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Brancazio

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(54) **SYSTEMS AND INTERFACES FOR BLOOD SAMPLING**

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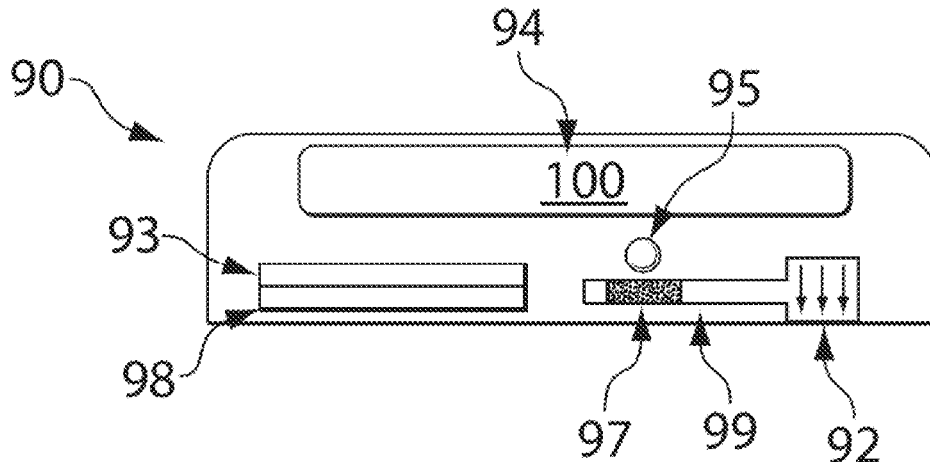
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(57) **ABSTRACT**

The present invention generally relates to systems and methods for delivering and/or receiving a substance or substances such as blood from subjects. In one aspect, the present invention is directed to devices and methods for receiving or extracting blood from a subject, e.g., from the skin and/or from beneath the skin, using devices containing a substance transfer component (for example, one or more needles or microneedles) and a reduced pressure or vacuum chamber having an internal pressure less than atmospheric pressure prior to receiving blood. In some embodiments, the device may contain a “snap dome” or other deformable structure, which may be used, at least in part, to urge or move needles or other suitable substance transfer components into the skin of a subject. In some cases, for example, the device may contain a flexible concave member and a needle mechanically coupled to the flexible concave member such that the needle may be urged or moved into the skin using the flexible concave member. Other aspects of the present invention are directed at other devices for receiving

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blood (or other bodily fluids, e.g., interstitial fluid), kits involving such devices, methods of making such devices, methods of using such devices, and the like.

24 Claims, 15 Drawing Sheets

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See application file for complete search history.

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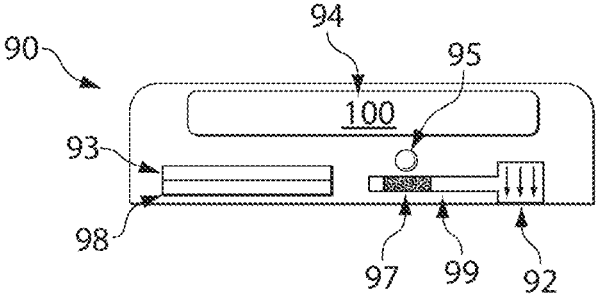


