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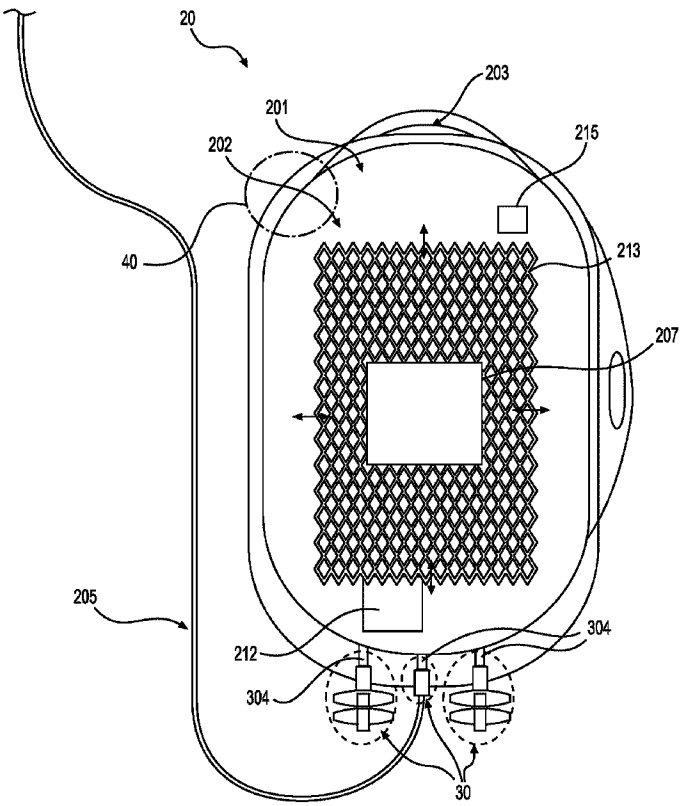
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(57) Abrégé/Abstract:
A blood storage container for the anaerobic storage of blood, having enhanced sealing methods and materials for the preservation of stored blood is provided.

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(54) Title: ANAEROBIC BLOOD STORAGE CONTAINERS

(57) Abstract: A blood storage container for the anaerobic storage of blood, having enhanced sealing methods and materials for the preservation of stored blood is provided.

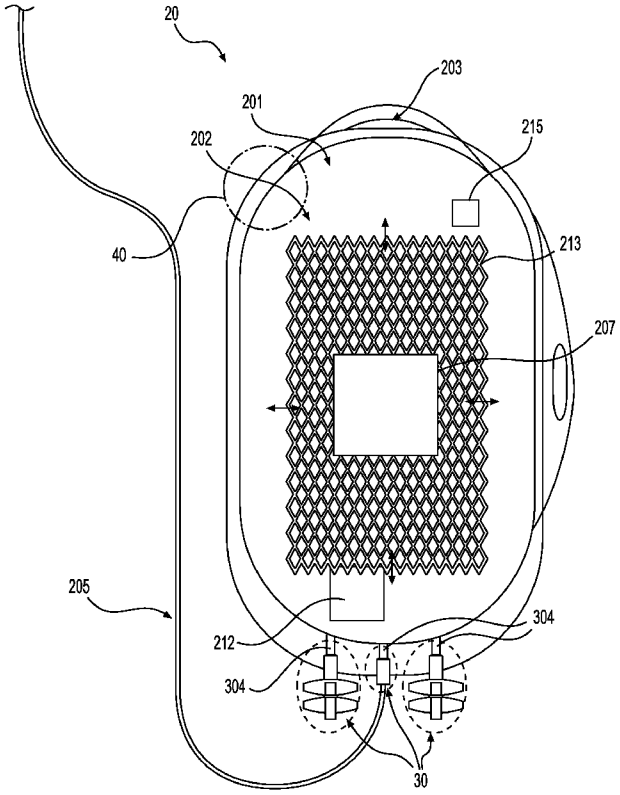


FIG. 1A

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ANAEROBIC BLOOD STORAGE CONTAINERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is related to U.S. Provisional Patent Application No. 62/151,957 filed April 23, 2015, and U.S Provisional Patent Application No. 62/151,839 filed April 23, 2015.

FIELD OF THE INVENTION

[0002] The present disclosure relates to an improved anaerobic storage bag (ASB) and methods for the improved preservation of whole blood and blood components. More particularly, the disclosure relates to improved devices and methods for the anaerobic storage of oxygen and oxygen and carbon dioxide depleted blood and blood components that provide for an extended shelf life prior to use, improved usability in a collection center, and reduced ingression of oxygen. The methods, devices and kits of the present disclosure provide for improved quality of blood and blood components for transfusion and improved patient safety and outcome.

BACKGROUND OF THE INVENTION

[0003] The supplies of liquid blood and blood components are currently limited by storage systems used in conventional blood storage practices. Using current systems, stored blood expires after a period of about 42 days of refrigerated storage at a temperature above freezing (*i.e.*, 4°C) as packed blood cell preparations. For example, in 2007, more than 45 million units of red blood cells (RBCs) were collected and stored globally (15.6 million in the US). During refrigerated storage, RBCs become progressively damaged by complicated biological changes collectively referred to as "storage lesions." When transfused within the current 6-week limit, stored RBCs have lower quality as well as potential toxicity, which can be manifested as side effects of transfusion therapy. Among the observed storage lesions are altered biochemical and physical parameters associated with stored red blood cells. Examples of these alterations include *in vitro* measured parameters such as reduced metabolite levels (adenosine triphosphate (ATP) and 2,3 diphosphoglycerate (2,3-DPG)), increased levels of cell-free iron, hemolysis, increased levels of microparticles, reduced surface area, echinocytosis, phosphatidylserine exposure, and reduced deformability. Expired blood cannot be used and must be discarded because it may harm the ultimate

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recipient. These reasons and others limit the amount of readily available high quality blood needed for transfusions.

[0004] When stored conventionally, stored blood undergoes a steady deterioration which is associated with various storage lesions including, among others, hemolysis, hemoglobin degradation, and reduced ATP and 2,3-DPG concentrations. When transfused into a patient, the effects of the steady deterioration during storage manifest, for example, as a reduction in the 24-hour *in vivo* recovery. Because of these and other medical sequelae of transfusion of stored blood, a variety of approaches have been developed to minimize the effects of storage on blood and to improve medical outcomes. See, for example, Zimring *et al.*, "Established and theoretical factors to consider in assessing the red cell storage lesion" in *Blood*, *125*:2185-90 (2015).

[0005] A number of approaches have been developed aimed at minimizing storage lesions and improving transfusion outcomes. One approach has been the development of additive solutions included during storage. Examples of this approach include U.S. Patent No. 4,769,318 to Hamasaki *et al.* and U.S. Patent No. 4,880,786 to Sasakawa *et al.* which are directed to additive solutions for blood preservation and activation. For example, Rejuvesol (available from Citra Lab LLC, Braintree, MA) is added to blood after cold storage (*i.e.*, 4°C) just prior to transfusion or prior to freezing (*i.e.*, at -80°C with glycerol) for extended storage. U.S. Patent No. 6,447,987 to Hess *et al.* is directed to additive solutions for the refrigerated storage of human red blood cells. An alternative approach is to freeze the blood and prevent the development of storage lesions. Storage of frozen blood is known in the art, but such frozen blood has limitations. U.S. Patent No. 6,413,713 to Serebrennikov is directed to a method of storing blood at temperatures below 0°C. See Chaplin *et al.*, "Blood Cells for Transfusion," *Blood*, *59*: 1118-20 (1982), and Valeri *et al.*, "The survival, function, and hemolysis of human RBCs stored at 4 degrees C in additive solution (AS-1, AS-3, or AS-5) for 42 days and then biochemically modified, frozen, thawed, washed, and stored at 4 degrees C in sodium chloride and glucose solution for 24 hours," *Transfusion*, *40*:1341-5 (2000). Another approach relates to the containers for blood storage as provided by U.S. Patent No. 4,837,047 to Sato *et al.*

[0006] One approach that has proven successful in improving blood quality and extending its utility is through the depletion of oxygen and storage under anaerobic conditions. U.S. Patent No. 5,624,794 to Bitensky *et al.*, U.S. Patent No. 6,162,396 to Bitensky *et al.*, and U.S. Patent No. 5,476,764 to Bitensky are directed to the storage of red blood cells under oxygen-

depleted conditions. U.S. Patent No. 5,789,151 to Bitensky *et al.* is directed to blood storage additive solutions. Among the benefits of storing blood under oxygen depleted conditions are improved levels of ATP and 2,3-DPG, reduced hemolysis. Storing blood under oxygen depleted conditions can also result in reduced microparticle levels, reductions in the loss of deformability, reduced lipid and protein oxidation and higher post transfusion survival when compared to blood stored under conventional conditions.

[0007] U.S. Patent No. 6,162,396 to Bitensky *et al.* (the '396 patent) discloses anaerobic storage bags for blood storage that comprise an oxygen impermeable outer layer, a red blood cell (RBC) compatible inner layer that is permeable to oxygen having an oxygen scrubber placed between the inner and outer layers. The blood storage device further comprises at least two ports for conventional sterile connections for introducing whole blood or RBCs into the device. The '396 patent generally discloses oxygen impermeable outer layers but does not provide guidance regarding specific types of materials or suitable construction methods. Similarly, the '396 patent discloses inner blood compatible layers generally but does not provide guidance regarding appropriate materials and construction methods. Similarly, the '396 patent does not provide guidance on tubing materials and methods to gain access to the inner blood bag and contents while maintaining a reduced oxygen environment.

[0008] During the course of research to develop an ASB for use in blood collection and blood banking operations, it was observed that additional considerations were necessary. First, in preparing oxygen impermeable outer layers, it was observed that not all of the materials identified as suitable in the '396 patent could be used in practicable devices. Specifically, it was observed that certain aluminum foil laminated membranes became compromised when creased, wrinkled or folded. More problematic, is that upon introduction of blood into such bags, the increase in volume directly led to the formation of such integrity compromising creases. To avoid this complication, appropriate materials having sufficient flexibility are required. Alternatively, ASBs having suitable expansion features that provide for the accommodation of the blood are required.

[0009] Also during the course of development, it was observed that the bag integrity needed to be maintained at the various ports to prevent ingress of oxygen prior to use and also during storage. Another source of oxygen ingress was observed at seams and joints wherein wider seals provided for both decreasing oxygen leakage and preventing outer and inner bag failure. It was further observed that the standard PVC tubing used in blood banking operations had significant permeability to oxygen and incompatibility with methods

to create an oxygen impermeable seal where it passed through the outer oxygen impermeable barrier. Even further, conventional blood collection kits require transfer tubing ranging in length from about greater than or equal to 200 mm as well as collection tubing having a length greater than or equal to 800 mm that are also potential sources of oxygen introgression. See ISO 3826-1:2013. Thus, blood collection kits for anaerobic storage of blood must account for this source of oxygen that can diminish the capacity of an oxygen sorbent placed in the ASB and significantly reduce the shelf life of the resulting bags.

[0010] Therefore, there is a need for improved anaerobic blood storage bags that provide for extended shelf life a blood collection kit including such bags. There is also a need for improved anaerobic storage bags that can provide for the ingression of oxygen through the tubing associated with blood collection kits. Finally, there is a need to identify suitable materials that can accommodate routine handling of blood storage bags that do not compromise the integrity of the oxygen barrier.

[0011] Finally, the integration of oxygen indicators into improved anaerobic blood storage bags provides additional levels of quality control that helps inform the users of possible oxygen ingress that are large enough to compromise the ability to the storage bag to maintain the depleted blood in an oxygen depleted condition.

SUMMARY OF THE INVENTION

[0012] The present disclosure provides for, and includes, a blood storage device for storing oxygen depleted blood comprising an outer receptacle substantially impermeable to oxygen, a collapsible blood container and at least one inlet/outlet passing through the outer receptacle and that is in fluid communication with the collapsible container and that is substantially impermeable to oxygen.

[0013] The present disclosure provides for, and includes, a blood storage device for storing oxygen depleted blood comprising an outer receptacle substantially impermeable to oxygen, a collapsible blood container and at least one inlet/outlet passing through the outer receptacle and that is in fluid communication with the collapsible container and that is substantially impermeable to oxygen, and an oxygen sorbent situated within the outer receptacle.

[0014] The present disclosure provides for, and includes, a blood storage device for storing oxygen depleted blood comprising a multilayered membrane that combines an outer receptacle substantially impermeable to oxygen, a collapsible blood container and at least one inlet/outlet passing through the outer receptacle and that is in fluid communication with the

collapsible container and that is substantially impermeable to oxygen, and an oxygen sorbent situated within the multilayered membrane.

[0015] The present disclosure provides for, and includes, a blood storage device for storing oxygen depleted blood comprising a blood compatible outer receptacle that is substantially impermeable to oxygen, a collapsible blood container and at least one inlet/outlet passing through the outer receptacle and that is in fluid communication with the collapsible container and that is substantially impermeable to oxygen wherein oxygen depleted blood having an oxygen saturation level of less than 20% is maintained in an oxygen depleted state for at least 64 days.

[0016] The present disclosure provides for, and includes, a method for storing deoxygenated blood comprising placing deoxygenated blood into a blood storage device as described herein.

[0017] The present disclosure provides for, and includes, a method of further reducing the oxygen saturation of blood during storage comprising transferring oxygen depleted blood for storage having an oxygen saturation level of less than 20% to a blood storage device and storing the oxygen depleted blood for storage for a time period wherein the time period is at least 1 week.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Some aspects of the disclosure are herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and are for purposes of illustrative discussion of aspects of the disclosure. In this regard, the description, taken with the drawings, makes apparent to those skilled in the art how aspects of the disclosure may be practiced.

[0019] Figures 1A to 1C illustrate an exemplary embodiment of an improved anaerobic storage bag according to the present disclosure.

[0020] Figures 2A and 2B illustrate an exemplary embodiment of an oxygen reduction disposable storage system having a blood depletion device having two or three compartments, respectively, and an anaerobic storage bag according to the present disclosure.

[0021] Figures 3A to 3C illustrate an exemplary embodiment of inlet/outlet barrier traversing tubes **305**.

[0022] Figure 3D is an illustration of an exemplary embodiment of a manifold **301** with 3 inlet/outlet ports to hold barrier traversing tubes **305**.

[0023] Figure 4A is an illustration of a bonding layer joining a barrier traversing tube **305** onto membrane 208 and creating a bond **302** with gap **209**.

[0024] Figure 4B is an illustration of a bonding layer joining multilayer barrier traversing tubes **305** with membrane **208**.

[0025] Figure 5A is an illustration of a blood storage device with barrier traversing tubes **305** bonded to create bond **302** according to an aspect of the present disclosure.

[0026] Figure 5B is an illustration of a blood storage device with bonding layer **302** joining manifold **301** with membrane **208**.

[0027] Figures 6A to 6F illustrate tubing management features according to aspects of the present disclosure.

[0028] Figure 7 illustrates an integrated handle **214** according to an aspect of the present disclosure.

[0029] Figure 8 illustrates an outer receptacle **201** incorporating an expansion feature **217** according to an aspect of the present disclosure.

[0030] Figure 9 illustrates an aluminum die **70,** according to an aspect of the present disclosure.

[0031] Figure 10 presents a graph of oxygen absorption that occurs in conventional storage bags.

[0032] Figure 11 presents a graphical presentation of sorbent test data according to example 9.

[0033] Figure 12 presents a graphical presentation of hand warmers test data according to example 10.

[0034] Figure 13 presents a graphical presentation of oxygen absorption that occurs in non-depleted blood during storage in conventional storage bags without an outer receptacle **201**.

[0035] Figure 14 presents a graphical presentation of oxygen absorption that occurs in an anaerobic storage container with sorbent (filled symbols) or without a sorbent.

[0036] Figure 15 presents a graphical presentation of partial pressure of oxygen in an anaerobic storage container with three inlet/outlets according to the prior art that is not substantially impermeable to oxygen.

[0037] Figure 16 presents a graphical presentation of partial pressure of oxygen in an anaerobic storage container with three inlets/outlets **30** having barrier traversing tubes **305**.

[0038] Corresponding reference characters indicate corresponding parts throughout the several views. The examples set out herein illustrate several embodiments of the invention but should not be construed as limiting the scope of the invention in any manner.

DETAILED DESCRIPTION

[0039] Unless defined otherwise, technical and scientific terms as used herein have the same meaning as commonly understood by one of ordinary skill in the art. One skilled in the art will recognize many methods can be used in the practice of the present disclosure. Indeed, the present disclosure is in no way limited to the methods and materials described. For purposes of the present disclosure, the following terms are defined below.

[0040] As used herein, the term "bag" refers to collapsible containers prepared from a flexible material and includes pouches, tubes, and gusset bags. As used herein, and included in the present disclosure, the term includes folded bags having one, two, three, or more folds and which are sealed or bonded on one, two, three, or more sides. Bags may be prepared using a variety of techniques known in the art including bonding of sheets of one or more materials. Methods of bonding materials to form bags are known in the art. Also included and provided for in the present disclosure are containers prepared by injection and blow molding. Methods to prepare blow molded and injection molded containers are known in the art. Preferred types of blow molded or injection molded containers are flexible containers that can be reduced in size for efficient packing and shipping while being capable of expanding to accommodate blood or blood components for reduction of oxygen. They also may be designed to conform to the volume of the blood until they are fully expanded. As used throughout the present disclosure, the bags are a form of collapsible container and the two terms are used interchangeably throughout the present disclosure.

[0041] As used herein, the term "collapsible container" includes bags, containers, enclosures, envelopes, pouches, pockets, receptacles, and other devices that can contain and retain a liquid or fluid. In certain aspects, the collapsible container may be manufactured by conventional means such as injection molding or insert molding. In other aspects, the collapsible container may be prepared from sheets of polymer materials that are bonded together using methods known in the art to prepare containers capable of holding a volume. Such collapsible containers are well known in the art. See, for example, U.S. Patent 3,942,529 issued to Waage; U.S. Patent 4,131,200 issued to Rinfret; and U.S. Patent 5,382,526 issued to Gajewski *et al.* Suitable methods for bonding polymer materials to

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prepare collapsible containers according to the present disclosure include heat welding, ultrasonic welding, radio frequency (RF) welding, and solvent welding. In certain aspects, multiple bonding methods may be used to prepare collapsible containers according to the present disclosure. Collapsible container according to the present disclosure include enclosures having one or more pleats, folds, diaphragms, bubbles, and gussets. Methods for preparing collapsible containers are known in the art. See, for example, U.S. Patent 3,361,041 issued to Grob; U.S. Patent 4,731,978 issued to Martensson; U.S. Patent 4,998,990 issued to Richter *et al.*; and U.S. Patent 4,262,581 issued to Ferrell. Also included and provided for in the present disclosure are containers having combinations of both flexible and inflexible parts, wherein the flexible parts allow for the expansion of the volume through, for example, pleats, folds or gussets and other similar geometric features in the packaging shape, whereas the inflexible parts may provide rigidity and geometry definition to the container. Methods and designs for preparing collapsible containers having both flexible and inflexible parts are known in the art, such as described by Randall in U.S. Patent 6,164,821 and by LaFleur in U.S. Patent 5,328,268. Others are described by Yeager in U.S. Patent 6,076,664 and by David in U.S. Patent Application Publication No. 2014/0248005A1, also known in the art as a "stand up pouch."

[0042] As used herein, the term "ingressed oxygen" refers to oxygen that enters the blood storage device during the period of storage of oxygen depleted blood. Ingressed oxygen further includes oxygen that enters the blood storage device during shelf storage. Such ingressed oxygen can render the blood storage device inoperative during shelf storage if not minimized or preferably eliminated. In an aspect, ingressed oxygen can result in the consumption of the gas binding capacity of the sorbent (either oxygen or carbon dioxide) rendering the device deficient and unable to maintain the blood storage device in an anaerobic state and further unable to maintain the oxygen reduced stored blood. Ingressed oxygen includes oxygen that enters the device through the substantially impermeable barriers of the device and it is recognized that absolute integrity in typical devices is either not possible or is cost prohibited. More generally, ingressed oxygen can enter the device through the seals or welds of the outer receptacle **201**, the inlet/outlet **30**, tubing **304**, and tubing **205**. More specifically, it was discovered that standard tubing used in blood collection devices (*e.g.*, collection and transfer tubes) were significant sources of ingressed oxygen that rendered anaerobic blood storage devices known previously in the art inadequate. As shown in the examples below, the tubing was the primary source of ingressed oxygen. Even further,

while the present design eliminates the majority of the ingressed oxygen observed in previous anaerobic storage bags, it will be appreciated that the absolute elimination of ingressed oxygen may not be possible. The problem of ingressed oxygen manifests in a significantly decreased shelf life of unused blood storage devices as well as the inability to maintain the blood in a suitably oxygen depleted state. Moreover, even with the incorporation of the elements of the blood storage device **20** of the present disclosure, it is preferable to include an oxygen sorbent **207** that is capable of absorbing not only any residual oxygen present in the oxygen depleted blood, but also that amount of unwanted ingressed oxygen that still enters into the system.

[0043] As used herein, the term "blood" refers to whole blood, leukoreduced RBCs, platelet reduced RBCs, and leukocyte and platelet reduced RBCs. The term blood further includes packed red blood cells, platelet reduced packed red blood cells, leukocyte reduced packed red blood cells (LRpRBC), and leukocyte and platelet reduced packed red blood cells. The temperature of blood can vary depending on the stage of the collection process, starting at the normal body temperature of 37 °C at the time and point of collection, but decreasing rapidly to about 30 °C as soon as the blood leaves the patient's body and further thereafter to room temperature in about 6 hours when untreated, and ultimately being refrigerated at between about 4 °C and 6 °C.

[0044] As used herein, the term "whole blood" refers to a suspension of blood cells that contains red blood cells (RBCs), white blood cells (WBCs), platelets suspended in plasma, and includes electrolytes, hormones, vitamins, antibodies, etc. In whole blood, white blood cells are normally present in the range between 4.5 and 11.0 x 10^9 cells/L and the normal RBC range at sea level is 4.6-6.2 x 10^{12}/L for men and 4.2-5.4 x 10^{12}/L for women. The normal hematocrit, or percent packed cell volume, is about 40-54% for men and about 38-47% for women. The platelet count is normally 150-450 x 10^9/L for both men and women. Whole blood is collected from a blood donor, and is usually combined with an anticoagulant. Whole blood, when collected is initially at about 37 °C and rapidly cools to about 30 °C during and shortly after collection, but slowly cools to ambient temperature over about 6 hours. Whole blood may be processed according to methods of the present disclosure at collection, beginning at 30-37 °C, or at room temperature (typically about 25 °C). As used herein, a "unit" of blood is about 450-500 ml including anticoagulant.

[0045] As used herein, "red blood cells" (RBCs) includes RBCs present in whole blood, leukoreduced RBCs, platelet reduced RBCs, and leukocyte and platelet reduced RBCs.

Human red blood cells *in vivo* are in a dynamic state. The red blood cells contain hemoglobin, the iron-containing protein that carries oxygen throughout the body and gives red blood its color. The percentage of blood volume composed of red blood cells is called the hematocrit. As used herein, unless otherwise limited, RBCs also includes packed red blood cells (pRBCs). Packed red blood cells are prepared from whole blood using centrifugation techniques commonly known in the art. As used herein, unless otherwise indicated, the hematocrit of pRBCs is about 70%.

[0046] As used herein the term "about" refers to ± 10 %.

[0047] The terms "comprises," "comprising," "includes," "including," "having," and their conjugates mean "including but not limited to."

[0048] The term "consisting of" means "including and limited to."

[0049] The term "consisting essentially of" means that the composition, method or structure may include additional ingredients, steps and/or parts, but only if the additional ingredients, steps and/or parts do not materially alter the basic and novel characteristics of the claimed composition, method or structure.

[0050] As used herein, the singular forms "a," "an," and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a compound" or "at least one compound" may include a plurality of compounds, including mixtures thereof.

[0051] Throughout this application, various aspects of this disclosure may be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosure. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as "from 1 to 6" should be considered to have specifically disclosed subranges such as "from 1 to 3," "from 1 to 4," "from 1 to 5," "from 2 to 4," "from 2 to 6," "from 3 to 6," etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

[0052] Whenever a numerical range is indicated herein, it is meant to include any cited numeral (fractional or integral) within the indicated range. The phrases "ranging/ranges between" a first indicate number and a second indicate number and "ranging/ranges from" a first indicate number "to" a second indicate number are used herein interchangeably and are meant to include the first and second indicated numbers and all the fractional and integral numerals therebetween.

[0053] As used herein the term "method" refers to manners, means, techniques, and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques, and procedures either known to or readily developed from known manners, means, techniques, and procedures by practitioners of the chemical, pharmacological, biological, biochemical, and medical arts.

[0054] Referring to Fig. 1A, there is provided an illustration of an exemplary aspect of the present disclosure. The blood storage device **20** includes an outer receptacle **201** substantially impermeable to oxygen, a collapsible blood container **202** comprising, at least one inlet/outlet **30** passing through said outer receptacle **201** comprising a seal adaptor **301** and a bond **302**, and an oxygen sorbent **207** situated within said outer receptacle **201**, wherein said seal adaptor **301** and said bond **302** are substantially impermeable to oxygen, and said inlet/outlet **30** is in fluid communication with said collapsible container **202**.

[0055] As used herein, the outer receptacles **201** are prepared from membrane materials **208** that are substantially impermeable to oxygen and optionally impermeable to carbon dioxide. In certain aspects, an outer receptacle **201** is prepared from flexible membrane materials **208**. As illustrated in non-limiting aspects of the present disclosure in Figure 1C, outer receptacle **201** may be prepared from one or more sheets of membrane material **208**. In other aspects, and as described below, outer receptacle **201** may be prepared as a tube and sealed at the ends to create an outer receptacle. Also provided by the present disclosure is an outer receptacle **201** comprising a single sheet of membrane material **208**, folded and sealed to prepare an outer receptacle **201**. In further aspects, outer receptacle **201** may comprise two sheets of a membrane material **208** joined together. In yet other aspects, outer receptacle **201** may be prepared from two different membrane materials **208**, each of which are substantially impermeable to oxygen and optionally impermeable to carbon dioxide. As discussed below, additional sheets of membrane material **208** may be joined together to prepare an outer receptacle **201** having an expansion feature **217** to accommodate an increase in volume of a collapsible blood container **202** that occurs upon transferring oxygen depleted blood to the blood storage device **20**. The present disclosure provides blood storage device **20** with a hanging feature **203**. The present disclosure also provides for and includes blow molded outer receptacles **201** comprising a suitable membrane material **208** that is substantially impermeable to oxygen and optionally impermeable to carbon dioxide.

[0056] The present disclosure provides for, and includes, an outer receptacle **201** substantially impermeable to oxygen. As used herein, an outer receptacle **201** that is

substantially impermeable to oxygen is sufficiently impermeable to oxygen to allow no more than 10 cc of oxygen inside the receptacle over a period of 3 months, and more preferably no more than 5 cc of oxygen over 6 months. As used herein, the term "substantially impermeable to oxygen" (SIO) refers to materials and compositions that provide a barrier to the passage of oxygen from one side of the barrier to the other, sufficient to prevent significant increases in the partial pressure of oxygen. In certain aspects, a substantially impermeable membrane suitable for use in the preparation of an outer receptacle **201** is characterized by a Barrer value of less than 1.0 Barrer. In other aspects, a substantially impermeable membrane suitable for use in the preparation of an outer receptacle **201** is characterized by a Barrer value of between 0.001 and 0.2 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.02 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.002 Barrer.

[0057] The present disclosure also provides for, and includes, an outer receptacle **201** that is substantially impermeable to oxygen having a permeability to oxygen of less than about 0.5 cc of oxygen per square meter per day. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 1.0 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.2 Barrer.

[0058] It is notable that few materials provide complete impermeability and that even the high impermeability of materials can be compromised when joining, welding, folding, and otherwise assembling an outer receptacle **201**. As will be discussed below, blood storage device **20** may further incorporate one or more inlets/outlets **30** comprising a seal adaptor **301** and a bond **302** to the outer receptacle **201**. In other aspects, the inlet/outlet **30** may comprise a single unitary tube that is substantially impermeable to oxygen that incorporates tubing **304**, bond **302**, and tubing **205**. In other aspects, the unitary tube substitutes for tubing **304** and tubing **205** and is bonded to the outer receptacle **201**. The outer receptacle **201** must also be designed to accommodate changes in volume of the inner collapsible blood container **202**. In aspects according to the present disclosure, integrity of the impermeable barrier can be maintained by including a manifold as a seal adapter **301** or inlet/outlet **30** formulated in a

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diamond wedge shape according to Figure 3C. Accordingly, special care is taken to incorporate specific design elements and manufacturing methods to ensure the integrity of the impermeable barrier.

[0059] In one aspect of the present disclosure, a manifold is a seal adapter **301**. In other aspects, the inlet/outlet **30** may be comprised of a plurality of inlet/outlets. In an aspect, the inlet/outlet **30** incorporates two barrier traversing tubes **305** and a manifold **301**. In an aspect, the inlet/outlet **30** incorporates three barrier traversing tubes **305** and a manifold **301**. An example of an manifold seal adaptor **301**having three inlet/outlets **30** and having three barrier traversing tubes **305** is provided in Figure 3D. The present disclosure further provides for, and includes, barrier traversing tubes **305** having different diameters and functions. In one aspect of the present disclosure a barrier traversing tube **305** is a bilayer tube, for example as illustrated in Figure 3C. In another aspect a barrier traversing tube(s) **305** is a trilayer tube, for example as illustrated in Figures 3A and 3B. In an aspect, an inlet/outlet **30** has a tube enabling a blood transfusion (*e.g.*, an outlet for flowing blood from the inner collapsible blood container **202**) and for spiking the inner collapsible blood container **202** of the blood storage device **20** with nutrients (*e.g.*, a spike port). Also provided for and included is the use of a such spike ports to introduce oxygen into the inner collapsible blood container **202** to re-oxygenate the blood prior to transfusion.

[0060] The present disclosure also provides for, and includes, an outer receptacle **201** that is substantially impermeable to oxygen having a permeability to oxygen of less than about 0.5 cc of oxygen per square meter per day. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 1.0 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.2 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.02 Barrer. In certain aspects, a membrane suitable for use in the preparation of an outer receptacle and other elements of the present disclosure are materials characterized by a Barrer value of less than 0.002 Barrer.

[0061] Materials and methods to prepare an outer receptacle **201** are known in the art. See, for example, U.S. Patent 7,041,800 issued to Gawryl *et al.*, U.S. Patent 6,007,529 issued to Gustafsson *et al.*, and U.S. Patent Application Publication No. 2013/0327677 by

McDorman. Impermeable materials are routinely used in the art and any suitable material can be used. In the case of molded polymers, additives are routinely added to enhance the oxygen (and CO_2) barrier properties. *See*, for example, U.S. Patent 4,837,047 issued to Sato *et al.* For example, U.S. Patent 7,431,995 issued to Smith *et al.* describes an oxygen- and carbon dioxide-impermeable receptacle composed of layers of ethylene vinyl alcohol copolymer and modified ethylene vinyl acetate copolymer, impermeable to oxygen and carbon dioxide ingress. In another aspect, the outer receptacle **201** is impermeable to oxygen and carbon dioxide.

[0062] In certain aspects, membranes that are substantially impermeable to oxygen may be laminated membranes. In an aspect, a laminated membrane that is substantially impermeable to oxygen is a laminated foil membrane. Membrane materials can be polymers or foil materials or multilayer constructions that are combinations of foils and polymers. In an aspect, a laminated membrane may be a polyester membrane laminated with aluminum. An example of a suitable aluminum laminated membrane, also known as a laminated foil, that is substantially impermeable to oxygen is known in the art. For example, U.S. Patent 4,798,728 to Sugisawa discloses aluminum laminated foils of nylon, polyethylene, polyester, polypropylene, and vinylidene chloride. Other laminated films are known in the art. For example, U.S. Patent 7,713,614 to Chow *et al.* discloses multilayer containers comprising an ethylene-vinyl alcohol copolymer (EVOH) resin that is substantially impermeable to oxygen. Additional materials suitable for an outer receptacle **201** include silicone oxide coated polyester, silicone oxide coated polypropylene, and silicone oxide coated nylon films. Suitable silicone oxide coated films include, but are not limited to, CERAMIS® silicone oxide coated films (available from Celplast Metallized Products Limited, Ontario, Canada). In an aspect, an outer receptacle **201** may be a barrier bag constructed by sealing three or four sides by means of heat sealing. The bag is constructed of a multilayer construction that includes materials that provide enhancement to O_2 and CO_2 barrier properties. The bag is constructed of a multilayer construction that includes materials that provide enhancement to O_2 and CO_2 barrier properties.

[0063] Table 1 below shows the oxygen transfer rate in Barrer for various bulk polymer materials tested at 23°C and 0% R.H. using 25.4 μm (1 mil) thick samples:

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Table 1: Oxygen transfer rate (OTR) in Barrer for various bulk polymer materials

Bulk Material Properties (25 μm, 23°C, 0% R.H.)	OTR (Barrer)
EVOH (ethylene vinyl alcohol)	0.00003 - 0.00007
Barex® 210 (acrylonitrile-methyl acrylate copolymer)	0.0001 - 0.0002
Barex® 218	0.0002
Biax Nylon-6	0.007 - 0.014
OPET (oriented polyester)	0.01 - 0.03
OPP (oriented polypropylene)	0.6 - 0.9
Cast PP (polypropylene)	0.8 - 1.1
HDPE (high density polyethylene)	0.8 - 1.1
OPS (oriented polystyrene)	1.6 - 2.2
LDPE (low density polyethylene)	2.5 - 3.0

[0064] Although EVOH has excellent barrier properties as a neat film, it rapidly loses these properties upon exposure to water vapor and especially with exposure to >70% R.H. Similarly, nylon-6 has good barrier properties that are susceptible to degradation in high moisture conditions. It is well known in the art to create multilayer laminated and/or coated structures to enhance the barrier properties over those of the bulk materials shown above. Such techniques and compositions include using a layer of EVOH disposed between layers of other polymers such as PA, PET, PE, PP or PVC to provide moisture protection to the EVOH layer and other desirable properties, thereby yielding a multilayer structure with excellent barrier properties. Such compositions are well known in the art and commercially available, such as the EVAL™ series of EVOH films from Kurary Company of America (Pasadena, TX).

