference will now be made to Figure 5, which depicts the flash chamber 34 dispensing blood 50 onto a blood test strip 70. The test strip 70 can be used to test for glucose, creatine, cystatin C test, or other such test at the point of care, the location of the patient. Such diagnosis can provide rapid diagnostic results at the point of care, without the need to withdraw a blood 50 sample via a syringe, vacuum tube, or other traditional device.

In some instances, the blood 50 can be dispensed into a diagnostic test device that performs diagnostic testing on the blood. In other instances, the blood 50 can be dispensed from the flash chamber 34 into a sterile vial or tube, such as a in-vitro test tube that is taken to a medical laboratory for testing.

[0045] The chamber body 44 of the flash chamber 34 can have various embodiments that can facilitate the dispensing blood 50 from the flash chamber 34. In some embodiments, at least a portion of the chamber body 44 is compressible to at least a small degree. When compressed, such as in an inward direction 72, the internal volume of the internal cavity 66 of the flash chamber 34 decreases, increasing the internal pressure of the internal cavity 66, and dispensing a sample of blood 50 from the distal opening 56. In some embodiments, the flash chamber 34 is rigid or semi-rigid. In some embodiments, only a portion of the flash chamber 34 is compressible. The compressible portion can be located and designed so that it does not compress during normal removal of the flash chamber 34 from the needle hub 36. In other embodiments, the chamber body 44 of the flash chamber 34 is a breakable ampoule, which when broken, dispenses blood 50 therefrom. In some embodiments, the distal opening 56 of the flash chamber 34 is shaped and sized so that a clinician can wick blood 50 therefrom using a test strip 70 or other device.

[0046] Reference will now be made to Figure 6, which depicts another embodiment of a connection between the needle hub 36 and the flash chamber 34. As shown, in some embodiments, the needle hub 36 includes a valve 80 that can prevent blood 50 from spilling out of the proximal opening 60 of the inner bore 62 of the needle hub 36 when the flash chamber 34 is removed therefrom. In some configurations, the valve 80 is flexible and selectively opens upon insertion of the flash chamber 34 therein. In some embodiments, the valve 80 is made of an elastomeric material, such as silicon rubber or the like. The valve 80 can selectively close and seal when the flash chamber 34 is removed therefrom. The valve 80 can provide a fluid tight connection between the flash chamber 34 and the valve 80 when the flash chamber 34 is inserted therein. As shown, in some embodiments, the flash chamber 34 can coupled directly into the valve 80 with a press fit connection. As further shown, in some embodiments, the flash chamber 34 is not coupled to, nor does it contact, the introducer needle 30.

[0047] As shown, in some embodiments, the valve 80 includes a connection portion 90 that is coupled to the inner surface of the needle hub 36 and a barrier portion 82. The barrier portion 82 spans a cross section of inner bore 62 to seal the inner bore 62 upon removal of the flash chamber 34. The barrier portion 82 can include a hole or slit that selectively open and

closes. The slit can be a straight slit, a Y-shaped slit, or a cross-shaped slit. The barrier portion 82 can also include an inward facing duckbill shape that at least partially can prevent the slit from opening in response to proximally oriented internal pressure on the valve 80. The valve 80 can retain the flash chamber 34 within the needle hub 36 until a threshold force is applied proximally 63 on the flash chamber. In some embodiments, the flash chamber 34 is retained in the needle hub 36 with a breakable connection 92, which breaks when a threshold force is applied proximally 63 on the flash chamber 34. The breakable connection 92 can be made of a breakable material. The breakable connection 92 can also have a scored line 94 and/or a stress riser that facilitates breaking at that point.

[0048] Referring still to Figure 6, in some embodiments, the needle hub 36 includes a latch member 86 that extends distally from the needle hub 36. The latch member 86 permits the needle hub 36 to be is drawn proximally 62 and distally within the safety barrel 40 until the latch member 86 is drawn proximally passed an inward ridge 84. The inward ridge 84 can have a steep proximal face 92 that restricts the latch member's 86 distal movement. As such, the latch member 86 and the inward ridge 84 can prevent the needle hub 34 from advancing the introducer needle 30 out the safety barrel 40. The shape and configuration of the latch member 86 and the inward ridge can be adjusted, anticipated, and/or changed. Furthermore, other such means for limiting the needle hub's 36 distal movement can be incorporated into the needle assembly 22.

[0049] Figure 9 depicts another embodiment of a flash chamber 34 that can be used with the valve 80 and needle hub 36 of Figure 6. This flash chamber 34 includes a distal connector portion 48 that includes a narrow nose extension 130. The narrow nose extension 130 can pierce through the valve 80 and allows for effective resealing of the valve 80 after the removal of the flash chamber 34.

[0050] Reference will now be made to Figure 7, which depicts yet another embodiment of a connection between the needle hub 36 and the flash chamber 34. As shown, flash chamber 34 is removably coupled to the needle hub 36. The distal connector portion 48 of the flash chamber 34 includes an annular flange 102 that extends outwardly from the flash chamber 34. This distal connector portion 48 is positioned within proximal portion of the inner bore 62 of the needle hub 36. A valve 80 is located within this proximal portion of the inner bore 62. The valve 80 includes an inner cavity 108 that receives the distal connector portion 48 therein. The annular flange 102 of the distal connector portion 48 is interlocked within an inner groove 100 of the valve 80. The valve 80 is disposed within a distal region 110 of the inner cavity 108. The valve 80 and/or the flash chamber 34 can longitudinally within this

distal region 110. This distal region is terminated at its distal end with an inward flange 104 of the needle hub 36. This inward flange 104 prevents the annular flange 102 of the flash chamber 34 from being withdrawn from the needle hub 36 until a threshold force is applied to the flash chamber 34. When a threshold force pulls the flash chamber 34, the proximal movement of the annular flange 102 forces the valve 80 and the inward flange 104 to flex outwardly into the space 106 between the needle hub 36 and the safety barrel 40. The characteristics, shapes, dimensions, and properties of the needle hub 36 and the valve 80 can be designed to require a certain threshold force that will allow a user to easily remove the flash chamber 34, while preventing the flash chamber 34 from falling out when it is slightly jarred, bumped, or touched.

[0051] In other embodiments, the flash chamber 34 is screwed onto the needle hub 36. As shown, the annular flange 102 can be angled to form one or more male threaded connectors and the inner groove 100 of the valve 80 and/or the inward flange 104 of the needle hub 36 can form a female threaded connector. Thus configured, the flash chamber 34 can be screwed into the needle hub 36. To remove the flash chamber 34 it can be unscrewed from the needle hub 36.

[0052] As shown in Figure 8, in some embodiments, the flash chamber 34 is connected to the needle hub 36 via a keyed connection. The distal connector portion 48 can include a one or more keyed connector components 120 that mates with keyed connector components 122 in the proximal opening 60 of the safety barrel 40 and/or the needle hub 36. For example, in some instances, the keyed distal connector portion 48 is inserted into the keyed safety barrel 40 and/or the needle hub 36 in a distal direction 124. When fully inserted, the flash chamber 34 can be rotated, for example in a clockwise direction 126, to lock it in place. To remove the flash chamber 34, the clinician rotates the flash chamber 34 in a counter-clockwise direction and withdraws the flash chamber 34 in the proximal direction 63. In addition to the connections between the flash chamber 34 and the needle hub 36 described herein, other such connecting means for connecting the flash chamber 34 to the needle hub 36 can be incorporated into the catheter assembly 20.

[0053] From the foregoing, it will be seen that the present devices and methods efficiently collect a blood sample from a flash chamber that is removably coupled to the proximal end of an introducer needle. Since blood is already collected in this chamber, the use of this blood can avoid the need for a separate blood sampling procedure. Once removed, blood can be dispensed from the flash chamber into a point-of care diagnostic device, for rapid, prompt test results, which can enable time-sensitive health information, such as the risk of diabetes or

impaired kidney function to be more quickly and easily acquired. Furthermore, the flash chamber can be sized for accommodate the needed blood sample. As such, the flash chamber can be enlarged, which increases the flashback visualization period.

[0054] The present invention may be embodied in other specific forms without departing from its structures, methods, or other essential characteristics as broadly described herein and claimed hereinafter. The described embodiments are to be considered in all respects only as illustrative, and not restrictive. The scope of the invention is, therefore, indicated by the appended claims, rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

CLAIMS

1. A needle hub comprising:

an introducer needle having a lumen extending therethrough;

a needle hub coupled to a proximal end of the introducer needle; and

a flash chamber removably coupled to the needle hub, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub.

2. The catheter assembly of claim 1, wherein at least a portion of the flash chamber is compressible.

3. The catheter assembly of claim 1, wherein the flash chamber comprises:

a chamber body defining an internal cavity; and

an air permeable membrane coupled to the chamber body and in fluid communication with the internal cavity.

4. The catheter assembly of claim 3, wherein the internal cavity of the chamber body of the flash chamber has in an internal volume between about 0.1 mL to about 10 mL.

5. The catheter assembly of claim 1, wherein the flash chamber is press fit into the needle hub or introducer needle.

6. The catheter assembly of claim 1, wherein the flash chamber is screwed onto the needle hub.

7. The catheter assembly of claim 1, wherein the flash chamber is selectively coupled to the needle hub or the introducer needle via a keyed connection.

8. The catheter assembly of claim 1, wherein the flash chamber is selectively coupled to the needle hub or the introducer needle via a breakable connection.

9. The catheter assembly of claim 1, wherein the flash chamber is a breakable ampoule.

10. A catheter assembly comprising:

an introducer needle having a lumen extending therethrough;

a needle hub coupled to a proximal end of the introducer needle;

a flash chamber selectively coupled to the needle hub or the introducer needle, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub, the flash chamber having an air permeable membrane and a distal connector portion;

the chamber body defining an internal cavity, the chamber body having at least a compressible portion that decreases the internal volume of the internal cavity when compressed;

the air permeable membrane coupled to the chamber body and in fluid communication with the internal cavity; and

the distal connector portion of the chamber body for selectively coupling to the needle hub.

11. The catheter assembly of claim 10, wherein at least a portion of the flash chamber is compressible.

12. The catheter assembly of claim 10, wherein the flash chamber has in an internal volume between about 0.1 mL to 10 mL.

13. The catheter assembly of claim 10, wherein the flash chamber is press fit into the needle hub or introducer needle.

14. The catheter assembly of claim 10, wherein the flash chamber is screwed onto the needle hub.

15. The catheter assembly of claim 10, wherein the flash chamber is selectively coupled to the needle hub or the introducer needle via a breakable connection, the breakable connection including at least one scored line and a stress riser.

16. The catheter assembly of claim 10, wherein the flash chamber is a breakable ampoule.

17. A method for providing a removable flash chamber of a catheter assembly, the method comprising:

providing a catheter assembly having a needle hub, the needle hub having an introducer needle coupled thereto;

providing an introducer needle coupled to the needle hub, the introducer needle having a lumen extending therethrough;

providing a flash chamber removably coupled to the needle hub, an interior of the flash chamber being in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub.

18. The method of claim 17, further comprising providing at least a single compressible portion of the flash chamber for selectively ejecting blood within the flash chamber from therefrom.

19. The method of claim 18, providing an inner cavity within a body of the flash chamber having an internal volume about 0.1 mL to 10 mL.

20. The method of claim 19, wherein the flash chamber has a distal connector portion, the distal connector portion having at least one of a press fit connector, screw threads, a keyed connection, and a breakable connection.

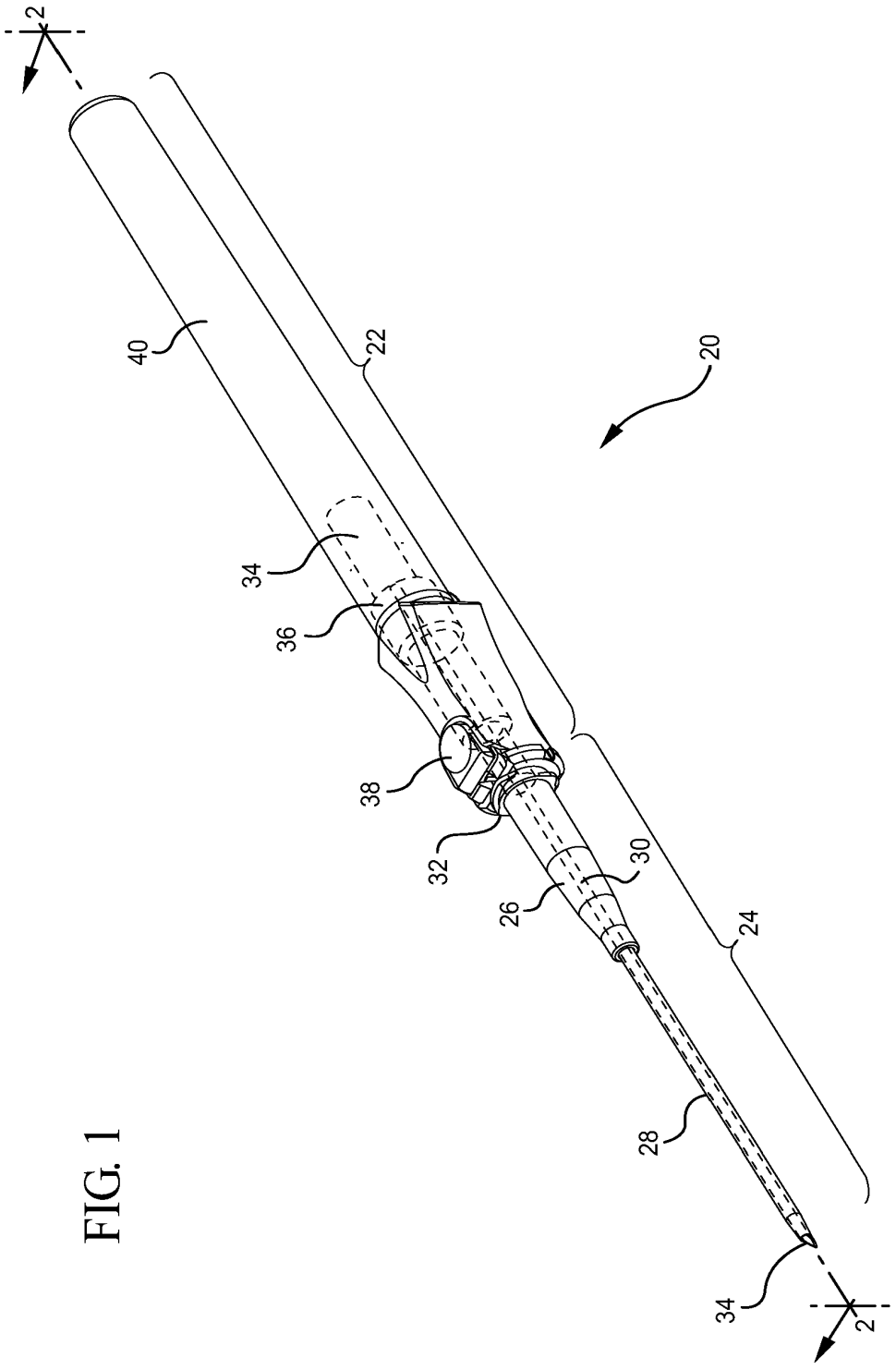


FIG. 1

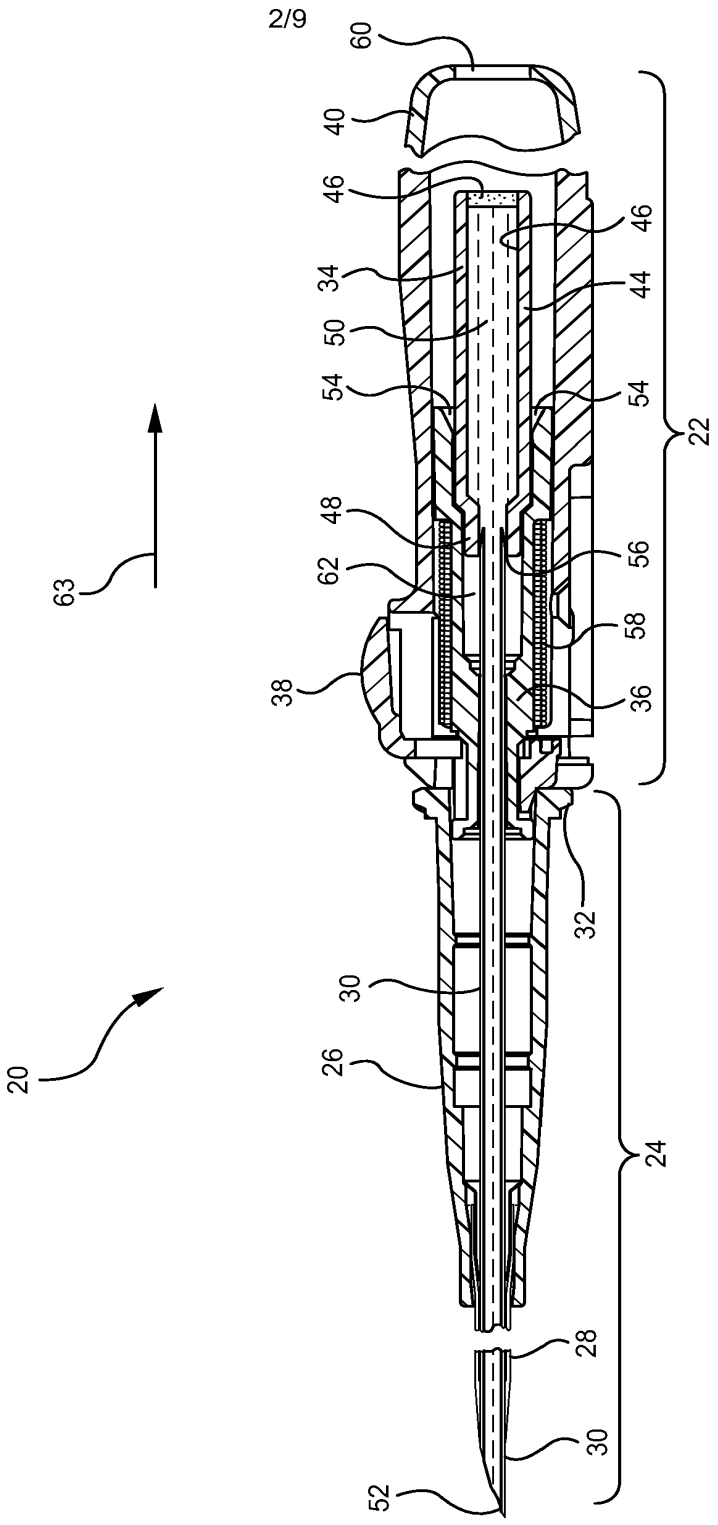

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FIG. 2

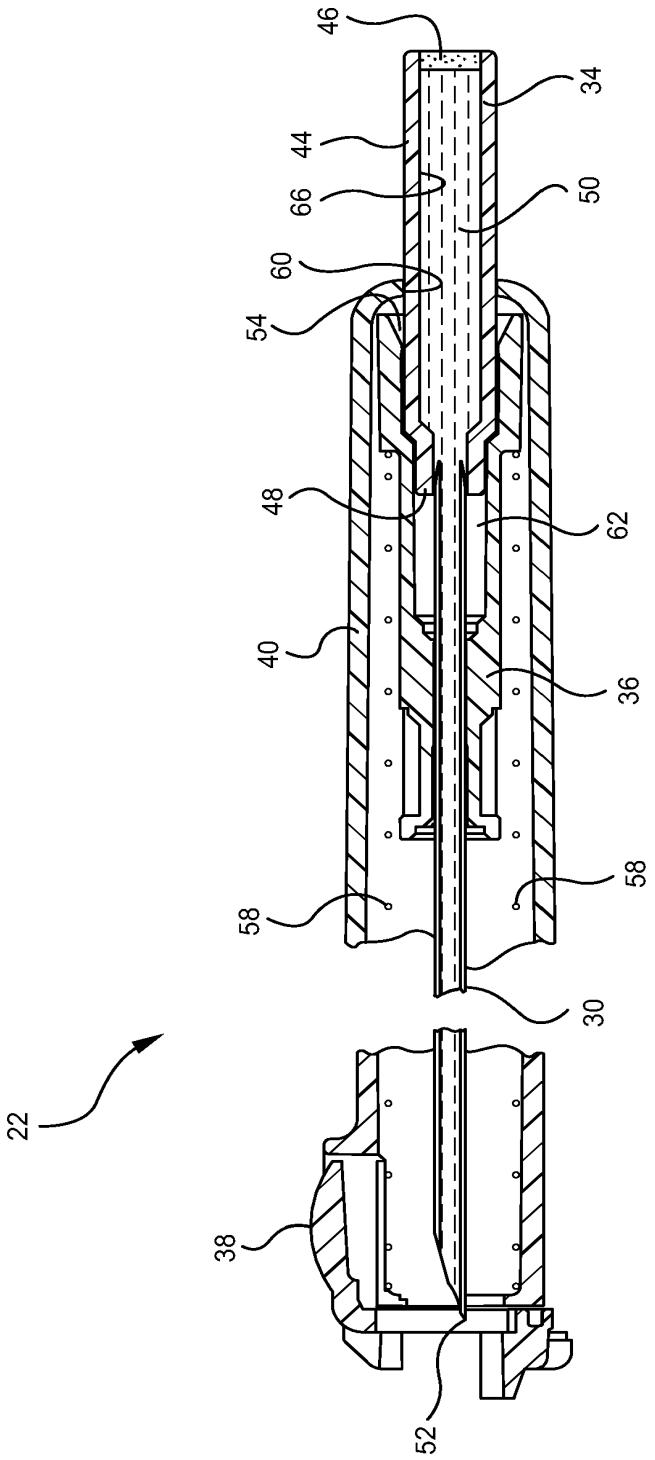


FIG. 3

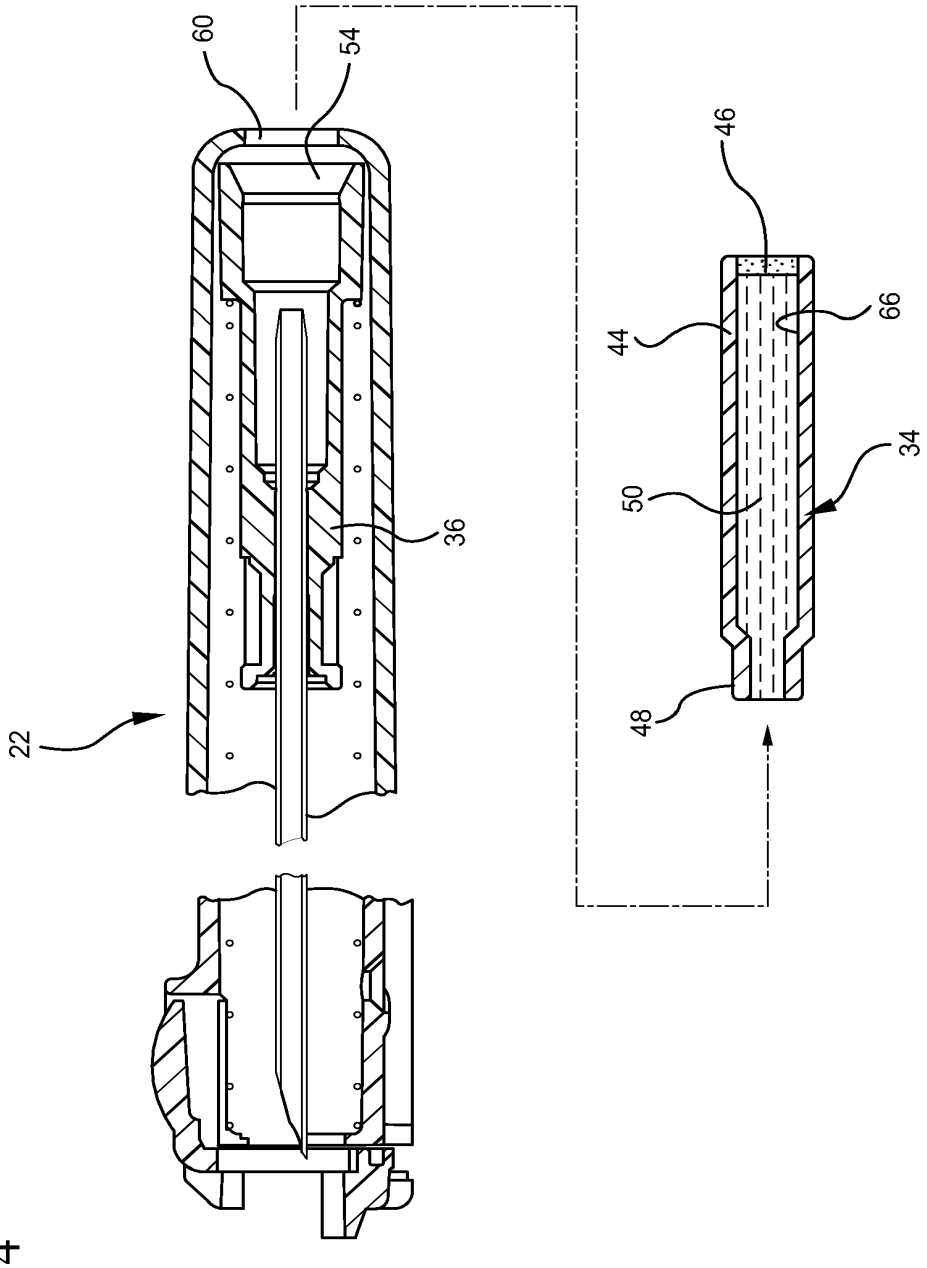


FIG. 4

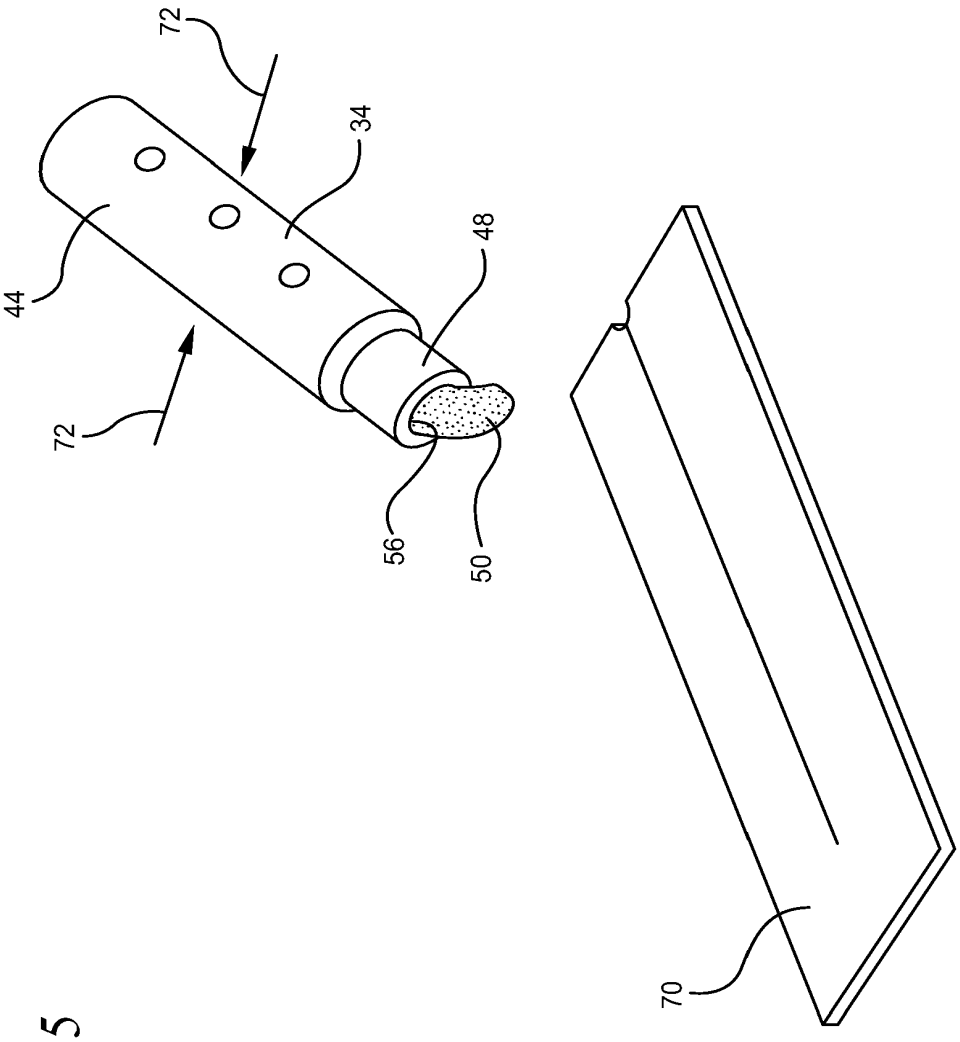


FIG. 5

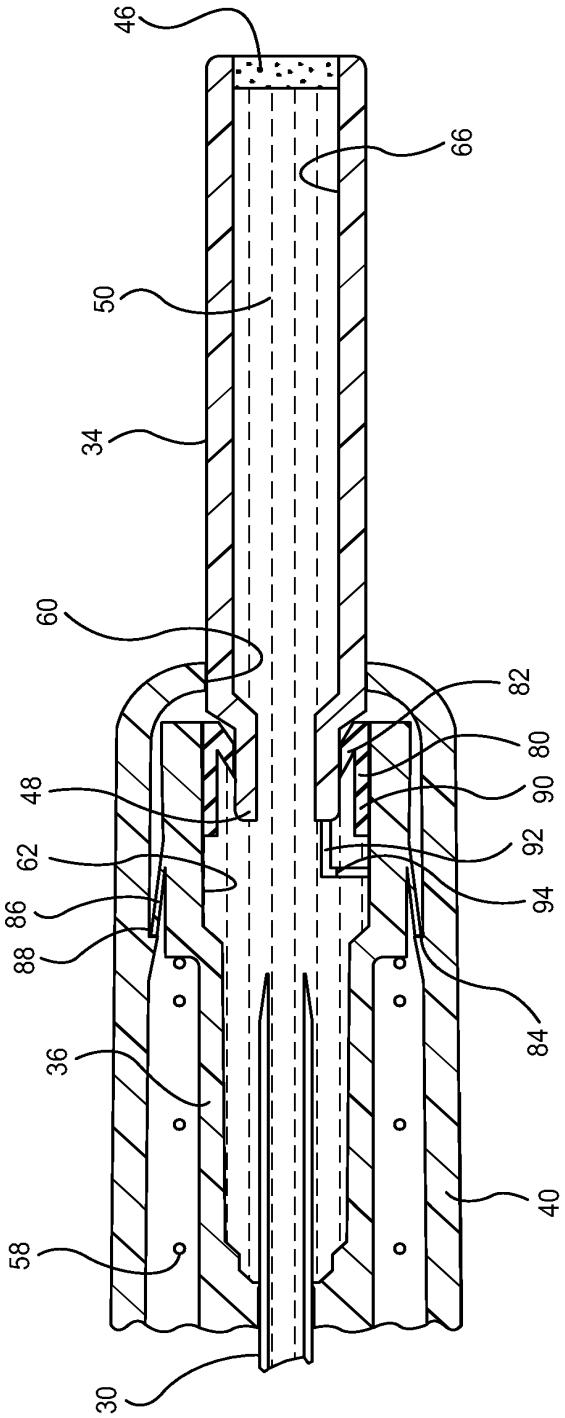


FIG. 6

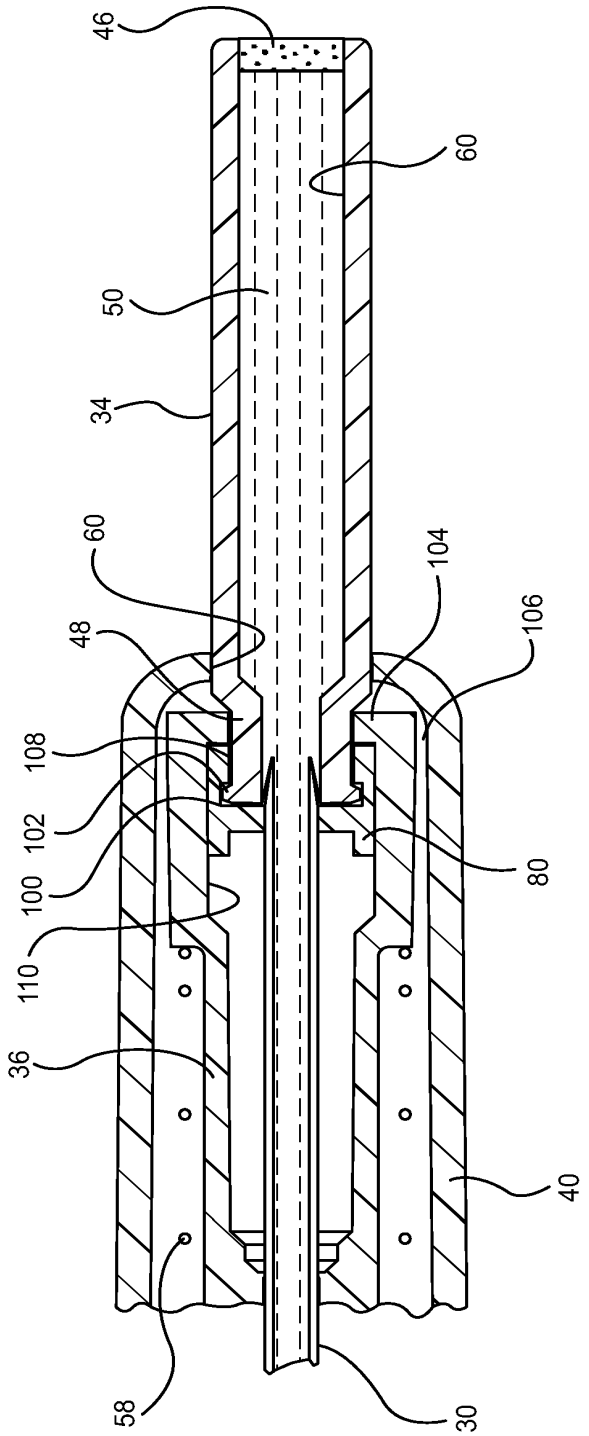


FIG. 7

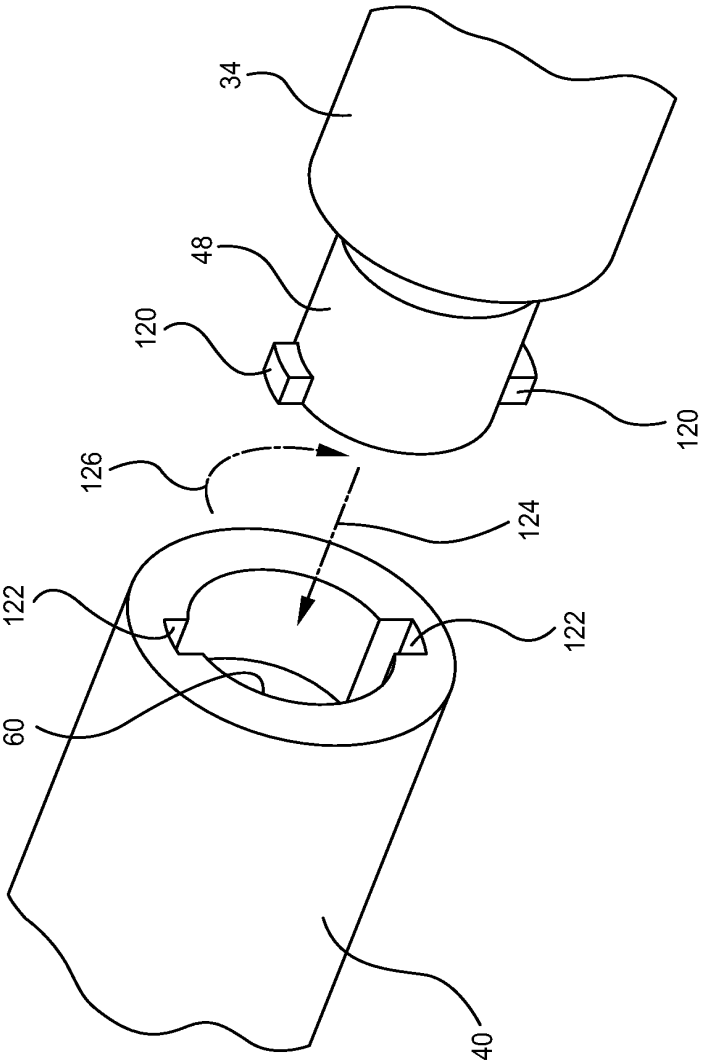


FIG. 8

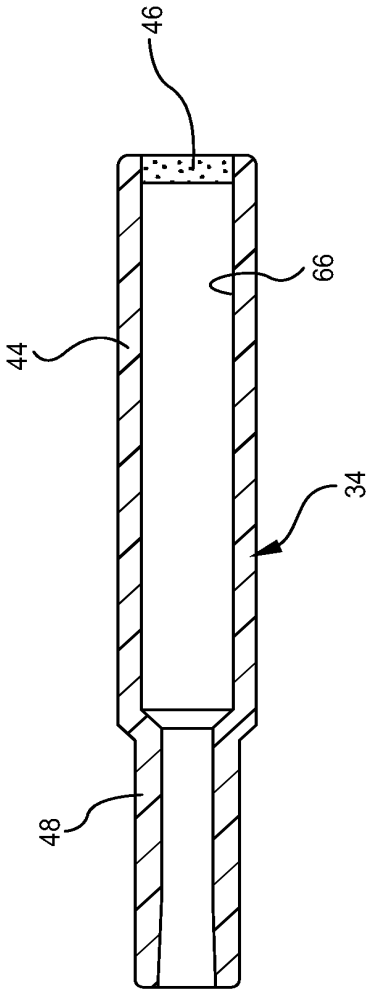


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/043892

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M25/06 A61B5/153
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)
A61M A61B

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 884 257 A1 (SHUE MING-JENG [TW]; HUANG DEBORAH [TW]; SHUE PHILLIP [TW]) 6 February 2008 (2008-02-06)	1,2,4-9, 17-20
Y	figures 3, 4, 30-35, 41-46 paragraph [0019] paragraph [0039] - paragraph [0041]	3,10-16
X	WO 01/12254 A1 (BECTON DICKINSON CO [US]) 22 February 2001 (2001-02-22)	1,3-9,17
Y	figures 1-6	3,10-16
A	page 4, line 4 - line 7 page 4, line 10 - page 6, line 16 page 6, line 19 - line 29	2,18-20
A	EP 0 812 601 A2 (BECTON DICKINSON CO [US]) 17 December 1997 (1997-12-17) column 3, line 35 - column 5, line 55; figures 1-6	1-20

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier 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
24 August 2011	31/08/2011

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	Przykutta, Andreas

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/043892

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

A needle hub (36) and catheter assembly are (20) disclosed herein. The needle hub includes an introducer needle (30) having a lumen extending therethrough. A needle hub is coupled to a proximal end of the introducer needle. A flash chamber (34) is removably coupled to the needle hub or the introducer needle. An interior of the flash chamber is in fluid communication with the lumen of the introducer needle when the flash chamber is coupled to the needle hub or the introducer needle. As such, the flash chamber can collect a sample of blood that can be accessed when the flash chamber is removed. In some instances, the blood can also be dispensed from the flash chamber into a test strip (70) or other testing device.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/043892

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007/191777 A1 (KING ALAN D [US]) 16 August 2007 (2007-08-16) paragraph [0015] - paragraph [0026]; figures 1-5 -----	1-20

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/043892

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1884257 A1	06-02-2008	NONE	
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		ES 2327679 T3	02-11-2009
		JP 2009526602 A	23-07-2009
		WO 2007094841 A1	23-08-2007

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

Bibliographic data: DE2541494 (A1) — 1977-03-31

Hypodermic needle blood taking device - has valves at needle end and at attachable evacuated chamber connection

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Classification: **- international:** ***A61B5/15; A61M39/02; A61M5/34;*** (IPC1-7): A61B5/14

- cooperative: **A61B5/15003 (EP)**; **A61B5/150221 (EP)**; **A61B5/150351 (EP)**; **A61B5/150389 (EP)**; **A61B5/150496 (EP)**; **A61B5/150732 (EP)**; **A61B5/150992 (EP)**; **A61B5/154 (EP)**; **A61M39/02 (EP)**; A61M2005/341 (EP); A61M2005/342 (EP); A61M5/346 (EP)

Application number: DE19752541494 19750917

Priority number(s): DE19752541494 19750917 ; FR19750025934 19750821 ; GB19750034265 19750818

Also published as: FR2321262 (A1) GB1506449 (A)

Abstract of DE2541494 (A1)

The blood-taking device is of the type where a hypodermic needle is inserted into a blood vessela nd one or more evacuated containers in successions are connected to the needle for collecting blood samples. The device has two valves. The first valve closes the proximal end of the needle section when a container is not connected to it and the second valve makes it possible to control the difference of pressure utilized for drawing blood from a subject. The second valve can be closed rapidly in the event it is discovered that the needle lies in tissue exterior to a blood vessel rather than in a blood vessel itself, thereby preventing extravasation and haematoma.

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DESCRIPTION DE2541494A1

[0001]

13 blood collection device

[0002]

17 The invention relates to a blood sampling device for draining blood from a blood vessel.

[0003]

21 It is routine in modern hospitals to draw blood samples from patients by sequentially inserting one or more evacuated test tubes into a holder having a double-tipped cannula; one pointed end of the kanttle pierces the patient's vein and the other pointed end pierces the stopper of the evacuated test tube, thereby allowing blood to flow from the vein into the evacuated tube.

[0004]

28 However, vacuum tube holders are relatively expensive and therefore not disposable; they are also bulky devices subject to contamination (see U.S. Patent 3,520,292).

30 Unless dual-tipped cannulas are already installed in the holders, they must be attached to the holders by a user.

32 However, handling these double-tipped cannulas is dangerous because the user could prick their fingers or infect the cannula.

34 In addition, double-ended needles do not readily permit the injection of soluble drugs into the vein. In medical practice, however, it is sometimes desirable to inject drugs after the blood has been drawn through the cannula in order to save the patient the pain of re-inserting a vein. Another disadvantage of using double-pointed cannulas is that when the tube is withdrawn,

some blood from the vein will flow back through the cannula to its inner end and soil the surrounding area. Of particular note when vacuum tubes are used with double-pointed cannulas is the risk that if the outer tip is not in a vein but in tissue, puncture of the inner tip of the cannula through the tube will result in blood leaking from the vein and a hematoma is coming. Then the user must pull out the cannula as quickly as possible. Even then, the user cannot grasp the situation quickly enough to avoid damage because the full pressure differential is applied to the outer tip of the cannula when the stopper of the evacuated tube is punctured.

[0005]

48 The conventional device has a holder surrounding the proximal end of the double-pointed cannula to receive the plugged end of the evacuated tube.

50 The diameter of the holder part is so large that the cannula penetrates the skin at a relatively acute angle, which increases the risk that the cannula will also puncture the other wall of the blood vessel, so that the tip of the cannula will then be in the tissue rather than in the blood vessel comes to rest. Even without an evacuated reservoir attached to the proximal end of the cannula, blood can clot at the tip, making the device inoperable if another sample is to be taken.

[0006]

58 The invention seeks to provide an improved blood sampling device that avoids the above deficiencies.

60 With the device according to the invention, it should be possible to take a plurality of blood samples with a single puncture of a cannula in a blood vessel without the risk of blood clotting in the space between the successive blood withdrawals. Furthermore, the angle at which the cannula penetrates the patient's skin should be determined by the device itself.

[0007]

67 In order to achieve this, the invention provides a blood sampling device as described in the characterizing part of the first claim.

[0008]

72 The device according to the invention has two valves.

73 The first valve closes the proximal end of the needle part when no container is connected; the second valve makes it possible to control the pressure difference used to aspirate blood from the patient.

76 The second valve can be quickly closed if it is discovered that the needle is not in a blood vessel but outside of it in the tissue. In this way, leakage of blood into the environment and a flamatoma are avoided.

[0009]

82 The device according to the invention consists of two composable parts; the first part comprises a cannula and a holder, the second part comprises an evacuated container closed with a stopper through which an axially slidable and rotatable tube passes.

85 The first and second parts, hereinafter referred to as the holder part and the container part, can be firmly joined together to form a continuous channel for blood to flow through the cannula, holder part and tube into the container. In the holder part is arranged the first valve, which is usually closed, so that when the tube and the container part are not connected to the holder part, the blood trapped in the holder part does not come into contact with air and thus possible infection is avoided. A second valve is mounted in the reservoir portion to allow control of the pressure differential acting across the distal tip of the cannula and to shut off negative pressure from the tip if the cannula is improperly seated in a blood vessel from which blood is being drawn to avoid the risk of a hematoma. The second valve is operated by rotating the container around the tube.

[0010]

98 The distal end of the tube can be inserted into the proximal end of the holder member so that a continuous channel is formed.

100 In one embodiment the distal end of the tube is provided with a protruding flange which opens the first valve when the container part and the holder part are connected to each other. In a second embodiment, the distal end of the tube itself opens the first valve and the container part can be detached from the holder part only when the second valve is closed.

[0011]

107 The invention thus has the advantage, among other things, that the negative pressure at the tip of a cannula is shut off by a valve if the cannula is not correctly positioned in a blood vessel.

109 The invention also eliminates the need for a holder and double-pointed needles by providing a novel vacuum container stopper and hypodermic applicator.

[0012]

114 The hypodermic applicator allows both the injection of soluble drugs into a blood vessel and the collection of blood samples without splashing back blood.

[0013]

119 Assembling the cannula containing part with the container part automatically opens the valve in the holder part so that a continuous and unobstructed channel is formed from the tip of the cannula to the proximal end of the tube which opens into the container.

122 Controlling the negative pressure applied to a vein can prevent the vein from collapsing.

[0014]

126 Further details and advantages of the invention result from the following description of exemplary embodiments with reference to the accompanying drawings.

128 1 shows a side view of a device according to the invention, in which the part containing the cannula is separated from the container part; Figure 2 shows a side elevation of the device according to the invention, in which the two parts are ready for assembly; Figure 3 is a side elevation showing the two parts of the device connected together and showing the valve in the container part closed; Figure 4 is a side elevation similar to Figure 3 but with the valve in the container part open; Figure 5 is a sectional view taken along line 5-5 of Figure 4; Figure 6 is a sectional view taken along line 6-6 of Figure 4; Figure 7 is a side perspective view of a second embodiment of the invention; Figure 8 is a partially sectioned view of the two parts of the second embodiment of the invention separated; Figure 9 is a view similar to Figure 8 but showing the two parts combined; Figure 10 shows the same two parts of the second embodiment but with the container advanced so that the second valve is open; Figure 11 is a view taken along line 11-11 of Figure 10; Figure 12 is a view taken along line 12-12 of Figure 10; and FIG. 13 is a sectional view taken along line 13-13 of FIG.

[0015]

144 The blood sampling device according to the invention consists of two parts that can be joined together, a holder part and a container part, which are shown separately from one another in FIG.

147 A cannula 23 has a tip 24 for piercing a blood vessel through a patient's skin.

148 The proximal end 25 (FIG. 2) of the cannula 23 is fastened in a holder part 22 through which a channel 26 runs. A flexible walled plug 27 sits in the end 28 of the channel. A flexible wall of the ben lies across an opening 29 so that the plug 27 simultaneously seals the opening 29 and the end 28 of the channel.

[0016]

155 The holder part 22 has a projection 30 which serves to hold the holder part at a certain distance from the patient's skin, thereby adjusting the angle at which the cannula 23 penetrates the skin and the manipulation of the holder part and the cannula is facilitated.

[0017]

161 A container 12 is closed with a stopper 10 having a flange 11 seated on the open end of the container 12 .

163 The plug 10 is penetrated by an axial passage in which is inserted a tube 14 which fits tightly

enough in the plug 10 to prevent air from entering between the tube 14 and the axial passage in the plug 10, yet is loose enough That they can move or rotate in the plug 10 in the axial direction.

[0018]

170 The tube 14 is closed at its proximal end, preferably with a disc cemented or otherwise secured onto the end of the tube 14 after the tube 14 is inserted into the stopper 10.

172 The washer 15 performs the dual function of sealing the end of the tube 14 and at the same time limiting the axial movement of the tube 14 away from the container 12.

174 The tube 14 also has a rigidly attached or molded stop 18 at a location such that the movement of the tube 14 axially toward the container 12 is limited.