Fig. 1A

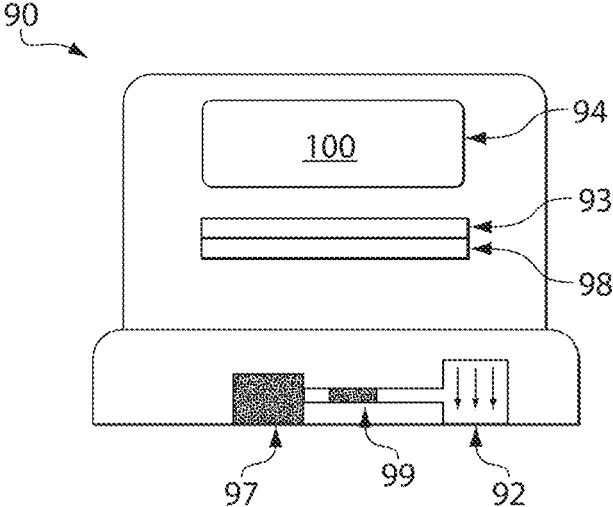


Fig. 1B

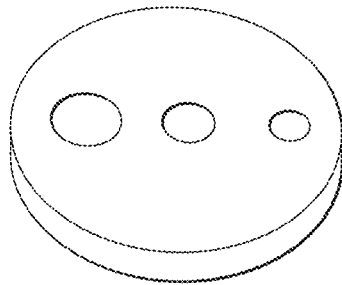


Fig. 2A

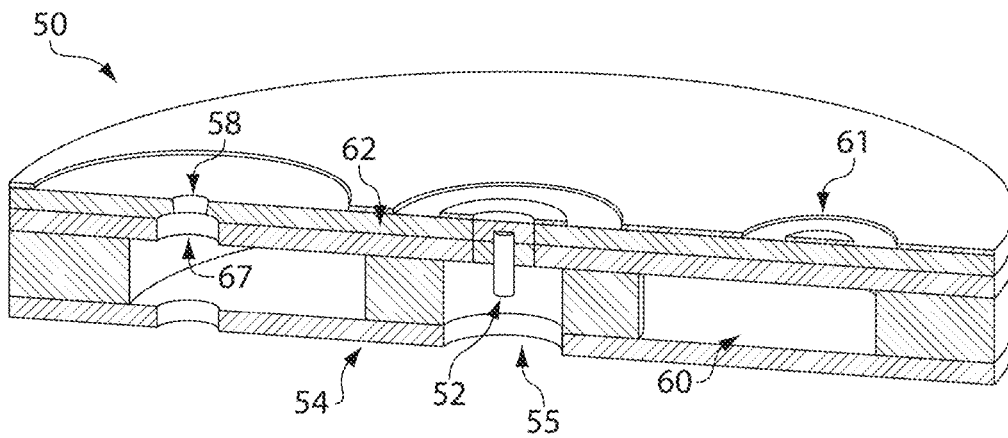


Fig. 2B

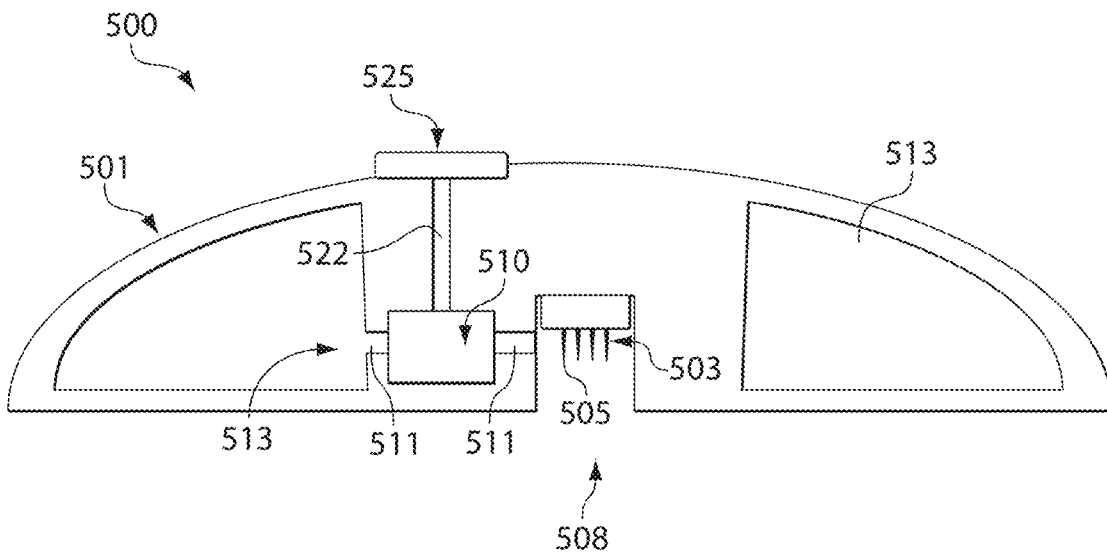


Fig. 2C

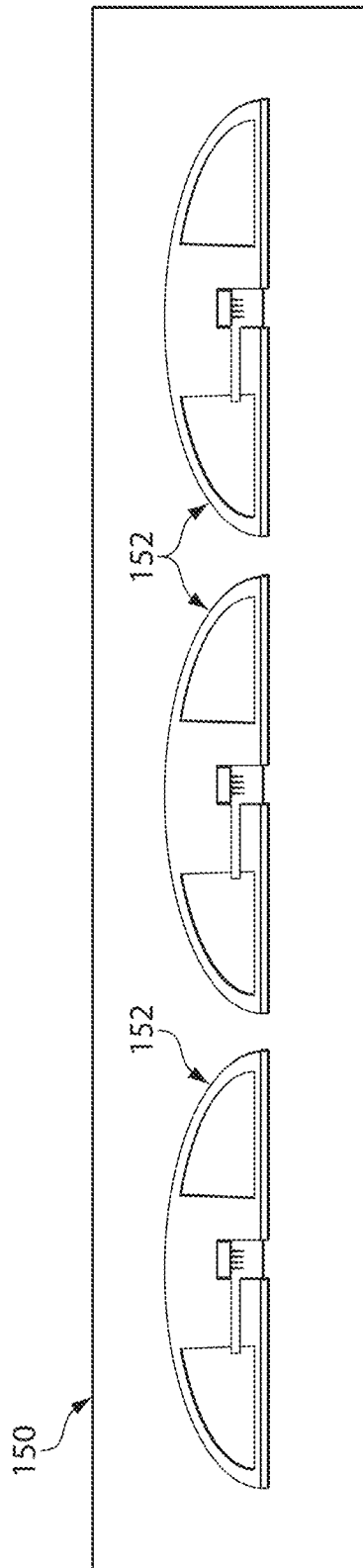


Fig. 2D

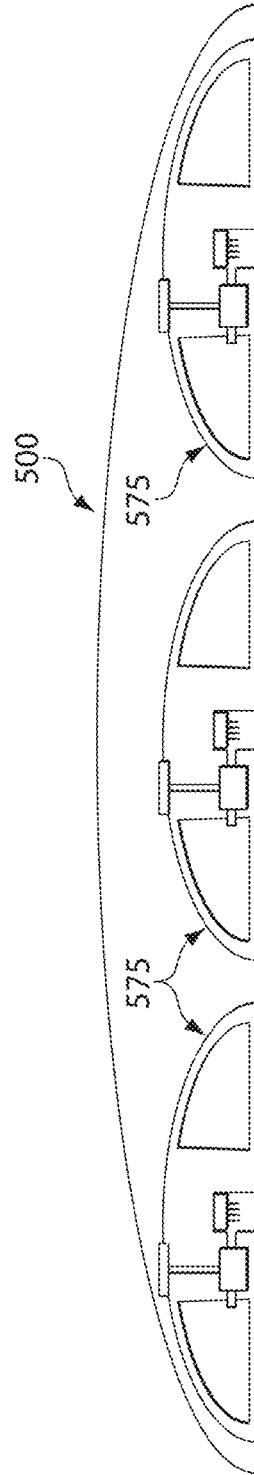


Fig. 2E

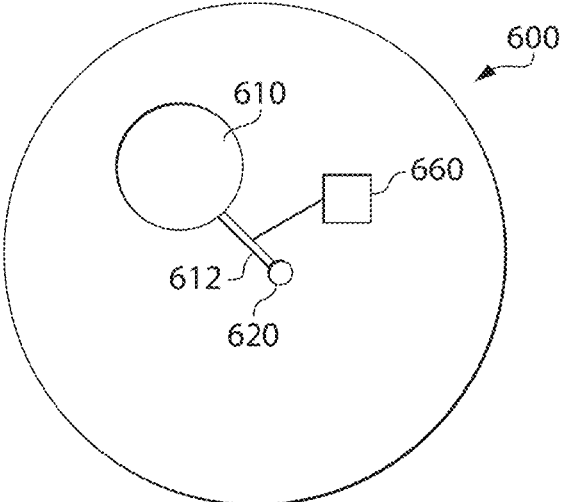


Fig. 3

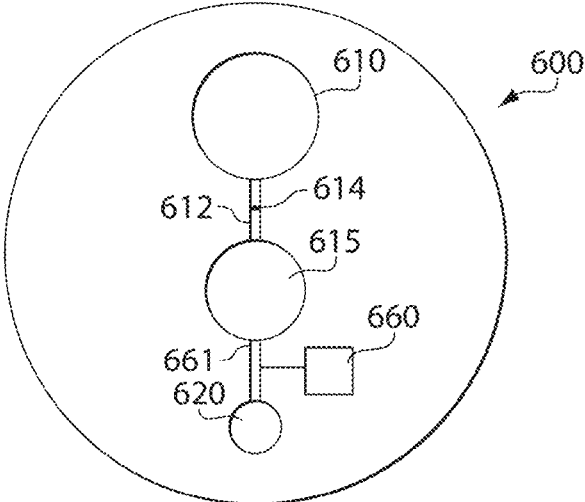


Fig. 4

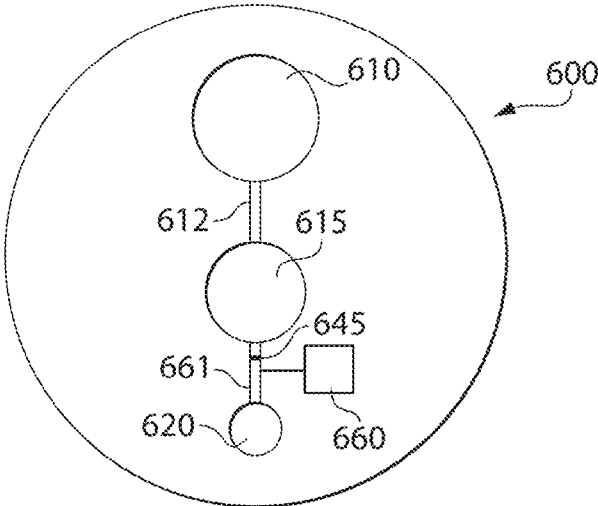


Fig. 5

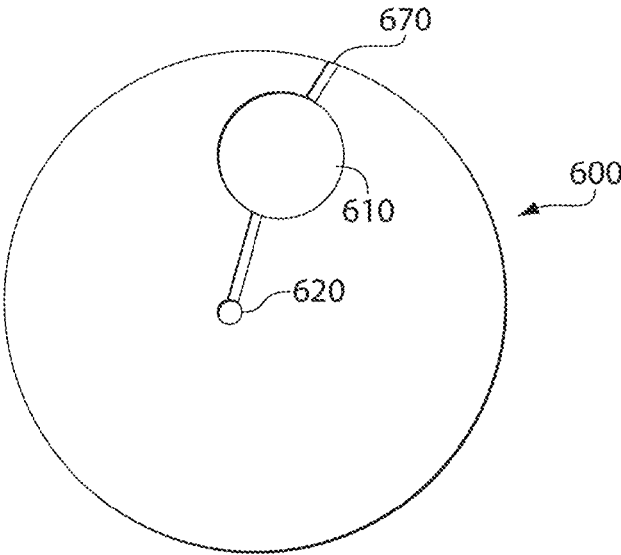


Fig. 7

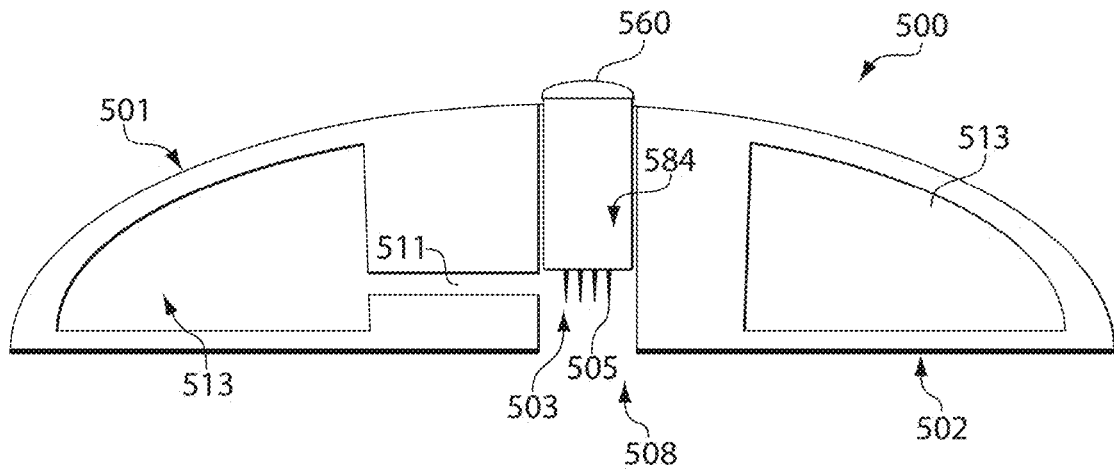


Fig. 6

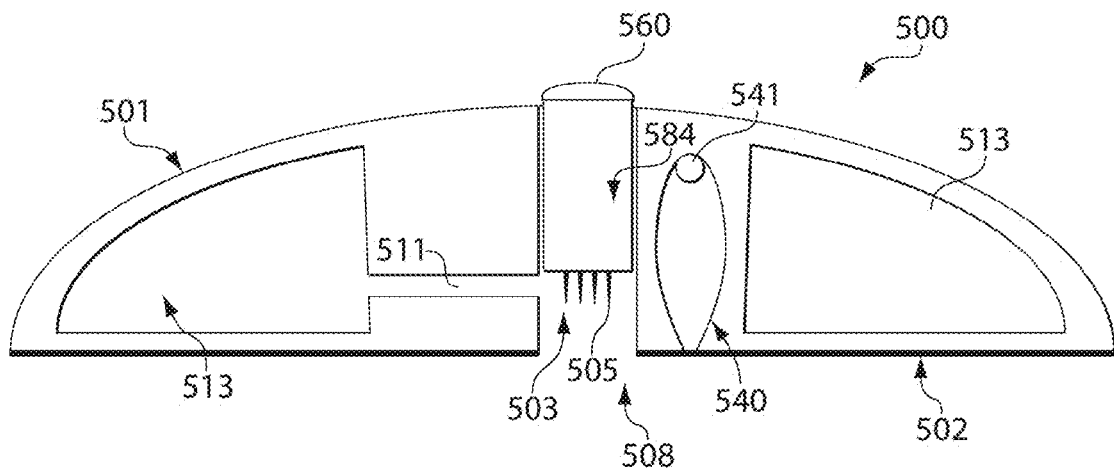


Fig. 8

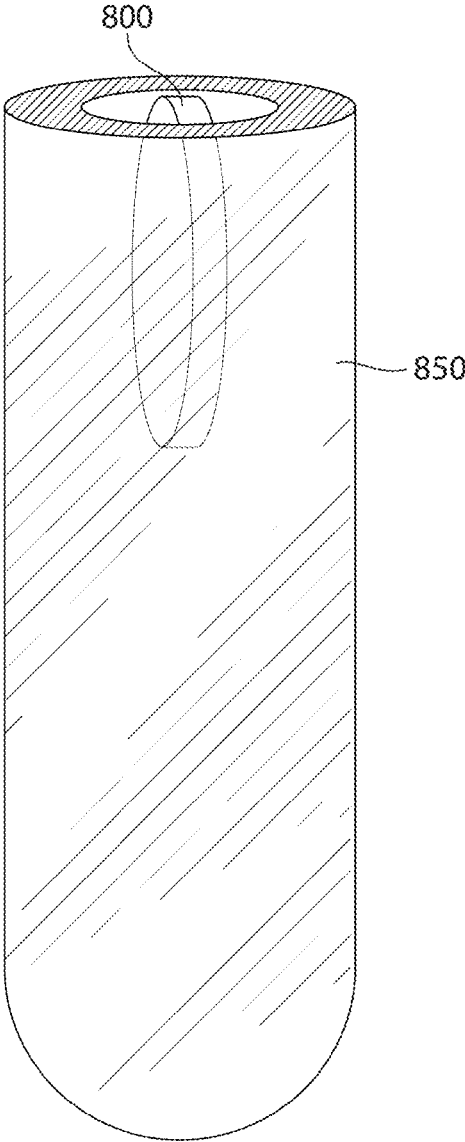


Fig. 9

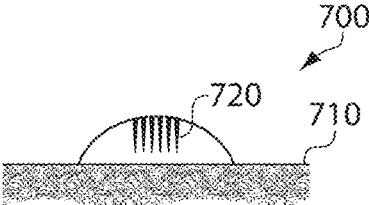


Fig. 10A

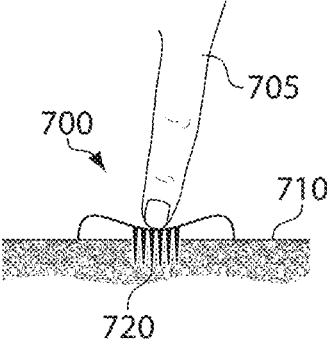


Fig. 10B

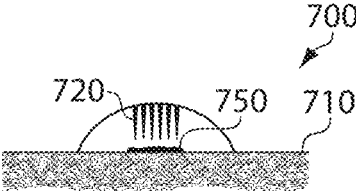


Fig. 10C

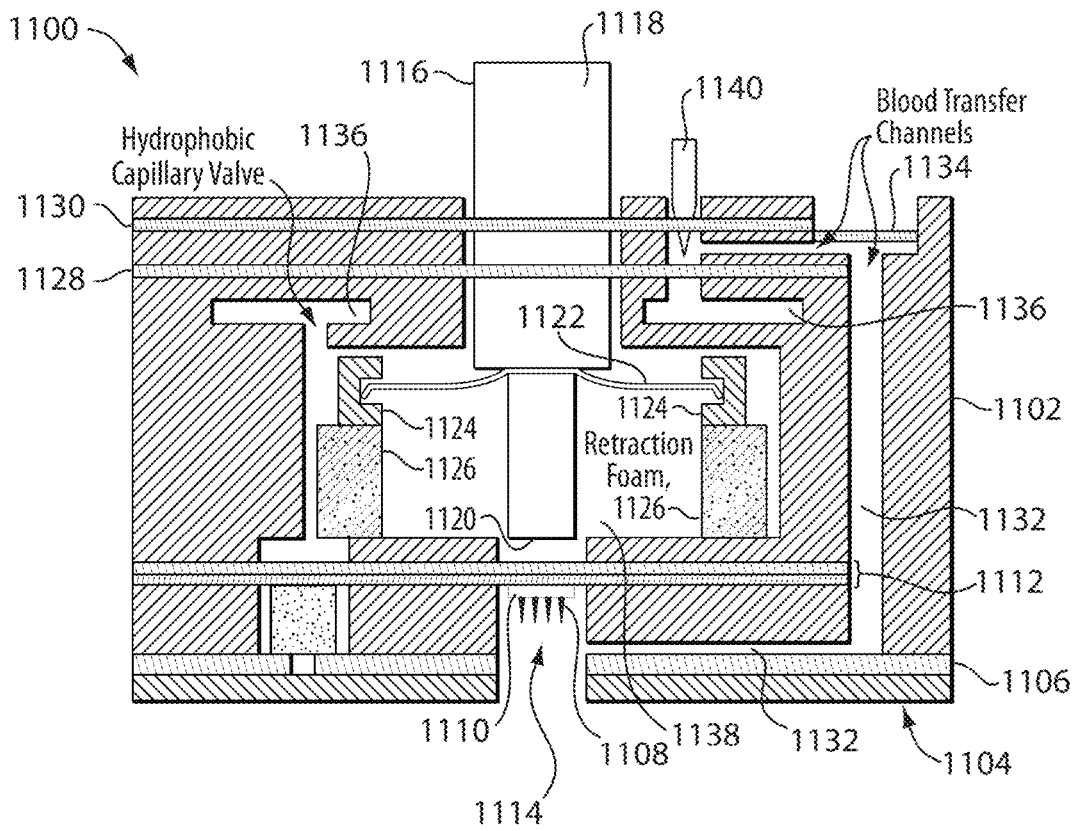


Fig. 11

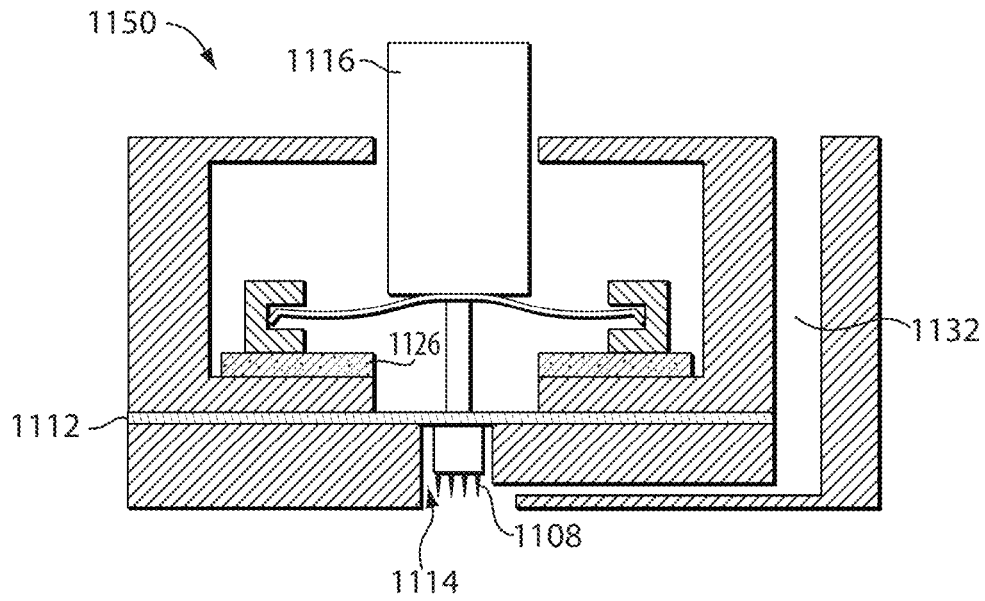


Fig. 12A

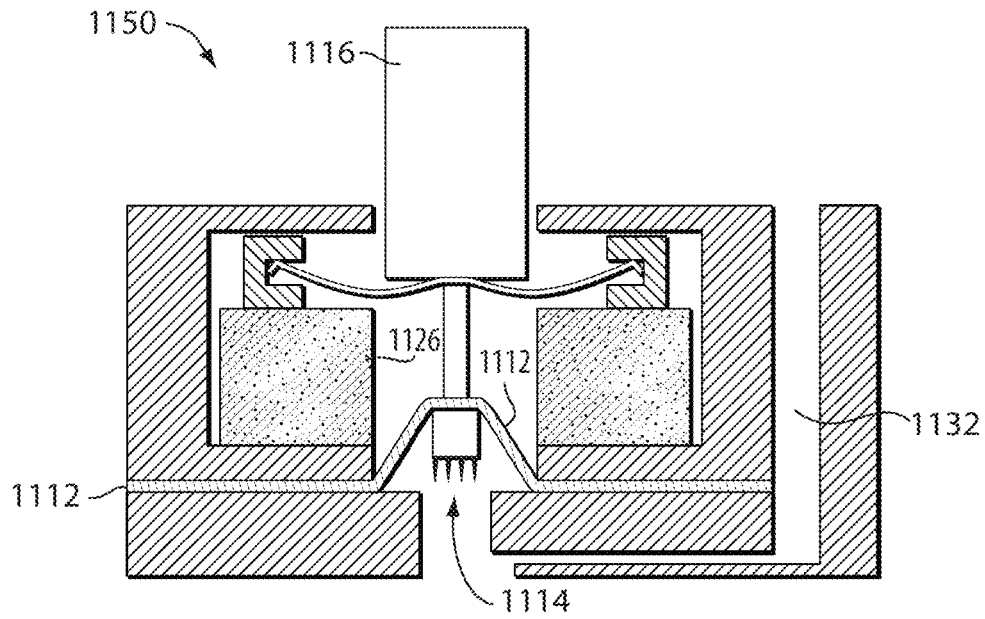


Fig. 12B

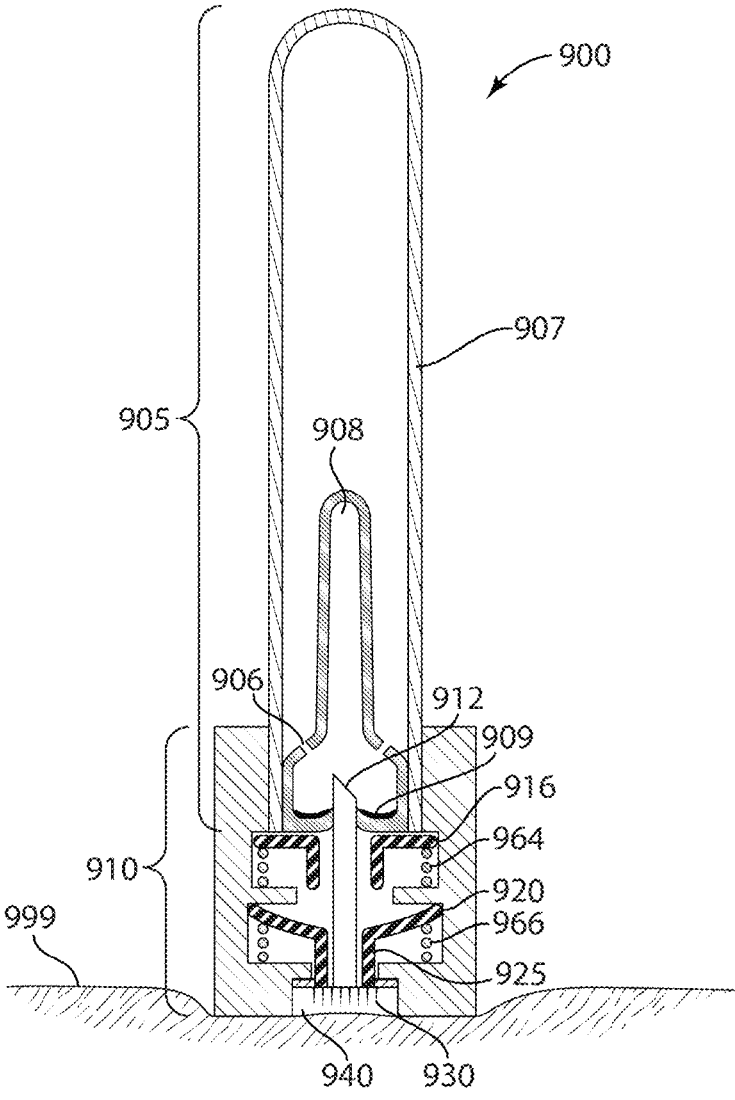


Fig. 13A

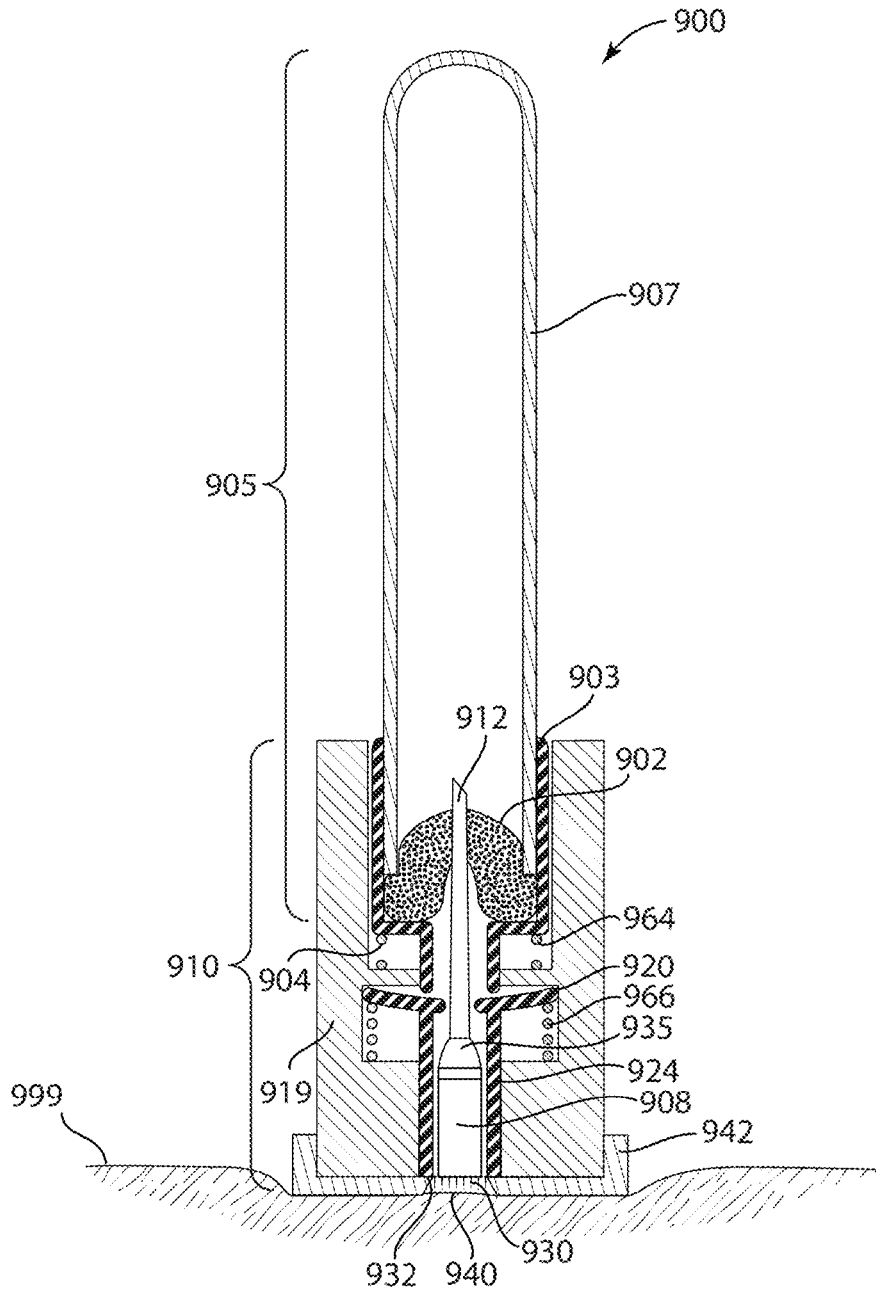


Fig. 13B

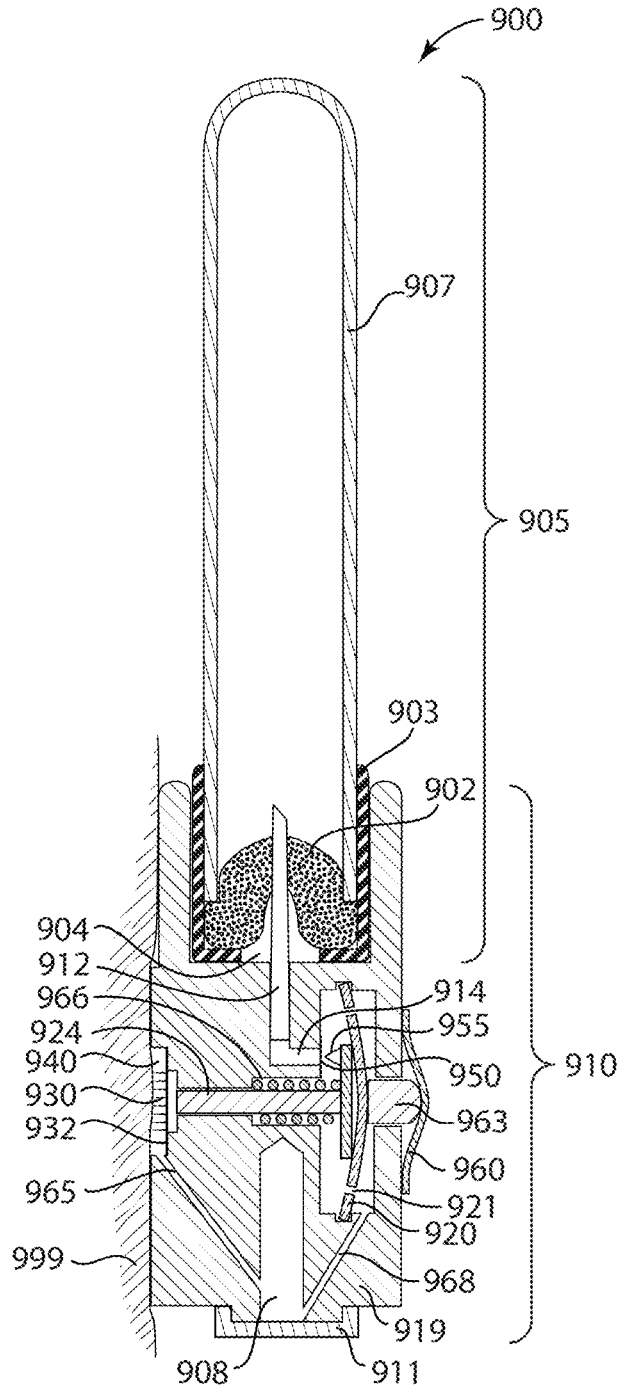


Fig. 13C

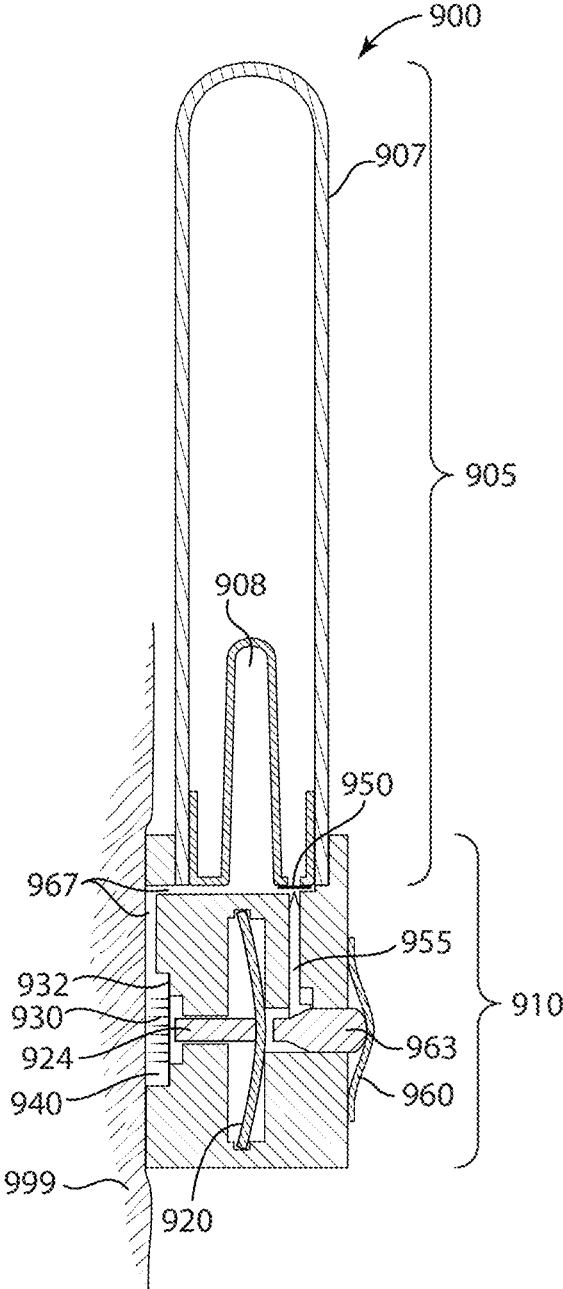


Fig. 13D

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SYSTEMS AND INTERFACES FOR BLOOD SAMPLING

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 17/396,549, filed Aug. 6, 2021, entitled "Systems and Interfaces for Blood Sampling," by David Brancazio, which is a continuation of U.S. patent application Ser. No. 15/297,253, filed Oct. 19, 2016, entitled "Systems and Interfaces for Blood Sampling," by David Brancazio, which is a continuation of U.S. patent application Ser. No. 14/327,987, filed Jul. 10, 2014, entitled "Systems and Interfaces for Blood Sampling," by David Brancazio, which is a continuation of U.S. patent application Ser. No. 13/292,254, filed Nov. 9, 2011, entitled "Systems and Interfaces for Blood Sampling," by David Brancazio, which claims the benefit of U.S. Provisional Patent Application Ser. No. 61/411,566, filed Nov. 9, 2010, entitled "Systems and Interfaces for Blood Sampling," by David Brancazio, each of which is incorporated herein by reference.

FIELD OF INVENTION

The present invention generally relates to systems and methods for delivering and/or receiving a substance or substances such as blood, from subjects, e.g., from the skin and/or from beneath the skin.

BACKGROUND

Phlebotomy or venipuncture is the process of obtaining intravenous access for the purpose of intravenous therapy or obtaining a sample of venous blood. This process is typically practiced by medical practitioners, including paramedics, phlebotomists, doctors, nurses, and the like. Substantial equipment is needed to obtain blood from a subject, including the use of evacuated (vacuum) tubes, e.g., such as the Vacutainer™ (Becton, Dickinson and company) and Vacuette™ (Greiner Bio-One GmbH) systems. Other equipment includes hypodermic needles, syringes, and the like. However, such procedures are complicated and require sophisticated training of practitioners, and often cannot be done in non-medical settings. Accordingly, improvements in methods of obtaining blood or other fluids from the skin are still needed.

SUMMARY OF THE INVENTION

The present invention generally relates to systems and methods for delivering and/or receiving a substance or substances such as blood, from subjects, e.g., from the skin and/or from beneath the skin. The subject matter of the present invention involves, in some cases, interrelated products, alternative solutions to a particular problem, and/or a plurality of different uses of one or more systems and/or articles.

In one aspect, the invention is generally directed to a device for receiving blood or other fluids from a subject. According to one set of embodiments, the device includes a flexible concave member moveable between a first configuration and a second configuration, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least

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when the needle is in the second position, and a vacuum chamber having a pressure less than atmospheric pressure. In some embodiments, movement of the flexible concave member from the first configuration to the second configuration creates a fluid communication pathway between the vacuum chamber and the applicator region.

The device, in another set of embodiments, includes a flexible concave member moveable between a first configuration and a second configuration, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least when the needle is in the second position, a piercing member mechanically coupled to the flexible concave member such that the piercing member is able to move when the flexible concave member moves from the first configuration to the second configuration, a vacuum chamber having a pressure less than atmospheric pressure, and a pierceable surface in fluidic communication with the vacuum chamber. In some embodiments, the piercing member is positioned to pierce the pierceable surface when the piercing member is moved by the flexible concave member.

In yet another set of embodiments, the device includes a flexible concave member moveable between a first configuration and a second configuration, an actuator able to move the flexible concave member between the first configuration and the second configuration when actuated, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least when the needle is in the second position, and a vacuum chamber having a pressure less than atmospheric pressure. In certain embodiments, the actuator, when actuated, is able to create a fluid communication pathway between the vacuum chamber and the applicator region.

The device, according to still another set of embodiments, includes a flexible concave member moveable between a first configuration and a second configuration, an actuator able to move the flexible concave member between the first configuration and the second configuration when actuated, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least when the needle is in the second position, a piercing member mechanically coupled to the actuator, a vacuum chamber having a pressure less than atmospheric pressure, and a pierceable surface in fluidic communication with the vacuum chamber. The piercing member, in some embodiments, is positioned to pierce the pierceable surface when moved by the actuator.

In accordance with yet another set of embodiments, the device includes a flexible concave member moveable between a first configuration and a second configuration, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least when the needle is in the second position, and a vacuum chamber. In some embodiments, movement of

the vacuum chamber creates a fluidic communication pathway between the vacuum chamber and the applicator region.

According to still another set of embodiments, the device includes a flexible concave member moveable between a first configuration and a second configuration, a needle mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in the first configuration and the needle is in a second position when the flexible concave member is in the second configuration, an applicator region containing the needle at least when the needle is in the second position, and a vacuum chamber. In certain embodiments, movement of the vacuum chamber causes movement of the flexible concave member from the first configuration to the second configuration.

In one aspect, the present invention is generally directed to a simple, one-piece, low-profile, high acceleration, high energy, actuation mechanism for inserting microneedles (or other objects) into the skin for the purpose of delivering or receiving bodily fluids, such as blood or interstitial fluid.

In one set of embodiments, a device of the invention is actuated by a deployment actuator which can provide advantage in ease of operation, speed of operation, reduction or elimination of pain, etc.

In another aspect, the present invention is generally directed to a device for receiving blood from the skin and/or from beneath the skin of a subject. According to one set of embodiments, the device includes a substance transfer component, a vacuum chamber having an internal pressure less than atmospheric pressure before blood is received into the device, and a storage chamber, separate from the vacuum chamber, for receiving blood from the subject via the substance transfer component when a negative pressure is applied to the skin of the subject. In another set of embodiments, the device includes at least 6 microneedles, and a storage chamber for receiving blood from the subject. In certain embodiments, the storage chamber has an internal pressure less than atmospheric pressure prior to receiving blood. The device, in yet another set of embodiments, includes a plurality of microneedles having a combined skin-penetration area of at least about 500 nm^2 , and a storage chamber for receiving blood from the subject through the plurality of microneedles. The area may also be larger, for example, at least about $2,500 \text{ micrometers}^2$. In some cases, the storage chamber has an internal pressure less than atmospheric pressure prior to receiving blood.

In one set of embodiments, the device includes a deployment actuator, a substance transfer component fastened to a deformable portion of the deformable structure, and a storage chamber for receiving blood from the subject via the substance transfer component. In certain instances, when the device is applied to the surface of the skin of a subject and the structure is deformed, the substance transfer component is driven into the skin of the subject. According to another set of embodiments, the device includes a deployment actuator, a substance transfer component fastened to the deployment actuator, and a storage chamber for receiving blood from the subject via the substance transfer component. In some cases, the deployment actuator can insert the substance transfer component into the skin at a speed of at least about 1 cm/s . Higher speeds may also be desirable in some embodiments, e.g., at least about 1 m/s .

In another set of embodiments, the device includes a substance transfer component, a first storage chamber for receiving blood from the subject via the substance transfer component, and a second storage chamber for receiving blood from the subject via the substance transfer component.

In various embodiments, the first storage chamber may comprise a first anticoagulant, and/or the second storage chamber may comprise a second anticoagulant.

The device, according to yet another set of embodiments, includes a substance transfer component, a first storage chamber for receiving blood from the subject via the substance transfer component, and a reaction entity contained within the first storage chamber able to react with an analyte contained within the blood. In some cases, a product of the reaction entity with the analyte is determinable, and in certain embodiments, the storage chamber has an internal pressure less than atmospheric pressure prior to receiving blood.

In one set of embodiments, the device includes a substance transfer component, a storage chamber for receiving blood from the subject via the substance transfer component, and a potassium sensor able to determine potassium ions within blood contained within the device. In some embodiments, the storage chamber has an internal pressure less than atmospheric pressure prior to receiving blood. In another set of embodiments, the device includes a substance transfer component, a storage chamber for receiving blood from the subject via the substance transfer component, and a flow controller able to control blood flow into the storage chamber. In certain cases, the storage chamber has an internal pressure less than atmospheric pressure prior to receiving blood.

According to yet another set of embodiments, the device includes a substance transfer component, and a storage chamber for receiving fluid from the subject via the substance transfer component. In some cases, the device carries a color indicative of a recommended bodily use site for the device. The device, in still another set of embodiments, includes a substance transfer component for receiving fluid from the subject, a storage chamber for receiving fluid from the subject via the substance transfer component, and an exit port for removing the fluid from the device, separate from the substance transfer component. According to yet another set of embodiments, the device includes a substance transfer component for receiving fluid from the subject, and a storage chamber for receiving fluid from the subject via the substance transfer component. In some embodiments, the device is constructed and arranged to reproducibly obtain from the subject, and deliver to an analysis device, a fluid sample of less than about 1 ml . In another set of embodiments, the device includes a fluid sample device comprising a substance transfer component for receiving fluid from the subject, and a storage chamber for receiving fluid from the subject via the substance transfer component.

Another aspect of the invention involves a device able to receive a substance or deliver a substance from or to a subject including a triggering mechanism able to move a substance transfer component, relative to the skin of a subject, in a short period of time, and/or at a relatively high velocity, and/or at a relatively high force, and/or at a relatively high pressure.

In yet another embodiment a device is provided in which a plurality of skin insertion objects that are relatively small, are inserted to a relatively complete depth into and/or through the skin in routine device operation.

According to another aspect, the invention is directed to an adaptor having a maximum length of no more than about 100 mm and a diameter of no more than about 16 mm . In some embodiments, the adaptor is able to immobilize a device having a largest lateral dimension of no more than about 50 mm , and/or a largest vertical dimension, extending

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from the skin of the subject when the device is applied to the subject, of no more than about 10 mm.

In yet another aspect, the invention is directed to a kit. In one set of embodiments, the kit includes a fluid sample device comprising a substance transfer component for receiving fluid from the subject and a storage chamber for receiving fluid from the subject via the substance transfer component, and an external analytical apparatus having a port for mating with a port on the fluid sample device.

In another aspect, the present invention is directed to a method of making one or more of the embodiments described herein, for example, devices for receiving blood from a subject. In another aspect, the present invention is directed to a method of using one or more of the embodiments described herein, for example, devices for receiving blood from a subject.

Other advantages and novel features of the present invention will become apparent from the following detailed description of various non-limiting embodiments of the invention when considered in conjunction with the accompanying figures. In cases where the present specification and a document incorporated by reference include conflicting and/or inconsistent disclosure, the present specification shall control. If two or more documents incorporated by reference include conflicting and/or inconsistent disclosure with respect to each other, then the document having the later effective date shall control.

BRIEF DESCRIPTION OF THE DRAWINGS

Non-limiting embodiments of the present invention will be described by way of example with reference to the accompanying figures, which are schematic and are not intended to be drawn to scale. In the figures, each identical or nearly identical component illustrated is typically represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. In the figures:

FIGS. 1A-1B illustrate devices according to certain embodiments of the invention;

FIGS. 2A-2C illustrate devices according to various embodiments of the invention;

FIG. 2D illustrates a kit containing more than one device, in yet another embodiment of the invention;

FIG. 2E illustrates a device according to still another embodiment of the invention;

FIG. 3 illustrates a device in one embodiment of the invention, having a vacuum chamber;

FIG. 4 illustrates a device in another embodiment of the invention, having a vacuum chamber and a storage chamber;

FIG. 5 illustrates a device in yet another embodiment of the invention, having a flow controller;

FIG. 6 illustrates a device according to another embodiment of the invention;

FIG. 7 illustrates a device in yet another embodiment of the invention, having an exit port;

FIG. 8 illustrates a device containing a fluid reservoir, in another embodiment of the invention;

FIG. 9 illustrates an adaptor according to one embodiment of the invention;

FIGS. 10A-10C illustrate a device in still another embodiment illustrating a deployment actuator;

FIG. 11 illustrates yet another embodiment of the invention in which a device is actuated by a deployment actuator;

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FIGS. 12A and 12B illustrate yet another embodiment of the invention, in which a device is actuated by a deployment actuator, at different stages of operation of the device; and

FIGS. 13A-13E illustrate several devices in accordance with various embodiments of the inventions.

DETAILED DESCRIPTION

The present invention generally relates to systems and methods for delivering and/or receiving a substance or substances such as blood from subjects. In one aspect, the present invention is directed to devices and methods for receiving or extracting blood from a subject, e.g., from the skin and/or from beneath the skin, using devices containing a substance transfer component (for example, one or more needles or microneedles) and a reduced pressure or vacuum chamber having an internal pressure less than atmospheric pressure prior to receiving blood. In some embodiments, the device may contain a "snap dome" or other deformable structure, which may be used, at least in part, to urge or move needles or other suitable substance transfer component into the skin of a subject. In some cases, for example, the device may contain a snap dome or other flexible concave member and a needle mechanically coupled to the flexible concave member such that the needle may be urged or moved into the skin using the flexible concave member. Other aspects of the present invention are directed at other devices for receiving blood (or other bodily fluids, e.g., interstitial fluid), kits involving such devices, methods of making such devices, methods of using such devices, and the like.

The received fluid may be any suitable bodily fluid, such as interstitial fluid, other skin-associated material, mucosal material or fluid, whole blood, perspiration, saliva, plasma, tears, lymph, urine, plasma, or any other bodily fluid, or combinations thereof. Substances received from a subject can include solid or semi-solid material such as skin, cells, or any other substance from the subject. Substances that can be delivered to a subject in accordance with some embodiments of the invention include diagnostic substances, therapeutic substances such as drugs, and the like. Various embodiments of the invention are described below in the context of delivering or receiving a fluid, such as blood, from or through the skin. It is to be understood that in all embodiments herein, regardless of the specific exemplary language used (e.g., receiving blood), the devices and methods of other embodiments of the invention can be used for receiving any substance from the skin and/or from beneath the skin of the subject, and/or for delivering any substance to the subject, e.g. to the skin and/or a location beneath the skin of the subject.

In one aspect, the present invention is generally directed to devices and methods for receiving or extracting blood or other bodily fluids from a subject, e.g., from the skin and/or from beneath the skin, using devices containing a substance transfer component (for example, one or more microneedles). The device may also contain, in some embodiments, a storage chamber having an internal pressure less than atmospheric pressure prior to receiving blood or other bodily fluids. In some cases, the device may pierce the skin of the subject, and fluid can then be delivered and/or received from the subject. The subject is usually human, although non-human subjects may be used in certain instances, for instance, other mammals such as a dog, a cat, a horse, a rabbit, a cow, a pig, a sheep, a goat, a rat (e.g., *Rattus norvegicus*), a mouse (e.g., *Mus musculus*), a guinea

pig, a hamster, a primate (e.g., a monkey, a chimpanzee, a baboon, an ape, a gorilla, etc.), or the like.

In some cases, the device can be applied to the skin, and activated to receive fluid from the subject. The device, or a portion thereof, may then be processed to determine the fluid and/or an analyte within the fluid, alone or with an external apparatus. For example, fluid may be received from the device, and/or the device may contain sensors or agents able to determine the fluid and/or an analyte suspected of being contained in the fluid.

The invention, in one set of embodiments, involves the determination of a condition of a subject. Bodily fluids and/or other material associated with the skin may be analyzed, for instance, as an indication of a past, present and/or future condition of the subject, or to determine conditions that are external to the subject. Determination may occur, for instance, visually, tactilely, by odor, via instrumentation, etc. In one aspect, accordingly, the present invention is generally directed to various devices for delivering and/or receiving blood, or other bodily fluids, from the skin and/or from beneath the skin of a subject. Accordingly, in the description that follows, the discussion of blood is by way of example only, and in other embodiments, other fluids may be received from the skin in addition to and/or instead of blood.

In one set of embodiments, the device includes a substance transfer component able to deliver or receive fluid from the subject into the device. As used herein, "substance transfer component" is any component or combination of components that facilitates movement of a fluid from one portion of the device to another, and/or from the device to the subject or vice versa. The substance transfer component may include an opening of any size and/or geometry that is constructed to receive fluid into the device. For example, an opening of a substance transfer component may lie in a two-dimensional plane or the opening may include a three-dimensional cavity, hole, groove, slit, etc. In some embodiments, the substance transfer component may also include one or more microneedles or other skin insertion objects, arranged to cause fluid to be released from the subject, e.g., by piercing the skin of a subject.

For example, at or near the skin, a substance transfer component can include a hollow needle or a solid needle. If a solid needle is used, then if fluid migrates along the needle due to surface forces (e.g., capillary action), then the solid needle can be part of a substance transfer component. If fluid (e.g. blood or interstitial fluid) partially or fully fills an enclosure surrounding a needle after puncture of skin (whether the needle is or is not withdrawn from the skin after puncture), then the enclosure can define at least part of a substance transfer component. A substance transfer component may include any other suitable fluid transporter or flow activator. Other components including partially or fully enclosed channels, microfluidic channels, tubes, wicking members, vacuum containers, etc. can be, or be a part of, substance transfer components.

The fluid may be received from and/or through the skin of a subject (or other mucosal surface). The substance transfer component may include, for example, one or more needles and/or microneedles, a hygroscopic agent, a cutter or other piercing element, an electrically-assisted system, or the like, as discussed in detail herein. If needles or microneedles are used, they may be solid or hollow, i.e., blood or other fluid may travel in and/or around the needles or microneedles into the device. In some cases, the needles or microneedles may also be removed from the subject, e.g., after insertion into the skin, for example, to increase the flow of blood or other

fluids from the subject. In one set of embodiments, the substance transfer component includes solid needles that are removed from the skin and a cup or channel to direct the flow of blood or other bodily fluids.

In some aspects, the device may include a support structure, such as a housing. The housing may be used, as discussed herein, for applying the substance transfer component to the surface of the skin of the subject, e.g., so that fluid may be delivered and/or received from the skin of the subject. In some cases, the housing may immobilize the substance transfer component such that the substance transfer component cannot move relative to the housing; in other cases, however, the substance transfer component, or a portion thereof, may be able to move relative to the housing. In one embodiment, as a non-limiting example, the substance transfer component is immobilized relative to the housing, and the deployment actuator is positioned within the device such that application of the device to the skin causes at least a portion of the substance transfer component to pierce the skin of the subject. In some cases, as previously discussed, the housing encloses a deployment actuator.

In some embodiments, the deployment actuator, or a portion of the deployment actuator, may move from a first position to a second position. For example, the first position may be one where the deployment actuator has attached thereto a substance transfer component that does not contact the skin (e.g., a skin insertion object of the substance transfer component may be contained within a recess of the substance transfer component), while the second position of the deployment actuator may be one where the substance transfer component does contact the skin, and in some cases, the substance transfer component may pierce the skin. The deployment actuator may be moved using any suitable technique, e.g., manually, mechanically, electromagnetically, using a servo mechanism, or the like. In one set of embodiments, for example, the deployment actuator may be moved from a first position to a second position by pushing a button on the device, which causes the deployment actuator to move (either directly, or through a mechanism linking the button with the deployment actuator). Other mechanisms (e.g., dials, levers, sliders, etc., as discussed herein) may be used in conjunction of or instead of a button. In another set of embodiments, the deployment actuator may be moved from a first position to a second position automatically, for example, upon activation by a computer, upon remote activation, after a period of time has elapsed, or the like. For example, in one embodiment, a servo connected to the deployment actuator is activated electronically, moving the deployment actuator from the first position to the second position. In some cases, the deployment actuator may include a triggering mechanism that initiates deployment.