[0065] Another method of producing an enhanced multilayer structure that is known in the art is by coating or metalizing a polymer substrate. Examples of such enhanced barrier films are shown in Table 2 below; since these are composite structures, the OTR is not dependent on the bulk film properties or thickness. An example of a suitable aluminum laminated membrane, also known as a laminated foil, that is substantially impermeable to oxygen is obtainable from Protective Packaging Corp. (Carrollton, TX).

Table 2: Enhanced Barrier Films

Enhanced Barrier Films (23°C, 0% R.H.)	OTR (Barrer)

Metallized OPET (oriented polyester)	0.022 - 0.24
PVOH-coated OPP (ExxonMobil AOH)	0.04
Metallized biax Nylon-6	0.11
PVDC (polyvinylidene chloride)-coated OPET	0.7 - 1.1
High Barrier PVDC-coated OPP	0.7 - 1.3
PVDC -coated biax Nylon-6	0.7 - 1.1
Metallized OPP	2.7 - 22.5
Sealable PVDC-coated OPP	3.2 - 7.6
(source: Polyprint.com)	

[0066] Another method of producing an enhanced multilayer structure that is known in the art is by coating a polymer substrate with a barrier coating of silica or alumina, followed by an additional coating or polymer laminate to protect the silica or alumina coating. In an aspect, the silica can be silicon oxide (SiOx). Examples of such enhanced barrier films are shown in Table 3 below.

Table 3: RollPrint® ClearFoil® Enhanced Barrier Films

RollPrint® ClearFoil® Enhanced Barrier Films	OTR (Barrer)	MVTR (gm/m^2-day-bar)
ClearFoil® V2	0.022	0.47
ClearFoil® D	0.131	0.93
ClearFoil® V	0.110	0.31
ClearFoil® M	0.044	0.31
ClearFoil® F	0.007	0.31
ClearFoil® A	0.087	0.62
ClearFoil® W3	0.015	0.062
ClearFoil® X	0.008	0.047
ClearFoil® Z	0.002	0.012
(source: Rollprint.com)		

[0067] The preferred structures include a PET base polymer outer layer, having good inherent oxygen barrier properties as a bulk material, coated with a middle layer of alumina to provide enhanced oxygen barrier properties over the PET and better optical clarity over a

silica middle layer, followed by a polyethylene inner layer for heat sealability in fabricating the outer receptacle **201**. The relative thickness of the alumina or silica layer primarily determines the oxygen barrier properties of the final structure of the film used in the fabrication of the outer receptacle **201**.

[0068] In another aspect, a preferred structure includes a PET base polymer outer layer, having good inherent oxygen barrier properties as a bulk material, coated with a middle layer of alumina to provide enhanced oxygen barrier properties over the PET and better optical clarity over silica middle layer, followed by a PVC inner layer for bonding to other PVC components and having good blood compatibility. In some aspects, the PVC can be plasticized with DEHP to provide for enhanced blood compatibility when blood is stored in contact with the surface.

[0069] Other manufacturers make similar products with similar oxygen transmission rates, such as Renolit Solmed Wrapflex® films (American Renolit Corp., City of Commerce, CA) and Celplast Ceramis® films (Celplast Metallized Products, Toronto, Ontario, Canada).

[0070] Another approach applicable to the preparation of SIO materials includes multilayer graphitic films made by gentle chemical reduction of graphene oxide laminates with hydroiodic and ascorbic acids. *See* Su *et al.*, "Impermeable barrier films and protective coatings based on reduced graphene oxide," *Nature Communications* 5, Article number: 4843 (2014). Nanoparticles to enhance oxygen barrier properties are also known in the art, for example, the multilayer barrier stack films provided by Tera-Barrier (Tera-Barrier Films Pte, Ltd, The Aries, Singapore) and described by Rick Lingle in *Packaging Digest Magazine* on August 12, 2014.

[0071] In aspects according to the present disclosure, an outer receptacle **201** may be prepared from a gas impermeable plastic. In an aspect, the gas impermeable plastic may be a laminate. In certain aspects, the laminate may be a transparent barrier film, for example, a nylon polymer or ethylene vinyl acetate (EVA). In an aspect, the laminate may be a polyester film. In an aspect, the laminate may be Mylar®. In certain aspects, the laminate may be a metalized film. In an aspect, the metalized film may be coated with aluminum. In another aspect, the coating may be aluminum oxide. In another aspect, the coating may be silicon oxide. In another aspect, the coating may be an ethylene vinyl alcohol copolymer (EVOH) laminated between layers of low density polyethylene (LDPE).

[0072] An outer receptacle **201** of the present disclosure may be formed of one or more parts prepared from a gas impermeable material including a plastic or other durable

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lightweight material. In some aspects, an enclosure may be formed of more than one material. In an aspect, an outer receptacle **201** may be formed of a material and coated with a gas impermeable material to prepare a gas impermeable enclosure. In an aspect, a rigid or flexible outer receptacle **201** may be prepared from a plastic that may be injection molded or blow molded. In aspects according to the instant disclosure, the plastic may be selected from polystyrene, polyvinyl chloride, or nylon. In an aspect, outer receptacle **201** materials may be selected from the group consisting of polyester (PES), polyethylene terephthalate (PET), polyethylene napthalate (PEN), polyethylene (PE), high-density polyethylene (HDPE), polyvinyl chloride (PVC), polyvinylidene chloride (PVDC), low-density polyethylene (LDPE), polypropylene (PP), polystyrene (PS), high impact polystyrene (HIPS), polyamides (PA) (*e.g.*, nylon), acrylonitrile butadiene styrene (ABS), polyacrylonitrile (PAN), polycarbonate (PC), polycarbonate/acrylonitrile butadiene styrene (PC/ABS), polyurethanes (PU), melamine formaldehyde (MF), plastarch material, phenolics (PF), polyetheretherketone (PEEK), polyetherimide (PEI) (Ultem), polylactic acid (PLA), polymethyl methacrylate (PMMA), polytetrafluoroethylene (PTFE), and urea-formaldehyde ethylvinyl acetate (EVA). In some aspects, ethylene vinyl alcohol copolymer (EVOH) may be used when part of a multilayered laminate. In certain aspects, outer receptacle **201** comprises polyethylene terephthalate (PET). In certain aspects, outer receptacle **201** comprises nylon-6. In certain aspects, the outer receptacle **201** may be polyethylene. In some aspects, the polyethylene outer receptacle **201** may comprise one or more polyethylene components that are welded together.

[0073] The present disclosure provides for, and includes, the preparation of outer receptacles **201** and inner collapsible blood container **202** from a membrane or film. As used herein, membranes generally refer to materials used to prepare an inner collapsible blood container **202** and films are used to refer to materials used to prepare outer receptacle **201**. A membrane comprises one or more layers of materials in the form of a sheet that allows or prevents one or more substances to pass through from one side of the sheet to the other side of the sheet. As used herein, membranes may also be prepared as tubes suitable for connecting together components of blood storage devices **20**, blood collection kits, or connecting together elements of blood collection devices, additive solution bags, leukocyte reduction filters, and depletion devices including depletion devices provided in U.S. Provisional Application No. 62/131,130, filed March 15, 2015. As used throughout, it is understood that a membrane of the present disclosure may be formed as a sheet or a tube

depending on the application. Also as previously provided, membranes to prepare outer receptacles **201** are substantially impermeable to oxygen while an inner collapsible blood container **202** is permeable to oxygen.

[0074] The present disclosure provides for and includes the preparation of outer receptacles **201** using heat sealing, blow molding, and injection molding techniques. Suitable materials for preparing outer receptacles **201** using heat sealing, blow molding, vacuum forming and injection molding include PET, standard and multilayer, polypropylene, polyethylene, polycarbonate, ABS, and other polymers known to those skilled in the art. Methods to prepare blow molded and injection molded outer receptacles **201** are known in the art, for example, a multilayer structure comprised of a barrier layer of ethylvinyl alcohol (EVOH or EVA) situated between two layers of polypropylene (PP) and offered by Kortec (Kortec, Inc., Rowley, MA) and also as described in U.S. Patent 5,906,285 issued to Slat. Additives that strengthen the oxygen and CO_2 barrier properties of the polymers prior to molding or during their formulation or during setup are known in the art. One example is multilayer polymer co-injection resulting in a multilayer PET. Such a barrier resin is typically incorporated at the preform stage as an inner layer with PET on both sides, making PET the liquid contact layer as well as the outside layer. As provided below, suitable blow molded or injection molded outer receptacles **201** are impermeable to oxygen. In certain aspects, suitable heat sealed, vacuum formed, blow molded, or injection molded outer receptacles **201** are substantially impermeable both oxygen and carbon dioxide.

[0075] The present disclosure provides for, and includes, two types of materials for the preparation of either permeable or substantially impermeable membranes. In an aspect, permeable membranes according to the present disclosure provide for the passage of substances through the material, specifically but not necessarily exclusively, oxygen. In certain aspects, membranes are selected to permit the passage of oxygen and carbon dioxide while preventing the passage of water, proteins, salts (*e.g.*, plasma components) and cells (*e.g.*, red blood cells, white blood cells, and platelets). The rate of passage through a material depends on one or more properties including particle size, phase of material (liquid vs. gas), hydrophilicity, hydrophobicity, or solubility. The rate of passage, or flux, through a material also depends on the presence or absence of a driving force such as a difference in pressure (or partial pressure), differences in temperature, or differences in concentration between one side of the membrane and the other. The flux through a membrane is known as the membrane

permeation flux. The membrane permeation flux of substances through a membrane is inversely proportional to the thickness of the membrane.

[0076] Membrane permeation flux, for a gas, is defined as the volume flowing through the membrane per unit area per unit time. The SI unit used is $m^3/m^2 \cdot s$. For gases and vapors, the volume is strongly dependent on pressure and temperature. Accordingly, permeation fluxes for gases are often given in terms of standard temperature and pressure (STP) which is defined as 0 °C and 1 atmosphere (1.0013 bar) (*e.g.*, 273 °K and 760 Torr). As noted above, the rate of passage depends on a driving force or difference between the two sides of the membrane, and this dependence is incorporated in the permeability coefficient, P, or simply the permeability.

[0077] Permeability (P) is defined as the permeability flux per unit of driving force per unit of membrane thickness. The SI unit for the permeability coefficient P is provided in Table 4 A common unit for gas separation, as in the present disclosure, is the Barrer and is also presented in Table 4. The term "cm^3 gas (STP)/cm^2s" refers to the volumetric trans-membrane flux of the diffusing species in terms of standard conditions of 0 °C and 1 atmosphere pressure, the term cm refers to the membrane thickness, and cm-Hg refers to the trans-membrane partial pressure driving force for the diffusing species. Permeability must be experimentally determined.

Table 4: Permeability Units

	Units of Permeability
"Volumetric" permeability	$1\ Barrer = \frac{10^{-10} \cdot cm^3\ gas(STP) \cdot (cm\ membrane\ thickness)}{(cm^2\ membrane\ area) \cdot s \cdot (cmHg\ pressure)}$
"Molar" permeability	$\frac{mol}{m \cdot Pa \cdot s}(SI\ units) = \frac{(mol,\ permeating) \cdot (m\ membrane\ thickness)}{(m^2\ membrane\ area) \cdot s \cdot (Pa\ pressure)}$

[0078] Membranes suitable for the methods and devices according to the present disclosure include dense membranes, porous membranes, asymmetric membranes, and composite membranes. In certain aspects, suitable membranes may be multilayered membranes. In other aspects, suitable membranes are prepared from inorganic materials. Dense membranes are membranes prepared from solid materials that do not have pores or voids. Materials permeate dense membranes by processes of solution and diffusion. Examples of dense membranes include standard blood bag materials such as PVC, PVC-DEHP, PVC-Citrate, PVC-DINCH, polyolefins such as PE, LDPE, UHMWPE, PP, and OPP,

urethanes, and silicone membranes (polydimethyl siloxane, or PDMS). Also included and provided for in the present disclosure are porous membranes that have pores of a particular range of sizes that separate on the basis of size exclusion. Examples of porous membranes suitable for use according to the present disclosure include PVDF and polysulfone membranes. Examples of composite membranes suitable for use according to the present disclosure are EMD Millipore's GVHP hydrophobic PVDF having 1.0 μm or 0.22 μm pore sizes.

[0079] Included and provided for by the present disclosure are composite membranes that are made of more than one material, often as laminates, wherein a dense material is applied to a porous support layer. Examples of composite membranes suitable for use according to the present disclosure are EMD Millipore's GVSP superhydrophobic PVDF having 1.0 μm or 0.22 μm pore sizes.

Table 5: Permeability of Fluoropolymers (200 μm thick; 23 °C):

	Silicone	PTFE	PFA	FEP	ETFE	CTFE	ECTFE	PVDF	PVF	THV
Water vapor	36000	5	8	1	2	1	2	2	7	1.73
Oxygen	500	1500	n/a	2900	350	60	100	20	12	696
Nitrogen	280	500	n/a	1200	120	10	40	30	1	217
CO_2	2700	15000	7000	4700	1300	150	400	100	60	2060

[0080] The present disclosure provides for, and includes, inner collapsible blood containers **202** prepared from membranes **206** that are characterized primarily by their permeability to oxygen. Unless indicated otherwise, a "substantially impermeable membrane" refers to membranes that are substantially impermeable to oxygen. However, in certain devices and methods, the membranes may be further characterized by the permeability or impermeability to carbon dioxide. For certain applications, the membrane material is substantially impermeable to oxygen and provides a barrier to the introduction of oxygen to the blood, blood component, or a blood collection kit comprised of multiple components. Such substantially impermeable membranes are generally used to prepare outer receptacles of the present disclosure. Suitable substantially impermeable membranes may also be used to prepare tubing for connective components of the devices and kits. Substantially impermeable membranes may comprise a monolayer or be laminated sheets or tubes having two or more layers.

[0081] The present disclosure provides for, and includes, inner collapsible blood containers **202** having a permeability of at least 3 Barrer. In certain aspects, the collapsible

blood container **202** is substantially permeable to oxygen and has a permeability between 3 and 350 Barrer. In certain aspects, the inner collapsible blood container **202** is substantially permeable to oxygen and has a permeability between 3 and 11 Barrer. In certain aspects, the inner collapsible blood container **202** is substantially permeable to oxygen and has a permeability of between 11 and 350 Barrer. In certain aspects, the inner collapsible blood container **202** is substantially permeable to oxygen and has a permeability of between 11 and 99 Barrer. In certain aspects, the inner collapsible blood container **202** is substantially permeable to oxygen and has a permeability of between 99 and 250 Barrer.

[0082] Applications for using inner collapsible blood containers **202** having a permeability of between 3 and 350 Barrer include those wherein the blood transferred into and contained within the inner collapsible blood container has a suitably reduced oxygen content and protection from oxygen ingress during storage is desired. In certain aspects, an inner collapsible blood container **202** has a permeability of between 3 and 11 Barrer. In certain aspects, an inner collapsible blood container **202** has a permeability of between 11 and 350 Barrer. In certain aspects, the inner collapsible blood container **202** is substantially permeable to oxygen and has a permeability of between 11 and 99 Barrer. In certain aspects, an inner collapsible blood container **202** has a permeability of between 99 and 250 Barrer. In an aspect, an inner collapsible blood container 202 does not have a permeability of more than 350 Barrer. In another aspect, an inner collapsible blood container 202 does not have a permeability of 350 to 500 Barrer.

[0083] The present disclosure provides for, and includes, inner collapsible blood containers **202** having membranes **206** that have an oxygen permeability of between 3 and 11 Barrer. In certain aspects, the inner collapsible blood container is permeable to oxygen and has a permeability of 3 to 11 Barrer, and are exemplified by inner collapsible blood containers made from PVC-DEHP, PVC- Citrate, or PVC-DINCH. In certain aspects, the inner collapsible blood container is permeable to oxygen and has a permeability of 4.3 Barrer, and is exemplified by inner collapsible blood containers made from PVC-DEHP.

[0084] In certain aspects, the use of an oxygen permeable inner collapsible blood container **202** having a permeability of between 3 and 11 Barrer include those wherein the ingress of oxygen into the blood through inlet tube **205** may be removed by gas transfer through the inner collapsible blood container **202** and adsorbed by the oxygen sorbent **207**. In certain aspects, the use of an oxygen permeable inner collapsible blood container **202** having a permeability of between 11 and 99 Barrer include those wherein the ingress of

oxygen into the blood through inlet tube **205** may be removed by gas transfer through the inner collapsible blood container **202** and adsorbed by the oxygen sorbent **207**.

[0085] The present disclosure also provides for, and includes, inner collapsible blood containers **202** having membranes **206** that are substantially permeable to oxygen. Membranes **206** that are substantially permeable to oxygen are generally used in the present disclosure for the preparation of inner collapsible blood containers **202**. Substantially permeable membranes **206** may comprise a monolayer or may comprise a laminated structure having two or more layers.

[0086] In an aspect, oxygen permeable membranes **206** having a permeability to oxygen of greater than 11 Barrer are used for the preparation of a collapsible blood container **202**. In another aspect, oxygen permeable membranes **206** having a permeability to oxygen greater than 99 Barrer are used for the preparation of a collapsible blood container **202**. In yet another aspect, oxygen permeable membranes **206** have a permeability to oxygen of greater than 200 Barrer. In certain aspects, oxygen permeable membranes **206** suitable for use in the preparation of a collapsible blood container **202** are characterized by a Barrer value of greater than 3. In other aspects, oxygen permeable membranes **206** suitable for use in the preparation of a collapsible blood container **202** are characterized by a Barrer value of greater than 11. In certain other aspects, oxygen permeable membranes **206** suitable for use in the preparation of a collapsible blood container **202** are characterized by a Barrer value of greater than 99. Examples of oxygen permeable membranes **206** suitable for use in the preparation of a collapsible blood container **202** include Membrana Accurel® PP flat sheet membranes (Membrana division of Celgard, LLC, Charlotte, NC), PP flat sheet membranes from Sterlitech (Kent, WA), Metricel® PP hydrophobic filter membranes (Pall Corp., Port Washington, NY), Propafilm™ RGP, RF and RGN series of biaxially oriented polypropylene (BOPP) films from Innovia (Innovia Films, Inc., Atlanta, GA), P-Derm™ PS-1033 and PS-1045 silicone sheets from Polymer Sciences (Polymer Sciences, Inc., Monticello, IN), Silpuran® silicone sheets from Wacker (Wacker Silicones, Inc., Adrian MI), PVDF microporous membranes such as the GVHP and GVSP series from Millipore (EMD Millipore, Bedford, MA), and polysulfone microporous membranes such as from Pacific Membranes (Pacific Membranes, Inc., San Diego, CA) or the MicroPES® membrane from Membrana.

[0087] In an aspect, a membrane **206** that is substantially permeable to oxygen can be dense membranes prepared from non-porous materials. Examples of suitable materials that

are capable of high oxygen permeability rates include silicones, polyolefins, epoxies, and polyesters. In another aspect, membranes that are substantially permeable to oxygen can be porous membranes prepared from organic polymers. A membrane **206** that is substantially permeable to oxygen may be prepared from a material selected from the group consisting of PVDF rendered hydrophobic, polytetrafluoroethylene (PTFE), polyamide (nylon), cellulose esters, polysulfone, polyethersulfone, polypropylene rendered hydrophobic, and polyacrylonitrile.

[0088] The present disclosure provides for, and includes, preparing membranes **206** that are substantially permeable to oxygen, not only by selecting the material, but also by selecting and controlling the thickness. As provided above, permeability is proportional to the thickness of the membrane. Accordingly, improved permeability may be achieved by decreasing the thickness of the membrane. In certain aspects, the minimum thickness is determined by its strength and resistance to puncture and tearing.

[0089] The present disclosure also provides for, and includes, membranes **206** that are substantially permeable to oxygen that are prepared using blow molding and injection molding techniques. Suitable materials for preparing inner collapsible blood containers **202** using blow molding and injection molding include silicone materials such as Bluestar 4350, 50 durometer, Silbione grade liquid silicone rubber and Shin-Etsu KEG-2000-40A/B Liquid Silicone. The silicone durometer choice is carefully chosen for collapsibility and permeability, followed by a well controlled wall thickness. Thinner materials will have a higher permeability. Methods to prepare blow molded and injection molded collapsible blood containers **202** are known in the art, for example, U.S. Patent 4,398,642 issued to Okudaira *et al.*; U.S. Patent 7,666,486 issued to Sato *et al.*; U.S. Patent 8,864,735 issued to Sano *et al.*; and U.S. Patent Application Publication No. 2012/0146266 by Oda *et al.* In an aspect, a blow molded collapsible blood container **202** can be prepared using LDPE used in the manufacture of collapsible water containers. As provided below, suitable blow molded or injection molded collapsible blood containers **202** have a permeability to oxygen of at least 3 Barrer.

[0090] Applications for using oxygen permeable inner collapsible blood containers **202** having a permeability of between 3 and 350 Barrer include those wherein the blood transferred into and contained within the inner collapsible blood container have reduced oxygen content, wherein further oxygen reduction during storage is desired.

[0091] The present disclosure provides for, and includes, a membrane **206** that is substantially permeable to oxygen and may further be permeable to water vapor. Those of skill in the art would recognize that permeability to oxygen is often, but not always, accompanied by permeability to water vapor, as well other gases. Further, a person of skill in the art would recognize that as the permeability to oxygen increases, without more, the permeability to water vapor may also increase. According to the present disclosure, a membrane **206** may be selected based on its selective permeability for oxygen or oxygen and carbon dioxide while minimizing the permeability to water. Membranes **206** for use in collapsible blood containers **202** are selected to minimize water vapor permeability and to prevent the escape of water from the plasma or additive solutions during storage. In order to properly preserve the blood in the storage container for extended periods, up to and including 64 days, the blood should not be allowed to lose significant amounts of moisture from its content plasma. Accordingly the collapsible blood containers **202** are prepared from membranes **206** that are selected with consideration of the Moisture Vapor Transfer Rate (MVTR) of the material. In aspects according to the present disclosure, membranes **206** that are substantially permeable to oxygen have measured MVTR of 30 g/m^2/24hrs or less when tested at 23°C and 100% R.H.. MVTR's above 30, without more, are unsuitable above 30 g/m^2 /24hrs.

[0092] The MVTR of materials being used at temperatures and conditions lower than those typically used for standard MVTR testing, such as in ASTM F-1249, notably the temperatures and conditions used for the refrigerated storage of blood and blood components, have actual MVTR's much lower than the values reported for the standardized tests conducted at higher temperatures. The MVTR of most materials is strongly dependent on the temperature being used or tested. For example, Propafilm® RHX heavy duty barrier coated film (PVDC-coated BOPP, Innovia Films, Inc., Atlanta, GA) has a MVTR of 2.9 g/m^2/24 hrs. when tested at 38°C and 90% R.H., but only a MVTR of 0.3 g/m^2/24 hrs. when tested at 23°C and 85% R.H.

[0093] The OTR (Oxygen Transmission Rate) of most materials is not dependent on the R.H. conditions. For example, Propafilm® RHX heavy duty barrier coated film (PVDC-coated BOPP, Innovia Films, Inc., Atlanta, GA) has an OTR of 2.1 Barrer when tested at either 23°C and 85% R.H. or when tested at 25°C and 0% R.H. per ASTM F-1927.

[0094] The moisture loss performance of an exemplary collapsible blood container membrane, Renolit ES-3000 (PVC-DEHP), which has a reported MVTR of 8.06 g/m^2/24hrs

at standardized test conditions of 23°C and 100% R.H. per ASTM F-1249, is well known and accepted in the industry for refrigerated storage of blood and routinely provides less than 2% weight loss for a plastic blood storage container as required per ISO 3826-1:2013. Other exemplary membranes used for the processing and storage of blood and blood components include Renolit ES-4000 (PVC-Citrate) having a reported MVTR of 26.4 g/m^2/24hrs at 23°C and 100% R.H., Renolit 3406 (PVC-DINCH) having a reported standard MVTR of 5.5 g/m^2/24hrs at 23°C and 100% R.H., and Renolit 8300 (polyolefin-elastomer blend), having a reported MVTR of 3.5 g/m^2/24hrs at 23°C and 100% R.H.

[0095] The outer receptacle **201** provides further moisture barrier protection in addition to the oxygen barrier protection of the inner collapsible blood container **202**. Due to the added protection of the outer receptacle **201**, materials having higher MVTR's relative to the exemplary Renolit ES-3000 PVC-DEHP material are suitable for use in fabricating the collapsible inner blood container **202** while providing for higher OTR for the deoxygenation of the stored blood.

[0096] In aspects according to the present disclosure, a collapsible blood container **202** is prepared from a membrane material **206** having an MVTR of between 30 and 0.001 g/m^2/day. On certain aspects, the MVTR is between 0.1 and 10 g/m^2/day. In yet other aspects, the MVTR is between 1 and 8 g/m^2/day.

[0097] In aspects according to the present disclosure, the MVTR is measured in g/m^2/day at 23°C and 100% R.H., and the collapsible blood container **202** is prepared from membrane material **206** that is PVC having a MVTR of about 3 g/m^2/day. In other aspects, the PVC may contain DEHP and have a MVTR of about 8 g/m^2/day. In other aspects, the PVC may contain DINCH and have a MVTR of about 5 g/m^2/day. In other aspects, the PVC may contain Citrate and have a MVTR of about 10 g/m^2/day. Membrane material **206** may also be prepared from foil films such as an aluminum foil films that allow for very little moisture loss and can provide an MVTR as low as 0.001 g/m^2/day.

[0098] Polyethylene films are well known for having good moisture barrier properties, but relatively poor oxygen barrier properties. For example, LDPE is reported to have a MVTR of 17 g/m^2-day but an OTR of 2500 cc/m^2-day, while in comparison nylon is reported to have a MVTR of 260 g/m^2-day and an OTR of 95 cc/m^2-day. The barrier performance of polyethylene is proportional to the polymer density, thus low density PE materials have lower barrier performance properties than high density PE materials. Films such as 76 micrometer thick polyethylene providing MVTR of 6 g/m^2/day provide breathability of oxygen without

compromising moisture content. Also films of MVTR of 52 or 97 g/m²/day can provide good moisture barrier for the blood products. Polyethylene and other polyolefin materials having good moisture barrier characteristics are suitable for use as a permeable membrane **206** in preparing inner collapsible blood container **202**.

Table 6: Water vapor permeability and water vapor/N2 selectivity for various polymers at 30 °C extrapolated to water vapor activity 0

Polymer	Abbreviation	H2O Permeability (Barrer)	Selectivity [H2O/N2]
Polyethylene	(PE)	12	5.71
Polyvinylalcohol	(PVA)	19	33,300
Polypropylene	(PP)	68	230
Polyamide 6 (Nylon 6)	(PA-6)	275	11,000
Polyvinylchloride	(PVC)	275	12,500
Polyacrylonitril	(PAN)	300	1,875,000
Polyimide (Kapton)	(PI)	640	5,333,300
Polystyrene	(PS)	970	400
Polycarbonate	(PC)	1,400	4,700
Polysulfone	(PSF)	2,000	8,000
Natural rubber	(NR)	2,600	300
Polyethersulfone	(PES)	2,620	10,480
Polyphenyleneoxide	(PPO)	4,060	1,070
Cellulose acetate	(CA)	6,000	24,000
Sulfonated polyethersulofon	(SPES)	15,000	214,300
Ethyl cellulose	(EC)	20,000	6,060
Polydimethylsiloxane	(PDMS)	40,000	140
Sulfonated polyetheretherketon	(SPEEK)	61,000	10,166,700
1000PEO40PBT60	PEO-PBT	104,000	40,000

[0099] As used herein, an inner collapsible blood container **202** is permeable to oxygen. In certain aspects, an inner collapsible blood container **202** is permeable to oxygen and carbon dioxide. In other aspects, an inner collapsible blood container **202** is permeable to oxygen and impermeable to carbon dioxide.

[00100] The permeability of an inner collapsible blood container **202** need only be sufficient to provide for the transfer of oxygen away from stored blood that may leak into the stored blood from, for example tube **205**. In other aspects, the permeability of an inner collapsible blood container **202** may be sufficiently permeable to provide for additional deoxygenation of stored blood when combined with a sufficient amount of sorbent **207**. In certain aspects, the outer receptacle **201** and collapsible blood container **202** may be a single

integrated device **20** comprising a multilayered membrane having a substantially impermeable layer and an innermost blood compatible layer. A single integrated device **20** may further include a sorbent **207** comprising as a layer between the substantially impermeable layer and the innermost blood compatible layer.

[00101] In the course of development of blood storage devices **20** of the present disclosure, it was observed that by the appropriate selection and design of inlet/outlet **30**, tubing **304**, tubing **205** and combinations thereof, the necessity to efficiently and continually remove ingressed oxygen could be significantly reduced. The selection of inner collapsible blood containers **202** having a permeability of between 3 and 11 Barrer is provided in devices wherein the ingressed oxygen has been essentially reduced or eliminated. Not to be limited by theory, it is believed that the ingressed oxygen enters the system largely through tubing **205** or its bond **302,** which can form gap **209,** and is transported to the collapsible blood container **202**. In order to maintain the oxygen depleted state of the blood, it needs to be removed by passing out of an oxygen permeable collapsible blood container **202**, diffusing through the headspace and binding to oxygen sorbent **207**. Accordingly, the materials used to prepare collapsible blood container **202** should be selected to be as permeable as possible. In contrast, when ingressed oxygen can be largely eliminated, the choice of materials suitable for collapsible blood container **202** can include less permeable materials as provided herein.

[00102] As used herein, inner collapsible blood containers that are significantly less permeable to oxygen, are collapsible blood container **202** that have a permeability of between 3 and 11 Barrer.

[00103] The present disclosure provides for, and includes, a collapsible blood container **202** that is relatively permeable to oxygen and is a membrane **206** prepared from polyvinyl chloride (PVC). In aspects according the present disclosure, the collapsible blood container **202** can be prepared from a PVC membrane **206** having a thickness of between 25 μm and 450 μm, preferably from 50 μm to 400 μm, and more preferably between 150 μm and 400 μm. In some aspects, the collapsible blood container **202** can be prepared from a PVC membrane **206** having a thickness of between 25 μm and 250 μm. In other aspects, the collapsible blood container **202** can be prepared from a PVC membrane **206** having a thickness of between 350 μm and 450 μm. In some aspects, the collapsible blood container **202** is prepared from a PVC membrane **206** having a thickness of 381 μm.

[00104] The use of PVC in the manufacture of collapsible blood containers is well known in the art. The use of various plasticizers in various PVC formulations is also well known in

the art, and includes the use of diethylhexyl phthalate (DEHP) for long term storage of red blood cells. In addition to increasing the flexibility of the PVC, DEHP also increases the permeability of PVC to oxygen. Accordingly, the present disclosure provides for, and includes, a collapsible blood container **202** comprising PVC doped with DEHP to increase permeability. Typical manufacture of collapsible blood containers from PVC-DEHP utilizes radiofrequency (RF) welding of a pair of films to conveniently fabricate a bag structure, with such individual films having a thickness of 350 μm to 400 μm. An exemplary PVC-DEHP film is the Renolit ES-3000 film (American Renolit Corp., City of Commerce, CA).

[00105] Due to the relatively low oxygen permeability of such films and the need for higher oxygen permeability for platelet storage, other plasticizers for PVC have found utility in the fabrication of collapsible blood containers and include the use of citrate, among others (see, for example, "The Role of Poly(Vinyl Chloride) in Healthcare" by Colin R. Blass, copyright 2001 Rapra Technology, Ltd., ISBN:1-85957-258-8). A suitable example of a PVC-citrate film is the Renolit ES-4000 film (American Renolit Corp., City of Commerce, CA). The plasticity of PVC and the permeability of PVC may also be increased by the inclusion of DINCH, bis(7-methyloctyl) cyclohexane-1,2-dicarboxylate (also identifiable as E.C. Number 431-890-2 and available from BASF as Hexamoll® DINCH). A collapsible blood container **202** of the present disclosure may be comprised of PVC doped with DINCH to increase oxygen permeability. Among the advantages of using citrate or DINCH in a collapsible blood container **202** is that some concerns have been raised regarding the safety of DEHP, even while DEHP improves the storability of red blood cells. Not to be limited by theory, it is believed that deoxygenation of the red blood cells allows for the removal of DEHP from the blood storage system while not compromising the quality and storability of the red blood cells that would otherwise be provided by DEHP.

[00106] The present disclosure provides for suitable PVC materials for use in a collapsible blood container **202** that is permeable to oxygen. The use of a PVC-citrate film such as Renolit ES-4000 having a thickness of from 25 μm to 450 μm, preferably from 50 μm to 400 μm, and more preferably from 150 μm to 400 μm is suitable for providing a collapsible blood container having the desired characteristics of relatively high oxygen permeability for PVC membranes, having an oxygen permeability of at least 3 Barrer, and having good RF welding and joining characteristics and high tensile strength. In certain aspects the present disclosure provides for a collapsible blood container **202** prepared from a PVC membrane **206** that is relatively permeable to oxygen having a thickness of from 25 μm to 450 μm, suitable for the

continued reduction of oxygen of the blood contained therein over the duration of storage for 42 days, or up to 64 days. In certain aspects the present disclosure provides for a collapsible blood container **202** prepared from a PVC membrane **206** that is relatively permeable to oxygen having a thickness of from 350 μm to 400 μm, suitable for the maintenance of the reduced oxygen level of the blood contained therein over the duration of storage for 42 days, or up to 64 days.