[0019]

179 The tube 14 is provided with a side opening 16 located a small distance from the sealed tube end.

181 As shown in Figure 2, the opening 16 lies within the passage through the stopper 10 so that the container 12 is protected against ingress of air during evacuation. In a convenient embodiment, the axial passage through the plug 10 is threaded from its outer part to just short of where the orifice 16 lies when the disc 15 is brought into contact with the plug 10. In this case, of course, the tube 14 must also be equipped with a suitable thread.

[0020]

189 Figure 2 shows the container part of the device being assembled with the holder part.

190 The connection is made by inserting the distal end 19 of the tube 14 into a socket 29. The tube end and socket are shaped to fit flush and prevent air from entering between them. A flange 20 is attached to the tube end 19 which bears against the flexible wall 29' of the plug 27 when the two parts are joined together. When the tube end 19 is pushed into the receptacle 29, the flange 20 pushes aside the top of the stopper 27 so that a continuous channel is established between the tip of the cannula 23 and the interior of the tube 14. This can be seen in Figure 3 where the top wall of the flexible plug 27 is depressed by the flange 20. The appearance of the holder portion of the device after insertion of the tube end 19 into the socket 29 is shown in the sectional views of Figs.

[0021]

202 When a blood sample is to be taken, the container 12 is gently rotated in the direction indicated by the arrow in FIG.

204 The axial movement of the container 12 towards the stop 18 results from the fact that the tube 14 is provided with a thread 13 which engages with a threaded part 13' of the stopper 10.

[0022]

209 It should be noted that the plug 10 has an unthreaded portion at its proximal end which ensures a tight seal when the opening 16 is within the plug 10.

[0023]

214 If blood does not flow through the opening 16 into the container 12 substantially immediately, the container 12 is rotated in the opposite direction to bring the opening 16 back into the stopper 10, thereby avoiding the full pressure differential being applied to the tissue in where the cannula must lie.

218 This avoids extravasation of blood and the resulting hematoma.

219 The cannula can then be pulled out and properly inserted again so that its tip comes to rest in a blood vessel.

[0024]

224 Then the container 12 is turned again according to FIG. 4 in order to start again with the blood collection.

226 If blood flows through the opening 16, the container 12 is rotated further until the stopper 10 meets the stop 18 on the holder part 22. The container then remains in this position until the desired amount of blood has been aspirated or until the container is filled.

[0025]

232 A second embodiment of the invention is shown in FIGS.

233 Again the device consists of two parts, a holder part, generally designated 221, containing the cannula, and a container part, generally designated 351. The container part 351 has a container 121 which is closed with a stopper 101 in which a through hole is made. A tube 141 having a threaded portion 131 is mounted in the bore of plug 101 . The tube 141 has two parts 141a and 141b which form an angle with each other. A passage 161a through tube 141 is closed at its end by a conical portion 151 which fits into a corresponding portion 151a of the bore in plug 101. A lateral opening 161 is provided in the channel 161a near the conical part 151 . The threaded portion 131 of the tube 141 terminates short of the side opening 161 so that when the container 121 is in a position such that the conical portion 151 is snugly received in section 151a, the opening 161 passes through the cylindrical portion of the stopper 101 is tightly closed.

[0026]

247 To assemble the holder portion and container portion of the device, end 191 of tube 141 is

inserted into a receptacle 291 in holder portion 221, lugs 301a slide into grooves 301b in holder portion 221, and rotation of container portion 351 establishes a bayonet fitting between lugs 301a and 301a grooves 301b.

251 In addition, the receptacle 29a has a spherical portion 311b which mates with a corresponding spherical portion 311a on the tube 141 to provide a tight seal between the holder portion and the container portion.

[0027]

257 When the tube end 191 is inserted into the socket 291 and the bayonet fitting is made, the pointed tube end 191 pushes down the top of a flexible plug 271 which is preferably hollow.

259 In doing so, the pointed end of the tube itself serves as a means to push the upper part 271' of the plug 271 aside. This displacement creates an uninterrupted line between the channel 161a in the container part and the cannula 23. The hollow plug 271 closes the end of the socket 291 and acts as a valve upon insertion of the tube end 191 due to the depressed top plug wall 271'. A portion 401 of the tube end is preferably received in a snug fit in receptacle 29a so that a seal is formed between these portions.

[0028]

268 When the container 121 is rotated in the direction indicated by an arrow in Fig. 10, it moves distally as shown in Fig. 10 and communicates the side opening 161 with the container interior; so that a connection is made from the cannula 23 to the container.

271 If the container is evacuated before the two parts are joined, then blood will flow through the cannula and through the associated channels into the container 121 after the side opening 161 enters the conical portion of the bore in the stopper 101. The range of movement of the container in a distal direction - the threads on the tube 141 are right-hand in this case - is restricted by the contact between the plug 101 and the rear part 321 of the border of the holder part 221.

[0029]

280 Conveniently, the plug 271 carries a ridge 271a which nests in a groove 271b in the retainer portion 221 to help hold the plug 271 in place.

[0030]

285 The manner in which the lugs 301a are fixed in the grooves 301b can be clearly seen from FIGS.

287 The path by which liquid enters the container 121 from the cannula is clear from FIGS. 10 and 12.

[0031]

292 Once the container is filled, the tip 191 of the tube 141 is removed from the channel, i. pulled out of the socket 29a and the flexible wall of the plug 27a springs back so that it blocks a channel 261 in the holder part 221.

295 This process can be repeated any number of times, each time using a new container to collect a sample.

[0032]

300 The distance between the border 321 of the holder part 221 and the outer surface 38a of the plug 101 is chosen so that the container part cannot lift off the corner 361 until the conical part 151 seals tightly in the bore portion 151a, and this sealing engagement is achieved by Turning the container 351 produced with simultaneous displacement of the same in the proximal direction.

305 The dashed curve shows how the distance at which the tip 371 of the plug 101 clears the corner 361 is determined.

307 The purpose of this arrangement is to ensure that the container is properly sealed before container portion 351 is removed from holder portion 221.

[0033]

312 The container portion can then be handled separately without risk of contamination of its contents.

[0034]

317 It should be noted that the seal between the tube end portion 401 and the receptacle 291 prevents air ingress when unlocking the bayonet fitting if unlocking is attempted when the container portion 351 at the side opening 161 is only partially closed.

[0035]

323 If desired, a soluble drug can be injected without causing pain to the patient by drawing the drug into an ordinary syringe fitted with a thin gauge needle and piercing the stopper 271 through an opening 28a with the needle tip of the syringe.

326 The drug is then injected into the channel 26a and from there goes to the cannula 23, to its tip 24 and finally into the patient's blood vessel, provided that the passageway serving as receptacle 291 remains sealed.

329 A new reservoir portion can be attached to the holder portion 221 that remains in place to aspirate more blood, or the cannula 23 can be withdrawn from the blood vessel and then discarded.

332 The filled part of the container is sent to an appropriate biochemical laboratory, where the valve of the side opening 161 is first opened, after which the plug 101 can be easily removed, the tests can be carried out and the whole unit can then be destroyed.

[0036]

338 Since receptacle 291 is blocked each time a container is removed, blood cannot continue to ooze out of channel 261, nor is it drawn back into the blood vessel.

[0037]

343 The object of the invention is thus fulfilled.

344 Modifications are possible with respect to the exemplary embodiments described.

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CLAIMS DE2541494A1

1.

13 L n 8 p r u c h e 9 Blood extraction device for draining blood from a blood vessel, characterized in that it consists of a holder part (22, 221) and a container part (351), that the holder part has a cannula (23) with a pointed distal end (24) and a proximal end (25) and is traversed by a channel (26, 261), in whose distal end the proximal end (25) of the cannula is received in a sealed manner and which communicates with an opening (29, 291) of the holder part and that a first valve (27, 271) is seated in the proximal end of the duct (26, 261) to close the duct, normally blocking communication between the opening (29, 291) and the duct, that further the container part has an evacuatable container (12, 121), the opening of which is closed by a stopper (10, 101), and that a tube (14, 141) is provided, the proximal end of which passes through the stopper (10, 101). and is connected at its distal end to the opening (29, 291) in the holder part in such a way that a sealing connection can be established between the tube and the holder part at this opening, and that at the distal end of the tube an actuating element (20, 191) is provided which opens the first valve (27, 271) thereby connecting the orifice (29, 291) to the channel (26, 261) when the tube (14, 141) is attached to the holder part (22, 221) with the plug (10,101) being attached to the container (12,121) so that it is movable with the container relative to the tube but is sufficiently tight in the container opening to prevent air ingress between the two prevent sharing.

2.

33 Device according to Claim 1, characterized in that the first valve consists of a flexible plug (27, 271) which fits into the proximal end (28, 281) of the channel (26, 261) and closes this end (28, 281). and which extends across the opening (29, 291) and completely seals this opening when the tube (14, 141) is not connected to the holder part (22, 221).

3.

40 Apparatus according to claim 2 characterized in that the actuator on the tube (14) is a flange (20) projecting from the distal end of the tube and positioned to engage that portion (29) of the hollow flexible plug (27) blocking the opening (29), pushing aside and thereby establishing communication with the channel (26) so that blood can flow through the holder part (22) into the tube (14).

4.

48 Apparatus according to any one of the preceding paragraphs characterized in that the opening (29, 291) is shaped as a socket and the distal end of the tube (14, 141) is receivable in the socket-shaped opening with a snug fit.

5.

54 Device according to one of the preceding claims, characterized in that the holder part is provided with a projection (30) which can be placed on the surface into which the cannula (2#) is to be inserted and thus defines the angle under which the cannula is inserted into the surface, and also maintains the holder portion at a distance from the surface and provides a means for more conveniently retaining the holder portion.

6.

62 Device according to any one of the preceding claims, characterized in that the plug (10, 101) is traversed by an axial channel in which the tube (14, 141) fits tightly enough to permit a flow of fluid between the tube and the channel wall preventing, and that the tube (14, 141) is closed at its proximal end and has an opening (16, 161) in its side wall near the proximal end, and that the container (12, 121) relative to this proximal end of the tube is axially movable sufficiently so that in a first position the opening (16, 161) is within the container and communicates between the tube and the container and in a second position within the channel in the stopper (10, 101) and thus the container is sealed against the ingress of air or liquid from the tube into the container, the opening (16, 161) in the side wall of the tube constituting a second valve.

7.

74 Device according to claim 6, characterized in that the distal end of the channel in the stopper (10, 101) and the proximal end of the tube are externally provided with mating threads (13, 13'; 131, 131') so that through Rotating the container around the tube gradually establishes a connection between the tube and the container or the connection can be broken.

8.

81 Device according to claim 6 or 7, characterized in that the tube (14) is provided on both sides of the stopper (10) with protruding parts (18, 15) serving as stops to limit the relative axial freedom of movement of the container and the stopper to limit the tube.

9.

87 A device according to any one of claims 6 to 8, characterized in that the proximal end of the tube and the proximal end of the channel in the stopper are shaped to match each other so that a seal is formed between the two parts when the tube is inserted into the channel.

10.

93 Apparatus according to claim 9, characterized in that the mating parts (151, 151a) of the tube and duct are conically shaped.

11.

98 Apparatus according to any one of the preceding claims characterized in that the first valve is a hollow plug (27, 271) through which a hypodermic needle can be inserted to inject fluid into a patient once the patient's skin has been punctured for blood collection .

12.

104 Device according to one of claims 6 to 11, characterized in that the axial range of movement of the container (121) relative to the tube (141) in the proximal direction is determined by the contact of the proximal end (151) of the tube with the stopper (101) and in the distal Direction is limited by the contact of the plug (101) with the holder part (221).

13.

111 Device according to Claim 12, characterized in that the distance between the holder part (221) and the stopper (101) is selected in such a way that the container part (351) can only be removed from the holder part (221) if the container has reached the am position furthest from the holder part, which position corresponds to the limit of movement of the container in the proximal direction, thereby ensuring that the second valve (161) is closed.

(51) Int. Cl. 2: A 61 B 5/14

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

DT 25 41 494 A 1

Behördeneigentum

(11) Offenlegungsschrift 25 41 494

(21) Aktenzeichen: P 25 41 494.2

(22) Anmeldetag: 17. 9. 75

(43) Offenlegungstag: 31. 3. 77

(30) Unionspriorität:

(32) (33) (31) —

(54) Bezeichnung: Blutentnahmevorrichtung

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Ansprüche

1. Blutentnahmevorrichtung zum Abzapfen von Blut aus einem Blutgefäß, dadurch gekennzeichnet, daß sie aus einem Halterteil (22, 221) und einem Behälterteil (351) besteht, daß der Halterteil eine Kanüle (23) mit einem zugespitzten distalen Ende (24) und einem proximalen Ende (25) aufweist und von einem Kanal (26, 261) durchzogen ist, in dessen distalem Ende das proximale Ende (25) der Kanüle dichtend aufgenommen ist und der mit einer Öffnung (29, 291) des Halterteils in Verbindung steht, und daß ein erstes Ventil (27, 271) in dem proximalen Ende des Kanals (26, 261) sitzt, um den Kanal zu schließen, das normalerweise die Verbindung zwischen der Öffnung (29, 291) und dem Kanal sperrt, daß ferner der Behälterteil einen evakuierbaren Behälter (12, 121) aufweist, dessen Öffnung durch einen Stöpsel (10, 101) verschlossen ist, und daß eine Röhre (14, 141) vorgesehen ist, die mit ihrem proximalen Ende durch den Stöpsel (10, 101) tritt und an ihrem distalen Ende derart mit der Öffnung (29, 291) in dem Halterteil verbunden ist, daß an dieser Öffnung eine abdichtende Verbindung zwischen der Röhre und dem Halterteil herstellbar ist, und daß an dem distalen Ende der Röhre ein Betätigungselement (20, 191) vorgesehen ist, das das erste Ventil (27, 271) öffnet und dabei die Öffnung (29, 291) mit dem Kanal (26, 261) verbindet, wenn die Röhre (14, 141) an den Halterteil (22, 221) angeschlossen wird, wobei der Stöpsel (10, 101) derart an dem Behälter (12, 121) angebracht ist, daß er mit dem Behälter relativ zur Röhre bewegbar ist, aber fest genug in der Behälteröffnung sitzt, um ein Eindringen von Luft zwischen den beiden Teilen zu verhindern.

2. Vorrichtung nach Anspruch 1, dadurch gekennzeichnet, daß das erste Ventil aus einem flexiblen Stopfen (27, 271) besteht, der in dem proximalen Ende (28, 281) des Kanals (26, 261) sitzt und dieses Ende (28, 281) verschließt und der sich quer über die Öffnung (29, 291) erstreckt und die-

se Öffnung vollständig abdichtet, wenn die Röhre (14, 141) nicht mit dem Halterteil (22, 221) verbunden ist.

3. Vorrichtung nach Anspruch 2, dadurch gekennzeichnet, daß das Betätigungselement an der Röhre (14) ein Flansch (20) ist, der vom distalen Ende der Röhre absteht und eine solche Lage hat, daß er denjenigen Teil (29) des hohlen flexiblen Stopfens (27), der die Öffnung (29) versperrt, beiseitedrückt und dadurch eine Verbindung mit dem Kanal (26) herstellt, so daß Blut durch den Halterteil (22) in die Röhre (14) fließen kann.

4. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß die Öffnung (29, 291) als Muffe geformt ist und das distale Ende der Röhre (14, 141) im Paßsitz in der muffenförmigen Öffnung aufnehmbar ist.

5. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß der Halterteil mit einem Vorsprung (30) versehen ist, der an der Oberfläche, in die die Kanüle (23) eingeführt werden soll, aufsetzbar ist und damit den Winkel festlegt, unter dem die Kanüle in die Oberfläche eingeführt wird, und zudem den Halterteil in einem Abstand von der Oberfläche hält und ein Mittel zum bequemeren Festhalten des Halterteils darstellt.

6. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß der Stöpsel (10, 101) von einem axialen Kanal durchzogen ist, in dem die Röhre (14, 141) fest genug sitzt, um einen Fluß von Fluid zwischen der Röhre und der Kanalwand zu verhindern, und daß die Röhre (14, 141) an ihrem proximalen Ende verschlossen ist und in ihrer Seitenwand nahe dem proximalen Ende eine Öffnung (16, 161) hat, und daß der Behälter (12, 121) relativ zu diesem proximalen Ende der Röhre in Achsrichtung weit genug bewegbar ist, so daß die Öffnung (16, 161) in einer

ersten Stellung sich in dem Behälter befindet und eine Verbindung zwischen der Röhre und dem Behälter herstellt und in einer zweiten Stellung innerhalb des Kanals in dem Stöpsel (10, 101) liegt und damit der Behälter gegen das Eindringen von Luft oder Flüssigkeit aus der Röhre in den Behälter abgedichtet ist, wobei die Öffnung (16, 161) in der Seitenwand der Röhre ein zweites Ventil darstellt.

7. Vorrichtung nach Anspruch 6, dadurch gekennzeichnet, daß das distale Ende des Kanals im Stöpsel (10, 101) und das proximale Ende der Röhre auf der Außenseite mit zusammenpassenden Gewinden (13, 13'; 131, 131') versehen sind, so daß durch Drehen des Behälters um die Röhre allmählich eine Verbindung zwischen der Röhre und dem Behälter herstellbar ist bzw. die Verbindung unterbrechbar ist.

8. Vorrichtung nach Anspruch 6 oder 7, dadurch gekennzeichnet, daß die Röhre (14) zu beiden Seiten des Stöpsels (10) mit vorstehenden Teilen (18, 15) versehen ist, die als Anschläge dienen, um den axialen Bewegungsspielraum des Behälters und des Stöpsels relativ zur Röhre zu begrenzen.

9. Vorrichtung nach einem der Ansprüche 6 bis 8, dadurch gekennzeichnet, daß das proximale Ende der Röhre und das proximale Ende des Kanals im Stöpsel zueinander passend geformt sind, so daß beim Einsetzen der Röhre in den Kanal eine Abdichtung zwischen beiden Teilen zustandekommt.

10. Vorrichtung nach Anspruch 9, dadurch gekennzeichnet, daß die zusammenpassenden Teile (151, 151a) von Röhre und Kanal konisch geformt sind.

11. Vorrichtung nach einem der vorangehenden Ansprüche, dadurch gekennzeichnet, daß das erste Ventil ein hohler Stopfen (27, 271) ist, durch den eine Injektionsnadel eingeführt werden kann, um Fluid einem Patienten zu injizieren,

wenn die Haut des Patienten zur Blutentnahme bereits einmal durchstochen ist.

12. Vorrichtung nach einem der Ansprüche 6 bis 11, dadurch gekennzeichnet, daß der axiale Bewegungsspielraum des Behälters (121) relativ zur Röhre (141) in proximaler Richtung durch den Kontakt des proximalen Endes (151) der Röhre mit dem Stöpsel (101) und in distaler Richtung durch den Kontakt des Stöpsels (101) mit dem Halterteil (221) begrenzt ist.

13. Vorrichtung nach Anspruch 12, dadurch gekennzeichnet, daß der Abstand zwischen dem Halterteil (221) und dem Stöpsel (101) so gewählt ist, daß ein Wegnehmen des Behälterteils (351) vom Halterteil (221) nur dann möglich ist, wenn der Behälter die am weitesten von dem Halterteil entfernte Lage einnimmt, wobei diese Lage der Bewegungsgrenze des Behälters in proximaler Richtung entspricht, wodurch sichergestellt ist, daß das zweite Ventil (161) geschlossen ist.

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Blutentnahmevorrichtung

Die Erfindung betrifft eine Blutentnahmevorrichtung zum Abzapfen von Blut aus einem Blutgefäß.

In modernen Krankenhäusern gehört es zur Routine, von Patienten Blutproben zu entnehmen, indem man eine oder mehrere evakuierte Teströhren nacheinander in einen Halter einsetzt, der eine Kanüle mit zwei Spitzen hat; das eine zugespitzte Ende der Kanüle sticht in die Vene des Patienten ein und das andere spitze Ende durchsticht den Stöpsel der evakuierten Teströhre, um auf diese Weise Blut aus der Vene in die evakuierte Röhre fließen zu lassen.

Halter für Vakuumröhren sind jedoch verhältnismäßig teuer und daher keine Wegwerfartikel; außerdem sind sie unhandliche Geräte, die einer Verunreinigung ausgesetzt sind (siehe US-PS 3 520 292). Wenn in den Haltern nicht bereits Kanülen mit zwei Spitzen eingebaut sind, müssen sie von einem Benützer an den Haltern angebracht werden. Die Handhabung dieser Kanülen mit zwei Spitzen ist jedoch gefährlich, weil der Benützer sich in die Finger stechen oder die Kanüle infizieren kann. Außerdem erlauben doppelseitig zugespitzte Kanülen nicht ohne weiteres die Injektion von löslichen Arzneimitteln in die Vene. In der medizinischen Praxis ist es jedoch manchmal erwünscht, nach der Blutentnahme durch die Kanüle Arzneimittel zu injizieren,

weil man so dem Patienten den Schmerz beim nochmaligen Einstechen in eine Vene erspart. Ein weiterer Nachteil in der Verwendung doppelt zugespitzter Kanülen ist, daß beim Herausziehen der Röhre etwas Blut aus der Vene durch die Kanüle zu deren innerem Ende zurückfließt und die Umgebung beschmutzt. Besonders beachtlich ist bei der Verwendung von Vakuumröhren zusammen mit doppelt zugespitzten Kanülen die Gefahr, daß, wenn die äußere Spitze nicht in einer Vene sondern im Gewebe liegt, es beim Durchstechen der inneren Spitze der Kanüle durch die Röhre zu einem Blutaustritt aus der Vene und einem Hämatom kommt. Dann muß der Benützer die Kanüle so rasch wie möglich herausziehen. Selbst dann kann der Benützer die Situation nicht schnell genug erfassen, um Schaden zu vermeiden, weil der volle Druckunterschied an die äußere Spitze der Kanüle angelegt wird, wenn der Stöpsel der evakuierten Röhre durchstochen wird.

Das herkömmliche Gerät hat einen Halter, der das proximale Ende der doppelt zugespitzten Kanüle umgibt, um das zugestöpselte Ende der evakuierten Röhre aufzunehmen. Der Durchmesser des Halterteils ist so groß, daß die Kanüle in die Haut unter einem verhältnismäßig spitzen Winkel eindringt, was die Gefahr erhöht, daß die Kanüle auch noch die andere Wand des Blutgefäßes durchsticht, so daß die Spitze der Kanüle dann im Gewebe statt im Blutgefäß zu liegen kommt. Auch wenn auf dem proximalen Ende der Kanüle kein evakuierter Behälter angebracht ist, kann es an der Spitze zu einer Blutgerinnung kommen, wodurch die Funktion des Gerätes gestört ist, wenn eine weitere Probe entnommen werden soll.

Die Erfindung will eine verbesserte Blutentnahmevorrichtung schaffen, die die obigen Mängel vermeidet. Mit der erfindungsgemäßen Vorrichtung sollen mit einem einzigen Einstich einer Kanüle in ein Blutgefäß mehrere Blutproben entnommen werden können, ohne daß die Gefahr einer Blutgerinnung in dem Zwischenraum zwischen den aufeinanderfolgenden Blutentnahmen besteht. Ferner soll der Winkel, unter dem die Kanüle in die

Haut des Patienten eindringt, durch das Gerät selbst festgelegt sein.

Um dies zu erreichen, sieht die Erfindung eine Blutentnahmevorrichtung vor, wie sie im kennzeichnenden Teil des ersten Anspruchs beschrieben ist.

Die erfindungsgemäße Vorrichtung hat zwei Ventile. Das erste Ventil schließt das proximale Ende des Nadelteils, wenn kein Behälter angeschlossen ist; das zweite Ventil macht es möglich, den Druckunterschied, der zum Absaugen von Blut aus dem Patienten genützt wird, zu steuern. Das zweite Ventil kann rasch geschlossen werden, falls man entdeckt, daß die Nadel nicht in einem Blutgefäß sondern außerhalb desselben im Gewebe liegt. Auf diese Weise wird ein Blutaustritt in die Umgebung und ein Hämatom vermieden.

Die erfindungsgemäße Vorrichtung besteht aus zwei zusammensetzbaren Teilen; der erste Teil umfaßt eine Kanüle und einen Halter, der zweite Teil umfaßt einen evakuierten Behälter, der mit einem Stöpsel geschlossen ist, durch den eine axial verschiebbare und drehbare Röhre tritt. Der erste und zweite Teil, die nachstehend als der Halterteil und der Behälterteil bezeichnet werden, können fest miteinander vereinigt werden, so daß ein durchgehender Kanal für das fließende Blut durch die Kanüle, den Halterteil und die Röhre in den Behälter gebildet ist. In dem Halterteil ist das erste Ventil angeordnet, das gewöhnlich geschlossen ist, so daß, wenn die Röhre und der Behälterteil nicht mit dem Halterteil verbunden sind, das in dem Halterteil eingeschlossene Blut nicht mit Luft in Berührung kommt und somit eine mögliche Infizierung vermieden ist. In dem Behälterteil ist ein zweites Ventil angebracht, das die Steuerung der Druckdifferenz, die an der distalen Spitze der Kanüle wirksam wird, ermöglicht und den Unterdruck von der Spitze absperren kann, falls die Kanüle nicht ordnungsgemäß in einem Blutgefäß liegt, aus dem Blut entnommen werden soll, um so die Gefahr eines Hämatoms auszuschließen. Das zweite Ven-

til wird durch Drehung des Behälters um die Röhre betätigt. Das distale Ende der Röhre kann in das proximale Ende des Halterteils eingesetzt werden, so daß ein durchgehender Kanal gebildet wird. In einer Ausführungsform ist das distale Ende der Röhre mit einem vorstehenden Flansch versehen, der das erste Ventil öffnet, wenn der Behälterteil und der Halterteil miteinander verbunden werden. In einer zweiten Ausführungsform öffnet das distale Ende der Röhre selbst das erste Ventil und der Behälterteil kann von dem Halterteil nur dann abgenommen werden, wenn das zweite Ventil geschlossen ist.

Die Erfindung hat also u.a. den Vorteil, daß der Unterdruck an der Spitze einer Kanüle von einem Ventil abgesperrt wird, falls die Kanüle nicht richtig in einem Blutgefäß liegt. Die Erfindung macht außerdem durch einen neuartigen Stöpsel für einen Vakuumbehälter und einen neuartigen hypodermischen Applikator einen Halter und doppelt zugesptitze Kanülen überflüssig. Der hypodermische Applikator erlaubt sowohl die Injizierung löslicher Arzneimittel in ein Blutgefäß als auch das Entnehmen von Blutproben, ohne ein Verspritzen von rückschießendem Blut. Durch das Zusammensetzen des die Kanüle enthaltenden Teils mit dem Behälterteil wird automatisch das Ventil in dem Halterteil geöffnet, so daß ein durchgehender und unbehinderter Kanal von der Kanülenspitze bis zum proximalen Ende der Röhre, das in den Behälter mündet, gebildet ist. Durch die Steuerung des an eine Vene angelegten Unterdruckes kann ein Kollaps der Vene vermieden werden.

Weitere Einzelheiten und Vorzüge der Erfindung ergeben sich aus der nachfolgenden Beschreibung von Ausführungsbeispielen anhand der beigefügten Zeichnungen. Darin zeigen:

Fig.1 eine Seitenansicht einer erfindungsgemäßen Vorrichtung, in der der die Kanüle enthaltende Teil von dem Behälterteil getrennt ist;

Fig.2 einen Seitenriß der erfindungsgemäßen Vorrichtung, in dem die beiden Teile in der Lage zum Zusammensetzen sind;

Fig.3 einen Seitenriß, der die zwei Teile der Vorrichtung miteinander verbunden zeigt und in dem das Ventil im Behälterteil geschlossen dargestellt ist;

Fig.4 einen der Fig.3 ähnlichen Seitenriß, bei dem jedoch das Ventil im Behälterteil offen ist;

Fig.5 eine Schnittansicht nach der Linie 5-5 der Fig.4;

Fig.6 eine Schnittansicht nach der Linie 6-6 der Fig.4;

Fig.7 eine perspektivische Seitenansicht einer zweiten Ausführungsform der Erfindung;

Fig.8 eine teilweise geschnittene Ansicht der beiden Teile der zweiten Ausführungsform der Erfindung im getrennten Zustand;

Fig.9 eine der Fig.8 ähnliche Ansicht, in der jedoch die beiden Teile vereinigt sind;

Fig.10 die gleichen beiden Teile der zweiten Ausführungsform, wobei jedoch der Behälter vorgeschoben ist, so daß das zweite Ventil offen ist;

Fig.11 eine Ansicht nach der Linie 11-11 der Fig.10;

Fig.12 eine Ansicht nach der Linie 12-12 der Fig.10; und

Fig.13 eine Schnittansicht nach der Linie 13-13 der Fig.9.

Die erfindungsgemäße Blutentnahmevorrichtung besteht aus zwei zusammenfügbaren Teilen, einem Halterteil und einem Behälterteil, die in Fig.1 getrennt voneinander dargestellt sind. Eine Kanüle 23 hat eine Spitze 24 zum Einstechen in ein Blutgefäß durch die Haut eines Patienten. Das proximale Ende 25 (Fig.2) der Kanüle 23 ist in einem Halterteil 22 befestigt, der von einem Kanal 26 durchzogen ist. Ein Stopfen 27 mit flexiblen Wänden sitzt im Ende 28 des Kanals. Eine flexible Wand desselben liegt quer über einer Öffnung 29, so daß der Stopfen 27 zugleich die Öffnung 29 und das Ende 28 des Kanals abdichtet. Der Halterteil 22 hat einen Vorsprung 30, der dazu dient, den Halterteil in einem bestimmten Abstand von der Haut des Patien-

ten zu halten, wodurch der Winkel eingestellt wird, unter dem die Kanüle 23 in die Haut eindringt, und die Handhabung des Halterteils und der Kanüle erleichtert wird.

Ein Behälter 12 ist mit einem Stöpsel 10 verschlossen, der einen auf dem offenen Ende des Behälters 12 aufsitzenden Flansch 11 hat. Der Stöpsel 10 ist von einem axialen Kanal durchzogen, in dem eine Röhre 14 steckt, die fest genug in dem Stöpsel 10 sitzt, um ein Eindringen von Luft zwischen die Röhre 14 und den axialen Kanal im Stöpsel 10 zu verhindern, aber andererseits doch so locker, daß sie sich im Stöpsel 10 in Achsrichtung verschieben oder drehen kann.

Die Röhre 14 ist an ihrem proximalen Ende verschlossen, vorzugsweise mit einer Scheibe, die auf dem Ende der Röhre 14 festgekittet oder sonstwie befestigt wird, nachdem die Röhre 14 in den Stöpsel 10 eingeführt ist. Die Scheibe 15 erfüllt eine doppelte Aufgabe, nämlich das Ende der Röhre 14 abzudichten und zugleich den axialen Bewegungsspielraum der Röhre 14 von dem Behälter 12 weg zu begrenzen. Die Röhre 14 hat auch noch einen starr angebrachten oder angeformten Anschlag 18 an einer solchen Stelle, daß der Bewegungsspielraum der Röhre 14 in axialer Richtung zum Behälter 12 hin begrenzt wird.

Die Röhre 14 ist mit einer seitlichen Öffnung 16 versehen, die in einem kleinen Abstand von dem abgedichteten Röhrenende angeordnet ist. Wie in Fig.2 gezeigt, liegt die Öffnung 16 innerhalb des den Stöpsel 10 durchziehenden Kanals, so daß der Behälter 12 gegen ein Eindringen von Luft beim Evakuieren geschützt ist. In einer zweckmäßigen Ausführungsform ist der axiale Kanal durch den Stöpsel 10 von seinem äußeren Teil bis kurz vor die Stelle, wo die Öffnung 16 zu liegen kommt, wenn die Scheibe 15 mit dem Stöpsel 10 in Kontakt gebracht ist, mit einem Gewinde versehen. Selbstverständlich ist in diesem Fall auch die Röhre 14 mit einem passenden Gewinde auszustatten.

Fig.2 zeigt den Behälterteil der Vorrichtung gerade beim Zu-

sammenfügen mit dem Halterteil. Die Verbindung wird in der Weise hergestellt, daß das distale Ende 19 der Röhre 14 in eine Aufnahme 29 eingesetzt wird, Das Röhrenende und die Aufnahme sind so geformt, daß sie bündig zusammenpassen und keine Luft zwischen ihnen eindringen kann. An dem Röhrenende 19 ist ein Flansch 20 angebracht, der sich gegen die flexible Wand 29' des Stopfens 27 anlegt, wenn die beiden Teile miteinander vereinigt sind. Wenn das Röhrenende 19 in die Aufnahme 29 eingeschoben wird, drückt der Flansch 20 den oberen Teil des Stopfens 27 beiseite, so daß ein durchgehender Kanal zwischen der Spitze der Kanüle 23 und dem Inneren der Röhre 14 hergestellt wird. Dies ist in Fig.3 zu sehen, in der die obere Wand des flexiblen Stopfens 27 von dem Flansch 20 niedergedrückt ist. Das Aussehen des Halterteils der Vorrichtung nach dem Einführen des Röhrenendes 19 in die Aufnahme 29 ist in den Schnittansichten der Fig.5 und 6 gezeigt.

Wenn eine Blutprobe entnommen werden soll, wird der Behälter 12 vorsichtig in der durch den Pfeil in Fig.4 angegebenen Richtung gedreht, bis die Öffnung 16 eben von dem proximalen Ende des Stöpsels 10 freikommt. Die axiale Bewegung des Behälters 12 in Richtung zum Anschlag 18 ergibt sich aus der Tatsache, daß die Röhre 14 mit einem Gewinde 13 versehen ist, das mit einem Gewindeteil 13' des Stöpsels 10 im Eingriff ist. Zu beachten ist, daß der Stöpsel 10 an seinem proximalen Ende einen gewindefreien Teil hat, wodurch eine feste Abdichtung sichergestellt ist, wenn sich die Öffnung 16 innerhalb des Stöpsels 10 befindet.

Wenn nicht praktisch sofort Blut durch die Öffnung 16 in den Behälter 12 fließt, wird der Behälter 12 in der entgegengesetzten Richtung gedreht, um die Öffnung 16 wieder in den Stöpsel 10 zurückzubringen, wodurch man vermeidet, daß die volle Druckdifferenz auf das Gewebe einwirkt, in dem die Kanüle liegen muß. Auf diese Weise werden eine Extravasation von Blut und das dabei entstehende Hämatom vermieden. Die Kanüle kann dann herausgezogen und noch einmal richtig eingestochen wer-

den, so daß ihre Spitze in einem Blutgefäß zu liegen kommt. Dann wird der Behälter 12 wieder gemäß Fig.4 gedreht, um noch einmal mit der Blutentnahme zu beginnen. Falls Blut durch die Öffnung 16 fließt, wird der Behälter 12 weitergedreht, bis der Stöpsel 10 auf den Anschlag 18 am Halterteil 22 trifft. In dieser Lage bleibt dann der Behälter, bis die gewünschte Blutmenge abgesaugt ist oder bis der Behälter gefüllt ist.

In den Fig.7-12 ist eine zweite Ausführungsform der Erfindung dargestellt. Wieder besteht die Vorrichtung aus zwei Teilen, einem die Kanüle enthaltenden Halterteil, der insgesamt mit 221 bezeichnet ist, und einem insgesamt mit 351 bezeichneten Behälterteil. Der Behälterteil 351 weist einen Behälter 121 auf, der mit einem Stöpsel 101 verschlossen ist, in dem eine durchgehende Bohrung angebracht ist. Eine Röhre 141, die einen Gewindeteil 131 hat, ist in der Bohrung des Stöpsels 101 angebracht. Die Röhre 141 hat zwei Teile 141a und 141b, die miteinander einen Winkel bilden. Ein die Röhre 141 durchziehender Kanal 161a ist an seinem Ende mit einem konischen Teil 151 verschlossen, das in einen entsprechenden Abschnitt 151a der Bohrung im Stöpsel 101 paßt. In dem Kanal 161a ist nahe dem konischen Teil 151 eine seitliche Öffnung 161 vorgesehen. Der Gewindeteil 131 der Röhre 141 hört kurz vor der seitlichen Öffnung 161 auf, so daß, wenn der Behälter 121 eine solche Lage hat, daß das konische Teil 151 im Paßsitz im Abschnitt 151a aufgenommen ist, die Öffnung 161 durch den zylindrischen Teil des Stöpsels 101 dichtend verschlossen ist.

Um den Halterteil und den Behälterteil der Vorrichtung zusammenzufügen, wird das Ende 191 der Röhre 141 in eine Aufnahme 291 im Halterteil 221 eingeführt. Nasen 301a schieben sich in Nuten 301b im Halterteil 221 und eine Drehung des Behälterteils 351 stellt einen Bajonettverschluß zwischen den Nasen 301a und Nuten 301b her. Außerdem hat die Aufnahme 29a einen kugeligen Teil 311b, der mit einem entsprechenden kugeligen Teil 311a an der Röhre 141 zusammenpaßt, so daß eine feste Abdich-

tung zwischen dem Halterteil und dem Behälterteil zustande kommt.

Wenn das Röhrenende 191 in die Aufnahme 291 eingeschoben und der Bajonettverschluß hergestellt ist, drückt das zugespitzte Röhrenende 191 den oberen Teil eines flexiblen Stopfens 271 nach unten, der vorzugsweise hohl ist. Dabei dient das zugespitzte Röhrenende selbst als ein Mittel, um den oberen Teil 271' des Stopfens 271 beiseite zu schieben. Durch diese Verlagerung entsteht eine ununterbrochene Leitung zwischen dem Kanal 161a im Behälterteil und der Kanüle 23. Der hohle Stopfen 271 schließt das Ende der Aufnahme 291 und wirkt beim Einführen des Röhrenendes 191 als Ventil infolge der herabgedrückten oberen Stopfenwand 271'. Ein Teil 401 des Röhrenendes ist vorzugsweise im Paßsitz in der Aufnahme 29a aufgenommen, so daß zwischen diesen Teilen eine Abdichtung hergestellt ist.

Wenn der Behälter 121 in der durch einen Pfeil in Fig.10 angedeuteten Richtung gedreht wird, bewegt er sich gemäß Fig.10 in distaler Richtung und verbindet die seitliche Öffnung 161 mit dem Behälterinnenraum; damit ist eine Verbindung von der Kanüle 23 zum Behälter hergestellt. Falls der Behälter vor dem Vereinigen der beiden Teile evakuiert ist, fließt dann Blut durch die Kanüle und durch die verbundenen Kanäle in den Behälter 121, nachdem die seitliche Öffnung 161 in den konischen Abschnitt der Bohrung im Stöpsel 101 gelangt ist. Der Bewegungsspielraum des Behälters in distaler Richtung - das Gewinde an der Röhre 141 ist in diesem Fall rechtsgängig - wird durch den Kontakt zwischen dem Stöpsel 101 und dem hinteren Teil 321 der Begrenzung des Halterteils 221 eingeschränkt.

Zweckmäßigerweise trägt der Stopfen 271 einen Wulst 271a, der sich in eine Nut 271b im Halterteil 221 einbettet, um dazu beizutragen, daß der Stopfen 271 in seiner Lage gehalten wird.

Auf welche Weise die Nasen 301a sich in den Nuten 301b festsetzen, ist deutlich aus den Fig.11 und 12 ersichtlich. Der

Weg, auf dem Flüssigkeit von der Kanüle in den Behälter 121 gelangt, wird aus den Fig.10 und 12 deutlich.

Sobald der Behälter gefüllt ist, wird die Spitze 191 der Röhre 141 von dem Kanal, d.i. aus der Aufnahme 29a herausgezogen und die flexible Wand des Stopfens 27a schnellt zurück, so daß sie einen Kanal 261 im Halterteil 221 versperrt. Dieser Vorgang kann beliebig oft wiederholt werden, wobei man jedesmal einen neuen Behälter zum Entnehmen einer Probe verwendet.

Der Abstand zwischen der Begrenzung 321 des Halterteils 221 und der Außenfläche 38a des Stöpsels 101 ist so gewählt, daß der Behälterteil von der Ecke 361 nicht abheben kann, bevor nicht das konische Teil 151 fest in dem Bohrungsabschnitt 151a abdichtet, und diese dichtende Anlage wird durch Drehen des Behälters 351 mit gleichzeitiger Verschiebung desselben in proximaler Richtung hergestellt. Die gestrichelte Kurve zeigt, wie der Abstand, bei dem die Spitze 371 des Stöpsels 101 von der Ecke 361 freikommt, bestimmt wird. Zweck dieser Anordnung ist es, sicherzustellen, daß der Behälter gut abgedichtet ist, bevor der Behälterteil 351 vom Halterteil 221 weggenommen wird. Der Behälterteil kann dann getrennt gehandhabt werden, ohne daß die Gefahr einer Verunreinigung seines Inhalts besteht.

Zu beachten ist, daß die Abdichtung zwischen dem Röhrenendenteil 401 und der Aufnahme 291 ein Eindringen von Luft beim Entriegeln des Bajonettverschlusses verhindert, falls ein Entriegeln versucht wird, wenn der Behälterteil 351 an der seitlichen Öffnung 161 nur teilweise verschlossen ist.

Nach Wunsch kann ein lösliches Arzneimittel ohne Schmerzen für den Patienten injiziert werden, indem man das Arzneimittel in eine übliche Spritze aufzieht, an der eine dünnkalibrige Nadel angesetzt ist, und den Stopfen 271 durch eine Öffnung 28a hindurch mit der Nadelspitze der Spritze durchsticht. Das Arzneimittel wird dann in den Kanal 26a eingespritzt und geht

von dort zur Kanüle 23, zu deren Spitze 24 und schließlich in das Blutgefäß des Patienten, vorausgesetzt, daß der als Aufnahme 291 dienende Durchgang abgedichtet bleibt. An den am Ort bleibenden Halterteil 221 kann ein neuer Behälterteil angesetzt werden, um mehr Blut abzusaugen, oder es kann auch die Kanüle 23 aus dem Blutgefäß herausgezogen und dann weggeworfen werden. Der gefüllte Behälterteil wird an ein entsprechendes biochemisches Labor geschickt, wo das Ventil der seitlichen Öffnung 161 zuerst geöffnet wird, worauf der Stöpsel 101 ohne weiteres entfernt, die Untersuchungen vorgenommen und die ganze Einheit dann vernichtet werden kann.

Da die Aufnahme 291 jedesmal versperrt wird, wenn ein Behälter weggenommen wird, kann Blut weder weiter aus dem Kanal 261 aussickern, noch wird es in das Blutgefäß zurückgesaugt.

Die der Erfindung gestellt Aufgabe ist somit erfüllt. Gegenüber den beschriebenen Ausführungsbeispielen sind Abänderungen möglich.