In some cases, the deployment actuator and/or the substance transfer component may also be moved from the second position to the first position. For example, after fluid has been delivered and/or received from the skin, e.g., using a substance transfer component the deployment actuator may be moved, which may move the substance transfer component away from contact with the skin. The deployment actuator may be moved from the second position to the first position using any suitable technique, including those described above, and the technique for moving the deployment actuator from the second position to the first position may be the same or different as that moving the deployment actuator from the first position to the second position.

In some cases, the device may be able to draw skin towards the substance transfer component. For example, in one set of embodiments, the device may include a vacuum

interface or region. The interface or region may be connected with a vacuum source (external and/or internal to the device), and when a vacuum is applied, skin may be drawn towards the device, e.g., for contact with a substance transfer component, such as one or more needles or microneedles.

In one set of embodiments, the device includes a deployment actuator able to drive a substance transfer component or a substance transfer component into the skin, e.g., so that the substance transfer component can receive a fluid from the skin and/or from beneath the skin of a subject, and/or so that the substance transfer component can deliver a substance to a subject, e.g. deliver a substance to the skin and/or to a location beneath the skin of a subject. The deployment actuator may be a structure that can be deformed using unaided force (e.g., by a human pushing the structure), or other forces (e.g., electrically-applied forces, mechanical interactions or the like), but is able to restore its original shape after the force is removed or at least partially reduced. For example, the deployment actuator may restore its original shape spontaneously, or some action (e.g., heating) may be needed to restore the structure to its original shape. The deployment actuator may be formed out of a suitable elastic material, in some cases. For instance, the deployment actuator may be formed from a plastic, a polymer, a metal, etc. In one set of embodiments, the deployment actuator may have a concave or convex shape. For instance, the edges of the deployment actuator may be put under compressive stress such that the structure “bows” out to form a concave or convex shape. A person pushing against the concave or convex shape may deform the deployment actuator, but after the person stops pushing on the deployment actuator, the deployment actuator may be able to return to its original concave or convex shape, e.g., spontaneously or with the aid of other forces as previously discussed. In some cases, the deployment actuator may be bistable, i.e., having two different positions in which the deployment actuator is stable.

In one set of embodiments, the deployment actuator may include a flexible concave member or a reversibly deformable structure that is moveable between a first configuration and a second configuration. For instance, the first configuration may have a concave shape, such as a dome shape, and the second configuration may have a different shape, for example, a deformed shape (e.g., a “squashed dome”), a convex shape, an inverted concave shape, or the like. See, for example, FIG. 10B. The flexible concave member (or a deployment actuator) may be moved between the first configuration and the second configuration manually, e.g., by pushing on the flexible concave member using a hand or a finger, and/or the flexible concave member may be moved using an actuator such as is described herein. In some cases, the flexible concave member may be able to spontaneously return from the second configuration back to the first configuration, e.g., as is shown in FIG. 10. In other cases, however, the flexible concave member may not be able to return to the first configuration, for instance, in order to prevent accidental repeated uses of the flexible concave member. The flexible concave member, in some embodiments, may be a deployment actuator, although in other embodiments, it need not be.

The flexible concave member (or a deployment actuator, in some embodiments) may be mechanically coupled to one or more needles (e.g., microneedles), or other substance transfer components such as those discussed herein. If needles are used, the needles can be hollow or solid, and there may be one or more than one needle. (It should be understood that in any embodiments described herein, references to a needle are by way of simplicity, and in other

embodiments, the device can include more than one needle (e.g., as in an array of needles), and/or the needle may be a microneedle.) The needle may be directly immobilized on the flexible concave member, or the needles can be mechanically coupled to the flexible concave member using bars, rods, levers, plates, springs, or other suitable structures. The needle (or other substance transfer component), in some embodiments, is mechanically coupled to the flexible concave member such that the needle is in a first position when the flexible concave member is in a first configuration and the needle is in a second position when the flexible concave member is in a second configuration. Thus, movement of the flexible concave member (or deployment actuator) is able to cause the needle to move from a first position to a second position. For instance, the first position of the needle may be a withdrawn position while the second position may be a deployed position where the needles are able to contact and/or be inserted into the skin of a subject, for example, in an applicator region, for example, a recess within the device.

In some cases, relatively high speeds and/or accelerations may be achieved, and/or insertion of the needle may occur in a relatively short period of time, e.g., as is discussed herein. The first position and the second position, in some cases, may be separated by relatively small distances. For example, the first position and the second position may be separated by a distance of less than about 10 mm, less than about 9 mm, less than about 8 mm, less than about 7 mm, less than about 6 mm, less than about 5 mm, less than about 4 mm, less than about 3 mm, or less than about 2 mm, etc. However, even within such distances, in certain embodiments, high speeds and/or accelerations such as those discussed herein can be achieved.

During use, a device may be placed into contact with the skin of a subject such that a recess or other suitable applicator region is proximate or in contact with the skin. By moving the flexible concave member (or deployment actuator) between a first configuration and a second configuration, because of the mechanical coupling, the flexible concave member is able to cause a needle (or other substance transfer component) to move to a second position within the recess or other applicator region and to contact or penetrate the skin of the subject.

In some embodiments, the device may also include a retraction mechanism able to move the needle (or other substance transfer component) away from the skin after the flexible concave member (or a deployment actuator) reaches a second configuration. Retraction of the flexible concave member may, in some embodiments, be caused by the flexible concave member itself, e.g., spontaneously returning from the second configuration back to the first configuration, and/or the device may include a separate retraction mechanism, for example, a spring, an elastic member, a collapsible foam, or the like. In some embodiments, the retraction mechanism may be useable only once or a limited number of times. For example, a spring or a collapsible foam may be used that includes a “breakaway” component, preventing reuse, or the spring may be “pre-packaged” within the device so that it can only be used once, and no mechanism is available within the device that allows the spring to be re-compressed.

The needle (or other substance transfer component) may be used for delivering and/or receiving a substance or substances such as blood, from a subject, e.g., from the skin and/or from beneath the skin. For example, in some cases, a vacuum chamber having a reduced pressure or an internal pressure less than atmospheric pressure prior to receiving blood or other bodily fluids (e.g., interstitial fluid) may be

used to assist in the receiving of the fluid from the skin after the needle (or other substance transfer component) has penetrated the skin. The fluid received from the skin may be collected in the vacuum chamber and/or in a collection chamber. The collection chamber may be separated from the vacuum chamber using a gas permeable membrane (e.g., one that is substantially impermeable to blood or other bodily fluids), a hydrophilic membrane, a porous structure, a dis-

solvable interface, or the like, e.g., as is discussed herein. In some cases, movement of a deployment actuator and/or a flexible concave member from a first configuration to a second configuration may be used to create a fluid communication pathway between a vacuum chamber and an applicator region such as a recess that contains or is able to contain needles or other substance transfer components for contact or insertion into the skin of the subject. For example, a flexible concave member and/or a deployment actuator may be mechanically coupled to a piercing member such that the piercing member is able to move when the flexible concave member moves from the first configuration to the second configuration. The piercing member may be, for example, a needle, a microneedle, a blade, a wire, or the like. As the flexible concave member or deployment actuator moves, e.g., from a first configuration to a second configuration, the piercing member may be inserted or slid past or into a pierceable surface. For example, the pierceable surface may be a foil or an airtight seal that is pierced, sliced, punctured, peeled, ripped, etc., or otherwise disrupted due to the movement of the piercing member, e.g., into and/or across the pierceable surface. The pierceable surface may separate a vacuum chamber from an applicator region such that, when disrupted, a fluid communication pathway is thereby created between the vacuum chamber and the applicator region. In some cases, other methods may be used to disrupt the pierceable surface. In some embodiments, movement of a vacuum chamber, e.g., pushing on the vacuum chamber manually, or actuation involving movement of the vacuum chamber, may be used to cause disruption of the pierceable surface.

An example of a deployment actuator is now illustrated with respect to FIG. 10. In FIG. 10A, structure 700 has a generally concave shape, and is positioned on the surface of skin 710. In some cases, structure 700 may be a flexible concave member. Structure 700 also contains a plurality of substance transfer components 720 for insertion into the skin. In FIG. 10B, a person (indicated by finger 705) pushes onto structure 700, deforming at least a portion of the structure and thereby forcing substance transfer components 720 into at least a portion of the skin. In FIG. 10C, after the person releases structure 700, the structure is allowed to return to its original position, e.g., spontaneously, lifting substance transfer components 720 out of the skin. In some cases, e.g., if the substance transfer components are sufficiently large or long, blood or other fluids 750 may come out of the skin through the holes created by the substance transfer components, and optionally the fluid may be collected by the device for later storage and/or use, as discussed herein.

As another example, referring now to FIG. 11, a device 1100 is illustrated schematically in which a substance transfer component comprising a substance transfer component is driven by a deployment actuator, such as a flexible concave member. In FIG. 11, device 1100 includes a housing 1102 defining a plurality of chambers and channels. In other embodiments (not shown) a plurality of components that can be separable from and attachable to each other (e.g., modular components) can together define the device and together

define a series of channels and compartments necessary for device function. See, e.g., U.S. patent application Ser. No. 12/716,233, filed Mar. 2, 2010, entitled "Systems and Methods for Creating and Using Suction Blisters or Other Pooled Regions of Fluid within the Skin," by Levinson, et al.; U.S. patent application Ser. No. 12/716,226, filed Mar. 2, 2010, entitled "Techniques and Devices Associated with Blood Sampling," by Levinson, et al.; or U.S. patent application Ser. No. 12/716,229, filed Mar. 2, 2010, entitled "Devices and Techniques Associated with Diagnostics, Therapies, and Other Applications, Including Skin-Associated Applications," by Bernstein, et al., each incorporated herein by reference.

In the specific device illustrated, device 1100 includes a surface 1104 for positioning the device proximate the skin of a subject during use. Where desired in certain embodiments, the device can include an adhesive layer 1106 where the adhesive is selected to be suitable for retaining the device in a relatively fixed position relative to the skin during use, but may allow for relatively easy removal of the device from the skin following use. Specific non-limiting examples of adhesives are discussed below. The adhesive also can be selected to assist in maintaining a vacuum within portions of the device proximate the skin as will be understood.

In FIG. 11, device 1100 includes a skin insertion object 1108. The skin insertion objects may be, for example, a substance transfer component and/or a skin insertion object as discussed herein. Specific non-limiting examples include needles or microneedles, e.g., as shown in FIG. 11. The substance transfer component can be or include, as described elsewhere herein and in other documents incorporated herein by reference, any of a variety of components able to receive a substance from the skin and/or from beneath the skin of a subject, and or deliver a substance to the skin and/or to a location beneath the skin of the subject. For example, the substance transfer component may include one or more needles and/or microneedles, a hygroscopic agent, a cutter or other piercing element, an electrically-assisted system, or the like. In the specific device illustrated, skin insertion objects 1108 define an array of microinsertion objects such as solid or hollow microneedles. In one set of embodiments, skin insertion object 1108 is selected to have a particular size and profile for a particular use. For example, the skin insertion objects may include an array of insertion or microinsertion objects which, in the device illustrated, emanate from a base 1110 which will be described further below.

In certain embodiments, a plurality of skin insertion objects 1108 are relatively small, and are relatively completely driven into the skin. Examples of skin insertion objects include needles or microneedles, e.g., as described in greater detail below. The skin insertion objects may be positioned to address the skin of the subject, each protruding from a base and defining a length from the base, and are able to be inserted into or through the skin to a depth essentially equal to their length but are prevented, by the base, from inserting at a depth greater than their length. In some embodiments, the plurality of skin insertion objects have an average length (measured from the base) of no more than about 1,000 microns or more than about 2,000 microns, although lengths can differ between individual skin insertion objects. In one set of embodiments, the skin insertion objects are of relatively uniform length, together defining an average length and each differing from the average length by no more than about 50%, about 40%, about 30%, about 10%, or about 5%. The average length of the skin insertion objects, in other embodiments, are no more than about 1,500

microns, no more than about 1,000 microns, no more than about 900 microns, no more than about 800 microns, no more than about 750 microns, no more than about 600 microns, no more than about 500 microns, no more than about 400 microns, or no more than about 350 microns. In some embodiments, a triggering mechanism as discussed herein is provided that is able to move the skin insertion objects from a fully predeployed position to a fully deployed position with a force sufficient to insert the plurality of skin insertion object into or through the skin to an average depth of at least about 50% the average length of the plurality of skin insertion objects. In other embodiments, the triggering mechanism is able to insert the plurality of skin insertion objects to an average depth of at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 92%, about 94%, about 96%, or about 98% of the average length of the plurality of skin insertion objects.

In the device illustrated, skin insertion objects **1108** are mounted on a flexible structure **1112** which, as illustrated, is maintained relatively rigidly through various aspects of the device but which mounts skin insertion objects **1108** flexibly for up/down movement relative to the skin. Flexible structure **1112** can be a membrane, a single or multi-layer structure selected from various polymers, metals, or the like to provide sufficient properties such as any combination of flexibility, elasticity, gas permeability or impermeability, fluid permeability or impermeability, or the like for desired operation. Portions of flexible structure **1112**, skin insertion objects **1108**, and other interior walls of the device define a region **1114** which allows for movement of skin insertion objects **1108** relative to the skin for delivery of a substance to and/or receiving of a substance from the skin or beneath the skin, and, where a substance is received from the skin or from beneath the skin, region **1114** can serve as a reservoir for introduction of the substance into the device. Where a vacuum is used to receive a substance from the subject (as in the embodiment illustrated in FIG. 11), region **1114**, when positioned against the skin, can expose vacuum to that portion of the skin proximate surface **1104** of the device and abutting the chamber.

Device **1100** also includes a device actuator **1116** which, as illustrated, includes a proximate portion **1118** which can be addressed by a user of the device (who may be the same or different from the subject the device is administered to) and a distal portion **1120** for addressing skin insertion objects **1108** via flexible structure **1112**. Proximal portion **1118** and distal portion **1120** are, in the device illustrated, opposite ends of a single component but, as would be understood by those of ordinary skill in the art, the actuator can include a plurality of individual components operably linked in any way necessary to perform actuation as will be described.

As will be understood, FIG. 11 is a cross-section of a device illustrating various components and channels within the device. As will also be understood by those of ordinary skill in the art, different arrangements of devices and channels are contemplated herein so long as the purpose of the device described herein is met. In this figure, device actuator **1116** is directly connected to or otherwise operably linked to a deployment actuator **1122** which, in the device illustrated, is in the form of a "snap dome," the function and use of which will be described below. The snap dome in this figure has an approximately circular profile, and may define in some embodiments a flexible concave member. The structure may define an interior and a periphery which, if not

circular, may include a plurality of tabs, protrusions, or the like sufficient for support of structure **1122** within the device. As illustrated, a plurality of tabs (or the essentially circular perimeter of) the device are supported within holders **1124**, and the center, snap dome portion of the device is operably linked to device actuator **1116**, such that movement of the central portion of snap dome **1122** and the periphery of the snap dome can be controlled independently of each other. Holders **1124** are directly connected to or otherwise operably linked to an actuator retraction component **1126** which, in the device illustrated, can be a ring-shaped structure positioned under and supporting holders **1124**. Holders **1124** can be individual holders and/or a ring-like structure surrounding the periphery of snap dome **1122**. A series of one, two, or more support members (e.g., **1130**) are positioned near the top of device **1100** and serve to define a series of channels for sample flow, vacuum control, or the like as will be described.

Turning now to channels defined within the device, as described above, region **1114**, when the device is positioned against skin, can serve to expose a portion of the skin defined by the periphery of the region to a vacuum, to skin insertion objects **1108** as they move toward and/or away from the skin, and/or to transfer a substance from or to the subject. Region **1114** can house a substance for transfer to the subject, in the form of a pharmaceutical composition or the like, optionally loaded on skin insertion objects **1108**. Where blood and/or interstitial fluid is drawn from a subject, region **1114** can serve to introduce the substance into the device from the subject.

A channel **1132** connects region **1114** to other portions of the device in this example. Channel **1132** can be used to deliver a substance to region **1114** for transfer to a subject, or for application of a vacuum to region **1114**, and/or for receiving a substance from a subject. The remainder of the description of device **1100** will be made within the context of receiving a substance such as blood and/or interstitial fluid from a subject, but it is to be understood that substances can also be delivered via various channels. Channel **1132** typically emanates in one direction from region **1114** although a plurality of channels can emanate from the region, arranged radially or otherwise relative to the center of the device. In device **1100**, channel **1132** first passes laterally from the center of the device and then upwardly where, near the top of the device, it can, optionally, include one wall defining a window **1134** through which a user of the device can observe transfer of a substance, or through which analysis of a substance may occur. It can also itself define a reservoir, in whole or in part, or be connected to an internal or an external reservoir for maintaining, storing, and/or transferring a substance drawn from a subject. As shown here, it can be connected to a substance collection reservoir **1136** which, as illustrated, is a disc-shaped reservoir formed in the device housing and surrounding the center of the device including device actuator **1116** and related components.

Device **1100**, illustrated as one example of devices provided by the invention, includes a vacuum chamber for applying a vacuum proximate the skin of a subject for receiving a substance from the skin. As illustrated, vacuum chamber **1138** is positioned in a central portion of the device surrounding device actuator **1116**, although it can be provided anywhere in or proximate the device. The vacuum chamber can be evacuated to an appropriate level just prior to use, or the device can be pre-packaged under vacuum as described elsewhere herein. As illustrated, vacuum chamber **1138** is in fluid communication with substance collection

reservoir **1136** but, in its initial state and prior to use, a membrane or other component, such as support member **1128**, separates channel **1132** connecting it to region **1102**. In the device illustrated, a vacuum actuation component **1140** can be actuated to puncture the membrane or other component (e.g., **1128**) and thereby connect vacuum chamber **1138** with channel **1132**, at an appropriate time during use of the device. In other embodiments, device actuator **1116** and vacuum actuation component **1140** can be combined into a single button or operably linked so that only one operation is needed to actuate both the microinsertion objects and the vacuum.

Deployment actuator (or, as shown, a snap dome or other flexible concave member) **1122** can be provided in a variety of forms including a monostable or bistable configuration. In the embodiment illustrated, a bistable configuration is illustrated including first and second low energy or stable configurations separated by a relatively high energy or unstable configuration. As shown, deployment actuator **1122** is shown in a “cocked” or predeployed position.

The deployment actuator (or the flexible concave member) may be formed from any suitable material, for example, a metal such as stainless steel (e.g., 301, 301LN, 304, 304L, 304LN, 304H, 305, 312, 321, 321H, 316, 316L, 316LN, 316Ti, 317L, 409, 410, 430, 440A, 440B, 440C, 440F, 904L), carbon steel, spring steel, spring brass, phosphor bronze, beryllium copper, titanium, titanium alloy steels, chrome vanadium, nickel alloy steels (e.g., Monel 400, Monel K 500, Inconel 600, Inconel 718, Inconel x 750, etc.), a polymer (e.g., polyvinylchloride, polypropylene, polycarbonate, etc.), a composite or a laminate (e.g., comprising fiberglass, carbon fiber, bamboo, Kevlar, etc.), or the like. The deployment actuator may be of any shape and/or size. In one embodiment, the deployment actuator is a flexible concave member. The deployment actuator may have, for instance, a generally domed shape (e.g., as in a snap dome), and be circular (no legs), or the deployment actuator may have other shapes, e.g., oblong, triangular (3 legs), square (4 legs), pentagonal (5 legs), hexagonal (6 legs), spiderlegged, starlike, clover-shaped (with any number of lobes, e.g., 2, 3, 4, 5, etc.), or the like. The deployment actuator may have, in some embodiments, a hole, a port, a slot, dimple, or button in the middle. The deployment actuator may also have a serrated disc or a wave shape. In some cases, the skin insertion objects may be mounted on the deployment actuator. In other cases, however, the skin insertion objects are mounted on a separate structure which is driven or actuated upon movement of the deployment actuator.

In one set of embodiments, the deployment actuator is not planar, and has a portion that can be in a first position (a “cocked” or predeployed position) or a second position (a “fired” or deployed position), optionally separated by a relatively high energy configuration. In some cases, both the first position and the second position are stable (i.e., the structure is bistable), although conversion between the first position and the second position requires the structure to proceed through an unstable configuration.

In some cases, surprisingly, the distance or separation between the first position and the second position of the deployment actuator or the flexible concave member is relatively small. Such distances or separations may be achieved using snap domes or other configurations such as those described herein, in contrast to springs or other devices which require longer translational or other movements. For example, the perpendicular distance (i.e., in a direction away from the skin) in the deployment actuator between the top of the structure and the bottom of the structure (excluding the

skin insertion objects) when the device containing the structure is placed on the skin of a subject may be no more than about 5 mm, no more than about 4 mm, no more than about 3 mm, no more than about 2 mm, no more than about 1 mm in some cases, no more than about 0.8 mm, no more than about 0.5 mm, or no more than about 0.3 mm. In one set of embodiments, the distance is between about 0.3 mm and about 1.5 mm. In another set of embodiments, the deployment actuator may have a greatest lateral dimension (parallel to the skin) when the device containing the structure is placed on the skin of a subject of no more than about 50 mm, no more than about 40 mm, no more than about 30 mm, no more than about 25 mm, no more than about 20 mm, no more than about 15 mm, no more than about 5 mm, no more than about 4 mm, no more than about 3 mm, no more than about 2 mm, no more than about 1 mm in some cases, no more than about 0.8 mm, no more than about 0.5 mm, or no more than about 0.3 mm. In one set of embodiments, the distance is between about 0.3 mm and about 1.5 mm.

Use of device **1100** will now be described in the context of receiving a substance such as blood from a subject. Device **1100** is placed against the skin of a subject such that at least a portion of surface **1104** contacts the skin. Prior to use, a cover member (not shown) can cover surface **1104** of the device and can cover region **1114**, to protect surface **1104** and region **1114** from contaminants, etc. optionally maintaining the interior of the device in a sterile condition. The cover can be peeled off or otherwise removed from the device, and the device placed against the skin, optionally adhering to the skin. Vacuum actuation component **1140** can be actuated to expose channel **1132** and region **1114** to vacuum at any time, including before, simultaneously, or after actuation of skin insertion objects **1108**. In one arrangement, vacuum actuation component **1140** is actuated to apply vacuum to region **1114** prior to actuation to skin insertion objects **1108**, thereby to create a vacuum against the skin proximate region **1114** prior to use. Actuation of device actuator **1116** can take place before or after deployment of vacuum.

When device actuator **1116** is actuated by a user (e.g., when proximal portion **1118** is depressed downwardly as shown in the figure), distal portion **1120** engages skin insertion objects **1108** (optionally via flexible structure **1112**) to drive them toward the skin. In some embodiments, foil **1128** is first broken, then component **1126** is compressed, then component **1126** is broken, before flexible structure **1112** is stretched and the deployment actuator **1122** of the device fires or is actuated. Membranes or other members **1112**, **1128**, or **1130** may have, in some cases, sufficient flexibility and/or elasticity to allow device actuator **1116** to drive skin insertion objects **1108** sufficiently distally (downwardly, as shown) to engage the skin of the subject and carry out the desired function of the device. Various gaskets, bearings, or membranes as shown can be used for this function. Where support member **1128** is a foil or the like used for the purpose of initially separating vacuum reservoir **1138** from channel **1132** (e.g., prior to use), when device actuator **1116** is moved downwardly, vacuum actuation component **1140** may rupture support member **1128** proximate device actuator **1116**, or flexibly deform as needed, so long as member **1130** (or another component) serves to allow device actuator **1116** to move slidably within the device while maintaining sufficient vacuum in vacuum reservoir **1138** and related channels for use of the device.

When skin insertion objects **1108** engage the skin of the subject and facilitates receiving a substance from the skin and/or from beneath the skin of the subject, a vacuum can

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draw the substance into region **1114**, through channel or channels **1132**, and into substance collection reservoir **1136**. In this process, device actuator **1116** first urges or moves structure **1122** from its first stable configuration to a relatively unstable configuration and beyond that point, at which point the structure **1122** rapidly moves to a second stable configuration associated with downward driving of device actuator **1116** to quickly drive access skin insertion objects **1108** proximate the skin.

After that point, if it is desirable for skin insertion objects **1108** to be withdrawn from the skin, then a variety of techniques can be used to do so. In the device illustrated, retraction component **1126** drives holder **1124** upwardly, retracting structure **1122** and device actuator **1116** from skin insertion objects **1108**. At that point, device actuator **1116** can be operably linked to skin insertion objects **1108** and receive the transfer component, or it can move freely relative to skin insertion objects **1108**, whereby flexible structure **1112** (e.g., an elastic membrane) or other component can withdraw skin insertion objects **1108** from the skin. Again, in the device illustrated, retraction component **1126** can itself be a deployment actuator such as a leaf spring, coil spring, foam, or the like. During use, when device actuator **1116** is driven downwardly, retraction component **1126** is first compressed and, depending upon the size and arrangement of components **1126**, **1124**, **1122**, **1116** and **1108**, during compression, skin insertion objects **1108** can be driven downwardly to some extent. At the point at which retraction component **1126** is compressed and provides a sufficient resistance force, deployment actuator **1122** can be urged or moved from its first configuration through an unstable configuration and can return to its second configuration, driving skin insertion objects **1108** against the skin. Then, upon release of user pressure (or other actuation, which can be automatic) from device actuator **1116**, retraction component **1126** can expand and, with structure **1122** optionally remaining in its second, downwardly-driven low-energy configuration, device actuator **1116** can be retracted and skin insertion objects **1108** retracted from the skin.

Referring now to FIGS. **12A** and **12B**, device **1150** is illustrated schematically. Device **1150** is similar to and can be considered essentially identical to device **1100** in all aspects other than those described here with respect to FIGS. **12A** and **12B**. As such, the reader will observe that not all components are provided, although other components similar to those of device **1100** can exist. One way in which device **1150** differs from device **1100** is that in device **1150**, in the pre-deployment or post-deployment retracted configuration, membrane **1112** is drawn proximally (upwardly) as illustrated in FIG. **12B**. Membrane **1112** is in a less-stressed lower-energy configuration as shown in FIG. **12A** when retraction component **1126** is compressed and skin insertion objects **1108** are driven proximate the skin. Devices **1100**, **1150**, and other similar devices are one way to enact a triggering mechanism that can move skin insertion objects **1108** or other similar transfer component relative to the skin in particularly advantageous ways. Examples of triggering mechanisms include, in addition to the examples shown in FIGS. **11** and **12**, blasting caps, explosives, other chemical reactions, solenoids or other electrical interactions, pneumatics (e.g., compressed air), other thermal interactions or mechanical interactions, or the like.

In one set of embodiments, the triggering mechanism may move skin insertion objects **1108** from a fully predeployed position (e.g., as shown in FIG. **11**) to a fully deployed position in which skin insertion objects **1108** are fully engaged with the skin, in a short period of time. In one

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embodiment, that period of time is less than about 0.01 seconds, and in other embodiments, less than about 0.009 seconds, less than about 0.008 seconds, less than about 0.007 seconds, less than about 0.006 seconds, less than about 0.005 seconds, less than about 0.004 seconds, less than about 0.003 seconds, less than about 0.002 seconds, less than about 0.001 seconds, less than about 0.0005 seconds, less than about 0.00025, or less than about 0.0001 seconds.

In another embodiment, skin insertion objects **1108** move quickly relative to skin during deployment via the triggering mechanism, reaching a speed of at least about 4 m/s, at least about 5 m/s, at least about 6 m/s, at least about 7 m/s, at least about 8 m/s, at least about 10 m/s, at least about 12 m/s, at least about 15 m/s, or at least about 20 m/s at the point at which skin insertion objects **1108** first touch the skin during deployment.

In some cases, skin insertion objects **1108** achieve relatively high accelerations due to the triggering mechanism, for example, at least about 4 m/s², about 6 m/s², about 8 m/s², about 10 m/s², about 12 m/s², about 15 m/s², or about 20 m/s², at least about 30 m/s², at least about 50 m/s², at least about 100 m/s², at least about 300 m/s², at least about 500 m/s², at least about 1,000 m/s², at least about 3,000 m/s², at least about 5,000 m/s², at least about 10,000 m/s², at least about 30,000 m/s², at least about 50,000 m/s², at least about 100,000 m/s², at least about 200,000 m/s², or at least about 300,000 m/s². In some embodiments, the skin insertion objects **1108** are accelerated for relatively short periods of time, e.g., less than about 1 s, less than about 300 ms, less than about 100 ms, less than about 30 ms, less than about 10 ms, less than about 3 ms, or less than about 1 ms, and/or over relatively short distances, e.g., less than about 5 mm, less than about 4 mm, less than about 3 mm, less than about 2 mm, less than about 1 mm, less than about 800 micrometers, less than 600 micrometers, less than 500 micrometers, less than 400 micrometers, less than about 300 micrometers, less than about 200 micrometers, less than about 100 micrometers, less than about 50 micrometers, etc.

Significant forces can be applied to skin insertion objects **1108** as they move relative to the skin via the triggering mechanism. In another set of embodiments, skin insertion objects **1108**, at the point at which they first contact the skin, are driven by a force created at least in part by the triggering mechanism of at least about 6 micronewtons, about 8 micronewtons, about 10 micronewtons, about 12 micronewtons, or about 15 micronewtons.