[00107] The present disclosure provides for, and includes, a collapsible blood container **202** that is substantially permeable to oxygen and is a membrane **206** prepared from silicone. In aspects according the present disclosure, the collapsible blood container **202** can be prepared from a silicone membrane **206** having a thickness of between 20 μm and 500 μm. In other aspects, the collapsible blood container **202** can have a thickness of between 30 μm and 400 μm. In other aspects, the collapsible blood container **202** can have a thickness of between 30 μm and 200 μm. In another aspect the collapsible blood container **202** is between 50 μm and 150 μm thick. In certain aspects, the present disclosure provides for a collapsible blood container **202** prepared from a silicone membrane **206** that is substantially permeable to oxygen having a thickness of from 50 μm to 150 μm, suitable for the continued reduction of oxygen of the blood contained therein over the duration of storage for 42 days, or up to 64 days.

[00108] In aspects according the present disclosure, the collapsible blood container **202** can be prepared from a silicone membrane **206** having a thickness of between 20 μm and 400 μm. In other aspects, the collapsible blood container **202** can have a thickness of between 20 μm and 200 μm. In other aspects, the collapsible blood container **202** can have a thickness of between 40 μm and 300 μm. In another aspect, the collapsible blood container **202** is between 40 μm and 400 μm thick. In yet another aspect, the collapsible blood container **202** is between 300 μm and 450 μm thick. In a further aspect, the thickness of the collapsible blood container **202** can be between 350 μm and 450 μm. The present disclosure provides for, and includes, a collapsible blood container **202** that is 450 μm in thickness. In another aspect, the collapsible blood container **202** is 425 μm thick. In yet another aspect, the collapsible blood container **202** is 400 μm thick. In an additional aspect, the collapsible blood container **202** is 350 μm thick. In certain aspects the present disclosure provides for a collapsible blood container **202** prepared from a silicone membrane **206** that is substantially permeable to oxygen having a thickness of from 350 μm to 500 μm, suitable for the

maintenance of the reduced oxygen level of the blood contained therein over the duration of storage for 42 days, or up to 64 days.

[00109] Suitable silicone membranes **206** include commercially available membranes. Non-limiting examples of silicone membranes are available from Wacker Silicones, such as the Silpuran® brand of medical grade silicone sheet membranes (Wacker Silicones, Adrian, MI) and Polymer Sciences PS-1033 and PS-1044 P-Derm® silicone elastomer membranes (Polymer Sciences, Inc., Monticello, IN). In an aspect, the silicone membrane may be Polymer Sciences PS-1033 or Silpuran® 6000 silicone. Silicone membranes can be prepared from various liquid silicone rubber (LSR) materials, which are available from a number of silicone suppliers, such as Wacker Silicones (Adrian, MI), Shin-Etsu Silicones of America (Akron, OH), NuSil Technology (Carpenteria, CA), and Blue Star Silicones (East Brunswick, NJ), to name a few.

[00110] In an aspect according to the present disclosure, a collapsible blood container **202** can be manufactured from silicone by various molding methods such as compression molding, injection molding, and insert molding, and also adhesive bonding of silicone sheets using silicone adhesives. In one aspect according to the present disclosure, a pair of silicone sheets are bonded together around the periphery with a section of silicone inlet tubing in place in the seam using silicone adhesive. In another aspect according to the present disclosure, a silicone liquid rubber is injection molded over a form to create a three-sided shape, which is then further bonded to closure on the remaining fourth side around a silicone inlet tube using a silicone adhesive. In another aspect according to the present disclosure, a silicone liquid rubber is injection molded over a form to create a three-sided shape, which is then insert molded onto a closure shape on the remaining fourth side that incorporates an inlet tubing into the closure shape. In another aspect according to the present disclosure, a silicone liquid rubber is diluted in a suitable solvent, such as xylene, hexane or tetrahydrofuran, and dip coated over a form to create a three-sided shape, which is then insert molded onto a closure shape on the remaining fourth side that incorporates an inlet tubing into the closure shape.

Mixed Membrane inner bags

[00111] The present disclosure provides for, and includes, a collapsible blood container **202** that is prepared from more than one type of membrane **206**. In an aspect, a collapsible blood container **202** comprises a first membrane **206** and a second different membrane **206** suitably bonded to prepare a container. In another aspect, a collapsible blood container **202** comprises

a membrane **206** combined with a second membrane **206** that has a permeability of less than about 30% of the permeability of first membrane **206**. In an aspect, the second membrane **206** may comprise a rigid structure joined to an oxygen permeable membrane **206**. In aspects according to the present disclosure, the second membrane **206** is heat sealed, laminated or boned to membrane **206**.

[00112] The present disclosure provides for, and includes, a collapsible blood container **202** that is substantially permeable to oxygen and is a microporous membrane **206** prepared from polytetrafluoroethylene, or polyvinylidene fluoride, also known as polyvinylidene difluoride (PVDF). In certain aspects, the PVDF membrane is a hydrophobic microporous membrane that is substantially permeable to oxygen.

[00113] In aspects according to the present disclosure, the microporous PVDF membrane **206** comprises pores having a range of between 0.01 μm and 2.0 μm. In other aspects, the microporous PVDF membrane **206** comprises pores having a range of between 0.01 μm and 1.0 μm. In some aspects, a microporous PVDF membrane **206** has a pore size of between 0.03 μm and 1.0 μm in diameter. In other aspects, a microporous PVDF membrane **206** has a pore size of between 0.03 μm and 0.45 μm in diameter.

[00114] In aspects according to the present disclosure, the void fraction of a PVDF membrane **206** used to prepare a collapsible blood container **202** is between 20 and 80%. In another aspect, the void fraction of a PVDF membrane **206** used to prepare a collapsible blood container **202** is between 35 and 50%.

[00115] In certain aspects, the permeability of PVDF membranes **206** having micropores greater than about 1.0 μm may allow fluid to permeate through the membrane, compromising both the fluid containment as well as the oxygen and carbon dioxide permeability. To overcome this permeability at high pore sizes, so called "super-hydrophobic" membranes can be employed wherein the contact angle is greater than 150°. As used herein and known in the art, the contact angle quantifies the wettability of a solid surface and is theoretically described by Young's equation. In certain aspects according the present disclosure, the use of non-hydrophobic PVDF materials is not recommended as the surface tension of the material is lower and allows for fluid to seep through the pores even at the ranges stated above.

[00116] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a PVDF permeable membrane **206** having a pore size of between 0.1 and 0.8 μm in diameter. In other aspects, micropores of porous PVDF membranes may be from 0.22 to 0.8 μm in diameter. In an aspect, the micropores of porous

PVDF membranes are from 0.2 to 1.0 μm. In another aspect, the micropores of porous PVDF membranes may be greater than 0.1 and less than 1.0 μm. In a further aspect, the micropore of the porous PVDF membrane ranges from 0.05 to 1.0 μm. In some aspects, the micropores of porous PVDF membranes may be greater than 0.3 or 0.4 μm. In other aspects, the micropores of porous PVDF membranes may be greater than 0.5 or 0.6 μm.

[00117] In aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of less than 1.0 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of less than 0.8 μm. In certain aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of less than 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of less than 0.45 μm.

[00118] In an aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.1 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.22 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.20 μm. In a further aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.45 μm. In yet a further aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a PVDF membrane **206** having a micropore size of 0.8 μm.

[00119] In aspects according to the present disclosure, the PVDF membrane may be less than 250 μm thick. In certain aspects, the membrane is greater than 10 μm thick. In some aspects, the PVDF membrane may be between 10 and 250 μm thick. In other aspects, the PVDF membrane may be between 10 and 125 μm thick or between 25 and 150 μm thick. In an aspect, the PVDF membrane may be between 50 and 125 μm thick, 75 and 125 μm thick,

50 and 150 μm thick, 75 and 150 μm thick, 100 and 125 μm thick, 150 and 250 μm thick, or between 25 and 150 μm thick. In an aspect, the membrane **206** of inner collapsible blood container **202** is 20 μm thick. In another aspect, the membrane **206** of inner collapsible blood container **202** is 30 μm thick. In yet another aspect, the membrane **206** of inner collapsible blood container **202** is 50 μm thick. In a further aspect, the membrane **206** of inner collapsible blood container **202** is 76 μm thick. In an aspect, the membrane **206** of inner collapsible blood container **202** is 120 μm thick.

[00120] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a PVDF permeable membrane **206** that is between 100 and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a PVDF permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 100 and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a PVDF permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 50 and 150 μm thick.

[00121] Examples of suitable PVDF membranes for the preparation of inner collapsible blood containers that are permeable to oxygen according to the present disclosure include VVSP 115 μm thick/0.1 μm pore; GVSP 115 μm thick/0.22 μm pore; HVSP 115 μm thick/0.45 μm pore; DVSP 115 μm thick/0.65 μm pore; BVSP 115 μm thick/1.0 μm pore; VVHP 107 μm thick/0.1 μm pore; GVHP 125 μm thick/0.22 μm pore; HVHP 115 μm thick/0.45 μm pore; or DVHP 115 μm thick/0.65 μm pore.

[00122] Suitable PVDF membranes **206** include commercially available membranes. Non-limiting examples of PVDF membranes **206** are available from Millipore Corporation, Bedford, MA. In an aspect, the PVDF membrane **206** may be obtained from Millipore Corporation, Bedford, MA. An example of such a PVDF membrane **206** is the VVSP, GVSP, HVSP, DVSP, BVSP, VVHP, GVHP, HVHP, or DVHP.

[00123] The present disclosure provides for, and includes, a collapsible blood container **202** that is substantially permeable to oxygen and is a microporous membrane **206** prepared from polysulfone. In certain aspects, the polysulfone membrane **206** is a hydrophobic microporous membrane **206** that is substantially permeable to oxygen.

[00124] In aspects according to the present disclosure, the microporous polysulfone membrane **206** comprises pores having a range of between 0.01 μm and 2.0 μm. In other aspects, the microporous polysulfone membrane **206** comprises pores having a range of

between 0.01 μm and 1.0 μm. In some aspects, a microporous polysulfone membrane **206** has a pore size of between 0.03 μm and 1.0 μm in diameter. In other aspects, a microporous polysulfone membrane **206** has a pore size of between 0.03 μm and 0.45 μm in diameter.

[00125] In aspects according to the present disclosure, the void fraction of a polysulfone membrane **206** used to prepare a collapsible blood container **202** is between 20 and 80%. In another aspect, the void fraction of a polysulfone membrane **206** used to prepare a collapsible blood container **202** is between 35 and 50%.

[00126] In certain aspects, the permeability polysulfone membranes having micropores greater than about 0.2 μm may allow fluid to permeate through the membrane, compromising both the fluid containment and the oxygen and carbon dioxide permeability. To overcome this permeability at high pore sizes, so called "super-hydrophobic" membranes can be employed wherein the contact angle is greater than 150°. As used herein and known in the art, the contact angle quantifies the wettability of a solid surface and is theoretically described by Young's equation. In certain aspects according the present disclosure, the use of non-hydrophobic polysulfone materials is not recommended as the surface tension of the material is lower and allows for fluid to seep through the pores even at the ranges stated above.

[00127] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polysulfone permeable membrane **206** having a pore size of between 0.03 μm and 0.8 μm in diameter. In other aspects, micropores of porous polysulfone membranes may be from 0.22 μm to 0.8 μm in diameter. In an aspect, the micropores of porous polysulfone membranes are from 0.2 μm to 1.0 μm. In another aspect, the micropores of porous polysulfone membranes may be greater than 0.1 μm and less than 1.0 μm. In a further aspect, the micropore of the porous polysulfone membrane ranges from 0.05 μm to 1.0 μm. In some aspects, the micropores of porous polysulfone membranes may be greater than 0.3 μm or 0.4 μm. In other aspects, the micropores of porous polysulfone membranes may be greater than 0.5 μm or 0.6 μm.

[00128] In aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of less than 1.0 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of less than 0.8 μm. In certain aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of less

than 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of less than 0.45 μm.

[00129] In an aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.1 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.22 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.20 μm. In a further aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.45 μm. In yet a further aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.8 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.03 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 0.05 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polysulfone membrane **206** having a micropore size of 1.2 μm.

[00130] In aspects according to the present disclosure, the polysulfone membrane may be less than 250 μm thick. In certain aspects, the membrane is greater than 10 μm thick. In some aspects, the polysulfone membrane may be between 10 and 250 μm thick. In other aspects, the polysulfone membrane may be between 10 and 125 μm thick or 25 and 150 μm thick. In an aspect, the polysulfone membrane may be between 50 and 125 μm thick, 75 and 125 μm thick, 50 and 150 μm thick, 75 and 150 μm thick, 100 and 125 μm thick, 150 and 250 μm thick, or between 25 and 150 μm thick. In an aspect, the membrane **206** of inner collapsible blood container **202** is 20 μm thick. In another aspect, the membrane **206** of inner collapsible blood container **202** is 30 μm thick. In yet another aspect, the membrane **206** of inner collapsible blood container **202** is 50 μm thick. In a further aspect, the membrane **206**

of inner collapsible blood container **202** is 76 μm thick. In an aspect, the membrane **206** of inner collapsible blood container **202** is 120 μm thick.

[00131] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polysulfone permeable membrane **206** that is between 100 and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polysulfone permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 100 and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polysulfone permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 50 and 150 μm thick.

[00132] Examples of suitable polysulfone membranes **206** for the preparation of inner collapsible blood containers that are permeable to oxygen according to the present disclosure include SS003AH 10-250 μm thick/0.03 μm pore; SS005AH 10-250 μm thick/0.05 μm pore; SS010AH 10-250 μm thick/0.1 μm pore; SS020AH 10-250 μm thick/0.2 μm pore; SS045AH 10-250 μm thick/0.45 μm pore; SS065AH 10-250 μm thick/0.65 μm pore; SS080AH 10-250 μm thick/0.8 μm pore; or SS120AH 10-250 μm thick/1.2 μm pore.

[00133] Suitable polysulfone membranes **206** include commercially available membranes. Non-limiting examples of polysulfone membranes **206** are available from Pacific Membranes. In an aspect, the polysulfone membrane may be SS120AH, SS080AH, SS065AH, SS045AH, SS020AH, SS010AH, SS005AH, or SS003AH.

[00134] The present disclosure provides for, and includes, a collapsible blood container **202** that is substantially permeable to oxygen and is a microporous membrane **206** prepared from polyolefin. The present disclosure also provides for, and includes, a collapsible blood container **202** that is impermeable to oxygen prepared from a polyolefin film. In certain aspects, the polyolefin membrane is a hydrophobic microporous membrane that is substantially permeable to oxygen. Examples of oxygen permeable polyolefin membranes **206** suitable for use in the preparation of a collapsible blood container **202** include Membrana Accurel® PP flat sheet membranes (Membrana division of Celgard, LLC, Charlotte, NC), PP flat sheet membranes from Sterlitech (Kent, WA), Metricel® PP hydrophobic filter membranes (Pall Corp., Port Washington, NY), Propafilm™ RGP, RF and RGN series of biaxially oriented polypropylene (BOPP) films from Innovia (Innovia Films, Inc., Atlanta, GA). In certain aspects, the polyolefin membrane is a biaxially oriented polypropylene (BOPP) film that is substantially permeable to oxygen. Examples of suitable polyolefin films

include the Propafilm™ RGP, RF and RGN series of biaxially oriented polypropylene (BOPP) coextruded films from Innovia (Innovia Films, Inc., Atlanta, GA), having an oxygen permeability of 140 to 450 Barrer.

[00135] In aspects according to the present disclosure, the microporous polyolefin membrane **206** comprises pores having a range of between 0.01 μm and 2.0 μm. In other aspects, the microporous polyolefin membrane **206** comprises pores having a range of between 0.01 μm and 1.0 μm. In some aspects, a microporous polyolefin membrane **206** has a pore size of between 0.03 μm and 1.0 μm in diameter. In other aspects, a microporous polyolefin membrane **206** has a pore size of between 0.1 μm and 0.45 μm in diameter.

[00136] In certain aspects according to the present disclosure, the use of non-hydrophobic polyolefin materials is not recommended as the surface tension of the material is lower and allows for fluid to seep through the pores even at the ranges stated above.

[00137] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polyolefin permeable membrane **206** having a pore size of between 0.1 μm and 0.45 μm in diameter. In other aspects, micropores of porous polyolefin membranes may be from 0.1 μm to 0.2 μm in diameter.

[00138] In aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of less than 1.0 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of less than 0.5 μm. In certain aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of less than 0.2 μm.

[00139] In an aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of 0.1 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of 0.2 μm. In a further aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a polyolefin membrane **206** having a micropore size of 0.45 μm.

[00140] In aspects according to the present disclosure, the polyolefin membrane may be less than 250 μm thick. In certain aspects, the membrane is greater than 50 μm thick. In

some aspects, the polyolefin membrane may be between 50 and 250 μm thick. In other aspects, the polyolefin membrane may be between 75 and 110 μm thick or between 140 and 180 μm thick.

[00141] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polyolefin permeable membrane **206** that is between 50 and 250 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polyolefin permeable membrane **206** having a pore size of between 0.1 μm and 0.45 μm in diameter and that is between 75 μm and 200 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polyolefin permeable membrane **206** having a pore size of between 0.1 μm and 0.2 μm in diameter and that is between 75 μm and 200 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a polyolefin permeable membrane **206** having a pore size of between 0.2 μm and 0.45 μm in diameter and that is between 140 μm and 200 μm thick.

[00142] Examples of suitable polyolefin membranes for the preparation of inner collapsible blood containers that are permeable to oxygen according to the present disclosure include those described in U.S. Patent 4,440,815 issued to Zomorodi *et al.*, Membrana Accurel® PP flat sheet membranes (Membrana division of Celgard, LLC, Charlotte, NC), PP flat sheet membranes from Sterlitech (Kent, WA), Metricel® PP hydrophobic filter membranes (Pall Corp., Port Washington, NY), Propafilm™ RGP, RF and RGN series of biaxially oriented polypropylene (BOPP) films from Innovia (Innovia Films, Inc., Atlanta, GA).

[00143] In certain aspects, suitable membranes **206** that are substantially permeable to oxygen may be multilayered membranes. In certain aspects, the multilayered membranes are hydrophobic microporous membranes that are substantially permeable to oxygen. Suitable multilayered membranes **206** include multilayered membranes having two or more materials selected from the group consisting of PVDF rendered hydrophobic, PTFE, nylon, cellulose esters, polysulfone, polyethersulfone, polypropylene rendered hydrophobic, and polyacrylonitrile.

[00144] The present disclosure provides for, and includes, a collapsible blood container **202** that is substantially permeable to oxygen and is a microporous membrane **206** prepared from an extruded, woven, non-woven single layer or multilayered membrane. In certain aspects, the multilayered membrane is a hydrophobic microporous membrane that is substantially permeable to oxygen.

[00145] In aspects according to the present disclosure, the microporous multilayered membrane comprises pores having a range of between 0.01 μm and 2.0 μm. In other aspects, the microporous multilayered membrane **206** comprises pores having a range of between 0.01 μm and 1.0 μm. In some aspects, a microporous multilayered membrane **206** has a pore size of between 0.03 μm and 1.0 μm in diameter. In other aspects, a microporous multilayered membrane **206** has a pore size of between 0.03 μm and 0.45 μm in diameter.

[00146] In aspects according to the present disclosure, the void fraction of a multilayered membrane **206** used to prepare a collapsible blood container **202** is between 20 and 80%. In another aspect, the void fraction of a multilayered membrane **206** used to prepare a collapsible blood container **202** is between 35 and 50%.

[00147] In certain aspects, the permeability of multilayered membranes having micropores greater than about 1.0 μm may allow fluid to permeate through the membrane, compromising both the fluid containment and the oxygen and carbon dioxide permeability. To overcome this permeability at high pore sizes, so called "super-hydrophobic" membranes can be employed wherein the contact angle is greater than 150°. As used herein and known in the art, the contact angle quantifies the wettability of a solid surface and is theoretically described by Young's equation. In certain aspects according the present disclosure, the use of non-hydrophobic multilayered materials is not recommended as the surface tension of the material is lower and allows for fluid to seep through the pores even at the ranges stated above.

[00148] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a multilayered permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter. In other aspects, micropores of porous multilayered membranes may be from 0.22 μm to 0.8 μm in diameter. In an aspect, the micropores of porous multilayered membranes are from 0.2 μm to 1.0 μm. In another aspect, the micropores of porous multilayered membranes may be greater than 0.1 μm and less than 1.0 μm. In a further aspect, the micropore of the porous multilayered membrane ranges from 0.05 μm to 1.0 μm. In some aspects, the micropores of porous multilayered membranes may be greater than 0.3 or 0.4 μm. In other aspects, the micropores of porous multilayered membranes may be greater than 0.5 or 0.6 μm.

[00149] In aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of less than 1.0 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a

multilayered membrane **206** having a micropore size of less than 0.8 μm. In certain aspects according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of less than 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of less than 0.45 μm.

[00150] In an aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.1 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.22 μm. In another aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.20 μm. In a further aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.45 μm. In yet a further aspect, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.65 μm. In another aspect according to the present disclosure, a blood storage device **20** comprises an inner collapsible blood container **202** comprising a multilayered membrane **206** having a micropore size of 0.8 μm.

[00151] In aspects according to the present disclosure, the multilayered membrane **206** may be less than 250 μm thick. In certain aspects, the membrane is greater than 10 μm thick. In some aspects the multilayered membrane **206** may be between 10 and 250 μm thick. In other aspects, the multilayered membrane may be between 10 and 125 μm thick or 25 and 150 μm thick. In an aspect, the multilayered membrane **206** may be between 50 and 125 μm thick, 75 and 125 μm thick, 50 and 150 μm thick, 75 and 150 μm thick, 100 and 125 μm thick, 150 and 250 μm thick or between 25 and 150 μm thick, 100 and 125 μm thick, 150 and 250 μm thick or between 25 and 150 μm thick. In another aspect, the membrane **206** of inner collapsible blood container **202** is 30 μm. In yet another aspect, the membrane **206** of inner collapsible blood container **202** is 50 μm. In a further aspect, the membrane **206** of inner collapsible blood container **202** is 76 μm. In an aspect, the membrane **206** of inner collapsible blood container **202** is 120 μm thick

[00152] In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a multilayered permeable membrane **206** that is between 100

and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a multilayered permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 100 μm and 125 μm thick. In certain aspects according to the present disclosure, the collapsible blood container **202** is prepared from a multilayered permeable membrane **206** having a pore size of between 0.1 μm and 0.8 μm in diameter and that is between 50 μm and 150 μm thick.

[00153] The present disclosure provides for, and includes, a collapsible blood container **202** having resistance to tearing. As used herein, "tear resistance" or "tear strength" is measured in kN/m. In aspects according the present disclosure, the collapsible blood container **202** should be prepared from oxygen permeable materials that are also resistant to tearing. Measures of tear resistance are known in the art, for example, ASTM D-412, which can also be used to measure tensile strength, modulus, and elongations. In certain aspects, collapsible blood container **202** should be prepared from oxygen permeable materials that are resistant to the formation of a tear (*e.g.*, tear initiation). Methods of measuring tear initiation and tear propagation are known in the art, for example, ASTM D-624. Other methods include measuring the tensile strength and the elongation at break according to DIN 53 504-S1.

[00154] In an aspect according to the present disclosure, a collapsible blood container **202** should be prepared from oxygen permeable materials having a tear strength of at least 10 N/mm according to test method ASTM D-1004. In an aspect, the tear strength is at least 25 N/mm. In some aspects, the tear strength is at least 50 N/mm. In some aspects, the tear strength is at least 100 N/mm. The blood storage devices **20** further provide for, and include, collapsible blood containers **202** prepared from materials having a tear strength of between 10 to 100 N/mm. In aspects of the present disclosure, a reduced tear strength is provided for collapsible blood containers **202** wherein the outer receptacle **201** has a tear strength of at least 50 N/mm. Generally, the tear strength of a collapsible blood container **202** decreases with increasing permeability. It will be appreciated by those of skill in the art, that materials are to be selected to maintain the overall integrity of the blood storage device **20** so that the potentially biohazardous blood materials are contained should the device **20** be mishandled during processing (e.g., dropped or crushed).

[00155] The present disclosure includes and provides for a blood storage device **20** having an inner collapsible blood container **202** and further including one or more spacers **213** that ensure the separation of the outer receptacle **201** and the inner collapsible blood container **202**. The spacer **213** provides for the maintenance of the headspace in the blood storage

device **20** to ensure efficient diffusion of the oxygen to the sorbent **207**. A spacer **213** can be prepared from one or more of the materials selected from the group consisting of a mesh, a molded mat, a woven mat, a non-woven mat, a strand veil, and a strand mat. In certain aspects, the spacer **213** can be integrated directly into the collapsible blood container **202** as ribs, dimples, or other raised feature that maintains a separation between the outer receptacle **201** and the inner collapsible blood container **202**. The present specification also includes and provides for a spacer **213** to be integrated into the outer receptacle **201** as ribs, dimples, or other suitable raised feature capable of maintaining a separation between the outer receptacle **201** and the inner collapsible blood container **202**. In certain aspects, the presence of spacer **213** provides consistency to the assembly from a standpoint of manufacturing technique and layering of the inner and outer films allowing for repeatable oxygen level maintenance. In other aspects, the presence of spacer **213** facilitates further oxygen reduction for during a storage period. By providing a spacer **213**, an inner membrane **206** can be prevented from become laminated or "stuck to" the membrane or material of outer receptacle **201** via mechanical or physical means. Not to be limited by theory, it is thought that if sticking or lamination were to occur, the oxygen preservation or further oxygen reduction of the assembly may be compromised as the oxygen encounters additional barriers to diffusion.

[00156] In certain aspects, the spacer **213** can also provide for a protective surrounding layer around the collapsible blood container **202**, increasing the resistance to burst fracture of the collapsible blood container, such as when inadvertently dropped or subjected to other traumatic forces in handling. In an aspect, a spacer **213** providing a protective layer includes an open cell reticulated polyurethane foam as the spacer **213** material. Such spacer **213** material can have from about 10 pores per inch (ppi) to about 100 ppi. In an aspect, the spacer **213** has 45 ppi with a height of 3.2 mm (0.125 in).

[00157] In addition to the pores, a spacer **213** providing a protective layer has a height from about 3.2 mm (0.125 in) to about 12.8 (0.5 in). In another aspect the spacer **213** has a height of about 6.4 mm (0.25 in). In another aspect the spacer **213** has a height from about 1.5 mm (0.064 in) to about 12.8 mm (0.50 in). In another aspect, spacer **213** has a height from about 1.2 mm (0.05 in) to about 10 mm (0.4 in). In another aspect, spacer **213** has a height from about 1.2 mm (0.05 in) to about 12.8 mm (0.5 in).

[00158] The present disclosure provides for and includes blood storage devices **20** for storing oxygen depleted blood comprising an outer receptacle **201**, a collapsible blood container **202**, at least one inlet/outlet **30**, and an oxygen sorbent **207** situated within said

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outer receptacle **201**. In certain aspects, the oxygen sorbent **207** is situated between outer receptacle **201** and the collapsible blood container **202**. In other aspects, the oxygen sorbent is located within the collapsible blood container **202** and contained in a second blood compatible container. In yet other aspects, the oxygen sorbent **207** is situated as a layer in a multilayered membrane, wherein the outer layer is outer receptacle **201** and the innermost layer is collapsible blood container **202**.

[00159] The present disclosure provides for, and includes, sorbents **207** capable of binding to and removing oxygen from an environment. Unless provided otherwise, the term "sorbent" refers to oxygen sorbents and scavengers. As used herein, "oxygen scavenger" or "oxygen sorbent" is a material that binds irreversibly to or combines with O_2 under the conditions of use. The term "oxygen sorbent" may be used interchangeably herein with "oxygen scavenger." In certain aspects according the present disclosure, a material may bind to or combines with oxygen irreversibly. In other aspects, oxygen may bind to a sorbent material and have a very slow rate of release, k_{off}. In an aspect, the oxygen may chemically react with some component of the material and be converted into another compound. Any material where the off-rate of bound oxygen is much less than the residence time of the blood can serve as an oxygen scavenger.

[00160] As used herein, the amount of sorbent is provided as having a certain binding capacity of oxygen as measured by volume (*e.g.*, cubic centimeters (cc) or milliliters (ml)) at standard temperature and pressure (*e.g.*, 0 °C (273.15 Kelvin) and $1.01x10^5$pa (100 kPa, 1 bar, 0.986 atm, 760 mmHg) of pressure). In other aspects, oxygen sorbents and scavengers are further capable of binding to and removing carbon dioxide from an environment. In certain aspects, sorbent **103** may be a mixture of non-toxic inorganic and/or organic salts and ferrous iron or other materials with high reactivity toward oxygen, carbon dioxide, or oxygen and carbon dioxide. In certain aspects, an oxygen sorbent or scavenger is combined with a carbon dioxide sorbent. In other aspects, the presence or absence of carbon dioxide binding capabilities of an oxygen sorbent is not necessary.

[00161] Suitable oxygen sorbents or scavengers are known in the art. Suitable oxygen sorbents according to the present disclosure have minimum oxygen adsorption rates of 0.8 ml/min. Sorbents having suitable adsorption profiles bind at least 45 ml O_2 within 60 minutes, 70 ml O_2 within 120 minutes, and 80 ml O_2 within 180 minutes. Suitable sorbents may have both higher capacity and binding rates.

[00162] Non-limiting examples of oxygen scavengers or sorbents include iron powders and organic compounds. Examples of O_2 sorbents include chelates of cobalt, iron, and Schiff bases. Additional non-limiting examples for O_2 sorbents may be found in U.S. Patent 7,347,887 issued to Bulow *et al.*, U.S. Patent 5,208,335, issued to Ramprasad *et al.*, and U.S. Patent 4,654,053 issued to Sievers *et al.*, U.S. Patent 4,366,179 issued to Nawata *et al.* Oxygen sorbent materials may be formed into or incorporated in fibers, microfibers, microspheres, microparticles, and foams.

[00163] In certain aspect$_s$, suitable sorbents include those obtainable from Multisorb Technologies (Buffalo, NY), Sorbent Systems/Impak Corporation (Los Angeles, CA), Dessicare, Inc. (Reno, NV) or Mitsubishi Gas Chemical America (MGC) (New York, NY). Exemplary oxygen sorbents include iron-based oxygen scavengers, such as Multisorb Technologies StabilOx® packets, Sorbent Systems P/N SF100PK100 100 cc oxygen absorber, and Mitsubishi Gas Chemical America (MGC) Ageless® SS-200 oxygen absorber. MGC also provides sorbents suitable for the methods and devices of the present disclosure. Such suitable oxygen sorbents include the MGC Ageless® SS-200 oxygen absorber.

[00164] In aspects according to the present disclosure, a sorbent may be an oxidizable organic polymer having a polymeric backbone and a plurality of pendant groups. Examples of sorbents with a polymeric backbone include a saturated hydrocarbon (< 0.01% carbon-carbon double bonds). In some aspects, the backbone can contain monomers of ethylene or styrene. In an aspect, a polymeric backbone may be ethylenic. In another aspect, an oxidizable organic compound may be ethylene/vinyl cyclohexene copolymer (EVCH). Additional examples of substituted moieties and catalysts are provided in U.S. Patent Publication No. 2003/0183801 by Yang *et al.* In additional aspects, an oxidizable organic polymer can also comprise substituted hydrocarbon moieties. Examples of oxygen scavenging polymers include those described by Ching *et al.*, International Patent Publication WO 99/48963. Oxygen scavenging materials may include those provided in U.S. Patent 7,754,798 issued to Ebner *et al.*, U.S. Patent 7,452,601 issued to Ebner *et al.*, or U.S. Patent 6,387,461 issued to Ebner *et al.*

[00165] As used herein, sorbents of the present disclosure may be either free or contained in a permeable enclosure, container, envelope, *etc.* In certain aspects, sorbent is provided in

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one or more sachets made of materials having high porosity and essentially no resistance to the transport of gases. Examples of such materials include spun polyester films, perforated metallic foils, spun polyethylene films (Tyvek®), perforated foils, polymers, paper, and combinations thereof.

[00166] The present disclosure further includes, and provides for, sorbent **207** incorporated as one or more laminated layers of an outer receptacle **201** substantially impermeable to oxygen. Polymeric sorbents such as those described above may be laminated to sheets used to prepare an outer receptacle using methods known in the art, including soft contact lamination, thermal lamination, or solvent lamination.

[00167] The present disclosure further includes, and provides for, sorbents **207** formed inside the pores of porous micro-glass fibers or encapsulated in other inert materials. The encapsulation of transition-metal complexes within the pores of a porous material may be achieved by using a ship-in-a-bottle synthesis in which the final molecule is prepared inside the pores by reacting smaller precursors. Examples of such encapsulated sorbents are known in the art, for example, as described by Kuraoka *et al.*, "Ship-in-a-bottle synthesis of a cobalt phthalocyanine/porous glass composite membrane for oxygen separation," *Journal of Membrane Science, 286(1-2)*:12-14 (2006). In some aspects, porous glass fibers may be manufactured as provided in U.S. Patent 4,748,121 issued to Beaver *et al.* In another aspect, a sorbent can formed as a porous sheet product using papermaking/non-woven wet-laid equipment. Sheets with O_2 scavenging formulations may be as described in U.S. Patent 4,769,175 issued to Inoue, which can be formed and then encapsulated with a silicone film.