17-

FIG. 1

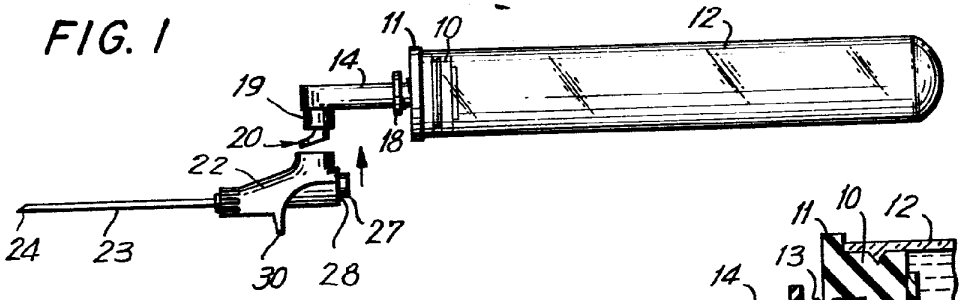


FIG. 2

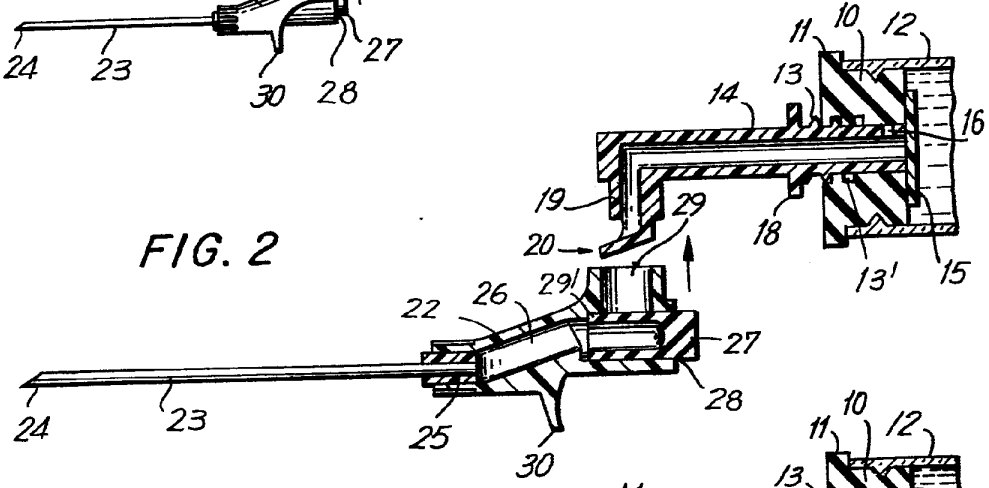


FIG. 3

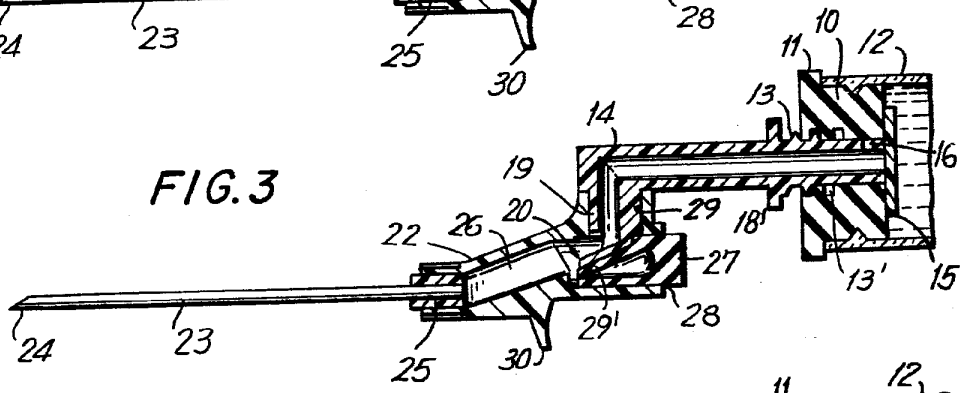


FIG. 4

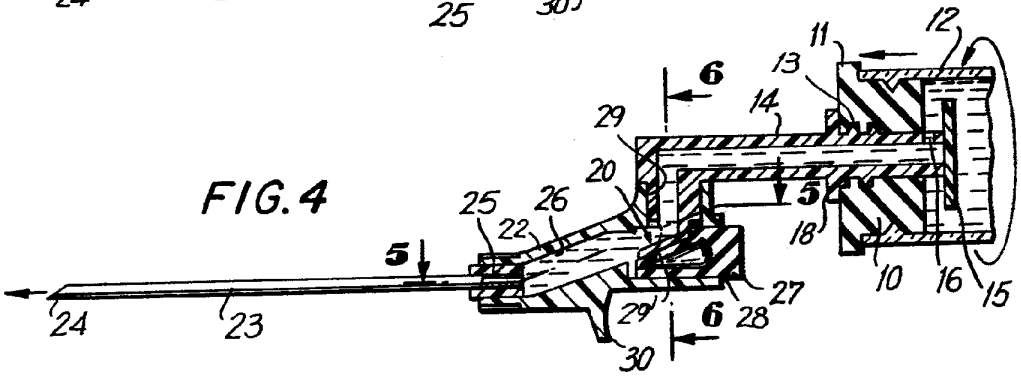


FIG. 5

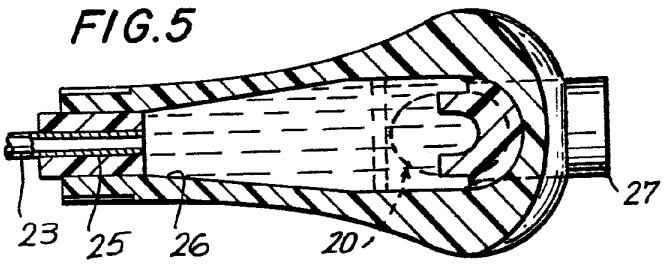
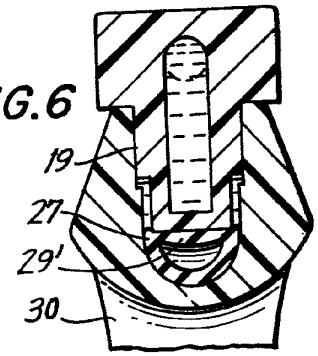


FIG. 6



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FIG. 7

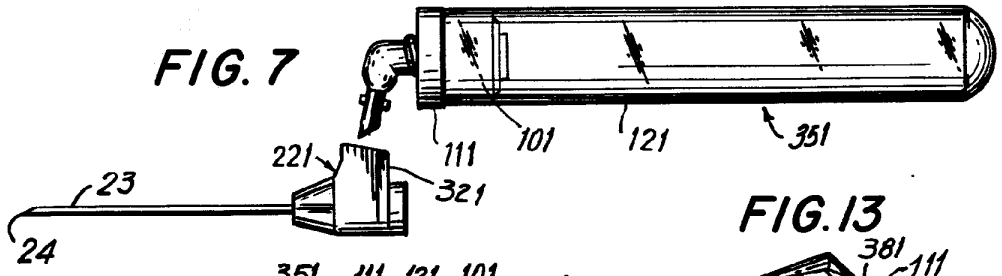


FIG. 13

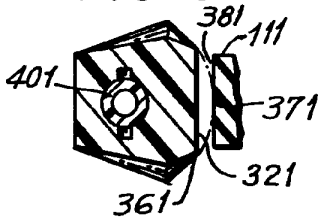


FIG. 8

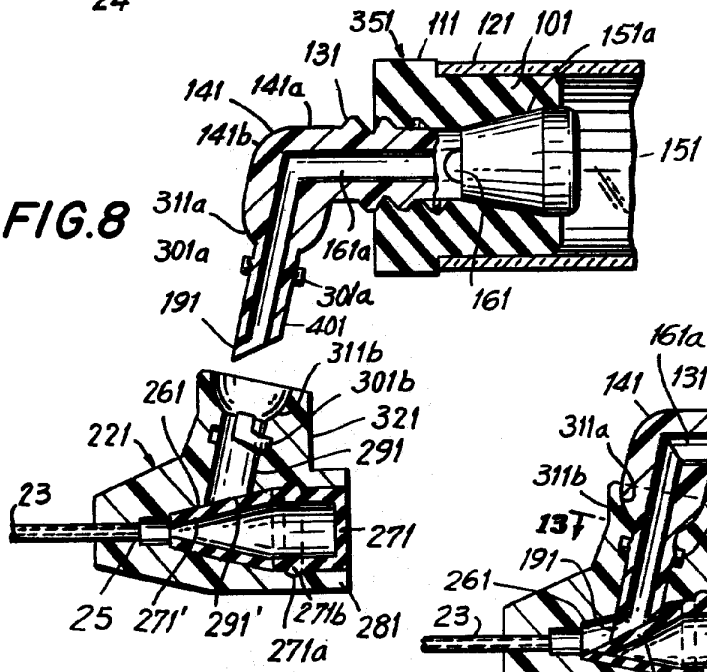


FIG. 9

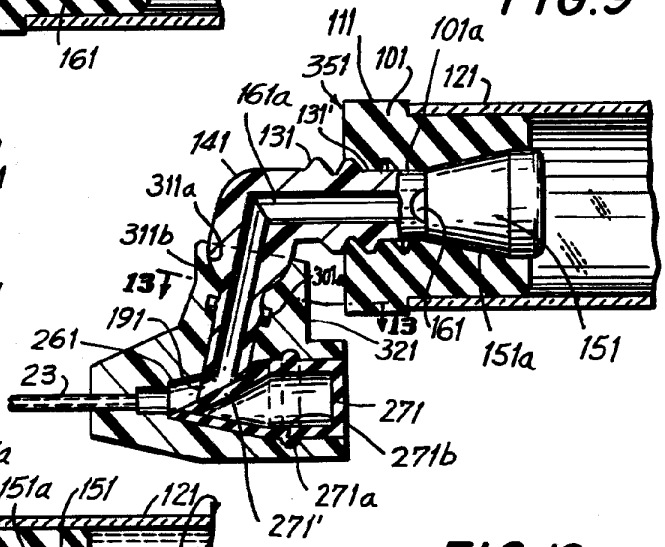


FIG. 10

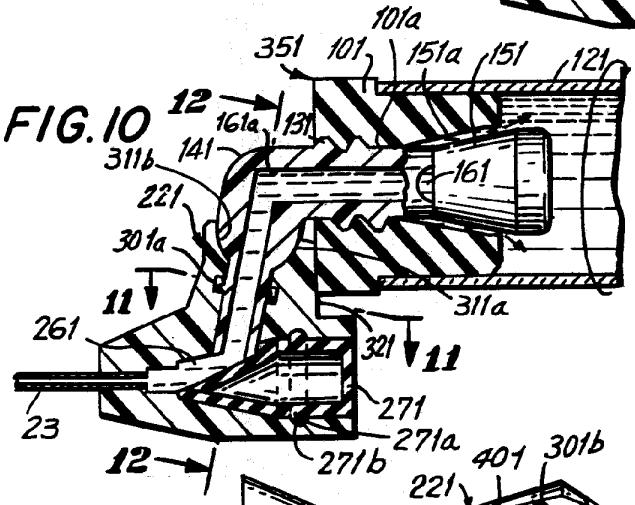


FIG. 12

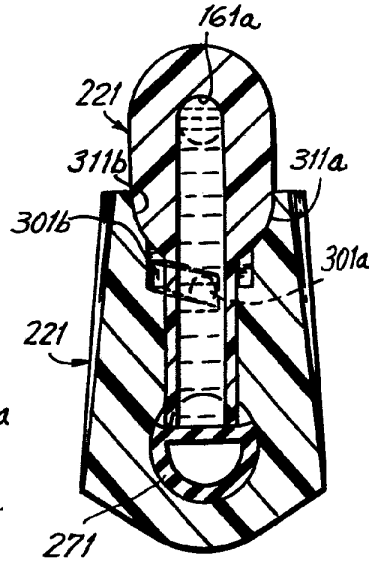
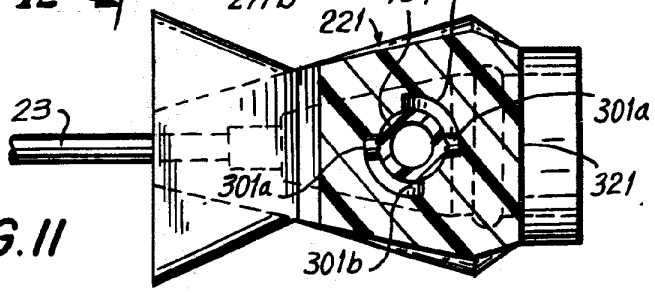


FIG. 11



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bibliography close

(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Published patent publication (A)
(11) [Publication number] JP 2012-16496 (P2012-16496A)
(43) [Published date] January 26, 2012 (2012.1.26)
(54) [Title of Invention] Sampling Port
(51) [International Patent Classification]
A61B 5/15 (2006.01)
A61B 5/154 (2006.01)
A61M 39/02 (2006.01)
[FI]
A61B 5/14 300Z
A61B 5/14 300E
A61M 5/14 459P
[Request for examination] Unclaimed
[Number of claims] 5
[Application form] OL
[Total number of pages] 12

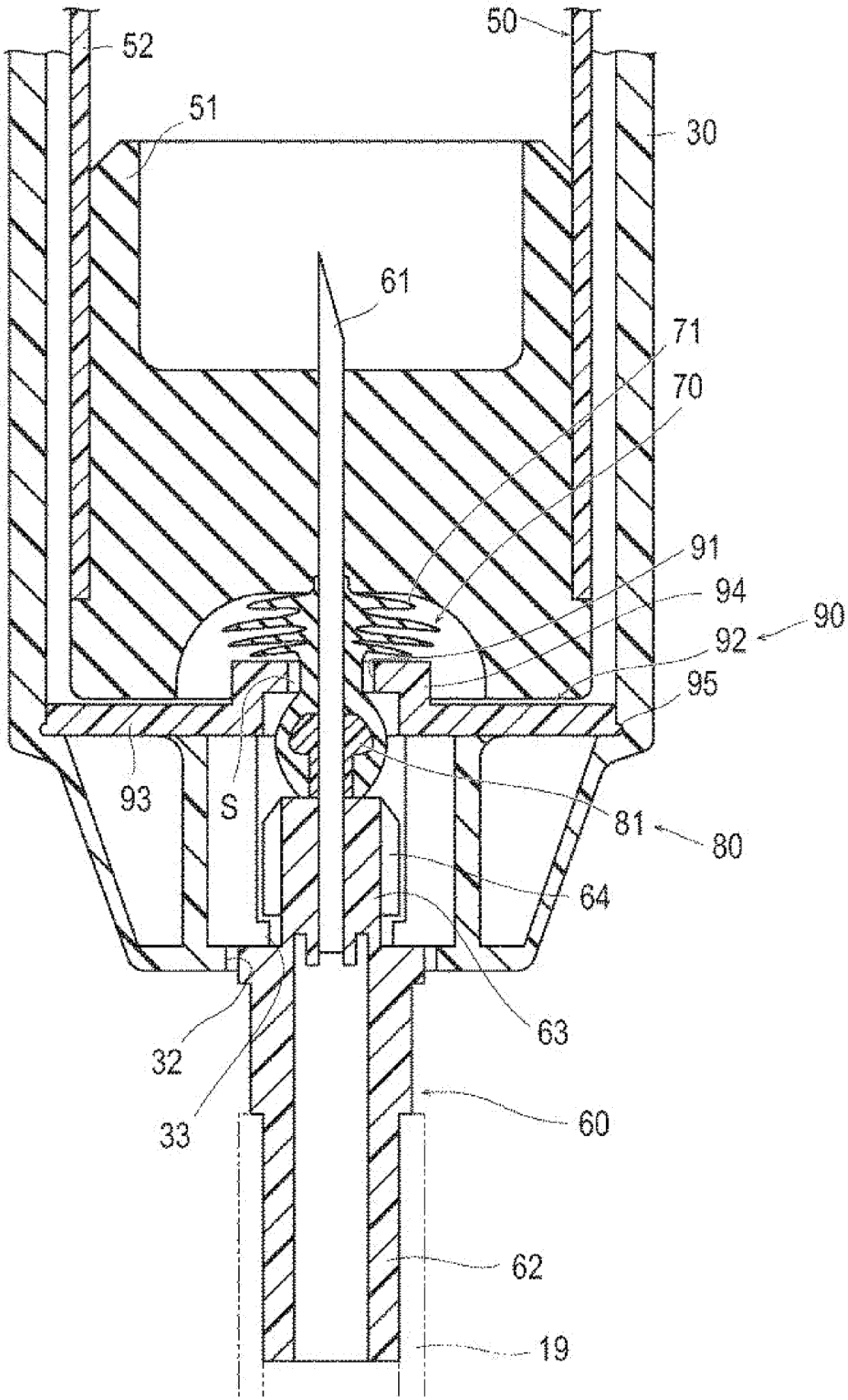
(21) [Application number] Patent Application 2010-156165 (P2010-156165)
(22) [Filing Date] July 8, 2010 (2010.7.8)
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[Theme code (reference)]
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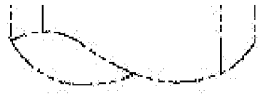
wrap up close

(57) [Summary]
[Problem] To hold a rubber cap on a needle assembly even when the rubber cap is elastically contracted and wrinkled as a hollow needle is passed through a rubber plug of a blood collecti on tube. To provide a sampling port capable of maintaining force and sufficiently preventing le akage of blood.

A sampling port (20) includes a main body (30) formed with an opening (31) for inserting a bl ood collection tube (50) having a rubber plug (51), a hollow needle (61) that can be freely ins erted into the rubber plug of the blood collection tube, and a hollow needle. a needle assembl y 60 attached to the main body, comprising a hub 64 supporting the proximal end of the need le, an elastic rubber cap 70 covering the hollow needle, and a holding portion 80 holding the r ubber cap; A through hole 91 through which a hollow needle covered with a rubber cap penetr ates is provided, and wrinkles 71 generated by elastic contraction of the rubber cap accompan ying insertion of the hollow needle into the rubber stopper are suppressed from reaching the holding portion. and a plate 92 as a suppressing member 90 .

[Selection drawing] Fig. 4


50
52
51
30
61
71
70
91
94
90
92
95
93
S
81
80
64
63
32
33
60
62
19



The scope of the claims open ----

What is claimed is

: 1.

A main body having an opening for inserting a blood collection tube having a rubber plug, a hollow

needle that can be inserted through the rubber plug of the blood collection tube, and the holl ow needle. a needle assembly attached to the main body, comprising: a hub for supporting th e proximal end of the hollow needle; an elastic rubber cap placed on the hollow needle; and a holding portion for holding the rubber cap

; A through hole is provided through which the hollow needle covered with a rubber cap pen etrates, and wrinkles generated by elastic contraction of the rubber cap as the hollow needle i s inserted into the rubber plug reach the holding portion. and a suppression member that sup presses the sampling port.

2.

The body portion is rotatably attached to the needle assembly,

the suppressing member is fixed to the body portion, and between the through hole and the rubber cap, 2. The sampling port of claim 1, having clearance to allow rotation of said body po rtion.

3.

The main body has a cylindrical shape, and

the suppressing member has a disc shape, and has a projection projecting toward the openi ng of the main body. 3. The sampling port of claim 2.

4.

The sampling port according to any one of claims 1 to 3, wherein a ring-shaped projection pr otruding radially outward is provided on the outer peripheral edge of said suppressing membe r.

[Claim 5]

The body portion is made of a resin material that shrinks more than the resin material formi ng the suppressing member when heat is applied, and the suppressing member is shrunk to t he body portion by applying heat for sterilization. A sampling port according to any one of clai ms 1 to 4, fixed with respect to

detailed description open ----

Description: BACKGROUND OF THE INVENTION 1.

Field of the Invention The present invention relates to sampling ports for holding blood collec tion tubes. 2. Description of the Related Art When blood is collected using a blood collection tube with a rubber stopper, a sampling port for holding the blood collection tube is used (see Patent Document 1). The sampling port has a main body with an opening for inserting a blood collection tube, and a needle assembly having a hollow needle that can be freely inserted into the rubber stopper of the blood collection tube is attached to the main body. there is The hollo w needle is covered with an elastic rubber cap to prevent leakage of blood. [0003] As the bl ood collection tube is inserted into the main body of the sampling port and the hollow needle i s passed through the rubber plug, the rubber cap is elastically contracted and wrinkled to exp ose the hollow needle. The exposed hollow needle is used to collect blood into a collection tub e. When the blood collection tube is pulled out after blood collection, the rubber cap is elastica lly stretched from the shrunk state so as to smooth out the wrinkles, and restores to the state where it can be put over the hollow needle again. This prevents leakage of blood from the holl ow needle. The rubber cap is held on the needle assembly by, for example, fitting the root por tion to the needle assembly. [Prior Art Document] [Patent Document] [Patent Document 1] J apanese Patent Application Laid-Open No. 2002-291724 [Summary of the Invention]

[0005] However, when the hollow needle is passed

through the rubber plug of the blood collection tube, the wrinkles caused by the elastic contr action of the rubber cap may reach the base of the rubber cap. There is In such a case, the ro ot portion of the rubber cap swells, weakening the holding force for holding the rubber cap to the needle assembly. For this reason, if the tip of the rubber cap is biting into the small inserti on hole of the rubber stopper of the blood collection tube, the rubber cap will be pulled togeth

er when the blood collection tube is pulled out, and the position of the rubber cap will be affec ted. There is a risk that the blood will not be sufficiently prevented from leaking.

[0006]

The present invention was made in order to solve the above-mentioned problems associated with the prior art. When a hollow needle is passed through a rubber plug of a blood collection tube, the rubber cap is elastically contracted and wrinkled. It is an object of the present inven tion to provide a sampling port capable of maintaining a holding force for holding a rubber cap to a needle assembly even when the needle assembly is closed, thereby sufficiently preventin g leakage of blood. [0007] A sampling port of the present

invention for achieving the above objects comprises a main body having an opening for inser ting a blood collection tube having a rubber stopper, and the blood collection tube . a hollow needle that can be freely inserted into the rubber plug of the above, a hub that supports the b ase end of the hollow needle, an elastic rubber cap that covers the hollow needle, and a holdi ng portion that holds the rubber cap a needle assembly attached to the main body, and a thro ugh hole through which the hollow needle covered with the rubber cap passes, wherein the r ubber cap is elastic as the hollow needle is inserted into the rubber plug a restraining member that restrains wrinkles generated by the contraction from reaching the holding portion.

[0008] The suppressing

member suppresses wrinkles generated by elastic contraction of the rubber cap as the hollo w needle is passed through the rubber stopper of the blood collection tube from reaching the holding portion. , the rubber cap does not swell at the holding part, and the holding force for holding the rubber cap to the needle assembly does not weaken. Therefore, even if the rubber cap is pulled together when the blood collection tube is pulled out after blood collection, the p osition of the rubber cap will not be displaced, and blood leakage can be sufficiently prevente d. Thus, even if the rubber cap is elastically contracted and wrinkled as the hollow needle is p assed through the rubber plug of the blood collection tube, the holding force for holding the ru bber cap to the needle assembly can be maintained, Thus, a sampling port that can sufficientl y prevent blood leakage can be provided.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009]

FIG. 1 is a block diagram showing a blood bag system incorporating a sampling port;

2 is a perspective view showing the initial blood bag shown in FIG. 1 and a sampling port; FI G.

FIG. 3 is a cross-sectional view showing essential parts of a sampling port before a blood colle

ction tube is inserted;

FIG. 4 is a cross-sectional view showing the essential parts of the sampling port after the bloo d collection tube has been inserted;

5(A) is a perspective view showing a plate as a suppressing member, FIG. 5(B) is a cross-sect ional view along line 5B-5B in FIG. 5(A), and FIG. It is sectional drawing which expands and s hows 5C part of FIG.5(B).

6A and 6B are cross-sectional views showing how a plate as a suppressing member is fixed to the main body; FIG.

FIG. 7A is a conceptual diagram for explaining the action of the present embodiment, and FI G. 7B is a conceptual diagram for explaining the action in the case of contrast without a plate;

8A to 8D are cross-sectional views showing modified examples of the plate; FIG.

9A and 9B are plan views showing further modifications of the plate; FIG.

DETAILED DESCRIPTION OF THE INVENTION Embodiments of the present invention will now

be described with reference to the accompanying drawings. In the description of the drawing s, the same elements are denoted by the same reference numerals, and overlapping descripti ons are omitted. Also, the dimensional ratios in the drawings are exaggerated for convenience of explanation, and may differ from the actual ratios.

Referring to FIG .

1, the illustrated blood bag system 10 removes the initial flow (initial blood flow) of the colle cted blood when collecting blood, and uses the initial blood flow as test blood. It is a blood coll ection device. Bacteria present on and under the skin enter along with the skin fragments at t he time of puncture, so the initial blood flow is removed. A blood bag system 10 includes a b lood collecting needle 11, a blood bag 12 containing blood collected through the blood collecti ng needle 11, a blood collecting tube 13 connecting the blood collecting needle 11 and the blo od bag 12, and a blood collecting tube

.

13, an initial blood flow bag 16 communicating with the blood collection tube 13 via a branch t ube 15 connected to the branch connector 14, and a sampling port 20 connected to the end of the initial blood flow bag 16. ,have. The branch connector 14 is provided with a sealing memb er 17 that seals communication with the blood bag 12 . The sealing member 17 seals the com munication with the blood bag 12 until the collection of the initial blood flow into the initial blo od bag 16 is completed. The branch tube 15 is provided with a clamp member 18 that blocks blood flow to the initial blood bag 16 . After collecting the initial blood flow, the clamp membe r 18 clamps the branch tube 15 to block the blood flow to the initial blood bag 16 . After that, the sealing member 17 is opened to start collecting blood into the blood bag 12 .

[0013]

FIG. 2 shows a state in which the initial blood contained in the initial blood bag 16 is collecte d as test blood. A sampling port 20 is connected to a blood extraction tube 19 connected to a

n initial blood bag 16 . A lid member 40 that opens and closes the opening 31 is rotatably con nected to the sampling port 20 via a hinge 41 . When collecting the initial blood contained in t he initial blood bag 16 as test blood, a reduced-pressure blood collection tube 50 (correspondi ng to a blood collection tube) having a rubber plug 51 is inserted into the sampling port 20 thr ough the opening 31 .

A reduced

-pressure blood collection tube 50 is an instrument for collecting the initial blood that is stor ed in the initial blood bag 16 . The vacuum blood collection tube 50 has a blood collection tub e body 52 and a rubber plug 51 fitted into the opening of the blood collection tube body 52 . T he vacuum blood collection tube 50 is in a vacuum or a reduced pressure state. When the vac uum blood collection tube 50 is connected to the sampling port 20 , the rubber stopper 51 is p ierced by the hollow needle 61 . As a result, the inside of the vacuum blood collection tube 50 and the blood extraction tube 19 are communicated, and the initial blood flow from the blood extraction tube 19 is collected in the vacuum blood collection tube 50 .

[0015]

With reference to FIGS. 3 and 4, the sampling port 20 according to the embodiment is gener ally composed of a body portion 30 formed with an opening 31 for inserting a blood collection tube 50 having a rubber plug 51, a blood collection tube A hollow needle 61 that can be freely inserted into the rubber plug 51 of 50, a hub 64 that supports the proximal end of the hollow needle 61, an elastic rubber cap 70 that covers the hollow needle 61, and a holder that holds the rubber cap 70. and a needle assembly 60 attached to the body portion 30 with a portion 8 0 . The sampling port 20 further suppresses wrinkles 71 (see FIG. 4) caused by elastic contra ction of the rubber cap 70 accompanying the insertion of the hollow needle 61 into the rubber stopper 51 from reaching the holding portion 80. It has a member 90 . The suppressing mem ber 90 has a through hole 91 through which the hollow needle 61 covered with the rubber cap 70 passes. 3 and 4, the upper side in the drawings is defined as the "upper side" of each mem ber, and the lower side in the drawings is defined as the "lower side" of each member. Details are given below. The body portion 30 has a cylindrical shape and has a tapered shape on the lower side

.

The main body part 30 has

, an insertion port 32 for inserting the needle assembly 60, and an engaging portion 33 for pr eventing the inserted needle assembly 60 from coming off.

Body

portion 30 is rotatably attached to needle assembly 60 . By making it rotatable, the body po rtion 30 can be rotated with respect to the needle assembly 60 to easily finely adjust the posit ion of the lid member 40 with respect to the initial blood flow bag 16 . A needle assembly 60 includes a hollow needle 61 having a sharp tip at its tip, a connecting portion 62 connected to the blood extraction tube 19, a boss portion 63 holding the proximal end portion of the hollow

needle 61

,

have. The hub 64 is provided so as to protrude radially outward from the boss portion 63 . Th e needle assembly 60 is attached to the body portion 30 with the hub 64 overcoming the locki ng portion 33 when it is inserted into the insertion port 32 of the body portion 30 . The upper end of the hub 64 in the figure is formed into an inclined surface so that it can easily get over the engaging portion 33 when it is inserted. In order to pivotally attach the body portion 30 t o the needle assembly 60, the clearance between the connecting portion 62 of the needle ass embly 60 and the receptacle 32 of the body portion 30 and the outer circumference of the hu b 64

are

and the body portion 30 are adjusted. As the blood collection tube 50 is inserted into the ma in body 30 and the hollow needle 61 is passed through the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrinkles 71, thereby exposing the hollow needle 61

.

Let When the blood collection tube 50 is pulled out, the rubber cap 70 is elastically stretched f rom the shrunk state so as to smooth out the wrinkles 71, and restores to the state where it c overs the hollow needle 61 again. This prevents blood from leaking from the hollow needle 61

.

[0021]

The holding portion 80 includes a lock member 81 through which the hollow needle 61 is ins erted and which is attached to the boss portion 63 of the needle assembly 60 . The locking m ember 81 has an undercut shape in which the base end side of the hollow needle 61 has a sm aller diameter than the tip end side. The undercut shape of the locking member 81 holds the r ubber cap 70 .

5(A) and 5(B), restraining member 90 includes a disk -

shaped flat plate portion 93 fitted in main body portion 30 and a center portion of flat plate portion 93 protruding upward. It consists of a plate 92 with a projection 94 . A through-hole 9 1 through which the hollow needle 61 with the rubber cap 70 is attached is formed in the conv ex portion 94 . As shown in FIG. 5C , a ring-shaped projection 95 projecting radially outward i s provided integrally with the flat plate portion 93 on the outer peripheral edge of the flat plat e portion 93 . 3 and 4, the plate 92 is mounted inside the main body 30 at a position above t he lock member 81 forming the holding portion 80. As shown in FIG

.

As the blood collection tube 50 is inserted into the main body 30 and the hollow needle 61 is passed through the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrin kles 71, thereby exposing the hollow needle 61. . A clearance S between the through hole 91 of the plate 92 and the rubber cap 70 is relatively small. Therefore, the plate 92 prevents the wrinkles 71 generated by the elastic contraction of the rubber cap 70 from reaching the holdin

g portion 80 (FIG. 4).

[0024]

As described above, the body portion 30 is rotatably attached to the needle assembly 60 . A clearance S is provided between the through hole 91 of the plate 92 fixed to the main body 30 and the rubber cap 70 to allow the main body 30 to rotate. By setting the clearance S to a di mension that does not hinder the rotation of the main body 30, the rotational position of the main body 30 with respect to the needle assembly 60, the position of the lid member 40 with respect to the initial blood bag 16, and the like can be easily finely adjusted. becomes possibl e.

By providing the plate 92 with the protrusions 94, it is possible to increase the area of the ru bber cap 70 in the longitudinal direction that is not affected by the wrinkles 71. As shown in F IG . As a result, a decrease in holding force for holding the rubber cap 70 to the needle assem bly 60 can be further suppressed. Even if the arrangement position of the plate 92 is shifted u pward from the position shown in FIG. 4, the area in the longitudinal direction of the rubber c ap 70 that is not affected by the wrinkles 71 can be increased. However, in this case, since th e position of the blood collection tube 50 is also shifted upward, it may be necessary to slightl y increase the longitudinal dimension of the main body 30 . Therefore, by providing the plate 92 with the convex portion 94 projecting toward the opening 31 side of the body portion 30, while maintaining the length of the body portion 30 in the longitudinal direction, It is possible to secure a sufficient holding force for holding the rubber cap 70 to the needle assembly 60 b y increasing the area not affected by the wrinkles 71 .

[0026]

The material of the main body 30, the cover member 40, the needle assembly 60 excluding t he hollow needle 61, the holding part 80, and the plate 92 is not particularly limited, but exa mples thereof include polycarbonate, polyethylene, polypropylene, ethylene- Examples include polyolefins such as vinyl acetate copolymers and modified polyolefins. The material of the ho llow needle 61 is not particularly limited, but examples include various metal materials such a s stainless steel, aluminum or aluminum alloys, titanium or titanium alloys, superelastic alloys such as Ni--Ti alloys, polyphenylene sulfide, and the like

.

and various hard resin materials.

[0028]

The material constituting the rubber cap 70 is not particularly limited, but examples include natural rubber, isoprene rubber, butadiene rubber, styrene-butadiene rubber, nitrile rubber, chl oroprene rubber, butyl rubber, acrylic rubber, ethylene-propylene rubber, hydrin rubber, Variou s rubber materials such as urethane rubber, silicone rubber, and fluororubber can be used.

FIGS.

6A and 6B show how the plate 92 is fixed to the body portion 30. FIG. In this embodiment, t

he body portion 30 is made of a resin material that shrinks more than the resin material formi ng the plate 92 when heat is applied. This is because the plate 92 can be fixed to the body po rtion 30 by applying heat for sterilization. More specifically, as shown in FIG. 6A, before heat is applied, the inner diameter of the main body 30 is relatively large, and the ring-shaped proj ection 95 of the plate 92 bites into the main body 30 by a small amount

.

I'm in. Since the plate 92 can be inserted into the main body 30 relatively easily, the assembl y work of the plate 92 can be easily performed.

Then ,

as shown in FIG. 6(B), when heat is applied for sterilization, for example, in a high-pressure steam sterilization method (autoclave), the main body 30 shrinks more than the plate 92 doe s. As a result, the ring-shaped protrusion 95 of the plate 92 further bites into the body portion 30 , and the plate 92 can be easily fixed to the body portion 30 . As an example of a combin ation of resin materials as described above, for example, polypropylene can be used as the m olding material for the main body 30 and polycarbonate can be used as the molding material f or the plate 92

. [0033]

The operation of this embodiment will be described. When collecting blood, the blood collec tion tube 50 is inserted into the body portion 30 of the sampling port 20, and is hollow

.

A needle 61 is passed through the rubber stopper 51 . As the hollow needle 61 is inserted thr ough the rubber stopper 51, the rubber cap 70 is elastically contracted to form wrinkles 71, th ereby exposing the hollow needle 61. As shown in FIG. Referring to FIG. 7(B), in the case of contrast without plate 92, rubber cap 170 is elastically closed as hollow needle 161 is inserted into rubber plug 51 of blood collection tube 50

.

Wrinkles 171 caused by shrinking may reach the base of the rubber cap 170 . In such a case, the base portion of rubber cap 170 swells, and the holding force for holding rubber cap 170 to needle assembly 160 is weakened. Therefore, when the blood collection tube 50 is pulled out, the rubber cap 170 may be pulled together, and the position of the rubber cap 170 may be dis placed, resulting in insufficient prevention of blood leakage. On the other hand, referring to FIGS. 4 and 7A, in the present embodiment, the plate 92 is positioned above the locking mem ber 81 forming the holding portion 80, and the main

body

It is installed inside the part 30 . The plate 92 prevents wrinkles 71 generated by elastic contr action of the rubber cap 70 as the hollow needle 61 is inserted into the rubber plug 51 of the

blood collection tube 50 from reaching the locking member 81 . Since the rubber cap 70 does not swell at the portion of the lock member 81, the holding force for holding the rubber cap 7 0 to the needle assembly 60 is not weakened.

[0037]

The exposed hollow needle 61 is inserted through the rubber stopper 51 and blood is collect ed into the blood collection tube 50 . When the blood collection tube 50 is pulled out after blo od collection, the rubber cap 70 elastically expands from the shrunk state so as to smooth out the wrinkles 71 and restores to the state where it covers the hollow needle 61 again. This pre vents blood from leaking from the hollow needle 61 . The rubber cap 70 is held by the needle assembly 60 at the locking member 81 .

When the tip of the rubber cap 70 bites into the

minute insertion hole of the rubber stopper 51 of the blood collection tube 50 and the blood collection tube 50 is pulled out, the rubber cap 70 is pulled together. However, since the portio n of the locking member 81 is not affected by the wrinkles 71, the holding force remains set a t the initial stage. Therefore, the rubber cap 70 does not come off from the hollow needle 61 and the blood collection tube 50 is released from biting into the rubber plug 51 . As a result, t he position of the rubber cap 70 is not displaced, and blood leakage can be sufficiently preven ted.

As described

above, even if the rubber cap 70 is elastically contracted as the hollow needle 61 is inserted into the rubber stopper 51 of the blood collection tube 50 and wrinkles 71 are generated, the rubber cap 70 is attached to the needle assembly 60. It is possible to provide the sampling po rt 20 which can maintain a holding force for holding and thereby sufficiently prevent leakage o f blood. Main body 30 is rotatably attached to needle assembly 60 , plate 92 is fixed to main body 30 , and main body 30 is positioned between through hole 91 and rubber cap 70

.

Since there is a clearance S that allows rotation, it is possible to easily finely adjust the rotatio n position of the main body 30 with respect to the needle assembly 60 .

[0041]

In addition, since the plate 92 has a convex portion 94 that protrudes toward the opening 31 side of the body portion 30, the longitudinal length of the rubber cap 70 is increased while ma intaining the length of the body portion 30 in the longitudinal direction. It is possible to secure a sufficient holding force for holding the rubber cap 70 to the needle assembly 60 by enlargin g the area that is not affected by the wrinkles 71 . In addition, since the ring-shaped projecti on 95 projecting radially outward is provided on the outer peripheral edge of the plate 92, the plate 92 is attached to the body portion 30 so that the ring-shaped projection 95 bites into th e body portion 30 by a small amount

.

It can be inserted into the plate 30, and the work of assembling the plate 92 can be easily per

formed.

becomes possible. The main body 30 is made of a resin material that shrinks more than the resin material forming the plate 92 when heat is applied

.

Since it is fixed to the body portion 30, the plate 92 can be relatively easily inserted into the b ody portion 30 before heat is applied, and the plate 92 can be easily assembled. On the other hand, when heat is applied for sterilization, the body portion 30 contracts more than the plate 92 . This makes it possible to easily fix the plate 92 to the body portion 30 .

(

Modified Example of Plate)

The plate has a through hole 91 through which the hollow needle 61 with the rubber cap 70 attached passes. As long as wrinkles 71 generated by elastic contraction of 70 are prevented f rom reaching holding portion 80, the shape can be modified as appropriate.

For example, referring to FIG. 8, a plate 92a (FIG. 8A) in which

a projection 94 smoothly protrudes from a flat plate portion 93, a plate 92b with a thicker ov erall thickness and a flat upper surface, 92c (FIGS. 8B and 8C), and a cap-shaped plate 92d (FIG. 8D) that covers the holding portion 80 without covering the entire bottom surface of the main body portion 30 can be exemplified. Further, referring to FIG. 9, a plate 92e (FIG. 9A) i n which the flat plate portion 93 is not formed with the through portion, and a plate 92f (FIG. 9A) in which the flat plate portion 93 is formed with the through portion 96 are provided

.

(B)).

(

Other modifications)

Although the lock member 81 having an undercut shape has been exemplified as the holding portion 80 that holds the rubber cap 70, the holding portion 80 is not limited to this case. The holding part 80 can be appropriately modified as long as it has a function of preventing the ru bber cap 70 from coming off and holding it in the needle assembly 60 . For example, the holdi ng part 80 uses a form in which the rubber cap 70 is adhered to the hollow needle 61 with an adhesive to hold it, a form in which the rubber cap 70 is held by being fused to the hollow nee dle 61 by ultrasonic fusion, or a clip. For example, a configuration in which the rubber cap 70 i s held on the hollow needle 61 by fitting is exemplified. These holding portions 80 may be use d alone, or may be a holding portion 80 in which two or more types are combined.

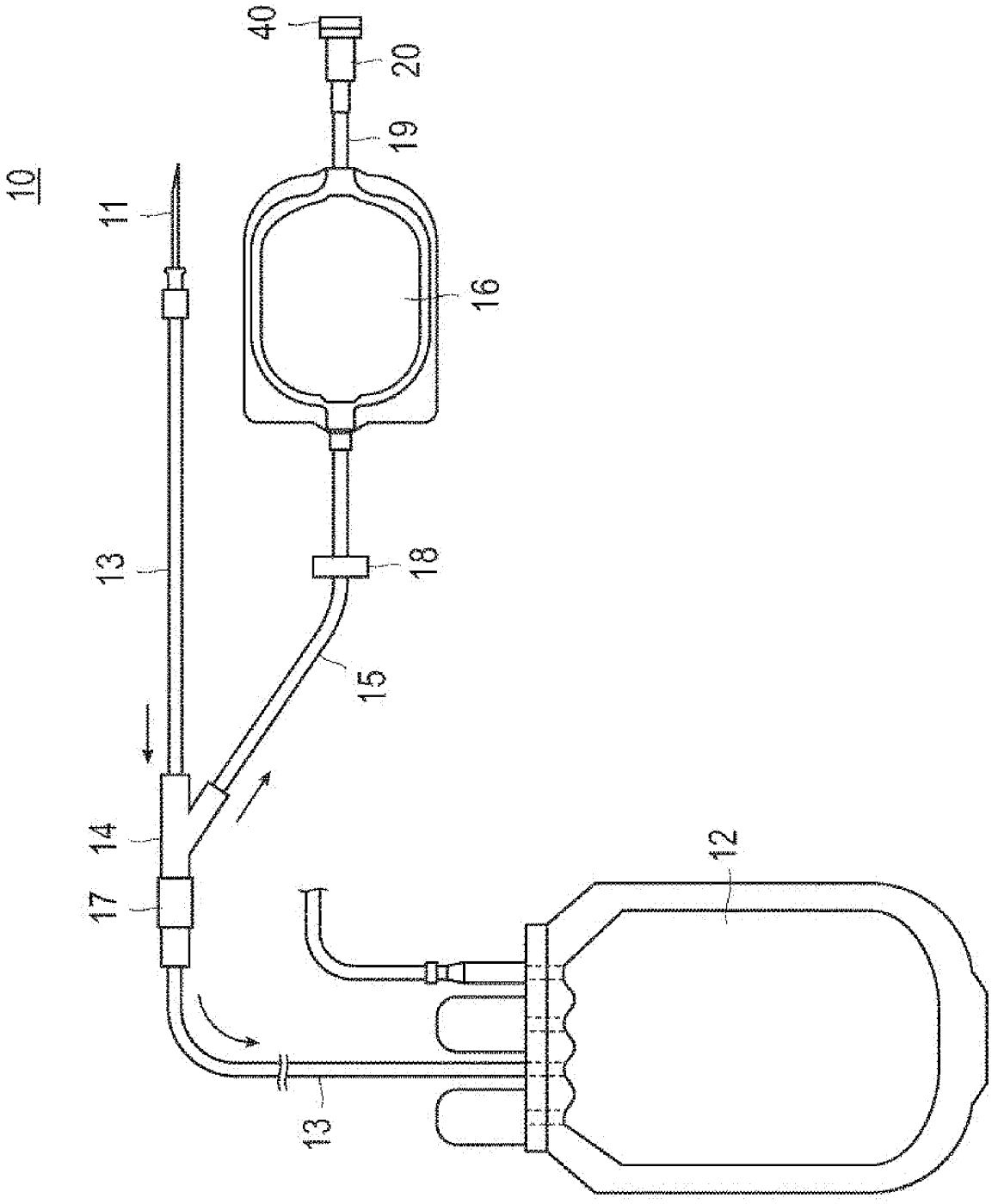
20 sampling port 30 main body 31 opening 50 vacuum

blood collection tube (collection tube) 51 rubber plug 60 needle assembly 61 hollow needle 64 hub 70 rubber cap 71 wrinkles 80 holding part 81 locking member 90 suppressing member 91 through hole 92 plate (suppressing member);

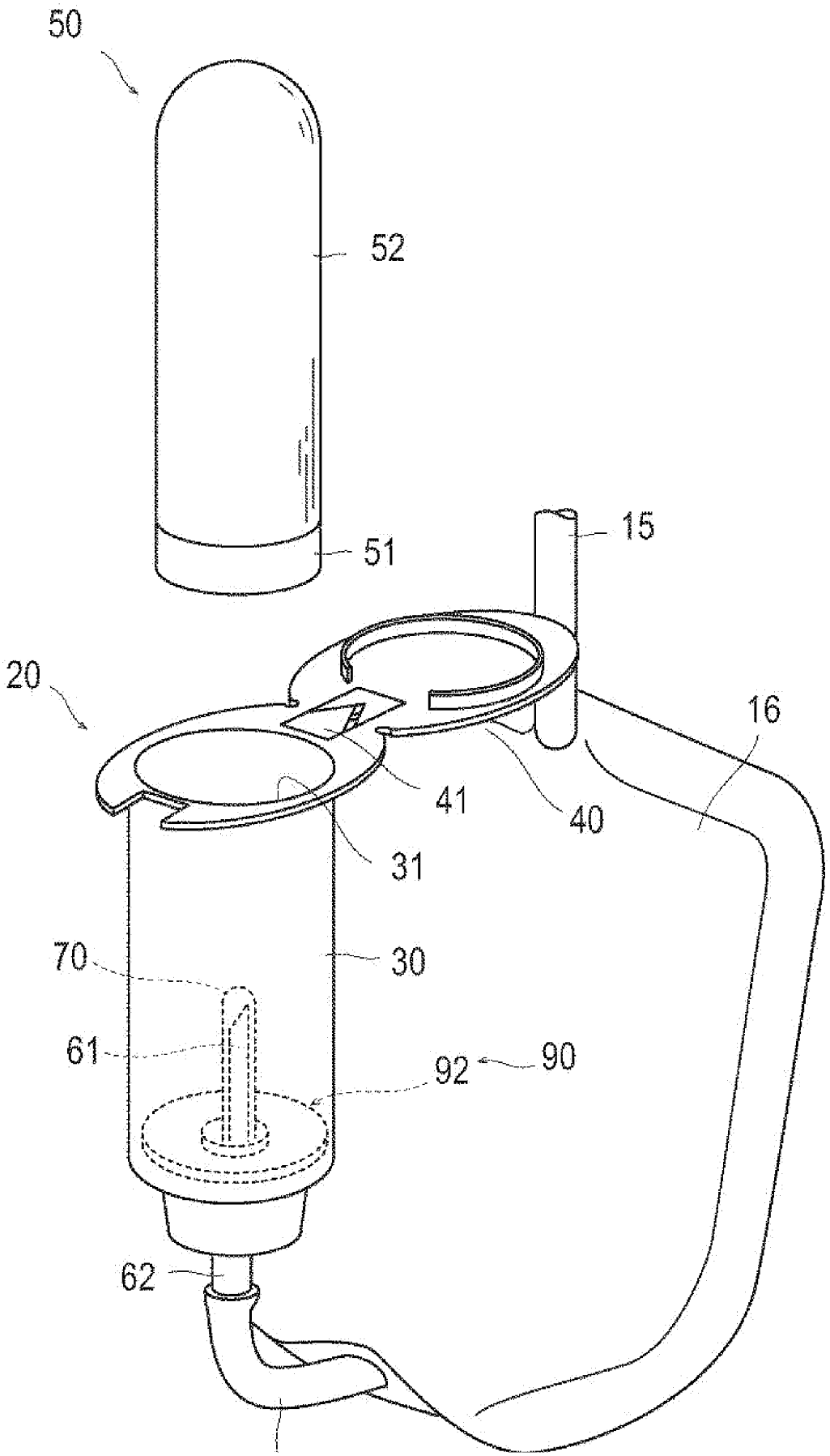
93 flat plate portion,
94 convex portion,
95 ring-shaped projection,
S clearance.

drawing open —

[Fig. 1]

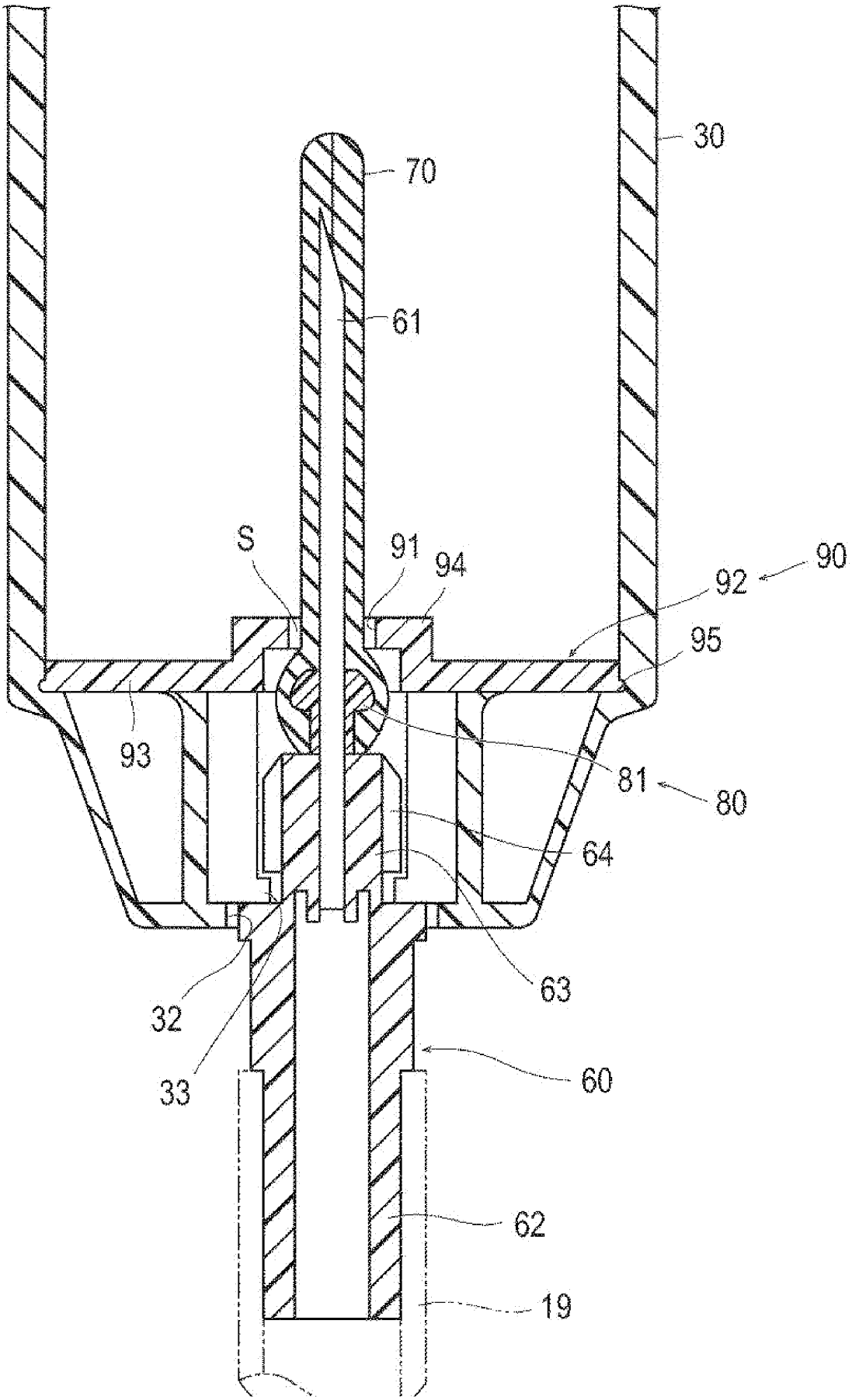


[Figure 2]


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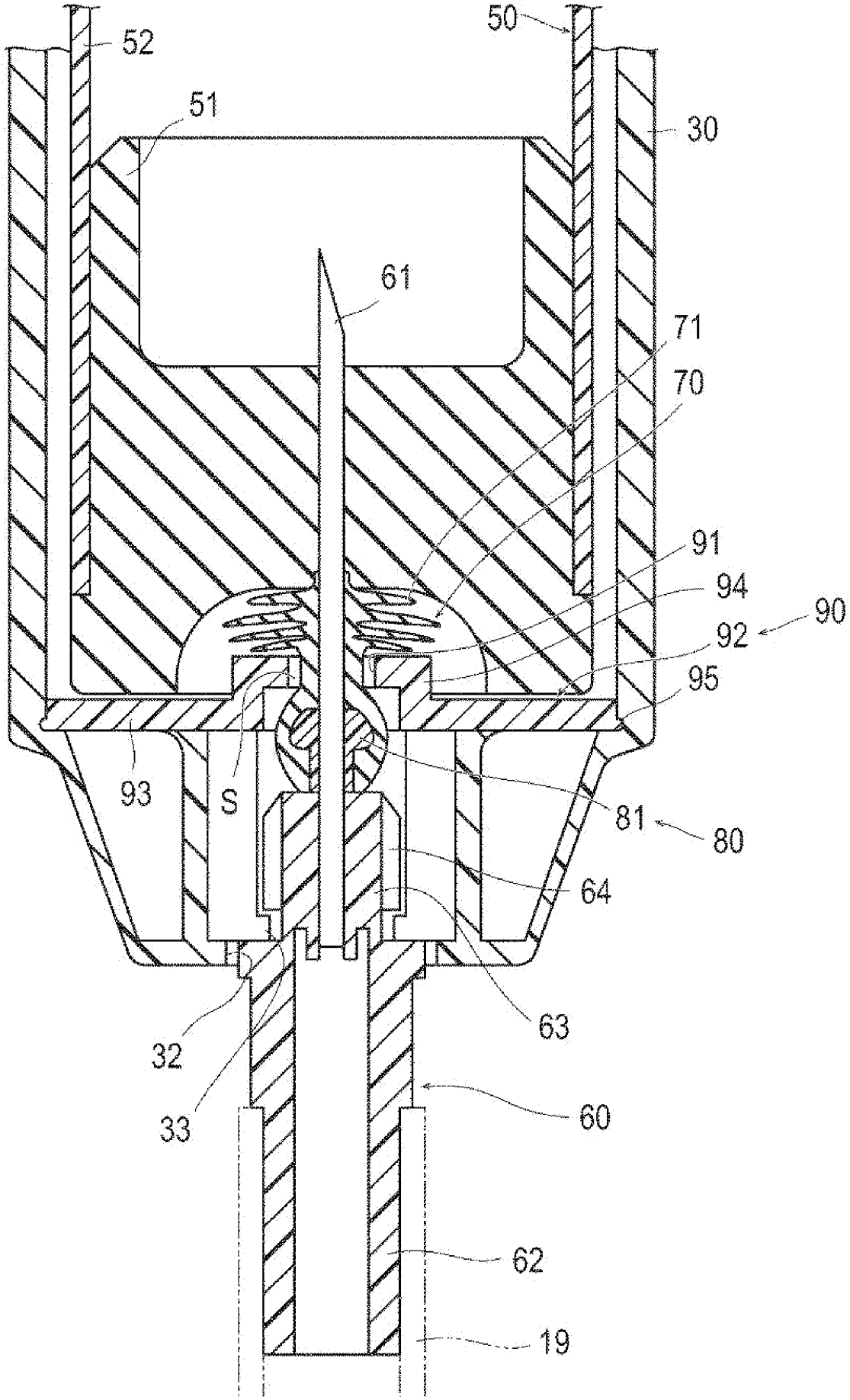
[Figure 3]