In another set of embodiments, skin insertion objects **1108** apply a pressure to the skin, during deployment caused by the triggering mechanism, of at least about 100 N/m², at least about 300 N/m², at least about 1,000 N/m², at least about 3,000 N/m², etc. In force assessment, the area can be measured as the area of skin displaced by the transfer component at full deployment, e.g., the area of the skin ruptured by the total of the cross sectional area of all skin insertion objects inserted into the skin, at the top surface of the skin.

In some cases, the skin insertion objects are forced into the skin via the triggering mechanism with a force sufficient to insert the skin insertion objects into or through the skin to an average depth of at least about 60% of the skin insertion object (or the average length of the skin insertion objects, if more than one is used, e.g., as in an array of microneedles). In some cases, the depth is at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% of the skin

insertion objects, e.g., the length of the needle or the microneedle inserted into the skin.

Referring now to FIG. 13, various examples of devices including flexible concave members are now discussed. In FIG. 13A, a device 900 for receiving blood or other fluids from a subject is shown positioned onto the skin 999 of a subject. Device 900 includes first module 905 and second module 910. First module 905 includes vacuum chamber 907, and optionally, collection chamber 908, which can be used to collect blood or other bodily fluids from the subject. When the device is used to fluids from a subject, vacuum chamber 907 may be used to urge or move the fluid from the subject into the device, and into collection chamber 908 and/or vacuum chamber 907.

First module 905 can, in some embodiments, be detached from second module 910, and replaced with a fresh first module 905, for example, for repeated uses of the device. First module 905, as is shown in FIG. 13A, includes a substantially cylindrical vacuum chamber 907, and, within vacuum chamber 907, collection chamber 908. In other embodiments, however collection chamber 908 may be positioned elsewhere within the device besides within vacuum chamber 907, including within module 910. Vacuum chamber 907 may be, for example, a Vacutainer™ tube, a Vacuette™ tube, or other similar vacuum tube, many of which are commercially available.

As mentioned, in some cases, collection chamber 908 may be positioned within the vacuum chamber 907. Collection chamber 908 may thus have a shape that fits substantially inside of vacuum chamber 907. In some cases, collection chamber 908 may also be removable from vacuum chamber 907, for example, for analysis of blood or other bodily fluids received from the subject. In other cases, however, collection chamber 908 may not be easily removed from vacuum chamber 907.

As is shown in FIG. 13A, passages 906 allow vacuum chamber 907 and collection chamber 908 to be in fluidic communication. Passages 906 may be, for example, holes, tubes, or other suitable openings that allow the two chambers to be in fluidic communication with each other. Thus, the two chambers may have substantially the same pressure (i.e., substantially the same reduced pressure), such that, when the reduced pressure causes blood or other bodily fluids to flow into first module 905, the fluid first enters the collection chamber 908. In some cases, collection chamber 908 may be separated from vacuum chamber 907 using a gas permeable membrane, a hydrophilic membrane, a porous structure, a dissolvable interface, or the like, i.e., to prevent blood or other bodily fluids from exiting collection chamber 908 into vacuum chamber 907. Passage 906 could be positioned anywhere along chamber 908, including the top of chamber 908 in the orientation shown in FIG. 13A.

First module 905 also contains, at one end, a surface or a seal 909 that can be pierced as is discussed below. Before use, first module 905 may be separate from second module 910, and this end of first module 905 may be sealed using surface 909, thereby preventing the loss of reduced pressure from within vacuum chamber 907, prior to use of the first module 905 within device 900. The pierceable surface may be, for example, a foil, a metal, a polymer, rubber, a rubber septum, or the like that can be pierced by a piercing member 912 from second module 910, as is discussed below.

First module 905 may be connected to second module 910 to form device 900. When first module 905 is connected to second module 910, piercing member 912 is inserted into pierceable surface 909 as first module 905 and second module 910 are connected to each other. Piercing member

912 may be, for example, a needle, a microneedle, a blade, or other piercing structure that is able to penetrate the pierceable surface 909 when first module 905 and second module 910 are connected. Piercing member 912 may be, e.g., a hollow needle, and in some cases, piercing member is in fluidic communication with applicator region 940. Once piercing member 912 has been inserted into (or otherwise disrupted) pierceable surface 909, a fluidic connection may be formed between vacuum chamber 907, and a fluid received from the skin of a subject, e.g., within applicator region 940, as is discussed below.

When first module 905 and second module 910 are connected, a surface of first module 905 pushes down on one or more activation members 916 as is shown in FIG. 13A. In this example activation member 916 has a generally cylindrical shape that is pushed down onto flexible concave member 920. Activation members 916 then can be used to move flexible concave member 920, as is discussed below. In other embodiments, other mechanical couplings may be used in addition to or instead of activation members, for example, levers, gears, or the like. The surface used to move activation members 916, as is shown in FIG. 13A, is the same pierceable surface as discussed above that is pierced by piercing member 912 when first module 905 and second module 910 are connected. However, in other embodiments, other surfaces may be used, or the portions used to push activation members 916 may be different than the pierceable surface of first module 905 that is pierced by piercing member 912.

Activation members 916, in the example illustrated in FIG. 13A, push a flexible concave member 920, e.g., a “snap dome,” or other suitable structure, for example, a deformable structure (e.g., a deployment actuator) such as described herein. In the example of FIG. 13A, flexible concave member 920 can be in either a first configuration or a second configuration, where the first configuration is “concave down” while the second configuration is “concave up.” In FIG. 13A, the second configuration of flexible concave member 920 is shown. Due to the concave shape of the flexible concave member, and/or the materials used to form the flexible concave member, the flexible concave member cannot adopt a stable configuration in a position midway between the first configuration and the second configuration, or in other words, the flexible concave member is able to “snap” from the first configuration to the second configuration. This movement of flexible concave member 920 from the first configuration to the second configuration, as shown in FIG. 13A, is caused by activation members 916 pushing against a surface of the flexible concave member. Accordingly, by connecting first module 905 and second module 910, the activation members 916 are pushed by a surface of first module 905 into flexible concave member 920, thereby causing flexible concave member 920 to “snap” from the first configuration to the second configuration. In some cases, this action may be quite rapid, as is discussed herein. In other embodiments (not shown here), the connection of the components may be used to load the device by compressing a component. In some cases, the actual firing is controlled by a release mechanism (e.g., a button).

Flexible concave member 920, in the example shown in FIG. 13A, is mechanically coupled to a microneedle array 930 via activation ring 925. In this case, microneedles 930 may be formed or attached to a plate 932 that can be moved as activation ring 925 and/or flexible concave member 920 are moved. In other embodiments, however, other mechanical couplings may be used to mechanically couple the flexible concave member and the microneedle array, or in

some cases, microneedles **930** may be directly attached to flexible concave member **920**. Examples of other mechanical coupling systems that can be used include, but are not limited, activation members, levers, gears, or the like. In addition, although an array of microneedles **930** is shown in FIG. **13A** (connected to plate **932**), the invention is not so limited, and in other embodiments, other substance transfer components can be used, for example, needles or other substance transfer components as discussed herein. In this example, when flexible concave member **920** moves from the first configuration to the second configuration, due to the transfer of energy or momentum from flexible concave member **920** to plate **932** via activation ring **925**, the microneedles **930** are driven rapidly downward. Initially, activation ring **925** would be in a raised position in FIG. **13A**, and would be pushed downward during actuation, e.g., to activate plate **932** and microneedles **930** by momentum transfer or the like. In some cases, spring **964** may be used to hold activation ring **925** in a raised position prior to use. In this example, such movement causes the microneedles to become moved to a lower position in which the microneedles are able to contact the skin of a subject in applicator region **940**, and preferably inserted or penetrated into the skin of the subject. In some cases, optionally, the microneedles may also be withdrawn from the skin after insertion, for example, due to the flexible concave member returning to the first configuration, and/or due to the presence of a retraction mechanism. For example, as is shown in FIG. **13A**, when module **905** is attached to module **910**, module **905** may be pushed hard enough to compress spring **964**, which allows activation members **916** to press down on flexible concave member **920**. This in turn compresses spring **966**, positioning needles **930** above the skin **999**. With additional force, activation members **916** causes flexible concave member **920** to snap into its second configuration, which inserts needles **930** into the skin **999**. When force is released from module **905**, spring **966** raises activation members **916** and module **905**, and spring **966** raises flexible concave member **920**, causing plate **932** and needles **930** to retract from skin **999**. In some embodiments, however, plate **932** may be elastomeric and thus could also function as a retraction mechanism (or as part of a retraction mechanism, e.g., in combination with the configuration shown in FIG. **13A**).

Once microneedles **930** have been inserted into the skin, bleeding may occur. In the example illustrated in FIG. **13A**, the blood may flow from the skin into applicator region **940**. In this figure, piercing member **912** is a hollow shaft that extends from vacuum chamber **907** through second module **910** to applicator region **940**. Because of the action of the vacuum from vacuum chamber **907**, blood is drawn through hollow piercing member **912** into collection chamber **908** to be collected therein. Other configurations for the removal of blood or other fluids may be used in other embodiments. For instance, a channel that circumvents the needle array and snap dome may be used in some cases.

In some cases, vacuum chamber **907** and/or collection chamber **908** may be clear or substantially clear, thereby allowing monitoring of the receiving fluids such as blood from the subject to occur. Thus, for example, when collection chamber **908** is filled or partially filled to a certain extent, the device can be removed from the skin of the subject.

After a suitable time, for example, when collection chamber **908** is filled with blood, or partially filled to a certain or predetermined extent, device **900** can be removed from the skin of the subject. In addition, first module **905** and second

module **910** may be removed from each other, so that the blood within blood collection chamber **908** can be analyzed using suitable techniques such as those described herein. For example, vacuum chamber **907** may be a Vacutainer™ tube or a Vacuette™ tube as previously described, and first module **905** may thus be interfaced with standard commercially-available equipment able to process Vacutainer™ tubes or a Vacuette™ tubes. In some cases, the collection chamber may be removed from the vacuum chamber **907** for later analysis.

Another example of a device including a flexible concave member is illustrated in FIG. **13B**. Like the device illustrated in FIG. **13A**, FIG. **13B** shows device **900** positioned on skin **999**, including a first module **905** and a second module **910** that can be connected to each other to form device **900**. In this figure, first module **905** includes vacuum chamber **907**, which may be a Vacutainer™ tube or a Vacuette™ tube, or other similar tube or vacuum chamber as is described herein. Many other components, including collection chamber **908**, are present within second module **910**. In this example, vacuum chamber **907** has a septum **902** that covers an end of vacuum chamber **907**, and thereby allows vacuum chamber **907** to retain its reduced pressure prior to use. In some cases, septum **902** may be part of the Vacutainer™ tube or a Vacuette™ tube. Optionally, a cap may be present on first module **905**, as is illustrated with cap **903** in FIG. **13B**. In some cases, cap **903** may include an opening **904** to allow the insertion of a piercing member **912** into septum **902**. At the end of second module **910** may be a cap **903** (or a shield in some cases) that can be used to at least partially protect an end of second module **910**, including needles **930**, e.g., before or after use. Cap **903** may form a seal with vacuum chamber **907** and also may be able to slide into body **919** of second module **910** while keeping such a seal intact.

During use, first module **905** is connected to second module **910** such that piercing member **912** on first module **905** is inserted through septum **902** of second module **910** into the reduced pressure environment of vacuum chamber **907**. Piercing member **912** can be, for example, a hollow needle, and insertion of piercing member **912** allows a fluidic connection with the reduced pressure within vacuum chamber **907** to be formed.

Second module **910** contains similar components as those previously described with respect to FIG. **13A**, including a flexible concave member **920** that is moved from a first configuration to a second configuration upon the connection of second chamber **907** with second module **910**. The second configuration is illustrated in FIG. **13B**. The body **919** of second module **910** may be formed out of any suitable material, for example, a polymer, rubber, or the like. Unlike FIG. **13A**, in FIG. **13B**, no activation members are used, and cap **903** is directly used to move the flexible concave member from a first configuration to a second configuration, e.g., by having a portion of cap **903** pushing against a portion of flexible concave member **920**. Spring **964** is used in FIG. **13B** to push cap **903** back to its original position once spring **964** is compressed due to movement of cap **903** downwardly into flexible concave member **920**. However, spring **966** is compressed and can function as a retraction mechanism when flexible concave member **920** is moved from the first configuration to a second configuration, similar to the above discussion with reference to FIG. **13A**.

As flexible concave member **920** is moved from the first configuration to a second configuration, flexible concave member **920** is able to move activation members **924**, which causes plate **932** having one or more needles **930** attached thereon to move from a first position to a second position.

Thus, needles **930** are in a first position when flexible concave member **920** is in a first configuration, and needles **930** are in a second position when flexible concave member **920** is in a second configuration. The second position is shown in FIG. 13B. Needles **930** are present within applicator region **940**, which, in this example, is present as a recess within device **900**.

As the needles move from the first position to the second position, the needles may contact or may be inserted into the skin of a subject, in some cases allowing blood to be drawn from the subject. The blood from the subject is then urged or moved into second module **910**, and in particular, into collection chamber **908** within second module **910**. Collection chamber **908** is positioned such that it is in fluidic communication with piercing member **912**, which, in this embodiment, is a hollow needle, i.e., blood flows from applicator region **940** directly into a first end collection chamber **908**, while an opposing end of collection chamber **908** is in fluidic communication with the reduced pressure environment of vacuum chamber **907** via piercing member **912**, thereby providing the driving force for blood to flow into collection chamber **908**. However, blood entering collection chamber **908** cannot move into vacuum chamber **907** due to the presence of gas-permeable membrane **935** that is present at the opposing end of piercing member **912**, which connects the piercing member to collection chamber **908**. Accordingly, the blood that is drawn into device **900** remains and can be collected within collection chamber **908**, without contaminating vacuum chamber **907** or first module **905**. In some embodiments, a removable cap and needle assembly, which may contain plate **932** and needles **930** (for example, microneedles), can be removed and disposed, then replaced with a closed cap for transportation and/or storage (not shown). The cap could be removed prior to placing the device **900** in an analysis machine, for example.

A different configuration is illustrated in FIG. 13C, in another embodiment of the invention. In this example, device **900** is positioned on skin **999** (shown sideways in this figure). First module **905** includes vacuum chamber **907**, similar to the embodiment described above with respect to FIG. 13B. For example, vacuum chamber **905** may be a Vacutainer™ tube or a Vacuette™ tube, or another similar vacuum chamber. However, in this embodiment, the vacuum chamber is not positioned perpendicular with respect to the surface of the skin, as in FIGS. 13A and 13B, but instead is positioned substantially parallel to the skin when device **900** is used. Applicator region **940** containing needles **930**, such as microneedles, is positioned on the right side of device **900** as is shown in FIG. 13C, rather than on the bottom of the device as shown in FIGS. 13A and 13B, i.e., the device is depicted in a sideways orientation in FIG. 13C with skin **999** on the right of the device as shown in this figure. However, it should be understood that devices as discussed herein may work over a range of orientations, including horizontal, vertical, upside down, at an angle, etc. This feature is important since the device may be applied to any suitable location on the body of a subject while the subject is in any suitable (or comfortable) position, e.g., standing, sitting, lying down, etc., and thus, the device may be applied at any suitable angle necessary to access the skin of the subject at the desired location.

As with FIG. 13B, in FIG. 13C, first module **905** including a vacuum chamber **907** can be connected to second module **910**. First module **905** also includes a septum **902** for maintaining the reduced pressure inside vacuum chamber **907**, and optionally cap **903** for protection. Cap **903** may include an opening **904** to allow the insertion of a piercing

member **912** into septum **902**. In some cases, cap **903** may be supplied as part of the Vacutainer™ tube or a Vacuette™ tube, e.g., to hold a septum in place prior to use.

Upon connection of first module **905** and second module **910**, septum **902** of first module **905** is penetrated by piercing member **912** from second module **910**. However, unlike in FIGS. 13A and 13B, connecting first module **905** and second module **910** does not immediately result in the receiving of blood by the device. Instead, piercing member **912**, in this embodiment a hollow tube, is connected to a small chamber **914** which is blocked at one end by pierceable surface **950**. As long as pierceable surface **950** remains intact, even when first module **905** is connected to second module **910** such that septum **902** is pierced by piercing member **912**, device **900** is still able to maintain a reduced pressure within vacuum chamber **907**, prior to use.

The body **919** of second module **910** may be formed out of any suitable material, for example, a polymer, rubber, or the like. Second module **910** also includes a flexible concave member **920**. In this embodiment, flexible concave member **920** has characteristics similar to those previously described, e.g., flexible concave member **920** can adopt a first configuration or a second configuration, although flexible concave member **920** is not able to adopt a stable configuration in a position midway between the first configuration and the second configuration. Mechanically coupled to flexible concave member **920** is piercing member **955**. Piercing member **955** may be directly attached to flexible concave member **920**, or piercing member **955** may be positioned such that movement of flexible concave member **920** from a first configuration to a second configuration causes piercing member **955** to move, as is illustrated in FIG. 13C. In this figure, as flexible concave member **920** moves from the first position to the second configuration, flexible concave member **920** pushes piercing member **955** downwards (i.e., to the right in FIG. 13C), which causes piercing member **955** to come into contact with pierceable surface **950**, causing pierceable surface **950** to be pierced or otherwise be disrupted. Disruption of pierceable surface **950** thus allows fluidic communication with reduced pressure within vacuum chamber **907** to occur.

In the embodiment shown in FIG. 13C, device **900** also includes a retraction mechanism that is able to urge or move flexible concave member **920** to move from the second configuration back to the first configuration. The retraction mechanism may cause retraction of the flexible concave member away from the skin, and/or the retraction mechanism may be able to move the flexible concave member from the second configuration to the first configuration. For example, in some cases, the retraction mechanism may be designed only to cause retraction of the flexible concave member away from the skin, without being able to return the flexible concave member to the first configuration. In this example, the retraction mechanism takes the form of a spring **966**, which is positioned around activation member **924**. When flexible concave member **920** is moved from the first configuration to the second configuration, spring **966** is compressed, and the compressed spring subsequently tries to expand, thereby pushing flexible concave member **920** from the second configuration back to the first configuration, thus illustrating a configuration in which the retraction mechanism is able to both retract the flexible concave member away from the skin and return it to the first configuration. Spring **966** may be, in some embodiments, initially partially compressed, then addition force, e.g., caused by moving flexible concave member **920** from the first configuration to the second configuration, may be used to further compress

the spring, and/or to be able to cause subsequent configuration changes to occur, e.g., as previously discussed. In other embodiments, other retraction mechanisms may be used in addition to or besides a spring, for example, a compressible foam.

In FIG. 13C, activation member 924 mechanically couples flexible concave member 920 to needles 930 attached to plate 932. As previously noted, mechanical coupling is performed via activation members 924 in this example, although in other embodiments, other mechanical coupling systems may be used. In this embodiment, as flexible concave member 920 moves from the first configuration to the second configuration, thereby pushing activation member 924 to the right in FIG. 13C, needles 930 are pushed downwardly (i.e., to the right in FIG. 13C) through applicator region 940, for insertion into the skin of a subject. After insertion, the activation member may be withdrawn due to mechanical action of spring 966 or another retraction mechanism, withdrawing plate 932 and needles 930 away from the skin (i.e., to the left in FIG. 13C), and thereby allowing blood to flow from the subject.

Flexible concave member 920 may be actuated using any suitable actuator, for example, buttons, dials, levers, sliders, or the like. In FIG. 13C, an example of an actuator having the form of a button that is pushed by a user is illustrated. In this figure, a button dome 960 is illustrated covering activation member 963. The button dome may be made out of any suitable material, e.g. a rubber or a polymer. By pushing button dome 960, activation member 963 is pushed into flexible concave member 920, thereby causing flexible concave member 920 to move from the first configuration to the second configuration, compressing spring 966 and pushing activation member 924 to the right to move plate 932 and needles 930 into the skin of a subject.

Blood released from the skin of a subject, after insertion of needles 930, may flow into applicator region 940 and into transfer channel 965. From transfer channel 965, the blood (or other received fluid) may flow into collection chamber 908, positioned in this example at the top of second module 910 in FIG. 13C covered by a cap 911. Cap 911 may subsequently be removed, e.g., for access of blood or other fluid within collection chamber 908. Transfer channel 968 fluidically connects collection chamber 908 to a region surrounding flexible concave member 920, which is in fluidic communication with vacuum chamber 907 through the piercing of pierceable surface 950 by piercing member 955 and piercing member 912, as noted above. In some cases, fluidic access may be facilitated by holes or other structures within flexible concave member 920, as is indicated by holes 921 in FIG. 13C. Accordingly, by piercing surface 950 using member 955, which is activated by the movement of flexible concave member 920 from a first configuration to a second configuration (e.g., upon pushing of button 960, as noted above), a fluidic pathway is created from vacuum chamber 907 through piercing member 912, pierceable surface 950, holes 921 in flexible concave surface 920, through channel 968 to collection chamber 908, and from collection chamber 908 through channel 965 to applicator region 940. Thus, the reduced pressure from vacuum chamber 907 is able to urge or move blood within applicator region 940 to move through channel 965 and into collection chamber 908. In some cases, transfer channel 968 may be separated from collection chamber 908, e.g., to prevent blood or other bodily fluids from flowing through the rest of second module 910, using an appropriate separator, such as a gas-permeable membrane, a hydrophilic membrane, a porous structure, or the like (not shown in FIG. 13C).

A similar configuration is illustrated in FIG. 13D, in accordance with another embodiment of the invention. Device 900 is positioned on the surface of skin 999, and like the device shown in FIG. 13C, includes first module 905, comprising a Vacutainer™ tube or a Vacuette™ tube, or other suitable vacuum chamber, and second module 910 containing various other components. In this example, however, first module 905 also contains collection chamber 908, and the routing in this device of blood or other bodily fluids received from the skin of a subject is somewhat different than the device shown in FIG. 13C. In this figure, collection chamber 908 may have a shape that fits substantially inside vacuum chamber 907, and in certain embodiments, collection chamber 908 may also be removable from vacuum chamber 907, for instance, for analysis of blood or other bodily fluids that are received from the subject. In other embodiments, however, collection chamber 908 may not be easily removable from vacuum chamber 907.

It should be noted that in FIG. 13D, a septum is not used to maintain vacuum within vacuum chamber 907, and instead, the opening of vacuum chamber 907 of first module 905 is sealed using a combination of collection chamber 908 and pierceable surface 950. Thus, first module 905 and second module 910 can be connected together to form device 900 without releasing the reduced pressure within vacuum chamber 907. Pierceable surface 950, in this embodiment, can be pierced by piercing member 955. Upon piercing of pierceable surface 950 by piercing member 955, a fluidic communication pathway is formed from vacuum chamber 907, through channel 967, to applicator region 940.

The device in FIG. 13D also requires a button to be pushed to activate the device. As previously discussed, other actuators may also be used to activate the device, including dials, levers, sliders, or the like. In this example, button dome 960 may be pushed to move activation member 963, causing it to push flexible concave member 920 from a first configuration to a second configuration. Flexible concave member 920 cannot adopt a stable configuration in a position midway between the first configuration and the second configuration. In FIG. 13D, flexible concave member 920 is illustrated in the first configuration. When flexible concave member 920 is moved from the first configuration to a second configuration, flexible concave member 920 moves activation member 924 (i.e., to the right in FIG. 13D), which causes movement of plate 932 and needles 930 immobilized with respect to plate 932. In other embodiments, other substance transfer components may be used instead of and/or in addition to needles 930. Needles 930 are then moved through applicator region 940 and can be inserted into the skin of a subject. Optionally, a retractor mechanism (not shown) may be used to move flexible concave member 920 away from the skin, and/or to return flexible concave member 920 from the second configuration to the first configuration, moving activator rods 924 away from the skin (i.e., to the left in FIG. 13D), withdrawing needles 930 from the skin of the subject.

The insertion of needles into the skin of the subject may cause blood or other bodily fluids to be released into applicator region 940. The fluids may then flow through channels 967 into collection chamber 908, for example, due to action of the vacuum from second chamber 907, which is released when activation member 963 pushes piercing member 955 downwardly into pierceable surface 950, thereby causing a fluidic connection with vacuum chamber 907 to be formed with applicator region 940. In some cases, collection chamber 908 may be separate from vacuum chamber 907

using a gas-permeable membrane, a hydrophilic membrane, a porous structure or the like (not shown).

A somewhat different configuration is illustrated in FIG. 13E. In this example, device 900 may be prepackaged with an internal vacuum, e.g., within chamber 971. The vacuum may initially be charged in the device using a septum (970) during manufacture. In addition, device 900 does not include separate modules in this example. The body 919 of device 900 may be formed out of any suitable material, for example, a polymer, rubber, or the like.

Vacuum or reduced pressure is introduced in the embodiment shown in FIG. 13E via port 970, which is located on one side of device 900. A vacuum may be present within first chamber 971 of the device, which is separated from collection chamber 908 of the device due to the presence of pierceable surface 950 dividing the two chambers. Pierceable surface 950 may be pierced using one or more piercing members 955 which are connected, either directly or indirectly, to a button on top of device 900 that can be pushed by a user to activate device 900. For example, the button may be connected to an actuator rod to cause piercing member 955 to pierce pierceable surface 950. Thus, when button 960 is pushed, piercing members 955 are inserted into pierceable surface 950 to create fluidic communication between first chamber 971 and collection chamber 908.

In addition, by pushing button 960, activation member 963 is also moved, which in turn pushes on activation plate 961 and flexible concave member 920, causing it to move from a first configuration to a second configuration. Flexible concave member 920 cannot adopt a stable configuration in a position midway between the first configuration and the second configuration, and thus moves into a second configuration, which pushes activation member 924 downwardly, which in turn causes plate 932 and needles 930 on plate 932 to also move downwardly through applicator region 940 and into the skin of a subject to which the device is applied. Optionally, device 900 may also include a retraction mechanism such as those previously discussed, although such a retraction mechanism is not illustrated in FIG. 13E.

Blood or other bodily fluids entering applicator region 940 can enter channel 967 under influence of the reduce pressure from the reduced pressure in chamber 971, which is in fluidic communication with collection chamber 908. Thus, blood or other bodily fluids may flow from applicator region 940, through channel 967, and into collection chamber 908 to be collected therein.

Also shown in FIG. 13E is an optional support tube 980, shown here in dashed outline. Optional support tube 980 may be used to protect applicator region 940 of the device prior to use, or simply to allow the device to be placed on a surface before or after use. In some cases, support tube 980 may be of a size similar to a Vacutainer™ tube or a Vacuette™ tube, which may be used to interface device 900 with commercially-available phlebotomy equipment able to process or handle Vacutainer™ or Vacuette™ tubes. In some embodiments, support tube 980 may be attached and cap 960 may be removed in order to allow a sample contained within the device to be processed on automated diagnostic equipment designed for use with Vacutainer™ and/or Vacuette™ tubes.

In some cases, the device may be constructed and arranged to interface with various test strips, cartridges, or cuvettes, including those that are commercially available. Non-limiting examples of such systems include i-STAT Cartridges, Hemocue cuvettes, Hemopoint cuvettes, Novobiomed test strips, Cholestech cartridges, or the like. For

example, in one set of embodiments, the device may be constructed and arranged such that blood or other bodily fluids received from the skin of a subject may be delivered to a cartridge or a cuvette, e.g., for subsequent insertion into a meter, e.g., into an i-STAT Cartridge. As another example, blood received from a subject as is discussed herein may be placed on a Hemocue or Hemopoint cuvette (e.g., manually, or by insertion of the cuvette into the device as is discussed herein, similar in manner to a test strip), or a test strip such as a test strip used in a Novobiomed handheld device.

Devices of the invention can provide significant advantage according to some embodiments. For example, triggering mechanisms able to move substance transfer components or skin insertion objects in short time periods, and/or at high velocities, and/or with high forces, and/or with high pressure, and/or drive relatively short skin insertion objects such as microinsertion objects or microneedles relatively deeply into the skin and/or through the skin, and/or any combination of the above can provide significant advantage. In some embodiments, these features can provide better control of substance delivery or receiving. Better mechanical stability can be provided in some cases by shorter skin insertion objects (e.g., bending and/or buckling can be avoided) and relatively shorter skin insertion objects, designed to be driven relatively completely (for example, through nearly all of their entire length) into the skin may offer better control of penetration in some embodiments. If better control of penetration can be achieved, better delivery or receiving can also be achieved in some cases, for example, resulting in less pain or essentially painless deployment.

Moreover, if skin insertion objects are used to deliver a substance such as a pharmaceutical composition into or through the skin, more precise delivery can be provided, according to certain embodiments. With better, precise control over depth of insertion of the skin insertion objects (e.g., by using devices designed to insert the skin insertion objects essentially fully), and/or the skin insertion objects contain and/or are coated with a pharmaceutical composition, then more control exists over the amount of pharmaceutical substance inserted into the skin by the skin insertion objects, in some embodiments. Furthermore, quick and/or high velocity, and/or high force and/or pressure application of skin insertion objects to the skin may in certain embodiments result in lower pain or painless deployment.