[00168] The present disclosure provides for, and includes, a suitable amount of sorbent **207** sufficient to absorb and retain residual oxygen present after manufacture, ingressed oxygen ingressed during storage of the device **20** and prior to use, oxygen introduced during filling of device **20**, residual oxygen contained in the oxygen depleted blood, and oxygen that ingresses during the blood storage period. Prior anaerobic blood storage devices, such as those described by Bitensky, do not recognize nor address the problem of oxygen ingress, particularly through the transfer tubing and collection tubing. Traditional inlets and outlets fail to provide a sufficient oxygen barrier. Moreover, while the present disclosure provides for certain elements that minimize, or even largely eliminate oxygen ingress, absolute impermeability is not practicable. Accordingly, the blood storage devices **20** of the present

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disclosure incorporate sorbent **207** having both sufficient capacity and appropriate binding kinetics to ensure that the anaerobic environment is maintained. In addition, in certain aspects, sorbent **207** may be further provided to further reduce the level of oxygen in oxygen depleted blood. Finally, the amount of sorbent **207** must also provide for a reliable and reproducible shelf life of blood storage devices **20**.

[00169] In aspects according to the present disclosure, a blood storage device **20** has an amount of oxygen sorbent **207** having an oxygen binding capacity of at least 20 cc oxygen. In an aspect, the oxygen binding capacity of sorbent **207** in a blood storage device **20** is at least 30 cc oxygen. In an aspect, the oxygen binding capacity of sorbent **207** in a blood storage device **20** is at least 50 cc oxygen. In an aspect, the oxygen binding capacity of sorbent **207** in a blood storage device **20** is at least 100 cc oxygen. In another aspect, the oxygen binding capacity of sorbent **207** is at least 25 or 30 cc oxygen. In yet further aspects, the oxygen binding capacity of sorbent **207** is at least 30 or 45 cc oxygen.

[00170] In aspects according to the present disclosure, the oxygen capacity of sorbent **207** is at least 20 cc. In an aspect, the oxygen capacity of sorbent **207** is at least 20 cc but less than 100 cc. In an aspect, the oxygen capacity of sorbent **207** is at least 20 cc but less than 75 cc. In an aspect, the oxygen capacity of sorbent **207** is at least 30 cc but less than 50 cc. In an aspect, the oxygen capacity of sorbent **207** is at least 20 cc but less than 250 cc. In certain aspects, the oxygen capacity of sorbent **207** is between 50 and 200 cc. In other aspects, the oxygen capacity of sorbent **207** is between 100 and 200 cc. In other aspects, the oxygen capacity of sorbent **207** is between 20 and 50 cc.

[00171] In other aspects according to the present disclosure, the oxygen capacity of sorbent **207** may be little as 6 cc. In certain aspects, the oxygen capacity of sorbent **207** is between 6 cc and 20 cc. In other aspects, the oxygen capacity of sorbent **207** is about 6 cc. In an aspect, the oxygen capacity of sorbent **207** is between 6 and 10 cc. In another aspect, the oxygen capacity of sorbent **207** is 10 cc. The present disclosure provides for, and includes, an oxygen sorbent **207** having a suitable capacity and suitable rate of oxygen binding to maintain oxygen depleted blood in its depleted state and ensure an appropriate shelf life of blood storage device **20**. In aspects according to the present disclosure, sorbent **207** has a minimal oxygen absorption rate of at least 11 cc/week/gram. In another aspect, sorbent **207**, having an oxygen absorption rate of at least 11 cc/week/gram and can bind at least 22 cc of oxygen within 2 weeks. In an aspect, sorbent **207**, having an oxygen absorption rate of at least 11 cc/week/gram and can bind at least 54 cc of oxygen within 4 weeks. In yet another

aspect, sorbent **207**, having an oxygen absorption rate of at least 11 cc/week/gram and can bind at least 99 cc of oxygen within 9 weeks.

[00172] As used herein, "carbon dioxide scavenger" is a material that binds to or combines with carbon dioxide under the conditions of use. The term "carbon dioxide sorbent" may be used interchangeably herein with "carbon dioxide scavenger." In certain aspects, carbon dioxide sorbents may be non-reactive, or minimally reactive with oxygen. In other aspects, oxygen sorbents may exhibit a secondary functionality of carbon dioxide scavenging. Carbon dioxide scavengers include metal oxides and metal hydroxides. Metal oxides react with water to produce metal hydroxides. The metal hydroxide reacts with carbon dioxide to form water and a metal carbonate. In certain aspects according the present disclosure, a material may bind to or combine with CO_2 irreversibly. In aspects according to the present disclosure, a material may bind CO_2 with higher affinity than hemoglobin. In other aspects, a sorbent material may bind CO_2 with high affinity such that the carbonic acid present in the blood or RBC cytoplasm is released and absorbed by the sorbent. In other aspects, CO_2 binds to a sorbent material and has a very slow rate of release, k_{off}. In an aspect, the carbon dioxide can chemically react with some component of the material and be converted into another compound.

[00173] Carbon dioxide scavengers are known in the art. In certain aspects according to the present disclosure, a carbon dioxide scavenger may be calcium oxide. Reaction of calcium oxide with water produces calcium hydroxide that may react with carbon dioxide to form calcium carbonate and water. In certain aspects according the present disclosure, the water for the production of calcium hydroxide is obtained via diffusion of blood derived water vapor through the inner oxygen permeable container. In another aspect, the water may be provided by the environment through the outer receptacle that is substantially impermeable to oxygen. In yet another aspect, the water may be included with the outer receptacle of the oxygen depletion device.

[00174] Non-limiting examples of CO_2 scavengers include oxygen scavengers and carbon dioxide scavengers provided by Multisorb Technologies (Buffalo, NY) and Sodasorb® from Grace. Oxygen scavengers may exhibit a secondary functionality of carbon dioxide scavenging.

[00175] In aspects according to the present disclosure, O_2 depletion media and CO_2 depletion media may be blended to a desired ratio to achieve desired results. In another aspect, the sorbent chemistry may have an affinity to both O_2 and CO_2.

[00176] The present disclosure further includes and provides for sorbents contained in sachets. As used herein, a "sachet" is any enclosure that encloses and contains an oxygen sorbent, a carbon dioxide sorbent, or a combination of oxygen and carbon dioxide sorbent(s). Sachets according the present disclosure are contained within overwrap material that is both oxygen and carbon dioxide permeable. In certain aspects, the overwrap material may be a combination of two or more materials, at least one of the materials being oxygen and carbon dioxide permeable. Suitable overwrap materials have a known biocompatible profile or meet ISO 10993.

[00177] Sachets are sealed so that the sorbent contents are wholly contained within the overwrap material and do not allow the sorbent to leak, leach, migrate, or otherwise exit its overwrap package. Sachets may take any shape, though typically take a rectangular or square shape. In an aspect, the sachet is about 50 x 60 mm. In an aspect, the oxygen sorbent **207** binds 20 cc oxygen per sachet at STP. In an aspect, the oxygen sorbent **207** binds 10 cc oxygen per sachet at STP. In an aspect, the oxygen sorbent **207** binds 25 cc oxygen per sachet at STP. In an aspect, the oxygen sorbent **207** binds from 10 to 50 cc oxygen per sachet at STP. In an aspect, the oxygen sorbent **207** binds from 10 to 75 cc oxygen per sachet at STP. In an aspect, the oxygen sorbent **207** binds from 10 to 20 cc oxygen per sachet at STP. In certain aspects according to the present disclosure, a sachet has a total oxygen adsorption capacity of 50 cc O_2 at STP. In certain other aspects of the present disclosure, a sachet has a total oxygen absorption capacity of at least 100 cc O_2 at STP.

[00178] In aspects according to the present disclosure, the oxygen sorbent **207** may be provided in one or more sachets. In another aspect, the oxygen sorbent **207** is provide in a single larger sachet. In other aspects, the oxygen sorbent **207** is provided in two sachets distributed within the headspace between the inner collapsible container **202** and the outer receptacle **201**. In yet other aspects, the oxygen sorbent **207** is provided in four sachets distributed within the headspace between the inner collapsible container **202** and the outer receptacle **201**. In aspects according to the present disclosure, a blood storage device **20** may comprise 2 to 20 sorbent packages.

[00179] In aspects according to the present disclosure, a blood storage device **20** includes from 0.5 to 150 grams of sorbent **207** contained in one or more sachets. Suitable sorbents are provided above at [00161] to [00164]. In an aspect, a blood storage device **20** includes from 0.5 to 5 grams of sorbent **207** contained in one or more sachets. In other aspects, a blood storage device **20** includes from 8 to 24 grams of sorbent **207** contained in one or more

sachets. In another aspect, a blood storage device **20** includes 8, 16, or 24 grams of sorbent **207**. In an aspect, a blood storage device **20** includes of 8 grams of SS-200 sorbent **207**, or its equivalent contained in one sachet. In another aspect, a blood storage device **20** includes 16 grams of SS-200 sorbent **207**, or its equivalent contained in two sachets. In another aspect, a blood storage device **20** includes 24 grams of SS-200 sorbent **207**, or its equivalent contained in three sachets. In a further aspect, a blood storage device **20** includes 14 grams of sorbent **207** contained in one Dessicare pack or its equivalent. In an aspect, a blood storage device **20** includes about 1 grams of sorbent **207**. In yet another aspect, a blood storage device **20** includes about 2 grams of sorbent **103**. In an aspect, a blood storage device **20** includes about 3 or 4 grams of sorbent **207** contained in one or more sachets. In an aspect, a blood storage device **20** includes about 0.75 or 1.0 grams of sorbent **207** contained in one or more sachets. The sachets can be square, rectangular, circular, or elliptical.

[00180] In aspects according to the present disclosure, the blood storage device **20** includes an oxygen indicator **215** that can serve as an early warning for users that the storage device has become compromised. In aspects according to the present disclosure, compromise of the outer barrier bag **102** or the inlet/outlets **30** results in oxygen within the outer bag headspace. Such unwanted oxygen ingress can occur prior to use (*e.g.*, during shelf storage) or after the device **20** is filled with oxygen depleted blood. An oxygen indicator **215** according to the present disclosure includes devices that are usually constructed of a chemistry on paper or tablet form and enclosed in an oxygen permeable film pack. As used herein, an oxygen indicator **215** is sensitive enough to detect levels of oxygen above 1 Torr of partial oxygen pressure. In the presence of oxygen, an indicator will change color (for example, from pink to purple). This alerts the user of a device **20** that the oxygen impermeable protection may be compromised and to take additional precautions as appropriate. In an aspect, blood in a compromised device **20** may be treated as regular conventional blood during or at storage end. As provided herein, an oxygen indicator **215** is typically integrated into the blood storage bag during bag manufacture. In certain aspects, an oxygen indicator **215** is laminated to a transfer tape such as 3M 1524A and dispensed into the outer bag side facing the inner bag. A exemplary oxygen indicator **215** includes, but is not limited to, the Dry Pak Wondersensor (Dry Pak Industries, Inc., Encino, CA).

[00181] The present disclosure provides for, and includes, tubing **205** to connect a blood storage device **10**, and other components of a blood collection kit together. Tubing **205** provides a number of functions in a blood collection kit, including but not limited to

preventing contamination of blood collection kit and providing for sterile transfer and sterile docking when connections to external sterile tubing is necessary. In the course of development of anaerobic storage bags and as illustrated below in Example 8, it became evident that the primary source of ingressed oxygen both prior to, and during, blood storage device use was tubing **205**. Accordingly, the devices and methods of the present disclosure overcome the limitations of the prior art and minimize the impact of oxygen in the storage environment.

[00182] In aspects according to the present disclosure, tubing **205** is prepared from materials that are substantially impermeable to oxygen and optionally impermeable to carbon dioxide. In many aspects, tubing **205** is prepared from dense materials that do not have pores or voids. In other aspects, tubing **205** is prepared as a barrier traversing tube **305** as illustrated in Figure 3 having at least one oxygen barrier layer **307** and at least one blood compatible layer **306**. In certain aspects, an oxygen barrier layer **307** and blood compatible layer **306** are the same layer. Also provided for and included in the present disclosure is barrier traversing tube **305**, having an inner blood compatible layer **306**, an intermediate oxygen barrier layer **307**, and outer layer **308**. In certain aspects, outer layer **308** provides protection for the oxygen barrier layer **307** and prevents the formation of holes, cracks or other breaches in the oxygen barrier. In certain aspects, outer layer **308** also provides for the formation of bond **302**. The present disclosure provides for a barrier traversing tube **305,** having a bilayer of a blood compatible layer **306** and a outer layer **308**. In certain aspects, an oxygen barrier layer **307** and outer layer **308** are the same layer. In certain aspects, outer layer **308** is suitable to act as a seal adapter **301**. In addition to permeability, tubing **205** should be suitable for sterile welding which provides for joining two opposing ends of the tube while maintaining a sterile fluid pathway. In some aspects, tubing **205** is comprised of a barrier traversing tube **305** suitable for sterile welding. In further aspects, tubing **205** should be resistant to kinking, twisting and collapsing. As discussed above, it would be understood by one of ordinary skill in the art that the thickness of the tubing wall is proportional to the permeability of the tubing. Accordingly, while many materials may be suitable when provided with sufficient thickness, such materials may not be suitable as they would lack flexibility or simply be too bulky or unwieldy for use in a blood collection set or to dock with other tubing.

[00183] As used herein, tubing **205** that is substantially impermeable to oxygen are materials characterized by a Barrer value of less than 1 Barrer, and preferably less than 0.2

Barrer. In other aspects, tubing **205** that is substantially impermeable to oxygen are materials characterized by a Barrer value of less than 0.01 Barrer. In other aspects, tubing **205** that is substantially impermeable to oxygen are materials characterized by a Barrer value of less than 0.002 Barrer. In other aspects, tubing **205** that is substantially impermeable to oxygen has an oxygen transmission rate of less than 100 cc/mil•100in^2•day•atm. In other aspects, tubing **205** that is substantially impermeable to oxygen has an oxygen transmission rate of less than 80 cc/mil•100in^2•day•atm. In other aspects, tubing **205** that is substantially impermeable to oxygen has an oxygen transmission rate of less than 35 cc/mil•100in^2•day•atm. Examples of tubing suitable for use include PVC tubing, such as Renolit Medituub 3467 (American Renolit Corp., City of Commerce, CA) and Qosina T4306 (Qosina Corp., Edgewood, NY). In some aspects according to the present disclosure, tubing **205** has an oxygen permeability of between 0.002 and 1 Barrer. In aspects according to the present disclosure, tubing **205** has an oxygen permeability of between 0.002 and 0.20 Barrer. In some aspects according to the present disclosure, tubing **205** has an oxygen permeability of between 0.01 and 0.10 Barrer.

[00184] In aspects according to the present disclosure, tubing **205** may be prepared from materials selected from the group consisting of ethylene-vinyl acetate (EVA), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyurethane (PU), polyester (PES), polyethylene terephthalate (PET), polyethylene (PE), high-density polyethylene (HDPE), polyvinyl chloride (PVC), polyvinylidene chloride (PVDC), low-density polyethylene (LDPE), polypropylene (PP), polystyrene (PS), high impact polystyrene (HIPS), polyamides (PA) (*e.g.*, nylon), acrylonitrile butadiene styrene (ABS), polycarbonate (PC), polycarbonate/acrylonitrile butadiene styrene (PC/ABS), polyurethanes (PU), melamine formaldehyde (MF), plastarch material, phenolics (PF), polyetheretherketone (PEEK), polyetherimide (PEI) (Ultem), polylactic acid (PLA), polymethyl methacrylate (PMMA), polytetrafluoroethylene (PTFE), urea-formaldehyde, ethylene vinyl alcohol copolymer (EVOH), and polyamide. In an aspect, tubing **205** is prepared from polyethylene. In an aspect, tubing **205** is prepared from polyvinyl chloride.

[00185] The present disclosure also provides for and includes a blood storage device **20** having tubing **205** that is a barrier traversing tube **305** having at least one layer selected from the group consisting of ethylene-vinyl acetate (EVA), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), biaxially oriented polypropylene (BOPP), biaxially oriented nylon, ethylvinyl alcohol (EVOH), polyethylene terephthalate (PET), polyethylene napthalate

(PEN), polyurethane (PU), polyethylene (PE), polyvinylidene chloride (PVDC), and polyamide. In an aspect, a barrier traversing tube **305** used for tubing **205** includes an oxygen barrier layer **307** comprising PET. In another aspect, a barrier traversing tube **305** used for tubing **205** includes an oxygen barrier layer **307** comprising EVA. In another aspect, a barrier traversing tube **305** used for tubing **205** includes an oxygen barrier layer **307** comprising EVOH. In certain aspects, tubing **205** comprises a blood compatible inner layer **306** comprising PVC. In certain aspects, the barrier traversing tube **305** used for tubing **205** is comprised of an outer layer **308** of polyethylene (PE), and inner layer **306** of PVC (polyvinyl chloride), and an oxygen barrier layer **307** of EVA (ethyl-vinyl-acetate) (Pexco, Inc. Athol, MA). In some aspects, the barrier traversing tube **305** used for tubing **205** is comprised of an outer layer **308** of polyethylene (PE), and inner layer **306** of PVC (polyvinyl chloride), and an oxygen barrier layer **307** of EVA (ethyl-vinyl-acetate), wherein the PE outer layer **308** has a thickness of 150 μm, the EVA oxygen barrier layer **307** has a thickness of 10 μm, and the PVC inner layer **306** has a thickness of 350 μm, thereby providing a multilayer tubing that is easily used with current sterile tubing connection devices. Additives that strengthen the oxygen and CO_2 barrier properties of the polymers prior to molding or during their formulation or during setup are known in the art. Current blood collection kits employ PVC in tubing that is equivalent to the tubing **205** of the present disclosure. Such PVC tubing is not suitable for use in some aspects of the blood storage devices of the present disclosure and would be a considerable source of ingressed oxygen if used as tubing **205**. Such PVC tubing typically allows approximately 1 cc oxygen ingress per day over a 1 m length of tubing at ambient conditions; thus blood collection systems and kits of the present invention would require an oxygen barrier overpack with an oxygen sorbent to protect and maintain the internal spaces and volumes of the blood collection kit from undesired oxygen ingress. Since the majority of PVC tubing in the blood collection kit is discarded after collection and processing, and the anaerobic storage device **20** only has 150 mm length of exposed inlet tubing remaining prior to storage, the oxygen ingress rate through the remaining 150 mm length of exposed PVC tubing is limited to about 0.16 cc/day at ambient conditions, or about 7 cc oxygen at ambient conditions over 42 days and about 10 cc after 64 days. The actual amount of oxygen ingress is much lower at the refrigerated storage temperature of 4°C used for long term blood storage than the amount of oxygen ingress measured at ambient conditions.

[00186] The present disclosure includes, and provides for, a blood storage device 10 having unitary tubing design that is substantially impermeable to oxygen that combines and incorporates tubing **205**, bond **302**, and tubing **304** into a single structure. The advantage of this design is that it decreases the number of individual parts and eliminates potential sources of oxygen ingress. Moreover, the incorporation of a unitary tubing design comprising a multilayered, oxygen impermeable tube provides for the preparation of simplified blood storage device **20** comprising a blood compatible outer receptacle **201** capable of storing oxygen depleted blood bonded directly to one or more inlets or outlets comprising the impermeable tubing. By essentially eliminating the potential sources of oxygen, suitably oxygen depleted blood may be stored directly in the blood compatible outer receptacle **201** while eliminating the collapsible blood container **202** and the oxygen sorbent **207**. The present disclosure also provides for the preparation of a blood storage device comprising a multilayered container which combines the outer receptacle **201**, oxygen sorbent **207**, and the collapsible blood container **202** as a single multilayered device bonded to one or more tubings **205** through an oxygen impermeable bond.

[00187] In aspects according to the present disclosure, the outer receptacle **201** includes one or more inlets/outlets **30**. In certain aspects, the one or more inlet/outlets **30** further comprise a spike port **303**. In some aspects, the outer receptacle **201** includes a second inlet/outlet **30** in fluid communication with said collapsible blood container **202**. In yet other aspects, the outer receptacle **201** includes a third inlet/outlet **30** in fluid communication with said collapsible blood container **202**. Each inlet/outlet **30** may further include a spike port **303**.

[00188] It is notable that few materials provide complete impermeability and that even the high impermeability of materials can be compromised when joining, welding, folding, or otherwise assembling an outer receptacle **201**. As will be discussed below, blood storage device **20** may further incorporate optional spike ports **303** and inlets/outlets **30** and must also be designed to accommodate changes in volume of the inner collapsible blood container **202**. Accordingly, special care is taken to incorporate specific design elements and manufacturing methods to ensure the integrity of the impermeable barrier and the maximization of material performance integrity.

[00189] Spike ports **303** for use in blood collection kits and systems are commonly known in the art and include products such as Vitalmed # 20391 (Vitalmed, Inc., Lakeville, MA) and Qosina # 65842 (Qosina Corp., Edgewood, NY). These ports are typically molded from PVC

and have a removable cap that provides for a sterile barrier before use, and also provides for some degree of oxygen impermeability to the contents. In some aspects, a spike port **303** is covered by a sealed, frangible section of the outer receptacle film, thereby providing for a sterile barrier and also providing an additional degree of oxygen impermeability. Improved oxygen impermeability is desirable as it increases the shelf life of kits and systems having a blood storage device **20**.

[00190] As will be appreciated, conventional ports, inlets, and outlets are potential sources of unwanted oxygen ingression that depend both on the selection of the material and the methods used to bond the port, inlet, or outlet to the outer receptacle **201**. Methods of bonding materials to prepare a bond **302** are well known in the art. As provided herein, inlet/outlet **30** comprises a seal adaptor **301** joined to the outer receptacle **201** using bond **302** which creates an oxygen impermeable seal to the outer receptacle **201**. In one aspect of the present disclosure, a manifold is a seal adapter **301**. As used herein, a bond **302** that is substantially impermeable to oxygen has a Barrer value of less than 1 Barrer, preferably less than 0.10 Barrer, and more preferably less than 0.01 Barrer.

[00191] As provided in the present disclosure, a bond **302** that is substantially impermeable to oxygen may be solvent sealed, heat sealed, adhesive bonded, ultrasonic welded, or radio frequency welded. In an aspect, bond **302** is achieved by using constant heat sealing dies heated to and maintained at about 260 °F. In an aspect, films are placed between heated dies and clamped together for about 3 to 7 seconds to achieve a thermally welded seam. In certain aspects, a heat seal is created in about 5 seconds. In certain aspects, the sealing dies have a grooved section machined out of them to accommodate an intermediary component. In some aspects seal adaptor **301** comprises an intermediary component that may be a length of barrier traversing tubing as discussed below or a small block of machined, extruded, molded or laminated polymer wedge. In aspects according to the present disclosure, the groove is dimensioned about 5% smaller than the features of the component, thereby providing for compression and material flow during sealing.

[00192] In some aspects, an oxygen impermeable bond is comprised of a section of barrier traversing tube (*e.g.*, seal adaptor **301**) that is heat sealed into the seam of the outer receptacle **201**. In certain aspects, the barrier traversing tube is comprised of an outer layer of EVA (ethyl-vinyl-acetate) and an inner layer of PVC (polyvinyl chloride) (Pexco, Inc., Athol, MA). In certain aspects, the barrier traversing tube is comprised of an outer layer of polyethylene, and inner layer of PVC (polyvinyl chloride), and an intermediary layer of EVA

(ethyl-vinyl-acetate) (Extrusion Alternatives, Inc., Portsmouth, NH). In some aspects, additional sections of PVC tubing are solvent bonded into the multilayer tube using, for example, cyclohexanone.

[00193] In some aspects, an inlet/outlet **30** is comprised of a seal adaptor **301** that is a small device that is a machined, extruded, molded or laminated polymer wedge or a block. The molded device may be prepared from a polyolefin, such as polyethylene, for example Dowlex® 2517 resin. In other aspects the machined, extruded, molded or laminated polymer device may be prepared from a polyether block amide (e.g., PEBAX®). In yet another aspect, the machined, extruded, molded or laminated polymer may be ethylene-vinyl acetate (e.g., EVA). In certain aspects, the machined, extruded, molded or laminated polymer device may be a small diamond, oval or other suitably shaped, block of polymer, with a hole through the center, such that the shaped device is heat sealed into the seam of the outer receptacle to provide an oxygen impermeable bond **302** while the center through-hole provides for fluid connectivity with the contents. In an aspect, a section of PVC tubing is bonded into the center hole of a diamond shaped seal adaptor **301** using an oxygen impermeable adhesive capable of bonding to polyethylene, such as Loctite 4310, Masterbond X17, or 3M Scotchweld 4693, thereby providing for fluid connectivity through the oxygen impermeable outer receptacle to the contents therein. In other aspects, a barrier traversing tubing can be bonded to the center hole of the diamond shaped seal adaptor **301** using methods known in the art. In other aspects, barrier traversing tubing can be insert molded into a diamond shaped seal adaptor **301** using methods known in the art. In other aspects, barrier traversing tubing can be utilized in place of standard PVC intravenous tubing to provide for enhanced oxygen barrier properties.

[00194] The present disclosure provides for and includes a locating feature to align the outer receptacle **201**, collapsible blood container **202** and inlet/outlet **30** and ensure the integrity of the oxygen impermeable barrier. Misalignment can result in breaches to the barrier and ingress of oxygen during storage and prior to use. In accordance with the present disclosure, the locating feature may be selected from the group consisting of a geometric cutout, a tactile surface marking, die cut fiducials, spacers, interlocking cutouts, tubing fittings, and a printed marking.

[00195] The present disclosure provides for and includes an expansion feature **217** to accommodate the volume of blood and to avoid creases and folds. During the development of anaerobic storage bags, it was observed that creases and folds that developed during the

filling of certain anaerobic storage bags, for example foil coated bags, results in breaches of the impermeable barrier. Such folds and creases result in unacceptable levels of oxygen ingress and leads to unacceptable increases in oxygen saturation in stored blood during storage. Expansion features also provide for unrestricted filling of the storage device **20**, the outer enclosure **201**, and the collapsible blood container **202**.

[00196] In aspects according to the present disclosure, an expansion feature **217** is selected from a group consisting of a pleat, a diaphragm, a bubble, one or more folds, a folded pouch, and a geometric expansion in the packaging shape. In some aspects, the expansion feature **217** is comprised of a gusseted fold along one or more edges of the outer receptacle **201**. In an aspect, a fold of about 1/8 to 1/4 inch is adequate to provide for expansion of the inner container **202**, and the pleats of the fold are sealed into the seams at the ends. In some aspects, and as illustrated in Figure 8, the expansion feature **217** is comprised of a third panel or trifold of barrier film sealed along the bottom of the outer receptacle **201**, providing for a three-dimensional bag.

[00197] In certain aspects, the collapsible blood container **202** may also include expansion features to facilitate filling of the container, though the oxygen impermeable integrity of the container **202** is obviously not of concern.

[00198] The present disclosure provides for and includes methods and systems to manage the tubing **205** and other tubes that are associated with a complete blood collection kit. A blood storage device **20** having an outer receptacle **201**, collapsible blood container **202** at least one inlet/outlet **30**, and oxygen sorbent **207** may further comprise tube management component **40**. Tube management component **40** may be selected from the group consisting of a separate clip or strap as illustrated in Figure 6A and 6B, a strap attached to the outer surface of said outer receptacle such as that illustrated in Figure 6C and 6D, and a hook and loop fastener (VELCRO®). In certain aspects, and as illustrated for example in Figure 6E and 6F, tube management component **40** is a cut out feature of the outer surface of said outer receptacle. In another aspect, tube management component **40** is a clip attached outer surface of said outer receptacle.

[00199] The present disclosure provides for and includes an integrated handle **214** in the outer receptacle **201**, for example as illustrated in Figure 7.

[00200] The present disclosure provides for and includes one or more transparent or translucent windows **212** to provide for the visual inspection of the blood. Such a window

allows for the inspection of the color of the blood, and also for visualizing undesirable features or contaminants, such as blood clots or bacterial colonies, if present in the blood.

[00201] Among other factors, the shelf life and stability of a blood storage device **20** can be significantly affected by temperature. Specifically, a blood storage device **20**, or one or more of the components thereof, may degrade when exposed to high temperatures. Such degraded devices are unsuitable for the storage of blood and may result in unwanted patient outcomes. As would be known to a person of skill in the art, the amount of time the device is exposed to undesirable temperatures is important as well. Accordingly, the present disclosure provides for devices that further include temp-time monitors. Such monitors are known in the art for example as provided in U.S. Patent Nos. 7,517,146, 6,042,264, and 5,709,472. In an aspect, a BT-10 time strip from Genesis (GenesisBPS, Ramsey, NJ) can be incorporated on the collapsible blood container to monitor the duration of any temperature incursions above 10 °C.

[00202] The present disclosure provides for an includes a blood storage device **20** for storing oxygen depleted blood that provide for maintaining a headspace comprising a volume between said outer receptacle **201** and said collapsible blood container **202** at a low partial pressure of oxygen during a storage period. In some aspects, the blood storage device can maintain the headspace of the blood storage device **20** without the need to include sorbent **207**, however such configurations required a higher level of oxygen barrier integrity. As provided by the present disclosure, a blood storage device **20** maintains the headspace at a partial pressure of oxygen of about 1 mmHg , or less, for a period of 64 days when stored at a temperature of between 2 to 6 °C. In some aspects, a blood storage device **20** maintains the headspace at a partial pressure of oxygen of about 1 mmHg, or less, for a period of 64 days when stored at a temperature of between 2 to 6 °C, without the inclusion of sorbent **207**. The present disclosure also provides for an includes a blood storage device that maintains a partial pressure of oxygen in the headspace of 1 mmHg or less for at least 6 months prior to use.

[00203] The present disclosure further includes a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen that maintains the headspace at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 21 days. In some aspects, a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** that maintains the headspace at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 21 days without sorbent **207**. The present disclosure also provides for a blood storage device **20** having an inlet/outlet **30** that is

substantially impermeable to oxygen is a blood storage device **20** wherein the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 28 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a storage period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 21 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 48 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 48 days without sorbent **207**. In another aspect, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 56 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a period of at least 56 days without sorbent **207**. In another aspect, is maintained at a partial pressure of oxygen 1 mmHg, or less, for a storage period of at least 64 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 1 mmHg, or less, for a storage period of at least 64 days without sorbent **207**.

[00204] The present disclosure further includes a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen that maintains the headspace at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 21 days. In some aspects, a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** that maintains the headspace at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 21 days without sorbent **207**. The present disclosure also provides for a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** wherein the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 28 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a storage period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 21 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 48 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 48 days without sorbent **207**. In another aspect, the headspace is

maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 56 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a period of at least 56 days without sorbent **207**. In another aspect, is maintained at a partial pressure of oxygen 3 mmHg, or less, for a storage period of at least 64 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 3 mmHg, or less, for a storage period of at least 64 days without sorbent **207**.

[00205] The present disclosure further includes a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen that maintains the headspace at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 21 days. In some aspects, a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** that maintains the headspace at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 21 days without sorbent **207**. The present disclosure also provides for a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** wherein the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 28 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a storage period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 21 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 48 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 48 days without sorbent **207**. In another aspect, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 56 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a period of at least 56 days without sorbent **207**. In another aspect, is maintained at a partial pressure of oxygen 5 mmHg, or less, for a storage period of at least 64 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 5 mmHg, or less, for a storage period of at least 64 days without sorbent **207**.

[00206] The present disclosure further includes a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen that maintains the headspace at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 21 days. In some aspects, a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable

to oxygen is a blood storage device **20** that maintains the headspace at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 21 days without sorbent **207**. The present disclosure also provides for a blood storage device **20** having an inlet/outlet **30** that is substantially impermeable to oxygen is a blood storage device **20** wherein the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 28 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a storage period of at least 28 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 21 days without sorbent **207**. In further aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 48 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 48 days without sorbent **207**. In another aspect, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 56 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a period of at least 56 days without sorbent **207**. In another aspect, is maintained at a partial pressure of oxygen 15 mmHg, or less, for a storage period of at least 64 days. In some aspects, the headspace is maintained at a partial pressure of oxygen 15 mmHg, or less, for a storage period of at least 64 days without sorbent **207**.

[00207] The present disclosure provides for and includes, a blood storage device 20 comprising an outer receptacle **201**, a collapsible blood container **202**, at least one inlet/outlet **30** and an oxygen sorbent **207**, wherein blood stored in said collapsible blood container **202** maintains an oxygen saturation level (SO2) during a storage period that is approximately equal to the oxygen saturation level at the beginning of storage. In an aspect, the storage period is 21 days and the initial SO2 level is 20% or less. In another aspect, the storage period is 28 days and the initial SO2 level is 20% or less. In a further aspect, the storage period is 42 days and the initial SO2 level is 20% or less. In a further aspect, the storage period is 56 days and the initial SO2 level is 20% or less. In yet another aspect, the storage period is 64 days and the initial SO_2 level is 15% or less. In an aspect, the storage period is 21 days and the initial SO2 level is 15% or less. In another aspect, the storage period is 28 days and the initial SO2 level is 15% or less or the storage period is 42 days and the initial SO2 level is 15% or less. In a further aspect, the storage period is 56 days and the initial SO2 level is 15% or less or the storage period is 64 days and the initial SO2 level is 15% or less.

In an aspect, the storage period is 21 days and the initial SO2 level is 10% or less or the storage period is 28 days and the initial SO2 level is 10% or less. In a further aspect, the storage period is 42 days and the initial SO2 level is 10% or less. In a further aspect, the storage period is 56 days and the initial SO2 level is 10% or less or the storage period is 64 days and the initial SO2 level is 10% or less. In an aspect, the storage period is 21 days and the initial SO2 level is about 5%. In another aspect, the storage period is 28 days and the initial SO2 level is about 5% or the storage period is 42 days. In a further aspect, the storage period is 56 days and the initial SO2 level is about 5%, or the storage period is 64 days. In yet another aspect, the storage period is 21 days and the initial SO_2 level is about 3%. In another aspect, the storage period is 28 days and the initial SO2 level is about 3% or the storage period is 42 days and the initial SO2 level is about 3%. In a further aspect, the storage period is 56 days and the initial SO2 level is about 3%. In yet another aspect, the storage period is 64 days and the initial SO2 level is about 3%.