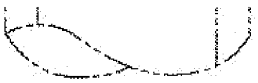

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[Figure 4]

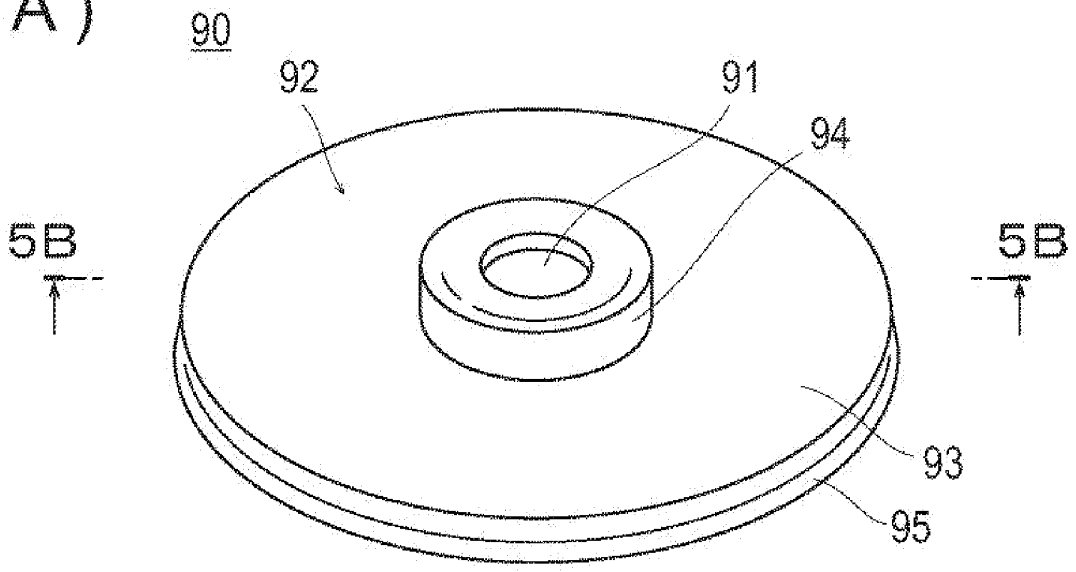



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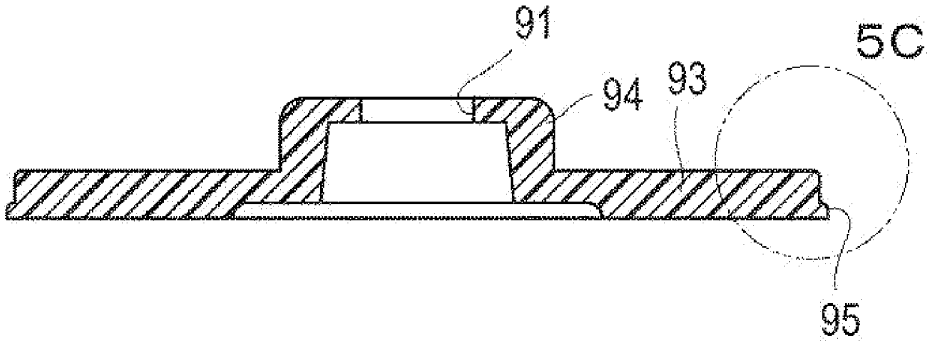
[Figure 5]



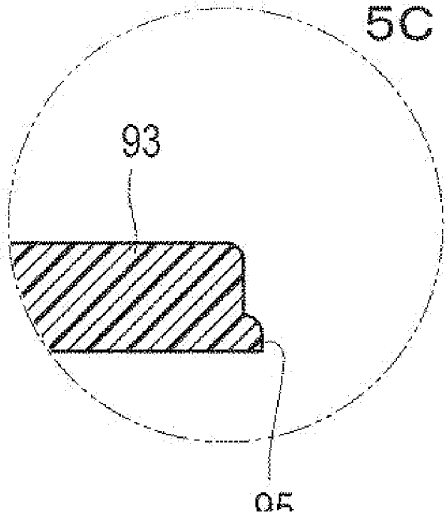
(A)



(B)

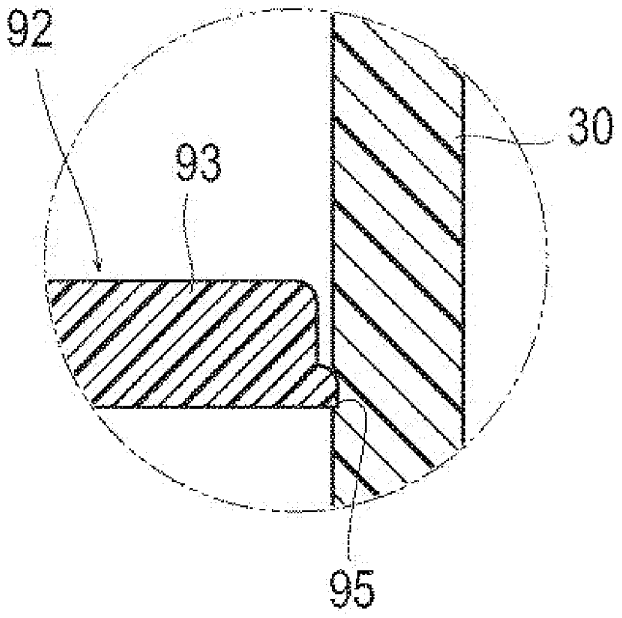


(C)

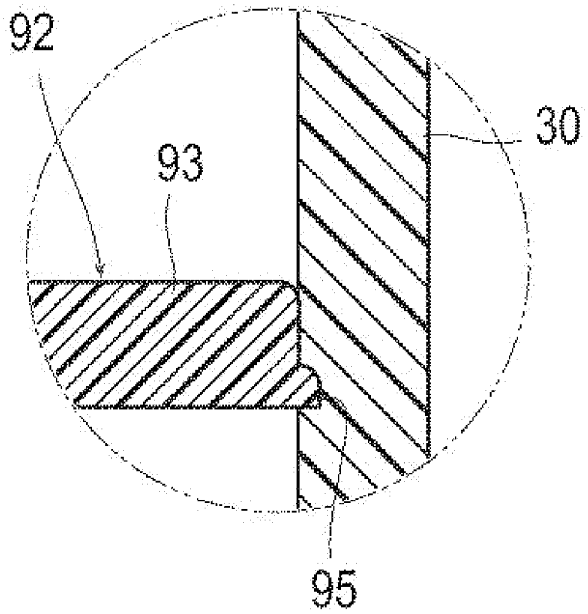


[Fig. 6]

(A)

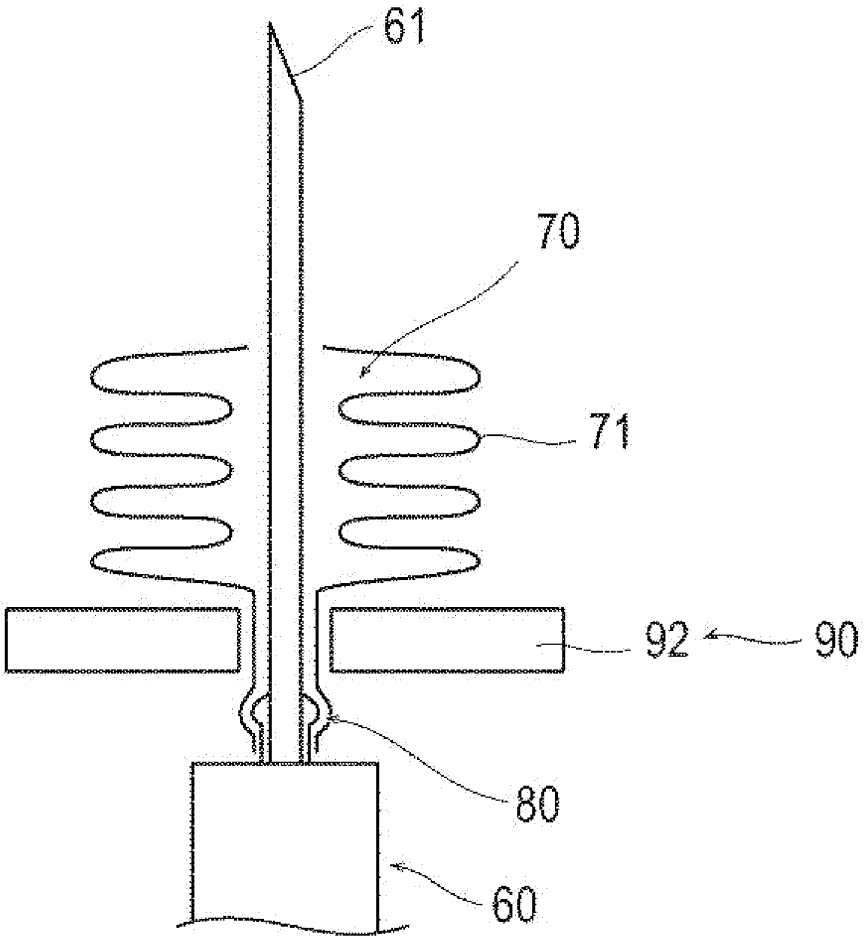


(B)

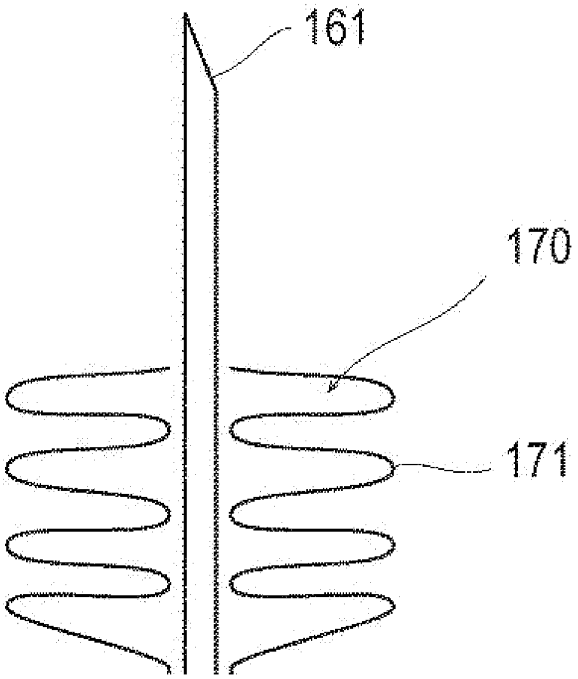


[Fig. 7]

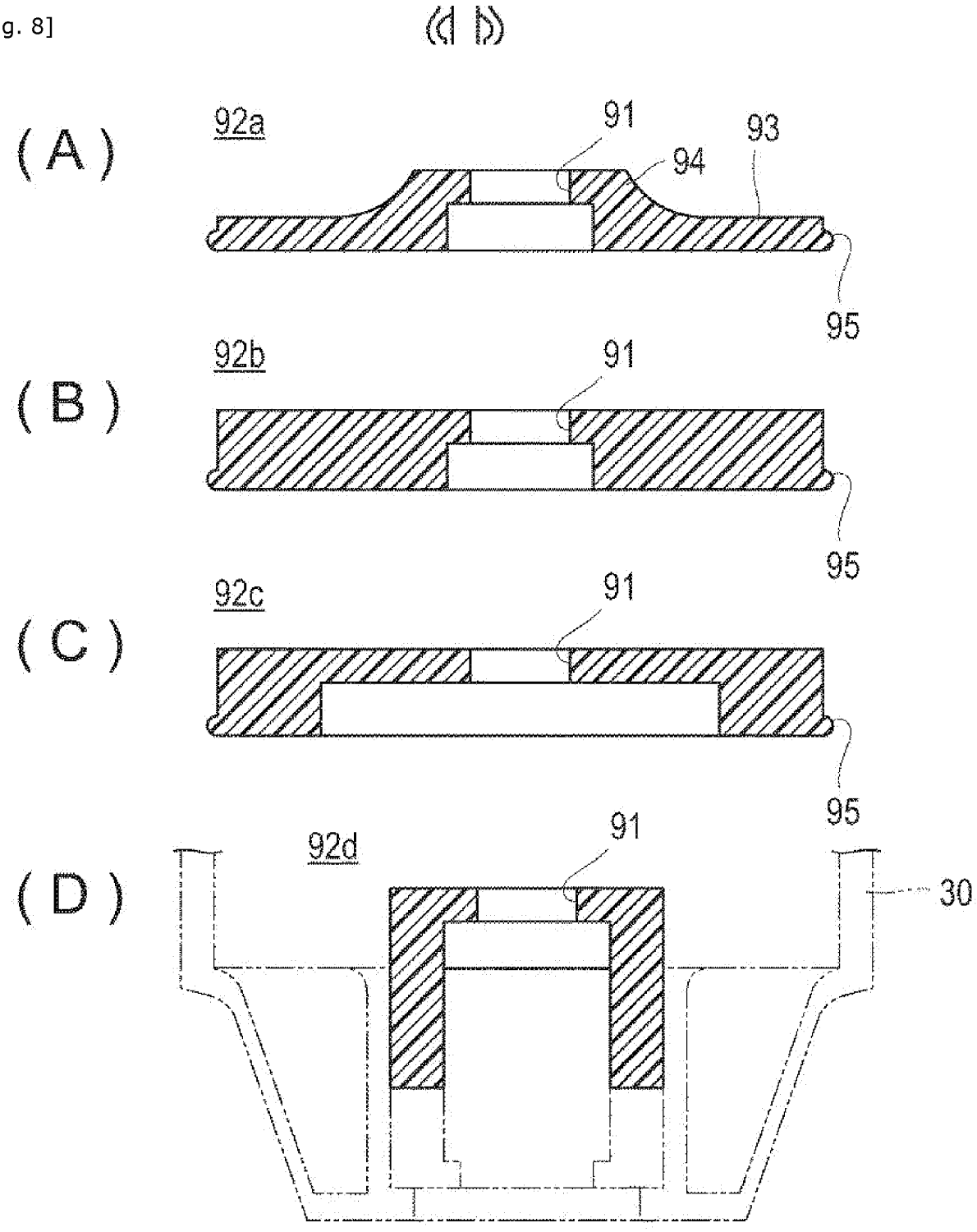
(A)



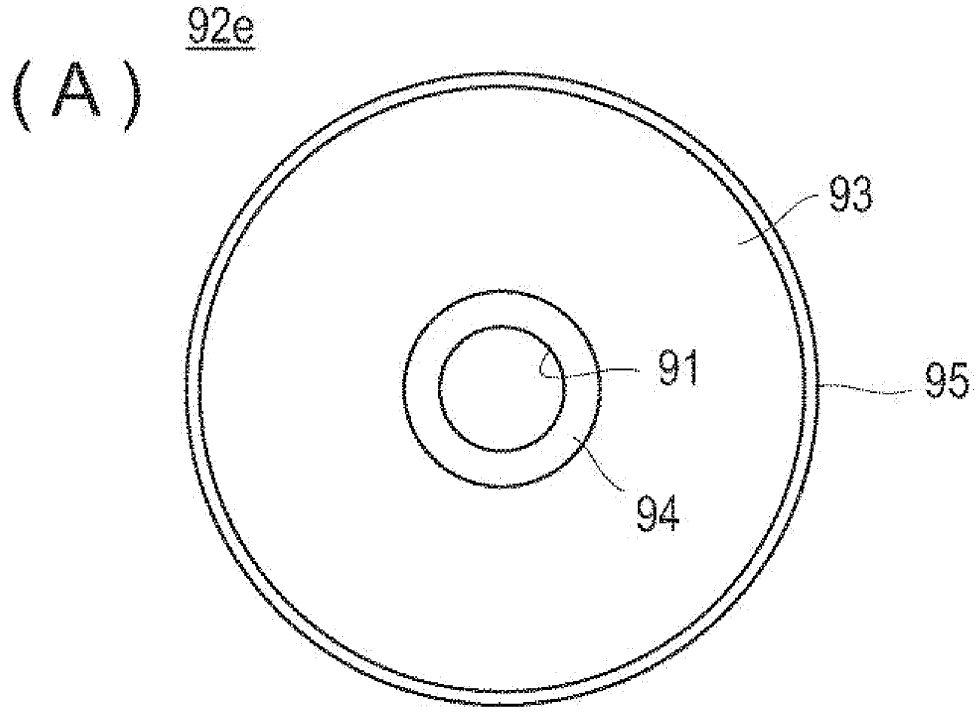
(B)

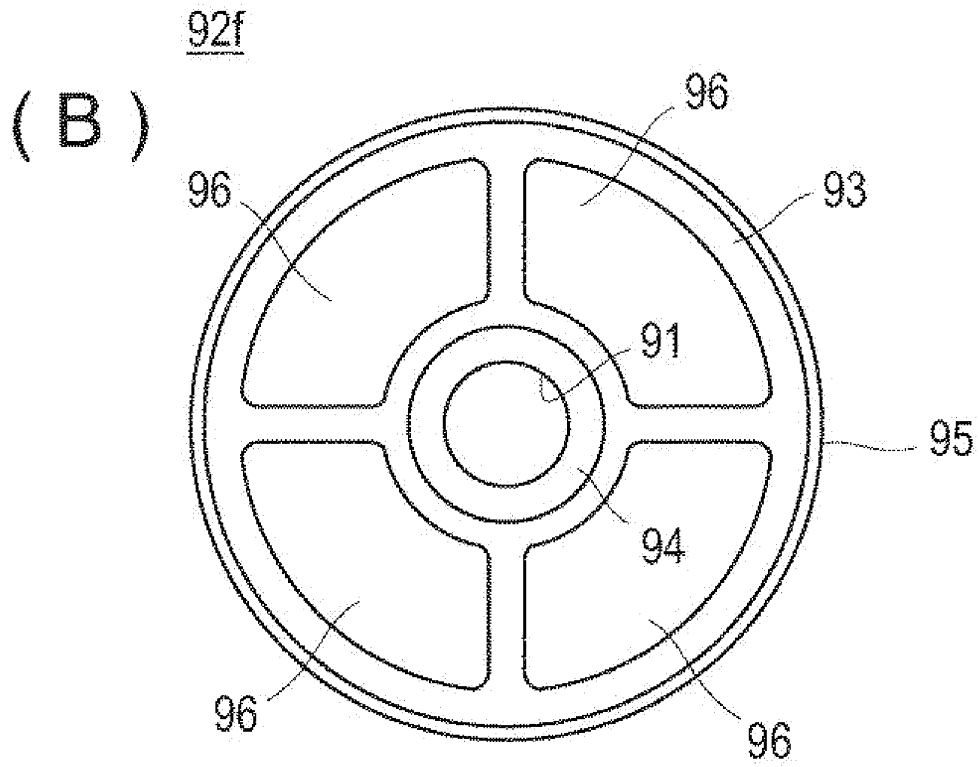


[Fig. 8]



[Fig. 9]

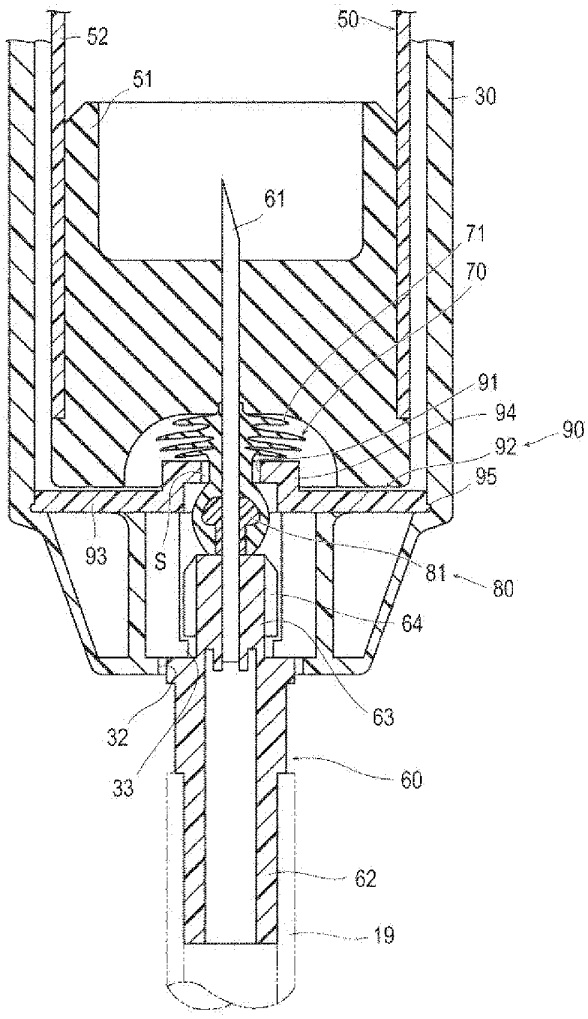

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drawing open

Representative drawing 1 2 3 Four Five 6 7 8 9

Magnify and Rotate



Representative drawing

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(19)日本国特許庁(JP)　(12)公開特許公報(A)　(11)特許出願公開番号
特開2012-16496
(P2012-16496A)
(43)公開日　平成24年1月26日(2012.1.26)

(51)Int.Cl.		F I			テーマコード（参考）
A61B 5/15	***(2006.01)***	A61B	5/14	300Z	4C038
A61B 5/154	***(2006.01)***	A61B	5/14	300E	4C066
A61M 39/02	*(2006.01)*	A61M	5/14	459P	

審査請求 未請求　請求項の数 5　OL　（全 12 頁）

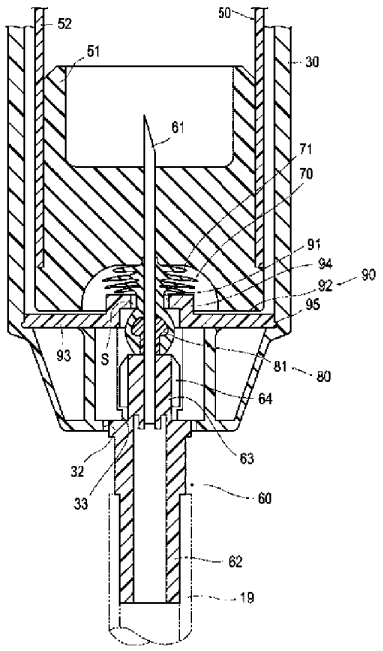
(21)出願番号　特願2010-156165 (P2010-156165)
(22)出願日　平成22年7月8日 (2010.7.8)

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最終頁に続く

(54)【発明の名称】サンプリングポート

(57)【要約】
【課題】採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポートを提供する。
【解決手段】サンプリングポート２０は、ゴム栓５１を備える採血管５０を挿入するための開口部３１が形成された本体部３０と、採血管のゴム栓に挿通自在な中空針６１と、中空針の基端部を支持するハブ６４と、中空針に被せられた弾性を有するゴムキャップ７０と、ゴムキャップを保持する保持部８０と、を備え、本体部に取り付けられた針組立体６０と、ゴムキャップが被せられた中空針が貫通する貫通孔９１を備え、ゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺７１が保持部に達することを抑制する抑制部材９０としてのプレート９２と、を有している。
【選択図】図４



【特許請求の範囲】
【請求項１】
ゴム栓を備える採血管を挿入するための開口部が形成された本体部と、
前記採血管の前記ゴム栓に挿通自在な中空針と、前記中空針の基端部を支持するハブと、前記中空針に被せられた弾性を有するゴムキャップと、前記ゴムキャップを保持する保持部と、を備え、前記本体部に取り付けられた針組立体と、
前記ゴムキャップが被せられた前記中空針が貫通する貫通孔を備え、前記ゴム栓への前記中空針の挿通に伴って前記ゴムキャップが弾性的に縮められることによって生じる皺が前記保持部に達することを抑制する抑制部材と、を有することを特徴とするサンプリングポート。
【請求項２】
前記本体部は、前記針組立体に対して回動自在に取り付けられ、
前記抑制部材は、前記本体部に固定されており、前記貫通孔と前記ゴムキャップとの間に、前記本体部の回動を許容するクリアランスを有する、請求項１に記載のサンプリングポート。
【請求項３】
前記本体部は、円筒形状であり、
前記抑制部材は、円盤形状であり、前記本体部の前記開口部の側に向けて突出する凸部を備えている、請求項１または請求項２に記載のサンプリングポート。
【請求項４】
前記抑制部材の外周縁には、径方向外方に突出するリング状突起が設けられている、請求項１～３のいずれか１つに記載のサンプリングポート。
【請求項５】
前記本体部は、熱を印加したときに前記抑制部材を形成する樹脂材料よりも大きく収縮する樹脂材料から形成されており、滅菌のための熱を印加することによって、前記抑制部材を前記本体部に対して固定する、請求項１～４のいずれか１つに記載のサンプリングポート。
【発明の詳細な説明】
【技術分野】
【０００１】
本発明は、採血管を保持するサンプリングポートに関する。
【背景技術】
【０００２】
ゴム栓を備える採血管を用いて採血するときには、採血管を保持するサンプリングポートが使用される（特許文献１を参照）。サンプリングポートは、採血管を挿入するための開口部が形成された本体部を有し、この本体部には、採血管のゴム栓に挿通自在な中空針を備えた針組立体が取り付けられている。中空針には、血液の漏洩を防止するために、弾性を有するゴムキャップが被せられている。
【０００３】
サンプリングポートの本体部に採血管を挿入し、中空針をゴム栓に挿通させるのに伴って、ゴムキャップは、弾性的に縮められて皺を生じながら中空針を露出させる。露出した中空針は、採血管に採血する。採血後に採血管を引き抜くと、ゴムキャップは、縮んだ状態から、皺を伸ばすように弾性的に伸び、中空針に再び被せられる状態まで復元する。これによって、中空針からの血液の漏洩を防止する。ゴムキャップは、例えば根元部分を針組立体に密着させることによって、針組立体に保持されている。
【先行技術文献】
【特許文献】
【０００４】
【特許文献１】特開２００２－２９１７２４
【発明の概要】

【発明が解決しようとする課題】
【０００５】
しかしながら、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺が、ゴムキャップの根元部に達することがある。このような場合には、ゴムキャップの根元部が膨らんでしまい、ゴムキャップを針組立体に保持するための保持力が弱くなる。このため、採血管のゴム栓の微小な挿通孔にゴムキャップの先端部が食い込んでいるような場合においては、採血管を引き抜くときにゴムキャップが一緒に引っ張られてしまい、ゴムキャップの位置などがずれてしまい、血液の漏洩の防止が不十分になる虞がある。
【０００６】
本発明は、上記従来技術に伴う課題を解決するためになされたものであり、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポートを提供することを目的とする。
【課題を解決するための手段】
【０００７】
上記目的を達成するための本発明のサンプリングポートは、ゴム栓を備える採血管を挿入するための開口部が形成された本体部と、
前記採血管の前記ゴム栓に挿通自在な中空針と、前記中空針の基端部を支持するハブと、前記中空針に被せられた弾性を有するゴムキャップと、前記ゴムキャップを保持する保持部と、を備え、前記本体部に取り付けられた針組立体と、
前記ゴムキャップが被せられた前記中空針が貫通する貫通孔を備え、前記ゴム栓への前記中空針の挿通に伴って前記ゴムキャップが弾性的に縮められることによって生じる皺が前記保持部に達することを抑制する抑制部材と、を有している。
【発明の効果】
【０００８】
抑制部材によって、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められることによって生じる皺が保持部に達することが抑制されているので、保持部の部分でゴムキャップが膨らむことがなく、ゴムキャップを針組立体に保持するための保持力が弱くならない。このため、採血後に採血管を引き抜くときにゴムキャップが一緒に引っ張られてしまっても、ゴムキャップの位置などがずれることがなく、血液の漏洩を十分に防止することが可能となる。このように、採血管のゴム栓への中空針の挿通に伴ってゴムキャップが弾性的に縮められて皺が生じても、ゴムキャップを針組立体に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポートを提供できる。
【図面の簡単な説明】
【０００９】
【図１】サンプリングポートが組み込まれた血液バッグシステムを示す構成図である。
【図２】図１に示される初流血バッグと、サンプリングポートとを示す斜視図である。
【図３】採血管を挿入する前のサンプリングポートの要部を示す断面図である。
【図４】採血管を挿入した後のサンプリングポートの要部を示す断面図である。
【図５】図５（Ａ）は、抑制部材としてのプレートを示す斜視図、図５（Ｂ）は、図５（Ａ）の５Ｂ－５Ｂ線に沿う断面図、図５（Ｃ）は、図５（Ｂ）の５Ｃ部分を拡大して示す断面図である。
【図６】図６（Ａ）（Ｂ）は、抑制部材としてのプレートを本体部に対して固定する様子を示す断面図である。
【図７】図７（Ａ）は、本実施形態の作用の説明に供する概念図、図７（Ｂ）は、プレートを設けていない対比例の場合の作用の説明に供する概念図である。
【図８】図８（Ａ）～（Ｄ）は、プレートの改変例を示す断面図である。
【図９】図９（Ａ）（Ｂ）は、プレートのさらなる改変例を示す平面図である。

【発明を実施するための形態】
【００１０】
以下、添付した図面を参照しながら、本発明の実施形態を説明する。なお、図面の説明において同一の要素には同一の符号を付し、重複する説明を省略する。また、図面の寸法比率は、説明の都合上誇張されており、実際の比率とは異なる場合がある。
【００１１】
図１を参照して、図示する血液バッグシステム１０は、血液を採取する際に、採取された血液の初流（初流血）を除去し、その初流血を検査用血液として利用する採血器具である。皮膚上や皮下に存在する細菌が穿刺時の皮膚のかけらとともに侵入するため、初流血を除去している。
【００１２】
血液バッグシステム１０は、採血針１１と、採血針１１を介して採取された血液を収納する血液バッグ１２と、採血針１１と血液バッグ１２とを連通する採血チューブ１３と、採血チューブ１３の途中に配置した分岐コネクタ１４と、分岐コネクタ１４に接続した分岐チューブ１５を介して採血チューブ１３に連通する初流血バッグ１６と、初流血バッグ１６の端部に接続されたサンプリングポート２０と、を有している。分岐コネクタ１４には血液バッグ１２への連通を封止する封止部材１７が設けられている。初流血バッグ１６への初流血の採血が終わるまで、封止部材１７は血液バッグ１２への連通を封止している。分岐チューブ１５には、初流血バッグ１６への血流を遮断するクランプ部材１８が設けられている。初流血の採血が終わると、クランプ部材１８によって分岐チューブ１５をクランプし、初流血バッグ１６への血流が遮断される。その後、封止部材１７を開放し、血液バッグ１２への採血を開始する。
【００１３】
図２には、初流血バッグ１６に収納した初流血を検査用血液として回収するときの状態が示されている。初流血バッグ１６に接続された血液取出チューブ１９にサンプリングポート２０が接続されている。サンプリングポート２０には、開口部３１を開閉する蓋部材４０がヒンジ４１を介して回動自在に接続されている。初流血バッグ１６に収納した初流血を検査用血液として回収するときには、ゴム栓５１を備える減圧採血管５０（採血管に相当する）が開口部３１からサンプリングポート２０内に挿入される。
【００１４】
減圧採血管５０は、初流血バッグ１６内に貯留された初流血を採取するための器具である。この減圧採血管５０は、採血管本体５２と、この採血管本体５２の開口に嵌め込まれているゴム栓５１と、を有している。減圧採血管５０内は、真空または減圧状態になっている。減圧採血管５０は、サンプリングポート２０に接続されたとき、ゴム栓５１が中空針６１によって刺通される。これによって、減圧採血管５０内と血液取出チューブ１９とが連通し、当該血液取出チューブ１９からの初流血が減圧採血管５０に回収される。
【００１５】
図３および図４を参照して、実施形態に係るサンプリングポート２０は、概説すれば、ゴム栓５１を備える採血管５０を挿入するための開口部３１が形成された本体部３０と、採血管５０のゴム栓５１に挿通自在な中空針６１と、中空針６１の基端部を支持するハブ６４と、中空針６１に被せられた弾性を有するゴムキャップ７０と、ゴムキャップ７０を保持する保持部８０と、を備え、本体部３０に取り付けられた針組立体６０と、を有している。サンプリングポート２０はさらに、ゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１（図４を参照）が保持部８０に達することを抑制する抑制部材９０を有している。抑制部材９０は、ゴムキャップ７０が被せられた中空針６１が貫通する貫通孔９１を備えている。なお、図３および図４において図中上側を各部材における「上部側」とし、図中下側を各部材における「下部側」とする。以下詳述する。
【００１６】
本体部３０は、円筒形状を有し、下部側は先細りの形状を有している。本体部３０には

、針組立体６０を差し込むための差込口３２と、差し込まれた針組立体６０の抜けを防止する係止部３３とが設けられている。

【００１７】

本体部３０は、針組立体６０に対して回動自在に取り付けられている。回動自在にすることによって、本体部３０を針組立体６０に対して回動させて、初流血バッグ１６に対する蓋部材４０の位置などを簡単に微調整することができる。

【００１８】

針組立体６０は、先端に鋭利な針先を有する中空針６１と、血液取出チューブ１９に接続される接続部６２と、中空針６１の基端部を保持するボス部６３と、を有している。ハブ６４は、ボス部６３の径方向外方へ突出するように設けている。針組立体６０は、本体部３０の差込口３２に差し込むときにハブ６４が係止部３３を乗り越えて、本体部３０に取り付けられる。ハブ６４の図中上端は、差し込むときに係止部３３を乗り越え易いように傾斜面に形成されている。

【００１９】

本体部３０を針組立体６０に対して回動自在に取り付けるために、針組立体６０の接続部６２と本体部３０の差込口３２との間のクリアランス、およびハブ６４の外周と本体部３０との間のクリアランスの寸法が調整されている。

【００２０】

ゴムキャップ７０は、本体部３０に採血管５０を挿入させ、中空針６１をゴム栓５１に挿通させるのに伴って、弾性的に縮められて皺７１を生じながら中空針６１を露出させる。採血管５０を引き抜くと、ゴムキャップ７０は、縮んだ状態から、皺７１を伸ばすように弾性的に伸び、中空針６１に再び被せられる状態まで復元する。これによって、中空針６１からの血液の漏洩を防止する。

【００２１】

保持部８０は、中空針６１が挿通されるとともに針組立体６０のボス部６３に取り付けられたロック部材８１から構成されている。ロック部材８１は、中空針６１の基端部側が先端側よりも小径部となったアンダーカット形状を有している。ロック部材８１におけるアンダーカット形状によって、ゴムキャップ７０を保持している。

【００２２】

図５（Ａ）（Ｂ）を参照して、抑制部材９０は、本体部３０内に嵌り込む円盤形状の平板部９３と、平板部９３の中央部分において上部側に向けて突出する凸部９４とを有するプレート９２から構成されている。凸部９４に、ゴムキャップ７０が取り付けられた中空針６１が貫通する貫通孔９１が形成されている。図５（Ｃ）に示すように、平板部９３の外周縁には、径方向外方に突出するリング状突起９５が、平板部９３と一体的に設けられている。

【００２３】

図３および図４を再び参照して、プレート９２は、保持部８０をなすロック部材８１よりも上部側の位置において、本体部３０内に取り付けられている。本体部３０に採血管５０を挿入し、中空針６１をゴム栓５１に挿通させるのに伴って、ゴムキャップ７０は、弾性的に縮められて皺７１を生じながら中空針６１を露出させている。プレート９２の貫通孔９１とゴムキャップ７０との間のクリアランスＳは比較的小さい。したがって、プレート９２によって、ゴムキャップ７０が弾性的に縮められることによって生じる皺７１が保持部８０に達することが抑制される（図４）。

【００２４】

前述のように本体部３０は、針組立体６０に対して回動自在に取り付けられている。そして、本体部３０に固定されたプレート９２の貫通孔９１とゴムキャップ７０との間に、本体部３０の回動を許容するクリアランスＳを設定してある。クリアランスＳを本体部３０の回動を阻害しない寸法に設定することによって、針組立体６０に対する本体部３０の回動位置や、初流血バッグ１６に対する蓋部材４０の位置などを簡単に微調整することが可能となる。

【００２５】
プレート９２に凸部９４を備えさせることによって、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくすることができる。その結果、ゴムキャップ７０を針組立体６０に保持するための保持力の低下をより一層抑えることができる。プレート９２の配置位置を図４に示される位置から上部側にずらしても、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくすることができる。但し、この場合には、採血管５０の位置も上部側にずれるため、本体部３０の長手方向の長さ寸法を若干大きくする必要が生じる場合がある。したがって、プレート９２に本体部３０の開口部３１の側に向けて突出する凸部９４を備えさせることによって、本体部３０の長手方向の長さを維持したまま、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくして、ゴムキャップ７０を針組立体６０に保持するための十分な保持力を確保することが可能となる。

【００２６】
本体部３０、蓋部材４０、中空針６１を除いた針組立体６０、保持部８０、およびプレート９２の構成材料としては、特に限定されないが、例えば、ポリカーボネート、ポリエチレン、ポリプロピレン、エチレン－酢酸ビニル共重合体等のポリオレフィン、変性ポリオレフィンが挙げられる。

【００２７】
中空針６１の構成材料としては、特に限定されないが、例えば、ステンレス鋼、アルミニウムまたはアルミニウム合金、チタンまたはチタン合金、Ｎｉ－Ｔｉ合金等の超弾性合金等の各種金属材料、ポリフェニレンサルファイド等の各種硬質樹脂材料等が挙げられる。

【００２８】
また、ゴムキャップ７０の構成材料としては、特に限定されないが、例えば、天然ゴム、イソプレンゴム、ブタジエンゴム、スチレン－ブタジエンゴム、ニトリルゴム、クロロプレンゴム、ブチルゴム、アクリルゴム、エチレン－プロピレンゴム、ヒドリンゴム、ウレタンゴム、シリコーンゴム、フッ素ゴムのような各種ゴム材料が挙げられる。

【００２９】
図６（Ａ）（Ｂ）に、プレート９２を本体部３０に対して固定する様子が示される。本実施形態においては、本体部３０は、熱を印加したときにプレート９２を形成する樹脂材料よりも大きく収縮する樹脂材料から形成してある。滅菌のための熱を印加することによって、プレート９２を本体部３０に対して固定することができるからである。

【００３０】
さらに詳しくは、図６（Ａ）に示すように、熱を印加する前では、本体部３０の内径が比較的大きく、プレート９２のリング状突起９５が若干寸法だけ本体部３０に食い込んでいる。プレート９２を比較的簡単に本体部３０内に挿入できることから、プレート９２の組み込み作業を行いやすい。

【００３１】
そして、図６（Ｂ）に示すように、滅菌のために行われる例えば高圧蒸気滅菌法（オートクレーブ）における熱を印加すると、本体部３０がプレート９２よりも大きく収縮する。これによって、プレート９２のリング状突起９５が本体部３０にさらに食い込み、プレート９２を本体部３０に対して簡単に固定することができる。

【００３２】
上記のような樹脂材料の組み合わせ例として、例えば、本体部３０の成形材料としてポリプロピレンを適用し、プレート９２の成形材料としてポリカーボネートを適用することができる。

【００３３】
本実施形態の作用を説明する。

【００３４】
採血するときには、サンプリングポート２０の本体部３０に採血管５０を挿入し、中空

針６１をゴム栓５１に挿通させる。ゴム栓５１に中空針６１が挿通するのに伴って、ゴムキャップ７０は、弾性的に縮められて皺７１を生じながら中空針６１を露出させる。

【００３５】

図７（Ｂ）を参照して、プレート９２を設けていない対比例の場合には、採血管５０のゴム栓５１への中空針１６１の挿通に伴ってゴムキャップ１７０が弾性的に縮められることによって生じる皺１７１が、ゴムキャップ１７０の根元部に達することがある。このような場合には、ゴムキャップ１７０の根元部が膨らんでしまい、ゴムキャップ１７０を針組立体１６０に保持するための保持力が弱くなる。このため、採血管５０を引き抜くときにゴムキャップ１７０が一緒に引っ張られてしまい、ゴムキャップ１７０の位置などがずれてしまい、血液の漏洩の防止が不十分になる虞がある。

【００３６】

これに対して、図４および図７（Ａ）を参照して、本実施形態にあっては、プレート９２を、保持部８０をなすロック部材８１よりも上部側の位置において、本体部３０内に取り付けている。このプレート９２によって、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１がロック部材８１に達することが抑制される。ロック部材８１の部分でゴムキャップ７０が膨らむことがないので、ゴムキャップ７０を針組立体６０に保持するための保持力が弱くならない。

【００３７】

露出した中空針６１は、ゴム栓５１に挿通されて、採血管５０に採血する。採血後に採血管５０を引き抜くと、ゴムキャップ７０は、縮んだ状態から、皺７１を伸ばすように弾性的に伸び、中空針６１に再び被せられる状態まで復元する。これによって、中空針６１からの血液の漏洩を防止する。ゴムキャップ７０は、ロック部材８１の部分で針組立体６０に保持されている。

【００３８】

採血管５０のゴム栓５１の微小な挿通孔にゴムキャップ７０の先端部が食い込んだ状態で採血管５０を引き抜くと、ゴムキャップ７０が一緒に引っ張られる。しかし、ロック部材８１の部分は皺７１の影響を受けていないので、保持力は初期に設定したままである。このため、ゴムキャップ７０は、中空針６１から抜けずに、採血管５０のゴム栓５１への食い込みが解除される。これによって、ゴムキャップ７０の位置などがずれることがなく、血液の漏洩を十分に防止することが可能となる。

【００３９】

このように、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められて皺７１が生じても、ゴムキャップ７０を針組立体６０に保持するための保持力を維持でき、もって、血液の漏洩を十分に防止し得るサンプリングポート２０を提供できる。

【００４０】

また、本体部３０は針組立体６０に対して回動自在に取り付けられ、プレート９２は本体部３０に固定されており、貫通孔９１とゴムキャップ７０との間に本体部３０の回動を許容するクリアランスＳを有するため、針組立体６０に対する本体部３０の回動位置などを簡単に微調整することが可能となる。

【００４１】

また、プレート９２は、本体部３０の開口部３１の側に向けて突出する凸部９４を備えているため、本体部３０の長手方向の長さを維持したまま、ゴムキャップ７０の長手方向のうち皺７１の影響を受けない範囲を大きくして、ゴムキャップ７０を針組立体６０に保持するための十分な保持力を確保することが可能となる。

【００４２】

また、プレート９２の外周縁に径方向外方に突出するリング状突起９５を設けているため、リング状突起９５を若干寸法だけ本体部３０に食い込ませるようにしてプレート９２を本体部３０内に挿入させることができ、簡単にプレート９２の組み込み作業を行うこと

が可能となる。

【００４３】

また、本体部３０は、熱を印加したときにプレート９２を形成する樹脂材料よりも大きく収縮する樹脂材料から形成されており、滅菌のための熱を印加することによって、プレート９２を本体部３０に対して固定するため、熱を印加する前ではプレート９２を比較的簡単に本体部３０内に挿入でき、プレート９２の組み込み作業を行いやすい。一方、滅菌のための熱を印加すると、本体部３０がプレート９２よりも大きく収縮する。これによって、プレート９２を本体部３０に対して簡単に固定することができる。

【００４４】

（プレートの改変例）

プレートは、ゴムキャップ７０が取り付けられた中空針６１が貫通する貫通孔９１を備え、採血管５０のゴム栓５１への中空針６１の挿通に伴ってゴムキャップ７０が弾性的に縮められることによって生じる皺７１が保持部８０に達することを抑制する限りにおいて適宜の形状に改変することができる。

【００４５】

例えば、図８を参照して、凸部９４を平板部９３から滑らかに突出させたプレート９２ａ（図８（Ａ））、全体の厚みを厚くし上面を平坦面としたプレート９２ｂ、９２ｃ（図８（Ｂ）（Ｃ））、本体部３０の底面全体を覆わずに保持部８０に被せるようなキャップ形状を有するプレート９２ｄ（図８（Ｄ））などを例示することができる。

【００４６】

また、図９を参照して、平板部９３に貫通部を形成しないタイプのプレート９２ｅ（図９（Ａ））、平板部９３に貫通部９６を形成したタイプのプレート９２ｆ（図９（Ｂ））とすることもできる。

【００４７】

（その他の改変例）

ゴムキャップ７０を保持する保持部８０として、アンダーカット形状を有するロック部材８１を例示したが、保持部８０はこの場合に限定されるものではない。保持部８０は、針組立体６０に設けられゴムキャップ７０の抜けを防止して保持する機能を有している限りにおいて適宜改変することができる。例えば、保持部８０は、接着剤によってゴムキャップ７０を中空針６１に接着させて保持する形態、超音波融着によってゴムキャップ７０を中空針６１に融着させて保持する形態、クリップなどを用いた嵌め込みによってゴムキャップ７０を中空針６１に保持する形態などを例示することができる。これらの保持部８０を単独で用いてもよいし、２種以上を組み合わせた保持部８０であってもよい。

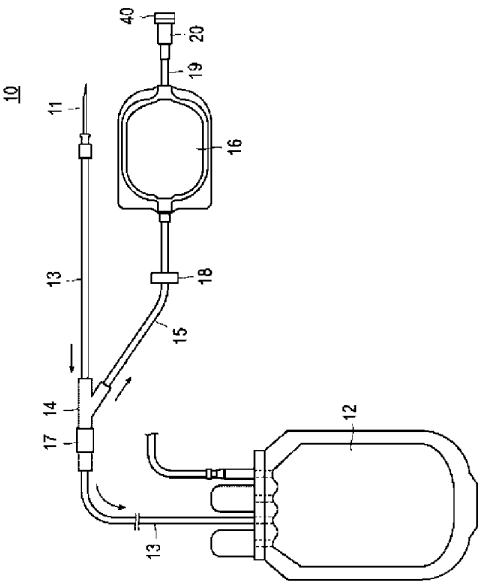
【符号の説明】

【００４８】

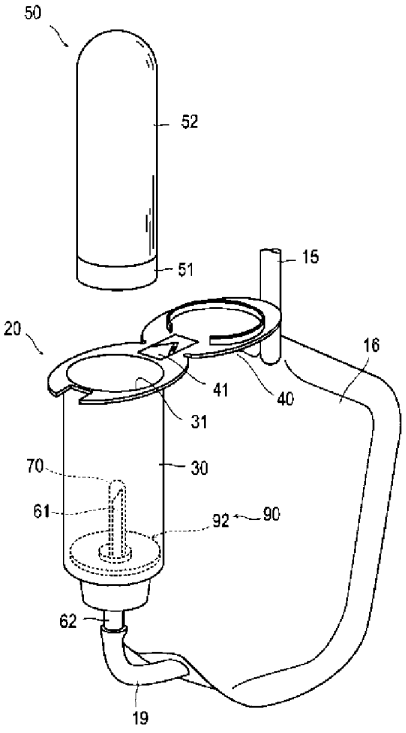
２０　サンプリングポート、
３０　本体部、
３１　開口部、
５０　減圧採血管（採血管）、
５１　ゴム栓、
６０　針組立体、
６１　中空針、
６４　ハブ、
７０　ゴムキャップ、
７１　皺、
８０　保持部、
８１　ロック部材、
９０　抑制部材、
９１　貫通孔、
９２　プレート（抑制部材）、