According to one set of embodiments, many devices as discussed herein use various techniques for delivering and/or receiving fluid, for example, in connection with fluid transporters, substance transfer components, skin insertion objects, microinsertion objects, or the like. For example, one or more needles and/or microneedles, a hygroscopic agent, a cutter or other piercing element, an electrically-assisted system, or the like may be used in conjunction with a snap dome or other device as described above. Additional examples of such techniques are described herein and/or in the applications incorporated herein. It is to be understood that, generally, fluids may be delivered and/or received in a variety of ways, and various systems and methods for delivering and/or receiving fluid from the skin are discussed below and/or in the applications incorporated herein. In some embodiments, for example, techniques for piercing or altering the surface of the skin to transport a fluid are discussed, for example, using a needle such as a hypodermic needle or microneedles, chemicals applied to the skin (e.g., penetration enhancers), jet injectors or other techniques such as those discussed below, etc.

As an example, in one embodiment, a needle such as a hypodermic needle can be used to deliver and/or receive fluid to or from the skin. Hypodermic needles are well-known to those of ordinary skill in the art, and can be obtained commercially with a range of needle gauges. For example, the needle may be in the 20-30 gauge range, or the needle may be 32 gauge, 33 gauge, 34 gauge, etc.

If needles are present, the needles may be of any suitable size and length, and may be solid or hollow. The needles may have any suitable cross-section (e.g., perpendicular to the direction of penetration), for example, circular, square, oval, elliptical, rectangular, rounded rectangle, triangular, polygonal, hexagonal, irregular, etc. For example, the needle may have a length of less than about 5 mm, less than about 4 mm, less than about 3 mm, less than about 2 mm, less than about 1 mm, less than about 800 micrometers, less than 600 micrometers, less than 500 micrometers, less than 400 micrometers, less than about 300 micrometers, less than about 200 micrometers, less than about 175 micrometers, less than about 150 micrometers, less than about 125 micrometers, less than about 100 micrometers, less than about 75 micrometers, less than about 50 micrometers, etc. The needle may also have a largest cross-sectional dimension of less than about 5 mm, less than about 4 mm, less than about 3 mm, less than about 2 mm, less than about 1 mm, less than about 800 micrometers, less than 600 micrometers, less than 500 micrometers, less than 400 micrometers, less than about 300 micrometers, less than about 200 micrometers, less than about 175 micrometers, less than about 150 micrometers, less than about 125 micrometers, less than about 100 micrometers, less than about 75 micrometers, less than about 50 micrometers, etc. For example, in one embodiment, the needle may have a rectangular cross section having dimensions of 175 micrometers by 50 micrometers. In one set of embodiments, the needle may have an aspect ratio of length to largest cross-sectional dimension of at least about 2:1, at least about 3:1, at least about 4:1, at least 5:1, at least about 7:1, at least about 10:1, at least about 15:1, at least about 20:1, at least about 25:1, at least about 30:1, etc.

In one embodiment, the needle is a microneedle. As an example, microneedles such as those disclosed in U.S. Pat. No. 6,334,856, issued Jan. 1, 2002, entitled "Microneedle Devices and Methods of Manufacture and Use Thereof," by Allen, et al., may be used to deliver and/or receive fluids or other materials to or from a subject. The microneedles may be hollow or solid, and may be formed from any suitable material, e.g., metals, ceramics, semiconductors, organics, polymers, and/or composites. Examples include, but are not limited to, pharmaceutical grade stainless steel, titanium, nickel, iron, gold, tin, chromium, copper, alloys of these or other metals, silicon, silicon dioxide, and polymers, including polymers of hydroxy acids such as lactic acid and glycolic acid polylactide, polyglycolide, polylactide-co-glycolide, and copolymers with polyethylene glycol, polyanhydrides, polyorthoesters, polyurethanes, polybutyric acid, polyvaleric acid, polylactide-co-caprolactone, polycarbonate, polymethacrylic acid, polyethylenevinyl acetate, polytetrafluoroethylene, polymethyl methacrylate, polyacrylic acid, or polyesters. In some cases, more than one microneedle may be used. For example, arrays of microneedles may be used, and the microneedles may be arranged in the array in any suitable configuration, e.g., periodic, random, etc. In some cases, the array may have 3 or more, 4 or more, 5 or more, 6 or more, 10 or more, 15 or more, 20 or more, 35 or more, 50 or more, 100 or more, or any other suitable number of microneedles. In some embodiments, the device may have at least 3 but no more than 5

needles or microneedles (or other substance transfer components), at least 6 but no more than 10 needles or microneedles, or at least 11 but no more than 20 needles or microneedles. Typically, a microneedle will have an average cross-sectional dimension (e.g., diameter) of less than about a micron. It should be understood that references to "needle" or "microneedle" as discussed herein are by way of example and ease of presentation only, and that in other embodiments, more than one needle and/or microneedle may be present in any of the descriptions herein.

Those of ordinary skill in the art can arrange needles relative to the skin for these purposes including, in one embodiment, introducing needles into the skin at an angle, relative to the skin's surface, other than 90°, i.e., to introduce a needle or needles into the skin in a slanting fashion so as to limit the depth of penetration. In another embodiment, however, the needles may enter the skin at approximately 90°.

In some cases, the microneedles may be present in an array selected such that the density of microneedles within the array is between about 0.5 needles/mm² and about 10 needles/mm², and in some cases, the density may be between about 0.6 needles/mm² and about 5 needles/mm², between about 0.8 needles/mm² and about 3 needles/mm², between about 1 needles/mm² and about 2.5 needles/mm², or the like. In some cases, the needles may be positioned within the array such that no two needles are closer than about 1 mm, about 0.9 mm, about 0.8 mm, about 0.7 mm, about 0.6 mm, about 0.5 mm, about 0.4 mm, about 0.3 mm, about 0.2 mm, about 0.1 mm, about 0.05 mm, about 0.03 mm, about 0.01 mm, etc.

In another set of embodiments, the microneedles may be chosen such that the area of the microneedles (determined by determining the area of penetration or perforation on the surface of the skin of the subject by the microneedles) allows for adequate flow of fluid to or from the subject. The microneedles may be chosen to have smaller or larger areas (or smaller or large diameters), so long as the area of contact for the microneedles to the skin is sufficient to allow adequate blood flow from the subject to the device. For example, in certain embodiments, the microneedles may be selected to have a combined skin-penetration area of at least about 500 nm², at least about 1,000 nm², at least about 3,000 nm², at least about 10,000 nm², at least about 30,000 nm², at least about 100,000 nm², at least about 300,000 nm², at least about 1 microns², at least about 3 microns², at least about 10 microns², at least about 30 microns², at least about 100 microns², at least about 300 microns², at least about 500 microns², at least about 1,000 microns², at least about 2,000 microns², at least about 2,500 microns², at least about 3,000 microns², at least about 5,000 microns², at least about 8,000 microns², at least about 10,000 microns², at least about 35,000 microns², at least about 100,000 microns², etc., depending on the application.

The microneedles may have any suitable length, and the length may be, in some cases, dependent on the application. For example, needles designed to only penetrate the epidermis may be shorter than needles designed to also penetrate into the dermis, or to extend beneath the dermis or the skin. In certain embodiments, the microneedles may have a maximum penetration into the skin of no more than about 3 mm, no more than about 2 mm, no more than about 1.75 mm, no more than about 1.5 mm, no more than about 1.25 mm, no more than about 1 mm, no more than about 900 micron, no more than about 800 microns, no more than about 750 microns, no more than about 600 microns, no more than about 500 microns, no more than about 400 microns, no

more than about 300 microns, no more than about 100 microns, no more than about 175 micrometers, no more than about 150 micrometers, no more than about 125 micrometers, no more than about 100 micrometers, no more than about 75 micrometers, no more than about 50 micrometers, etc. In certain embodiments, the needle may be selected so as to have a maximum penetration into the skin of at least about 50 micrometers, at least about 100 micrometers, at least about 300 micrometers, at least about 500 micrometers, at least about 1 mm, at least about 2 mm, at least about 3 mm, etc.

In one embodiment, the fluid is delivered and/or received manually, e.g., by manipulating a plunger on a syringe. In another embodiment, the fluid can be delivered and/or received from the skin mechanically or automatically, e.g., using a piston pump or the like. Fluid may also be received using vacuums such as those discussed herein. For example, vacuum may be applied to a conduit, such as a needle, in fluidic communication with a bodily fluid in order to draw up at least a portion of the fluid from the skin. In yet another embodiment, fluid is received using capillary action (e.g., using a microfluidic channel or hypodermic needle having a suitably narrow inner diameter). In still another embodiment, pressure may be applied to force fluid out of the needle.

As still another example, pressurized fluids may be used to deliver fluids or other materials into the skin, for instance, using a jet injector or a "hypospray." Typically, such devices produce a high-pressure "jet" of liquid or powder (e.g., a biocompatible liquid, such as saline) that drives material into the skin, and the depth of penetration may be controlled, for instance, by controlling the pressure of the jet. The pressure may come from any suitable source, e.g., a standard gas cylinder or a gas cartridge. A non-limiting example of such a device can be seen in U.S. Pat. No. 4,103,684, issued Aug. 1, 1978, entitled "Hydraulically Powered Hypodermic Injector with Adapters for Reducing and Increasing Fluid Injection Force," by Ismach.

In some embodiments, fluid may be received using a hygroscopic agent applied to the surface of the skin, or proximate the skin. For example, a device as described herein may contain a hygroscopic agent. In some cases, pressure may be applied to drive the hygroscopic agent into the skin. Hygroscopic agents typically are able to attract water from the surrounding environment, for instance, through absorption or adsorption. Non-limiting examples of hygroscopic agents include sugar, honey, glycerol, ethanol, methanol, sulfuric acid, methamphetamine, iodine, many chloride and hydroxide salts, and a variety of other substances. Other examples include, but are not limited to, zinc chloride, calcium chloride, potassium hydroxide, or sodium hydroxide. In some cases, a suitable hygroscopic agent may be chosen based on its physical or reactive properties, e.g., inertness or biocompatibility towards the skin of the subject, depending on the application.

In some embodiments, the device may comprise a cutter able to cut or pierce the surface of the skin. The cutter may comprise any mechanism able to create a path through which fluids may be delivered and/or received from the skin. For example, the cutter may comprise a hypodermic needle, a blade (e.g., a knife blade, a serrated blade, etc.), a piercing element (e.g., a lancet or a solid or a hollow needle), or the like, which can be applied to the skin to create a suitable conduit for the delivery and/or receiving of fluid from the skin. In one embodiment, a cutter is used to create such a pathway and removed, then fluid may be delivered and/or received via this pathway. In another embodiment, the cutter

remains in place within the skin, and fluid may be delivered and/or received through a conduit within the cutter.

In some embodiments, fluid may be received using an electric charge. For example, reverse iontophoresis may be used. Without wishing to be bound by any theory, reverse iontophoresis uses a small electric current to drive charged and highly polar compounds across the skin. Since the skin is negatively charged at physiologic pH, it acts as a permselective membrane to cations, and the passage of counterions across the skin induces an electroosmotic solvent flow that may carry neutral molecules in the anode-to-cathode direction. Components in the solvent flow may be analyzed as described elsewhere herein. In some instances, a reverse iontophoresis apparatus may comprise an anode cell and a cathode cell, each in contact with the skin. The anode cell may be filled, for example, with an aqueous buffer solution (i.e., aqueous Tris buffer) having a pH greater than 4 and an electrolyte (i.e. sodium chloride). The cathode cell can be filled with aqueous buffer. As one example, a first electrode (e.g., an anode) can be inserted into the anode cell and a second electrode (e.g., a cathode) can be inserted in the cathode cell. In some embodiments, the electrodes are not in direct contact with the skin.

A current may be applied to induce reverse iontophoresis, thereby receiving a fluid from the skin. The current applied may be, for example, greater than 0.01 mA, greater than 0.3 mA, greater than 0.1 mA, greater than 0.3 mA, greater than 0.5 mA, or greater than 1 mA. It should be understood that currents outside these ranges may be used as well. The current may be applied for a set period of time. For example, the current may be applied for greater than 30 seconds, greater than 1 minute, greater than 5 minutes, greater than 30 minutes, greater than 1 hour, greater than 2 hours, or greater than 5 hours. It should be understood that times outside these ranges may be used as well.

In one set of embodiments, the device may comprise an apparatus for ablating the skin. Without wishing to be bound by any theory, it is believed that ablation comprises removing a microscopic patch of stratum corneum (i.e., ablation forms a micropore), thus allowing access to bodily fluids. In some cases, thermal, radiofrequency, and/or laser energy may be used for ablation. In some instances, thermal ablation may be applied using a heating element. Radiofrequency ablation may be carried out using a frequency and energy capable of heating water and/or tissue. A laser may also be used to irradiate a location on the skin to remove a portion. In some embodiments, the heat may be applied in pulses such that a steep temperature gradient exists essentially perpendicular to the surface of the skin. For example, a temperature of at least 100° C., at least 200° C., at least 300° C., or at least 400° C. may be applied for less than 1 second, less than 0.1 seconds, less than 0.01 seconds, less than 0.005 seconds, or less than 0.001 seconds.

In some embodiments, the device may comprise a mechanism for taking a solid sample of tissue. For example, a solid tissue sample may be acquired by methods such as scraping the skin or cutting out a portion. Scraping may comprise a reciprocating action whereby an instrument is scraped along the surface of the skin in two or more directions. Scraping can also be accomplished by a rotating action, for example parallel to the surface of the skin and in one direction (i.e., with a roller drum) or parallel to the surface of the skin and in a circular manner (i.e., with a drilling instrument). A cutting mechanism may comprise a blade capable of making one or more incisions and a mechanism for removing a portion of tissue (i.e., by suction or mechanically picking up) or may use a pincer mechanism for cutting out a portion of

tissue. A cutting mechanism may also function by a coring action. For example, a hollow cylindrical device can be penetrated into the skin such that a cylindrical core of tissue may be removed. A solid sample may be analyzed directly or may be liquefied prior to analysis. Liquefaction can comprise treatment with organic solvents, enzymatic solutions, surfactants, etc.

The device may also contain, in some embodiments, a vacuum source. In some cases, the vacuum source is one that is self-contained within the device, i.e., the device need not be connected to an external vacuum source (e.g., a house vacuum) during use of the device to receive blood from the skin. For example, in one set of embodiments, the vacuum source may include a vacuum chamber having a pressure less than atmospheric pressure before blood (or other fluid) is received into the device, i.e., the vacuum chamber is at a “negative pressure” (that is, negative relative to atmospheric pressure) or a “vacuum pressure” (or just having a “vacuum”). For example, the vacuum in the vacuum chamber may be at least about 50 mmHg, at least about 100 mmHg, at least about 150 mmHg, at least about 200 mmHg, at least about 250 mmHg, at least about 300 mmHg, at least about 350 mmHg, at least about 400 mmHg, at least about 450 mmHg, at least about 500 mmHg, at least 550 mmHg, at least 600 mmHg, at least 650 mmHg, at least about 700 mmHg, or at least about 750 mmHg, i.e., below atmospheric pressure. Thus, the pressure within the vacuum is at a “reduced pressure” relative to atmospheric pressure, e.g., the vacuum chamber is a reduced pressure chamber. However, in other embodiments, it should be understood that other pressures may be used and/or that different methods may be used to produce other pressures (greater than or less than atmospheric pressure). As non-limiting examples, an external vacuum or a mechanical device may be used as the vacuum source; various additional examples are discussed in detail herein.

As a specific, non-limiting example, in one embodiment, a device may be used to receive fluid without an external power and/or a vacuum source. Examples of such devices include skin patches, strips, tapes, bandages, or the like. For instance, a skin patch may be contacted with the skin of a subject, and a vacuum created through a change in shape of a portion of the skin patch or other device (e.g., using a shape memory polymer), which may be used to deliver and/or receive fluid from the skin. As a specific example, a shape memory polymer may be shaped to be flat at a first temperature (e.g., room temperature) but curved at a second temperature (e.g., body temperature), and when applied to the skin, the shape memory polymer may alter from a flat shape to a curved shape, thereby creating a vacuum. As another example, a mechanical device may be used to create the vacuum. For example, springs, coils, expanding foam (e.g., from a compressed state), a shape memory polymer, shape memory metal, or the like may be stored in a compressed or wound released upon application to a subject, then released (e.g., unwinding, uncompressing, etc.), to mechanically create the vacuum.

Thus, in some cases, the device is “pre-packaged” with a suitable vacuum source (e.g., a pre-evacuated vacuum chamber); for instance, in one embodiment, the device may be applied to the skin and activated in some fashion to create and/or access the vacuum source. In yet another example, a chemical reaction may be used to create a vacuum, e.g., a reaction in which a gas is produced, which can be harnessed to provide the mechanical force to create a vacuum. In still another example, a component of the device may be able to create a vacuum in the absence of mechanical force. In

another example, the device may include a self-contained vacuum actuator, for example, chemical reactants, a deformable structure, a spring, a piston, etc.

In one set of embodiments, the device may be able to create a pressure differential (e.g. a vacuum). The pressure differential may be created by a pressure regulator. As used here, “pressure regulator” is a pressure controller component or system able to create a pressure differential between two or more locations. The pressure differential should be at least sufficient to urge or move the movement of fluid or other material in accordance with various embodiments of the invention as discussed herein, and the absolute pressures at the two or more locations are not important so long as their differential is appropriate, and their absolute values are reasonable for the purposes discussed herein. For example, the pressure regulator may produce a pressure higher than atmospheric pressure in one location, relative to a lower pressure at another location (atmospheric pressure or some other pressure), where the differential between the pressures is sufficient to urge or move fluid in accordance with the invention. In another example, the regulator or controller will involve a pressure lower than atmospheric pressure (a vacuum) in one location, and a higher pressure at another location(s) (atmospheric pressure or a different pressure) where the differential between the pressures is sufficient to urge or move fluid in accordance with the invention. Wherever “vacuum” or “pressure” is used herein, in association with a pressure regulator or pressure differential of the invention, it should be understood that the opposite can be implemented as well, as would be understood by those of ordinary skill in the art, i.e., a vacuum chamber can be replaced in many instances with a pressure chamber, for creating a pressure differential suitable for urging the movement of fluid or other material.

The pressure regulator may be an external source of vacuum (e.g. a lab, clinic, hospital, etc., house vacuum line or external vacuum pump), a mechanical device, a vacuum chamber, pre-packaged vacuum chamber, or the like. In some cases, vacuum may be created manually, e.g., by manipulating a syringe pump, a plunger, or the like, or the low pressure may be created mechanically or automatically, e.g., using a piston pump, a syringe, a bulb, a Venturi tube, manual (mouth) suction, etc., or the like. Vacuum chambers can be used in some embodiments, where the device contains, e.g., regions in which a vacuum exists or can be created (e.g. a variable volume chamber, a change in volume of which will affect vacuum or pressure). A vacuum chamber can include pre-evacuated (i.e., pre-packaged) chambers or regions, and/or self-contained actuators.

A “self-contained” vacuum (or pressure) regulator means one that is associated with (e.g., on or within) the device, e.g. one that defines an integral part of the device, or is a separate component constructed and arranged to be specifically connectable to the particular device to form a pressure differential (i.e., not a connection to an external source of vacuum such as a hospital’s, clinic’s, or lab’s house vacuum line, or a vacuum pump suitable for very general use). In some embodiments, the self-contained vacuum source may be actuated in some fashion to create a vacuum within the device. For instance, the self-contained vacuum source may include a piston, a syringe, a mechanical device such as a vacuum pump able to create a vacuum within the device, and/or chemicals or other reactants that can react to increase or decrease pressure which, with the assistance of mechanical or other means driven by the reaction, can form a pressure differential associated with a pressure regulator. Chemical reaction can also drive mechanical actuation with

or without a change in pressure based on the chemical reaction itself. A self-contained vacuum source can also include an expandable foam, a shape memory material, or the like.

One category of self-contained vacuum or pressure regulators of the invention includes self-contained assisted regulators. These are regulators that, upon actuation (e.g., the push of a button, or automatic actuation upon, e.g., removal from a package or urging a device against the skin), a vacuum or pressure associated with the device is formed where the force that pressurizes or evacuates a chamber is not the same as the actuation force. Examples of self-contained assisted regulators include chambers evacuated by expansion driven by a spring triggered by actuation, release of a shape-memory material or expandable material upon actuation, initiation of a chemical reaction upon actuation, or the like.

Another category of self-contained vacuum or pressure regulators of the invention are devices that are not necessarily pre-packaged with pressure or vacuum, but which can be pressurized or evacuated, e.g. by a subject, health care professional at a hospital or clinic prior to use, e.g. by connecting a chamber of the device to a source of vacuum or pressure. For example, the subject, or another person, may actuate the device to create a pressure or vacuum within the device, for example, immediately prior to use of the device.

The vacuum or pressure regulator may be a “pre-packaged” pressure or vacuum chamber in the device when used (i.e., the device can be provided ready for use by a subject or practitioner with an evacuated region on or in the device, without the need for any actuation to form the initial vacuum). A pre-packaged pressure or vacuum chamber regulator can, e.g., be a region evacuated (relative to atmospheric pressure) upon manufacture and/or at some point prior to the point at which it is used by a subject or practitioner. For example, a chamber is evacuated upon manufacture, or after manufacture but before delivery of the device to the user, e.g. the clinician or subject. For instance, in some embodiments, the device contains a vacuum chamber having a vacuum of at least about 50 mmHg, at least about 100 mmHg, at least about 150 mmHg, at least about 200 mmHg, at least about 250 mmHg, at least about 300 mmHg, at least about 350 mmHg, at least about 400 mmHg, at least about 450 mmHg, at least about 500 mmHg, at least about 550 mmHg, at least about 600 mmHg, at least about 650 mmHg, at least about 700 mmHg, or at least about 750 mmHg below atmospheric pressure.

In one set of embodiments, a device of the present invention may not have an external power and/or a vacuum source. In some cases, the device is “pre-loaded” with a suitable vacuum source; for instance, in one embodiment, the device may be applied to the skin and activated in some fashion to create and/or access the vacuum source. As one example, a device of the present invention may be contacted with the skin of a subject, and a vacuum created through a change in shape of a portion of the device (e.g., using a shape memory polymer), or the device may contain one or more sealed, self-contained vacuum chambers, where a seal is punctured in some manner to create a vacuum. For instance, upon puncturing the seal, a vacuum chamber may be in fluidic communication with a needle, which can be used to move the skin towards the device, receive fluid from the skin, or the like.

As another example, a shape memory polymer may be shaped to be flat at a first temperature (e.g., room temperature) but curved at a second temperature (e.g., body tem-

perature), and when applied to the skin, the shape memory polymer may alter from a flat shape to a curved shape, thereby creating a vacuum. As yet another example, a mechanical device may be used to create the vacuum. For example, springs, coils, expanding foam (e.g., from a compressed state), a shape memory polymer, shape memory metal, or the like may be stored in a compressed or wound released upon application to a subject, then released (e.g., unwinding, uncompressing, etc.), to mechanically create the vacuum. Non-limiting examples of shape-memory polymers and metals include Nitinol, compositions of oligo(epsilon-caprolactone)diol and crystallizable oligo(rho-dioxanone) diol, or compositions of oligo(epsilon-caprolactone)dimethylacrylate and n-butyl acrylate.

In yet another example, a chemical reaction may be used to create a vacuum, e.g., a reaction in which a gas is produced, which can be harnessed to provide the mechanical force to create a vacuum. In some embodiments, the device may be used to create a vacuum automatically, once activated, without any external control by a user.

In one set of embodiments, the device contains a vacuum chamber that is also used as a storage chamber to receive blood or other fluid received from the subject into the device. For instance, blood received from a subject through or via the substance transfer component may enter the vacuum chamber due to its negative pressure (i.e., because the chamber has an internal pressure less than atmospheric pressure), and optionally stored in the vacuum chamber for later use. A non-limiting example is illustrated in FIG. 3. In this figure, device 600 contains vacuum chamber 610, which is connected to substance transfer component 620 (which may be, e.g., one or more microneedles). Upon activation of vacuum chamber 610 (e.g., using actuator 660, as discussed below), vacuum chamber 610 may be put into fluidic communication with substance transfer component 620. Substance transfer component 620 may accordingly cause negative pressure to be applied to the skin of the subject, for instance, due to the internal pressure within vacuum chamber 610. Fluid (e.g., blood) exiting the skin via substance transfer component 620 may accordingly be drawn into the device and into vacuum chamber 610, e.g., through conduit 612. The fluid collected by the device can then be analyzed within the device or removed from the device for analysis, storage, etc.

In another set of embodiments, however, the device may include separate vacuum chambers and storage chambers (e.g., chambers to store fluid such as blood from the subject). The vacuum chamber and storage chambers may be in fluid communication, and may have any suitable arrangement. In some embodiments, the vacuum from the vacuum chamber may be used, at least in part, to receive fluid from the skin, which is then directed into a storage chamber, e.g., for later analysis or use, for example, as discussed below. As an example, blood may be received into the device, flowing towards a vacuum chamber, but the fluid may be prevented from entering the vacuum chamber. For instance, in certain embodiments, a material permeable to gas but not to a liquid such as blood may be used. For example, the material may be a membrane such as a hydrophilic or hydrophobic membrane having a suitable porosity, a porous structure, a porous ceramic frit, a dissolvable interface (e.g., formed from a salt or a polymer, etc.), or the like.

One non-limiting example is illustrated in FIG. 4. In this figure, device 600 contains vacuum chamber 610 and storage chamber 615. Vacuum chamber 610 can be put in fluidic communication with storage chamber 615 via conduit 612, which contains material 614. Material 614 may be any

material permeable to gas but not to a liquid in this example, e.g., material **614** may be a membrane such as a hydrophilic membrane or a hydrophobic membrane that has a porosity that allows gas exchange to occur but does not allow the passage of blood from the subject. When device **600** is actuated using actuator **660**, blood (or other fluid) flows through substance transfer component **620** via conduit **661** into collection chamber **615** because of the internal vacuum pressure from vacuum chamber **610**, which is not completely impeded by material **614** since it is permeable to gases. However, because of material **614**, blood (or other suitable bodily fluid) is prevented from entering vacuum chamber **610**, and instead remains in storage chamber **615**, e.g., for later analysis or use.

In some embodiments, the flow of blood (or other fluid) into the storage chamber may be controlled using a flow controller. The flow controller may be manually and/or automatically controlled to control the flow of blood. The flow controller may activate or deactivate when a certain amount or volume of fluid has entered the storage chamber in certain cases. For instance, the flow controller may stop blood flow after a predetermined amount or volume of blood has entered the storage chamber, and/or the flow controller may be able to control the internal pressure of the storage chamber, e.g., to a specific level, such as a predetermined level. Examples of suitable flow controllers for the device include, but are not limited to, a membrane, a valve, a dissolvable interface, a gate, or the like.

One non-limiting example of a flow controller is now illustrated with reference to FIG. 5. In this example figure, device **600** includes a vacuum chamber **610** and a storage chamber **615**. Fluid entering device **600** via substance transfer component **620** is prevented from entering storage chamber **615** due to flow controller **645** present within conduit **611**. However, under suitable conditions, flow controller **645** may be opened, thereby allowing at least some fluid to enter storage chamber **615**. In some cases, for instance, storage chamber **615** also contains at least a partial vacuum, although this vacuum may be greater or less than the pressure within chamber **610**. In other embodiments, flow controller **645** may initially be open, or be externally controllable (e.g., via an actuator), or the like. In some cases, the flow controller may control the flow of fluid into the device such that, after collection, at least some vacuum is still present in the device.

Thus, in some cases, the device may be constructed and arranged to reproducibly obtain from the subject a controlled amount of fluid, e.g., a controlled amount or volume of blood. The amount of fluid reproducibly obtained from the subject may be controlled, for example, using flow controllers, materials permeable to gas but not to liquids, membranes, valves, pumps, gates, microfluidic systems, or the like, as discussed herein. In particular, it should be noted that the volume of blood or other fluid obtained from the subject need not be strictly a function of the initial vacuum pressure or volume within the device. For example, a flow controller may initially be opened (e.g., manually, automatically, electronically, etc.) to allow fluid to begin entering the device; and when a predetermined condition is reached (e.g., when a certain volume or amount of blood has entered the device), the flow controller may be closed at that point, even if some vacuum pressure remains within the device. In some cases, this control of fluid allows the amount of fluid reproducibly obtained from the subject to be controlled to a great extent. For example, in one set of embodiments, the amount of fluid received from the subject may be controlled to be less than about 1 ml, may be less than about 300 microliters, less than

about 100 microliters, less than about 30 microliters, less than about 10 microliters, less than about 3 microliters, less than about 1 microliter, etc.

Further examples of various embodiments of the invention are illustrated in FIGS. 6 and 8. In FIG. 6, device **500** is illustrated. In this example, device **500** includes a deployment actuator **501**, an adhesive **502** for adhesion of the device to the skin, and a substance transfer component system **503**. In this figure, substance transfer component system **503** includes a plurality of microneedles **505**, although other substance transfer components as discussed herein may also be used. Microneedles **505** are contained within recess **508**. Also shown in FIG. 6 is vacuum chamber **513** which, in this example, is self-contained within device **500**. Vacuum chamber **513** is in fluidic communication with recess **508** via channel **511**, for example, as controlled by a controller or an actuator. Actuator **560** is shown at the top of device **500**. Actuator **560** may be, for example, a button, switch, slider, dial, etc. and may cause microneedles **505** to move towards the skin when the device is placed on the skin. For example, the microneedles may be moved mechanically (e.g., compression spring, Belleville spring, etc.), electrically (e.g., with the aid of a servo, which may be computer-controlled), pneumatically, etc. In some cases, actuator **560** (or another actuator) may be used to cause the microneedles to be withdrawn from the skin, and/or the microneedles may be withdrawn automatically after delivering and/or receiving fluid from the subject, e.g., without any intervention by the subject, or by another person. Non-limiting examples of such techniques are discussed in detail below.