[00208] The present disclosure provides for and includes, a blood storage device **20** comprising an outer receptacle **201**, a collapsible blood container **202**, at least one inlet/outlet **30**, and an oxygen sorbent **207**, that provides for an oxygen saturation level (SO2) during a storage period that is less than the oxygen saturation level at the beginning of storage, wherein said storage period is at least 1 week. In aspects according to the present disclosure, oxygen saturation level is 2% less after one week of storage than the oxygen saturation level at the beginning of storage. In other aspects, according to the present disclosure, the oxygen saturation level decreases at a rate of at least 0.00010 %SO2/minute. In certain aspects, the oxygen saturation level decreases at a rate of at least 0.00020 %SO2/minute. In other aspects, the oxygen saturation level decreases at a rate of between 0.0003 and 0.0001 $\%SO_2$/minute. In other aspects, the storage period is 21 days or 28 days. In yet other aspects, the storage period is 42 of 56 days. In other aspects, the blood storage device **20** provides for a decreased oxygen saturation level after 64 days.

[00209] The present disclosure provides for and includes, a blood storage device **20** comprising an outer receptacle **201**, a collapsible blood container **202**, at least one inlet/outlet **30**, wherein blood and said blood stored in said collapsible blood container **202** provides for an oxygen saturation level (SO2) during a storage period that increases less than 5% over the oxygen saturation level at the beginning of storage, wherein said storage period is 64 days. In other aspects, the oxygen saturation level (SO2) during a storage period that increases less

than 3% over the oxygen saturation level at the beginning of storage, wherein said storage period is 64 days.

[00210] The present disclosure provides for, and includes, different methods to manufacture a collapsible blood container **202**. In an aspect, a collapsible blood container **202** is prepared by blow molding. In another aspect, a collapsible blood container **202** is prepared by compression molding. In a further aspect, a collapsible blood container **202** is prepared by insert molding. Methods of blow molding, compression molding, or insert molding are known in the art, for example, "Rupture resistant blow molded freezer bag for containing blood products" in US Patent Application Publication No. 2004/0254560A1 and "Blowbag manufacturing method" in U.S. Patent No. 5,368,808 issued to Koike *et al.*, and "Blow or vacuum molding thermoplastic resins, then expanding or shaping using compressed air; medical equipment" in U.S. Patent No. 6,878,335.

[00211] In some aspects according to the present disclosure, a collapsible blood container **202** is prepared by heat sealing one or more membranes **206**. In another aspect, a collapsible blood container **202** is prepared by adhesive bonding one or more membranes **206**. In other aspects, a collapsible blood container **202** is prepared by ultrasonic welding one or more membranes **206**. In other aspects, a collapsible blood container **202** is prepared by radio frequency welding one or more membranes **206**. In yet other aspects, a collapsible blood container **202** is prepared by one or more methods selected from heat sealing, adhesive bonding, ultrasonic welding, or radio frequency welding.

[00212] In aspects according to the present disclosure, the collapsible blood container **202** is prepared from one or more membranes **206** that comprise one or more seals having a width of at least 1/8 inch.

[00213] In an aspect according to the present disclosure, the collapsible blood container **202** can be manufactured from microporous membrane **206** by various sealing methods such as heat sealing, thermal staking, and adhesive bonding. In one aspect according to the present disclosure, a pair of PVDF microporous membranes are bonded together around the periphery with a section of PVC inlet tubing in place in the seam using an adhesive such as Loctite 4011 in conjunction with an adhesive primer such as Loctite 770. In another aspect according to the present disclosure, a collapsible blood container can be manufactured from a pair of microporous membranes by heat sealing the 3 or 4 edges of the pair of membranes together with a section of multilayer tubing sealed into the seam to provide for fluid connectivity.

[00214] The present disclosure provides for, and includes, methods of using a blood storage device **20** to store deoxygenated blood for up to 64 weeks, resulting in reduced storage lesions relative to blood stored in the presence of oxygen. According to the methods of the present disclosure, a blood storage device **20** as described above is used to for blood storage. In an aspect, the blood comprises packed red blood cells. In other aspects, the blood comprises whole blood. In yet other aspects, the blood for storage comprises oxygen reduced packed red blood cells further comprising an additive solution.

[00215] In an aspect, according to a method of the present disclosure, deoxygenated blood, having an oxygen saturation of less than 20% is placed in a blood storage device **20**, and stored. In certain aspects, the storage period is between 1 day and 64 days. In other aspects, the storage period is one week. In another aspect the storage period is two weeks. In another aspect, the storage period is three of four weeks. On other aspects, the storage period is 8 weeks. In yet another aspect the storage period is 9 weeks. According to the methods of the present disclosure, the blood storage device **20** maintains the oxygen depleted state of the oxygen depleted blood at, or less than the initial saturation level, SO_2.

[00216] The present disclosure also provides for and includes, methods of blood storage, comprising placing oxygen reduced blood into a blood storage device **20** and storing the oxygen reduced blood for a period of 1 to 64 days, wherein the oxygen saturation of the blood is further reduced during the storage period. In an aspect, the SO_2 of the stored blood is reduced by at least 3% after one week of storage. In an aspect, the initial oxygen saturation of the oxygen reduced blood is about 20% SO2 and is reduced during storage. In other aspects, the initial SO_2 is about 15% and is reduced during storage. In yet another aspect, the initial SO_2 is about 10% and is reduced during storage. In aspects according to the present disclosure, the stored blood has an oxygen saturation level of less than 20% after one week. In another aspect, the stored blood has an oxygen saturation level of less than 10% after two weeks. In yet another aspect, the stored blood has an oxygen saturation level of less than 5% after three weeks.

[00216a] The present disclosure also provides for, and includes, an oxygen depletion device **10** for depleting oxygen from blood prior to anaerobic storage comprising an outer receptacle **101** substantially impermeable to oxygen; an oxygen indicator **104**, a spacer material **110**, and an oxygen sorbent **103** in between outer receptacle **101** and an inner collapsible blood container **102**. In certain aspects, an inner collapsible blood container **102** further comprises a window **112**. As used herein, a window **112** is made of a transparent material and is bonded or otherwise incorporated into the inner collapsible blood container **102**. In accordance with the present

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disclosure, suitable materials for window **112** are blood compatible. In certain aspects, materials suitable for a window **112** are oxygen impermeable. In other aspects, materials suitable for a window **112** are oxygen impermeable. The size of a window **112** need only be large enough to provide observation of the blood.

[00216b] The present disclosure also provides for, and includes, an oxygen depletion device **10** having tubing **106**.

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EXAMPLES

Example 1: Inner collapsible blood containers comprising PVC

[00217] A collapsible blood container **202** (blood bag) with two inlet/outlets **30** configured as spike ports and one inlet/outlet **30** configured as an I.V. inlet tube is fabricated from a pair of PVC sheets (Renolit Solmed ES-3000, Renolit America) by welding the edges together with radio frequency welding (RF welding). The blood bag is leak tested by insufflating with compressed air to 3 psig and submerging in water and observing for bubbles before use. Alternatively, the blood bag is leak tested by insufflating with compressed air and negative pressure changes are monitored with a pressure decay tester (Sprint MT, Zaxis). The leak-tested blood bag is then placed in an outer receptacle **201** fabricated from RollPrint Clearfoil® Z film #37-1275 having a heat sealable PE inner layer, and alumina barrier middle layer, and a PET outer layer (Rollprint Packaging Products, Inc., Addison, IL) as described in Example 2.

Example 2: Outer receptacle 201

[00218] An outer receptacle **201** that is substantially impermeable to oxygen ('barrier bag") is fabricated by heat sealing an oxygen impermeable section of tubing into one edge with a custom heat sealer, and sealing the other remaining edges using conventional heat sealing methods and equipment. The custom heat sealer is comprised of a pair of 1 inch square aluminum bars 12 inches long having a ½ inch wide by ¼ inch high sealing surface machined on one side of each bar. Each of the sealing bars are fitted with a pair of 3/8 inch diameter by 5 inch long 200 watt heater cartridges (4 total, McMaster Carr #3618K315, McMaster Carr, Inc., Robbinsville, NJ) and maintained at 260 °F by an Athena Controls temperature controller and a K-type thermocouple (McMaster Carr #9251T93, McMaster Carr, Inc., Robbinsville, NJ) inserted into a small hole drilled in one end of one of the aluminum bars. A transverse groove is machined into each of the two aluminum sealing bars with a 7/32 inch ball end mill to a depth of about 0.208 inches to provide for about 0.010 inches of compression when locating a seal adaptor comprising a section of oxygen impermeable tubing within the seal. The bars are bolted in opposition to each other on a Franklin Hot Stamp press, such that when the press is operated the transverse grooves and pair of sealing surfaces come into aligned contact with each other to provide a ½ inch wide seal along the 12 inch length of the aluminum sealing bars.

[00219] To prepare the outer receptacle **201**, a sheet of the barrier film about 11 x 12 inches is folded in half along the 12 inch dimension with the polyethylene layer inside and a gusset fold of about ¼ inch incorporated into the folded edge. The gusset fold is maintained in place with a small clamp at each end and then the film is placed into the custom heat sealer aligning one of the short edges in the sealing dies. A piece of oxygen impermeable multilayer tubing (seal adaptor **301**) having a polyethylene outer layer **308**, a PVC inner layer **306**, and an intermediary bonding layer of EVA **307**, (Extrusion Alternatives, Inc., Portsmouth, NH) 0.156" I.D. by 0.218" O.D. by about ½ inch long is placed onto a solid aluminum mandrel about 0.156" diameter by about 1 inch length and then placed between the films and located in the transverse groove **703** or **704** of the sealing die **70**. The press is activated and set to about 5 seconds duration at 80 pounds per square inch gage (psig) to create a continuous welded seal along the length of the dies, and sealing the short piece of multilayer tubing (seal adaptor **301**) in place with bond **302**. The combination of seal adaptor **301** and bond **302** short multilayer tubing provides for an oxygen impermeable seal around the outer diameter of the tubing while also providing fluid connectivity through the seal. The folded edge provides for expansion of the barrier bag when the collapsible blood container **202** is filled with fluid.

[00220] A length of standard I.V. tubing (PVC tubing 0.118 inch I.D. x 0.161 inch O.D. (Pexco, Inc., Athol, MA) about 12 inches long (tubing **205**) is solvent bonded using cyclohexanone into the multilayer tubing from the outside of the bag and heat sealed closed about ½ inch from the end. The inlet tubing (tubing **304**) of the inner blood bag is trimmed to about 2 inches in length and the inner blood bag is placed inside the barrier bag. The inlet tubing **304** is solvent bonded into the multilayer tubing, thereby providing for fluid connectivity of the inner blood bag inlet tube through the oxygen impermeable seal of the barrier bag to the 12 inch length of tubing **205** outside the barrier bag.

[00221] The remaining short edge of the barrier film is sealed with an impulse heat sealer (Accu-Seal model 530, Accu-Seal, Inc., San Marcos, CA), leaving the last remaining long edge of the barrier bag unsealed to place a sorbent **207**, plastic mesh spacer **213** configured as a plastic mesh, and oxygen sensor **215**. An oxygen sensor **215** (Mocon # 050-979, Mocon, Inc., Minneapolis, MN) is affixed to the inside of the barrier bag. A pair of plastic mesh spacers **213** (McMaster Carr #9314T29, NJ McMaster Carr, Inc., Robbinsville, NJ) are cut to about 5 x 7 inches and one sachet of oxygen sorbent **207** (SS-200 type, Mitsubishi Gas Chemical America, New York, NY) is affixed near the center of one piece of plastic mesh **213** prior to placing the plastic mesh spacers **213** between the blood bag **202** and barrier bag

201 and sealing the final long edge of the barrier bag with an impulse heat sealer (McMaster Carr # 2054T35, McMaster Carr, Inc., Robbinsville, NJ). Care is taken to minimize the assembly time to reduce the exposure to atmospheric oxygen by performing the assembly in a nitrogen atmosphere glove box.

Example 3: Conventional Storage Bags Allow for Blood Reoxygenation

[00222] The extent and rate of reoxygenation of blood during storage in conventional PVC blood storage bags is determined by transferring 150 ml of packed Red Blood Cells (pRBC) having an initial SO2 of about 60% to a conventional PVC blood transfer bag. The pRBC containing bag is placed at 4 °C under ambient atmospheric conditions and allowed to stand, unmixed. Samples are removed and the average SO2 determined at days 0, 7, 14, 21, 28, 52, and 56. Six independent samples are taken per time point. The results are presented in Table 7 and presented graphically in Figure 10.

Table 7: Reoxygenation of blood during storage in conventional PVC bags

Storage Time (days)	Average SO2 (%)
0	62.4
7	80.8
14	95.5
21	98.3
28	98.2
42	97.9
56	97.6

[00223] As shown in Table 7 and Figure 10, blood becomes saturated over the 56 day storage period. SO_2 increases consistently for 14-21 days, until it reaches ~98%, after which there are no significant ($n=6$; $p<0.001$) changes in SO_2 for the remainder of the storage period.

Example 4: Oxygen ingress occurs primarily through collection and transfer tubing

[00224] Based on calculations and comparing to a bag made from the RollPrint 37-1275, 8.53 ml oxygen ingresses over 42 days with the majority coming through the 6" length of inlet tubing. Accordingly, a 20 cc minimum sorbent capacity, based on the 8.53 ingress + 10 mL in blood is indicated.

Example 5: Continued Oxygen depletion during storage at 4 °C

[00225] The depletion of oxygen is significantly affected by temperature. To evaluate the ability to continue to deplete oxygen from blood during storage, conventional blood storage bags are prepared and filled with blood having differing initial levels of oxygen saturation. Packed red blood cells are prepared in PAGGSM or SAGM additive solution and are stored anaerobically within plastic canisters pressurized with ~5mmHg, 100% nitrogen gas; additionally, each canister containing 2 ZB sorbent sachets to assist in keeping oxygen levels negligible. As shown in Table 8, at higher levels of oxygen saturation, the rate of the reaction is about twice that of the reaction rate at lower levels of saturation.

Table 8: First order rate constants of oxygen depletion during cold storage

Initial (Day 0) SO_2	Kinetic Rate (%SO2/min)
3	-2.07917E-05
10	-0.000102393
20	-0.00019752
39	-0.000250115
48	-0.000270159
54	-0.000268709

[00226] There also appears to be a logarithmic relationship between the initial set-point of SO_2, and the total amount of O_2 removed during storage, as indicated by a coefficient of determination (R^2) of 0.98. Deriving the line of best fit from this data also allows for the extrapolation of predicted O_2 variance for a given initial SO_2 set-point to inform (Eq. 1).

$$\Delta SO_2 = 7.195 \ln(SO_{2,i}) - 6.99$$

Equation 1 Logarithmic equation relating initial SO_2 to total SO_2 loss during storage. Deriving the equation of line of best fit from the plot of change in SO_2 (ΔSO2) and initial SO_2 values ($SO_{2,i}$)

[00227] Additionally, the time-dependent loss of SO_2 can be predicted by plotting the slopes of a linear regression and deriving the line of best fit. There appears to be a logarithmic relationship between the initial SO_2 value at the start of storage, and the linear rate at which SO_2 is lost during anaerobic storage (Eq 2).

$$k = -0.131 \ln(SO_{2,i}) + 0.1241$$

Equation 2 Logarithmic equation relating initial SO_2 to linear rate of SO_2 loss during storage. Derived equation for the line of best fit from the plot of rate of SO_2 loss (k) versus initial SO_2 value ($SO_{2,i}$)

Example 6: Preparation of outer receptacles

[00228] Pairs of oxygen barrier films are heat sealed together on all four sides to yield pouches having inner dimensions of about 160 by 240 mm. The pouches are sealed using an impulse heat sealer having about a 3 mm (1/8") wide seal (McMaster Carr # 2054T35, McMaster Carr, Inc., Robbinsville, NJ). Samples are prepared from the following barrier films: Rollprint Clearfoil® Z film #37-1275 and Clearfoil® V film #27-1232 (Rollprint Packaging Products, Inc., Addison, IL), and Glenroy ESO 031-002 (Glenroy, Inc., Menomonee Falls, WI). Samples of the Rollprint Clearfoil® Z film are also prepared using an impulse heat sealer having about a 9.5 mm (3/8") wide seal (Accu-Seal model 530, Accu-Seal, Inc., San Marcos, CA).

[00229] Several samples of each configuration are prepared and tested for oxygen permeation using an Oxtran 2/61 oxygen permeability instrument (Mocon, Inc., Minneapolis, MN). For each configuration, two samples are selected for testing using a test gas comprising 100% oxygen at 50% relative humidity (RH) and 760 mmHg pressure. The carrier gas is 98% nitrogen/2% hydrogen at 100% RH and conducted at 23°C. The results are shown in the Table 9 below:

Table 9: Permeability of outer receptacles 201 prepared from different materials

Description	Sample # 1	Sample # 2
Rollprint 37-1275 3-mm seal	0.0053	0.0053
Rollprint 37-1275 9.5-mm seal	0.0049	0.0051
Rollprint 27-1237 3-mm seal	0.0457	0.0564
Glenroy 031-002 3-mm seal	0.0496	0.0504

[00230] While all samples showed a low oxygen ingress rate of less than 0.1 cc/package*day, the Clearfoil® Z film was clearly superior by an order of magnitude lower oxygen ingress rate than the other materials. The different two seal widths of the Rollprint Clearfoil® Z do not reveal a significant difference under the tested conditions.

Example 7: Blood Containers with anaerobic tube fitments

[00231] Collapsible inner blood bags are utilized for testing (model KS-500, KS Mfg., Avon, MA) and utilize PVC films (Renolit ES-3000, Renolit America). The KS-500 blood bag has two transfusion spike ports (Vitalmed # 20391, Vitalmed. Inc., Lakeville, MA) and one PVC inlet port adapted to accept standard I.V. inlet tubing having ~ 4-mm (0.161 inch) O.D.; the blood bags are supplied without any inlet tubing bonded to the inlet port **30**. The

blood bags are placed in outer barrier bags fabricated from RollPrint Clearfoil® Z film #37-1275 (Rollprint Packaging Products, Inc., Addison, IL) as follows.

[00232] For one group of samples an oxygen impermeable fitment adapter (reference NHS # A097-000 - "PE wedge") is machined from solid polyethylene having flat tapered sealing surfaces for mating with the barrier film and a through hole in the center for the inlet tubing **30** to pass through. For the other group of samples an oxygen impermeable fitment adapter (reference NHS # A121-000 – "Multilayer tube") is made from a trilayer tubing having a polyethylene outer layer **308**, for mating with the barrier film, a thin EVA intermediary bonding layer **307**, and an inner PVC layer **306**,for the inlet tubing to bond to.

[00233] Barrier bags about 150 by 270 mm are fabricated from pairs of sheets of Rollprint Clearfoil® Z film by first heat sealing the oxygen impermeable fitment adapter (either PE Wedge version or Multilayer Tube version) into the seam created on one of the short edges of the film pairs using a custom heat sealer having a cutout area to accept the specific type of fitment adapter. The other short edge and one long edge of the barrier bags are then sealed using conventional heat sealing methods and equipment, leaving one long edge of each bag open.

[00234] For the PE Wedge samples an 800 mm length of PVC inlet tubing (Qosina # T4306, Qosina Corp., Edgewood, NY) is pushed through the hole in the fitment adapter and pulled through to expose about 25-30 mm inside the barrier bag seam. For the multilayer barrier traversing tube (tube 305) samples a ~750 mm length of PVC inlet tubing (Qosina # T4306, Qosina Corp., Edgewood, NY) is solvent bonded to the exposed end of the multilayer barrier traversing tube **305**, outside the barrier bag using cyclohexanone. Another piece of PVC tube about 25-30 mm long is solvent bonded to the end of the multilayer barrier traversing tube **305**, inside the barrier bag.

[00235] The inner blood bag is then placed inside the barrier bag and the short section of PVC inlet tubing (tubing **304**) is solvent bonded into the PVC inlet port (inlet/outlet **30**) of the inner blood bag using cyclohexanone. For the PE wedge samples the inlet tube (tubing **304**) is bonded in place to the fitment adapter (PE Wedge) with Loctite 4310 adhesive (Henkel Corp., Rocky Hill, CT) and cured with UV light using a spot wand (Dymax PC-3 Lightwelder, Dymax Corp., Torrington, CT). No further bonding of the multilayer barrier traversing tube samples aside from the solvent bonding was performed.

[00236] The inlet tubing (tubing **304**) on all samples is then heat sealed closed about 150 mm from the fitment adapter and at 50 mm intervals thereafter to create 12 dummy pilot

sample segments as required for blood sampling by ISO 3826-1 using a tube sealer (Genesis SE340, Genesis BPS, Ramsey, NJ). Sealing of the remaining long edge of the barrier film is then performed with an impulse heat sealer (Accu-Seal model 530, Accu-Seal, Inc., San Marcos, CA) after squeezing as much air as possible out of the headspace between the bags.

[00237] Several such sample blood storage containers are sent to Mocon, Inc. for oxygen permeation testing using an Oxtran 2/21 oxygen permeability instrument (Mocon, Inc., Minneapolis, MN). To understand the sources of oxygen ingress, some samples are tested as prepared; some samples have the inlet tube trimmed off near the fitment face and the inlet tubing I.D. plugged with metalized epoxy; some samples have the inlet tubing (tubing **304**) trimmed off and the fitment face/barrier bag seam area masked with metallized epoxy. A pair of each configuration is selected for testing. The test gas is 100% oxygen at 50% R.H. and 760 mmHg pressure, and the carrier gas is 98% nitrogen/2% hydrogen at 100% R.H.; the test is conducted at 23°C. The results of the testing for oxygen ingress (cc/package*day) of 100% O_2 is presented in Table 10:

Table 10: Oxygen ingress testing of seal adaptors

Description	Sample # 1	Sample # 2
Full Pouch w/PE Wedge Adapter	0.275*	0.880
With Inlet Tube Plugged	0.275*	0.0378
With Fitment Masked	0.149*	0.027
Full Pouch w/Multilayer Tube Adapter	0.977	0.978
With Inlet Tube Plugged	0.0192	0.0174
With Tube Masked	0.0185	0.0150

*Results of sample # 1 with the polyethylene fitment adapter indicate a blockage in the tubing at a point close to the fitment, as well as a potential leak in the oxygen barrier pouch itself caused by the copper tubing used for gas introduction during testing. This leads to inconsistent results.

[00238] These results indicate that under ambient conditions (21% O_2, 23°C) the blood container will introduce about 7.7 - 8.6 cc oxygen over 42 days, and 11.8 – 13.1 over 64 days, however most of oxygen this ingress is due to the PVC tubing. At the refrigerated temperature of 4°C used for blood storage, these ingress rates will be greatly reduced. For the anaerobically sealed package with the inlet tube plugged near the seal, only about 0.15 - 0.24 cc of oxygen ingress is expected over 42 days duration, and about 0.23 – 0.36 cc oxygen over 64 days.

Example 8: Oxygen Ingress of Tubing

[00239] Several samples of PVC inlet tubing (Qosina # T4306, Qosina Corp., Edgewood, NY) are trimmed to either ~150 mm (6 inch) length or ~200 mm (8 inch) length and sealed at one end. In addition, the longer 200 mm samples are sealed again about 50 mm (2 inches) from the sealed end to mimic a pilot sample section. Several such samples are sent to Mocon, Inc. for oxygen permeation testing using an Oxtran 2/21 oxygen permeability instrument (Mocon, Inc., Minneapolis, MN). A pair of each configuration are selected for testing. The test gas is 100% oxygen at 50% R.H. and 760 mmHg pressure, and the carrier gas is 98% nitrogen/2% hydrogen at 100% R.H.; the test was conducted at 23°C. The testing results are presented in Table 11 for oxygen ingress (cc/day) of 100% O_2:

Table 11: Oxygen ingress testing of PVC inlet tubing

Description	Sample # 1	Sample # 2	Mean
Qosina T4306 tubing 150-mm sealed one end	0.959	0.965	0.962
Qosina T4306 tubing 200-mm sealed one end with 50-mm pilot sample	0.934	0.957	0.946

[00240] These results are consistent with the previous blood container testing, and show an oxygen ingress through the PVC tubing at ambient conditions (21% O_2, 23°C) of about 8.2 – 8.5 cc over 42 days duration, and 12.6 – 13.0 cc oxygen over 64 days. Under the conditions tested, no substantial difference is observed between the shorter samples without a pilot segment and the longer samples with a pilot segment.

Example 9: Dynamic Oxygen Absorption of Commercial Sorbents

[00241] Three exemplary sorbents are tested for their ability to absorb oxygen in a dynamic test. The test chamber consists of a 4 inch diameter by 4 inch length 304 stainless steel quick flange fitting (McMaster Carr # 4322K35) with end caps, wherein one end cap is modified for the connection of sensors, nitrogen purge and oxygen test gas inlets. A cylindrical polyethylene insert is made to reduce the interior chamber volume to about 50 cc total volume. A PreSens Fibox 3 Gas Analyzer fitted with a PSt6 oxygen sensor and a PT1000 temperature sensor (PreSens Precision Sensing GmbH, Regensburg, Germany) are used for the testing.

[00242] The system is purged with a 1% oxygen /balance nitrogen gas mixture and then a 100% nitrogen gas for two-point calibration before use. A sachet of the sorbent **207** under test is placed in the system in a nitrogen atmosphere glove box, the system sealed (cover

clamped in place) and then purged with 100% nitrogen before removing from the glove box. A syringe pump with a Hamilton gas tight syringe is filled with >5 cc of 100% oxygen; the syringe line to the test chamber is purged by activating the syringe pump, leaving 5 cc of oxygen in the syringe. The syringe line valve is closed and connected to the system. The dynamic test is started by activating the syringe pump to inject 5cc of oxygen over a period of 60 minutes. After 60 minutes the syringe pump line valve is closed and the sorbent allowed to continue to absorb the residual oxygen in a static test.

[00243] The test is performed at ambient conditions (23°C) using a single sachet each of the following commercially available iron-based oxygen scavengers: Mitsubishi Gas Chemical America (MGC) Ageless® SS-200 sorbent (200cc capacity, designed to work in cold environments), O-Buster® (300cc capacity, standard grade) (Hsiao Sung Non-Oxygen Chemical Co., Ltd., Taiwan), and Sorbent Systems LTECC1K500CS (1000cc capacity, "fast acting" – designed to work in cold environments) (Impak Corp., Los Angeles, CA).

[00244] Figure 11 shows that the introduction of oxygen rises to about 0.7 - 0.8 % oxygen in about 10 minutes for each type of sorbent. At about 10 – 15 minutes both the O-Buster® and Sorbent Systems sorbents are able to reduce the level of oxygen in the system from about 0.75% to about 0.3 – 0.5% oxygen. The SS-200 sorbent is not able to reduce the oxygen level, which continued to increase up to about 1% oxygen at 60 minutes.

[00245] After 60 minutes, when the dynamic introduction of oxygen is terminated and the system is under static test, all sorbents showed continued reduction of the oxygen level. The SS-200 shows a dramatic increase in the rate of oxygen reduction under static conditions, whereas the Sorbent Systems sorbent shows a slight increase in the rate of oxygen reduction under static conditions; the O-Buster® sorbent shows no difference in the rate of oxygen reduction under static conditions. It is noted that the capacity of the sorbents, as claimed by the manufacturers, do not appear to have a direct impact on the rate of oxygen absorption, as evidenced by the relative performance of the 300cc O-Buster® sorbent compared to the 1000cc capacity Sorbent Systems sorbent. The two sorbents formulated to perform well in cold conditions (MGC SS-200 and Sorbent Systems LTECC1K500CS), as claimed by the manufacturers, did appear to perform more poorly than the standard O-Buster® sorbent. Test data is not performed or collected at temperatures other than 23°C.

Example 10: Dynamic Oxygen Absorption of Commercial Hand Warmers

[00246] Several commercially available hand warmers are tested for their ability to absorb oxygen in a dynamic test, using the same system and conditions as described in Example 9 above. Hand warmers are iron-based oxygen scavengers designed to react with ambient oxygen and generate heat. The iron-based chemistry is the same of commercially available sorbents used for food preservation as tested in Example 9, but the formulations may vary slightly to modify the kinetics of the reactions.

[00247] Figure 12 shows the data for several commercially available hand warmers tested as described above. The data shown in the table below shows that the introduction of oxygen raises the level to about 0.25 % to about 0.75 % oxygen in about 10 minutes, depending on the type of hand warmer. At about 10 – 15 minutes the data shows that all of the hand warmers are able to quickly reduce the oxygen level from the peak values, with noticeable variations between formulations. Most of the formulations appear to approach a steady state during the dynamic test, except for the Hot Hands (hand) and the Heat Works versions, which continued to reduce the oxygen levels to near zero under dynamic test conditions.

[00248] After 60 minutes, when the dynamic introduction of oxygen is terminated and the system is under static test, all sorbents showed a dramatic reduction of the oxygen level to near zero values, except for the Hot Hands (hand) and the Heat Works versions, which are already at near zero oxygen. These results show that the formulations used for the hand warmers have a faster rate of oxygen absorption than the food grade oxygen sorbents shown in Example 9, and are able to achieve lower oxygen levels over the period of study and conditions used in this test.

Example 11: Fabrication of Anaerobic Storage Bags

[00249] Several Anaerobic Storage Bags are fabricated as described in examples 1 and 2 above, and further completed by incorporating a sachet of SS-200 sorbent (Mitsubishi Gas Chemical America, New York, NY), a plastic spacer, and an oxygen sensor tab (Mocon, Inc., Minneapolis, MN) before heat sealing the final edge in a nitrogen atmosphere glove box. In addition, several Anaerobic Storage Bags were fabricated using Renolit ES-4000 PVC-Citrate and also using silicone sheets (McMaster Carr # 87315K61, McMaster Carr, Robbinsville, NJ) to fabricate the inner collapsible blood container **202**. The headspace oxygen level is measured through the outer receptacle film (Rollprint Clearfoil® Z) for several days after fabrication to verify the robustness of the seals. The results are shown in Table 12 to Table 14 below.

Table 12: ASB fabricated with Renolit ES-3000 Inner blood bag (Headspace oxygen in Torr)

ASB #	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
1	4.52	0.39	0.43	0.53	0.49	0.47
2	5.85	0.43	0.56	0.76	0.63	0.87
3	5.83	0.64	0.42	0.37	-	-
4	2.41	0.62	0.40	0.34	0.44	0.35
5	5.36	0.63	0.43	0.37	-	-
6	5.07	0.75	0.34	0.46	0.45	0.42
7	3.15	0.63	0.35	0.46	0.44	0.42
8	6.07	0.63	0.51	0.33	0.37	0.29
9	5.39	0.50	0.38	0.35	0.36	0.28
10	3.24	0.78	0.75	**7.50**	4.36	1.90
11	5.30	0.49	0.44	0.43	0.47	0.31
12	2.79	0.62	0.43	0.36	0.44	0.42

Table 13: ASB fabricated with Renolit ES-4000 Inner blood bag (Headspace oxygen in Torr)

ASB #	Day 0	Day 1	Day 2	Day 4
1	4.52	0.18	0.03	0.00
2	5.85	0.19	0.02	0.01
3	5.83	0.26	0.06	0.03
4	2.41	0.17	0.00	0.01
5	5.36	0.32	0.02	0.00
6	5.07	0.22	0.01	0.00
7	3.15	2.12	27.85	12.00
8	6.07	0.28	0.06	0.05
9	5.39	0.38	0.15	0.10
10	3.24	0.20	0.11	0.09

Table 14: ASB fabricated with Silicone Inner blood bag (Headspace oxygen in Torr)

ASB #	Day 0	Day 1	Day 2	Day 4
1	7.23	0.00	0.00	0.00
2	6.90	0.00	0.00	0.00
3	8.03	0.00	0.00	0.00
4	7.92	0.00	0.00	0.00
5	7.81	0.00	0.00	0.00
6	8.03	0.00	0.00	0.00
7	4.75	0.00	0.00	0.00
8	4.76	0.00	0.00	0.00
9	3.96	0.00	0.00	0.00
10	3.94	0.00	0.00	0.00

[00250] The mean oxygen level at day 0 is significantly higher for the silicone inner blood bag group vs. both of the PVC blood bag groups, with means of 6.33 Torr vs. 4.58 Torr (ES-3000) and 4.69 Torr (ES-4000), with $p<0.05$. The results also indicate that the sorbents are able to effectively reduce the headspace oxygen levels to less than 1 Torr oxygen, except in the case of sample #10 in the ES-3000 group and sample # 7 in the ES-4000 group. Upon closer examination of the seals on these samples, a small crease or wrinkle is observed in the seam of the final seal.

Example 12: Intermediary seal adaptor 301 with multilayer barrier traversing tubes for solvent bonding of tubing

[00251] An anaerobic storage container with a substantially impermeable joint having fluid connectivity is fabricated by first insert molding 3 pieces of multilayer barrier traversing tubing **305** into polyethylene (Dowlex™ 2517) in the shape of a bar about 5 mm wide by about 57 mm total length with tapered ends ("diamond wedge", a seal adaptor **301**) (Sonicron Corp., Westfield, MA). The multilayer barrier traversing tubes have a polyvinylchloride (PVC) inner layer **306**, suitable for solvent bonding to PVC tubing, a polyethylene (PE) outer layer **308**, suitable for heat bonding to PE and other heat weldable films, and an intermediary ethylvinylacetate (EVA) layer **307**, suitable for achieving bonding between the PVC and PE layers (Extrusion Alternatives, Inc., Portsmouth, NH). The multilayer barrier traversing tubes **305**, are suitably sized in inner diameter to accommodate solvent bonding to either standard

PVC blood line transfer tubing of about 3.0 mm by about 4.1 mm according to ISO 3826-1:2013, or a blood transfer device such as a PVC spike port, for example Vitalmed #20391 (Vitalmed, Inc., Lakeville, MA) or Qosina # 65842 (Qosina Corp., Edgewood, NY). The barrier traversing tubes **305** extend beyond the width of the diamond wedge by about 25 mm on both sides to facilitate these connections.