９３　　平板部、
９４　　凸部、
９５　　リング状突起、
Ｓ　　クリアランス。

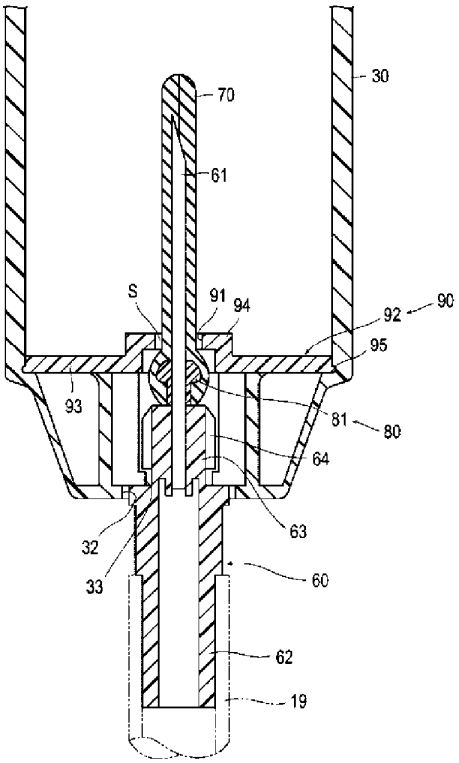
【図１】



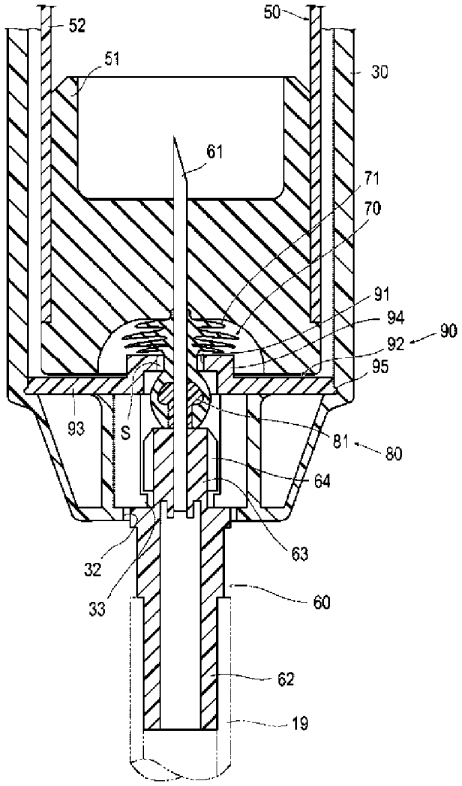
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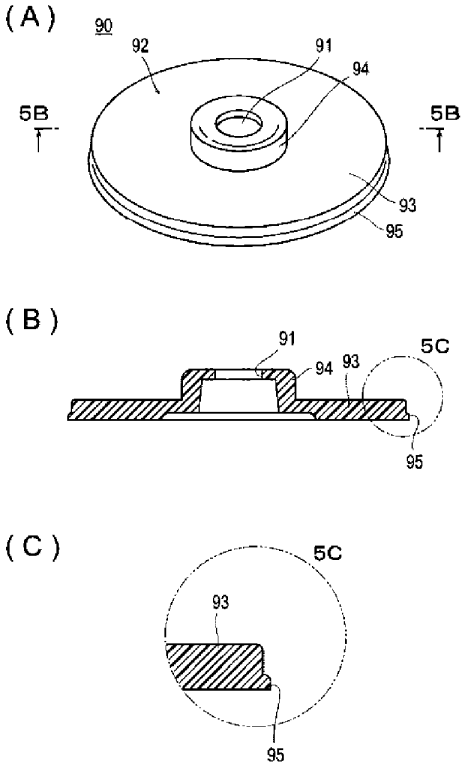
【図３】


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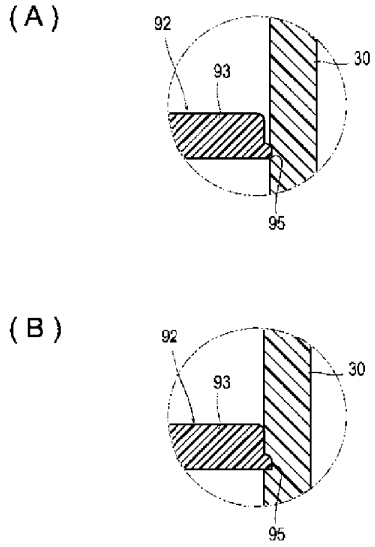
【図４】


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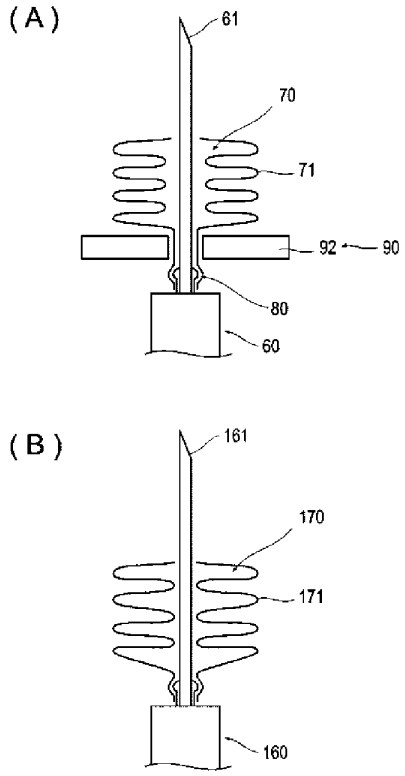
【図５】


(A)
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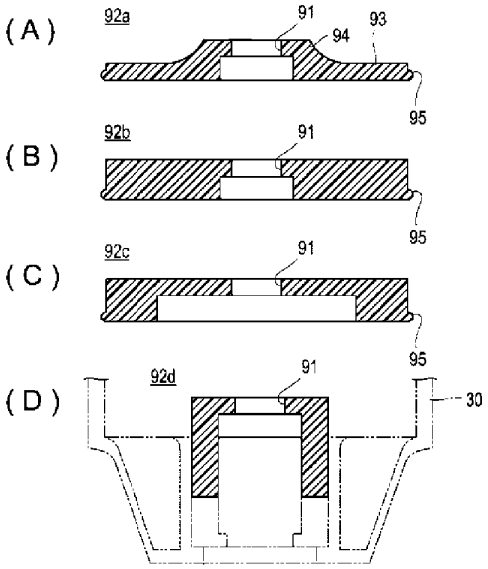
【図６】


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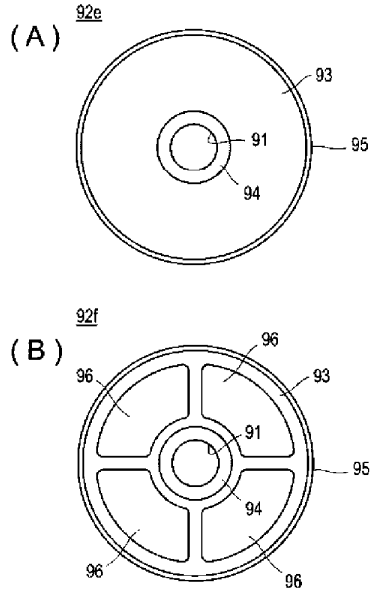
【図７】


(A)
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(B)
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【図８】


(A)
92a
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(B)
92b
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(C)
92c
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95
(D)
92d
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【図９】


(A)
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Ｆターム(参考) 4C038 TA01 TA10 UA10 UB07 UF03 UF11 UF14
4C066 AA07 BB10 FF05 JJ08

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Patent 6734490

bibliography close

(19) [Country of issue] Japan Patent Office (JP)
(12) [Type of publication] Patent publication (B2)
(11) [Patent number] Patent No. 6734490 (P6734490)
(24) [Registration date] Reiwa 2 July 13, 2020 (2020.7.13)
(45) [Date of issue] August 5, 2020 (2020.8.5)
(54) [Title of invention] Blood isolation device, body fluid isolation device, and blood isolation system
(51) [International Patent Classification]
A61B 5/15 (2006.01)
A61B 5/154 (2006.01)
[FI]
A61B 5/15 200
A61B 5/154 200
[Number of Claims] 26
[Foreign language application]
[All pages Number] 39
(21) [Application number] Patent application 2020-340 (P2020-340)

(22) [Application date] January 6, 2020 (2020.1.6)
(62) [Indication of division] Patent application Division of 2018-523384 (P2018-523384) [Original filing date] July 22, 2016 (2016.7.22) (65) [Publication number] JP 2020-96843 (P2020-96843A) (43) [Publication date]] June 25, 2020 (2020.6.25)

[Date of request for examination] January 31, 2020 (January 31, 2020)
(31) [Priority claim number] 62/238,636
(32) [Priority date] October 7, 2015 (October 7, 2015)
(33) [Country/region or organization claiming priority] United States (US)
(31) [Priority claim number] 62/318,194
(32) [Priority date] April 4, 2016 (2016.4.4)
(33) [Priority claiming country/region or organization] United States (US)
(31) [Priority claim number] 62/196,797
(32) [Priority date] July 24, 2015 (2015.7.24)
(33) [Priority Country/Territory or Organization] United States (US)
(31) [Priority claim number] 15/140,448
(32) [Priority date] April 27, 2016 (2016.4.27)
(33) [Priority claim Country/region or organization] United States (US)
(31) [Priority claim number] 15/140,443
(32) [Priority date] April 27, 2016 (2016.4.27)
(33) [Priority claim country/ Region or institution] United States (US)
[Application subject to accelerated examination]
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[Examiner] Hirokatsu Shimizu
(56) [Reference]
[Reference] Japanese Patent Application Laid-Open No. 58-025146 (JP, A) [Reference] Japanese Patent Application Laid-Open No. 58-067238 (JP, A) [Reference] Japanese Patent Application Laid- Open No. 2012-016496 (JP, A) [Document] JP-A-57-089869 (JP, A) [Document] JP-A-09-504726 (JP, A) [Document] JP-A-02-224742 (JP, A) 2005-349196 (JP, A) [Reference]

US Patent No. 04207870 (US, A)
[Reference] US Patent Application Publication No. 2013/0116599 (US, A1) [Reference] US Patent Application Publication No. 2011/0306899 (US, A1) (58) [Fields searched] (Int.Cl., DB name)A61B 5/153-5/154

The scope of the claims — open

(57) [Claims]
[Claim 1]
A blood isolation device comprising
an inlet port, an

outlet port, an

isolation chamber and a sampling channel, wherein each of the isolation chamber and the sa mpling channel has an isolation chamber connected to the inlet port via a bifurcation, the isol ation chamber having a vent containing an air permeable blood barrier, and the sampling chan nel having a distal end connected to the outlet port; a sampling channel, and a housing contai ning

and defining the inlet port, the outlet port, the isolation chamber, and the sampling channel, wherein the isolation chamber, the sampling channel, and the bifurcation point are connecte d to the flow of blood. A first portion of blood flows into the isolation chamber toward the air p ermeable blood barrier for sequestration within the isolation chamber and a second portion of the blood flows into the isolation chamber and the blood isolated within the isolation chamber. A blood isolation device sized and configured to bypass the first portion and direct the samplin g channel toward the outlet port. 2. A blood isolation device, comprising: an inlet port;

an isolation chamber having an exit port,

a vent containing an air permeable blood barrier, a sampling channel

having a distal end connected to said exit port, said

entrance port, said exit port, said isolation chamber, and said a housing containing and defini ng a sampling flow path

,

each of said isolation chamber and said sampling flow path being connected to said inlet port via a bifurcation point, said bifurcation point connecting said first portion of blood to said isola tion fluid; a second portion of blood flowing into the chamber to expel air in the isolation cha mber through the air permeable blood barrier and to be isolated in the isolation chamber; a bl ood isolation device sized and configured to bypass the first portion of the blood that has been drawn and directed into the sampling flow path toward the outlet port.

3.

The blood isolation device of claim 1, wherein the air permeable blood barrier comprises an air permeable material that at least partially seals upon contact with blood.

4.

The blood isolation device of claims 1 or 2, wherein said isolation chamber includes an isolati on channel defined within said housing.

5. The housing

includes a lower member mating with an upper member, each of said lower member and sai d upper member being associated with each of said inlet port, said outlet port, said isolation c

hamber and said sampling channel. 4. A blood isolation device according to any one of claims 1 to 3, which defines part of a

6.

A blood isolation device connected to a blood collection path having a patient needle and a sample collection device, comprising:

an inlet port connected to the patient needle,

an isolation chamber and a sampling channel, wherein each of the isolation chamber and the sampling channel is connected to the inlet port through a branch point, and the isolation chamber is air permeable a vent including an air permeable blood barrier, the isolation chamber and the bifurcation configured to direct a first portion of blood into the isolation chamber toward the air permeable blood barrier; Having a distal end connected with an outlet port, the sampling channel and the branch point bypass the isolation chamber and the first portion of the blood with the second portion of blood isolated within the isolation chamber. , an isolation chamber and a sampling channel configured to allow the sampling channel to be directed toward the outlet port, the outlet port being connected with the sample-collecting device

;

A blood isolation device comprising a housing containing and defining an outlet port, said isolation chamber, and said sampling flow path .

7.

A blood isolation device connected to a blood collection path having a patient needle and a sample collection device, wherein an

inlet port connected to the patient needle and

an outlet port connected to the sample collection device;

an isolation chamber having a vent containing an air permeable blood barrier; a sampling channel

having a distal end connected to said outlet port;

said inlet port, said outlet port, said isolation chamber and said sampling channel; a housing containing and defining

;

Each of the isolation chamber and the sampling channel are connected to the inlet port via a branch point, the junction allowing a first portion of blood to flow into the isolation chamber and through the air permeable blood barrier to the isolation chamber. to expel the air inside and into the isolation chamber

allowing a second portion of blood to be sequestered, bypassing said isolation chamber and a first portion of said blood isolated within said isolation chamber, towards said outlet port and said sampling device; A blood isolation device sized and configured to allow it to be directed into a tract.

8. The blood isolation device of claim

6, wherein said entry port is connected to said patient needle through said first portion of sai

d blood collection path.

9.

A blood isolation device according to any one of claims 6 to 8, wherein said outlet port is con nected to said sample collection device via a second portion of said blood collection pathway.

10.

The blood isolation device of claim 6 or 7, wherein said air permeable blood barrier comprise s an air permeable material that at least partially seals upon contact with blood.

11.

The blood isolation device of claim 6 or 7, wherein said isolation chamber includes an isolatio n channel defined within said housing.

12. The blood isolation of claim 11,

wherein said isolation channel has a proximal end connected with said inlet port and a distal end with said vent containing an air permeable blood barrier. Device.

13. A

body fluid isolation device, comprising

an inlet port,

an outlet port connected to said inlet port, and an

isolation chamber connected to said inlet port via a branch point, wherein said air permeable body fluid barrier comprises: an isolation chamber having a vent containing

a housing containing and defining the inlet port, the outlet port, and the isolation chamber,

wherein the isolation chamber and the junction direct a first portion of bodily fluid from the i nlet port to the air permeable bodily fluid barrier; The air permeable bodily fluid barrier compr ises an air permeable material that forms a barrier to bodily fluids upon contact with bodily flu ids, such that contact with bodily fluids results in an increase in air flow within the isolating ch ambers. and a second portion of bodily fluid from the inlet port to the outlet port through the bifurcation bypasses the isolation chamber and the first portion of the bodily fluid. Become a b ody fluid isolation device.

14. A

body fluid isolation device, comprising

an inlet port,

an outlet port connected to said inlet port, and an

isolation chamber connected to said inlet port via a branch point, wherein said air permeable body fluid barrier comprises: and a housing containing and defining said inlet port, said outlet port, and said isolation chamber , said isolation chamber and said branch point

being adapted for a first flow of bodily fluid from said inlet port. configured to direct one po rtion toward said isolation chamber toward said air permeable body fluid barrier, said air perm eable body fluid barrier comprising an air permeable material that forms a barrier to body flui ds upon contact therewith, such that: Formation of the barrier permits isolation of a first porti

on of bodily fluid within the isolation chamber and allows a second portion of bodily fluid from the inlet port to pass through the junction toward the outlet port and into the isolation chamb er and into the isolation chamber. A bodily fluid isolation device configured to allow a first port ion of the bodily fluid to be bypassed.

15.
The body fluid isolation device of claim 13 or 14, wherein the air permeable body fluid barrie r comprises an air permeable material that seals upon contact with body fluids.
16.
A body fluid isolation device according to claim 13 or 14, wherein said isolation chamber incl udes an isolation channel defined within said housing.
17. The method according to claim
13 or 14, further comprising a blood collection path connected to said inlet port, said blood c ollection path conveying a second portion of said body fluid from said inlet port to said outlet port through said branch point. A bodily fluid isolation device as described.
18. The housing
includes a lower member mating with an upper member, the lower member and the upper m ember each defining a portion of each of the inlet port, the outlet port and the isolation cham ber. 15. A body fluid isolation device according to claim 13 or 14, wherein
19. A body fluid isolation device according to claim 13 or 14,
further comprising .
20. The housing
includes a lower member mating with an upper member, each of said lower member and sai d upper member being associated with each of said inlet port, said outlet port, said isolation c hamber and said sampling channel. 20. A bodily fluid isolation device according to claim 19, w hich defines a portion of a.
21.
A blood isolation system comprising:
a blood collection path having a patient needle and a sample collection device; and a
blood isolation device
, said blood isolation device comprising:
an isolation chamber having an inlet port connected to the patient needle; an
outlet port connected to the sample collection device; an
isolation chamber having a vent containing an air permeable blood barrier; and a
distal end connected to the outlet port. a sampling channel, a housing containing
and defining said inlet port, said outlet port, said isolation chamber, and said sampling chann el, said isolation chamber and said sampling channel each diverging through said branch poi nt; Connected with an inlet port, the junction allows a first portion of blood to flow into the iso

lation chamber, expel air within the isolation chamber through the air permeable blood barrier, and be sequestered within the isolation chamber. and a second portion of blood bypasses the i solation chamber and the first portion of blood isolated within the isolation chamber and is dir ected into the sampling channel toward the exit port and the sample collection device. A blood isolation system sized and configured to enable. 22. The blood isolation system of claim 21 , wherein said entry port is connected to said patient needle through said first portion of said bl ood collection path. 23. The blood isolation system of claim 21 , wherein said exit port is con nected to said sample collection device via a second portion of said blood collection pathway. 24. The blood isolation system of claim 21, wherein said air permeable blood barrier compris es an air permeable material that at least partially seals upon contact with blood. [Claim 25]

25. The blood isolation system of Claim 24, wherein the isolation chamber includes an isolati on channel defined within the housing. 26. The blood isolation of claim 25, wherein said isola tion channel has a proximal end connected with said inlet port and a distal end with said vent containing an air permeable blood barrier

.

system.

detailed description open —

Description:

CROSS -REFERENCE TO RELATED APPLICATIONS This application is entitled "Blood Sample Op timization System and Blood Contaminant Isolation Apparatus and Method," filed on Apr. 27, 2016

. U.S. Nonprovisional Application No. 15/140,443, entitled "Blood Sample Optimization Syste m and Blood Contaminant Isolation Apparatus and , 448, and both of these U.S. nonprovision al applications are U.S. Provisional Application Nos. 62/196,797, U.S. Provisional Application N o. 62/ 238,636 entitled "Blood Isolation System for Clean Blood Collection," filed Oct. 7, 201

5; No. 62/318,194, entitled "Blood Sample Optimization System and Blood Contaminant Isola tion Apparatus and Method," filed herein, the disclosure of which is incorporated herein by ref erence in its entirety. shall be included in the Bacteremia is the presence of microorganisms i n the blood. Sepsis, on the other hand, is bacteremia with clinical symptoms and signs such a s fever, tachycardia, tachypnea and hypotension. Bacteremia and sepsis are associated with hi gh mortality, hospitalization incidence and length of stay and associated costs. many bactere mia

, sepsis, fungemia, and other pathogens do occur in hospitals or other health care facilities, a nd
catheters and venipunctures are sources of contamination as potential carriers of these patho gens.

[0003] Blood cultures are the standard test used
to detect microbial pathogens associated with bacteremia and sepsis in the blood of patients .
The term blood
culture
refers to a single venipuncture from a peripheral site or central or arterial line in which blood i s inoculated into one or more blood culture bottles or vessels. One bottle is considered one bl ood culture and two or more are considered a set. Multiple
sets are obtained from multiple venipunctures and are associated with different sites in the pa tient.

[0004]
Although these methods enable microbial identification and susceptibility testing, which are i

mportant factors in the management of sepsis, their
lack of rapid results and low sensitivity to nasty pathogens pose challenges for
improvement . This
has .
[0005]
The collection of blood samples for blood culture is an important component of modern patie nt care, both positively impacting patient outcome by providing
an accurate diagnosis and eliminating unnecessary antibacterial treatments. It can also adversely therapy
affect .
[0006]
One consequence of the collection of blood cultures is contamination. Contamination of blood cultures can lead to false positive culture results and
and/or significantly increase healthcare-related costs. Sources of blood culture contamination include inadequate skin disinfection, inadequate collection tube disinfection, and contaminatio n of the initial blood draw, which
can skew results. Blood culture collection kits generally include a "butterfly" set, infusion set, or other type of venipuncture device provided
and an aerobic

It consists of a blood culture bottle and an anaerobic blood culture bottle. A variety of differen t bottles are also available depending on inspection
requirements . These bottles
are specially designed to optimize the collection of both aerobic and anaerobic organisms. In c onventional kits, the bottle used
is commonly known as a "vacutainer", which is used to create a
vacuum inside the tube to facilitate the collection of a predetermined amount of liquid, such a s blood. A blood collection tube formed from a sterile
glass .
False
positive blood cultures are generally the result of poor sampling techniques. They
cause antibiotics to be used when they are not needed, increasing hospital costs and patient a nxiety. Blood cultures
are taken from a needle prick into the skin, after which
a Vacutainer® . Contamination can result from improper
or . It can also result from the piercing of the skin by the needle during insertion, which draws pierced skin cells and associated contaminants into the sample . [0009] Blood flow through a hypodermic needle is laminar, which causes a flow velocity gradient across the flow tube wh

en . Strong aspiration of the blood or use of a very small hypodermic needle causes lysis and release of potassium from the red blood cells, thereby obtaining a blood sample.

The pull can become abnormal.

[0010]

In another example, some patients have delicate veins which are subject to pressure drop

or for the patient's condition. Can collapse under vacuum.

Such venous collapse is dangerous and very difficult to control because such a condition cannot be known in advance . Various strategies have been implemented to reduce the contamination rate of blood cultures, such as staff training in sterile collection techniques , feedback on contamination rates, and the introduction of blood culture collection kits

. Skin antisepsis can reduce contamination concerns, but more than 20% of skin microbes are located deep in the dermis and are not affected by antisepsis. Changing needles prior to bottle inoculation is not recommended as it increases the risk of needlestick injuries without reducing contamination rates. [0012] Some conventional systems and techniques for reducing contamination of blood cultures involve discarding the initial aliquot of blood taken from central venous catheters, venous punctures and other vascular access systems. . However, these systems either require the user to mechanically manipulate the intravascular device or require a complex series of steps that are difficult to ensure. SUMMARY OF THE INVENTION [Problem to be Solved by the Invention]

Presented herein are systems
and . In some implementations, the systems and methods can eliminate variability in user disi nfection
and also eliminate the risk of skin cells entering blood culture samples. Other than potentially indicating when to attach a Vacutainer® or other blood collection device (i.e., a syringe) to ob tain a contaminant-free blood sample, the systems and methods disclosed
herein are does not require changes to existing clinical processes. [0014] In some implemen tations of the systems and methods disclosed herein, blood sampling is accomplished passivel y through the use of the patient's own blood pressure, thereby reducing the risk of venous ru pture and reducing current practice. Eliminates additional user steps beyond duties. The syste m and method can be adapted to suit short-path direct puncture or butterfly venipuncture sys tems. catheter

It can also be used with samples taken through the tube.
SUMMARY OF THE INVENTION In
one
aspect, a blood isolation device is presented. A blood isolation device includes an inlet port a nd an outlet
port . The blood isolation device further includes an isolation chamber connected to the inlet p ort, the
isolation chamber having a vent including an air permeable blood barrier. The blood isolation 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 isolation device is described that is connected to a blood collectio n path. The blood collection path has a
patient needle and a sample collection device. The blood isolation device includes an entry por t connected to the patient needle and an
isolation chamber connected to the entry port, the isolation chamber having a vent including a n air permeable blood barrier . The blood isolation device further includes a sampling channel having a proximal end connected to the inlet port
, and an outlet port connected to the distal end of the sampling channel and the sample collec

tion device . [0017] In yet another aspect, a blood isolation device is described that interfac es with a blood collection system. The blood collection system includes a patient needle for all owing a blood sample to be drawn from a patient and a sample needle that is sealed and adap ted to receive an evacuated blood collection tube. A blood isolation device includes an inlet po rt connected to a patient needle for receiving a blood sample from . blood isolation device

The device is an isolation
chamber isolating an initial
portion of the blood sample before the sample needle is unsealed by the evacuated blood coll ection tube. further includes an isolation chamber for The blood isolation
device
further includes a sampling channel having a proximal end connected to the inlet port, the sa mpling channel carrying a subsequent portion of the blood sample when the sample needle is opened by the evacuated blood collection tube. . The blood isolation device further includes an exit port connected
with the distal end of the sampling channel for carrying subsequent portions of the blood sam ple 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 collection s ystem for enabling and obtaining one or more samples of a patient's blood, a blood collection system for potentially contaminated by the venipuncture process and a false pathogen in the patient's blood. a blood isolation device for receiving and isolating an initial portion of one or more samples of patient blood that may result in a positive identification . A blood collection s ystem includes a patient needle configured for venipuncture of a patient to enable withdrawa l of a sample of the patient's blood , a blood collection channel connected to the patient needl e for carrying the blood sample, and a blood sample. a sample needle configured to receive th e evacuated blood collection container for withdrawing and containing a subsequent portion of the sample . [0020]

In yet another aspect, a blood isolation device is disclosed and described. In some implementations, a blood isolation device can include an
inlet port, an outlet port connected to the inlet port, and an isolation chamber connected to the inlet port . The isolation chamber can have a vent
containing an air permeable blood barrier . A blood isolation device is connected along the blood collection path between the patient needle and the sample needle and includes an entry port for receiving a blood sample . A blood isolation device is an isolation chamber connected with an inlet port for receiving and an air permeable blood barrier to isolate at least a first portion of the initial volume of blood sample. further comprising an isolation chamber having a vent containing a . The blood sequestration device is a sampling , the sequestration chamber receiving at least a first portion of an initial volume of blood sample.

Further includes a sampling channel that, when isolated, conveys subsequent amounts of the blood sample to the evacuated blood collection container.
The blood isolation device further includes an outlet port connected to the distal end of the sampling channel for outputting a subsequent volume of the blood
sample . 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 specification 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.
1 shows a blood sample optimization system; FIG.

FIG. 2 shows a blood sample optimization system according to an alternative implementation;
FIG. 3 shows a blood sample optimization system according to another alternative implement ation;
FIG. 4 shows a blood sample optimization system according to another alternative implement ation;
FIG. 5 shows a blood sample optimization system according to another alternative implement ation;
FIG. 6 shows a blood sample optimization system according to an alternative implementation;
FIG. 7 is a flowchart of a method for optimizing blood culture quality;
FIG. 8A illustrates a blood isolation system for non-contaminated blood collection, according t o some implementations;
FIG. 8B illustrates a blood isolation system for clean blood collection, according to some imple mentations.
FIG. 8C illustrates a blood isolation system for clean blood collection, according to some imple mentations;
FIG. 8D illustrates a blood isolation system for clean blood collection, according to some imple mentations.
FIG. 8E illustrates a blood isolation system for clean blood collection, according to some imple mentations.
FIG. 9 shows a path splitter for use in a blood sequestration system;
FIG. 10A shows a blood isolation system for non-contaminated blood collection according to a n alternative implementation;
FIG. 10B shows a blood isolation system for non-contaminated blood collection according to a n alternative implementation;
FIG. 10C shows a blood isolation system for non-contaminated blood collection according to a n alternative implementation;
FIG. 10D shows a blood isolation system for non-contaminated blood collection according to a n alternative implementation;
FIG. 11A shows a blood isolation system for non-contaminated blood collection according to a nother alternative implementation;
FIG. 11B shows a blood isolation system for non-contaminated blood collection according to a nother alternative implementation;
FIG. 11C shows a blood isolation system for non-contaminated blood collection according to a nother alternative implementation;
FIG. 11D shows a blood isolation system for non-contaminated blood collection according to a nother alternative implementation;
FIG. 11E shows a blood isolation system for non-contaminated blood collection according to a nother alternative implementation;
FIG. 12A shows a blood sample optimization system including a blood isolation device accordi

ng to yet another alternative implementation;

12B shows a blood sample optimization system including a blood isolation device according to yet another alternative implementation; FIG.

FIG. 12C shows a blood sample optimization system including a blood isolation device accordi ng to yet another alternative implementation;

FIG. 12D shows a blood sample optimization system including a blood isolation device accordi ng to yet another alternative implementation;

FIG. 13A shows blood sample optimization system 1300 according to yet another alternative i mplementation.

FIG. 13B shows blood sample optimization system 1300 according to yet another alternative i mplementation.

FIG. 13C shows blood sample optimization system 1300 according to yet another alternative i mplementation.

FIG. 13D shows blood sample optimization system 1300 according to yet another alternative i mplementation.

FIG. 14A illustrates yet another implementation of a blood collection system that isolates cont aminants in the initial aliquot or sample to reduce false positives in blood cultures or tests per formed on patient blood samples.

FIG. 14B illustrates yet another implementation of a blood collection system that isolates cont aminants in the initial aliquot or sample to reduce false positives in blood cultures or tests per formed on patient blood samples.

FIG. 14C. False positives in blood cultures or tests performed on patient blood samples.

FIG. 10 illustrates yet another implementation of a blood collection system that isolates initial aliquots or samples of contaminants to reduce them.

FIG. 14D illustrates yet another implementation of a blood collection system that isolates cont aminants in the initial aliquot or sample to reduce false positives in blood cultures or tests per formed on patient blood samples.

FIG. 14E shows yet another implementation of a blood collection system that isolates contami nants in the initial aliquot or sample to reduce false positives in blood cultures or tests perfor med on patient blood samples.

15A-B illustrate a blood isolation device and method of using the same according to yet anoth er implementation.

15B illustrates a blood isolation device and method of using the same according to yet anothe r implementation; FIG.

FIG. 15C illustrates a blood isolation device and method of using the same according to yet an other implementation;

FIG. 15D illustrates a blood isolation device and method of using the same according to yet an other implementation;

FIG. 15E illustrates a blood isolation device and method of using the same according to yet an

other implementation;

Figure 15F illustrates a blood isolation device and method of using the same according to yet another implementation;

FIG. 15G shows a blood isolation device and method of using the same according to yet anoth er implementation;

FIG. 16A shows a blood isolation device according to yet another implementation;

16B shows a blood isolation device according to yet another implementation; FIG.

16C shows a blood isolation device according to yet another implementation; FIG.

16D shows a blood isolation device according to yet another implementation; FIG.

Figure 17A shows a lower member of a housing for a blood isolation device;

Figure 17B shows a lower member of a housing for a blood isolation device;

Figure 17C shows a lower member of a housing for a blood isolation device;

Figure 17D shows a lower member of a housing for a blood isolation device;

Figure 17E shows a lower member of a housing for a blood isolation device;

Figure 18A shows a top member of a housing for a blood isolation device;

Figure 18B shows a top member of a housing for a blood isolation device;

Figure 18C shows a top member of a housing for a blood isolation device;

Figure 18D shows a top member of a housing for a blood isolation device;

Figure 18E shows a top member of a housing for a blood isolation device;

Figure 18F shows a top member of a housing for a blood isolation device;

Figure 19A shows a blood isolation device having an upper member that mates with a lower member.

Figure 19B shows a blood isolation device having an upper member that mates with a lower member.

FIG. 20 shows a blood sample optimization system including a blood sequestration device;

Figure 21 shows a non-vented blood isolation device using a wicking material chamber.

Figure 22A shows the material composition of a filter for isolating blood in an isolation chamb er of a blood isolation device;

Figure 22B shows the material composition of a filter for isolating blood in an isolation chamb er of a blood isolation device;

FIG. 23A shows another implementation of a blood isolation device using vacuum force from a blood collection device;

Figure 23B shows another implementation of a blood isolation device using vacuum force from a blood collection device. Like numbers in the various drawings indicate like elements.

DETAILED DESCRIPTION OF THE INVENTION

[0024]

The present invention provides blood

sample optimization that reduces or eliminates contaminants in a drawn blood sample and, as a result, reduces or eliminates false positive readings in blood cultures or other tests of the dr

awn blood sample.

A system and method are described. In some implementations, the blood sample optimization system includes a patient needle for vascular access to the patient's bloodstream and a blood collection container such as a vacutainer or evacuated blood collection tube or other and a blood

isolation device positioned between the patient needle and the sample needle. The blood isola tor will remove the first aliquot of potentially contaminated blood.

and bypasses

the isolation chamber to carry potentially uncontaminated blood between the patient needle a nd the sample needle after the first aliquot of blood has been isolated in the isolation chambe r.

A sampling channel can be further included.

FIG .

1 shows a blood sample optimization system according to some implementations. The syste m includes a patient needle 1 for puncturing the patient's

skin to access the patient's vein and intravenous blood therein

.

The system is housed within

a resealable boot 10, luer-activated valve, or other collection interface or device and initially s ealed by the resealable boot 10, luer-activated valve, or other collection interface or device. It further includes a sample needle (ie

, a resealably sealed needle for use with a Vacutainer® or the like) 5, which may be included. The resealable boot 10 can be pushed

by or around the sample needle 5 by using a Vacutainer® bottle (not shown) for collecting th e patient's blood.

The system

can further include a low volume chamber 30 leading to the sample needle 5, but

also includes a hole or one or more channels 45 leading to the isolation chamber 55 formed b y the housing 50. FIG. Isolation chamber 55 is a chamber for receiving and holding an initial aliquot of the patient's blood, which can be

.

, channels, passages, locks, or other structures. Initial blood draws

generally contain or are more

susceptible to contain microorganisms or other pathogens that cause bacteremia and sepsis t han subsequent blood draws. The isolation chamber 55 can be contained within a rigid housin g, can be a container formed in or defined by the

housing itself, or

can be realized as a tube or lumen.

Isolation chamber 55 can have a predetermined volume, regardless of how it is formed and i mplemented. In some implementations

, the predetermined volume is based on the volume of the patient needle, i.e.,

ranges from a volume less than the volume of the patient needle to any volume to a volume g reater than 20 times the volume of the patient needle. can be done

.

The predetermined volume of isolation chamber 55 can also be set to conserve or minimize th e amount of blood that is isolated and disposed of . Isolation chamber 55 may be formed, co ntained, or housed within chamber housing 50 and may be made of plastic, rubber, steel, alu minum, or other suitable material

. For example, isolation chamber 55 can be formed from flexible tubing or other elastomeric material . The isolation chamber 55 further includes an air permeable blood barrier 20 that all ows air to exit the isolation chamber 55 . As used herein, the term "air permeable blood barri er " refers to an air permeable but substantially blood impermeable substance, material or str ucture.

means. Representative examples are hydrophobic membranes and coatings, hydrophilic mem branes or hydrophilic

coatings combination with hydrophobic membranes or coatings, meshes, filters, mechanical v alves

, antimicrobial materials, or the isolation chamber 55 is Any other means capable of expelling air from isolation chamber 55 when filled with blood may be included. In various exemplary e mbodiments

, the air permeable blood barrier can be formed by one or more materials

that allow , such materials comprising: Completely or partially sealed to prevent or block the passage of air and/or

liquids . In other words,

the material forms an air permeable barrier prior to contact with the liquid. After contact with liquid, the material

substantially or completely prevents further passage of air and/or liquid. Holes or channels 4 5 may be of any desired length, cross-sectional shape or size and/or be formed away from lo w volume chamber 30 at any desired angle or orientation

. can be done. The hole or channel 45 may also include a one-way flap or valve 60 that retain

s the first aliquot of blood sample within the isolation chamber 55 . In some particular implem entations , the holes or channels 45 allow unidirectional blood flow from the low volume cham ber 30 to the isolation chamber 55 .

can include a "duckbill" valve or flapper valve 60 or the like for Air permeable blood barrier 20 may also be constructed of a material that allows air to escape but seals upon cont act with blood , thereby not allowing outside air to enter isolation chamber 55 . This seal eliminates the need for valves.

Valve 60 can be any type of valve or opening/closing mechanism. Chamber 30 is designed to retain substantially no residual blood and can be configured to retain or pass a ce rtain volume or percentage of blood to isolation chamber 55 . Similarly, the isolation chamber 55 may also include any type of coating, such as an antimicrobial coating, or a coating that assists in identifying a nd/or diagnosing components of the isolated primary blood draw . Housings 50 and 40 may be formed from any suitable material, including plastics such as acrylonitrile butadiene styrene (ABS) or other thermoplastic or polymeric materials, rubber, steel, or aluminum . The air permeable blood barrier 20 is activated upon contact with blood from the first draw o r when the expulsion of air is stopped, or upon any combination of events and blood within th e isolation chamber 55. , color-providing substances or other signaling mechanisms. Air perm eable barriers may also include hydrophobic membranes or covers that block or prevent inadv ertent or premature sealing of the filter by external fluid sources, splashes, etc.

An outer layer can be included. The isolation chamber 55 can also be translucent or transpare nt to allow the user .

FIG.

2 shows a blood sample optimization system according to some alternative implementations. In the implementation shown in FIG. 2 , an isolation chamber 55 or waste chamber surrounds the patient needle 1 and an open-ended
cuff or housing is connected to the waste chamber and surrounds the sample needle housing base and
housing . The patient needle 1 and the sample needle 5 are connected to each other by a boo t 56
which forms a continuous blood collection flow path therethrough. Boot 56
includes a single hole or channel leading from the blood collection channel to isolation chambe r 55 .
The device can include multiple holes or channels in other implementations . Each hole or cha nnel can include a one-way valve
and can be sized and adapted for a predetermined amount of blood flow.
Isolation
chamber 55 contains an air permeable blood barrier. The
filter
may further include sensors or indicators, respectively, for sensing and/or indicating when a p redetermined volume of blood has been collected in the isolation chamber 55 .
The instructions alert the user to attach an evacuated blood collection tube or bottle, such as a Vacutainer®, to the sample needle 5 . The housing for the isolation chamber 55
can be of any size or shape, and the internal space within the housing or
can include any type of material to define the volume. The interior space is initially filled with air only, but
can also be coated with agents or substances such as decontamination agents, coagulants, an d the like. When the evacuated blood collection tube is attached to the sample needle 5, blood automatically
flows into the patient needle 1, through the blood collection channel and the sample needle 5 into the bottle. The sample needle 5
is
covered by a resealable boot, coating or membrane that seals the sample needle when no blo od collection bottle is attached to the sample needle.
FIG.
3 shows a blood sample optimization system according to some alternative implementations. In the illustrated implementation
, sample needle 5 is surrounded by a resealable boot or membrane and is also
connected . A blood flow path is formed through the sample needle and the patient needle.
The connection between
the sample needle and the patient needle includes a 'T' or 'Y' connector 102 that includes a flo w path, port or opening leading from the main blood flow path to the isolation chamber 104 .

The T or Y connector 102 includes a flap or one-way valve and has holes sized and adapted f or a predetermined flow rate of blood
. Isolation chamber 104 is formed from a tube

or can be formed by a rigid housing, initially filled with air. The isolation
chamber 104 receives blood
flowing . The isolation chamber 104 preferably includes an air permeable blood barrier 106 at the distal end of the tube forming the isolation chamber 104
and connected at the proximal end to the T or Y connector 102 . The T or Y connector 102 can branch at any desired angle
for most efficient blood flow , minimizing or eliminating mixing of the initial aliquot of blood wi th the main blood sample. To this end, the openings and junctions between the channels and t he main blood flow channel can be shaped to minimize. In some alternative implementation s, the sample needle is attached to any length of tubing whose opposite end is connected to a T or . I can . The isolation chamber 104 can be of any shape or volume so long as the initial al iquot contains a predetermined amount of blood sample . The T or Y connector 102 can also i nclude openings or channels 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 predeter mined amount of blood has been collected in the isolation chamber or when the released air h as reached a certain threshold, i.e. zero. can. The tube also includes a clip 109 that can be us ed to pinch and prevent fluid flow through the tube

can be done. Once the air permeable blood barrier and primary chamber are sealed, the first aliquot of blood is confined to the isolation chamber 104 and an evacuated blood collection tu be, such as a Vacutainer® bottle, is
used to obtain the sample. It is attached to the sample needle 5 . The blood collection tube ca n be removed and the sample needle 5 resealed. Any number of subsequent blood collection t

ubes can be attached for additional blood draws or samples. When all blood draws are comple ted, the system is discarded, leaving the first aliquot of blood trapped in isolation chamber 10 4 . FIG. 5 shows a blood sample optimization system according to some alternative impleme ntations. In the illustrated implementation , the sample needle 5 is connected by tubing to the patient needle. A "T" or "Y" connector 120 is added at any desired location along the tube to i nclude an opening, port or flow path leading to isolation chamber 204, substantially as describ ed above. FIG. 6 illustrates a blood sample according to some alternative implementations in which an isolation chamber 304 configured as the primary collection channel receives the first aliquot of blood and is provided adjacent to the blood collection channel. An optimization syst em is shown. The isolation chamber 304 can surround the blood collection channel, patient ne edle 1 and/or sample needle 5 . The primary collection channel may include T or Y connectors 120, or other types of openings or channels. The isolation chamber 304 is an air permeable bl ood barrier

and may also include an indication that a fluid, such as blood, has been contacted, as describe d above. In some implementations, either or both of the patient needle 1 or the sample nee dle 5 can be replaced with luer lock

or luer lock female connectors. However, in various implementations , the connector at the sa mple needle end of the blood sample optimization system is first sealed and the first aliquot al low to divert the blood of the In this way, the system passively and automatically uses the pat ient's own blood pressure to overcome the ambient air pressure in the isolation chamber, forc e air through the air permeable blood barrier, and replace the air in the isolation chamber with blood. FIG . 7 is a flowchart of an exemplary method for optimizing blood culture quality. At

702 , a clinician inserts a needle into a patient's vein. At 704, blood flows into the isolation ch amber, forcing . In some implementations, the volume of the isolation chamber is less than 0. 1 cubic centimeters (cc).

From full to 5 cubic centimeters (cc) or more. The isolation chamber is sized and adapted to c ollect
a second portion of the blood sample and other subsequent portions or a first portion of the bl ood sample that is more susceptible to contamination than subsequent collections .
The isolation chamber has an air permeable blood barrier
through which air can be expelled by the blood expelled from the patient's veins
so that such blood is
a vacutainer Before being drawn into or otherwise entering a ® or other bottle, it inevitably a nd
automatically flows into the isolation chamber. As the isolation chamber fills, blood collects o r otherwise contacts an air permeable blood barrier that
blocks or prevents blood from passing through. At 706, once the blood contacts the entire inte rnal surface area of the air permeable blood barrier, the air permeable blood barrier is closed and air no longer flows out or in. At 708, the clinician is provided an indication or can view the full chamber indicating that an evacuated blood collection tube , such as a Vacutainer®, can b e attached. The indicator may include visibility of the primary chamber to see if the primary c hamber is full , eg, a blood barrier that changes color, or other indicator . Since the fill time of the isolation chamber may be substantially instantaneous, such an indication, if present, may simply be that the isolation chamber is filled. [0042]

Before the evacuated blood collection tube is attached, communication between the needle, the sampling channel, and the isolation chamber
is restricted by the sealing of the isolation chamber's blood barrier, thus isolation does not allow air to re-enter
the system . Sealing of the communication path is accomplished by mechanical twisting or other
action , small hole or tortuous path,
obviating the need for a separate valve or mechanical action or manipulation by the clinician. At 710, the evacuated blood collection tube is removed, a self-
sealing membrane seals the sample needle, and at 712, a further subsequent evacuated blood collection tube
can be attached. At 714, once the sample has been taken, the device is removed from the patient and discarded
.

[0043]

Figures 8A-8E illustrate an exemplary blood sample optimization
system . Blood sample optimization system 800 includes an
entry port 802 that can be connected to tubing, a patient needle (or both), or other vascular or venous access device, and a
first exit to isolation chamber tubing 806 and sample collection tubing.
a path splitter 804 with a second exit to 808 ; One or both of isolation chamber tube 806 and sample collection
tube 808 can be formed from tubing. In some implementations , isolation chamber tube 806 is sized
to accommodate a specific amount of initial blood sample .
The sample collection tube 808 is used once the isolation chamber tube 806 is full.
When prompted, accept a blood sample. The sample collection tube 808 can be
connected to a Vacutainer® base or housing 810, or other blood sample collection device . Blood isolation system 800 further includes blood isolation device 812, which includes housing 818, shown in more detail in FIGS . It includes a sampling channel 820 that defines a pathway or is connected at either end with a clean sample collection tube 808 . The sampling flow path 820 can be curved through the housing 818 to better secure and stabilize the housing 818 in position along the clean sample collection tube 808 . Blood isolation device 812 further includes an isolation chamber 822 or other chamber connected with isolation chamber tube 806 .

Isolation chamber 822 terminates . The air-permeable blood barrier 824 also reacts upon full contact with blood as an indicator that proper collection of a blood sample (i.e., an uncontami nated blood sample) can begin.

It may contain a colorant that changes to a different color. Other indicators such as small light s, sound generating mechanisms, etc.
can be used. In some implementations, the air permeable blood barrier is positioned perpendi cular to
the orientation , but
may be positioned at any distance or orientation to conserve space and materials used for ho using 818. can Housing 818 and its contents
can be formed from any rigid or semi-rigid material or range of materials.
FIG.
9
shows a path splitter 900 for use in, for example, blood isolation systems such as those show n in FIGS. 8A-8E. Path splitter 900 includes inlet port 902 , main conduit outlet port 904
and isolation channel outlet port 906 .
The entry port 902 can be connected to a main tube that is also connected to the patient nee dle system or directly to the patient needle. The main line outlet port 904 can be connected to a
main line tube to a blood collection system, such as a Vacutainer® base or housing, or directl y to such a blood collection system.
The isolation channel
outlet port 906
can be connected to an isolation tube for receiving and isolating the first sample of blood up t o a measured volume or predetermined threshold. Alternatively, the isolation flow path outlet port

906 can connect to the isolation chamber. The isolation channel outlet port 906
is preferably angled from 20 to 70 degrees from the main conduit outlet port 904, while the m ain conduit outlet port
Port 904 is preferably in line with inlet port 902 . Once an initial blood
sample
has been isolated in an isolation tube or isolation chamber according to the mechanisms and t echniques described herein, subsequent blood samples flow into inlet port 902 unobstructed. directly out of the main conduit outlet port 904 at . 10A-10D show blood isolation device 100 0 according to another implementation
.
Blood isolation device 1000 includes
inlet port 1002 , main outlet port 1004 , and isolation flow port 1006
. Entry port 1002 can be connected with a patient needle or associated tubing.
The main exit port 1004 can be connected to a blood sampling device such as a Vacutainer®, associated tubing, or a luer-
actuated valve. An isolation flow port 1006
separates from the main exit port 1004 into an isolation chamber 1008 . In some implementa tions, isolation
chamber 1008 is formed as a spiral channel within housing or other container 1001 .
Isolation chamber 1008 is connected
at its distal end to air permeable blood barrier 1010, substantially as described above . Air w ithin the isolation chamber 1008 is expelled by the first aliquot of blood directed into the isolat ion flow path
port 1006
through .
Once the isolation chamber 1008 is filled, further
blood draws through the main exit port 1004 are accomplished and these samples are clean.
11A -
11E show blood isolation device 1100 according to another alternative implementation. Bloo d isolation device 1100 includes an
inlet port 1102 similar to the inlet ports described above, a main outlet port 1104
and an isolation flow port 1106 separate from main outlet port 1104 and inlet port 1102 .
The isolation flow port is connected to isolation chamber 1108 .
In the implementation shown in FIGS. 11A-11E , the blood isolation device
includes a base member 1101 having a flow path therein that functions as an isolation chamb er 1108 .
The flow path can be formed as a tortuous path through the base member 1101 while the bas e member 1101
is shaped and shaped to rest on the patient's limb. A portion of isolation chamber 1108 may p

rotrude from or near the top surface of the base member just prior to exiting air permeable . Indicator 1109 can be made of a transparent material or a material that changes color when in contact with blood . In some implementations, the blood isolation device 1100 includes a n ormally closed needle, vacutainer.RTM.