Another example is illustrated with reference to FIG. 8. In this figure, device **500** includes a deployment actuator **501**, an adhesive **502** for adhesion of the device to the skin, and a substance transfer component system **503**. In FIG. 8, substance transfer component system **503** includes a plurality of microneedles **505** within recess **508**, although other substance transfer components as discussed herein may also be used. Actuator **560** is shown at the top of device **500**. Actuator **560** may be, for example, a button, switch, slider, dial, etc. and may cause microneedles **505** to move towards the skin when the device is placed on the skin. For example, the microneedles may be moved mechanically (e.g., compression spring, Belleville spring, etc.), electrically (e.g., with the aid of a servo, which may be computer-controlled), pneumatically, etc., e.g., via component **584** (e.g., a piston, a screw, a mechanical linkage, etc.). In some cases, actuator **560** may also be able to withdraw the microneedles from the skin after use, e.g., after a fluid is delivered and/or received from the skin.

Chamber **513**, in this figure, is a self-contained vacuum chamber. Vacuum chamber **513** is in fluidic communication with recess **508** via channel **511**, for example, as controlled by a controller or an actuator. Also illustrated in FIG. 8 is fluid reservoir **540**, which may contain a fluid such as an anticoagulant. The fluid may be introduced into blood or other fluid received from the skin. Controlling fluid flow from fluid reservoir may be one or more suitable fluidic control elements, e.g., pumps, nozzles, valves, or the like, for example, pump **541** in FIG. 8.

In certain embodiments, the substance transfer component may be fastened on a deployment actuator. In some cases, the deployment actuator can bring the substance transfer component to the skin, and in certain instances, insert the substance transfer component into the skin. For example, the substance transfer component can be moved mechanically, electrically (e.g., with the aid of a servo, which may be computer-controlled), pneumatically, via a piston, a screw, a

mechanical linkage, or the like. In one set of embodiments, the deployment actuator can insert the substance transfer component into the skin at a speed of at least about 0.1 cm/s, at least about 0.3 cm/s, about 1 cm/s, at least about 3 cm/s, at least about 10 cm/s, at least about 30 cm/s, at least about 1 m/s, at least about 2 m/s, at least about 3 m/s, at least about 4 m/s, at least about 5 m/s, at least about 6 m/s, at least about 7 m/s, at least about 8 m/s, at least about 9 m/s, at least about 10 m/s, at least about 12 m/s, etc., at the point where the substance transfer component initially contacts the skin. Without wishing to be bound by any theory, it is believed that relatively faster insertion speeds may increase the ability of the substance transfer component to penetrate the skin (without deforming the skin or causing the skin to move in response), and/or decrease the amount of pain felt by the application of the substance transfer component to the skin. Any suitable method of controlling the penetration speed into the skin may be used, include those described herein.

As mentioned, in some embodiments, blood or other bodily fluids may be stored within the device for later use and/or analysis. For example, the device may be attached to a suitable external apparatus able to analyze a portion of the device (e.g., containing the fluid), and/or the external apparatus may remove at least some of the blood or other fluid from the device for subsequent analysis and/or storage. In some cases, however, at least some analysis may be performed by the device itself, e.g., using one or more sensors, etc., contained within the device.

For example, as discussed in detail below, in some cases, a storage chamber may contain a reagent or a reaction entity able to react with an analyte suspected of being present in the blood (or other fluid) entering the device, and in some cases, the reaction entity may be determined to determine the analyte. In some cases, the determination may be made externally of the device, e.g., by determining a color change or a change in fluorescence, etc. The determination may be made by a person, or by an external apparatus able to analyze at least a portion of the device. In some cases, the determination may be made without removing blood from the device, e.g., from the storage chamber. (In other cases, however, blood or other fluid may first be removed from the device before being analyzed.) For example, the device may include one or more sensors (e.g., ion sensors such as K^+ sensors, colorimetric sensors, fluorescence sensors, etc.), and/or contain "windows" that allow light to penetrate the device. The windows may be formed of glass, plastic, etc., and may be selected to be at least partially transparent to one or a range of suitable wavelengths, depending on the analyte or condition to be determined. As a specific example, the entire device (or a portion thereof) may be mounted in an external apparatus, and light from the external apparatus may pass through or otherwise interact with at least a portion of the device (e.g., be reflected or refracted via the device) to determine the analyte and/or the reaction entity.

In one aspect, the device may be interfaced with an external apparatus able to determine an analyte contained within a fluid in the device, for example within a storage chamber as discussed herein. For example, the device may be mounted on an external holder, the device may include a port for transporting fluid out of the device, the device may include a window for interrogating a fluid contained within the device, or the like. Examples may be seen in a U.S. provisional patent application filed on even date herewith, entitled "Sampling Device Interfaces," incorporated herein by reference in its entirety.

Thus, the device, in certain embodiments, may contain a portion able to determine a fluid removed from the skin. For

example, a portion of the device may contain a sensor, or reagents able to interact with an analyte contained or suspected to be present within the received fluid from the subject, for example, a marker for a disease state. The sensor may be embedded within or integrally connected to the device, or positioned remotely but with physical, electrical, and/or optical connection with the device so as to be able to sense a chamber within or fluid from the device. For example, the sensor may be in fluidic communication with fluid received from a subject, directly, via a microfluidic channel, an analytical chamber, etc. The sensor may be able to sense an analyte, e.g., one that is suspected of being in a fluid received from a subject. For example, a sensor may be free of any physical connection with the device, but may be positioned so as to detect the results of interaction of electromagnetic radiation, such as infrared, ultraviolet, or visible light, which has been directed toward a portion of the device, e.g., a chamber within the device. As another example, a sensor may be positioned on or within the device, and may sense activity in a chamber by being connected optically to the chamber. Sensing communication can also be provided where the chamber is in communication with a sensor fluidly, optically or visually, thermally, pneumatically, electronically, or the like, so as to be able to sense a condition of the chamber. As one example, the sensor may be positioned downstream of a chamber, within a channel such a microfluidic channel, on an external apparatus, or the like.

Thus, the invention provides, in certain embodiments, sensors able to determine an analyte. Such determination may occur within the skin, and/or externally of the subject, e.g., within a device on the surface of the skin, depending on the embodiment. "Determine," in this context, generally refers to the analysis of a species, for example, quantitatively or qualitatively, and/or the detection of the presence or absence of the species. "Determining" may also refer to the analysis of an interaction between two or more species, for example, quantitatively or qualitatively, and/or by detecting the presence or absence of the interaction, e.g. determination of the binding between two species. The species may be, for example, a bodily fluid and/or an analyte suspected of being present in the bodily fluid. "Determining" also means detecting or quantifying interaction between species.

Non-limiting examples of sensors include dye-based detection systems, affinity-based detection systems, micro-fabricated gravimetric analyzers, CCD cameras, optical detectors, optical microscopy systems, electrical systems, thermocouples and thermistors, pressure sensors, etc. Those of ordinary skill in the art will be able to identify other suitable sensors. The sensor can include a colorimetric detection system in some cases, which may be external to the device, or microfabricated into the device in certain cases. As an example of a colorimetric detection system, if a dye or a fluorescent entity is used (e.g. in a particle), the colorimetric detection system may be able to detect a change or shift in the frequency and/or intensity of the dye or fluorescent entity.

Examples of sensors include, but are not limited to, pH sensors, optical sensors, ion sensors, colorimetric sensors, a sensor able to detect the concentration of a substance, or the like, e.g., as discussed herein. For instance, in one set of embodiments, the device may include an ion selective electrode. The ion selective electrode may be able to determine a specific ion and/or ions such as K^+ , H^+ , Na^+ , Ag^+ , Pb^{2+} , Cd^{2+} , or the like. Various ion selective electrodes can be obtained commercially. As a non-limiting example, a potassium-selective electrode may include an ion exchange

resin membrane, using valinomycin, a potassium channel, as the ion carrier in the membrane to provide potassium specificity.

Examples of analytes that the sensor may be used to determine include, but are not limited to, pH or metal ions, proteins, nucleic acids (e.g. DNA, RNA, etc.), drugs, sugars (e.g., glucose), hormones (e.g., estradiol, estrone, progesterone, progesterin, testosterone, androstenedione, etc.), carbohydrates, or other analytes of interest. Other conditions that can be determined can include pH changes, which may indicate disease, yeast infection, periodontal disease at a mucosal surface, oxygen or carbon monoxide levels which indicate lung dysfunction, and drug levels, e.g., legal prescription levels of drugs such as coumadin, other drugs such as nicotine, or illegal such as cocaine. Further examples of analytes include those indicative of disease, such as cancer specific markers such as CEA and PSA, viral and bacterial antigens, and autoimmune indicators such as antibodies to double stranded DNA, indicative of Lupus. Still other conditions include exposure to elevated carbon monoxide, which could be from an external source or due to sleep apnea, too much heat (important in the case of babies whose internal temperature controls are not fully self-regulating) or from fever. Still other potentially suitable analytes include various pathogens such as bacteria or viruses, and/or markers produced by such pathogens.

As additional non-limiting examples, the sensor may contain an antibody able to interact with a marker for a disease state, an enzyme such as glucose oxidase or glucose 1-dehydrogenase able to detect glucose, or the like. The analyte may be determined quantitatively or qualitatively, and/or the presence or absence of the analyte within the received fluid may be determined in some cases. Those of ordinary skill in the art will be aware of many suitable commercially-available sensors, and the specific sensor used may depend on the particular analyte being sensed. For instance, various non-limiting examples of sensor techniques include pressure or temperature measurements, spectroscopy such as infrared, absorption, fluorescence, UV/visible, FTIR ("Fourier Transform Infrared Spectroscopy"), or Raman; piezoelectric measurements; immunoassays; electrical measurements, electrochemical measurements (e.g., ion-specific electrodes); magnetic measurements, optical measurements such as optical density measurements; circular dichroism; light scattering measurements such as quasi-electric light scattering; polarimetry; refractometry; chemical indicators such as dyes; or turbidity measurements, including nephelometry.

In one set of embodiments, a sensor in the device may be used to determine a condition of the blood present within the device. For example, the sensor may indicate the condition of analytes commonly found within the blood, for example, O₂, K⁺, hemoglobin, Na⁺, glucose, or the like. As a specific non-limiting example, in some embodiments, the sensor may determine the degree of hemolysis within blood contained within the device. Without wishing to be bound by any theory, it is believed that in some cases, hemolysis of red blood cells may cause the release of potassium ions and/or free hemoglobin into the blood. By determining the levels of potassium ions, and/or hemoglobin (e.g., by subjecting the device and/or the blood to separate cells from plasma, then determining hemoglobin in the plasma using a suitable colorimetric assay), the amount of blood lysis or "stress" experienced by the blood contained within the device may be determined. Accordingly, in one set of embodiments, the device may indicate the usability of the blood (or other fluid) contained within the device, e.g., by indicating the degree of

stress or the amount of blood lysis. Other examples of devices suitable for indicating the usability of the blood (or other fluid) contained within the device are also discussed herein (e.g., by indicating the amount of time blood has been contained in the device, the temperature history of the device, etc.).

For instance, fluids received from the subject will often contain various analytes within the body that are important for diagnostic purposes, for example, markers for various disease states, such as glucose (e.g., for diabetics); other example analytes include ions such as sodium, potassium, chloride, calcium, magnesium, and/or bicarbonate (e.g., to determine dehydration); gases such as carbon dioxide or oxygen; H⁺ (i.e., pH); metabolites such as urea, blood urea nitrogen or creatinine; hormones such as estradiol, estrone, progesterone, progesterin, testosterone, androstenedione, etc. (e.g., to determine pregnancy, illicit drug use, or the like); or cholesterol. Other examples include insulin, or hormone levels. As discussed herein, certain embodiments of the present invention are generally directed at methods for receiving fluids from the body, and optionally determining one or more analytes within the received fluid. Thus, in some embodiments, at least a portion of the fluid may be stored, and/or analyzed to determine one or more analytes, e.g., a marker for a disease state, or the like. The fluid received from the skin may be subjected to such uses, and/or one or more materials previously delivered to the skin may be subject to such uses.

Still other potentially suitable analytes include various pathogens such as bacteria or viruses, and/or markers produced by such pathogens. Thus, in certain embodiments of the invention, as discussed below, one or more analytes within the pooled region of fluid may be determined in some fashion, which may be useful in determining a past, present and/or future condition of the subject.

In some embodiments, the device may be connected to an external apparatus for determining at least a portion of the device, a fluid removed from the device, an analyte suspected of being present within the fluid, or the like. For example, the device may be connected to an external analytical apparatus, and fluid removed from the device for later analysis, or the fluid may be analyzed within the device in situ, e.g., by adding one or more reaction entities to the device, for instance, to a storage chamber, or to analytical chamber within the device. For example, in one embodiment, the external apparatus may have a port or other suitable surface for mating with a port or other suitable surface on the device, and blood or other fluid can be removed from the device using any suitable technique, e.g., using vacuum or pressure, etc. The blood may be removed by the external apparatus, and optionally, stored and/or analyzed in some fashion. For example, in one set of embodiments, the device may include an exit port for removing a fluid from the device (e.g., blood). In some embodiments, fluid contained within a storage chamber in the device may be removed from the device, and stored for later use or analyzed outside of the device. In some cases, the exit port may be separate from the substance transfer component. An example is shown with exit port **670** and substance transfer component **620** in device **600** in FIG. 7. As shown in this figure, the exit port can be in fluidic communication with vacuum chamber **610**, which can also serve as a fluid reservoir in some cases. Other methods for removing blood or other fluids from the device include, but are not limited to, removal using a vacuum line, a pipette, extraction through a septum instead of an exit port, or the like. In some cases, the device may also be positioned in a

centrifuge and subjected to various g forces (e.g., to a centripetal force of at least 50 g), e.g., to cause at separation of cells or other substances within a fluid within the device to occur.

In one set of embodiments, the device may include an anticoagulant or a stabilizing agent for stabilizing the fluid received from the skin. The anticoagulant may be located in a vacuum chamber and/or a collection chamber, depending on the application. For example, the fluid may be stored within the device for a certain period of time, and/or the device (or a portion thereof) may be moved or shipped to another location for analysis or later use. For instance, a device may contain anticoagulant or a stabilizing agent in a storage chamber. In some cases, more than one anticoagulant may be used, e.g., in the same storage chamber, or in more than one storage chamber.

As a specific non-limiting example, an anticoagulant may be used for blood received from the skin. Examples of anticoagulants include, but are not limited to, heparin, citrate, thrombin, oxalate, ethylenediaminetetraacetic acid (EDTA), sodium polyanethol sulfonate, acid citrate dextrose. Other agents may be used in conjunction or instead of anticoagulants, for example, stabilizing agents such as solvents, diluents, buffers, chelating agents, antioxidants, binding agents, preservatives, antimicrobials, or the like. Examples of preservatives include, for example, benzalkonium chloride, chlorobutanol, parabens, or thimerosal. Non-limiting examples of antioxidants include ascorbic acid, glutathione, lipoic acid, uric acid, carotenes, alpha-tocopherol, ubiquinol, or enzymes such as catalase, superoxide dismutase, or peroxidases. Examples of microbials include, but are not limited to, ethanol or isopropyl alcohol, azides, or the like. Examples of chelating agents include, but are not limited to, ethylene glycol tetraacetic acid or ethylenediaminetetraacetic acid. Examples of buffers include phosphate buffers such as those known to ordinary skill in the art.

In one set of embodiments, at least a portion of the device may be colored to indicate the anticoagulant(s) contained within the device. In some cases, the colors used may be identical or equivalent to that commercially used for Vacutainers™, Vacuettes™, or other commercially-available phlebotomy equipment. For example, lavender and/or purple may indicate ethylenediaminetetraacetic acid, light blue may indicate citrate, dark blue may indicate ethylenediaminetetraacetic acid, green may indicate heparin, gray may indicate a fluoride and/or an oxalate, orange may indicate a thrombin, yellow may indicate sodium polyanethol sulfonate and/or acid citrate dextrose, black may indicate citrate, brown may indicate heparin, etc. In other embodiments, however, other coloring systems may be used.

Other coloring systems may be used in other embodiments of the invention, not necessarily indicative of anticoagulants. For example, in one set of embodiments, the device carries a color indicative of a recommended bodily use site for the device, e.g., a first color indicative of a device suitable for placement on the back, a second color indicative of a device suitable for placement on a leg, a third color indicative of a device suitable for placement on the arm, etc.

As mentioned, in one set of embodiments, a device of the invention as discussed herein may be shipped to another location for analysis. In some cases, the device may include an anticoagulant or a stabilizing agent contained within the device, e.g., within a storage chamber for the fluid. Thus, for example, fluid such as blood received from the skin may be delivered to a chamber (e.g., a storage chamber) within the device, then the device, or a portion of the device (e.g., a

module) may be shipped to another location for analysis. Any form of shipping may be used, e.g., via mail.

Non-limiting examples of various devices of the invention are shown in FIG. 1. In FIG. 1A, device 90 is used for receiving a fluid from a subject when the device is placed on the skin of a subject. Device 90 includes sensor 95 and substance transfer component 92, e.g., a needle, a microneedle, etc., as discussed herein. In fluidic communication with substance transfer component 92 via fluidic channel 99 is sensing chamber 97. In one embodiment, sensing chamber 97 may contain agents such as particles, enzymes, dyes, etc., for analyzing bodily fluids, such as interstitial fluid or blood. In some cases, fluid may be received using substance transfer component 92 by a vacuum, for example, a self-contained vacuum contained within device 90. Optionally, device 90 also contains a display 94 and associated electronics 93, batteries or other power supplies, etc., which may be used to display sensor readings obtained via sensor 95. In addition, device 90 may also optionally contain memory 98, transmitters for transmitting a signal indicative of sensor 95 to a receiver, etc.

In the example shown in FIG. 1A, device 90 may contain a vacuum source (not shown) that is self-contained within device 90, although in other embodiments, the vacuum source may be external to device 90. (In still other instances, other systems may be used to deliver and/or receive fluid from the skin, as is discussed herein.) In one embodiment, after being placed on the skin of a subject, the skin may be drawn upward into a recess containing substance transfer component 92, for example, upon exposure to the vacuum source. Access to the vacuum source may be controlled by any suitable method, e.g., by piercing a seal or a septum; by opening a valve or moving a gate, etc. For instance, upon activation of device 90, e.g., by the subject, remotely, automatically, etc., the vacuum source may be put into fluidic communication with the recess such that skin is drawn into the recess containing substance transfer component 92 due to the vacuum. Skin drawn into the recess may come into contact with substance transfer component 92 (e.g., solid or hollow needles), which may, in some cases, pierce the skin and allow a fluid to be delivered and/or received from the skin. In another embodiment, substance transfer component 92 may be actuated and moved downward to come into contact with the skin, and optionally retracted after use.

Another non-limiting example of a device is shown in FIG. 1B. This figure illustrates a device useful for delivering a fluid to the subject. Device 90 in this figure includes substance transfer component 92, e.g., a needle, a microneedle, etc., as discussed herein. In fluidic communication with substance transfer component 92 via fluidic channel 99 is chamber 97, which may contain a drug or other agent to be delivered to the subject. In some cases, fluid may be delivered with a pressure controller, and/or received using substance transfer component 92 by a vacuum, for example, a self-contained vacuum contained within device 90. For instance, upon creating a vacuum, skin may be drawn up towards substance transfer component 92, and substance transfer component 92 may pierce the skin. Fluid from chamber 97 can then be delivered into the skin through fluid channel 99 and substance transfer component 92. Optionally, device 90 also contains a display 94 and associated electronics 93, batteries or other power supplies, etc., which may be used control delivery of fluid to the skin. In addition, device 90 may also optionally contain memory 98, transmitters for transmitting a signal indicative of device 90 or fluid delivery to a receiver, etc.

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Yet another non-limiting example of a device of the invention is shown in FIG. 2. FIG. 2A illustrates a view of the device (with the cover removed), while FIG. 2B schematically illustrates the device in cross-section. In FIG. 2B, device 50 includes a needle 52 contained within a recess 55. Needle 52 may be solid or hollow, depending on the embodiment. Device 50 also includes a self-contained vacuum chamber 60, which wraps around the central portion of the device where needle 52 and recess 55 are located. A channel 62 connects vacuum chamber 60 with recess 55, separated by a foil or a membrane 67. Also shown in device 50 is button 58. When pushed, button 58 breaks foil 67, thereby connecting vacuum chamber 50 with recess 55, creating a vacuum in recess 55. The vacuum may be used, for example, to draw skin into recess 55, preferably such that it contacts needle 52 and pierces the surface, thereby gaining access to an internal fluid. The fluid may be controlled, for example, by controlling the size of needle 52, and thereby the depth of penetration. For example, the penetration may be limited to the epidermis, e.g., to collect interstitial fluid, or to the dermis, e.g., to collect blood. In some cases, the vacuum may also be used to at least partially secure device 50 on the surface of the skin, and/or to assist in the receiving of fluid from the skin. For instance, fluid may flow into channel 62 under action of the vacuum, and optionally to sensor 61, e.g., for detection of an analyte contained within the fluid. For instance, sensor 61 may produce a color change if an analyte is present, or otherwise produce a detectable signal.

Other components may be added to the example of the device illustrated in FIG. 2, in some embodiments of the invention. For example, device 50 may contain a cover, displays, ports, transmitters, sensors, channels such as microfluidic channels, chambers, and/or various electronics, e.g., to control or monitor fluid transport into or out of device 50, to determine an analyte present within a fluid delivered and/or received from the skin, to determine the status of the device, to report or transmit information regarding the device and/or analytes, or the like, as is discussed in more detail herein. As another example, device 50 may contain an adhesive, e.g., on surface 54, for adhesion of the device to the skin.

Yet another non-limiting example is illustrated with reference to FIG. 2C. In this example, device 500 includes a deployment actuator 501, and an associated substance transfer component system 503. Substance transfer component system 503 includes a plurality of needles or microneedles 505, although other substance transfer components as discussed herein may also be used. Also shown in FIG. 5 is sensor 510, connected via channels 511 to recess 508 containing needles or microneedles 505. Chamber 513 may be a self-contained vacuum chamber, and chamber 513 may be in fluidic communication with recess 508 via channel 511, for example, as controlled by a controller or an actuator (not shown). In this figure, device 500 also contains display 525, which is connected to sensor 510 via electrical connection 522. As an example of use of device 500, when fluid is drawn from the skin (e.g., blood, interstitial fluid, etc.), the fluid may flow through channel 511 to be determined by sensor 510, e.g., due to action of the vacuum from vacuum chamber 513. In some cases, the vacuum is used, for example, to draw skin into recess 508, preferably such that it contacts needles or microneedles 505 and pierces the surface of the skin to gain access to a fluid internal of the subject, such as blood or interstitial fluid, etc. The fluid may be controlled, for example, by controlling the size of needle 505, and thereby the depth of penetration. For example, the

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penetration may be limited to the epidermis, e.g., to collect interstitial fluid, or to the dermis, e.g., to collect blood. Upon determination of the fluid and/or an analyte present or suspected to be present within the fluid, a microprocessor or other controller may display on display 525 a suitable signal. As is discussed below, a display is shown in this figure by way of example only; in other embodiments, no display may be present, or other signals may be used, for example, lights, smell, sound, feel, taste, or the like.

In some cases, more than one substance transfer component system may be present within the device. For instance, the device may be able to be used repeatedly, and/or the device may be able to deliver and/or receive fluid at more than one location on a subject, e.g., sequentially and/or simultaneously. In some cases, the device may be able to simultaneously deliver and receive fluid to and from a subject. A non-limiting example of a device having more than one substance transfer component system is illustrated with reference to FIG. 2E. In this example, device 500 contains a plurality of structures such as those described herein for delivering and/or receiving fluid from a subject. For example, device 500 in this example contains 3 such units, although any number of units are possible in other embodiments. In this example, device 500 contains three such substance transfer component systems 575. Each of these substance transfer component systems may independently have the same or different structures, depending on the particular application, and they may have structures such as those described herein.

In some embodiments, the device may be an electrical and/or a mechanical device applicable or affixable to the surface of the skin, e.g., using adhesive, or other techniques such as those described herein. The adhesive may be permanent or temporary, and may be used to affix the device to the surface of the skin. The adhesive may be any suitable adhesive, for example, a pressure sensitive adhesive, a contact adhesive, a permanent adhesive, a hydrogel, a cyanoacrylate, a glue, a gum, hot melts, an epoxy, or the like. In some cases, the adhesive is chosen to be biocompatible or hypoallergenic.

In another set of embodiments, the device may be mechanically held to the skin, for example, the device may include mechanical elements such as straps, belts, buckles, strings, ties, elastic bands, or the like. For example, a strap may be worn around the device to hold the device in place against the skin of the subject. In yet another set of embodiments, a combination of these and/or other techniques may be used. As one non-limiting example, the device may be affixed to a subject's arm or leg using adhesive and a strap.

As another example, the device may be a handheld device that is applied to the surface of the skin of a subject. In some cases, however, the device may be sufficiently small or portable that the subject can self-administer the device. In certain embodiments, the device may also be powered. In some instances, the device may be applied to the surface of the skin, and is not inserted into the skin. In other embodiments, however, at least a portion of the device may be inserted into the skin, for example, mechanically. For example, in one embodiment, the device may include a cutter, such as a hypodermic needle, a knife blade, a piercing element (e.g., a solid or hollow needle), or the like, as discussed herein.

Any or all of the arrangements described herein can be provided proximate a subject, for example on or proximate a subject's skin. Activation of the devices can be carried out in a variety of ways. In one embodiment, a device can be applied to a subject and a region of the device activated (e.g.,

pushed, pressed, or tapped by a user) to inject a needle or a microneedle so as to access interstitial fluid. The same or a different tapping or pushing action can activate a vacuum source, open and/or close one or more of a variety of valves, or the like. The device can be a simple one in which it is applied to the skin and operates automatically (where e.g., application to the skin accesses interstitial fluid and draws interstitial fluid into an analysis region) or the device can be applied to the skin and one tapping or other activation can cause fluid to flow through administration of a needle or a microneedle, opening of a valve, activation of vacuum, or any combination. Any number of activation protocols can be carried out by a user repeatedly pushing or tapping a location or selectively, sequentially, and/or periodically activating a variety of switches. In another arrangement, activation of needles or microneedles, creation of suction blisters, opening and/or closing of valves, and other techniques to facilitate one or more analysis can be carried out electronically or in other manners facilitated by the subject or by an outside controlling entity. For example, a device or patch can be provided proximate a subject's skin and a radio frequency, electromagnetic, or other signal can be provided by a nearby controller or a distant source to activate any of the needles, blister devices, valves or other components of the devices described so that any assay or assays can be carried out as desired.

In some embodiments, fluid may be delivered to the subject, and such fluids may contain materials useful for delivery, e.g., forming at least a portion of the fluid, dissolved within the fluid, carried by the fluid (e.g., suspended or dispersed), or the like. Examples of suitable materials include, but are not limited to, particles such as microparticles or nanoparticles, a chemical, a drug or a therapeutic agent, a diagnostic agent, a carrier, or the like.

As used herein, the term "fluid" generally refers to a substance that tends to flow and to conform to the outline of its container. Typically, fluids are materials that are unable to withstand a static shear stress, and when a shear stress is applied, the fluid experiences a continuing and permanent distortion. The fluid may have any suitable viscosity that permits at least some flow of the fluid. Non-limiting examples of fluids include liquids and gases, but may also include free-flowing solid particles, viscoelastic fluids, and the like. For example, the fluid may include a flowable matrix or a gel, e.g., formed from biodegradable and/or biocompatible material such as polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), etc., or other similar materials.

In some cases, fluids or other materials delivered to the subject may be used for indication of a past, present and/or future condition of the subject. Thus, the condition of the subject to be determined may be one that is currently existing in the subject, and/or one that is not currently existing, but the subject is susceptible or otherwise is at an increased risk to that condition. The condition may be a medical condition, e.g., diabetes or cancer, or other physiological conditions, such as dehydration, pregnancy, illicit drug use, or the like. In one set of embodiments, the materials may include a diagnostic agent, for example, one which can determine an analyte within the subject, e.g., one that is a marker for a disease state. As a specific non-limiting example, material delivered to the skin, e.g., to the dermis or epidermis, to a pooled region of fluid, etc., of a subject may include a particle including an antibody directed at a marker produced by bacteria.

In other cases, however, the materials delivered to the subject may be used to determine conditions that are exter-

nal to the subject. For example, the materials may contain reaction entities able to recognize pathogens or other environmental conditions surrounding the subject, for example, an antibody able to recognize an external pathogen (or pathogen marker). As a specific example, the pathogen may be anthrax and the antibody may be an antibody to anthrax spores. As another example, the pathogen may be Plasmodia (some species of which causes malaria) and the antibody may be an antibody that recognizes the Plasmodia.