[00252] The diamond wedge with insert-molded multilayer tubes is placed between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL) on a custom fabricated heat sealing die having a groove suitably sized and shaped to accept the diamond wedge shape and provide slight compression during heat sealing, which is performed on a modified Franklin model 2400 press (Franklin Mfg. Corp., Norwood, MA). The dies are constantly heated to about 140°C by a pair of internal cartridge heaters (McMaster Carr # 4877K143, McMaster Carr, Inc., Robbinsville, NJ) connected to a process controller (Omega model CNI-CB120-SB, Omega Engineering, Inc., Stamford, CT). The press is activated with the films and diamond wedge in the die to compress and heat the assembly for about 3-4 seconds to yield a completely sealed seam comprising one side of the outer receptacle **201**.

[00253] One end of each multilayer tube is then solvent bonded to a transition PVC tube to connect a flexible collapsible blood container **202** inside the outer receptacle **201**, and the other end of each multilayer tube is then solvent bonded to either a spike port or a section of standard blood line transfer tubing. A sachet of sorbent is then placed on a spacer sheet, which is then placed between the collapsible container and one of the outer receptacle films, and then the remaining three seams of the outer receptacle **201** are sealed using an impulse sealer to yield a completed anaerobic blood storage container.

Example 13: Intermediary Block insert molded with bilayer tubes for RF welding of tubing

[00254] Similar to example 12 above, an anaerobic storage container with a substantially impermeable inlet/outlet **30** having fluid connectivity is fabricated by first insert molding 3 pieces of barrier traversing tubing **305** into polyethylene (Dowlex™ 2517) in the shape of a bar about 5 mm wide by about 57 mm total length with tapered ends ("diamond wedge") (Sonicron Corp., Westfield, MA), as shown in Figure 3D.

[00255] In this example, however, the barrier traversing tube of example 12 is replaced with a bilayer barrier traversing tube comprised of a polyvinylchloride (PVC) inner layer **306**, and an outer EVA layer **307**, **308** (Extrusion Alternatives, Inc., Portsmouth, NH). Since EVA

is known to have both good RF (radiofrequency) and heat weldability, and good adhesion to both PVC and PE, the need for any transition connection tubes to the collapsible blood container are eliminated in this configuration. The thickness of the EVA outer layer can be varied as desired and need only meet a minimum thickness to ensure adhesion of the PVC during insert molding to the PE; that is about 0.05-0.10 mm minimum thickness. The bilayer tubes are also similarly sized in inner diameter according to example 12 and extend beyond the width of the diamond wedge by about 25 mm on both sides to facilitate connections, however, the outer diameter of the bilayer tubes are suitably sized to fit into RF welding dies for use in fabricating a collapsible blood container.

[00256] In the first step of assembly the tubes on one end of the insert molded diamond wedge are RF welded to PVC films to form a collapsible blood container as follows: the three tubes in the diamond wedge are placed onto brass mandrels to support each of them, and then placed between a pair of collapsible blood container **202** films (Renolit ES-3000, American Renolit Corp., City of Commerce, CA). The assembly is then placed onto a custom RF sealing die **70** having three grooves suitably sized and shaped to accept the three tubes. The RF sealing die also seals the PVC collapsible blood container films between the tubes, and the perimeter seal in the outline shape of the collapsible blood container **202**. The press is activated with the films and tubes in the dies to compress and heat the assembly for about 4-5 seconds by RF energy (Solidyne RF Welder, S/N 3657) to yield a completely sealed seam forming the collapsible blood container **202**, which also has a substantially impermeable joint (diamond wedge) in place around the fluidly connected inlet tubes ready for sealing to the barrier films of the outer receptacle **201** in the next step.

[00257] Similar to example 12, the collapsible blood container RF welded to the tubes of the diamond wedge is now placed between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL). The assembly is placed onto a custom fabricated heat sealing die and sealed on the Franklin press to yield a completely sealed seam comprising one side of the outer receptacle **201**, plus the fluidly connected collapsible blood container. In the remaining steps the spike ports and PVC blood inlet tubing (inlet/outlet **30**) are solvent bonded to the exposed remaining sections of bilayer tubes of the diamond wedge as in example 12, and the sorbent sachet and spacer are also similarly prepared before sealing the remaining three seams of the outer receptacle **201,** to yield a completed anaerobic blood storage container.

Example 14: Barrier traversing tubes heat sealed "3-at-once" for solvent bonding

tubing

[00258] An anaerobic storage container with a substantially impermeable joint having fluid connectivity is fabricated by simultaneously heat sealing three individual pieces of barrier traversing tubing between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL), as shown in Figure 4A. The barrier traversing tubes have a polyvinylchloride (PVC) inner layer **306**, suitable for solvent bonding to PVC tubing, a polyethylene (PE) outer layer **308**, suitable for heat bonding to PE and other heat weldable films, and an intermediary ethylvinylacetate (EVA) layer **307**, suitable for achieving bonding between the PVC and PE layers (Extrusion Alternatives, Inc., Portsmouth, NH). The barrier traversing tubes are suitably sized in inner diameter to accommodate solvent bonding to either standard PVC blood line transfer tubing of about 3.0 mm by about 4.1 mm according to ISO 3826-1:2013, or a blood transfer device such as a PVC spike port, for example Vitalmed # 20391 (Vitalmed, Inc., Lakeville, MA) or Qosina # 65842 (Qosina Corp., Edgewood, NY).

[00259] The barrier traversing tubes are solvent bonded to a short section of PVC tubing using cyclohexanone to connect each tube to the respective port on a collapsible blood container. Mandrels are inserted into the barrier traversing tubes, a sorbent sachet (Mitsubishi SS-200, Mitsubishi Gas Chemical America, Inc., NY, NY) is placed on a spacer sheet and the assembly is held between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL) on a custom fabricated heat sealing die. The sealing die (aluminum die **70)** has three grooves suitably sized by reducing the diameter by about 0.25 mm and suitably shaped by providing a 0.5-0.8 mm radius to the corners to accept the tubes and provide slight compression during heat sealing. The sealing process is performed on a modified Franklin model 2400 hot stamp press (Franklin Mfg. Corp., Norwood, MA) at 80-85 psig. The upper die 701 is fabricated from a solid block of aluminum machined into a complimentary shape slightly larger than the perimeter of the collapsible blood container. The center region of the upper die **705** is relieved to accept and nest the collapsible blood container **202**, and the die has grooves as described above for sealing the barrier traversing tubes. The upper die is heated by direct conduction to about 127°C by mounting the upper die to the heated top platen of the Franklin press.

[00260] The lower die **702** is comprised of a metal insert section surrounded by thermally insulating Garolite® G-10 material. The lower die is similarly shaped as compared to the upper die, providing a nest for the collapsible blood container **202** and a flat mating surface **705** for the upper die to press against, while the metal insert section provides the grooves

needed for sealing the barrier traversing tubes to the surrounding films to ensure a substantially impermeable seal. The lower die is constantly heated to about 132°C by an internal cartridge heater (McMaster-Carr P/N: 3618K412) connected to process controller (Omega model CNI-CB120-SB, Omega Engineering, Inc., Stamford, CT). Thus, the entire perimeter is heated from the top die and also from the insert portion **706** of the lower die.

[00261] The press is activated with the films, sorbent and spacer sheet, and tubes in place in the dies as described and held for about 2 seconds dwell time to yield a completely sealed seam on the outer receptacle **201,** having three barrier traversing tubes with substantially impermeable seals fluidly connected to the collapsible blood container **202** inside. The remaining end of each barrier traversing tube is then solvent bonded to either a spike port or a section of standard blood line PVC tubing (inlet/outlet **30)** to yield an anaerobic blood storage container.

Example 15: Extruded shape barrier traversing tubes heat sealed "3-at-once" for solvent bonding tubing

[00262] Similar to example 14 above, an anaerobic storage container with a substantially impermeable joint having fluid connectivity is fabricated by simultaneously heat sealing three individual pieces of barrier traversing tubing between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL). In this example the barrier traversing tubes have an outer layer of PE that is extruded in a diamond wedge shape, as shown in Figure 4B, rather than a round shape to facilitate edge sealing to the barrier film; the inner PVC layer retains a round inner diameter suitable for solvent bonding with other PVC tubing and fitments, such as a spike port.

Example 16: Individual Insert Molded Intermediary Blocks

[00263] Similar to example 12 and 14 above, an anaerobic storage container with a substantially impermeable joint having fluid connectivity is fabricated by simultaneously heat sealing three individual diamond wedges, each having only one barrier traversing tube insert molded therein, between a pair of barrier films (RollPrint ClearFoil® Z, RollPrint Packaging Products Inc., Addison, IL). In this embodiment the barrier traversing tube **305** has an inner layer **306** of PVC, an intermediary layer **307** of EVA, and an outer layer **308** of PE that is insert molded into a PE diamond wedge shape to facilitate edge sealing to the barrier film; the inner PVC layer retains a round inner diameter suitable for solvent bonding with other PVC

tubing and fitments, such as a spike port. Alternatively, the barrier traversing tube **305** can have an inner layer **306** of PVC and an outer layer **308** of EVA, similar to example 13 above.

Example 17: Inner PVC Storage Bags Allow for Blood Reoxygenation

[00264] Several inner PVC storage bags are fabricated as described in example 1 and containing a single traditional inlet. The extent of reoxygenation of blood during storage in the inner PVC storage bags is determined by transferring 330 ml packed pRBC having an initial SO2 of between 35 to 70% into the bags. The PVC bags containing the pRBC are placed at 4°C under ambient atmospheric conditions. Samples are removed from each bag at 1 and 6 weeks and the SO2 determined.

[00265] The results presented in Figure 13 show reoxygenation of blood occurs in all inner PVC storage bags.

Example 18: Reoxygenation in the Absence of a Sorbent

[00266] Five anaerobic storage bags **20** are fabricated as described in examples 1 and 2 above. Two of the five bags are further completed by incorporating a sachet of SS-200 sorbent (Mitsubishi Gas Chemical America, New York, NY). The extent of reoxygenation of blood during storage in the Anaerobic Storage Bags is determined by transferring 330 ml pRBC having an initial SO2 of approximately 5% into the anaerobic storage bags **20**. Samples are removed from each bag at 1 and 6 weeks and the SO2 determined. As presented in Figure 14, the anaerobic storage bags **20** containing the sorbent result in decreased SO2 compared to the anaerobic storage bags **20** without sorbent, which result in reoxygenation to approximately 15% by week 6.

Example 19: Blood storage bags having three inlet/outlets lacking an oxygen impermeable bond 302 according to the present disclosure (Two Spike Ports and One Blood Line)

[00267] Five anaerobic storage bags **20** are fabricated by first RF welding two Renolit ES-3000 sheets, with a thickness that is approximately 0.017 inch and three (3) PVC tubes, without an impermeable bond **302**, to form an inner collapsible bag **202**.

[00268] The inner collapsible bag with 3 inlet/outlet tubes is heat sealed to an outside barrier bag fabricated from RollPrint Clearfoil® Z film #37-1275 (Rollprint Packaging Products, Inc., Addison, IL).

[00269] The headspace oxygen level is measured through the outer receptacle **201** film (Rollprint Clearfoil® Z). As shown in Figure 15, all anaerobic storage bags **20** lacking three oxygen impermeable bonds **302** provided by the present disclosure present highly variable levels of oxygen over the measurement period (84 days) and are not suitable for anaerobic storage of blood.

Example 20: ASB with three inlet/outlets 30 (Two Spike Ports and One Blood Line)

[00270] Three anaerobic storage bags **20** are fabricated as by first RF welding two Renolit ES-3000 sheets, with a thickness that is approximately 0.017 inch and three (3) PVC tubes, with a length of approximately 0.75 inch to form the inner collapsible bag **202**. Multilayer barrier traversing tubing (with an inner PVC layer **306**, intermediate EVA layer **307**, and outer PE layer **308**) is solvent bonded to each outside diameter of the three (3) PVC tubes of the inner bag to provide the means to heat sealing the inner (PVC) bag to the outer (PE) barrier bag. The multilayer tubing is solvent bonded to the inner bag PVC tubes directly.

[00271] The inner collapsible bag with three multilayer barrier traversing tubes **305** is heat sealed to an outside barrier bag fabricated from RollPrint Clearfoil® Z film #37-1275 (Rollprint Packaging Products, Inc., Addison, IL), using an aluminum die **70** (as shown in Figure 9) that is mounted to the Franklin hot stamping press and a bottom G-10 base with an aluminum insert block to seal around the three (3) ports and seal the inner PVC bag **202** to the outer barrier bag **201**.

[00272] As shown in Figure 9, the aluminum die **70** features two (2) aluminum insert blocks, one mounted to the top aluminum part and the bottom G-10 block. The top aluminum block is heated by the Franklin press and the bottom block is heated by a heating rod (1/4'' diameter) connected to the temperature controller. The tool has alignment pins on the top half and matting bushing on the bottom half to provide alignment between the two halves.

[00273] The headspace oxygen level is measured through the outer receptacle **201** film (Rollprint Clearfoil® Z). As shown in Figure 16, all anaerobic storage bags **20** maintained a headspace of below 0.8 mmHg for up to 84 days.

[00274] While the invention has been described with reference to preferred aspects, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof to adapt to particular situations without departing from the scope of the invention. Therefore, it is intended that the invention not be limited to

the particular aspects disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all aspects falling within the scope and spirit of the appended claims.

CLAIMS:

1. A blood storage device (20) for storing oxygen depleted blood comprising:
an outer receptacle (201) substantially impermeable to oxygen;
an inner collapsible blood container (202); and
at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202) and that is substantially impermeable to oxygen,
wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen and that comprises tubing (304), bond (302), and tubing (205).

2. The blood storage device of claim 1, further comprising an oxygen sorbent (207) situated within said outer receptacle (201).

3. The blood storage device of claim 1, wherein said at least one inlet/outlet (30) comprises a seal adaptor (301) and a bond (302), wherein said seal adaptor (301) and said bond (302) are substantially impermeable to oxygen.

4. The blood storage device of claim 1, wherein said inner collapsible blood container (202) has a moisture vapor transmission rate (MVTR) of 10 $g/m^2/24hrs$ or less when tested at a temperature of 23 ± 2 °C.

5. The blood storage device of claim 3, wherein said seal adaptor (301) is connected to tubing (205) and tubing (304).

6. The blood storage device of claim 1, wherein said unitary tube is a barrier traversing tube (305) having at least one oxygen barrier layer (307) and at least one blood compatible layer (306).

7. The blood storage device of claim 6, wherein said at least one oxygen barrier layer of barrier traversing tube (305) is selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyvinylidene fluoride (PVDF), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

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8. The blood storage device of claim 1, wherein said tubing (205) comprises a barrier traversing tube (305) having at least one oxygen barrier layer (307) and at least one blood compatible layer (306).

9. The blood storage device of claim 1, wherein said tubing (205) comprises PVC having a Barrer value of less than 3 Barrer.

10. The blood storage device of claim 8, wherein said oxygen barrier layer (307) is selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyvinylidene fluoride (PVDF), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

11. The blood storage device of claim 1, wherein said outer receptacle (201) is substantially impermeable to oxygen and said inner collapsible blood container (202) further comprises a locating feature adapted to align said inner collapsible blood container (202) within the geometry of said outer receptacle (201).

12. The blood storage device of claim 3, wherein said seal adaptor (301) is a barrier traversing tubing that is substantially impermeable to oxygen or is a polyethylene, a polyether block amide, or an ethylene-vinyl acetate wedge that is machined, extruded, molded, or laminated.

13. The blood storage device of claim 5, wherein said tubing (205) and said tubing (304) comprise polyvinyl chloride (PVC) having a Barrer value of less than 1 Barrer.

14. The blood storage device of claim 5, wherein said tubing (304) is a barrier traversing tube having an oxygen barrier layer (307) selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyvinylidene fluoride (PVDF), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

15. The blood storage device of claim 5, wherein said tubing (205) is selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene

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chloride (PVDC), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

16. The blood storage device of claim 1, further comprising a spacer (213).

17. The blood storage device of claim 16, wherein said spacer (213) is a mesh.

18. The blood storage device of claim 16, wherein said spacer (213) is integrated into at least one of said inner collapsible blood container (202) or outer receptacle (201) as a rib, dimple, or other raised feature that maintains a separation between said outer receptacle (201) and said inner collapsible blood container (202).

19. The blood storage device of claim 5, wherein said outer receptacle (201) and said tubing (205) are substantially impermeable to oxygen and wherein a headspace comprising a volume between said outer receptacle (201) and said inner collapsible blood container (202) is maintained at a partial pressure of oxygen (PO_2) of less than 15 mmHg during a storage period of at least 64 days.

20. The blood storage device of claim 19, wherein said headspace is maintained at a partial pressure of oxygen (PO_2) of less than 15 mmHg during a storage period of at least 21 days.

21. The blood storage device of claim 5, wherein said blood stored in said inner collapsible blood container (202) maintains an oxygen saturation level (SO_2) during a storage period that is approximately equal to the oxygen saturation level at the beginning of storage.

22. The blood storage device of claim 19, wherein said storage period is 64 days.

23. The blood storage device of claim 5, wherein said outer receptacle (201), said inlet/outlet (30), and said tubing (205) are substantially impermeable to oxygen, and said blood stored in said inner collapsible blood container (202) provides for an oxygen saturation level (SO_2) during a storage period that is less than the oxygen saturation level at the beginning of storage, wherein said storage period is at least 1 week.

24. The blood storage device of claim 23, wherein said oxygen saturation level is 3% less after one week of storage than the oxygen saturation level at the beginning of storage.

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25. The blood storage device of claim 23, wherein said oxygen saturation level decreases at a rate of at least 0.00010 % SO_2/minute.

26. The blood storage device of claim 5, wherein said outer receptacle (201), said inlet/outlet (30), and said tubing (205) are substantially impermeable to oxygen, and said blood stored in said inner collapsible blood container (202) provides for an oxygen saturation level (SO_2) during a storage period that increases less than 5% over said oxygen saturation level at the beginning of storage, wherein said storage period is 64 days.

27. The blood storage device of claim 26, wherein said SO2 increases less than 5% wherein said storage period is 64 days.

28. The blood storage device of claim 2, wherein said oxygen sorbent (207) has a capacity of at least 20 cc oxygen.

29. The blood storage device of claim 28, wherein said oxygen sorbent (207) has a capacity of about 6 cc.

30. The blood storage device of claim 28, wherein said oxygen sorbent (207) has a minimum oxygen adsorption rate of 1 cc/week/per gram.

31. The blood storage device of claim 3, wherein said bond (302) that is substantially impermeable to oxygen is solvent sealed, heat sealed, adhesive bonded, ultrasonic welded, or radio frequency welded.

32. The blood storage device of claim 11, wherein said locating feature is selected from the group consisting of a geometric cutout, a tactile surface marking, die cut fiducials, spacers, interlocking cutouts, tubing fittings, and a printed marking.

33. The blood storage device of claim 1, wherein said inner collapsible blood container (202) is manufactured by blow molding, compression molding, or insert molding.

34. The blood storage device of claim 1, wherein said inner collapsible blood container (202) is manufactured by heat sealing, adhesive bonding, ultrasonic welding, or radio frequency welding.

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35. The blood storage device of claim 1, further comprising a second inlet/outlet (30) in fluid communication with said inner collapsible blood container (202).

36. The blood storage device of claim 1, further comprising an integrated handle (214).

37. The blood storage device of claim 1, wherein said outer receptacle (201) comprises an expansion feature (215).

38. The blood storage device of claim 37, wherein said expansion feature (217) allows for unrestricted filling of said inner collapsible blood container (202).

39. The blood storage device of claim 37, wherein said expansion feature (217) is selected from the group consisting of a pleat, a diaphragm, a bubble, one or more folds, a folded pouch, a trifold, a gusset, and a geometric expansion in the packaging shape.

40. The blood storage device of claim 1, wherein said inner collapsible blood container (202) has a permeability of between 3 and 11 Barrer.

41. The blood storage device of claim 1, wherein said inner collapsible blood container (202) is highly permeable to oxygen with a permeability of between 11 and 350 Barrer.

42. The blood storage device of claim 1, wherein said inner collapsible blood container (202) has an oxygen permeability of between 99 and 350 Barrer.

43. The blood storage device of claim 42, wherein said oxygen sorbent (207) is situated outside of said inner collapsible blood container (202).

44. The blood storage device of claim 43, wherein said oxygen sorbent (207) is provided as one or more sachets.

45. The blood storage device of claim 43, wherein said sorbent is provided as an oxygen absorbing film.

46. The blood storage device of claim 44, wherein said oxygen absorbing film is laminated to said outer receptacle (201).

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47. The blood storage device of claim 1, wherein said outer receptacle (201), said inner collapsible blood container (202), and said oxygen sorbent (207) comprise a multilayered film.

48. The blood storage device of claim 47, wherein said outer receptacle (201) of said multilayered film comprises polyethylene (PE), PET, or EVA.

49. The blood storage device of claim 47, wherein said inner collapsible blood container (202) of said multilayered film comprises one or more layers that are substantially permeable to oxygen.

50. The blood storage device of claim 1, further comprising a tube management component (40).

51. The blood storage device of claim 50, wherein said tube management component (40) is selected from the group consisting of a strap attached to the outer surface of said outer receptacle, a hook and loop fastener (VELCRO®), tape, and snap.

52. The blood storage device of claim 50, wherein said tube management component (40) is a cut out feature of the outer surface of said outer receptacle.

53. The blood storage device of claim 50, wherein said tube management component (40) is a clip attached to the outer surface of said outer receptacle.

54. The blood storage device of claim 1, wherein said inner collapsible blood container (202) comprises a transparent material selected from the group consisting of polyvinyl chloride (PVC), low-density polyethylene, polypropylene, polyethylene terephthalate (PET), silicone, ethylvinyl alcohol (EVOH), ethylenevinyl acetate (EVA), and polyurethane.

55. The blood storage device of claim 1, wherein said inner collapsible blood container (202) comprises opaque or non-transparent low-density polyethylene, polypropylene, polysulfone, PVDF or PET.

56. The blood storage device of claim 55, wherein said inner collapsible blood container (202) further includes a transparent or translucent window (212) on the surface.

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57. The blood storage device of claim 1, wherein said inner collapsible blood container (202) comprises a microporous membrane selected from the group consisting of polytetrafluoroethylene, polyvinylidenefluoride, polypropylene, and polysulfone microporous membrane.

58. The blood storage device of claim 57, wherein said polytetrafluoroethylene, PVDF, polypropylene or polysulfone (PSU) microporous membrane has a pore size selected from the group consisting of 0.03 μm, 0.05 μm, 0.1 μm, 0.2 μm, 0.23 μm, 0.45 μm, 0.5 μm and 1.0 μm.

59. The blood storage device of claim 58, wherein said polytetrafluoroethylene, PVDF, polypropylene or polysulfone (PSU) microporous membrane is reinforced via lamination, layering, or bonding.

60. The blood storage device of claim 1, further comprising a time-temperature indicator.

61. The blood storage device of claim 1, wherein said outer receptacle (201) is substantially impermeable to oxygen and comprises one or more seals having a width of at least 1/16 inch.

62. A blood storage device for storing oxygen depleted blood comprising:
an outer receptacle (201) that is substantially impermeable to oxygen;
an inner collapsible blood container (202); and
at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202) and that is substantially impermeable to oxygen;
wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen and that comprises tubing (304), bond (302), and tubing (205),
wherein oxygen depleted blood having an oxygen saturation level of less than 20% is maintained in an oxygen depleted state for at least 21 days.

63. The blood storage device of claim 62, wherein said outer receptacle that is substantially impermeable to oxygen is selected from the group consisting of polyolefin, polyvinylidene chloride (PVDC), Oriented Polypropylene (OPP), polyethylene, PET, EVA, and PVC.

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64. The blood storage device of claim 62, wherein said tubing is barrier traversing tubing.

65. The blood storage device of claim 62, further comprising an inner receptacle that is permeable to oxygen and contains an oxygen sorbent (207).

66. The blood storage device of claim 62, wherein said inner collapsible blood container comprises PVC.

67. The blood storage device of claim 66, wherein said inner collapsible blood container comprises PVC doped with a permeability enhancing additive selected from the group consisting of DEHP, citrate, and DINCH.

68. A method of storing deoxygenated blood comprising placing deoxygenated blood into a blood storage device (20) comprising: an outer receptacle (201) substantially impermeable to oxygen; an inner collapsible blood container (202); at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible blood container (202) and that is substantially impermeable to oxygen, wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen and that comprises tubing (304), bond (302), and tubing (205).

69. The method of claim 68, wherein said deoxygenated blood has an oxygen saturation level of less than 20%.

70. The method of claim 68, wherein said inner collapsible blood container (202) having a permeability of between 3 and 350 Barrer.

71. A method of further reducing the oxygen saturation of blood during storage comprising:
transferring oxygen depleted blood for storage having an oxygen saturation level of less than 20% to a blood storage device (20) comprising: an outer receptacle (201) substantially impermeable to oxygen; an inner collapsible blood container (202); at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible blood container (202) and that is substantially impermeable to oxygen, wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen;
storing said oxygen depleted blood for storage for a time period wherein said time period is at least 1 week.

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72. The method of claim 71, wherein said storing is at a temperature of about 2 to 6 °C.

73. The method of claim 72, wherein said blood has an oxygen saturation level of less than 20% after one week, less than 10% after two weeks, or less than 5% after three weeks.

74. The blood storage device of claim 1, further comprising an oxygen indicator.

75. The blood storage device of claim 74, further comprising a temperature and time sensitive indicator.

76. The blood storage device of claim 1, wherein said at least one inlet/outlet (30) comprises a manifold.

77. The blood storage device of claim 76, wherein said manifold comprises a premolded manifold having integrated tubing.

78. The blood storage device of claim 1, wherein said at least one inlet/outlet (30) passing through said outer receptacle (201) comprises a shaped tubing.

79. The blood storage device of claim 78, wherein said shaped tubing is sealed to said outer receptacle (201) to prepare an oxygen impermeable seal (302).

80. The blood storage device of claim 16, wherein said spacer (213) is selected from the group consisting of a molded mat, a woven mat, a non-woven mat, an open cell foam, a strand veil, and a strand mat.

81. A blood storage device (20) for storing oxygen depleted blood comprising:
outer receptacle (201) substantially impermeable to oxygen;
a mesh spacer (213);
an inner collapsible blood container (202); at least one inlet/outlet (30) that is substantially impermeable to oxygen passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202); and
an oxygen and carbon dioxide sorbent (207) situated within said outer receptacle (201),
wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen comprising tubing (304), bond (302), and tubing (205), wherein said unitary tube is a barrier traversing tube (305) comprising an outer layer (308), an inner layer (306), and an oxygen barrier layer (307).

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82. The blood storage device of claim 81, wherein said outer receptacle (201) that is substantially impermeable to oxygen consists of a heat sealable polyethylene (PE) inner layer, an alumina barrier middle later, and a polyethylene terephthalate (PET) layer.

83. The blood storage device of claim 81, wherein said outer receptacle that is substantially impermeable to oxygen comprises a polyethylene terephthalate (PET).

84. The blood storage device of claim 83, wherein said PET further comprises a barrier coating of silica or alumina.

85. The blood storage device of claim 83, wherein said outer receptacle further comprises a polyolefin inner layer.

86. The blood storage device of claim 81, wherein said collapsible blood container (202) comprises PVC with DEHP.

87. The blood storage device of claim 81, wherein said collapsible blood container (202) has a moisture vapor transmission rate (MVTR) of 10 g/m2/24hrs or less when tested at a temperature of 23 ± 2 °C.

88. The blood storage device of claim 81, wherein said oxygen and carbon dioxide sorbent (207) consists of iron powders.

89. The blood storage device of claim 81, wherein said oxygen and carbon dioxide sorbent (207) has a capacity of at least 100 cc oxygen.

90. The blood storage device of claim 81, wherein said blood storage device (20) includes from 0.5 to 150 grams of said oxygen and carbon dioxide sorbent (207) in one or more sachets.

91. The blood storage device of claim 90, wherein said oxygen and carbon dioxide sorbent (207) is provided as a single sachet comprising 8 grams of sorbent, situated outside of said collapsible blood container (202).

92. The blood storage device of claim 81, wherein said tubing (205) comprises PVC having a Barrer value of less than 3 Barrer.

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93. The blood storage device of claim 81, wherein said outer layer (308) consists of polythelene (PE), said inner lay (306) consists of PVC, and said oxygen barrier layer (307) consists of EVA.

94. The blood storage device of claim 81, further comprising a headspace comprising a volume between said outer receptacle (201) and said inner collapsible blood container (202) is maintained at a partial pressure of oxygen (PO2) of less than 15 mmHg during a storage period of at least 64 days.

95. The blood storage device of claim 81, further comprising an oxygen indicator.

96. The blood storage device of claim 81, further comprising hanging feature (203).

97. The blood storage device of claim 81, wherein said oxygen depleted blood stored in said inner collapsible blood container (202) maintains an oxygen saturation level (SO2) during a storage period that increases less than 5% over said oxygen saturation level at the beginning of storage.

98. The blood storage device of claim 81, wherein said collapsible blood container (202) has an oxygen permeability of between 3 and 350 Barrer.

99. The blood storage device of claim 98, wherein said collapsible blood container (202) has said oxygen permeability of between 3 and 11 Barrer.

100. The blood storage device of claim 81, further comprising a locating feature adapted to align said inner collapsible blood container (202) with the geometry of said outer receptacle (201).

101. A blood storage device (20) for storing oxygen depleted blood comprising:
an outer receptacle (201) substantially impermeable to oxygen;
an inner collapsible blood container (202); and
at least one inlet/outlet (30) that is substantially impermeable to oxygen passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202); and
an oxygen sorbent (207) situated within said outer receptacle (201),

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wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen comprising tubing (304), bond (302), and tubing (205), wherein said unitary tube is a barrier traversing tube (305) comprising an outer layer (308), an inner layer (306), and an oxygen barrier layer (307).

102. The blood storage device of claim 101, wherein said sorbent (207) situated within said outer receptacle (201) further comprises a carbon dioxide sorbent.

103. The blood storage device of claim 101, wherein said at least one oxygen barrier layer of barrier traversing tube (305) is selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyvinylidene fluoride (PVDF), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

104. The blood storage device of claim 101, wherein said tubing (304) is a barrier traversing tube having an oxygen barrier layer (307) selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyvinylidene fluoride (PVDF), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

105. The blood storage device of claim 101, wherein said tubing (205) is selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), polyvinylidene chloride (PVDC), polyurethane (PU), polyethylene terephthalate (PET), polyethylene napthalate (PEN), and polyamide.

106. The blood storage device of claim 101, wherein said tubing (205) comprises polyvinyl chloride (PVC) having a Barrer value of less than 3 Barrer.

107. The blood storage device of claim 101, wherein said tubing (304) comprises polyvinyl chloride (PVC) having a Barrer value of less than 3 Barrer.

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108. The blood storage device of claim 101, wherein said collapsible blood container (202) has a moisture vapor transmission rate (MVTR) of 10 $g/m^2/24hrs$ or less when tested at a temperature of 23 ± 2 °C.

109. The blood storage device of claim 101, further comprising a spacer (213) selected from the group consisting of a mesh, a molded mat, a woven mat, a non-woven mat, an open cell foam, a strand veil, and a strand mat.

110. A blood storage device (20) for storing oxygen depleted blood comprising:
outer receptacle (201) substantially impermeable to oxygen;
a spacer (213);
an oxygen sorbent (207) situated within said outer receptacle (201),
an inner collapsible blood container (202); at least one inlet/outlet (30) that is substantially impermeable to oxygen passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202).

111. The blood storage device of claim 110, wherein said sorbent (207) situated within said outer receptacle (201) further comprises a carbon dioxide sorbent.

112. The blood storage device of claim 110, wherein said spacer (213) is selected from the group consisting of a mesh, a molded mat, a woven mat, a non-woven mat, an open cell foam, a strand veil, and a strand mat.

113. The blood storage device of claim 110, wherein said spacer (213) is integrated into at least one of said inner collapsible blood container (202) or outer receptacle (201) as a rib, dimple, or other raised feature that maintains a separation between said outer receptacle (201) and said inner collapsible blood container (202).

114. The blood storage device of claim 110, wherein said outer receptacle (201) that is substantially impermeable to oxygen consists of a heat sealable polyethylene (PE) inner layer, an alumina barrier middle later, and a polyethylene terephthalate (PET) layer.

115. The blood storage device of claim 110, wherein said outer receptacle that is substantially impermeable to oxygen comprises a polyethylene terephthalate (PET).

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116. The blood storage device of claim 110, wherein said PET further comprises a barrier coating of silica or alumina.

117. The blood storage device of claim 110, wherein said outer receptacle further comprises a polyolefin inner layer.

118. The blood storage device of claim 110, wherein said collapsible blood container (202) comprises PVC with DEHP.

119. The blood storage device of claim 110, wherein said collapsible blood container (202) has a moisture vapor transmission rate (MVTR) of 10 $g/m^2/24hrs$ or less when tested at a temperature of 23 ± 2 °C.

120. The blood storage device of claim 110, wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen comprising tubing (304), bond (302), and tubing (205), wherein said unitary tube is a barrier traversing tube (305) comprising an outer layer (308), an inner layer (306), and an oxygen barrier layer (307).

121. A blood storage device (20) for storing oxygen depleted blood comprising:
an outer receptacle (201) substantially impermeable to oxygen;
an inner collapsible blood container (202); and
at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202) and that is substantially impermeable to oxygen,
wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen and that comprises tubing (304), bond (302), and tubing (205), wherein said tubing (205) comprises a barrier traversing tube (305) comprising an outer layer (308), an inner layer (306), and an oxygen barrier layer (307).