A blood collection device 1120, such as a shield or other collection device, may be included. Bl ood collection device 1 120 is manufactured and sold with blood isolation device 1100 for effic iency and convenience so that the
first aliquot of blood that may be contaminated by the patient needle insertion process can be isolated. be able to. Accordingly, the blood collection device 1120 can collect and ensure a cle an blood sample so as to reduce the risk of false positive tests . [0052] Figures 12A-12D illust rate a blood sample optimization system 1200 according to yet another alternative impleme ntation . System 1200 includes a blood isolation device 1202 for attachment to a blood collect ion device 1204, such as a Vacutainer® or other collection and sampling device. Blood isolatio n device 1202 receives an initial aliquot or volume of blood before a Vacutainer® container or vial is attached to the collection needle of blood collection device 1204 and transfers that initi al aliquot or volume to blood isolation device 1202 . Constructed and . [0053] In some imple mentations, the blood isolation device 1202 can include an inlet port 1212, a main outlet port, and an isolation flow path port. Entry port 1212 can be connected to a patient needle or assoc iated tubing . The main exit port 1214 is an evacuated blood collection container or vacutaine r.

can be connected to a normally closed needle or device to allow connection with other collecti on devices such as ®, associated tubing, luer connectors, syringes,
luer actuated valves
. The isolation flow port separates the isolation chamber 1218 from the main exit port. In so me implementations, isolation chamber 1218 is formed
. The isolation chamber 1218 can be a tortuous channel, such as a U-shaped channel, an S-sh aped channel, a spiral channel, or any other tortuous channel. Isolation device 1202 can inclu de a housing or other enclosure and one or more channels formed therein . As shown in FIGS. 12A and 12B, isolation device 1202 includes body 1206 and cap 1208 . One or more cavities o r channels are formed in the body 1206, and the cavities or channels are further formed with one or more arms 1210 extending from the cap 1208, the one or more arms 1210 extending f rom the cavities or channels of the body 1206. A primary collection port and a main outlet por t . [0055] Figures 13A-13D illustrate a blood sample optimization system 1300 according to yet another alternative implementation . System 1300 includes a blood isolation device 1302 f or attachment to a blood collection device 1304, such as a Vacutainer® or other body fluid col lection and sampling device. Blood isolation device 1302 is a Vacutainer® container or vial blo od collection device 1304 .

to receive an initial aliquot or volume of blood and sequester that
initial
constructed and arranged. Blood isolation device 1302 includes housing 1301 having inlet po rt 1314 , main outlet port 1312 and isolation flow path port 1316
. Entry port 1314 can be connected to a patient needle or associated tubing. The main exit po

rt 1312 is a normally closed needle or needle to allow connection with other collection devices such as evacuated blood collection containers or vacutainers, associated tubing, luer connecto rs , syringes, luer actuated valves. It can be connected to a device . An isolation flow port 131 6 separates from the main inlet port 1314 into an isolation chamber 1318 . In the embodime nt shown in FIGS. 13A-13D, isolation chamber 1318 is formed as a cavity or chamber within h ousing 1301 or by walls defining housing 1301 .

be done. The isolation chamber 1318 can be a
tortuous
defined by the cooperation and connection of the housing 1301 and the cap 1307. The cap 13 07
can
include protrusions 1305 that provide one or more walls or directors for the tortuous flow path within the isolation chamber 1318 . Projections 1305 from cap 1307
can be straight or curved,
can extend from cap 1307 at any angle or orientation. be able to.
When the cap 1307 is connected with the housing 1301 to complete the formation of
the isolation chamber 1318 , the projection 1305 forms at least a portion of the tortuous flow path
formed by the tortuous flow path within the isolation chamber 1318 . An initial aliquot or volu me of blood or
other bodily fluid is sequestered in the sequestration channel .
Isolation chamber 1318
includes air permeable blood barrier 1310 substantially as described above
.
Air within the isolation chamber 1318 is expelled through the air permeable blood barrier 131 0 by the first aliquot of blood supplied into the isolation chamber 1318 by the patient's blood pressure
. Once the isolation chamber 1318 is filled and the air within the isolation chamber 1318 is ex pelled,

a

The patient's blood pressure forces more blood into the blood isolation device 1302, and in pa rticular the exit port 1312 , until a force such as a vacuum or other pressure is provided

Inadequate to drive or provide.

Additional blood draws can be taken through the main exit port 1312 and these samples are not contaminated because any contaminants are sequestered in the isolatio n chamber 1318 along with the blood of the first aliquot.

FIGS. 14A-14E further illustrate a blood collection system 1400 for isolating contaminants of i nitial aliquots or samples to reduce false positives in

blood cultures or tests performed on patient blood samples. Show another implementation.

Blood collection system 1400 includes a blood isolation device 1401 that can be connected bet ween blood sample collection device 1 403 and a patient needle (not shown) . The blood sam ple collection device 1403 can . Blood isolation device 1401 includes an entry port 1402 that c an be connected to a patient needle that is inserted into the patient's vasculature for access t o and collection of a blood sample . Inlet port 1402 can also be connected to a tube or other c onduit that is also connected to a patient needle . Inlet port 1402 defines an opening to bloo d isolation device 1401, which opening can be of the same cross-sectional dimensions as a tu be or other conduit connected to the patient needle or the patient needle itself.

be. For example, the opening can be , but may be 0.01 inch (0.254 mm) to 0.2 inch (5.08 mm) or less. can have diameters equal to or greater than Blood isolation device 1401 further incl udes an exit port 1404 that defines an opening from blood isolation device 1 401 and to blood sam pling device 1403 . Exit port 1404 can also be connected to a tube or other conduit that is also connected to blood isolation device 1403 . The exit port 14 04 may be a connector such as an unthreaded interference or glue joint for attachment to a v ariety of devices including, but not limited to,

threaded caps,
luer connectors (male or female), tubing, and the like.
A device
can also be included. Blood isolation device 1401 further includes a sampling
serves as a blood sample pathway once the first aliquot of blood has been isolated. do. Sampli ng channel 1406 can be a channel or conduit of any size , shape or configuration. In some im plementations, sampling channel 1406 has a cross-sectional area substantially similar to the o pening of inlet port 1402 . other fruits

In practice, sampling channel 1406
can gradually diverge from inlet port 1402 to outlet port 1404 . Blood isolation device 1401 f urther includes isolation chamber 1408 , which is connected to and separated from sampling c hannel 1406 anywhere between inlet port 1402 and outlet port 1404
. or diverted, but preferably connected to the proximal end of the sampling channel 1406 near the inlet port 1402 and separated or diverted from . The isolation chamber 1408 is initially ma intained at atmospheric pressure and includes an air outlet 1412 at or near the distal end of t he isolation chamber 1408 opposite the turning point from the sampling channel 1406 . Air ou tlet 1412 includes air permeable blood barrier 1412 . The air permeable blood barrier 1412 ca n be covered with a protective cover 1416, as shown in FIG. 14B . The protective cover 1416 can be sized and configured to prevent a user from touching the air permeable blood barrier 1 412 with their fingers or other external instruments , while still allowing the patient's own blo od pressure to force the isolation chamber. A forced blood supply into 1408 allows air to exit t he air permeable . The protective cover 1416 also prevents or prevents accidental exposure of the air permeable blood barrier to surrounding fluids or droplets.

can be configured.
This can be done in a variety of mechanical ways including, but not limited to, adding a hydro phobic membrane to the protective cover . As shown in FIGS. 14C and 14D, the sampling cha nnel 1406 is cylindrical or frusto-conical in shape from smaller diameters to larger diameters t o minimize the possibility of
. can be done. Similarly, the sampling channel 1406 is formed with a minimal amount or no s harp bends or sharp angles that could lyse red blood cells. Sampling channel 1406 splits near inlet port 1402 through diverting path 1409 into isolation chamber 1408 . Diversion pathway 1409 can , but is preferably similar to the cross-sectional shape of at least a portion of inlet p ort 1402 . In some implementations, sampling channel 1406 and isolation chamber 1408 are formed by grooves, channels, locks or other pathways formed in housing 1414 . Housing 1 41 4 can be made of plastic, metal or other rigid or semi-rigid material. The housing 1414 can ha ve a lower member that sealably mates with the upper member. One or both of the lower and upper members includes a sampling channel 1406 and an isolation chamber 1408 as well as a diversion channel 1409, an inlet port 1402 and an outlet port 1404.

can be read. In some other embodiments,
one or more of diverting path 1409, inlet port 1402, and/or outlet port 1404 are
at least partially closed by a cap member connected to either end of housing 1414. can be for med in
In
membersome
can be connected together by laser welding, heat sealing, gluing, snapping, screwing, bolting,

or the like. In other implementations,
some
can be coated or filled with agents or substances such as decontamination agents, coagulants, and the like. For example, when the sequestration chamber 1408 fills and the first aliquot of b lood
returns to the diversion path 1409 , the final volume of sequestered blood clots, creating a barrier between the sequestration chamber 1408 and the sampling channel 1406 .
A coagulant can be provided in the turning path 1409 to create . 15A-15G show a blood isola tion device 1500. FIG
.
The blood isolation device 1500
is
a needle that is normally closed to allow connection with other collection devices such as evac uated blood collection containers or vacutainers, associated tubing, luer connectors, syringes, luer actuated valves, and the like. or connected to
the device .
Blood isolation device 1500 includes an entry port 1502 that can be connected to a patient ne edle that is inserted into the patient's vasculature
for access to and withdrawal of a blood sample . Entry port 1502 can also be . Entry port 15 02 defines an opening to blood isolation device 1500, which opening can be of the same cross -sectional dimensions as a tube or other conduit connected to the patient needle or the patien t needle itself. For example, the opening can be circular with , but may be 0.01 inch (0.254 m m) to 0.2 inch (5.08 mm) or It can have a larger diameter. Inlet port 1502 may also include a sealed or fluid tight connector or connection such as a threaded or luer fitting or the like . In some implementations, a tube or other conduit that is coupled to the patient needle can be int egrated with the entry port 1502, such as by co-molding, gluing, laser welding, or heat bondi ng the parts together. This allows the blood isolation device 1500 to be manufactured and sol d as a single unit with the patient needle, eliminating the need to connect the patient needle t o the blood isolation device 1500 during blood draw or sampling. The blood isolation device 1 500 has open connections from the blood isolation device 1500 and to the blood sampling de vice.

Further includes an exit port 1504 defining a mouth. Exit port 1504
may also be connected to a tube or other conduit that is also connected to a blood isolation d
evice and may include a sealed or fluid tight connector or connection such as a threaded or lu
er
fitting . Thus
, as noted above, the blood isolation device 1500 is manufactured and sold as a single unit wit
h the patient needle and/or tubing and blood
sample device, and
is attached to the patient needle and blood sample collection device during blood collection or
sampling. to the blood isolation device 1500
.
Blood isolation device 1500 further includes a sampling channel 1506 between
inlet port 1502 and outlet port 1504, which functions as a blood sample channel once the fir
st aliquot of blood has been isolated. do. Sampling channel 1506 can be a channel or conduit
of any size , shape, or configuration. In some implementations, sampling channel 1506 has a
cross-sectional area substantially similar to the opening of inlet port 1502 . In other implemen
tations, sampling channel 1506 can gradually diverge from inlet port 1502 to . Blood isolatio
n device 1500 further includes isolation chamber 1508 , which is connected to sampling chann
el 150 at any location between inlet port 1502 and outlet port 1504 .

6 and separated or diverted from the sampling channel 1506 , preferably connected
to and separated or diverted
from . In some implementations, the diversion channel includes a Y-junction. The isolation cha

mber 1508
is preferably maintained at atmospheric pressure and includes a
vent . Vent 1510 includes air permeable blood barrier 1512 . FIG. 15C shows blood isolation d evice 1500
with isolation chamber 1508 filled with an initial aliquot or sample of blood from a patient . A ir permeable blood barrier 1512 may be covered with protective cover 1516 . The protective c over 1516 can be sized and configured to prevent a user from touching the air permeable bloo d barrier 1 512 with their fingers or other external instruments , while still allowing the patien t's own blood pressure to force the isolation chamber. A forced blood supply allows air to exit t he air permeable blood barrier 1512 as the air is expelled from the isolation chamber. Protecti ve cover 1516 protects the filter from accidental contact with surrounding fluids or splashes.

can be configured to inhibit or prevent exposure to This can be
done in a variety of mechanical ways including, but not limited to, adding a hydrophobic mem brane to the protective cover. FIG. 15B is a perspective view of blood isolation device 1500 fr om the top of housing blood isolation device 1500 , showing the sampling flow path before th e sample collection device is activated. A first aliquot of blood fills isolation . Figure 15G is a p erspective view of the blood isolation device 1500 from the bottom of the housing 1501 and t he exit port 1504 of the blood isolation device 1500, initially while the sampling channel 1506 is empty before the sample collection device is activated. aliquot of blood fills isolation chamb er 1508 . FIG. 15C is another perspective view of blood isolation device 1500 from the top of housing 1501 including inlet port 1502 and vent 1510 of blood isolation device 1500 , with the isolated blood substantially within isolation chamber 1508 . Blood is drawn through sampling c hannel 1506 while remaining at . FIG . 15D is a cross-sectional view of blood isolation device 1500 according to some implementations, showing housing 1501 defining sampling channel 1 506 and isolation chamber 1508 . Figure 15E and

and 15F illustrate various form factors of housings for blood isolation devices according to one or more implementations described herein . Isolation chamber 1508 can have a larger cross-sectional area than sampling channel 1506 , and the cross-sectional area or length can be con figured such that a predetermined or specific blood volume is isolated or locked
. can. The sampling channel 1506 can be sized to fit tubing for either or both the patient need le tubing or the blood collection device tubing. Housing 1501 can be formed from multiple pi eces or from a single unitary piece. In some implementations, as shown in FIG. 15D, housing 1501 includes an upper member 1520 and a lower member 1522 that mate with each other, o ne or both of which are formed, for example, by an injection molding process or by etching, H aving grooves, channels, locks, conduits drilling or the like. The upper member 1520 may be attached by laser welding, thermal bonding, ultrasonic welding , adhesives, screws, rivets, bol ts, etc., or by latches, grooves, tongues, or the like. Other mating mechanisms, such as pins, flanges, etc., can connect with lower member 1522 . In some implementations, upper memb er 1520 includes grooves, channels, locks, guides, etc., as shown in FIG. 15D .

A tube or other passageway can be included, while the lower member 1522 is sized and adapt ed
to fit into at least one of a groove, channel, lock or other passageway in the upper member 1 520.
can include raised protrusions 1524 . Protrusions 1524 can provide surface features
such as
partial . In some implementations,
the protrusions 1524
can be formed with one or more slanted sides or faces to more closely fit within corresponding grooves, channels, locks or other pathways. can. In still other implementations, both the upper member 1520 and the lower member
can include grooves, channels, locks or other pathways, as well as one or more protrusions 15 24 . In some implementations, sampling channel 1506 and isolation chamber 1508 are form ed by grooves, channels, locks or other pathways formed in housing 1501
. Housing 1 501 may be made of any suitable material including rubber, plastic, metal or other material.

can be done. Housing 1501 can be formed from a transparent or translucent material, or from an opaque or non-
translucent material.
In other implementations, the housing 1501 can
be largely opaque or non-transparent, but the housing surfaces directly adjacent the sampling channel 1506 and/or the isolation chamber 1508 are transparent or translucent and initially A visual cue or sign that the isolation
chamber 1508 is filled to the required or desired degree
and/or is isolated while a subsequent uncontaminated blood sample is
taken Gives the
practitioner . Other visual cues or signs of isolation include, but are not limited to,
contact, penetration, or partial penetration of blood, causing the air permeable blood barrier 1 512 to
turn
color-coded tabs or indicators, audible, vibratory, or other signals at any location along or adj acent to the isolation chamber . After venipuncture by a patient needle (not shown), which ca n collect many pathogens from the patient's skin, the patient's own blood pressure overcomes the atmospheric pressure in isolation chamber 1508 to form an air permeable blood

barrier
. As the air in the isolation chamber 1508 is expelled through 1512, the initial volume of pati ent blood with these pathogens enters the blood isolation device 1500 inlet port 1502 and the most

It flows into isolation chamber 1508 by following the path of least resistance. The patient's blo od pressure
is not sufficient to overcome the rising air pressure within the sealed sampling channel 1506 . Ultimately, an isolation chamber 1508 of predetermined volume
is filled with blood that drives air out through the air permeable blood barrier 1 512 . When bl ood
impinges , the blood interacts with the material of air permeable blood barrier 1512
to completely or partially seal vent 1510 . A signal or indication can be provided that the pract itioner can now
utilize the VACUTAINER® capsule or other blood sampling device to obtain the next volume of the patient's blood for sampling.
The blood in the isolation chamber 1508
is now effectively isolated within the isolation chamber.
Upon filling blood isolation channel 1508 and prior to use of a Vacutainer
™ or other blood
sampling device, the patient's blood pressure
causes compression of air within sampling channel 1506, possibly A small amount of blood tra vels past the turning point to the isolation chamber 1508 and into
the sampling channel 1506 ,
queuing clean blood to be drawn through the sampling channel 1506 .
Figures 16-19
show yet another implementation of a blood isolation device. Figures 16A-16D illustrate a bl ood sample collection device, such as an evacuated blood collection container such as
a Vacutainer® (not shown), and a patient.
A blood isolation device 1600 that can be connected between a needle (not shown) and/or ass ociated tubing is
shown. FIG. 17 shows the lower member of the blood isolation device and FIG. 18 shows the upper member of the blood isolation
device , the upper and lower members
being interfitted and configured as described in more detail below. Inlet ports, outlet ports, iso lation chambers and sampling channels
can . Figures 19A and 19B show the upper and lower members mating together. 16-19 show

one exemplary method of constructing the blood isolation devices described herein, and it should be understood that other forms of construction are possible. 16A-16D, blood isolation device 1600 has an entry port that can . 1602 included. Inlet port 1602 can also be connected to a tube . The inlet port 1602 defines an opening to the blood isolation device 1600, which opening can be of the same cross-sectional dimensions as the tubing or other conduit connected to the patient needle or the patient needle itself. For example, the opening can be circular with a diameter of about 0.045 inch (1.143 mm), but may be 0.01 inch (0.254 mm) to 0.2 inch (5.08 mm) or less. can have a diameter of

.

Inlet port 1602 may

also include a sealed or fluid tight connector or connection such as a threaded or luer fitting or the like . In some implementations, a tube or other conduit coupled

to the patient needle can be integrated with the entry port 1602, such as by co-molding, gluing, laser welding, or heat bonding the parts together. This allows the blood isolation device 1600 to be manufactured and sold as a single unit along with the patient needle and/or tubing, eliminating the need to connect the patient needle to the blood isolation device 1600 during blood draw or sampling. . Blood isolation device 1600 further includes an exit port 1604 that defines an opening . Exit port 1604 may also be connected to a tube or other conduit that is also connected to a blood isolation device and may include a sealed or fluid tight connector or connection such as a threaded or luer fitting . Thus , as noted above, the blood isolation device 1600 is manufactured and sold as a single unit with the patient needle and/or tubing and blood sample device, and is attached to the patient needle and blood sample collection device during blood collection or sampling. to the blood isolation device 1600 . Blood isolation device 1600 has a sampling port between inlet port 1602 and outlet port 1604 .

and an isolation chamber 1608 connected to and separated or diverted from
the sampling
. Sampling channel 1606 functions as a blood collection path once the first
aliquot of blood is sequestered in sequestration chamber 1608 . Sampling
channel 1606 can be a channel or conduit of any size, shape or configuration
. In some implementations, sampling channel 1606
has a cross-sectional area substantially similar to the opening of inlet port 1602 . In other imp lementations, sampling channel 1606
can gradually widen from inlet port 1602 to outlet port 1604 . The isolation chamber 1608 wid ens toward the path of the isolation channel so that blood first attempts to enter the reservoir as opposed to entering the
smaller diameter of the sampling channel 1606, as shown in more detail in FIGS . It can have a larger cross-section to form a reservoir. In some exemplary implementations, the diversion between sampling channel 1606 and isolation chamber 1608 is accomplished by diversion jun ction 1607 . Turning junction 1607 can be substantially Y-shaped, T-shaped, or U-shaped. In s ome preferred exemplary implementations , redirection junction 1607 is configured such that flow from . isolation chamber

1608 can also include or form a curve or ramp to move the initial blood flow toward and into t he isolation chamber 1608 . The isolation chamber 1608 is preferably maintained at atmosp

heric pressure and includes a vent 1610 at or near the distal end of the isolation chamber 1608 . Vent 1610 can include an air permeable blood . Blood isolation device 1600 can include a housing 1601 that can be formed from multiple pieces or a single unitary piece . In some implementations, as shown in FIGS. 17A-17D and 18A-18F, housing 1601 includes an upper member 1620 and a lower . Blood isolation device 1600 includes a gasket or other sealing member such that when upper member 1620 is mechanically attached to lower member 1622, the interface therebetween is sealed by A member (not shown) may also be included.

17A-17D show the lower member 1622 of the housing for the blood isolation device 1600. FIG.

The lower member 1622 includes pre-formed grooves, channels, locks, or the like by an injection molding process or by etching, cutting, drilling, etc., to form the sampling channels 1606, the isolation chambers 1608, and the turning junctions
1607.

Conduits or other pathways may be included
.

Isolation chamber 1608
has a larger cross-section than sampling channel 1606
so that blood preferentially moves into the isolation chamber first as opposed
to can be done.

FIGS.
18A-18F may be connected by any mating or connecting mechanism such as using laser welding, thermal bonding, gluing, screws, rivets, bolts, etc.,
or by latches, grooves, tongues, pins, flanges, etc.

Upper member 1620 is
shown . Top member 1620 can include
some or all of grooves, channels, locks, conduits or other pathways to form sampling channels 1606 , isolation chambers 1608 and turning junctions 1607 .

In still other implementations,
both upper member 1620 and lower member 1622 can include grooves, channels, locks or oth

er pathways. In some implementations, sampling channel 1606 and isolation chamber 1608 are located in a housing

.

formed by grooves, channels, locks or other pathways formed in 1601; Housing 1
601 can be made of rubber, plastic, metal or any other suitable material
. Housing 1601 can be formed from a transparent or translucent material, or
from .
In other implementations, housing 1601 can be largely opaque or non-translucent, but housing surfaces directly adjacent sampling channel 1606 and/or isolation chamber 1608 can be transparent or translucent. , first a visual cue or sign that the isolation
chamber 1608 has been filled to the required or desired degree
, and/or subsequently while a clean blood sample is
taken through the sampling channel 1606. ,
giving the practitioner a visual cue or sign that the sequestered blood remains sequestered .
Other visual cues or signs of isolation include, but are not limited to,
contact, penetration, or partial penetration of blood, causing the air permeable blood barrier 1
612 to turn a different color
; Color-coded tabs or indicators at any location along or adjacent to the isolation chamber
, audible, vibratory, or other signals may be included. As shown in FIGS. 18A-18F, air perme able blood barrier 1612
can be covered or surrounded by protective member 1616 . Protective material

1616 can be sized and configured to prevent a user from
touching , while still
expelling air from the isolation chamber 1608.
allows air to exit the air permeable blood barrier 1612 . In some implementations, protective member 1616
includes protrusions that extend from the top surface of top member 1620 up and around air permeable blood barrier 1612 . The protective cover 1616 can be configured
to block or prevent accidental exposure of the filter to ambient fluids or splashes . This can be done in a variety of mechanical ways
including, but not limited to, adding a hydrophobic membrane to the protective cover . In use, blood isolation device 1600 includes sampling channel 1606 and isolation chamber 1608 . Bo th paths are initially filled with air at atmospheric pressure, but sampling channel 1 606 is initi ally sealed by The isolation chamber 1608 terminates in a vent 1610 to the atmosphere that i ncludes an air permeable blood barrier 1612 . [0093]

After
venipuncture with a patient needle (not shown), which can collect many pathogens from the patient's skin, an initial volume of the patient's blood with these pathogens is delivered to inle t port 1602 of blood isolation device 1600 .
pass through. This initial volume of potentially contaminated blood
preferentially enters isolation chamber 1608 by finding the path of least resistance. The patie nt's
own blood pressure overcomes the atmospheric pressure in the vented isolation chamber 160 8
and expels air within the isolation chamber 1608 through the air permeable blood barrier 161 2, but builds up in the sealed
sampling channel 1606. insufficient to overcome the air pressure that is present. In
various exemplary embodiments, the isolation chamber 1608 and sampling channel 1606 are configured such that the force generated by the patient's blood pressure is sufficient to overco me the effects of gravity regardless of the orientation of the blood isolation device. can be con figured to Ultimately , the isolation chamber 1608 fills with blood that drives . When blood c ontacts the air permeable blood barrier, the blood interacts with the material of air permeable blood barrier 1612 to completely or partially seal vent 1610 . A signal or indication can be pro vided that the practitioner can now utilize the Vacutainer® or other blood collection device .
Once the blood isolation path 1608 is satisfied, a Vacutainer™ or other blood sample collecti on is performed .

Prior to use of the aspiration device, the patient's blood pressure

causes , possibly
moving a small amount of blood past the turning point into the sampling channel 1606 and int o the sampling channel.
Queue .
FIG .
19A is a side view of blood isolation device 1600 and FIG. 19B is a cross-sectional view of bl ood isolation device 1600
showing upper member 1620 mating with lower member 1622 .
FIG.
20 illustrates a patient needle 2002 for vascular access to a patient's bloodstream, a blood s ample collection device 2004 facilitating the collection of one or more blood
samples patient needle 2002 and the blood
sample . Blood sample
optimization . In some implementations, the blood sample collection device 2004
includes a protective shield that includes a sealed collection needle such that once a sealed va cuum container is placed on the collection needle and the container is pierced once by the coll ection
needle, the patient needle is exposed to the patient needle. A blood sample is drawn from 200 2 through conduit 2006 with vacuum pressure
or force.
Blood sample optimization system 2000 further includes a blood isolation device 2008 located at any point on conduit 2006 between
patient needle 2002 and blood sampling device 2004, as described herein. . [0099]

FIG. 21 shows a non-vented blood isolation device 2100 that uses wicking material chamber s . Blood isolation device 2100 includes a housing 2101
having a sampling channel 2104 at least partially surrounded or abutted by an isolation cham ber 2102 filled with wicking material .
A first aliquot of blood is
drawn from the patient needle into the sampling channel 2104 where it immediately escapes i nto the
wicking . The wicking material and/or isolation chamber 2102 is filled with a predetermined vo lume such
that subsequent or subsequent blood draws flow past the wicking material and
through the sampling channel 2104 directly to a sampling device such as a vacutainer.
Dimensioned and adapted to receive and retain blood. The wicking

material can include substances such as solidifying agents, decontaminating agents, or other additives. As described herein, air permeable blood barriers can be of a wide variety of differ ent constructions and materials

.

can be made using a fee. As shown in Figures 22A and 22B, the
air permeable blood barrier 2202 of the blood isolation device 2200
can include a polymeric bead matrix 2204 that has been treated to render at least some of th e beads hydrophilic. Air permeable blood
barrier 2202
further comprises a self-sealing material 2206 such as carboxymethylcellulose (CMC) or cellul ose gum, or other sealing material. Air permeable blood barrier
2202
may further include voids 2208 that allow air flow prior to or during partial contact with a fluid such as blood. Upon contact with fluid, self-sealing material 2206
expands close void 2208 and occlude air flow through void 2208, completely or
partially sealing, as shown in FIG. 22B. Figures 23A and 23B show an entry port 2302 for co nnection with a patient needle, an exit port 2304 for connection with a blood sampling device, an isolation chamber 2306, an isolation chamber 2306 and a contamination to be isolated . 23 shows yet another implementation of a blood isolation device 2300 having a sampling ch annel 2308 that bypasses the isolation . The isolation chamber 2306 includes a hydrophobic pl ug 2312 at the distal end of the isolation chamber 2306 furthest from the inlet port 2302 . Ap plied from outlet port 2304, such as from a Vacutainer® or the like.

The applied vacuum or other suction force
draws blood into inlet port 2302 and directly into isolation chamber 2306 where a first aliquot of blood contacts hydrophobic plug 2312
, isolating the first aliquot of blood. Return to chamber 2306 and isolate there. A small amoun t of
blood
can enter sampling channel 2308 which is initially closed by valve 2308 . When valve 2308 is released, a subsequent volume of blood, under additional vacuum or other force, flows into inl et port 2302, bypasses isolation chamber 2306, and through

sampling channel 2308 to the outlet port.
It flows towards 2304 and is sent to the collection device. Sampling channel 2308 can have any suitable geometry and can be formed from plastic
tubing or any other suitable material. Valve 2308 can be a clip or other enclosing device to pin ch, deflect, bend, or otherwise close the sampling channel before the first aliquot of blood is s equestered in sequestration chamber 2306 . can. [0103] While various embodiments have b een described in detail above, other modifications are possible. Other embodiments may be wi thin the scope of the following claims.

drawing open ----

[Fig. 1]

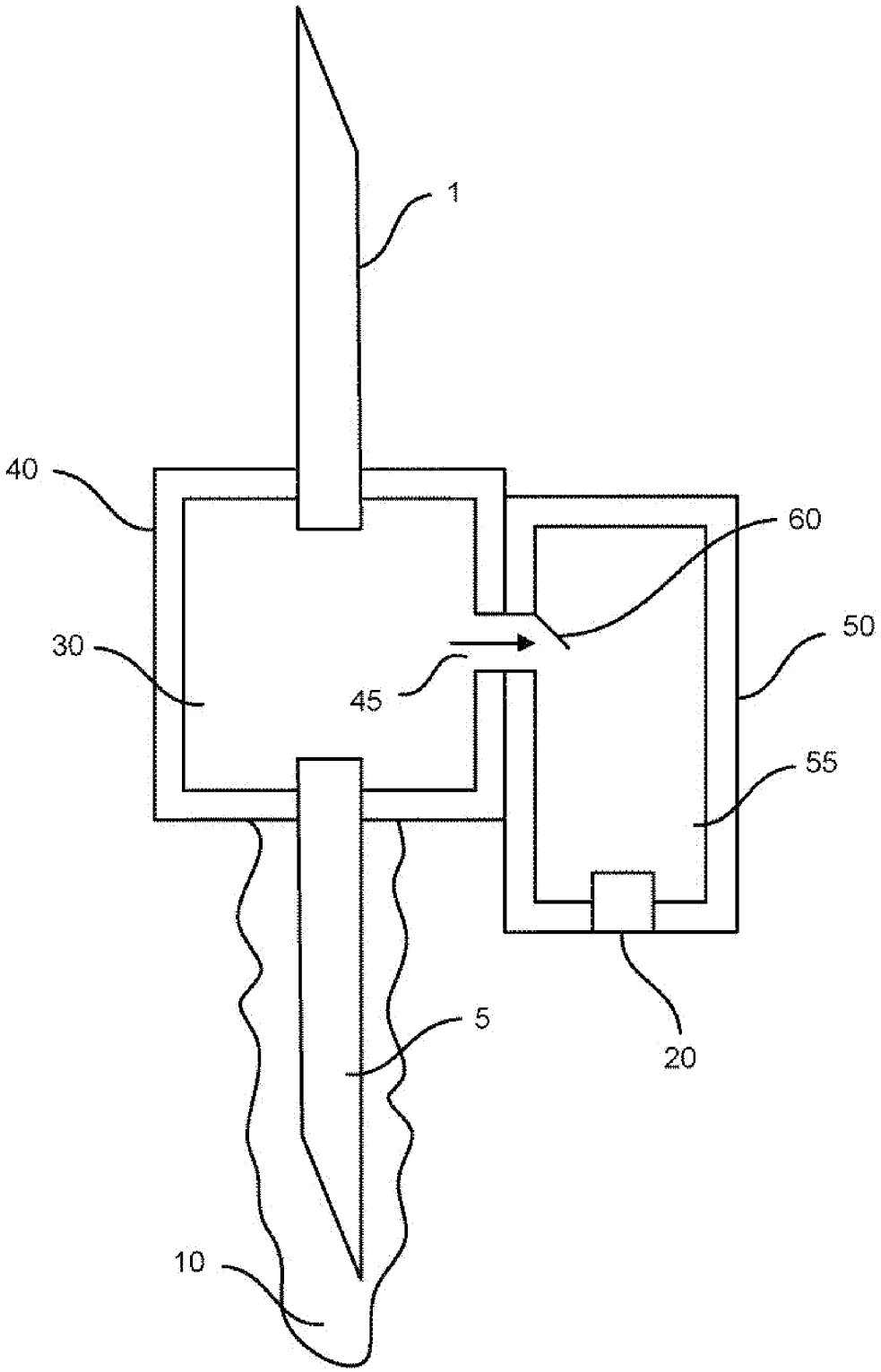


FIG. 1

[Figure 2]



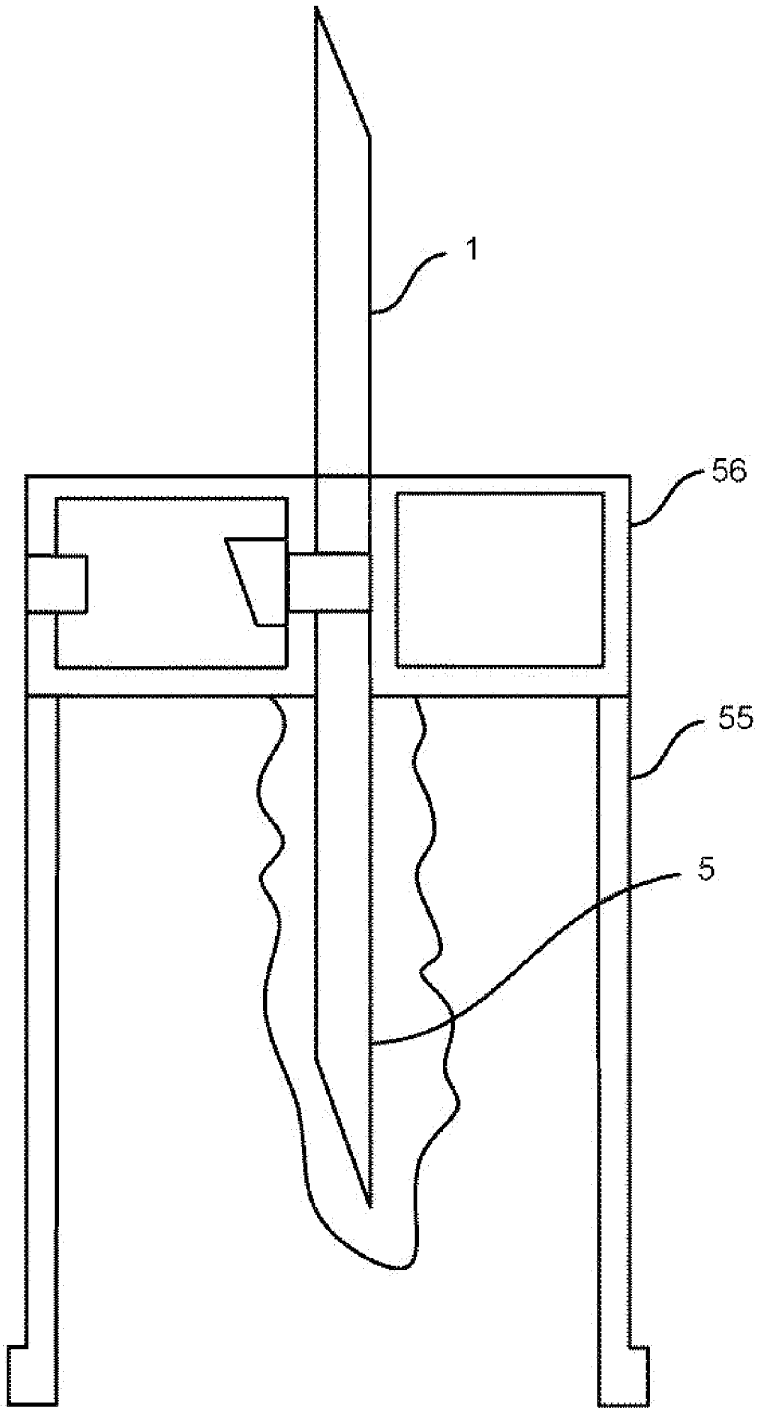


FIG. 2

[Figure 3]

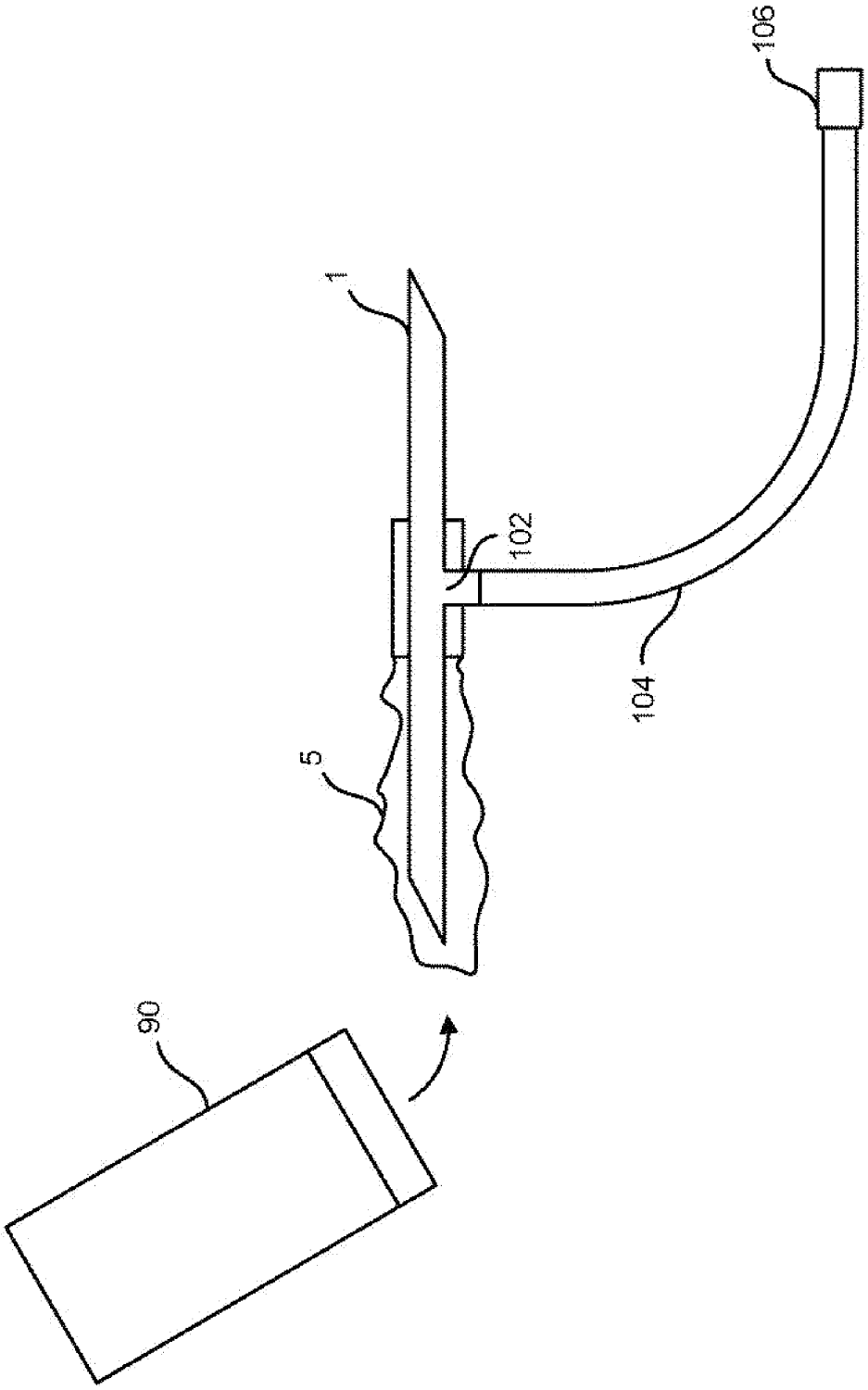


FIG. 3

[Figure 4]

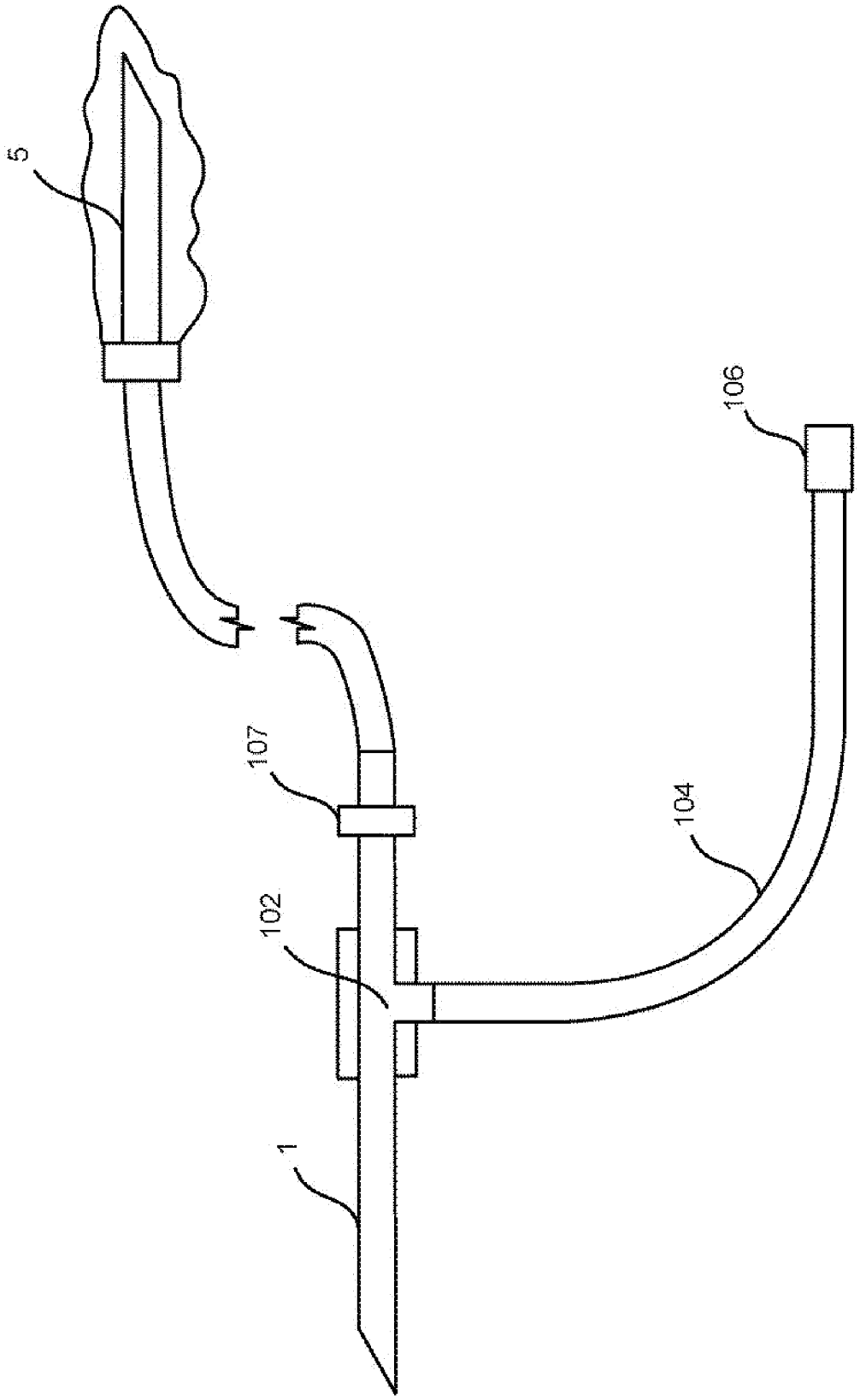


FIG. 4

[Figure 5]

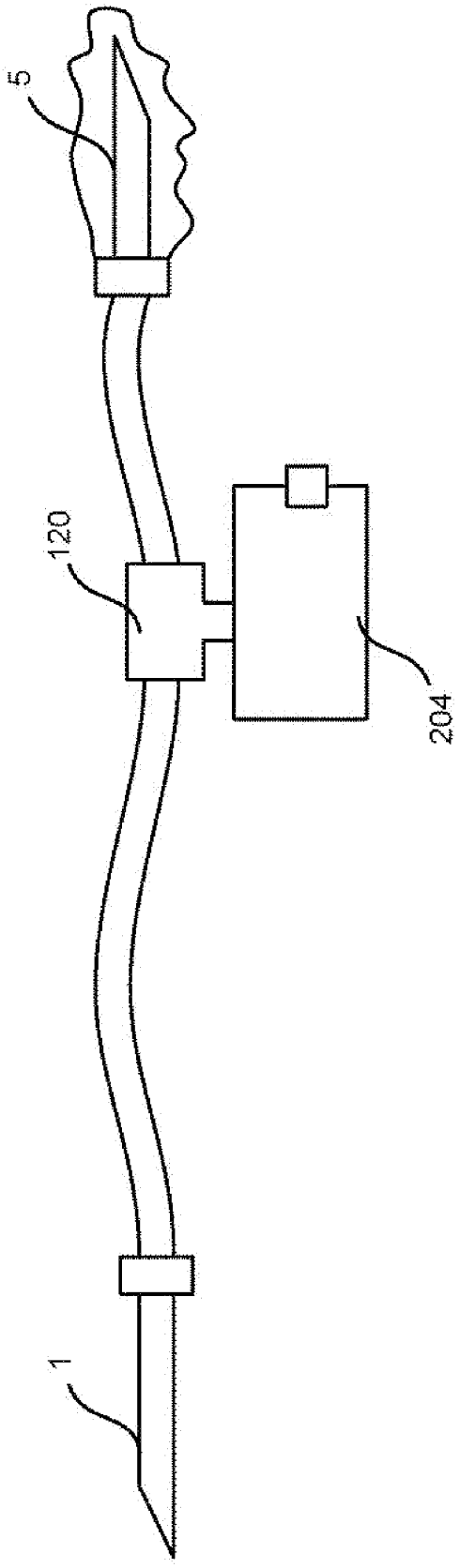


FIG. 5

[Fig. 6]

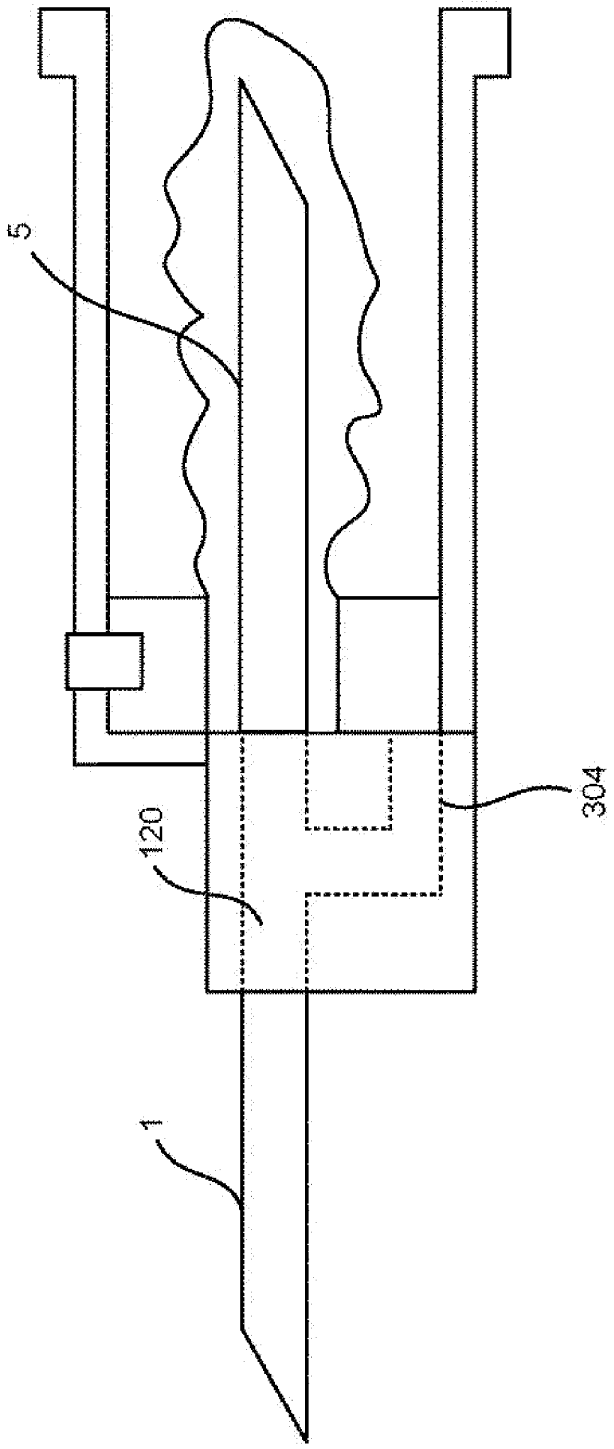


FIG. 6

[Fig. 7]