According to one aspect of the invention, the device is of a relatively small size. In some embodiments, the device may be sized such that it is wearable and/or carryable by a subject. For example, the device may be self-contained, needing no wires, cables, tubes, external structural elements, or other external support. The device may be positioned on any suitable position of the subject, for example, on the arm or leg, on the back, on the abdomen, etc. As mentioned, in some embodiments, the device may be affixed or held onto the surface of the skin using any suitable technique, e.g., using adhesives, mechanical elements such as straps, belts, buckles, strings, ties, elastic bands, or the like. In some cases, the device may be positioned on the subject such that the subject is able to move around (e.g., walking, exercising, typing, writing, drinking or eating, using the bathroom, etc.) while wearing the device. For example, the device may have a mass and/or dimensions such that the subject is able to wear the device for at least about 5 minutes, and in some cases for longer periods of time, e.g., at least about 10 minutes, at least about 15 minutes, at least about 30 minutes, at least about 45 minutes, at least about 1 hour, at least about 3 hours, at least 5 hours, at least about 8 hours, at least about 1 day, at least about 2 days, at least about 4 days, at least about 1 week, at least about 2 weeks, at least about 4 weeks, etc.

In some embodiments, the device is relatively lightweight. For example, the device may have a mass of no more than about 1 kg, no more than about 300 g, no more than about 150 g, no more than about 100 g, no more than about 50 g, no more than about 30 g, no more than about 25 g, no more than about 20 g, no more than about 10 g, no more than about 5 g, or no more than about 2 g. For instance, in various embodiments, the device has a mass of between about 2 g and about 25 g, a mass of between about 2 g and about 10 g, a mass of between 10 g and about 50 g, a mass of between about 30 g and about 150 g, etc.

The device, in some cases, may be relatively small. For example, the device may be constructed and arranged to lie relatively close to the skin. Thus, for instance, the device may have a largest vertical dimension, extending from the skin of the subject when the device is positioned on the skin, of no more than about 25 cm, no more than about 10 cm, no more than about 7 cm, no more than about 5 cm, no more than about 3 cm, no more than about 2 cm, no more than about 1 cm, no more than about 8 mm, no more than about 5 mm, no more than about 3 mm, no more than about 2 mm, no more than about 1 mm, or no more than about 0.5 mm. In some cases, the device may have a largest vertical dimension of between about 0.5 cm and about 1 cm, between about 2 and about 3 cm, between about 2.5 cm and about 5 cm, between about 2 cm and about 7 cm, between about 0.5 mm and about 7 cm, etc.

In another set of embodiments, the device may have a relatively small size. For example, the device may have a largest lateral dimension (e.g., parallel to the skin) of no more than about 25 cm, no more than about 10 cm, no more than about 7 cm, no more than about 5 cm, no more than about 3 cm, no more than about 2 cm, or no more than about

1 cm. In some cases, the device may have a largest lateral dimension of between about 0.5 cm and about 1 cm, between about 2 and about 3 cm, between about 2.5 cm and about 5 cm, between about 2 cm and about 7 cm, etc.

Combinations of these and/or other dimensions are also possible in other embodiments. As non-limiting examples, the device may have a largest lateral dimension of no more than about 5 cm, a largest vertical dimension of no more than about 1 cm, and a mass of no more than about 25 g; or the device may have a largest lateral dimension of no more than about 5 cm, a largest vertical dimension of no more than about 1 cm, and a mass of no more than about 25 g; etc.

In certain embodiments, the device may also contain an activator. The activator may be constructed and arranged to cause exposure of the substance transfer component to the skin upon activation of the activator. For example, the activator may cause a chemical to be released to contact the skin, a microneedle to be driven into the skin, a vacuum to be applied to the skin, a jet of fluid to be directed to the skin, or the like. The activator may be activated by the subject, and/or by another person (e.g., a health care provider), or the device itself may be self-activating, e.g., upon application to the skin of a subject. The activator may be activated once, or multiple times in some cases.

The device may be activated, for example, by pushing a button, pressing a switch, moving a slider, turning a dial, or the like. The subject, and/or another person, may activate the activator. In some cases, the device may be remotely activated. For example, a health care provider may send an electromagnetic signal which is received by the device in order to activate the device, e.g., a wireless signal, a radio signal, etc.

In one set of embodiments, the device may include channels such as microfluidic channels, which may be used to deliver and/or receive fluids and/or other materials into or out of the skin, e.g., within the pooled region of fluid. In some cases, the microfluidic channels are in fluid communication with a substance transfer component that is used to deliver and/or receive fluids to or from the skin. For example, in one set of embodiments, the device may include a hypodermic needle that can be inserted into the skin, and fluid may be delivered into the skin via the needle and/or received from the skin via the needle. The device may also include one or more microfluidic channels to contain fluid for delivery to the needle, e.g., from a source of fluid, and/or to receive fluid from the skin, e.g., for delivery to an analytical chamber within the device, to a reservoir for later analysis, or the like.

In some cases, more than one chamber may be present within the device, and in some cases, some or all of the chambers may be in fluidic communication, e.g., via channels such as microfluidic channels. In various embodiments, a variety of chambers and/or channels may be present within the device, depending on the application. For example, the device may contain chambers for sensing an analyte, chambers for holding reagents, chambers for controlling temperature, chambers for controlling pH or other conditions, chambers for creating or buffering pressure or vacuum, chambers for controlling or dampening fluid flow, mixing chambers, or the like.

Thus, in one set of embodiments, the device may include a microfluidic channel. As used herein, "microfluidic," "microscopic," "microscale," the "micro-" prefix (for example, as in "microchannel"), and the like generally refers to elements or articles having widths or diameters of less than about 1 mm, and less than about 100 microns (micrometers) in some cases. In some embodiments, larger channels

may be used instead of, or in conjunction with, microfluidic channels for any of the embodiments discussed herein. For examples, channels having widths or diameters of less than about 10 mm, less than about 9 mm, less than about 8 mm, less than about 7 mm, less than about 6 mm, less than about 5 mm, less than about 4 mm, less than about 3 mm, or less than about 2 mm may be used in certain instances. In some cases, the element or article includes a channel through which a fluid can flow. In all embodiments, specified widths can be a smallest width (i.e. a width as specified where, at that location, the article can have a larger width in a different dimension), or a largest width (i.e. where, at that location, the article has a width that is no wider than as specified, but can have a length that is greater). Thus, for instance, the microfluidic channel may have an average cross-sectional dimension (e.g., perpendicular to the direction of flow of fluid in the microfluidic channel) of less than about 1 mm, less than about 500 microns, less than about 300 microns, or less than about 100 microns. In some cases, the microfluidic channel may have an average diameter of less than about 60 microns, less than about 50 microns, less than about 40 microns, less than about 30 microns, less than about 25 microns, less than about 10 microns, less than about 5 microns, less than about 3 microns, or less than about 1 micron.

A "channel," as used herein, means a feature on or in an article (e.g., a substrate) that at least partially directs the flow of a fluid. In some cases, the channel may be formed, at least in part, by a single component, e.g. an etched substrate or molded unit. The channel can have any cross-sectional shape, for example, circular, oval, triangular, irregular, square or rectangular (having any aspect ratio), or the like, and can be covered or uncovered (i.e., open to the external environment surrounding the channel). In embodiments where the channel is completely covered, at least one portion of the channel can have a cross-section that is completely enclosed, and/or the entire channel may be completely enclosed along its entire length with the exception of its inlet and outlet.

A channel may have any aspect ratio, e.g., an aspect ratio (length to average cross-sectional dimension) of at least about 2:1, more typically at least about 3:1, at least about 5:1, at least about 10:1, etc. As used herein, a "cross-sectional dimension," in reference to a fluidic or microfluidic channel, is measured in a direction generally perpendicular to fluid flow within the channel. A channel generally will include characteristics that facilitate control over fluid transport, e.g., structural characteristics and/or physical or chemical characteristics (hydrophobicity vs. hydrophilicity) and/or other characteristics that can exert a force (e.g., a containing force) on a fluid. The fluid within the channel may partially or completely fill the channel. In some cases the fluid may be held or confined within the channel or a portion of the channel in some fashion, for example, using surface tension (e.g., such that the fluid is held within the channel within a meniscus, such as a concave or convex meniscus). In an article or substrate, some (or all) of the channels may be of a particular size or less, for example, having a largest dimension perpendicular to fluid flow of less than about 5 mm, less than about 2 mm, less than about 1 mm, less than about 500 microns, less than about 200 microns, less than about 100 microns, less than about 60 microns, less than about 50 microns, less than about 40 microns, less than about 30 microns, less than about 25 microns, less than about 10 microns, less than about 3 microns, less than about 1 micron, less than about 300 nm,

less than about 100 nm, less than about 30 nm, or less than about 10 nm or less in some cases. In one embodiment, the channel is a capillary.

In some cases, the device may contain one or more chambers or reservoirs for holding fluid. In some cases, the chambers may be in fluidic communication with one or more substance transfer components and/or one or more microfluidic channels. For instance, the device may contain a chamber for collecting fluid received from a subject (e.g., for storage and/or later analysis), a chamber for containing a fluid for delivery to the subject (e.g., blood, saline, optionally containing drugs, hormones, vitamins, pharmaceutical agents, or the like), etc.

After receiving the fluid into the device, the device, or a portion thereof, may be removed from the skin of the subject, e.g., by the subject or by another person. For example, the entire device may be removed, or a portion of the device containing the storage reservoir may be removed from the device, and optionally replaced with another storage reservoir. Thus, for instance, in one embodiment, the device may contain two or more modules, for example, a first module that is able to cause receiving of fluid from the skin into a storage reservoir, and a second module containing the storage module. In some cases, the module containing the storage reservoir may be removed from the device. Other examples of modules and modular systems are discussed below; other examples are discussed in U.S. Provisional Patent Application Ser. No. 61/256,931, filed Oct. 30, 2009, entitled "Modular Systems for Application to the Skin," incorporated by reference herein in its entirety.

As another example, the device may include at least two modules manually separable from each other, including a first module comprising a vacuum chamber, and a second module comprising other components such as those described herein. In some embodiments, the modules may be separable without the use of tools. For example, the second module may include one or more components such as a substance transfer component (e.g., a needle or microneedle), an applicator region such as a recess, a deployment actuator such as a flexible concave member, a collection chamber, a sensor, a processor, or the like. As a specific example, the first module may be defined entirely or partially by a vacuum chamber, and the first module may be removed and replaced with a fresh vacuum chamber, during or between uses. Thus, for instance, the first module may be inserted into the device when blood or other bodily fluids are desired to be received from a subject, and optionally, used to cause blood to be received from the subject, e.g., as discussed above with reference to FIG. 13A.

In one set of embodiments, the first module may be substantially cylindrical, and in some embodiments, the first module may be a Vacutainer™ tube, a Vacuette™ tube, or other commercially-available vacuum tube, or other vacuum source such as is described herein. In some embodiments, a Vacutainer™ or Vacuette™ tube that is used may have a maximum length of no more than about 75 mm or about 100 mm and a diameter of no more than about 16 mm or about 13 mm. The device, in certain embodiments, may also contain an adaptor able to hold or immobilize such tubes on the device, for example, a clamp. Other examples of adaptors are discussed in detail herein. In some cases, the device may have a shape or geometry that mimics a Vacutainer™ or Vacuette™ tube, e.g., one having the above dimensions. The device, in some embodiments, is substantially cylindrically symmetric.

The received fluid may then be sent to a clinical and/or laboratory setting, e.g., for analysis. In some embodiments,

the entire device may be sent to the clinical and/or laboratory setting; in other embodiments, however, only a portion of the device (e.g., a module containing a storage reservoir containing the fluid) may be sent to the clinical and/or laboratory setting. In some cases, the fluid may be shipped using any suitable technique (e.g., by mail, by hand, etc.). In certain instances, the subject may give the fluid to appropriate personnel at a clinical visit. For instance, a doctor may prescribe a device as discussed above for use by the subject, and at the next doctor visit, the subject may give the doctor the received fluid, e.g., contained within a device or module.

In some aspects, the device may contain an indicator. The indicator may be used for determining a condition of a fluid contained within the device, e.g., within a fluid storage chamber or a fluid reservoir. In some embodiments, the indicator may indicate one or more conditions associated with the introduction of fluid into the storage component and/or one or more conditions associated with storage of fluid in the storage component. For example, the indicator may indicate the condition of blood or ISF within the device, e.g., as the device is being transported or shipped to a clinical or a laboratory setting. The indicator may indicate the condition of the blood through any suitable technique, e.g., visually (such as with a color change), using a display, by producing a sound, etc. For instance, the indicator may have a display that is green if the fluid has not been exposed to certain temperatures or if there is no adverse chemical reaction present within the fluid (e.g., a change in pH, growth of microorganisms, etc.), but is yellow or red if adverse conditions are or have been present (e.g., exposure to temperatures that are too extreme, growth of microorganisms, etc.). In other embodiments, the display may display a visual message, a sound may be produced by the device, or the like.

In some cases, the indicator may be activated upon the accessing of fluid by the access component and/or introduction of fluid into the storage component. In one set of embodiments, the indicator may be activated upon the introduction of fluid within a fluid storage reservoir, upon activation of the device (e.g., to receive fluid from a subject, as discussed below), upon activation by a user (e.g., by the subject, or another person), etc.

In some cases, the indicator may determine the condition of fluid within a fluid storage reservoir within the device using one or more suitable sensors, for example, pH sensors, temperature sensors (e.g., thermocouples), oxygen sensors, or the like. For instance, a sensor may be present within or proximate the fluid storage reservoir for determining the temperature of the fluid within the fluid storage reservoir. In some cases, for example, more than one sensor measurement may be taken, e.g., at multiple points of time or even continuously. In some cases, the indicator may also record the sensor determinations, e.g., for analysis or later study.

In certain embodiments, time information may be determined and/or recorded by the indicator. For example, the time fluid enters a fluid storage reservoir may be recorded, e.g., using a time/date stamp (e.g., absolute time), and/or using the duration of time that fluid has been present within the fluid storage reservoir. The time information may also be recorded in some embodiments.

As discussed, in one set of embodiments, information from sensors and/or time information may be used to determine a condition of the fluid within the fluid storage reservoir. For example, if certain limits are met or exceeded, the indicator may indicate that, as discussed above. As a specific non-limiting example, if the temperature of the device is too low (e.g., reaches 0° C.) or too high (e.g.,

reaches 100° C. or 37° C.), this may be displayed by a display on the indicator. Thus, fluid exposed to temperature extremes may be identified, e.g., as being problematic or spoiled. As a another non-limiting example, it may be desired to keep the pH of fluid within the device within certain conditions, and if the pH is exceeded (e.g., too acidic or too basic), this may be displayed by a display on the indicator, for example, if the pH is less than 6 or 5, or greater than 8 or 9. In some cases, the time that fluid is present within the device may be kept within certain limits as well, as another condition. For example, the indicator may indicate that fluid has been present within the device for more than about 12 hours, more than about 18 hours, or more than about 24 hours, which may indicate the fluid as being problematic, spoiled, etc.

In one set of embodiments, conditions such as these may also be combined (e.g., time and temperature). Thus, for example, fluid exposed to a first temperature may be allowed to be present within the device for a first time, while fluid exposed to a second temperature may be allowed to be present within the device for a second time, before the indicator displays this.

In some embodiments, the indicator may record and/or transmit sensor or time information. This may be recorded and/or transmitted using any suitable format. For instance, the information may be transmitted using a wireless signal, a radio signal, etc., or recorded on any suitable electronic media, e.g., on a microchip, flash drive, optically, magnetically, etc.

A variety of materials and methods, according to certain aspects of the invention, can be used to form the device, e.g., microfluidic channels, chambers, etc. For example, various components of the invention can be formed from solid materials, in which the channels can be formed via micromachining, film deposition processes such as spin coating and chemical vapor deposition, laser fabrication, photolithographic techniques, etching methods including wet chemical or plasma processes, and the like. See, for example, Scientific American, 248:44-55, 1983 (Angell, et al).

In one set of embodiments, various components of the systems and devices of the invention can be formed of a polymer, for example, an elastomeric polymer such as polydimethylsiloxane ("PDMS"), polytetrafluoroethylene ("PTFE" or Teflon®), or the like. For instance, according to one embodiment, a microfluidic channel may be implemented by fabricating the fluidic system separately using PDMS or other soft lithography techniques (details of soft lithography techniques suitable for this embodiment are discussed in the references entitled "Soft Lithography," by Younan Xia and George M. Whitesides, published in the *Annual Review of Material Science*, 1998, Vol. 28, pages 153-184, and "Soft Lithography in Biology and Biochemistry," by George M. Whitesides, Emanuele Ostuni, Shuichi Takayama, Xingyu Jiang and Donald E. Ingber, published in the *Annual Review of Biomedical Engineering*, 2001, Vol. 3, pages 335-373; each of these references is incorporated herein by reference).

Other examples of potentially suitable polymers include, but are not limited to, polyethylene terephthalate (PET), polyacrylate, polymethacrylate, polycarbonate, polystyrene, polyethylene, polypropylene, polyvinylchloride, cyclic olefin copolymer (COC), polytetrafluoroethylene, a fluorinated polymer, a silicone such as polydimethylsiloxane, polyvinylidene chloride, bis-benzocyclobutene ("BCB"), a polyimide, a fluorinated derivative of a polyimide, or the like. Combinations, copolymers, or blends involving polymers including those described above are also envisioned.

The device may also be formed from composite materials, for example, a composite of a polymer and a semiconductor material.

In some embodiments, various components of the invention are fabricated from polymeric and/or flexible and/or elastomeric materials, and can be conveniently formed of a hardenable fluid, facilitating fabrication via molding (e.g. replica molding, injection molding, cast molding, etc.). The hardenable fluid can be essentially any fluid that can be induced to solidify, or that spontaneously solidifies, into a solid capable of containing and/or transporting fluids contemplated for use in and with the fluidic network. In one embodiment, the hardenable fluid comprises a polymeric liquid or a liquid polymeric precursor (i.e. a "prepolymer"). Suitable polymeric liquids can include, for example, thermoplastic polymers, thermoset polymers, waxes, metals, or mixtures or composites thereof heated above their melting point. As another example, a suitable polymeric liquid may include a solution of one or more polymers in a suitable solvent, which solution forms a solid polymeric material upon removal of the solvent, for example, by evaporation. Such polymeric materials, which can be solidified from, for example, a melt state or by solvent evaporation, are well known to those of ordinary skill in the art. A variety of polymeric materials, many of which are elastomeric, are suitable, and are also suitable for forming molds or mold masters, for embodiments where one or both of the mold masters is composed of an elastomeric material. A non-limiting list of examples of such polymers includes polymers of the general classes of silicone polymers, epoxy polymers, and acrylate polymers. Epoxy polymers are characterized by the presence of a three-membered cyclic ether group commonly referred to as an epoxy group, 1,2-epoxide, or oxirane. For example, diglycidyl ethers of bisphenol A can be used, in addition to compounds based on aromatic amine, triazine, and cycloaliphatic backbones. Another example includes the well-known Novolac polymers. Non-limiting examples of silicone elastomers suitable for use according to the invention include those formed from precursors including the chlorosilanes such as methylchlorosilanes, ethylchlorosilanes, phenylchlorosilanes, etc.

Silicone polymers are used in certain embodiments, for example, the silicone elastomer polydimethylsiloxane. Non-limiting examples of PDMS polymers include those sold under the trademark Sylgard by Dow Chemical Co., Midland, MI, and particularly Sylgard 182, Sylgard 184, and Sylgard 186. Silicone polymers including PDMS have several beneficial properties simplifying fabrication of the microfluidic structures of the invention. For instance, such materials are inexpensive, readily available, and can be solidified from a prepolymeric liquid via curing with heat. For example, PDMSs are typically curable by exposure of the prepolymeric liquid to temperatures of about, for example, about 65° C. to about 75° C. for exposure times of, for example, about an hour. Also, silicone polymers, such as PDMS, can be elastomeric and thus may be useful for forming very small features with relatively high aspect ratios, necessary in certain embodiments of the invention. Flexible (e.g., elastomeric) molds or masters can be advantageous in this regard.

One advantage of forming structures such as microfluidic structures of the invention from silicone polymers, such as PDMS, is the ability of such polymers to be oxidized, for example by exposure to an oxygen-containing plasma such as an air plasma, so that the oxidized structures contain, at their surface, chemical groups capable of cross-linking to other oxidized silicone polymer surfaces or to the oxidized

surfaces of a variety of other polymeric and non-polymeric materials. Thus, components can be fabricated and then oxidized and essentially irreversibly sealed to other silicone polymer surfaces, or to the surfaces of other substrates reactive with the oxidized silicone polymer surfaces, without the need for separate adhesives or other sealing means. In most cases, sealing can be completed simply by contacting an oxidized silicone surface to another surface without the need to apply auxiliary pressure to form the seal. That is, the pre-oxidized silicone surface acts as a contact adhesive against suitable mating surfaces. Specifically, in addition to being irreversibly sealable to itself, oxidized silicone such as oxidized PDMS can also be sealed irreversibly to a range of oxidized materials other than itself including, for example, glass, silicon, silicon oxide, quartz, silicon nitride, polyethylene, polystyrene, glassy carbon, and epoxy polymers, which have been oxidized in a similar fashion to the PDMS surface (for example, via exposure to an oxygen-containing plasma). Oxidation and sealing methods useful in the context of the present invention, as well as overall molding techniques, are described in the art, for example, in an article entitled "Rapid Prototyping of Microfluidic Systems and Polydimethylsiloxane," *Anal. Chem.*, 70:474-480, 1998 (Duffy et al.), incorporated herein by reference.

Another advantage to forming microfluidic structures of the invention (or interior, fluid-contacting surfaces) from oxidized silicone polymers is that these surfaces can be much more hydrophilic than the surfaces of typical elastomeric polymers (where a hydrophilic interior surface is desired). Such hydrophilic channel surfaces can thus be more easily filled and wetted with aqueous solutions than can structures comprised of typical, unoxidized elastomeric polymers or other hydrophobic materials.

As described herein, any of a variety of signaling or display methods, associated with analyses, can be provided including signaling visually, by smell, sound, feel, taste, or the like, in one set of embodiments. Signal structures or generators include, but are not limited to, displays (visual, LED, light, etc.), speakers, chemical-releasing chambers (e.g., containing a volatile chemical), mechanical devices, heaters, coolers, or the like. In some cases, the signal structure or generator may be integral with the device (e.g., integrally connected with a deployment actuator for application to the skin of the subject, e.g., containing a substance transfer component such as a needle or a microneedle), or the signal structure may not be integrally connected with the deployment actuator. As used herein, a "signal structure" or a "signal generator" is any apparatus able to generate a signal that is related to a condition of a medium. For example, the medium may be a bodily fluid, such as blood or interstitial fluid.

In some embodiments, signaling methods such as these may be used to indicate the presence and/or concentration of an analyte determined by the sensor, e.g., to the subject, and/or to another entity, such as those described below. Where a visual signal is provided, it can be provided in the form of change in opaqueness, a change in intensity of color and/or opaqueness, or can be in the form of a message (e.g., numerical signal, or the like), an icon (e.g., signaling by shape or otherwise a particular medical condition), a brand, logo, or the like. For instance, in one embodiment, the device may include a display. A written message such as "take next dose," or "glucose level is high" or a numerical value might be provided, or a message such as "toxin is present." These messages, icons, logos, or the like can be provided as an electronic read-out by a component of a

device and/or can be displayed as in inherent arrangement of one or more components of the device.

In some embodiments, a device is provided where the device determines a physical condition of a subject and produces a signal related to the condition that can be readily understood by the subject (e.g., by provision of a visual "OK" signal as described above) or can be designed so as not to be readily understandable by a subject. Where not readily understandable, the signal can take a variety of forms. In one form, the signal might be a series of letters or numbers that mean nothing to the subject (e.g., A1278CDQ) which would have meaning to a medical professional or the like (and/or be decodable by the same, e.g., with reference to a suitable decoder) and can be associated with a particular physiological condition. Alternatively, a signal in the form of bar code can be provided by a device such that, under a particular condition or set of conditions the bar code appears and/or disappears, or changes, and can be read by a bar code reader to communicate information about the subject or analyte. In another embodiment, the device can be designed such that an ultraviolet signal is produced, or a signal that can be read only under ultraviolet light (e.g., a simple spot or patch, or any other signal such as a series of number, letters, bar code, message, or the like that can be readily understandable or not readily understandable by a subject) can be provided. The signal may be invisible to the human eye but, upon application UV light or other excitation energy, may be readable. The signal can be easily readable or understandable by a user via visual observation, or with other sensory activity such as smell, feel, etc. In another set of embodiments equipment as described above may be needed to determine a signal provided by the device, such as equipment in a clinical setting, etc. In some cases, the device is able to transmit a signal indicative of the analyte to a receiver, e.g., as a wireless signal, a radio signal, etc.

In some embodiments, quantitative and/or qualitative analyses can be provided by a device. That is, the device in some cases may provide analyses that allow "yes/no" tests or the like, or tests that provide information on the quantity, concentration, or level of a particular analyte or analytes. Display configurations can be provided by the invention that reflect the amount of a particular analyte present in a subject at a particular point in time, or any other variable (presence of analysis over time, type of analyte, etc.) display configurations can take a variety of forms. In one example, a dial can be provided, similar to that of a speedometer with a series of level indications (e.g., numbers around the dial) and a "needle" or other device that indicates a particular level. In other configurations, a particular area of the device (e.g., on a display) can exist that is filled in to a greater or lesser extent depending upon the presence and/or quantity of a particular analyte present, e.g., in the form of a bar graph. In another arrangement a "color wheel" can be provided where the amount of a particular analyte present can control which colors of the wheel are visible. Or, different analytes can cause different colors of a wheel or different bars of a graph to become visible or invisible in a multiple analyte analysis. Multiple-analyte quantitative analyses can be reflected in multiple color wheels, a single color wheel with different colors per analyte where the intensity of each color reflects the amount of the analyte, or, for example, a plurality of bar graphs where each bar graph is reflective of a particular analyte and the level of the bar (and/or degree to which an area is filled in with visible color or other visible feature) is reflective of the amount of the analyte. As with all embodiments here, whatever signal is displayed can be understandable or not understandable to any number of participants.

For example, it can be understandable to a subject or not understandable to a subject. Where not understandable it might need to be decoded, read electronically, or the like. Where read electronically, for example, a device may provide a signal that is not understandable to a subject or not even visible or otherwise able to be sensed by a subject, and a reader can be provided adjacent or approximate the device that can provide a visible signal that is understandable or not understandable to the subject, or can transmit a signal to another entity for analysis.

In connection with any signals associated with any analyses described herein, another, potentially related signal or other display (or smell, taste, or the like) can be provided which can assist in interpreting and/or evaluating the signal. In one arrangement, a calibration or control is provided proximate (or otherwise easily comparable with) a signal, e.g., a visual calibration/control or comparator next to or close to a visual signal provided by a device and/or implanted agents, particles, or the like.

A visual control or reference can be used with another sensory signal, such as that of smell, taste, temperature, itch, etc. A reference/control and/or experimental confirmation component can be provided, to be used in connection with an in-skin test or vice versa. References/indicators can also be used to indicate the state of life of a device, changing color or intensity and/or changing in another signaling aspect as the device changes relative to its useful life, so that a user can determine when the device should no longer be relied upon and/or removed. For certain devices, an indicator or control can be effected by adding analyte to the control (e.g., from a source outside of the source to be determine) to confirm operability of the device and/or to provide a reference against which to measure a signal of the device. For example, a device can include a button to be tapped by a user which will allow an analyte from a reservoir to transfer to an indicator region to provide a signal, to demonstrate operability of the device and/or provide a comparator for analysis.

Many of the embodiments described herein involve a quantitative analysis and related signal, i.e., the ability to determine the relative amount or concentration of an analyte in a medium. This can be accomplished in a variety of ways. For example, where an agent (e.g. a binding partner attached to a nanoparticle) is used to capture and analyze an analyte, the agent can be provided in a gradient in concentration across a sensing region of the device. Or a sensing region can include a membrane or other apparatus through which analyte is required to flow or pass prior to capture and identification, and the pathway for analyte travel can vary as a function of position of display region. For example, a membrane can be provided across a sensing region, through which analyte must pass prior to interacting with a layer of binding and/or signaling agent, and the membrane may vary in thickness laterally in a direction related to "bar graph" readout. Where a small amount of analyte is present, it may pass through the thinner portion but not the thicker portion of the membrane, but where a larger amount is present, it may pass across a thicker portion. The boundary (where one exists) between a region through which analyte passes, and one through which it does not completely pass, can define the "line" of the bar graph. Other ways of achieving the same or a similar result can include varying the concentration of a scavenger or transporter of the analyte, or an intermediate reactive species (between analyte and signaling event), across a membrane or other article, gradient in porosity or selectivity of the membrane, ability to absorb or transport sample fluid, or the like. These principles, in combination

with other disclosure herein, can be used to facilitate any or all of the quantitative analyses described herein.