122. A blood storage device (20) for storing oxygen depleted blood comprising:
an outer receptacle (201) substantially impermeable to oxygen;
an inner collapsible blood container (202); and

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at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202) and that is substantially impermeable to oxygen,

wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen, wherein said unitary tube is a barrier traversing tube (305) having at least one oxygen barrier layer (307) and at least one blood compatible layer (306).

123. A blood storage device (20) for storing oxygen depleted blood comprising:

an outer receptacle (201) substantially impermeable to oxygen;

an inner collapsible blood container (202); and

at least one inlet/outlet (30) passing through said outer receptacle (201) and that is in fluid communication with said inner collapsible container (202) and that is substantially impermeable to oxygen,

wherein said at least one inlet/outlet (30) comprises a unitary tube that is substantially impermeable to oxygen and that comprises tubing (304), bond (302), and tubing (205),

wherein said tubing (304) is a barrier traversing tube comprising an oxygen barrier layer (307) selected from the group consisting of ethylene-vinyl acetate (EVA), ethyl vinyl alcohol (EVOH), poly(ethylene-vinyl) acetate (PEVA), polypropylene (PP), polyacrylonitrile (PAN), and polyvinylidene chloride (PVDC).

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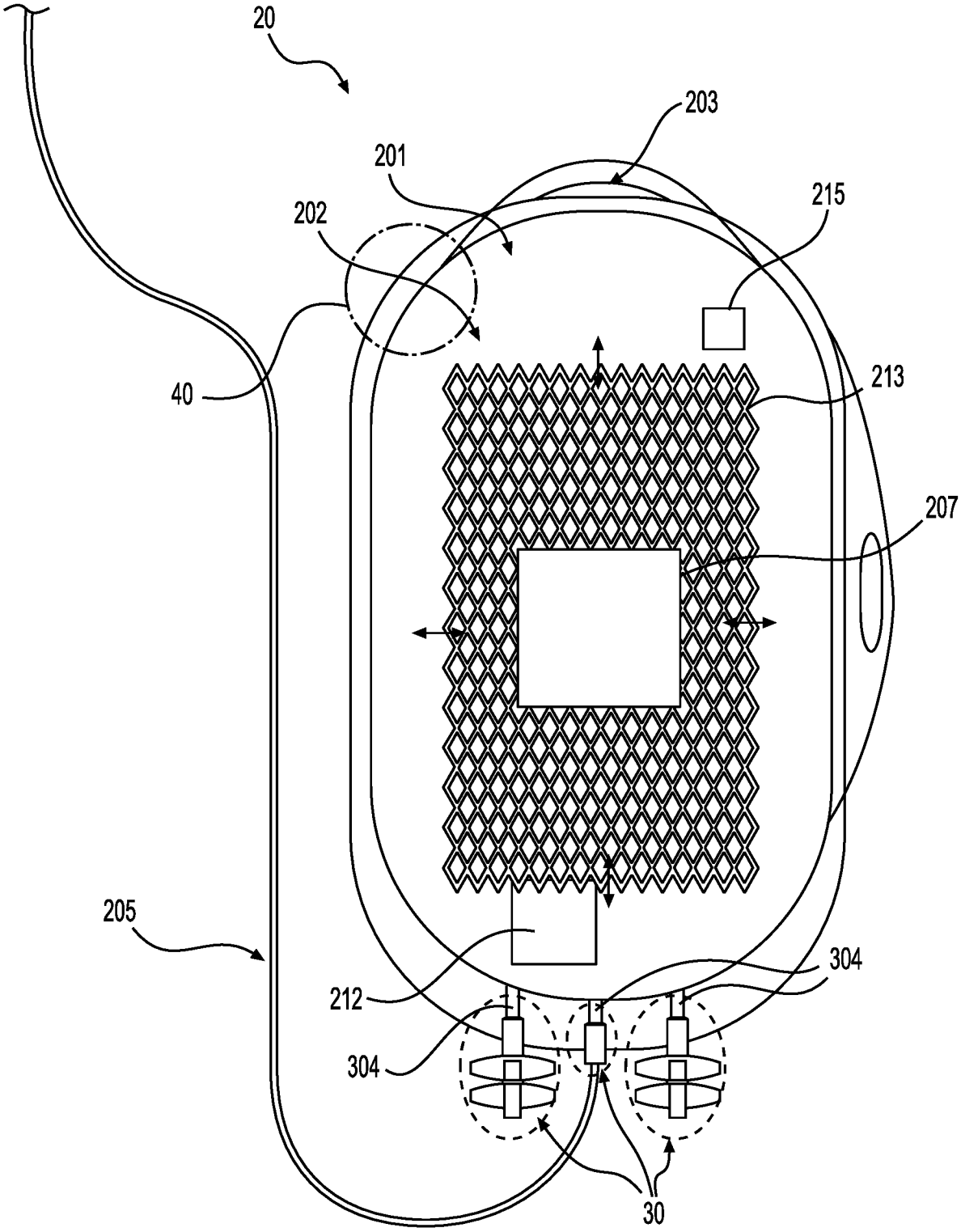