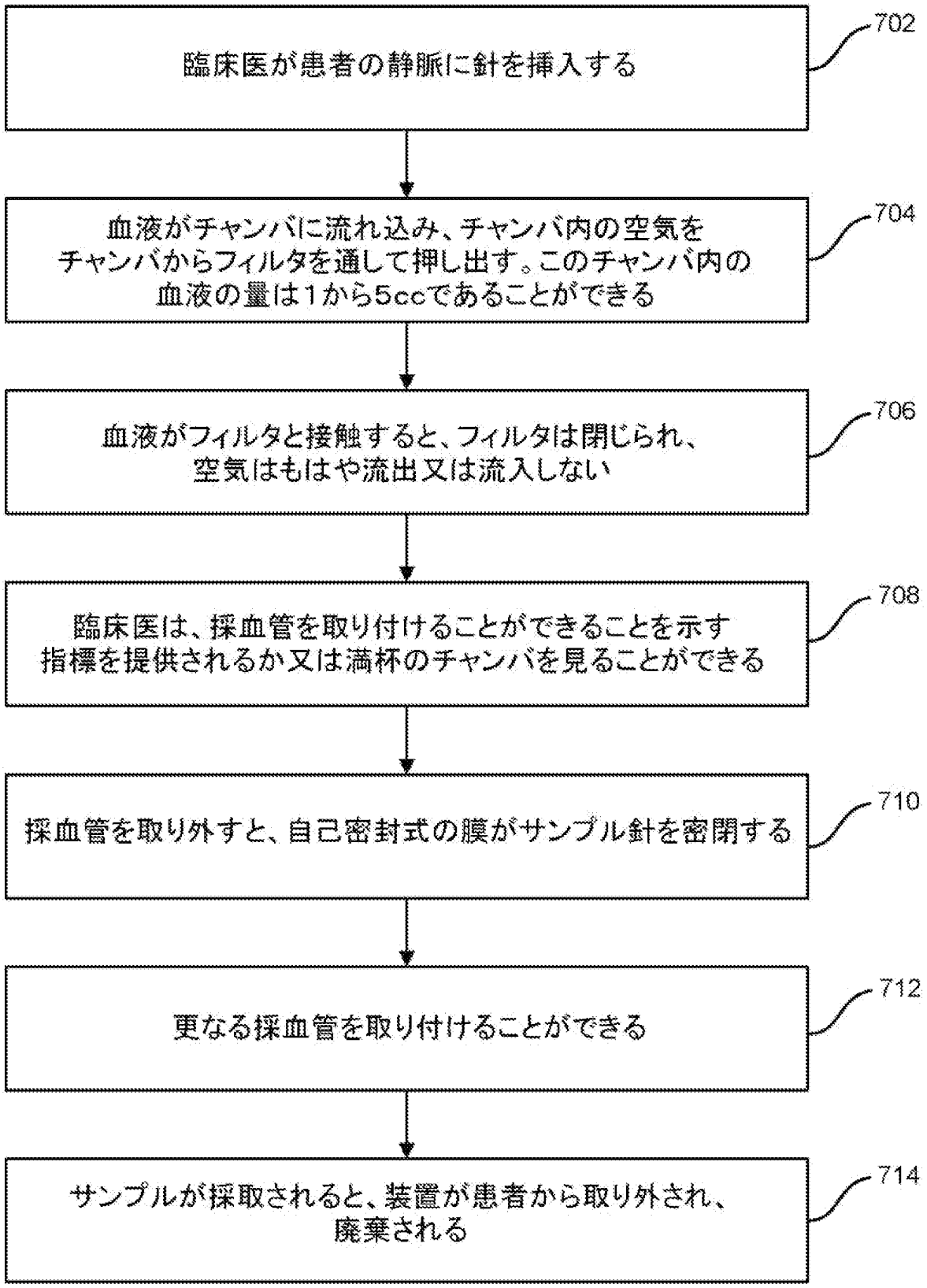

臨床医が患者の静脈に針を挿入する
702
血液がチャンバに流れ込み、チャンバ内の空気を
チャンバからフィルタを通して押し出す。このチャンバ内の
血液の量は1から5ccであることができる
704
血液がフィルタと接触すると、フィルタは閉じられ、
空気はもはや流出又は流入しない
706
臨床医は、採血管を取り付けることができることを示す
指標を提供されるか又は満杯のチャンバを見ることができる
708
採血管を取り外すと、自己密封式の膜がサンプル針を密閉する
710
更なる採血管を取り付けることができる
712
サンプルが採取されると、装置が患者から取り外され、
廃棄される
714

FIG. 7

[Fig. 8A]

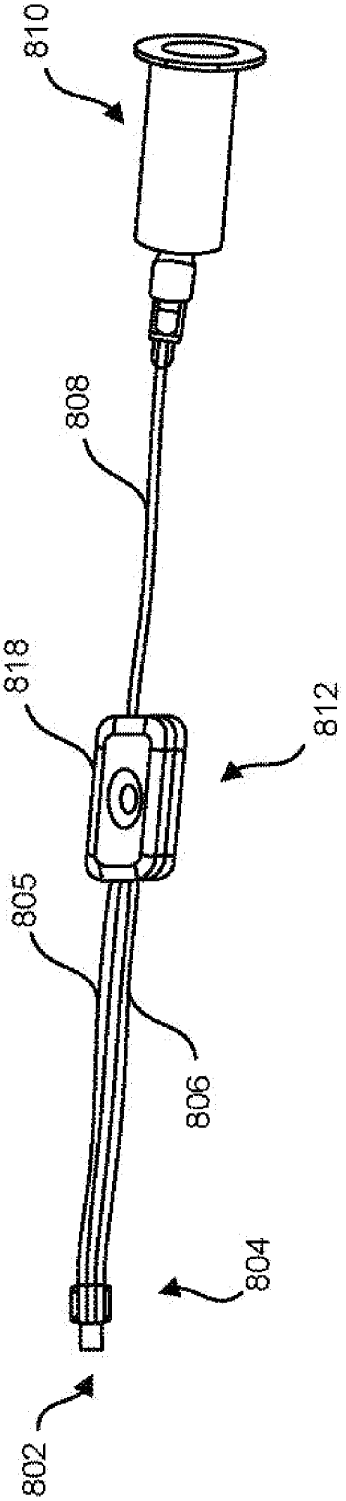


FIG. 8A

[Fig. 8B]

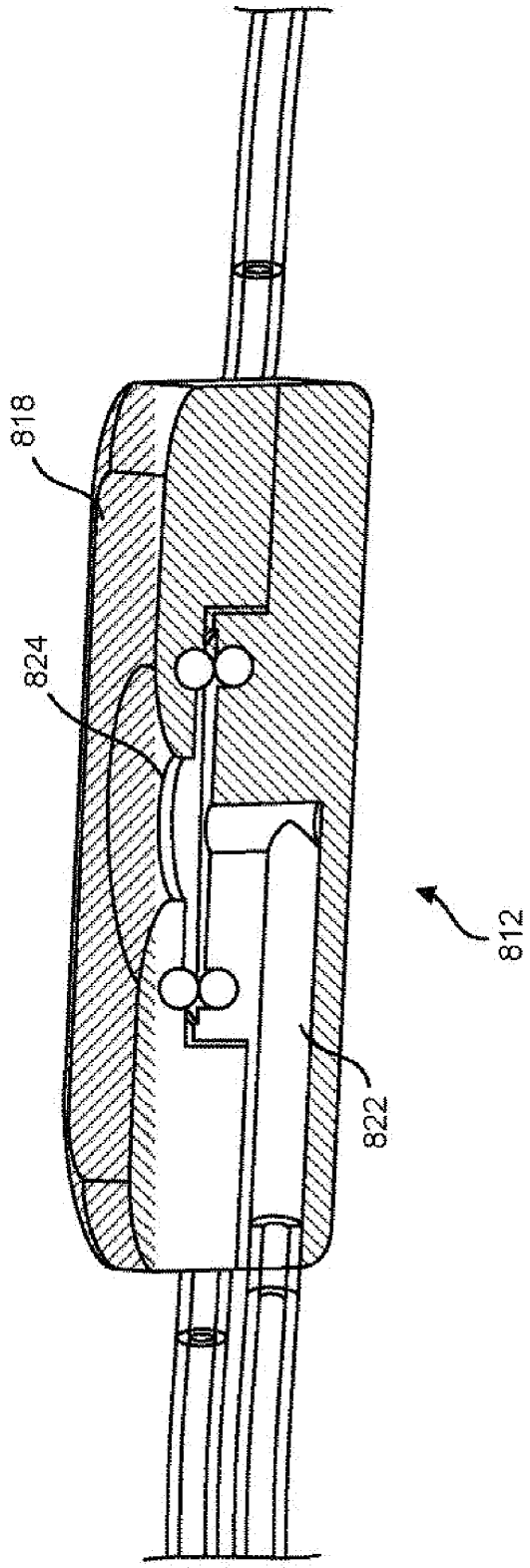


FIG. 8B

[Fig. 8C]

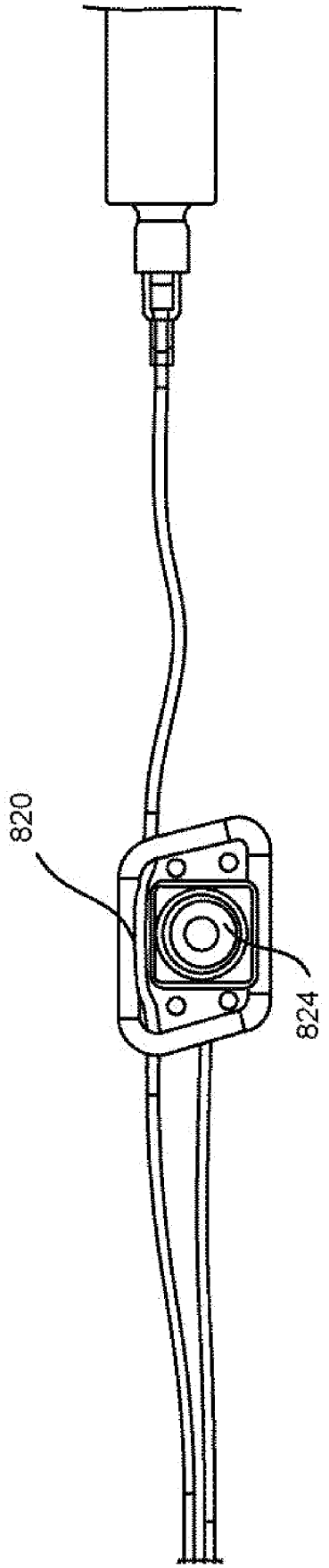


FIG. 8C

[Fig. 8D]



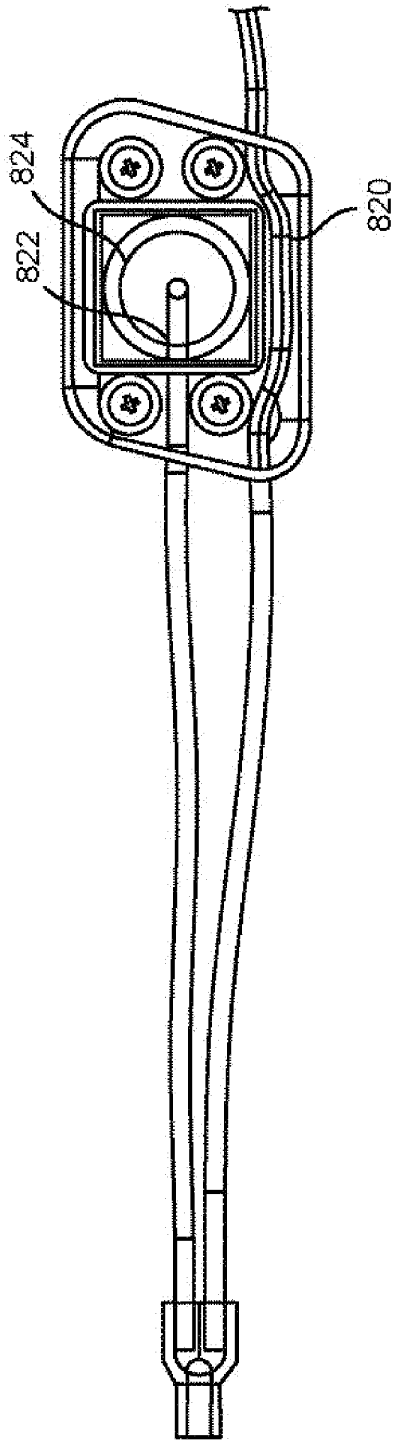


FIG. 8D

[Fig. 8E]

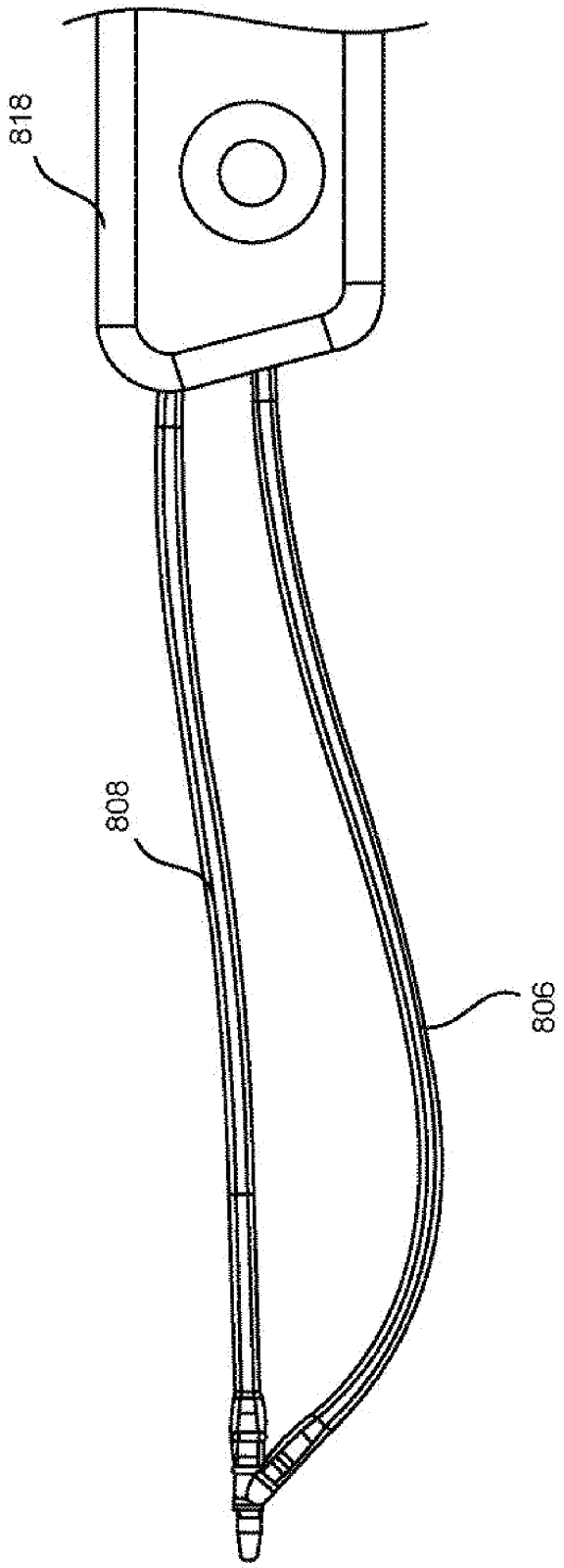


FIG. 8E

[Fig. 9]

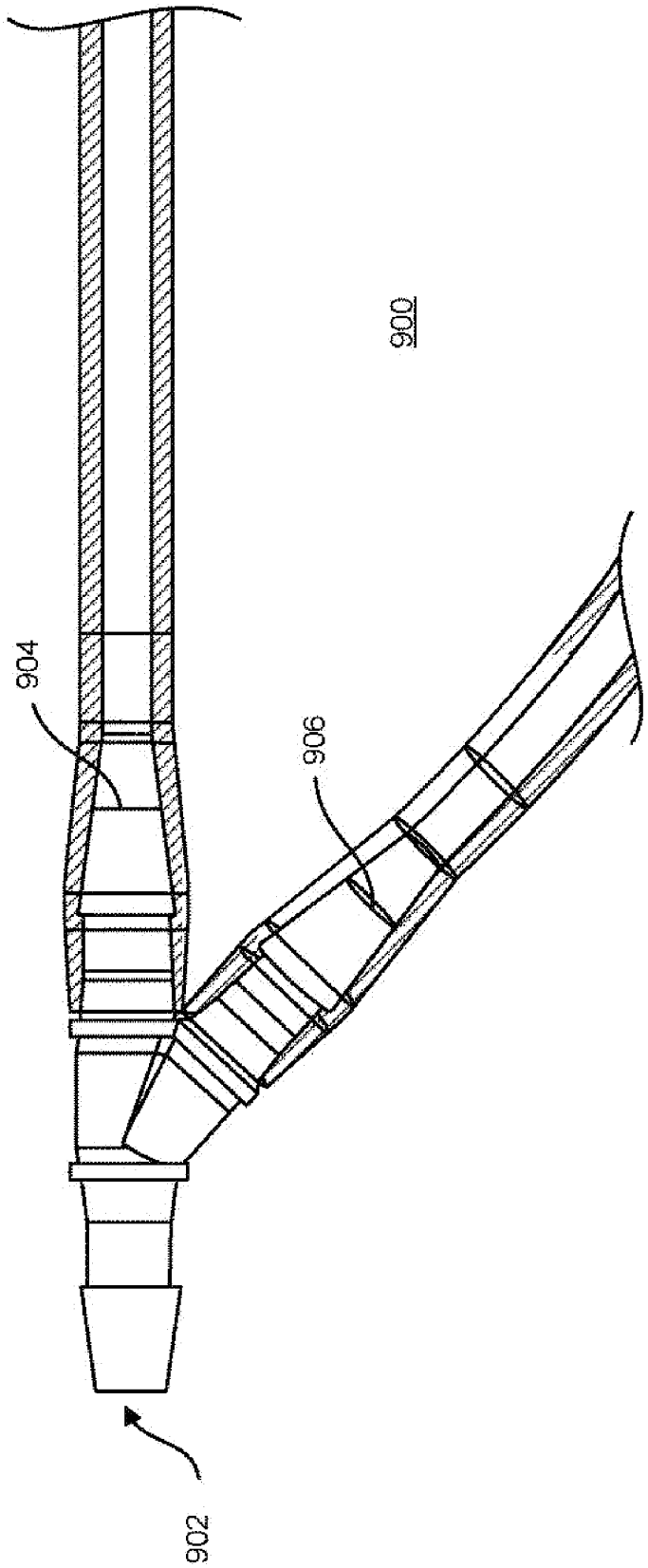


FIG. 9

[Fig. 10A]

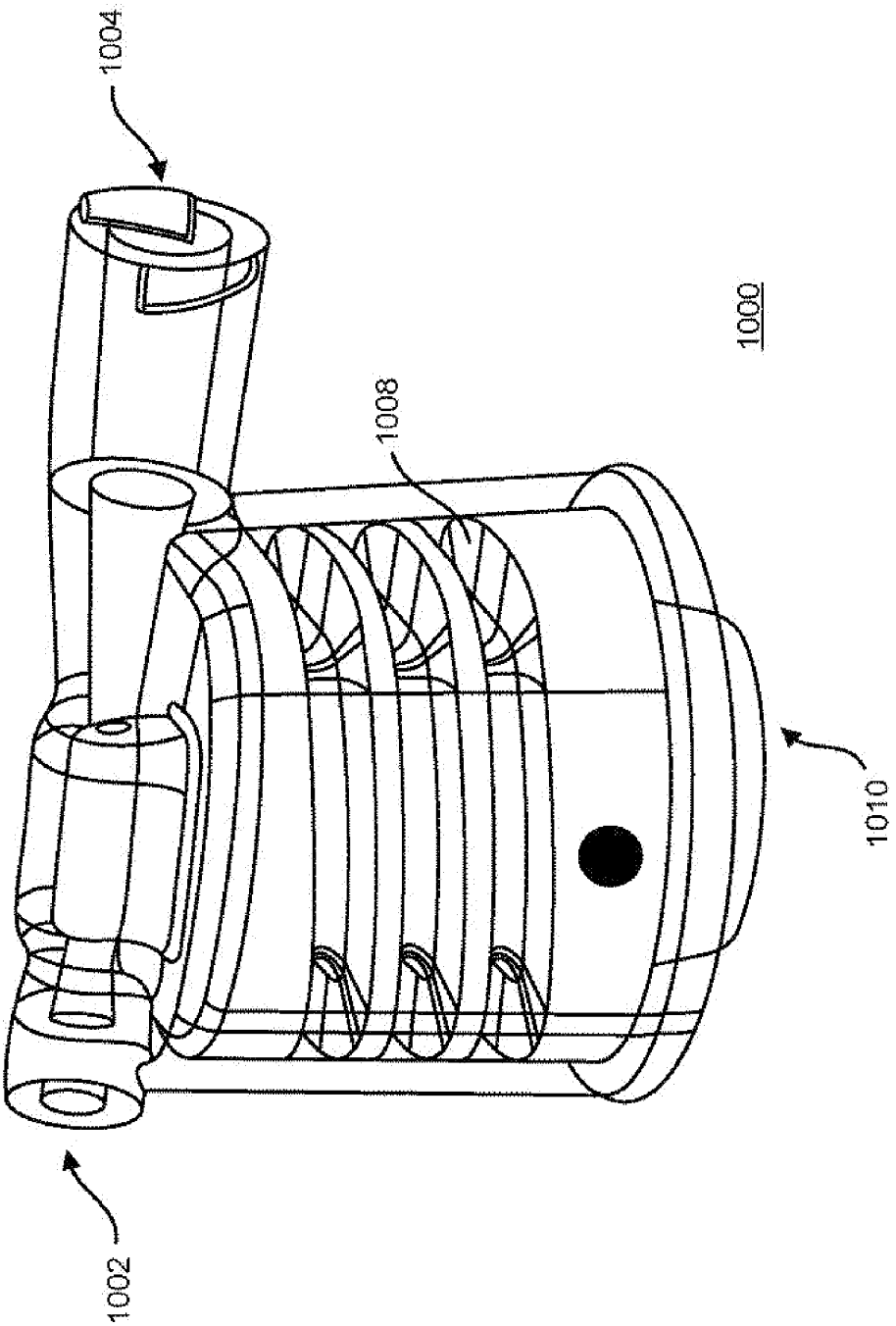


FIG. 10A

[Fig. 10B]

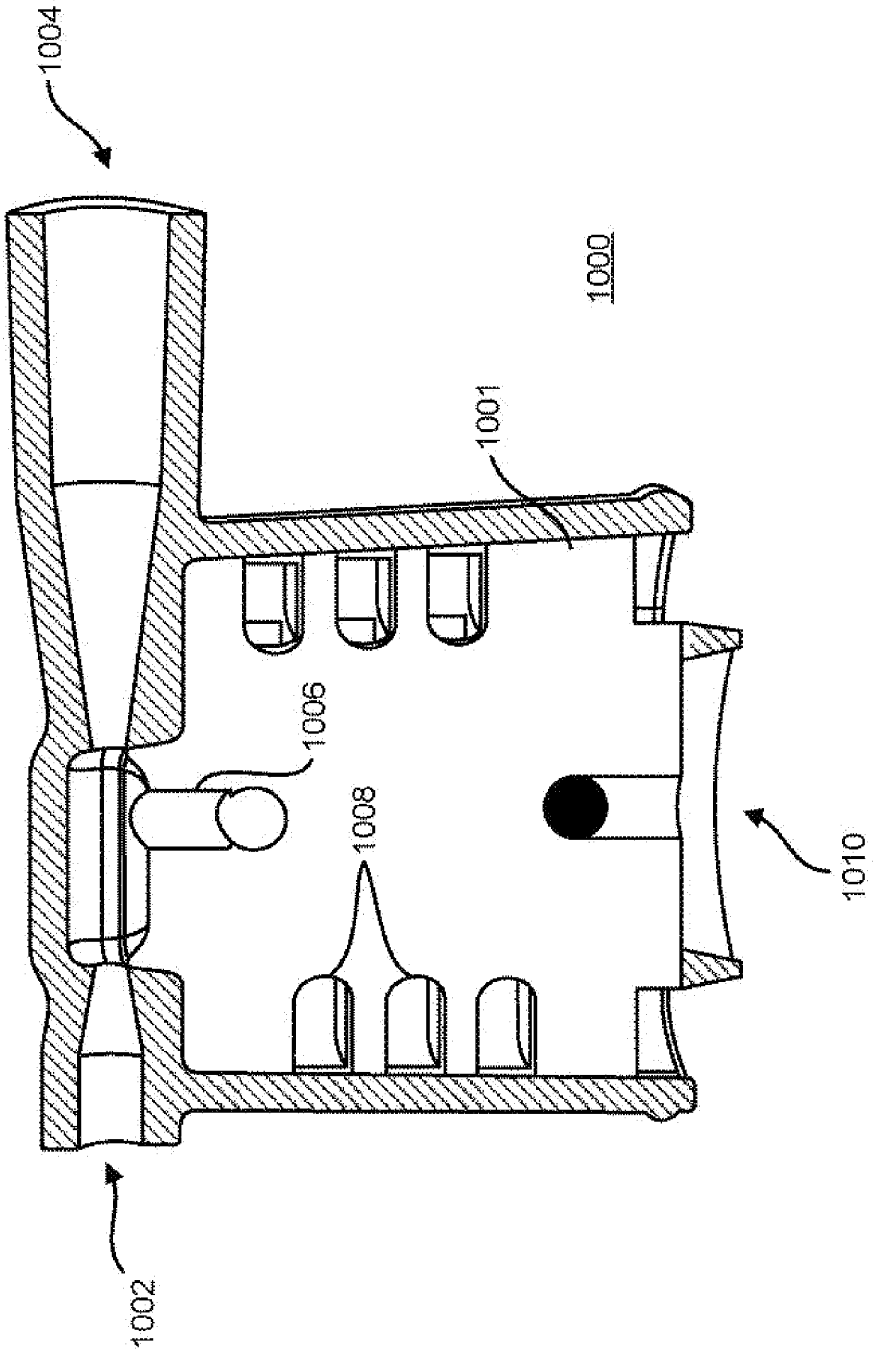


FIG. 10B

[Fig. 10C]

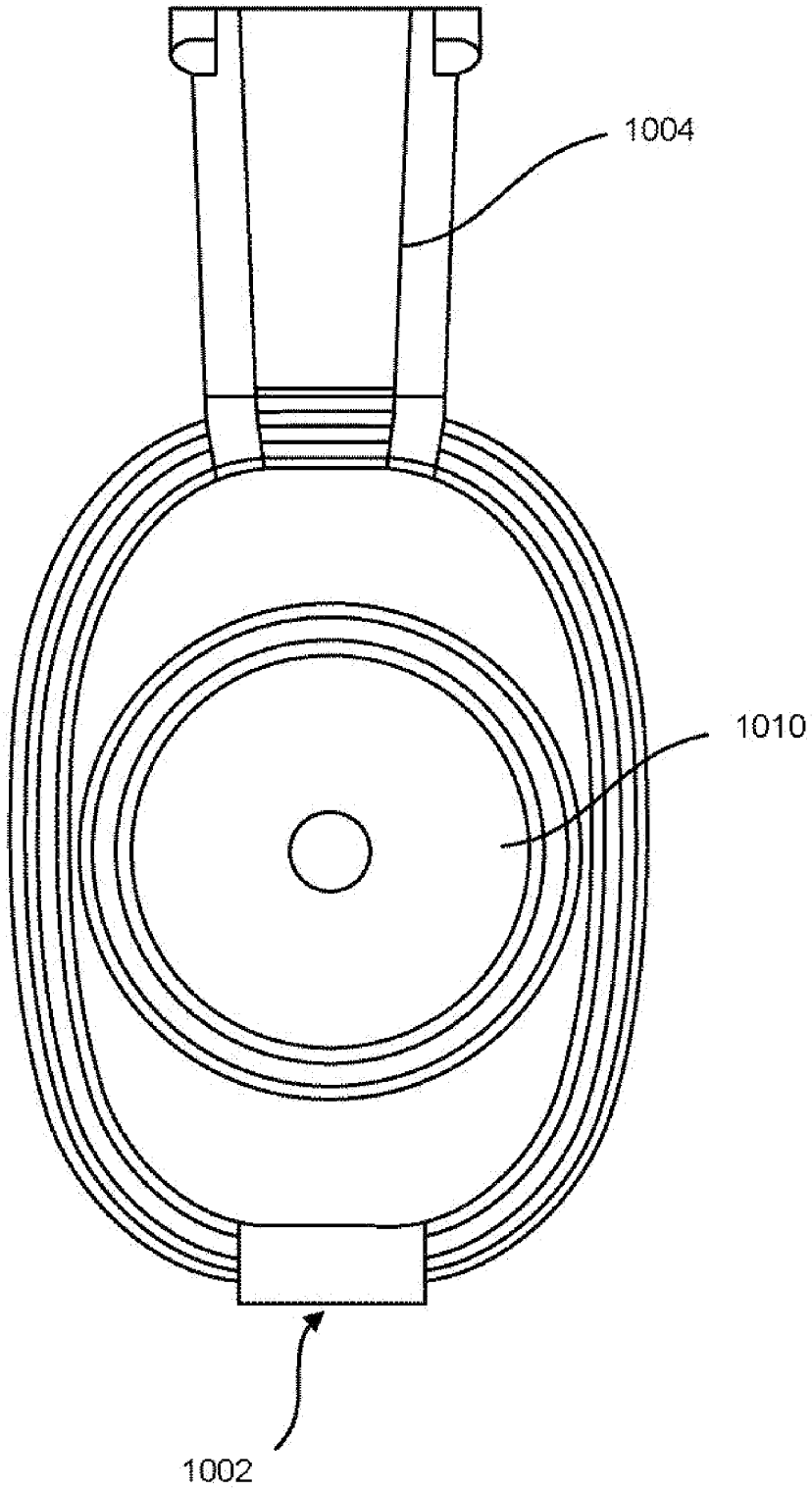
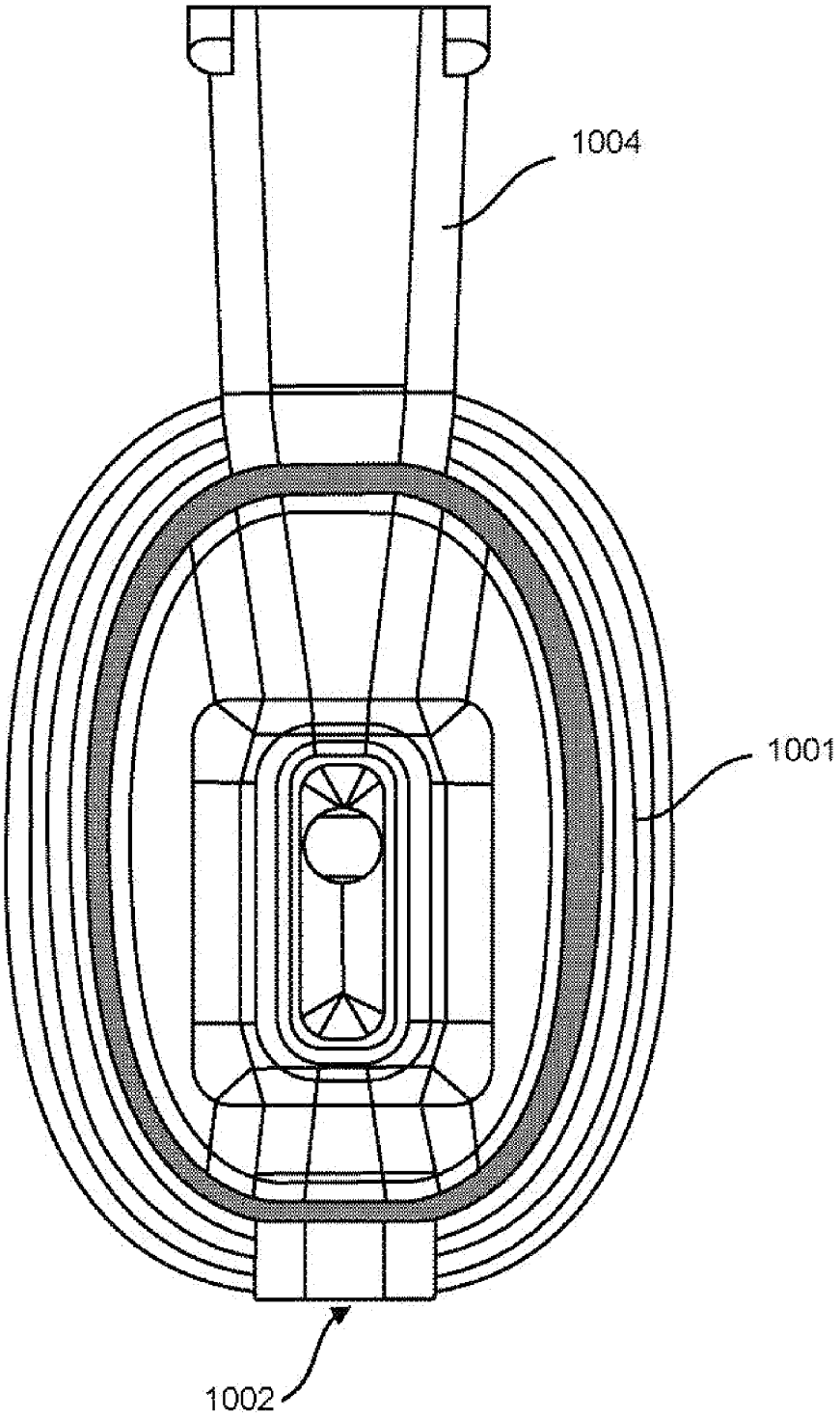


FIG. 10C

[Fig. 10D]


1004
1001
1002

[Fig. 11A]

FIG. 10D

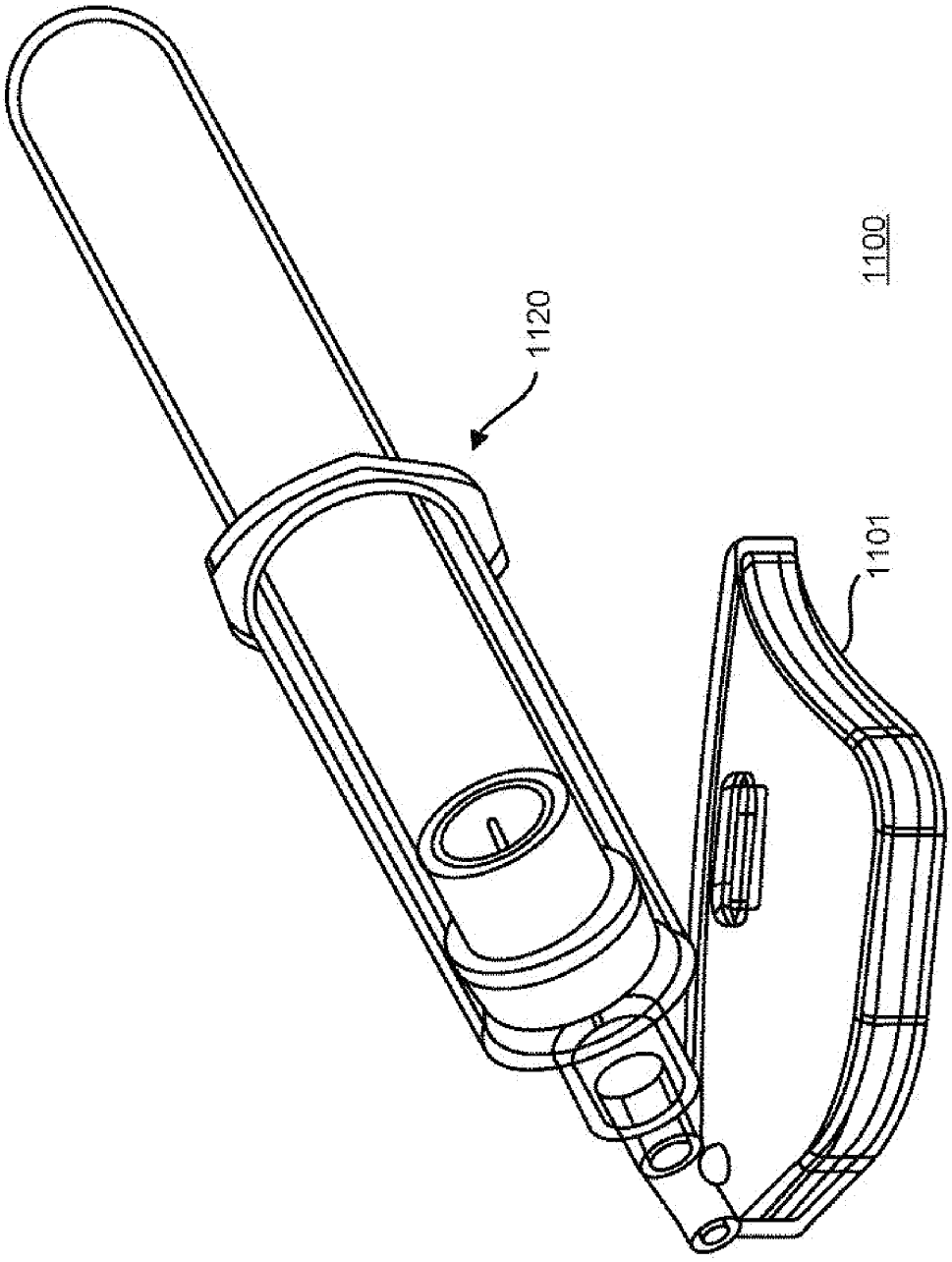


FIG. 11A

[Fig. 11B]

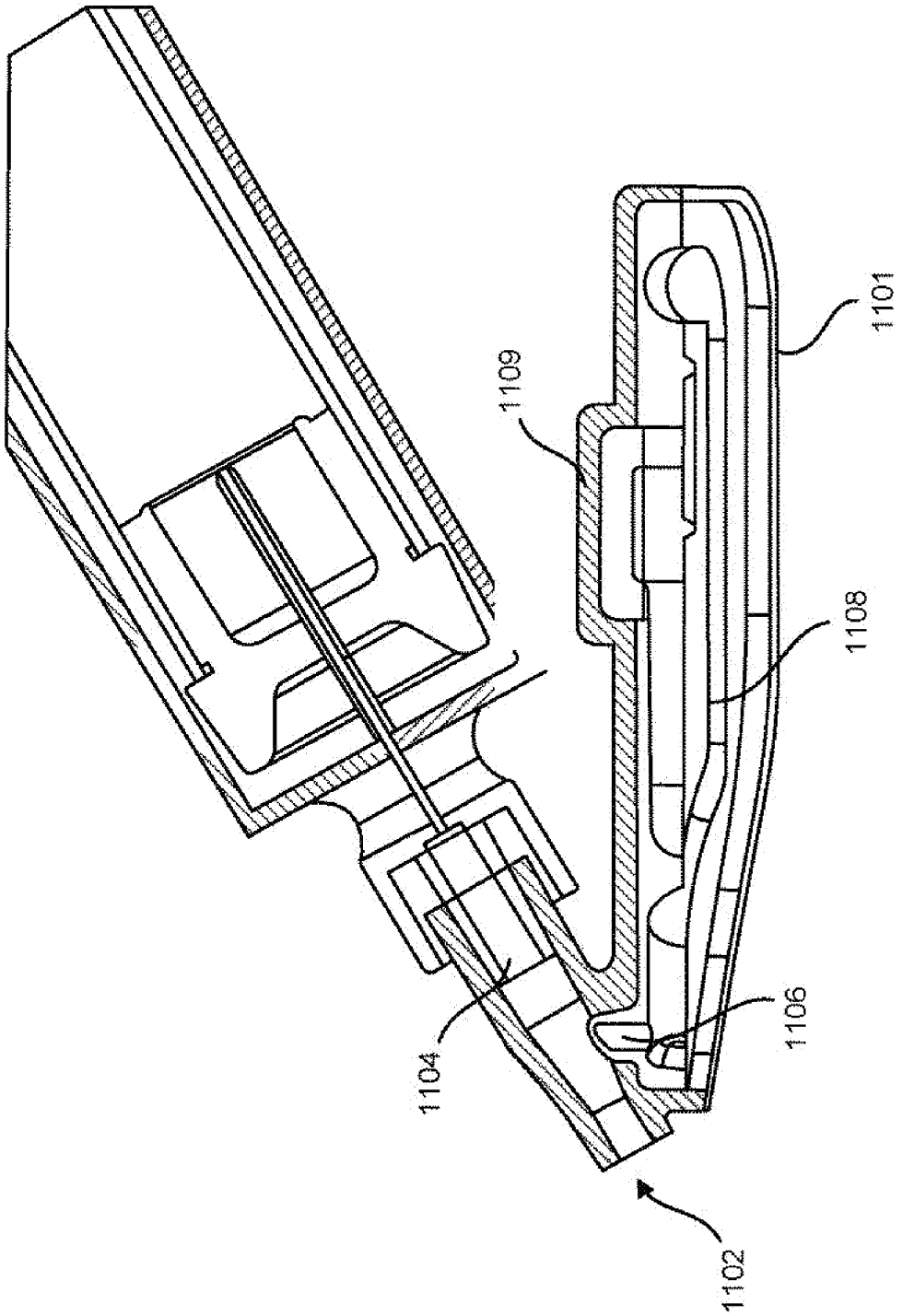
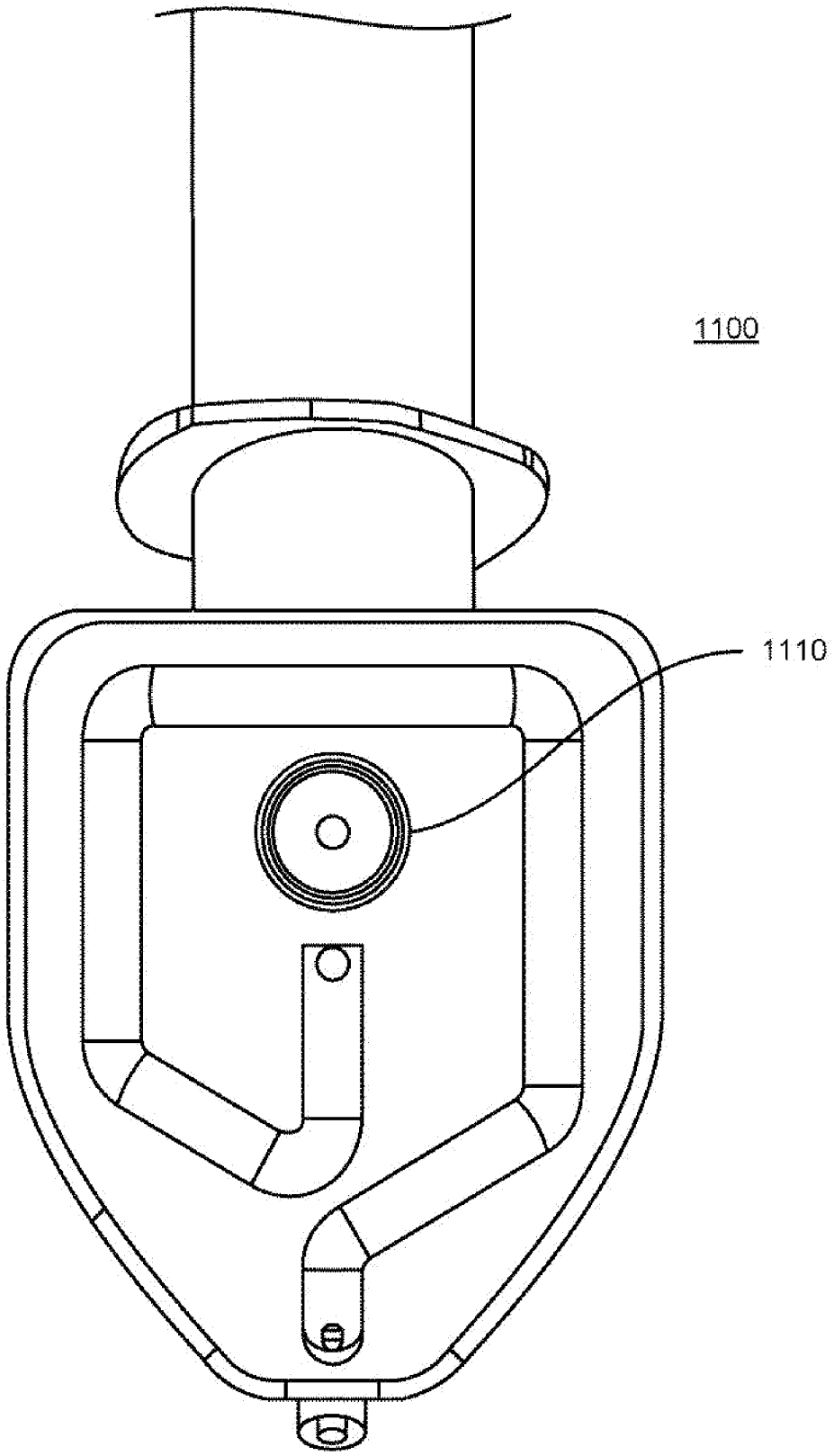


FIG. 11B

[Fig. 11C]


1100
1110

[Fig. 11D]

FIG. 11C

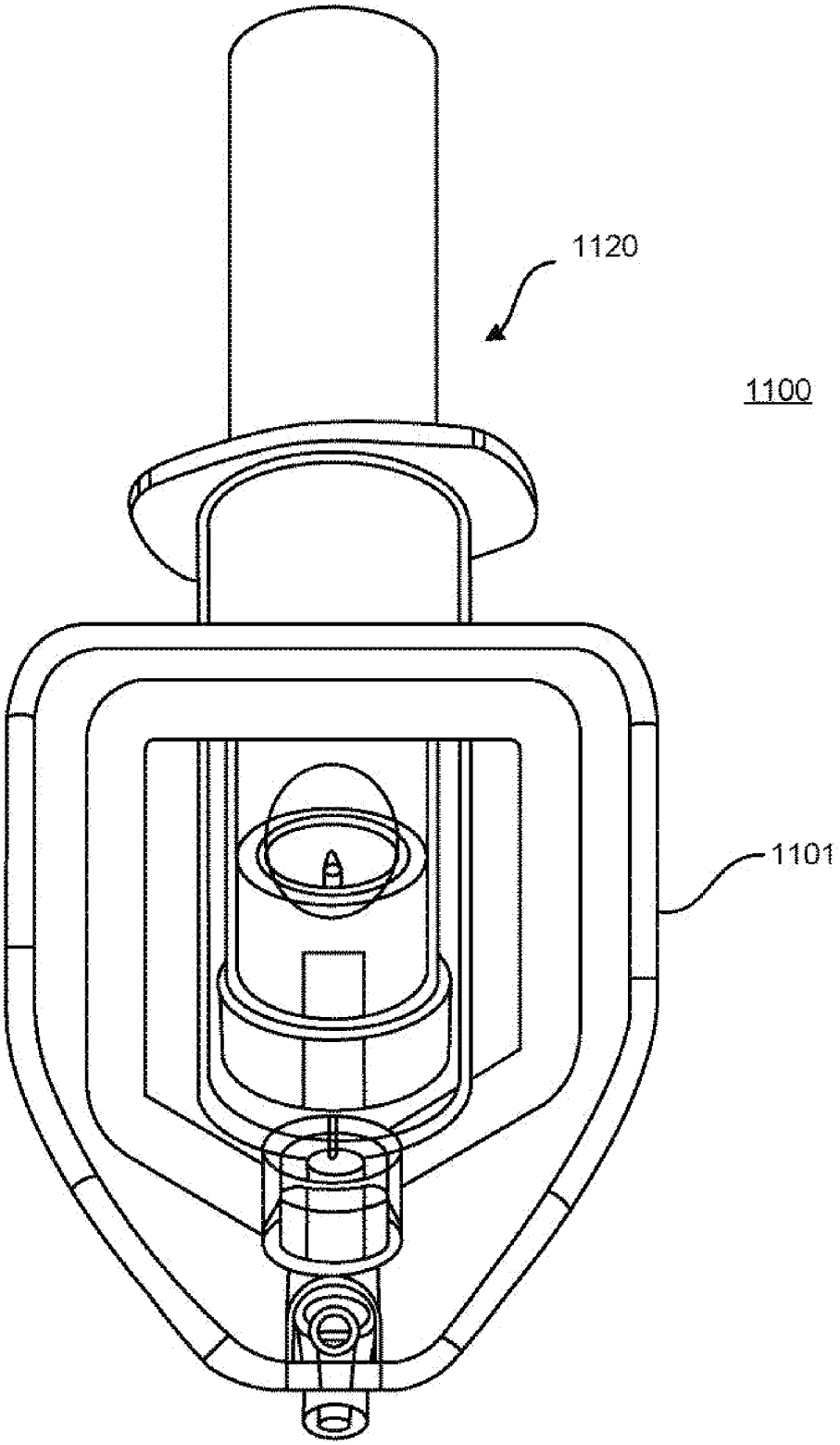


FIG. 11D

[Fig. 11E]