In one set of embodiments, a subject having a condition such as a physiological condition to be analyzed (or other user, such as medical personnel) reads and/or otherwise determines a signal from a device. For example, the device may transmit a signal indicative of a condition of the subject and/or the device. Alternatively, or in addition, a signal produced by a device can be acquired in the form of a representation (e.g. a digitized signal, or the like) and transmitted to another entity for analysis and/or action. For example, a signal can be produced by a device, e.g., based on a sensor reading of an analyte, based on fluid delivered and/or received from the skin, based on a condition of the device, or the like. The signal may represent any suitable data or image. For example, the signal may represent the presence and/or concentration of an analyte in fluid received from a subject, the amount of fluid received from a subject and/or delivered to the subject, the number of times the device has been used, the battery life of the device, the amount of vacuum left in the device, the cleanliness or sterility of the device, the identity of the device (e.g., where multiple devices are given unique identification numbers, to prevent counterfeiting, accidental exchange of equipment to incorrect users, etc.), or the like. For instance, in one set of embodiments, an image of the signal (e.g., a visual image or photograph) can be obtained and transmitted to a different entity (for example, a user can take a cell phone picture of a signal generated by the device and send it, via cell phone, the other entity).

The other entity that the signal is transmitted to can be a human (e.g., a clinician) or a machine. In some cases, the other entity may be able to analyze the signal and take appropriate action. In one arrangement, the other entity is a machine or processor that analyzes the signal and optionally sends a signal back to the device to give direction as to activity (e.g., a cell phone can be used to transmit an image of a signal to a processor which, under one set of conditions, transmits a signal back to the same cell phone giving direction to the user, or takes other action). Other actions can include automatic stimulation of the device or a related device to dispense a medicament or pharmaceutical, or the like. The signal to direct dispensing of a pharmaceutical can take place via the same used to transmit the signal to the entity (e.g., cell phone) or a different vehicle or pathway. Telephone transmission lines, wireless networks, Internet communication, and the like can also facilitate communication of this type.

As one specific example, a device may be a glucose monitor. As signal may be generated by the device and an image of the signal captured by a cell phone camera and then transmitted via cell phone to a clinician. The clinician may then determine that the glucose (or e.g., insulin) level is appropriate or inappropriate and send a message indicating this back to the subject via cell phone.

Information regarding the analysis can also be transmitted to the same or a different entity, or a different location simply by removing the device or a portion of the device from the subject and transferring it to a different location. For example, a device can be used in connection with a subject to analyze presence and/or amount of a particular analyte. At some point after the onset of use, the device, or a portion of the device carrying a signal or signals indicative of the analysis or analyses, can be removed and, e.g., attached to a record associated with the subject. As a specific example, a patch or other device can be worn by a subject to determine presence and/or amount of one or more analytes qualita-

tively, quantitatively, and/or over time. The subject can visit a clinician who can remove the patch (or other device) or a portion of the patch and attach it to a medical record associated with the subject.

According to various sets of embodiments, the device may be used once, or multiple times, depending on the application. For instance, obtaining samples for sensing, according to certain embodiments of the invention, can be done such that sensing can be carried out continuously, discretely, or a combination of these. For example, where a bodily fluid such as blood or interstitial fluid is accessed for determination of an analyte, fluid can be accessed discretely (i.e., as a single dose, once or multiple times), or continuously by creating a continuous flow of fluid which can be analyzed once or any number of times. Additionally, testing can be carried out once, at a single point in time, or at multiple points in time, and/or from multiple samples (e.g., at multiple locations relative to the subject).

Alternatively or in addition, testing can be carried out continuously over any number of points in time involving one or any number of locations relative to the subject or other multiple samples. As an example, one bolus or isolated sample, of fluid such as interstitial fluid can be obtained. From that fluid a test can be carried out to determine whether a particular analyte or other agent exists in the fluid. Alternatively, two or more tests can be carried out involving that quantity of fluid to determine the presence and/or quantity of two or more analytes, and any number of such tests can be carried out. Tests involving that quantity of fluid can be carried out simultaneously or over a period of time. For example, a test for a particular analyte can be carried out at various points in time to determine whether the result changes over time, or different analytes can be determined at different points in time.

In another example, a needle or a microneedle, or other device(s) can be used to access a fluid of a subject such as interstitial fluid. Fluid can be drawn to a point of analysis and analyzed in any manner described herein. For example, an analysis can be carried out once, to determine the presence and/or quantity of a single analyte, or a number of tests can be carried out. From a single sample of fluid, a particular test or number of tests can be carried out essentially simultaneously, or analyses can be carried out over time. Moreover, fluid can be drawn continuously from the subject and one or more tests can be carried out of any number of points in time. A variety of reasons for carrying out one or more tests over the course of time exists, as would be understood by those of ordinary skill in the art. One such reason is to determine whether the quantity or another characteristic of an analyte is constant in a subject, or changes over time. A variety of specific techniques for continuous and/or discrete testing will be described herein.

In one set of embodiments, one or more materials, such as particles, are delivered to the skin. Examples of suitable materials include, but are not limited to, particles such as microparticles or nanoparticles, a chemical, a drug or a therapeutic agent, a diagnostic agent, a carrier, or the like. The particles may be, for example, nanoparticles or microparticles, and in some cases, the particles may be anisotropic particles. In some cases, a plurality of particles may be used, and in some cases, some, or substantially all, of the particles may be the same. For example, at least about 10%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, or at least about 99% of the particles may have the same shape, and/or may have the same composition.

The particles may be used for a variety of purposes. For instance, the particles may contain a diagnostic agent or a reaction entity able to interact with and/or associate with an analyte, or another reaction entity, or other particles. Such particles may be useful, for example, to determine one or more analytes, such as a marker of a disease state, as discussed below. As another example, the particles may contain a drug or a therapeutic agent, positioned on the surface and/or internally of the particles, which may be released by the particles and delivered to the subject. Specific examples of these and other embodiments are discussed in detail below.

In some cases, materials such as particles may become embedded within the skin, for example, due to physical properties of the materials (e.g., size, hydrophobicity, etc.). Thus, in some cases, a depot of material may be formed within the skin, and the depot may be temporary or permanent. For instance, materials within the depot may eventually degrade (e.g., if the material is biodegradable), enter the bloodstream, or be sloughed off to the environment, e.g., as the cells of the dermis differentiate to form new epidermis and accordingly push the material towards the surface of the skin. Thus, the depot of material may be present within the subject on a temporary basis (e.g., on a time scale of days or weeks), in certain instances.

As mentioned, certain aspects of the present invention are generally directed to particles such as anisotropic particles or colloids, which can be used in a wide variety of applications. For instance, the particles may be present within the skin, or externally of the skin, e.g., in a device on the surface of the skin. The particles may include microparticles and/or nanoparticles. As discussed above, a "microparticle" is a particle having an average diameter on the order of micrometers (i.e., between about 1 micrometer and about 1 mm), while a "nanoparticle" is a particle having an average diameter on the order of nanometers (i.e., between about 1 nm and about 1 micrometer). The particles may be spherical or non-spherical, in some cases. For example, the particles may be oblong or elongated, or have other shapes such as those disclosed in U.S. patent application Ser. No. 11/851,974, filed Sep. 7, 2007, entitled "Engineering Shape of Polymeric Micro- and Nanoparticles," by S. Mitragotri, et al.; International Patent Application No. PCT/US2007/077889, filed Sep. 7, 2007, entitled "Engineering Shape of Polymeric Micro- and Nanoparticles," by S. Mitragotri, et al., published as WO 2008/031035 on Mar. 13, 2008; U.S. patent application Ser. No. 11/272,194, filed Nov. 10, 2005, entitled "Multi-phasic Nanoparticles," by J. Lahann, et al., published as U.S. Patent Application Publication No. 2006/0201390 on Sep. 14, 2006; or U.S. patent application Ser. No. 11/763,842, filed Jun. 15, 2007, entitled "Multi-Phasic Bioadhesive Nan-Objects as Biofunctional Elements in Drug Delivery Systems," by J. Lahann, published as U.S. Patent Application Publication No. 2007/0237800 on Oct. 11, 2007, each of which is incorporated herein by reference. Other examples of particles can be seen in U.S. patent application Ser. No. 11/272,194, filed Nov. 10, 2005, entitled "Multi-phasic Nanoparticles," by J. Lahann, et al., published as U.S. Patent Application Publication No. 2006/0201390 on Sep. 14, 2006; U.S. patent application Ser. No. 11/763,842, filed Jun. 15, 2007, entitled "Multi-Phasic Bioadhesive Nan-Objects as Biofunctional Elements in Drug Delivery Systems," by J. Lahann, published as U.S. Patent Application Publication No. 2007/0237800 on Oct. 11, 2007; or U.S. Provisional Patent Application Ser. No. 61/058,796, filed Jun. 4, 2008, entitled "Compositions and Methods for Diagnostics, Therapies, and Other Applications," by D.

Levinson, each of which is incorporated herein by reference. Other examples of particles can be seen in U.S. patent application Ser. No. 11/272,194, filed Nov. 10, 2005, entitled "Multi-phasic Nanoparticles," by J. Lahann, et al., published as U.S. Patent Application Publication No. 2006/0201390 on Sep. 14, 2006; U.S. patent application Ser. No. 11/763,842, filed Jun. 15, 2007, entitled "Multi-Phasic Bioadhesive Nan-Objects as Biofunctional Elements in Drug Delivery Systems," by J. Lahann, published as U.S. Patent Application Publication No. 2007/0237800 on Oct. 11, 2007; or U.S. Provisional Patent Application Ser. No. 61/058,796, filed Jun. 4, 2008, entitled "Compositions and Methods for Diagnostics, Therapies, and Other Applications," by D. Levinson, each of which is incorporated herein by reference.

In some cases, a pooled region of fluid, such as a suction blister, may be formed in the skin to facilitate delivery and/or receiving of fluid from the skin. Thus, certain aspects of the present invention are generally directed to the creation of suction blisters or other pooled regions of fluid within the skin. In one set of embodiments, a pooled region of fluid can be created between the dermis and epidermis of the skin. Suction blisters or other pooled regions may form in a manner such that the suction blister or other pooled region is not significantly pigmented in some cases, since the basal layer of the epidermis contains melanocytes, which are responsible for producing pigments. Such regions can be created by causing the dermis and the epidermis to at least partially separate, and as will be discussed below, a number of techniques can be used to at least partially separate the dermis from the epidermis.

In one technique, a pool of interstitial fluid is formed between layers of skin of a subject and, after forming the pool, fluid is drawn from the pool by accessing the fluid through a layer of skin, for example, puncturing the outer layer of skin with a microneedle. Specifically, for example, a suction blister can be formed and then the suction blister can be punctured and fluid can be drawn from the blister. In another technique, an interstitial region can be accessed and fluid drawn from that region without first forming a pool of fluid via a suction blister or the like. For example, a microneedle or microneedles can be applied to the interstitial region and fluid can be drawn there from.

Pooled regions of fluids may be formed on any suitable location within the skin of a subject. Factors such as safety or convenience may be used to select a suitable location, as (in humans) the skin is relatively uniform through the body, with the exception of the hands and feet. As non-limiting examples, the pooled region may be formed on an arm or a leg, on the chest, abdomen, or the back of the subject, or the like. The size of the pooled region of fluid that is formed in the skin and/or the duration that the pooled region lasts within the skin depends on a variety of factors, such as the technique of creating the pooled region, the size of the pooled region, the size of the region of skin to which the technique is applied, the amount of fluid received from the pooled region (if any), any materials that are delivered into the pooled region, or the like. For example, if vacuum is applied to the skin to create a suction blister, the vacuum applied to the skin, the duration of the vacuum, and/or the area of the skin affected may be controlled to control the size and/or duration of the suction blister. In some embodiments, it may be desirable to keep the pooled regions relatively small, for instance, to prevent an unsightly visual appearance, to allow for greater sampling accuracy (due to a smaller volume of material), or to allow for more controlled placement of particles within the skin. For example, the volume of the pooled region may be kept to less than about

2 ml or less than about 1 ml in certain cases, or the average diameter of the pooled region (i.e., the diameter of a circle having the same area as the pooled region) may be kept to less than about 5 cm, less than about 4 cm, less than about 3 cm, less than about 2 cm, less than about 1 cm, less than about 5 mm, less than about 4 mm, less than about 3 mm, less than about 2 mm, or less than about 1 mm.

A variety of techniques may be used to cause pooled regions of fluid to form within the skin. In one set of embodiments, vacuum is applied to create a suction blister, or otherwise used to collect interstitial fluid from a subject. In other embodiments, however, other methods may be used to create as a pooled region of fluid within the skin besides, or in addition to, the use of vacuum. When vacuum (i.e., the amount of pressure below atmospheric pressure, such that atmospheric pressure has a vacuum of 0 mmHg, i.e., the pressure is gauge pressure rather than absolute pressure) is used to at least partially separate the dermis from the epidermis to cause the pooled region to form, the pooled region of fluid thus formed can be referred to as a suction blister. For example, vacuums of at least about 50 mmHg, at least about 100 mmHg, at least about 150 mmHg, at least about 200 mmHg, at least about 250 mmHg, at least about 300 mmHg, at least about 350 mmHg, at least about 400 mmHg, at least about 450 mmHg, at least about 500 mmHg, at least about 550 mmHg, at least about 600 mmHg, at least about 650 mmHg, at least about 700 mmHg, or at least about 750 mmHg may be applied to the skin, e.g., to cause a suction blister and/or to collect interstitial fluid from a subject (as discussed, these measurements are negative relative to atmospheric pressure. Different amounts of vacuum may be applied to different subjects in some cases, for example, due to differences in the physical characteristics of the skin of the subjects.

The vacuum may be applied to any suitable region of the skin, and the area of the skin to which the vacuum may be controlled in some cases. For instance, the average diameter of the region to which vacuum is applied may be kept to less than about 5 cm, less than about 4 cm, less than about 3 cm, less than about 2 cm, less than about 1 cm, less than about 5 mm, less than about 4 mm, less than about 3 mm, less than about 2 mm, or less than about 1 mm. In addition, such vacuums may be applied for any suitable length of time at least sufficient to cause at least some separation of the dermis from the epidermis to occur. For instance, vacuum may be applied to the skin for at least about 1 min, at least about 3 min, at least about 5 min, at least about 10 min, at least about 15 min, at least about 30 min, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, etc. Examples of devices suitable for creating such suction blisters are discussed in more detail below. In other cases, however, bodily fluids such as blood or interstitial fluid may be received from the skin using vacuum without the creation of a suction blister. Other non-limiting fluids include saliva, sweat, tears, mucus, plasma, lymph, or the like.

Other methods besides vacuum may be used to cause such separation to occur. For example, in another set of embodiments, heat may be used. For instance, a portion of the skin may be heated to at least about 40° C., at least about 50° C., at least about 55° C., or at least about 60° C., using any suitable technique, to cause such separation to occur. The skin may be heated, for instance, using an external heat source (e.g., radiant heat or a heated water bath), a chemical reaction, electromagnetic radiation (e.g., microwave radiation, infrared radiation, etc.), or the like. In some cases, the radiation may be focused on a relatively small region of the

skin, e.g., to at least partially spatially contain the amount of heating within the skin that occurs.

In yet another set of embodiments, a separation chemical may be applied to the skin to at least partially cause separation of the dermis and the epidermis to occur. Non-limiting examples of such separation chemicals include proteases such as trypsin, purified human skin tryptase, or compound 48/80. Separation compounds such as these are commercially available from various sources. The separation chemical may be applied directly to the skin, e.g., rubbed into the surface of the skin, or in some cases, the separation chemical can be delivered into the subject, for example, between the epidermis and dermis of the skin. The separation chemical can, for example, be injected in between the dermis and the epidermis.

Another example of a separation chemical is a blistering agent, such as pit viper venom or blister beetle venom. Non-limiting examples of blistering agents include phosphene oxime, Lewisite, sulfur mustards (e.g., mustard gas or 1,5-dichloro-3-thiapentane, 1,2-bis(2-chloroethylthio)ethane, 1,3-bis(2-chloroethylthio)-n-propane, 1,4-bis(2-chloroethylthio)-n-butane, 1,5-bis(2-chloroethylthio)-n-pentane, 2-chloroethylchloromethylsulfide, bis(2-chloroethyl)sulfide, bis(2-chloroethylthio)methane, bis(2-chloroethylthiomethyl)ether, or bis(2-chloroethylthioethyl)ether), or nitrogen mustards (e.g., bis(2-chloroethyl)ethylamine, bis(2-chloroethyl)methylamine, or tris(2-chloroethyl)amine).

In still another set of embodiments, a device may be inserted into the skin and used to mechanically separate the epidermis and the dermis, for example, a wedge or a spike. Fluids may also be used to separate the epidermis and the dermis, in yet another set of embodiments. For example, saline or another relatively inert fluid may be injected into the skin between the epidermis and the dermis to cause them to at least partially separate.

These and/or other techniques may also be combined, in still other embodiments. For example, in one embodiment, vacuum and heat may be applied to the skin of a subject, sequentially and/or simultaneously, to cause such separation to occur. As a specific example, in one embodiment, vacuum is applied while the skin is heated to a temperature of between about 40° C. and about 50° C.

One aspect of the present invention is directed to an adaptor able to position a device of the invention in apparatuses designed to contain Vacutainer™ tubes or Vacuette tubes. In some cases, the Vacutainer or Vacuette tube sizes have a maximum length of no more than about 75 mm or about 100 mm and a diameter of no more than about 16 mm or about 13 mm. In some cases, the adaptor may be able to immobilize a device of the invention therein, e.g., for subsequent use or processing. In some cases, as previously discussed, devices of the invention may have a largest lateral dimension of no more than about 50 mm, and/or a largest vertical dimension, extending from the skin of the subject when the device is applied to the subject, of no more than about 10 mm. An example of such a device is shown in FIG. 9, with device 800 contained within adapter 850. The device may be contained within the adaptor using any suitable technique, e.g., using clips, springs, braces, bands, or the application of force to the device present within the adaptor.

In another aspect, the present invention is directed to a kit including one or more of the compositions previously discussed, e.g., a kit including a device for the delivery and/or receiving of fluid from the skin, a kit including a device able to create a pooled region of fluid within the skin of a subject, a kit including a device able to determine a fluid, or the like. An example of a kit containing more than one device of the

invention is illustrated in FIG. 2D, with kit 150 containing devices 152. A “kit,” as used herein, typically defines a package or an assembly including one or more of the compositions or devices of the invention, and/or other compositions or devices associated with the invention, for example, as previously described. For example, in one set of embodiments, the kit may include a device and one or more compositions for use with the device. Each of the compositions of the kit, if present, may be provided in liquid form (e.g., in solution), or in solid form (e.g., a dried powder). In certain cases, some of the compositions may be constitutable or otherwise processable (e.g., to an active form), for example, by the addition of a suitable solvent or other species, which may or may not be provided with the kit. Examples of other compositions or components associated with the invention include, but are not limited to, solvents, surfactants, diluents, salts, buffers, emulsifiers, chelating agents, fillers, antioxidants, binding agents, bulking agents, preservatives, drying agents, antimicrobials, needles, syringes, packaging materials, tubes, bottles, flasks, beakers, dishes, frits, filters, rings, clamps, wraps, patches, containers, tapes, adhesives, and the like, for example, for using, administering, modifying, assembling, storing, packaging, preparing, mixing, diluting, and/or preserving the compositions components for a particular use, for example, to a sample and/or a subject.

A kit of the invention may, in some cases, include instructions in any form that are provided in connection with the compositions of the invention in such a manner that one of ordinary skill in the art would recognize that the instructions are to be associated with the compositions of the invention. For instance, the instructions may include instructions for the use, modification, mixing, diluting, preserving, administering, assembly, storage, packaging, and/or preparation of the compositions and/or other compositions associated with the kit. In some cases, the instructions may also include instructions for the delivery and/or administration of the compositions, for example, for a particular use, e.g., to a sample and/or a subject. The instructions may be provided in any form recognizable by one of ordinary skill in the art as a suitable vehicle for containing such instructions, for example, written or published, verbal, audible (e.g., telephonic), digital, optical, visual (e.g., videotape, DVD, etc.) or electronic communications (including Internet or web-based communications), provided in any manner.

In some embodiments, the present invention is directed to methods of promoting one or more embodiments of the invention as discussed herein. As used herein, “promoted” includes all methods of doing business including, but not limited to, methods of selling, advertising, assigning, licensing, contracting, instructing, educating, researching, importing, exporting, negotiating, financing, loaning, trading, vending, reselling, distributing, repairing, replacing, insuring, suing, patenting, or the like that are associated with the systems, devices, apparatuses, articles, methods, compositions, kits, etc. of the invention as discussed herein. Methods of promotion can be performed by any party including, but not limited to, personal parties, businesses (public or private), partnerships, corporations, trusts, contractual or sub-contractual agencies, educational institutions such as colleges and universities, research institutions, hospitals or other clinical institutions, governmental agencies, etc. Promotional activities may include communications of any form (e.g., written, oral, and/or electronic communications, such as, but not limited to, e-mail, telephonic, Internet, Web-based, etc.) that are clearly associated with the invention.

In one set of embodiments, the method of promotion may involve one or more instructions. As used herein, “instructions” can define a component of instructional utility (e.g., directions, guides, warnings, labels, notes, FAQs or “frequently asked questions,” etc.), and typically involve written instructions on or associated with the invention and/or with the packaging of the invention. Instructions can also include instructional communications in any form (e.g., oral, electronic, audible, digital, optical, visual, etc.), provided in any manner such that a user will clearly recognize that the instructions are to be associated with the invention, e.g., as discussed herein.

The following documents are incorporated herein by reference: U.S. Provisional Patent Application Ser. No. 61/334,533, filed May 13, 2010, entitled “Rapid Delivery and/or Withdrawal of Fluids,” by Chickering, et al.; U.S. Provisional Patent Application Ser. No. 61/334,529, filed May 13, 2010, entitled “Sampling Device Interfaces,” by Chickering, et al.; U.S. Provisional Patent Application Ser. No. 61/357,582, filed Jun. 23, 2010, entitled “Sampling Devices and Methods Involving Relatively Little Pain,” by Chickering, et al.; U.S. Provisional Patent Application Ser. No. 61/367,607, filed Jul. 26, 2010, entitled “Microneedles and Techniques for Making and Using Same,” by Davis, et al.; U.S. Provisional Patent Application Ser. No. 61/373,764, filed Aug. 13, 2010, entitled “Clinical and/or Consumer Techniques and Devices,” by Chickering, et al.; U.S. Provisional Patent Application Ser. No. 61/058,796, filed Jun. 4, 2008, entitled “Compositions and Methods for Diagnostics, Therapies, and Other Applications”; U.S. Provisional Patent Application Ser. No. 61/163,791, filed Mar. 26, 2009, entitled “Composition and Methods for Rapid One-Step Diagnosis”; U.S. Provisional Patent Application Ser. No. 61/163,793, filed Mar. 26, 2009, entitled “Compositions and Methods for Diagnostics, Therapies, and Other Applications”; U.S. patent application Ser. No. 12/478,756, filed Jun. 4, 2009, entitled “Compositions and Methods for Diagnostics, Therapies, and Other Applications”; International Patent Application No. PCT/US09/046333, filed Jun. 4, 2009, entitled “Compositions and Methods for Diagnostics, Therapies, and Other Applications”; U.S. Provisional Patent Application Ser. No. 61/163,710, filed Mar. 26, 2009, entitled “Systems and Methods for Creating and Using Suction Blisters or Other Pooled Regions of Fluid within the Skin”; U.S. Provisional Patent Application Ser. No. 61/163,733, filed Mar. 26, 2009, entitled “Determination of Tracers within Subjects”; U.S. Provisional Patent Application Ser. No. 61/163,750, filed Mar. 26, 2009, entitled “Monitoring of Implants and Other Devices”; U.S. Provisional Patent Application Ser. No. 61/154,632, filed Mar. 2, 2009, entitled “Oxygen Sensor”; and U.S. Provisional Patent Application Ser. No. 61/269,436, filed Jun. 24, 2009, entitled “Devices and Techniques associated with Diagnostics, Therapies, and Other Applications, Including Skin-Associated Applications.” Also incorporated by reference herein are U.S. Provisional Patent Application Ser. No. 61/263,882, filed Nov. 24, 2009, entitled “Patient-Enacted Sampling Technique”; U.S. Provisional Patent Application Ser. No. 61/294,543, filed Jan. 13, 2010, entitled “Blood Sampling Device and Method”; U.S. patent application Ser. No. 12/716,222, filed Mar. 2, 2010, entitled “Oxygen Sensor,” by Levinson, et al.; U.S. patent application Ser. No. 12/716,233, filed Mar. 2, 2010, entitled “Systems and Methods for Creating and Using Suction Blisters or Other Pooled Regions of Fluid within the Skin,” by Levinson, et al.; U.S. patent application Ser. No. 12/716,226, filed Mar. 2, 2010, entitled “Techniques and Devices Associated with Blood Sampling,” by

Levinson, et al.; and U.S. patent application Ser. No. 12/716,229, filed Mar. 2, 2010, entitled “Devices and Techniques Associated with Diagnostics, Therapies, and Other Applications, Including Skin-Associated Applications,” by Bernstein, et al.

Also incorporated herein by reference is U.S. Provisional Patent Application Ser. No. 61/411,566, filed Nov. 9, 2010, entitled “Systems and Interfaces for Blood Sampling,” by David Brancazio.

While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

All definitions, as defined and used herein, should be understood to control over dictionary definitions, definitions in documents incorporated by reference, and/or ordinary meanings of the defined terms.

The indefinite articles “a” and “an,” as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean “at least one.”

The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B,” when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally,

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additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e. “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

What is claimed is:

1. A device for receiving blood from a subject, the device comprising:

- a surface configured to be positioned against skin of a subject;
- a device actuator;
- at least one cutter, wherein the at least one cutter is configured to move from a first position to a second position in response to actuation of the device actuator to cause blood to be drawn from a subject;
- an opening configured to receive fluid into the device, the opening being part of a first portion of the device;
- a collection chamber moveable relative to the opening, wherein when the collection chamber is coupled to the first portion of the device, the collection chamber extends in a direction parallel to the surface; and
- a vacuum source, wherein vacuum from the vacuum source is mechanically created.

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2. The device of claim 1, further comprising a spring configured to move the at least one cutter away from the second position.

3. The device of claim 1, wherein the at least one cutter comprises at least one needle.

4. The device of claim 1, wherein the at least one cutter comprises at least one microneedle.

5. The device of claim 1, wherein the at least one cutter comprises at least one blade.

6. The device of claim 1, further comprising a channel configured to guide fluid from the opening.

7. The device of claim 1, wherein the collection chamber is removeably coupleable to the device.

8. The device of claim 1, wherein the vacuum source comprises a deformable structure, and wherein vacuum from the vacuum source is mechanically created through a change in shape of a portion of the deformable structure.

9. The device of claim 1, wherein the vacuum source comprises a piston.

10. A device for receiving blood from a subject, the device comprising:

- a surface configured to be positioned against skin of a subject;

- a device actuator;

- at least one cutter, wherein the at least one cutter is moveable from a first position to a second position to cause blood to be drawn from a subject;

- an opening configured to receive fluid into the device, the opening being part of a first portion of the device;

- a collection chamber moveable relative to the opening, wherein when the collection chamber is coupled to the first portion of the device, the collection chamber extends in a direction parallel to the surface; and

- a flexible concave member, wherein the flexible concave member is moveable from a first configuration to a second configuration upon actuation of the device actuator.

11. The device of claim 10, further comprising a spring positioned beneath the flexible concave member, wherein when the flexible concave member is moved from the first configuration toward the second configuration, the spring compresses.

12. The device of claim 10, wherein the at least one cutter is positioned under the flexible concave member.

13. The device of claim 10, wherein the first configuration comprises a dome shape, and the second configuration comprises a deformed shape.

14. The device of claim 10, further comprising a spring configured to move the at least one cutter away from the second position.

15. The device of claim 10, wherein the at least one cutter comprises at least one needle.

16. The device of claim 10, wherein the at least one cutter comprises at least one microneedle.

17. The device of claim 10, wherein the at least one cutter comprises at least one blade.

18. The device of claim 10, wherein the collection chamber is removeably coupleable to the device.

19. A device for receiving blood from a subject, the device comprising:

- a device actuator;

- at least one cutter, wherein the at least one cutter is configured to move from a first position to a second position in response to actuation of the device actuator to cause blood to be drawn from a subject;

an opening configured to receive fluid into the device, wherein the opening lies in a two-dimensional plane, and wherein the opening is part of a first portion of the device;

a collection chamber moveable relative to the opening, wherein when the collection chamber is coupled to the first portion of the device, the collection chamber extends in a direction parallel to the two-dimensional plane; and

a vacuum source, wherein vacuum from the vacuum source is mechanically created.

20. The device of claim 19, further comprising a spring configured to move the at least one cutter away from the second position.

21. The device of claim 19, wherein the at least one cutter comprises at least one needle, at least one microneedle, or at least one blade.

22. The device of claim 19, wherein the collection chamber is removeably coupleable to the device.

23. The device of claim 19, wherein the vacuum source comprises a deformable structure, and wherein vacuum from the vacuum source is mechanically created through a change in shape of a portion of the deformable structure.

24. The device of claim 19, wherein the vacuum source comprises a piston.

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