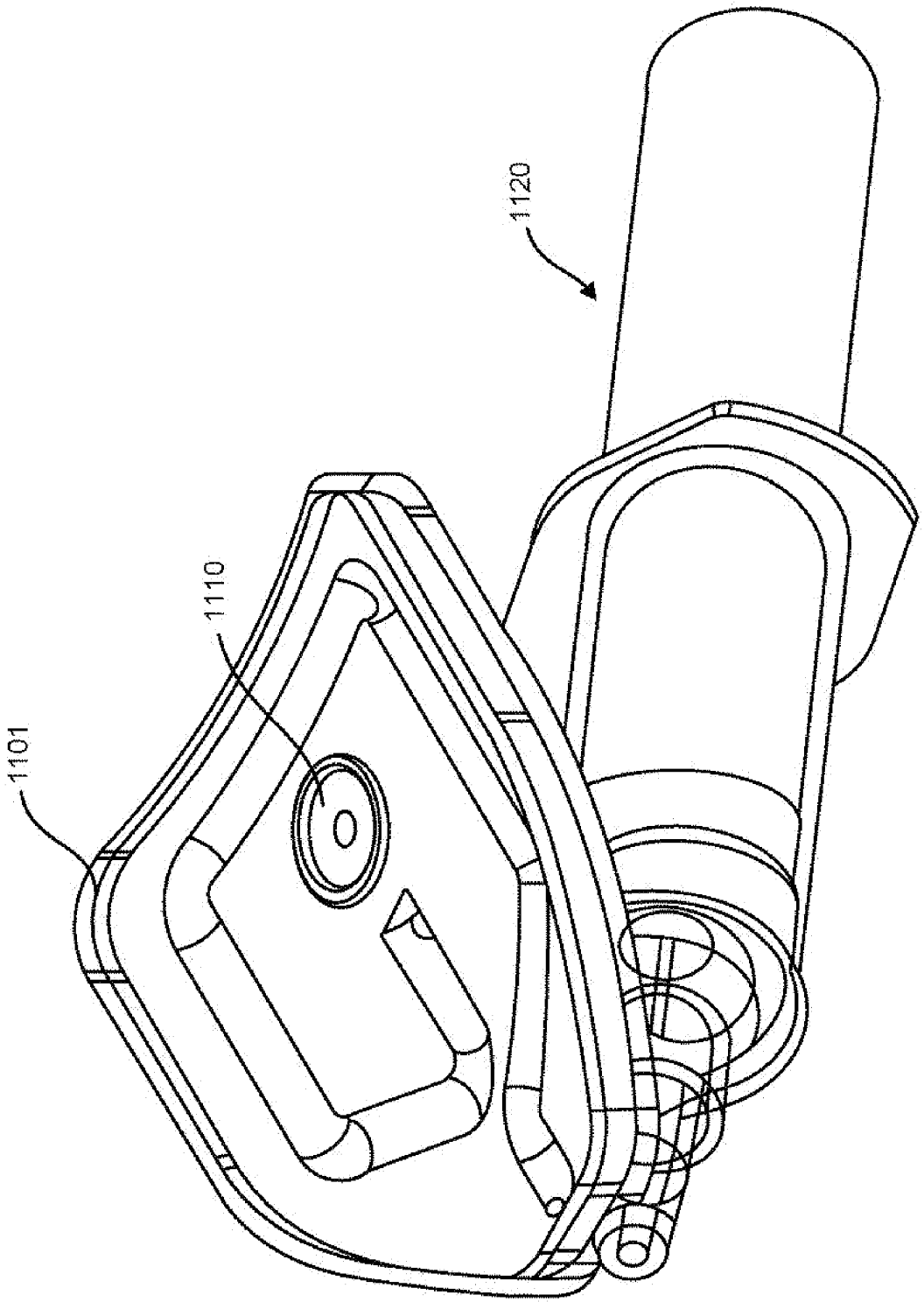


FIG. 11E

[Fig. 12A]

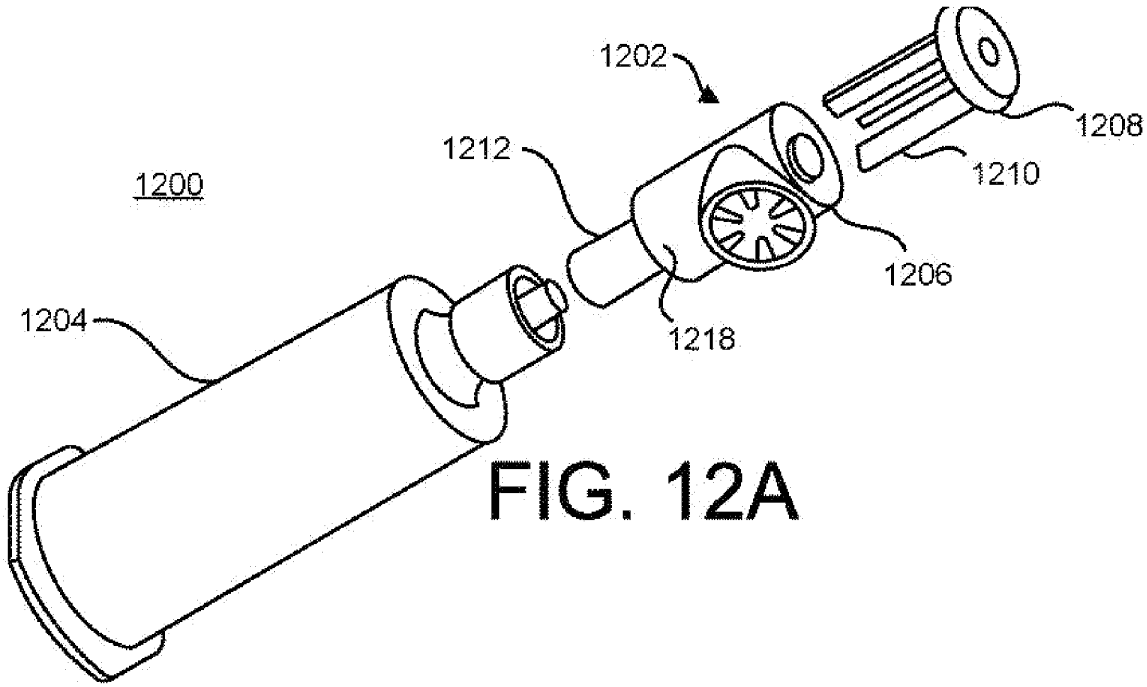


FIG. 12A

[Fig. 12B]

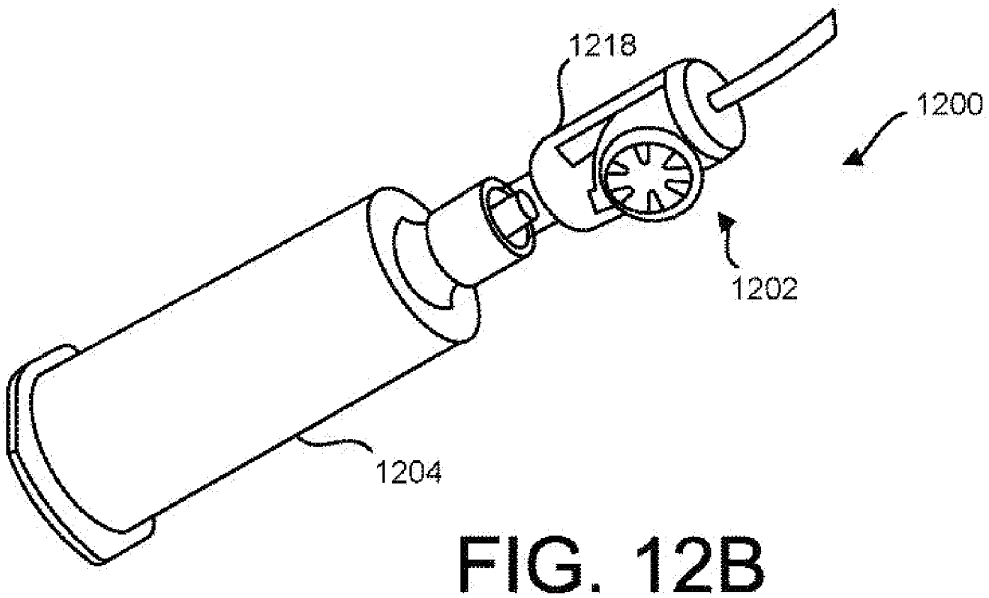


FIG. 12B

[Fig. 12C]

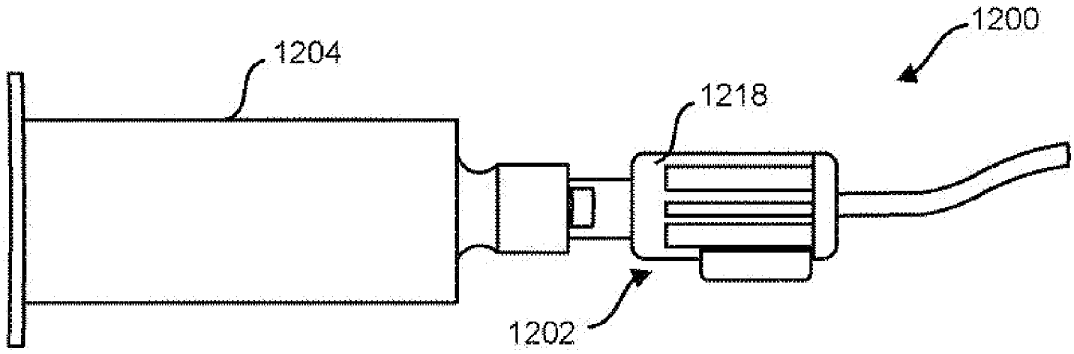


FIG. 12C

[Fig. 12D]

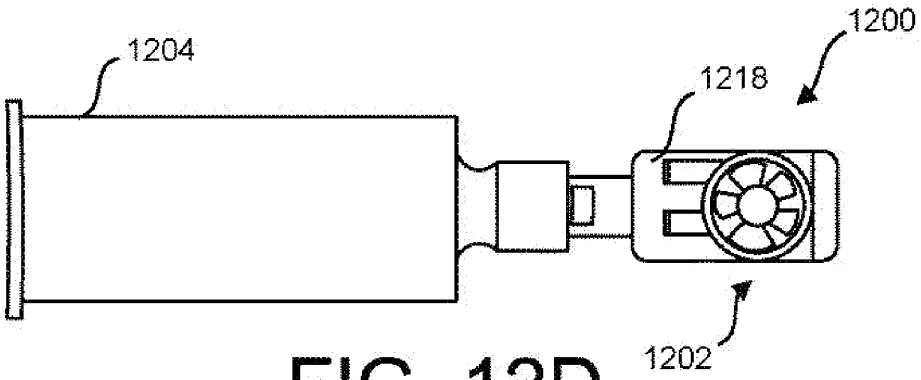


FIG. 12D

[Fig. 13A]

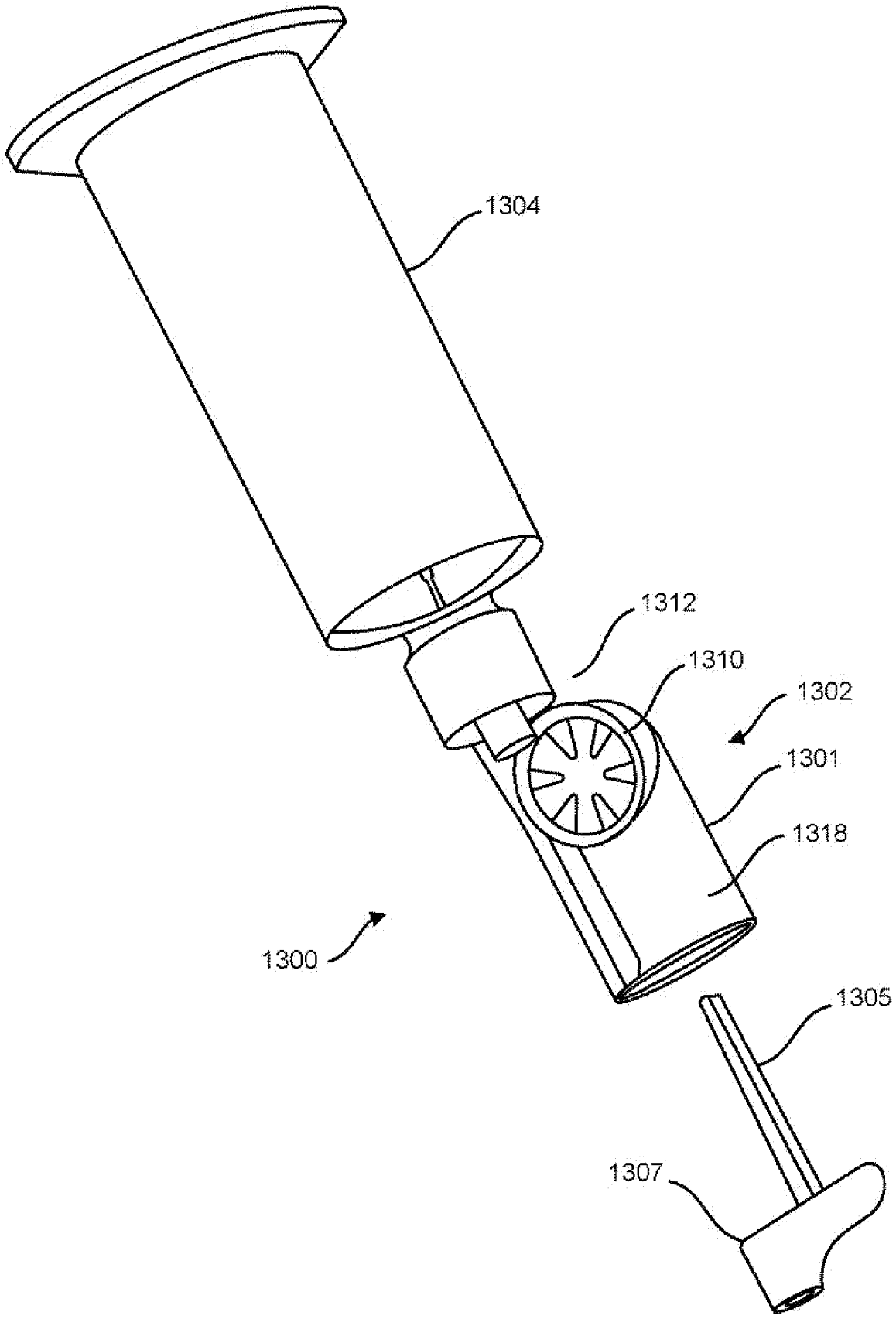


FIG. 13A

[Fig. 13B]

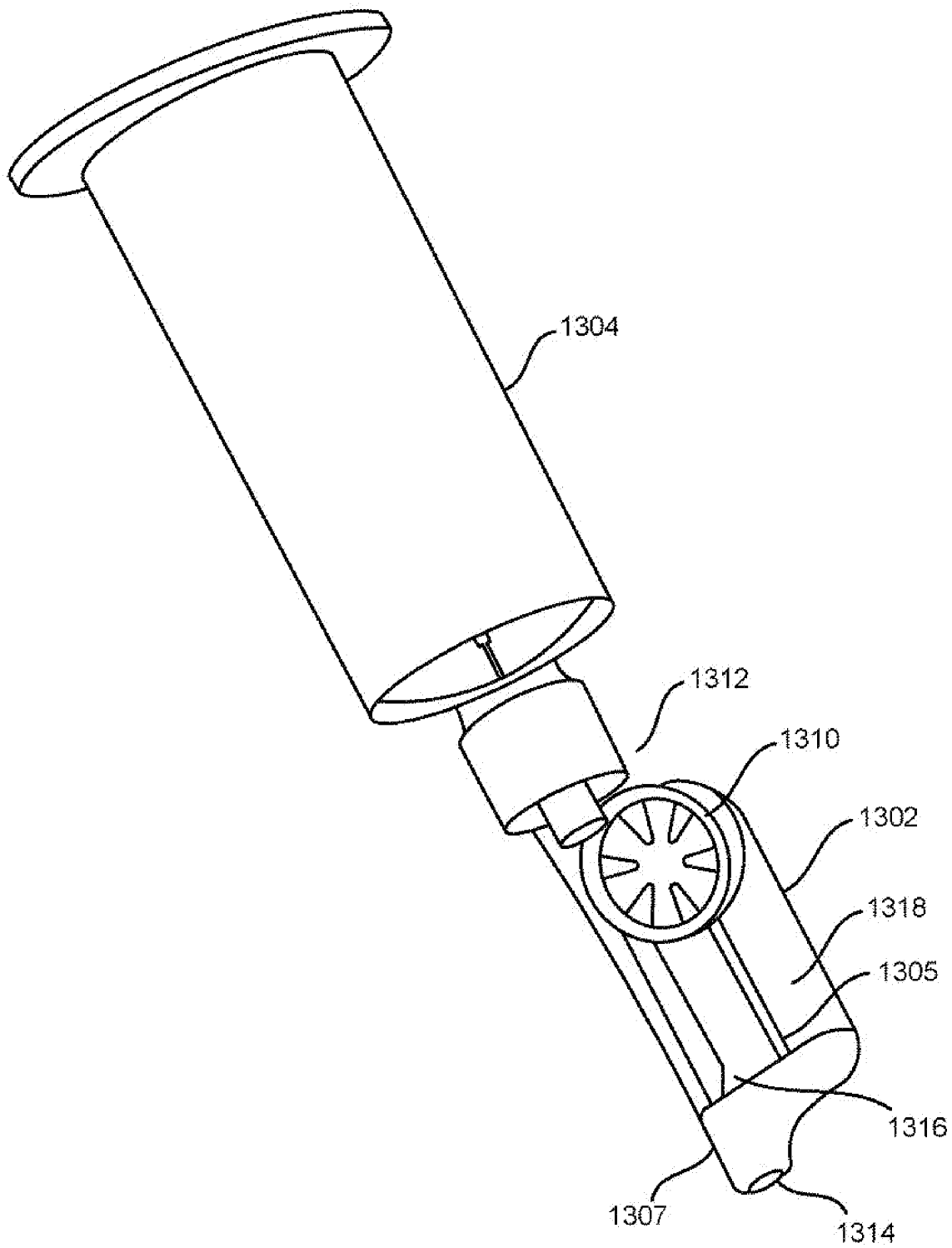


FIG. 13B

[Fig. 13C]

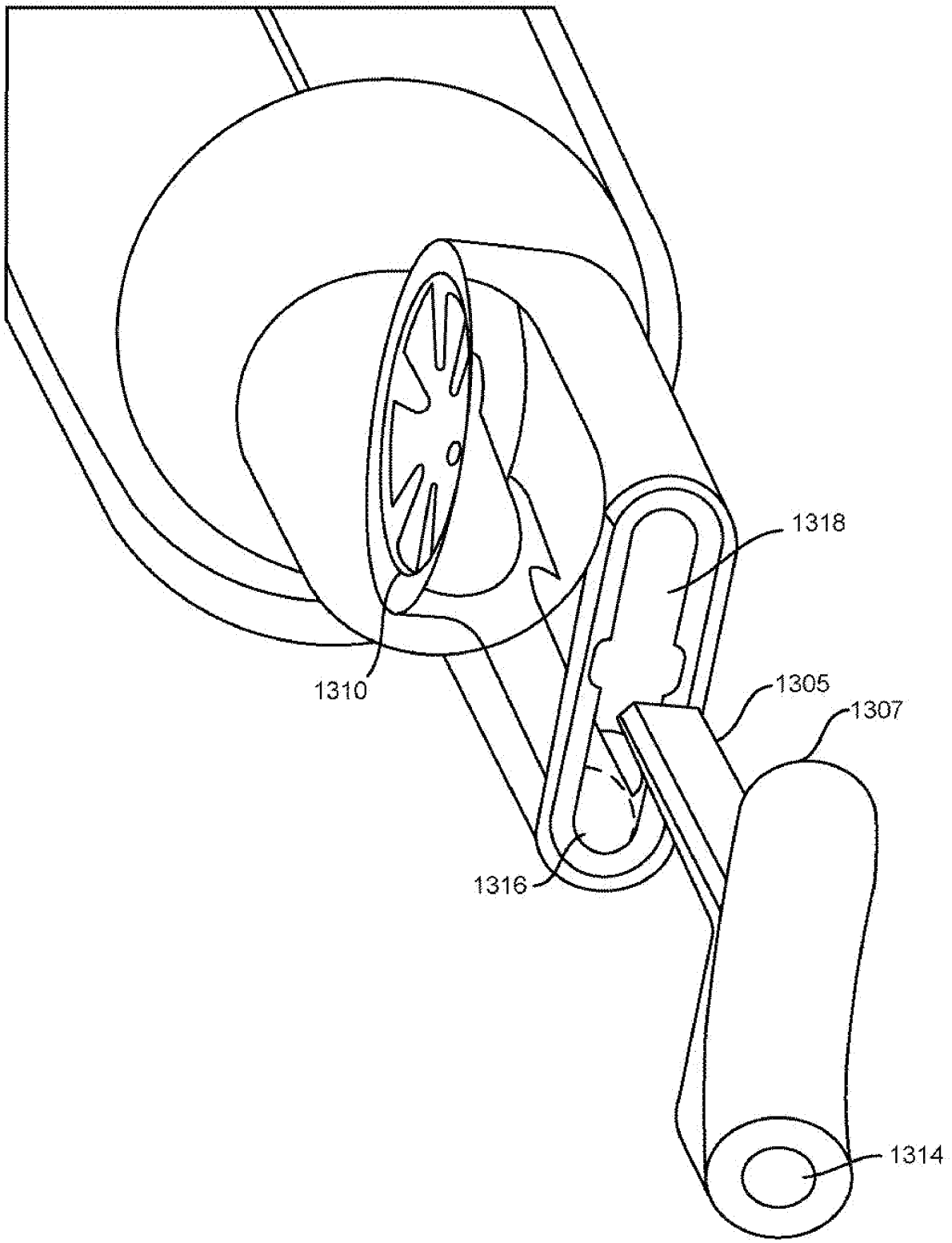
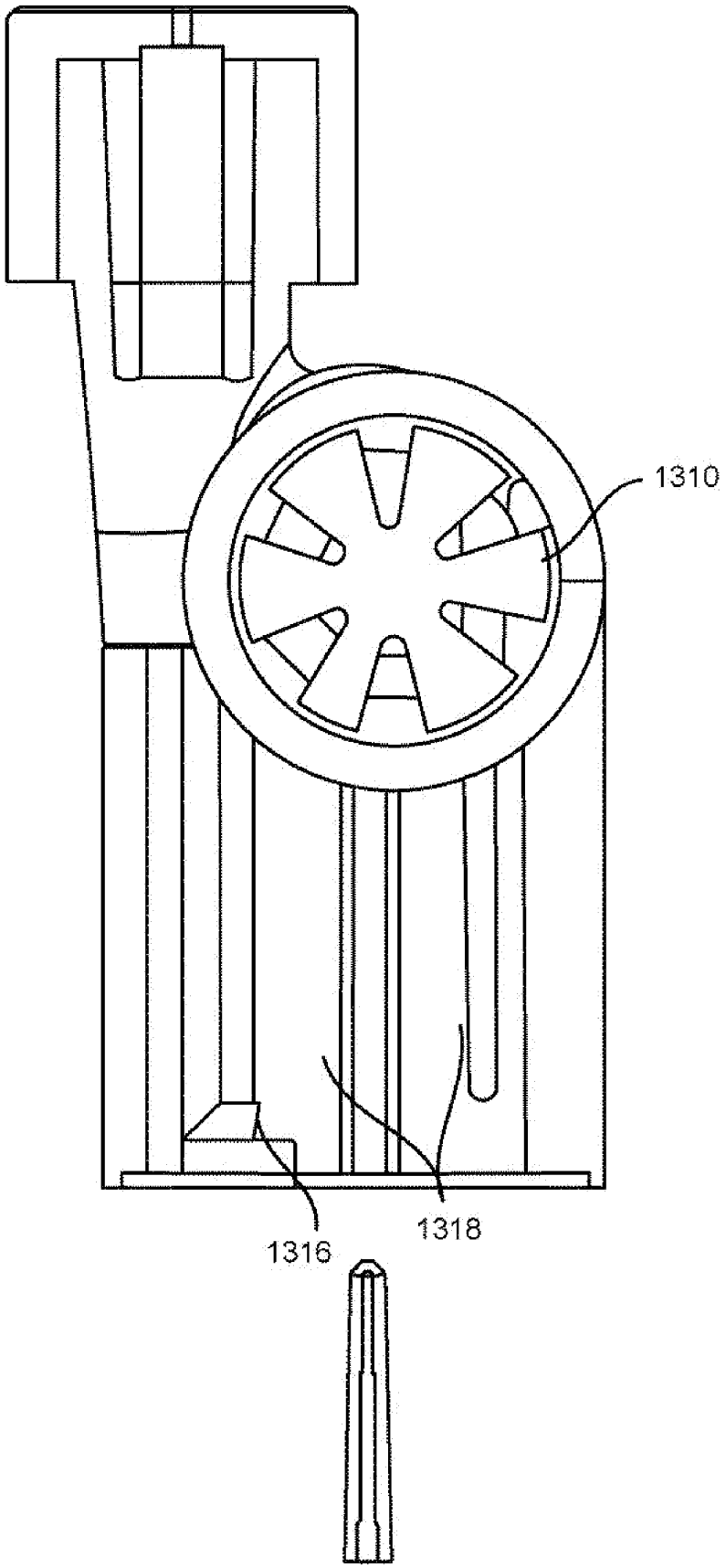


FIG. 13C

[Fig. 13D]


1310
1316
1318

[Fig. 14A]

FIG. 13D

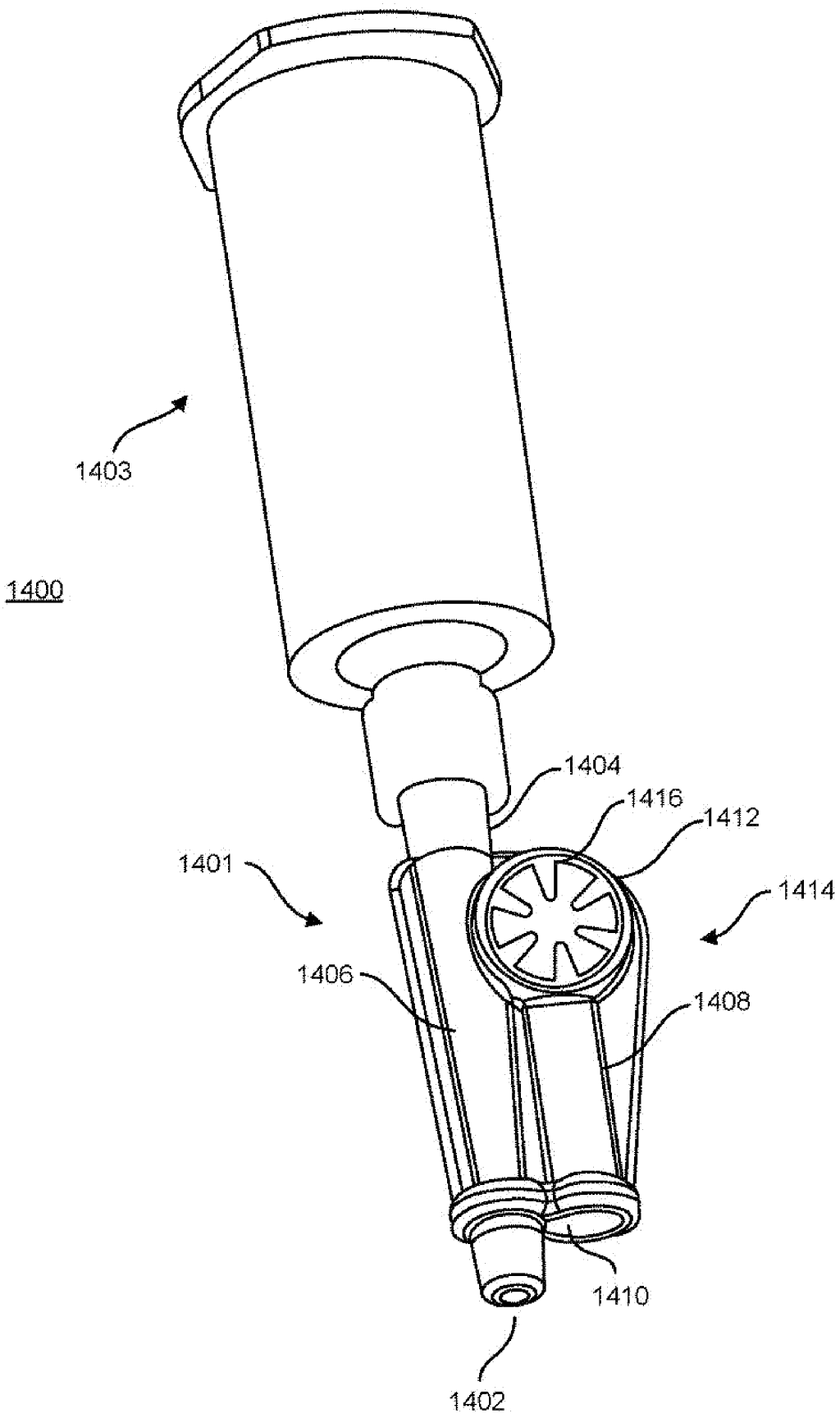
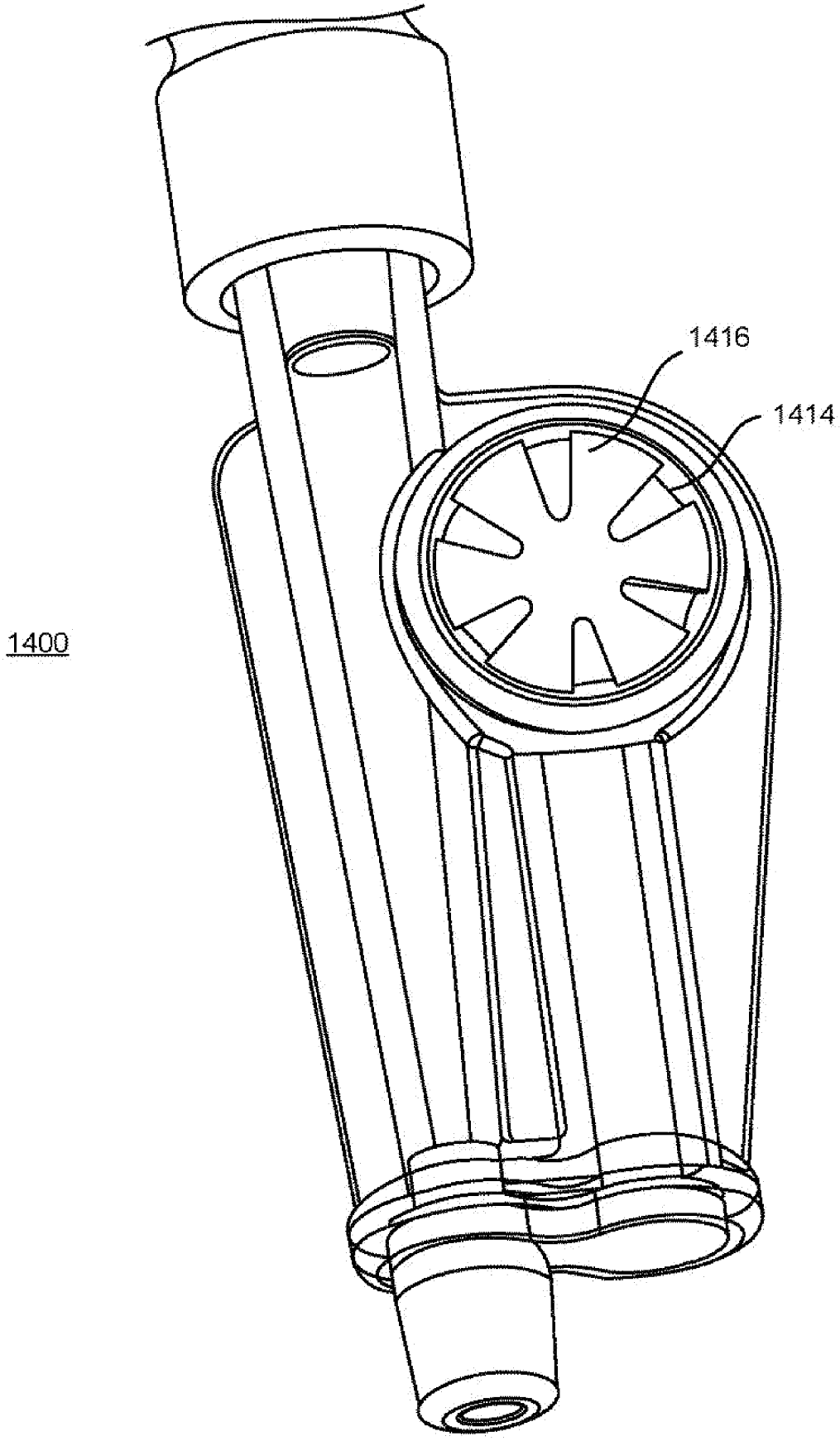


FIG. 14A

[Fig. 14B]


1416
1414
1400

[Fig. 14C]

FIG. 14B

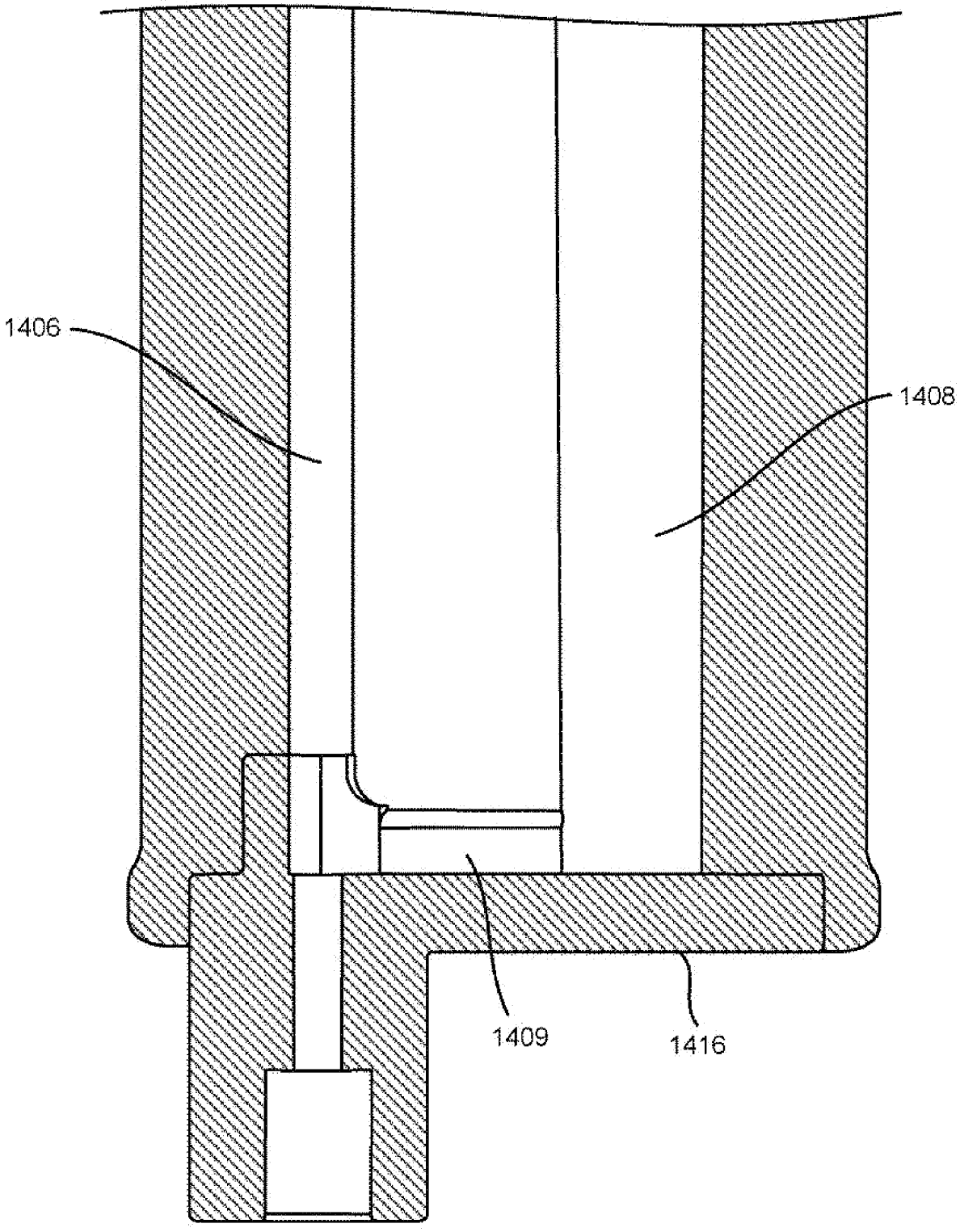
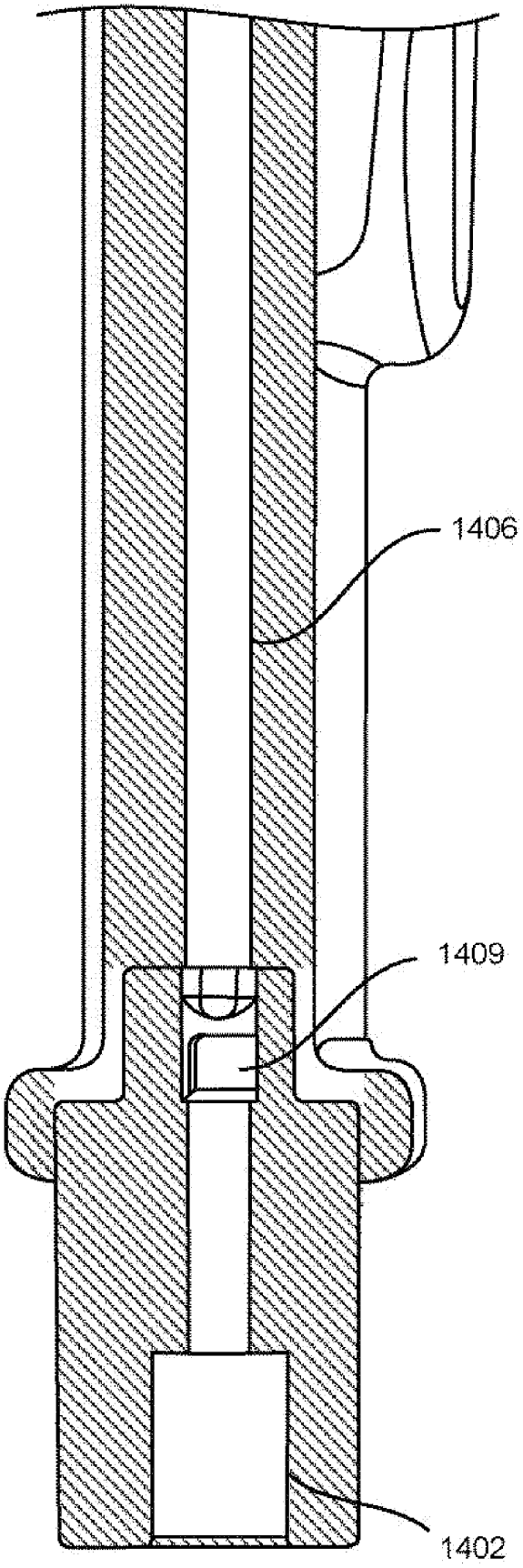


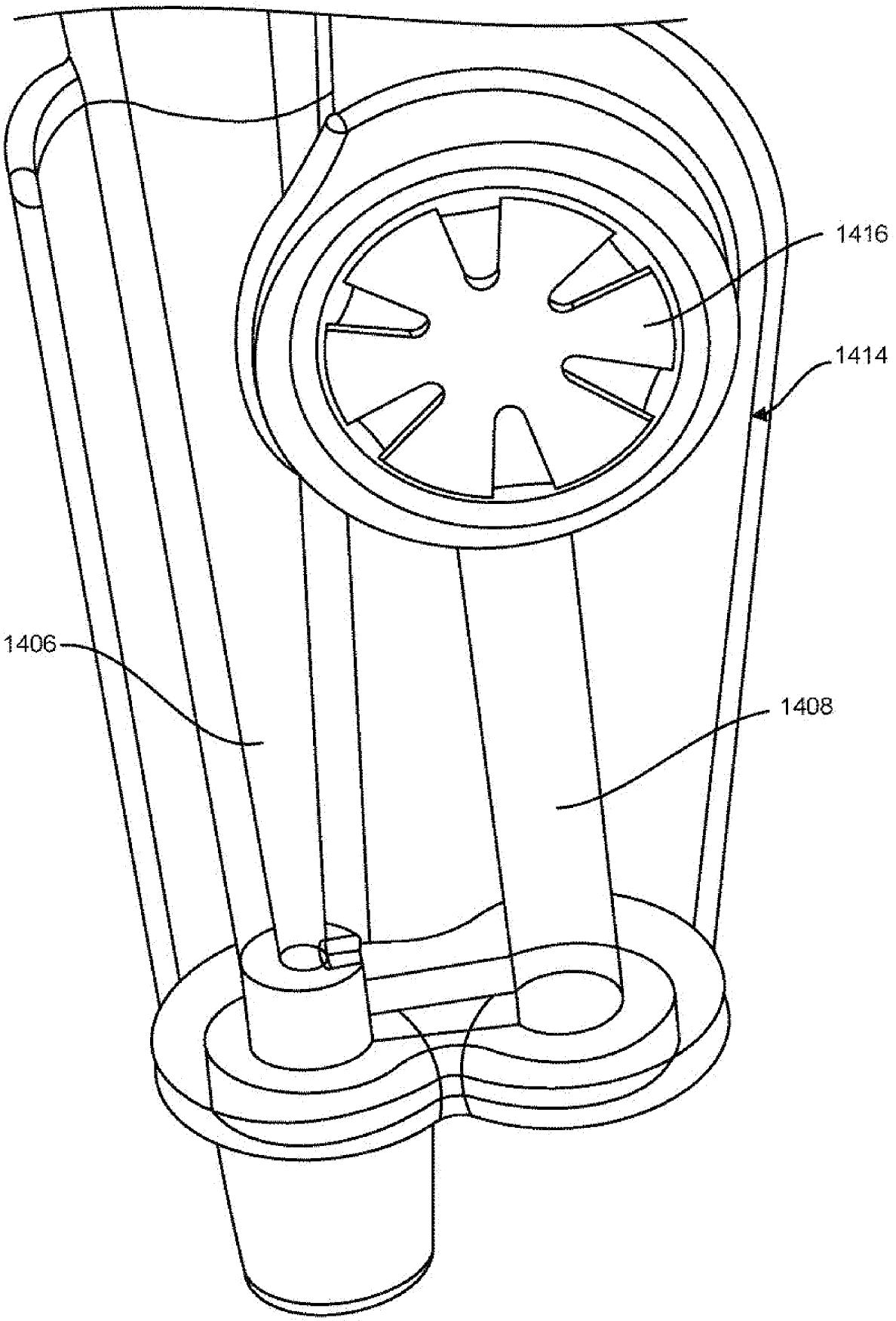
FIG. 14C

[Fig. 14D]


1406
1409
1402

[Fig. 14E]

FIG. 14D


1416
1414
1406
1408

[Fig. 15A]

FIG. 14E

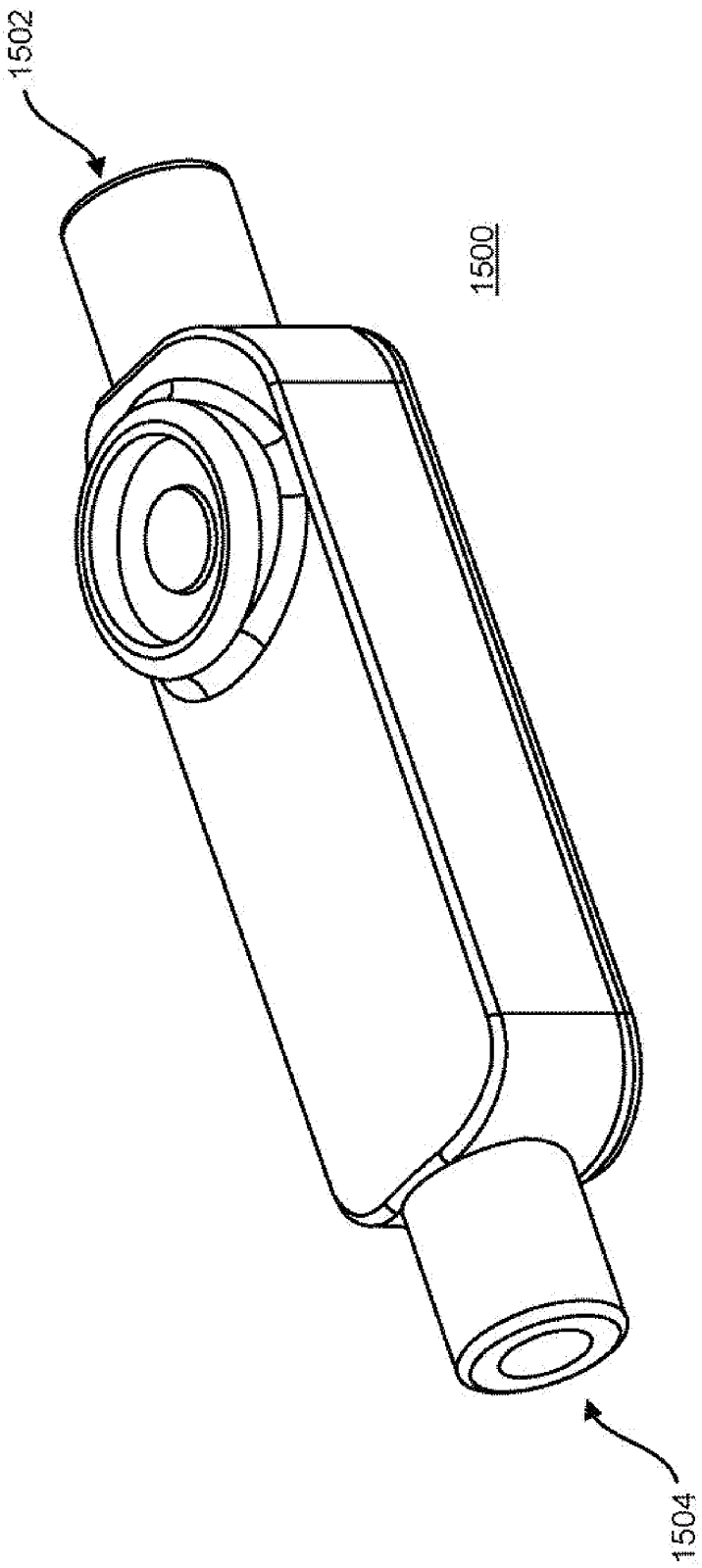


FIG. 15A