FIG. 1A

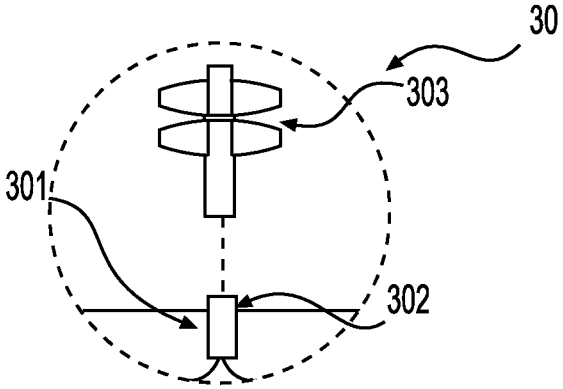

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FIG. 1B

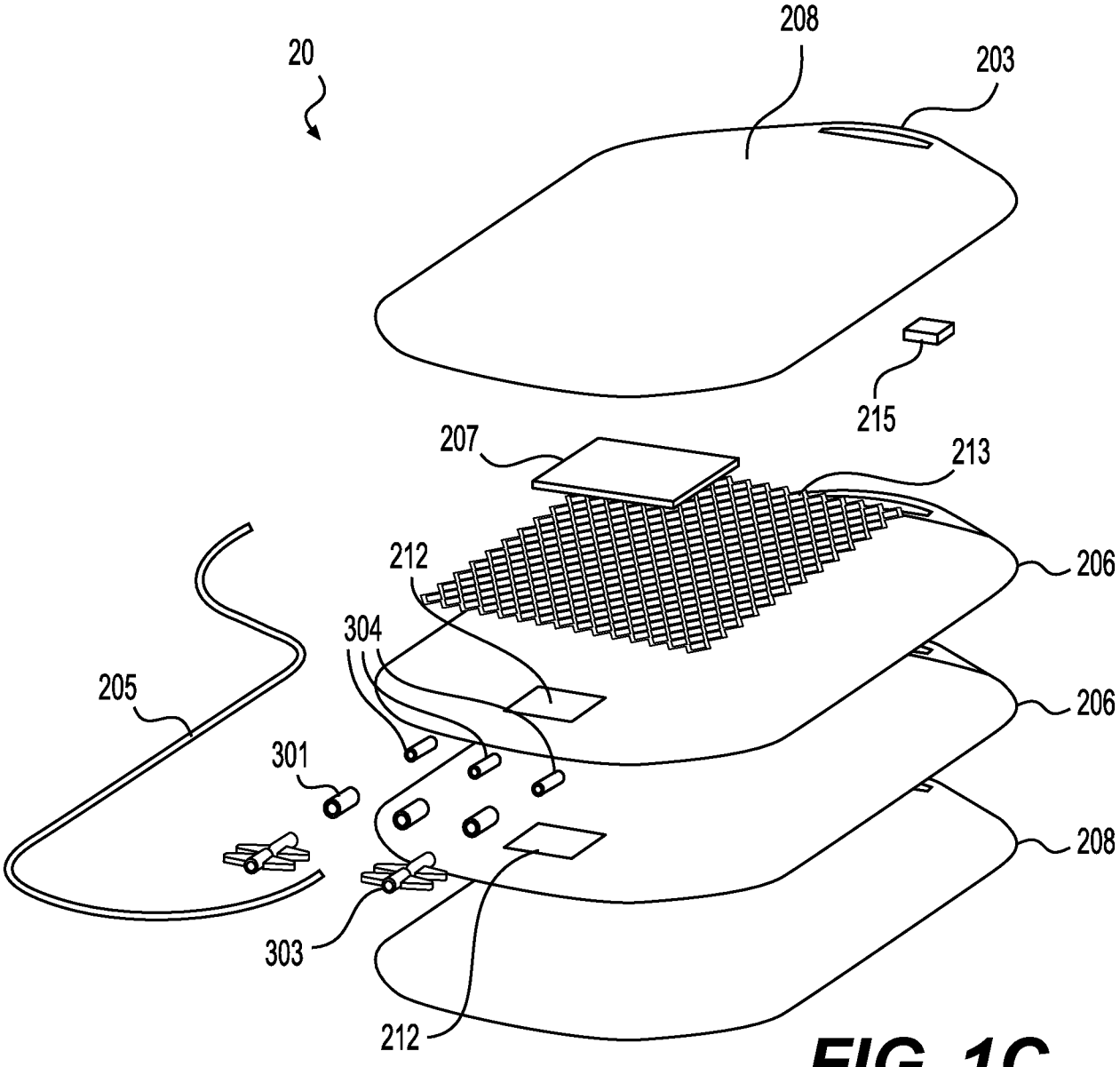

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FIG. 1C

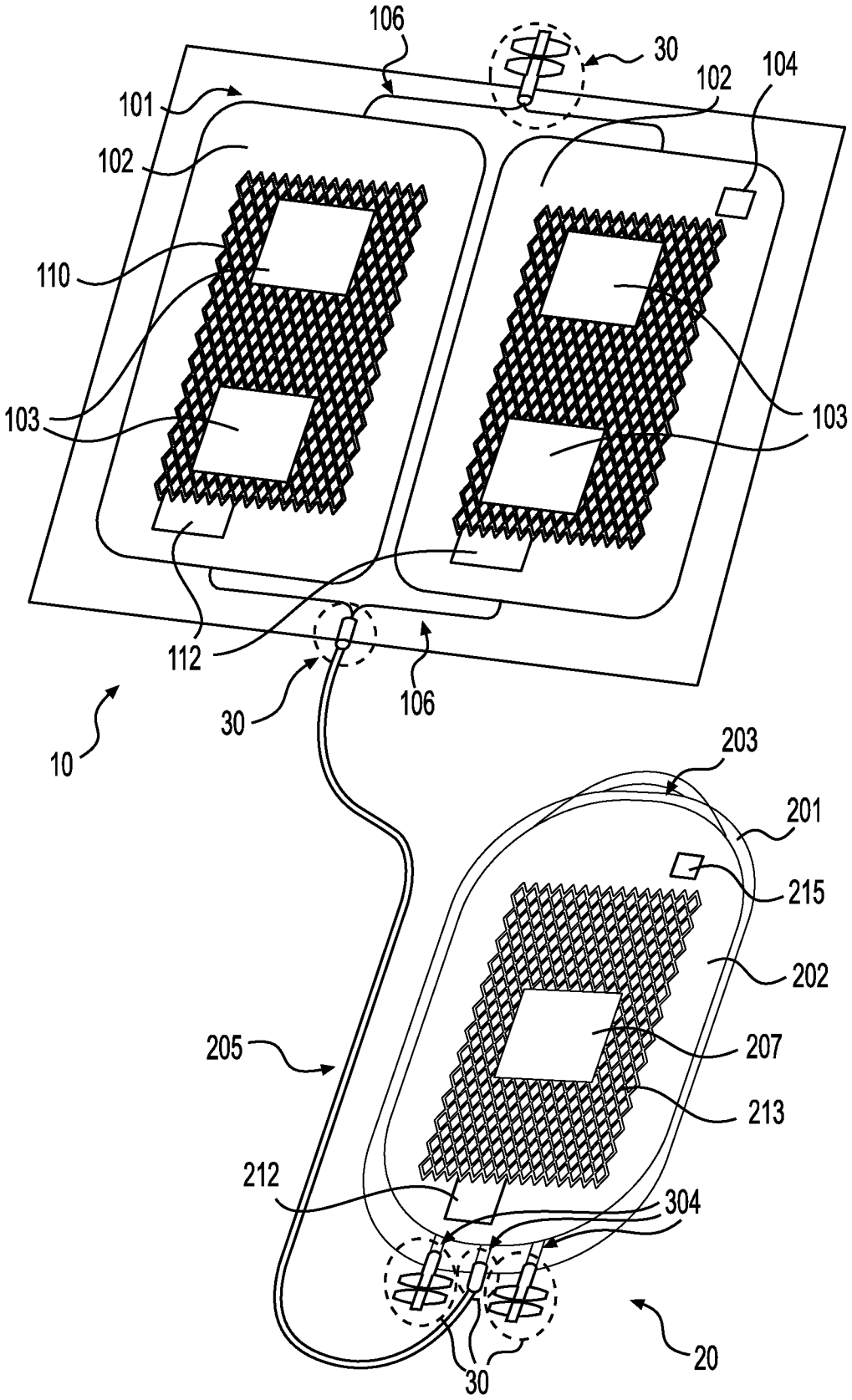

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FIG. 2A

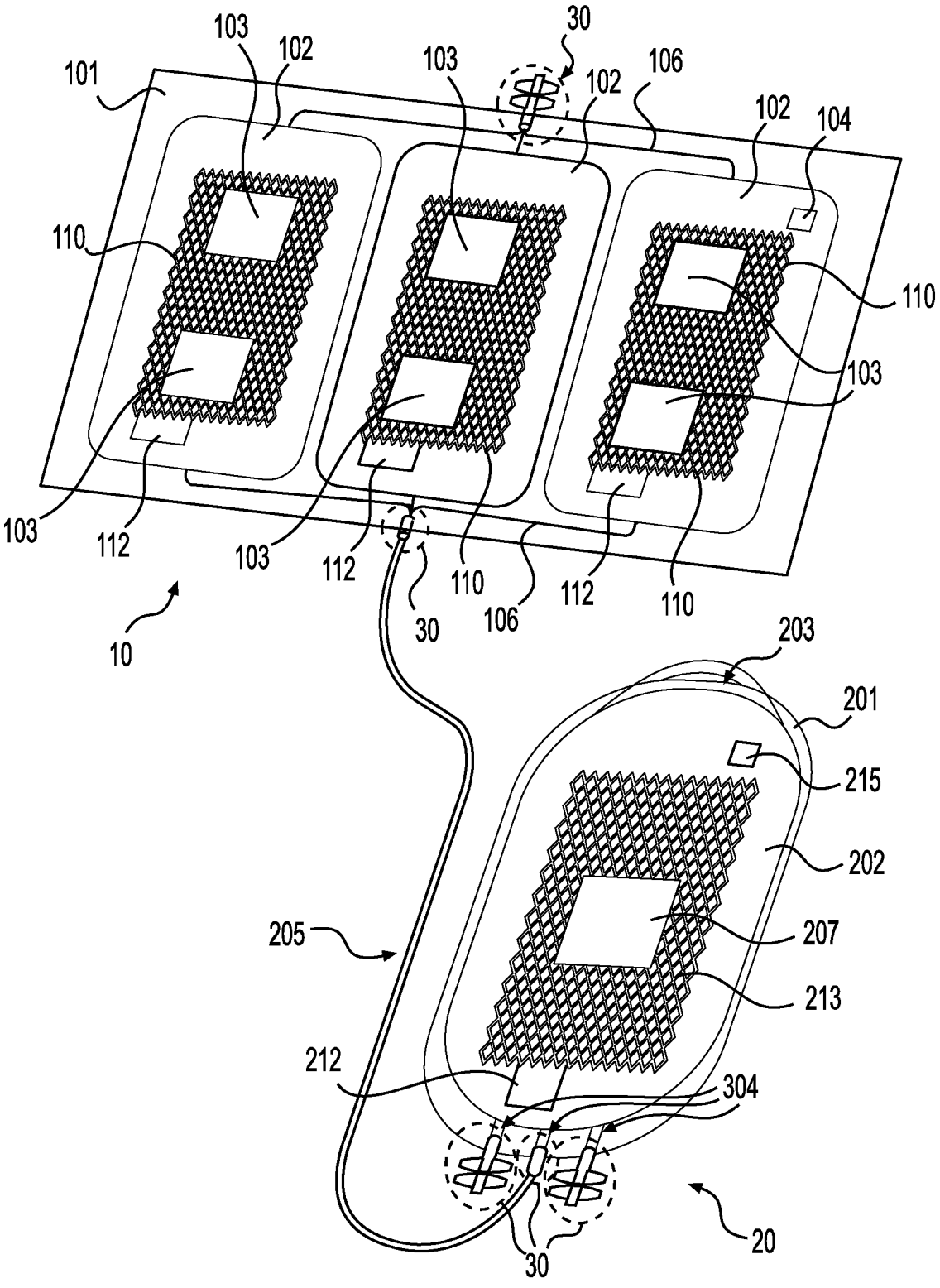

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FIG. 2B

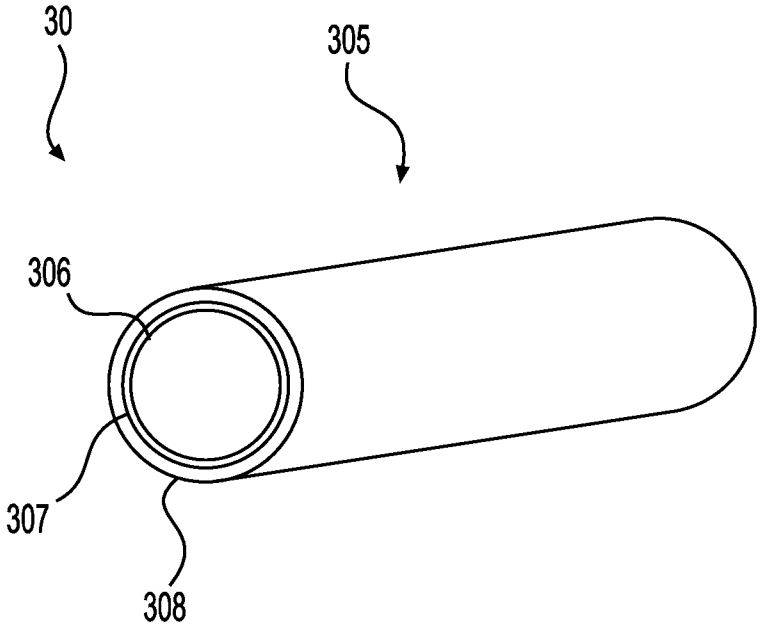


FIG. 3A

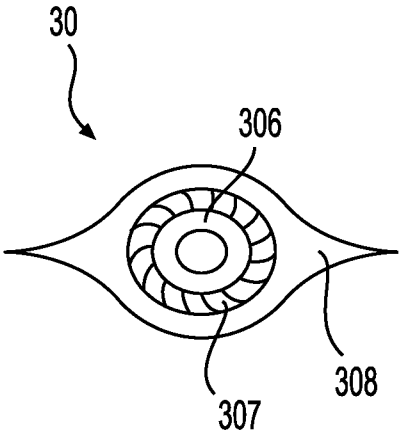


FIG. 3B

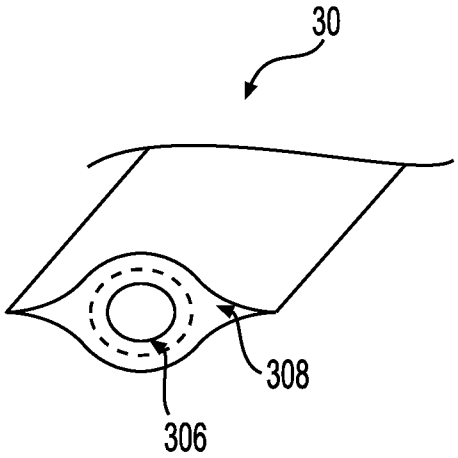


FIG. 3C

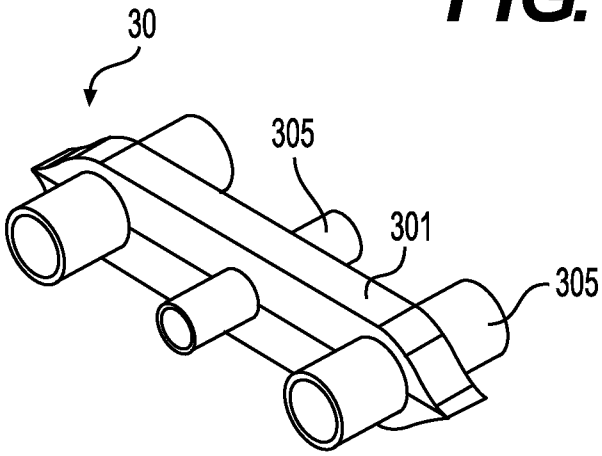


FIG. 3D

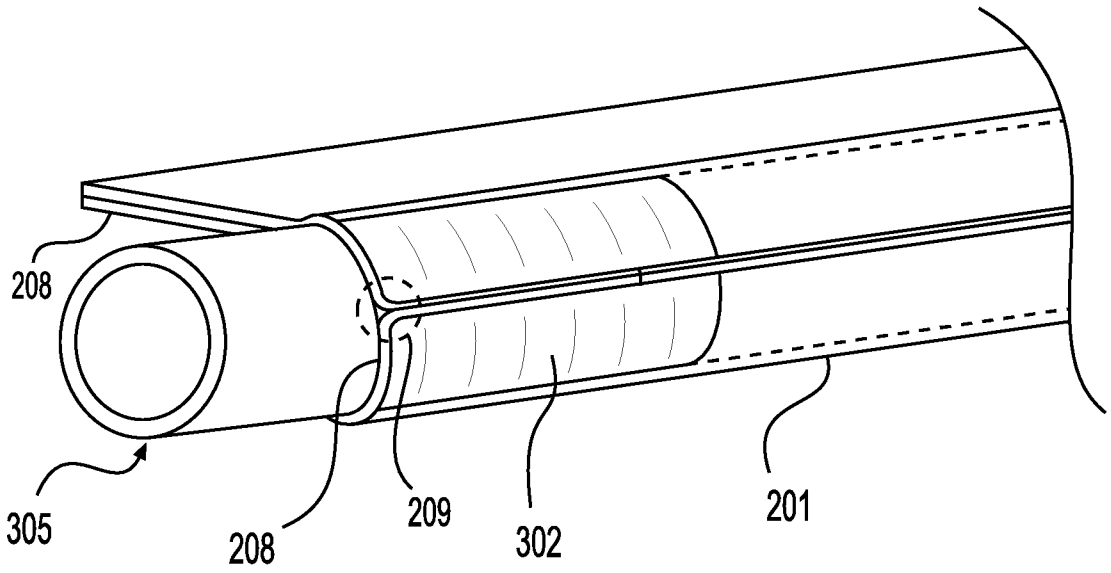


FIG. 4A

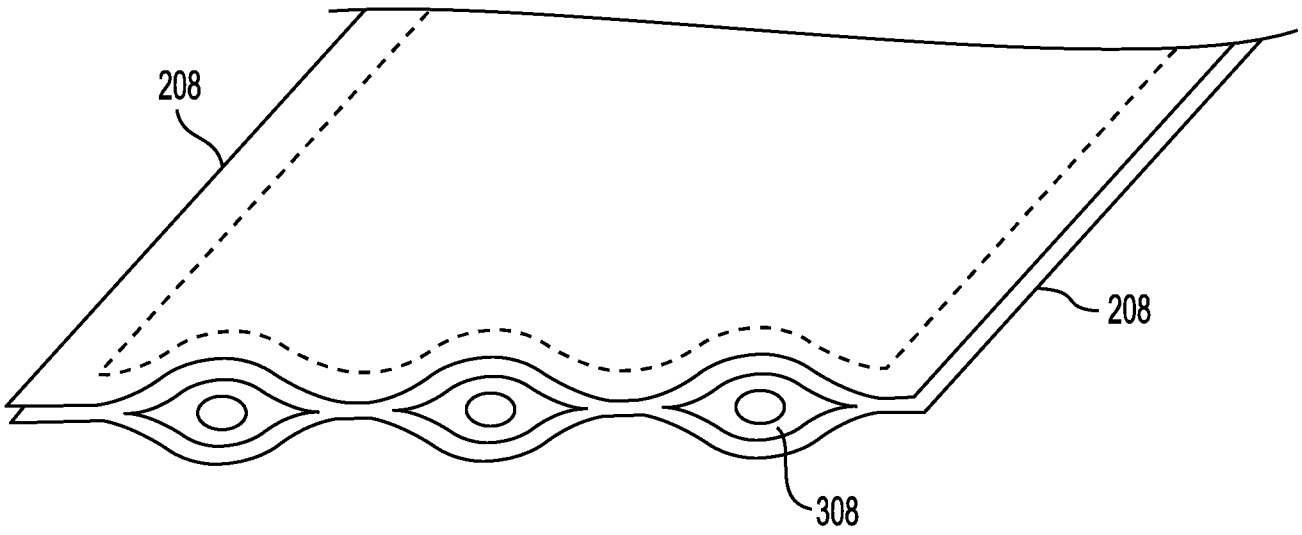


FIG. 4B

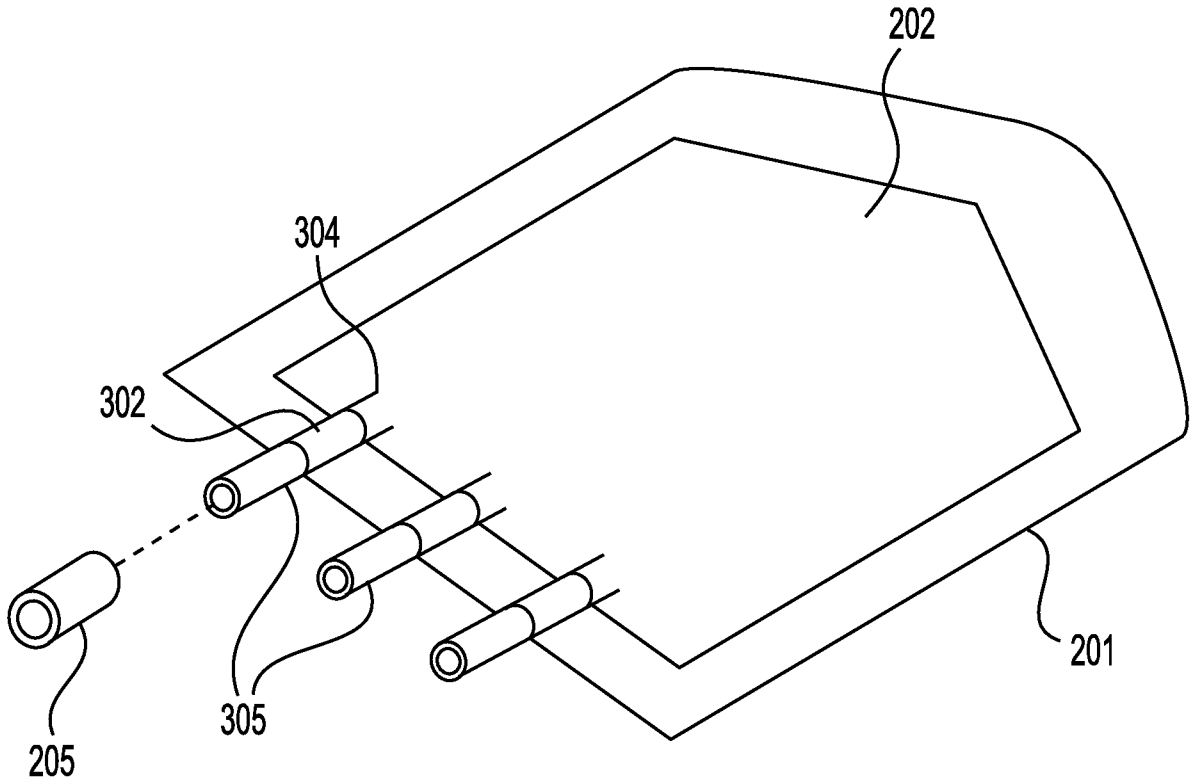


FIG. 5A

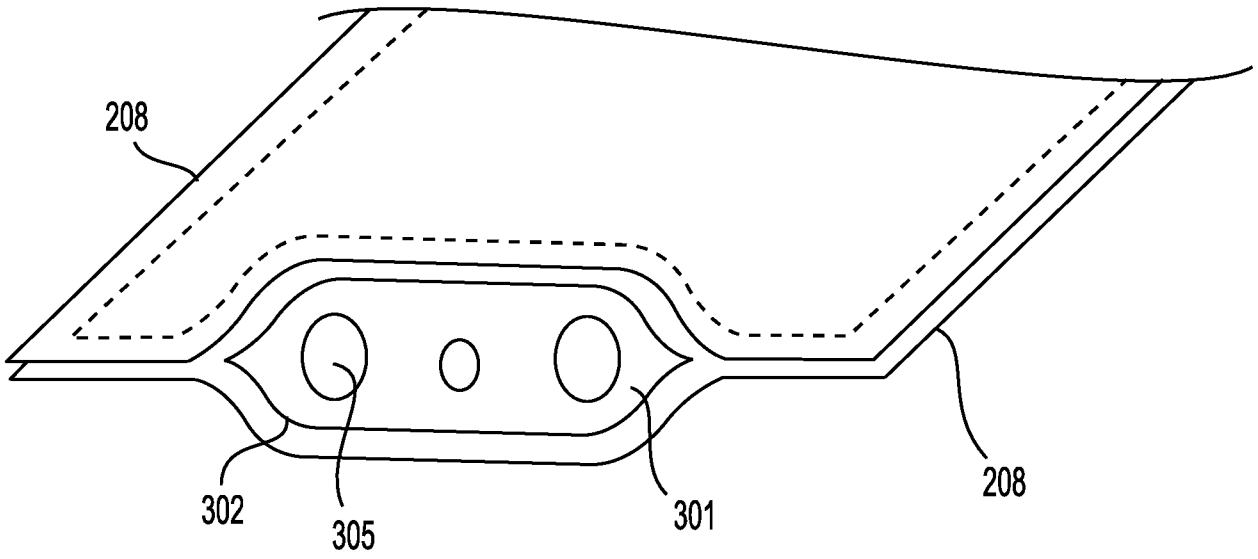


FIG. 5B

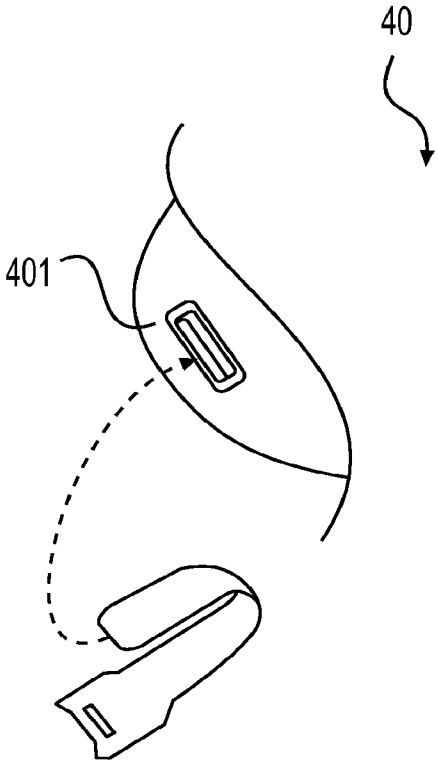


FIG. 6A

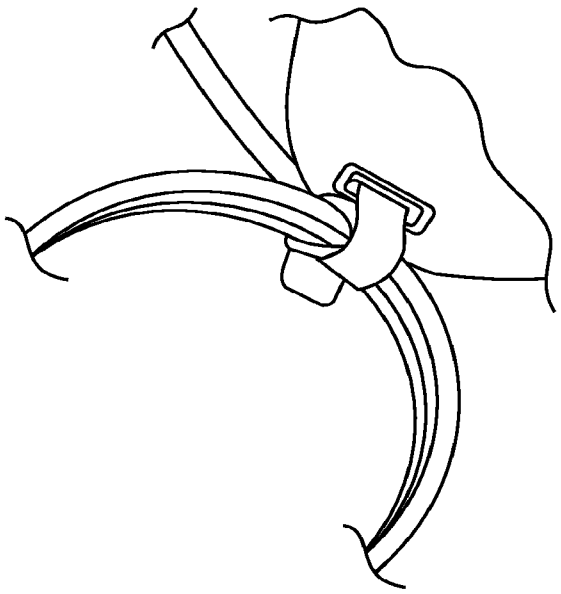


FIG. 6B

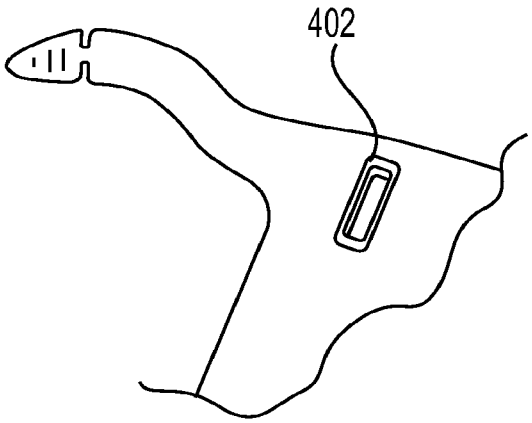


FIG. 6C

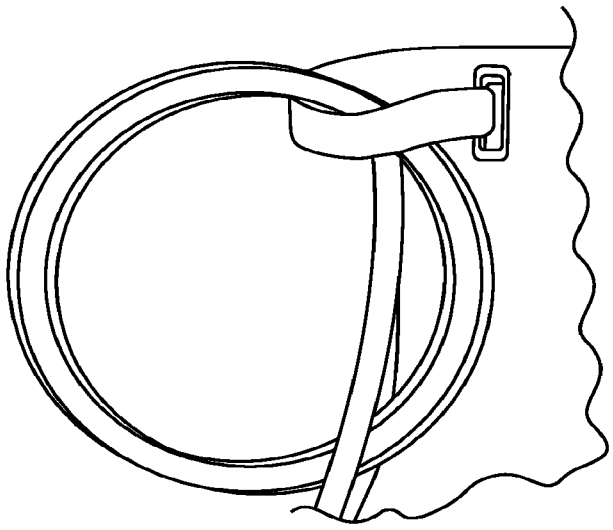


FIG. 6D

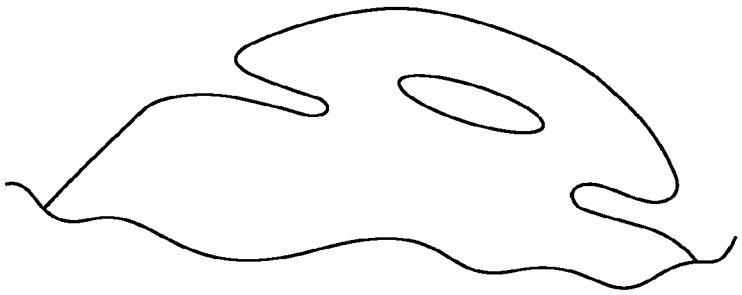


FIG. 6E

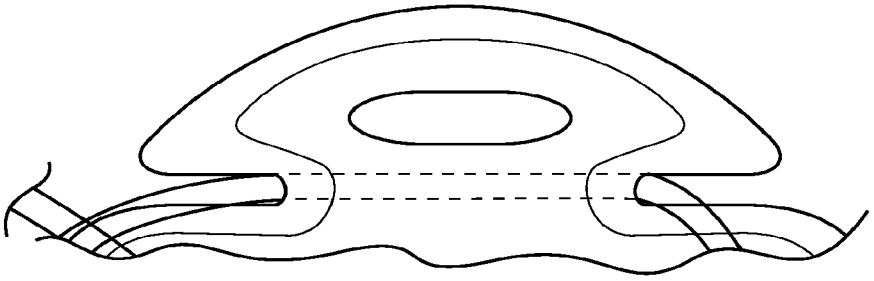


FIG. 6F

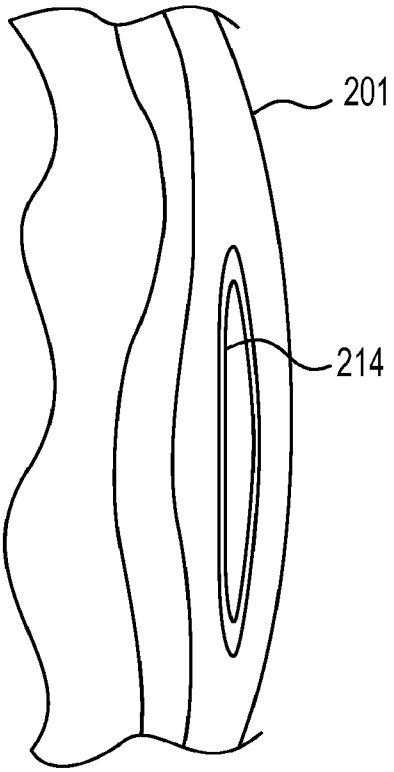


FIG. 7

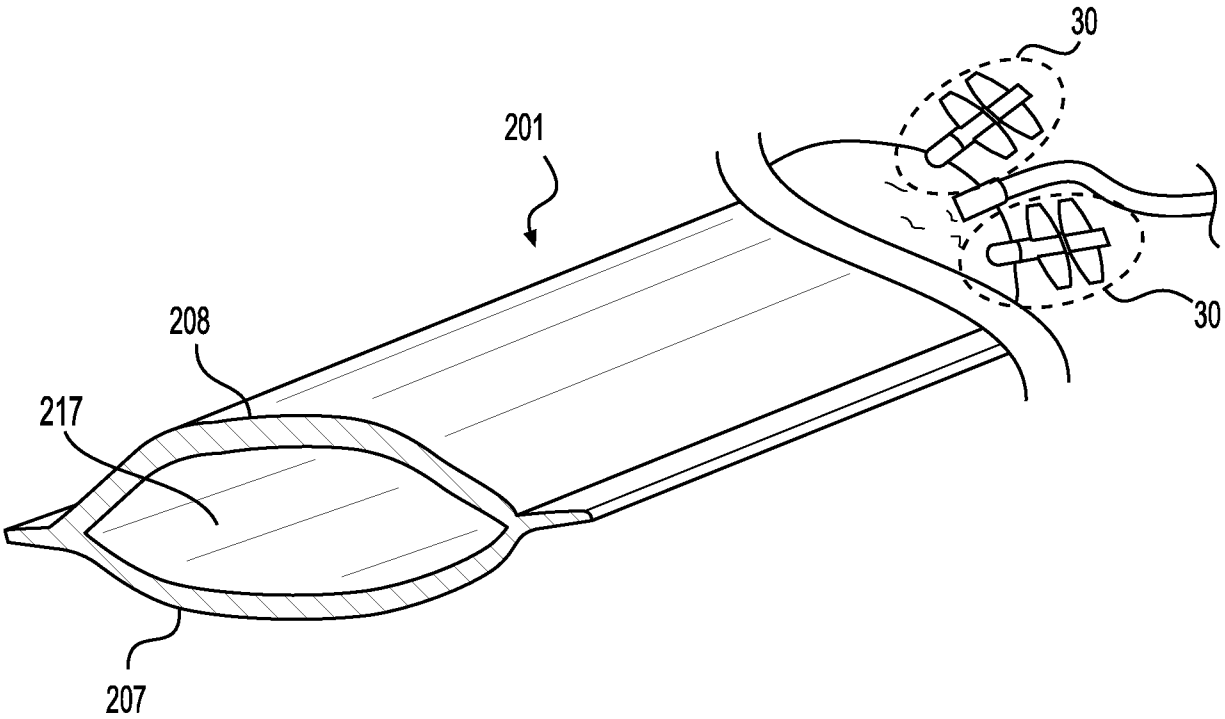


FIG. 8

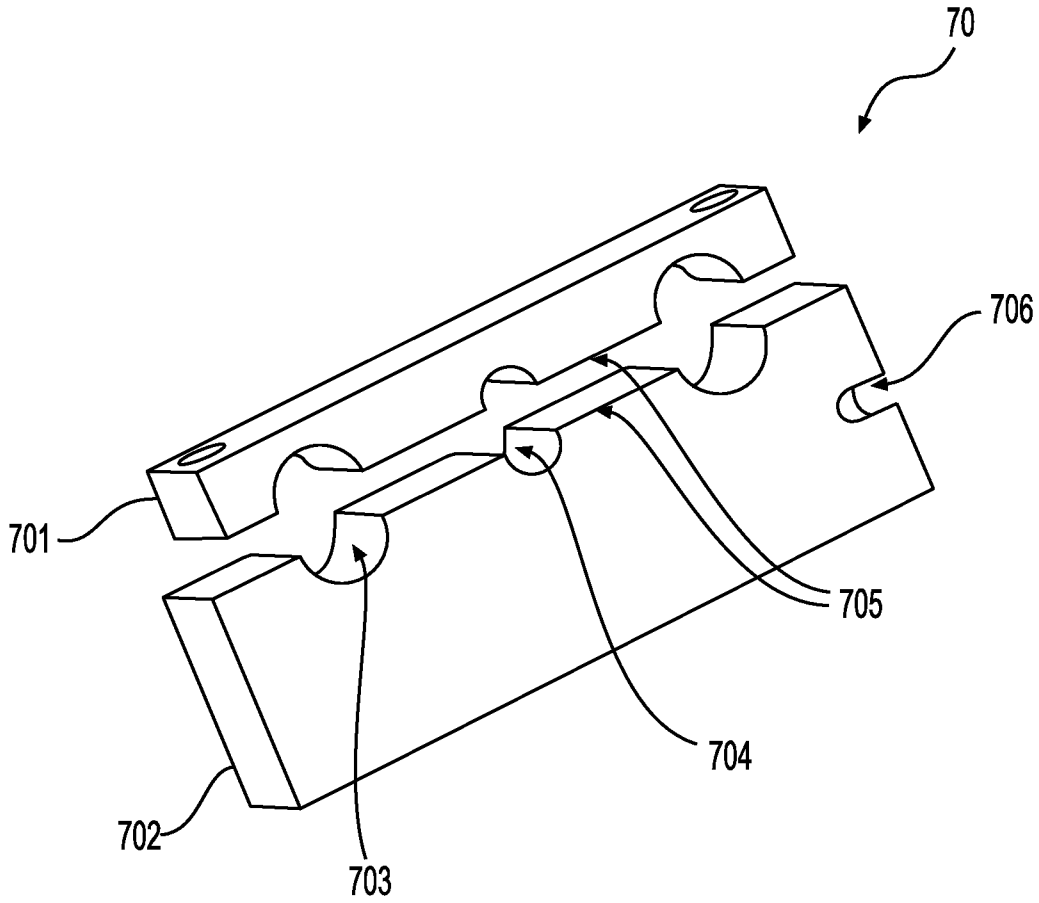


FIG. 9

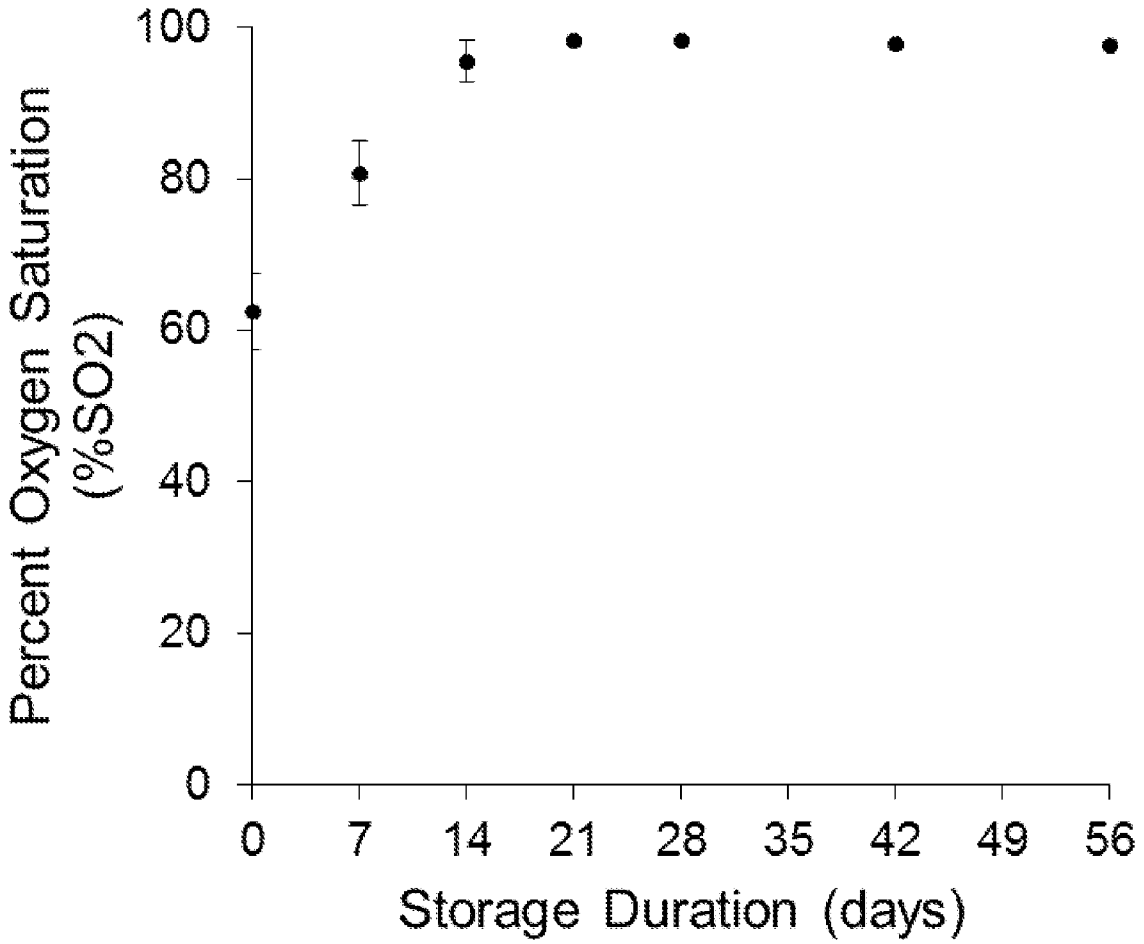

Percent Oxygen Saturation (%SO2)
100
80
60
40
20
0
0
7
14
21
28
35
42
49
56
Storage Duration (days)

FIG. 10

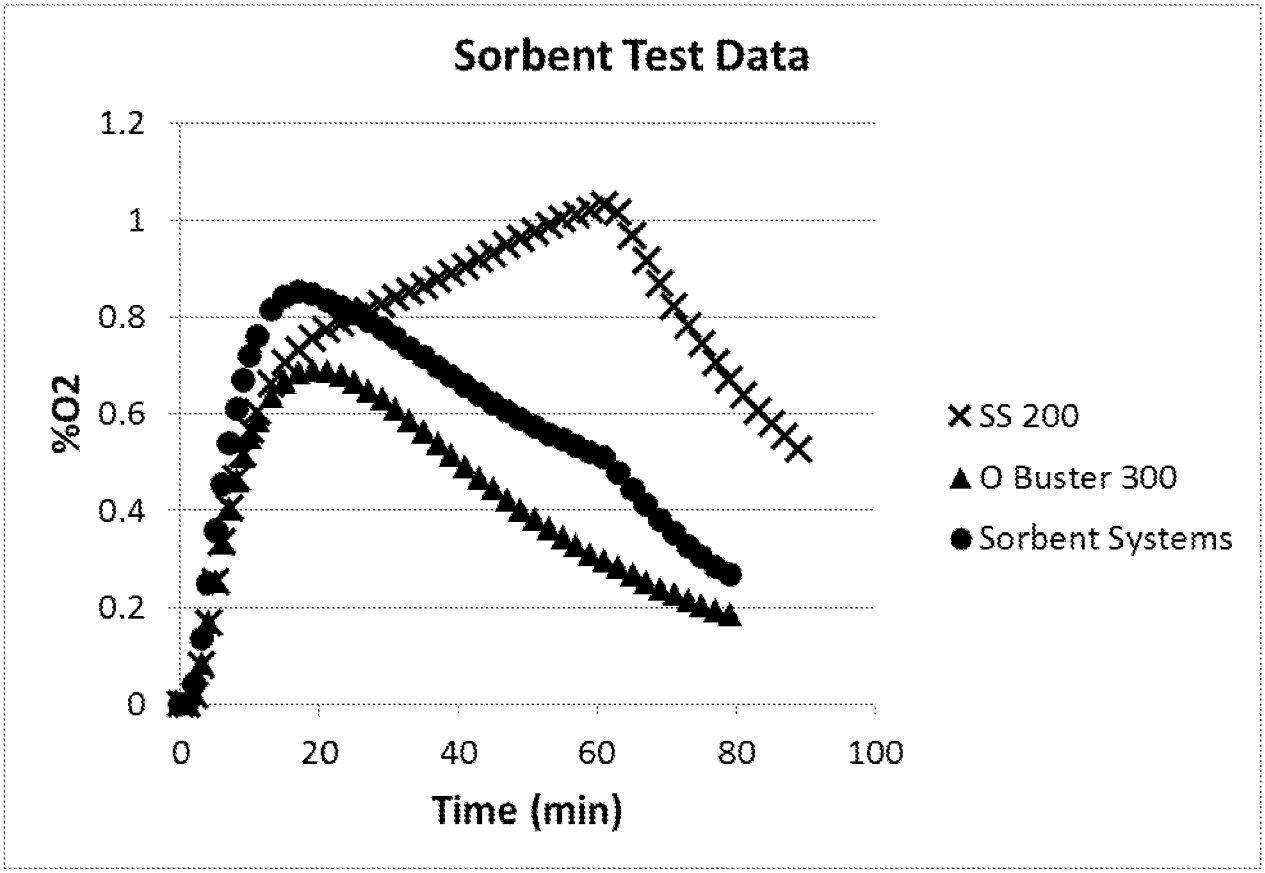

Sorbent Test Data
1.2
1
0.8
0.6
0.4
0.2
0
%O2
0
20
40
60
80
100
Time (min)
SS 200
O Buster 300
Sorbent Systems

FIG. 11

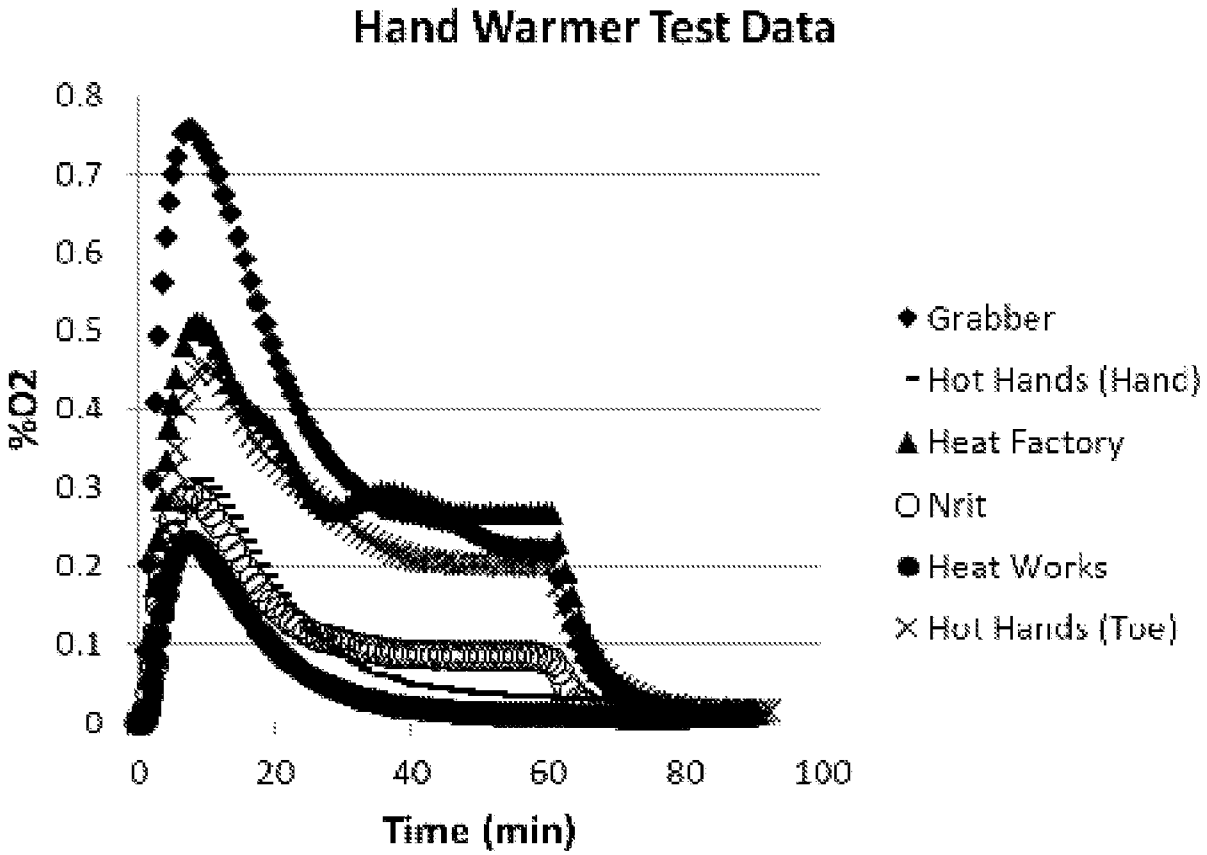

Hand Warmer Test Data
%O2
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
Time (min)
Grabber
Hot Hands (Hand)
Heat Factory
Nrit
Heat Works
Hot Hands (Toe)

FIG. 12

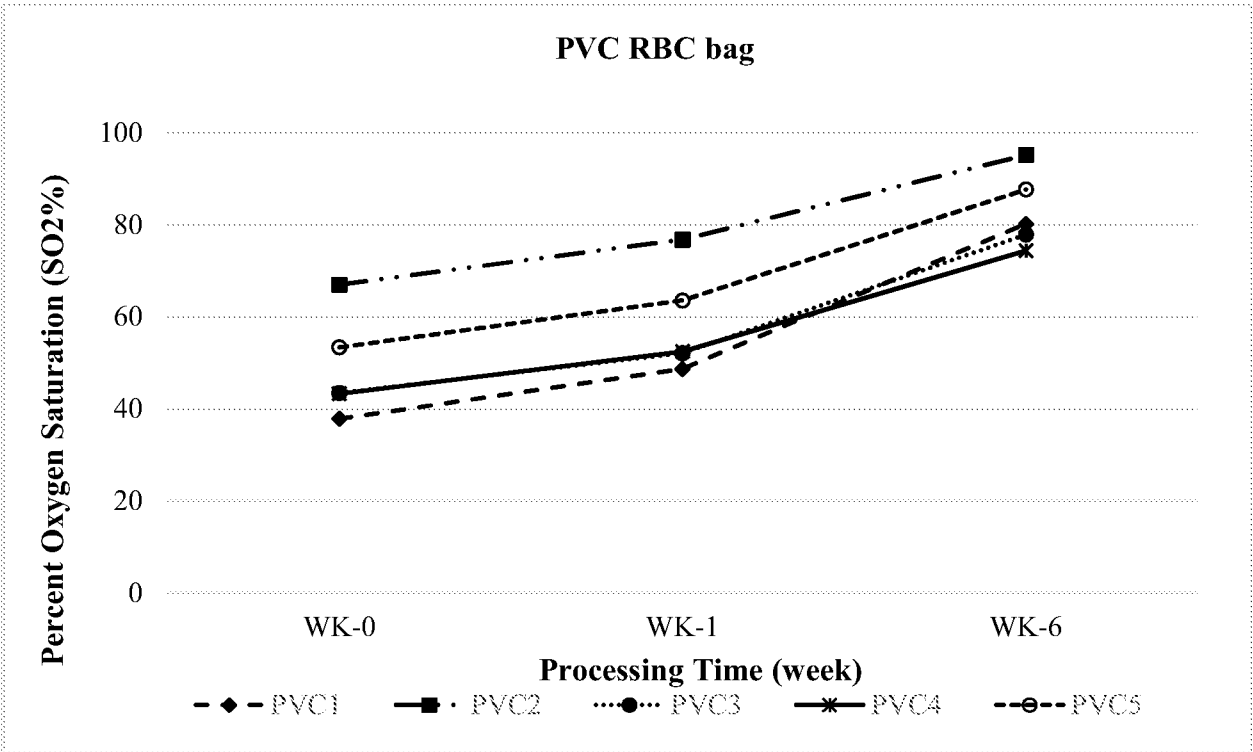

PVC RBC bag
Percent Oxygen Saturation (SO2%)
100
80
60
40
20
0
WK-0
WK-1
WK-6
Processing Time (week)
PVC1
PVC2
PVC3
PVC4
PVC5

FIG. 13

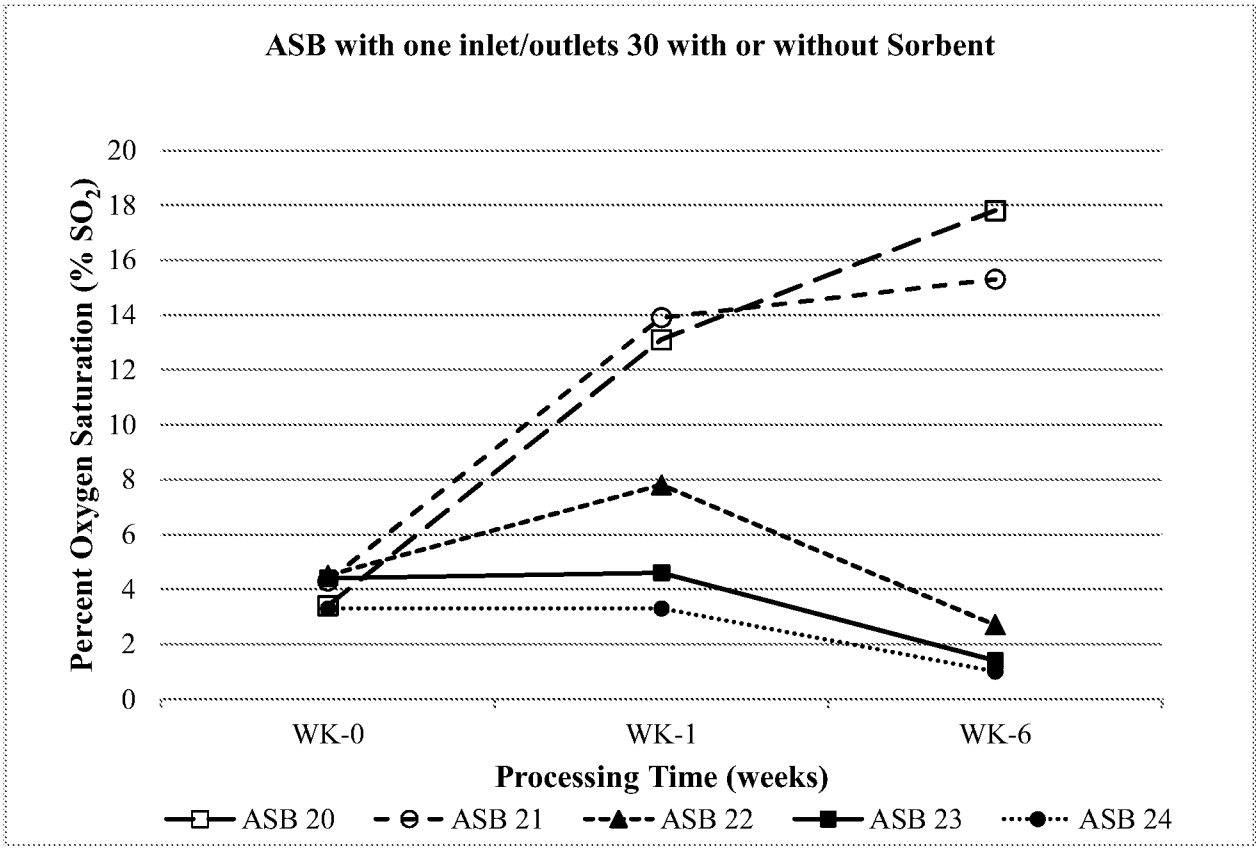

ASB with one inlet/outlets 30 with or without Sorbent
Percent Oxygen Saturation (% SO_2)
20
18
16
14
12
10
8
6
4
2
0
WK-0
WK-1
WK-6
Processing Time (weeks)
ASB 20
ASB 21
ASB 22
ASB 23
ASB 24

FIG. 14

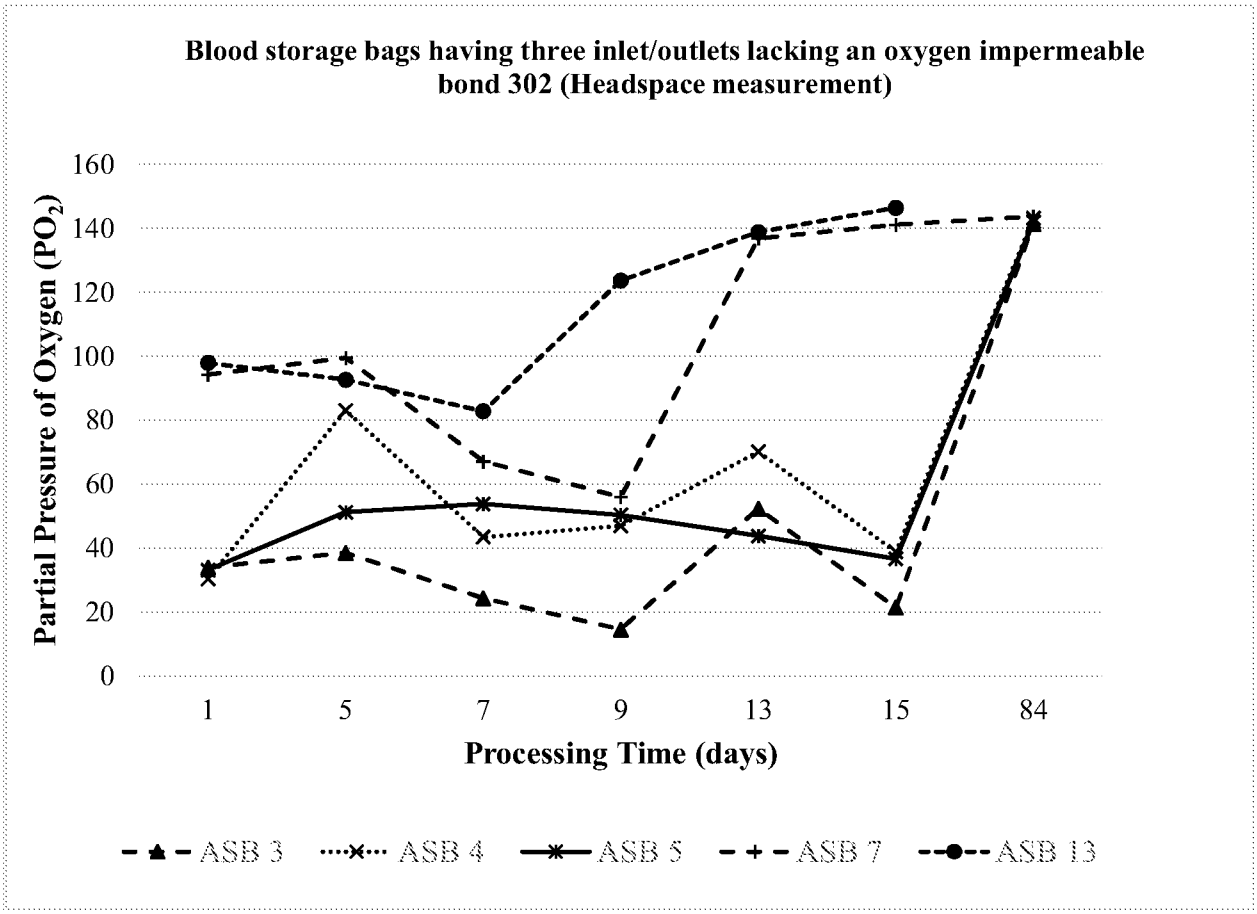

Blood storage bags having three inlet/outlets lacking an oxygen impermeable bond 302 (Headspace measurement)
Partial Pressure of Oxygen (PO_2)
160
140
120
100
80
60
40
20
0
1
5
7
9
13
15
84
Processing Time (days)
ASB 3
ASB 4
ASB 5
ASB 7
ASB 13

FIG. 15

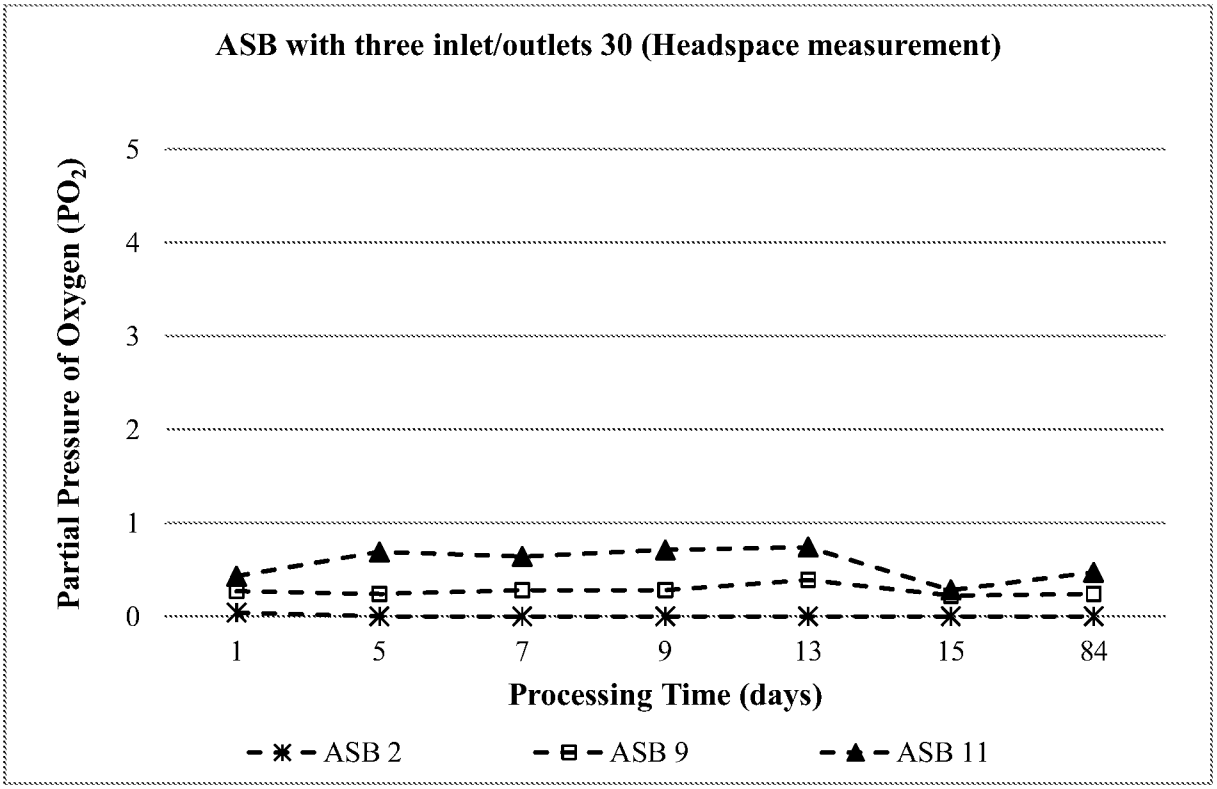
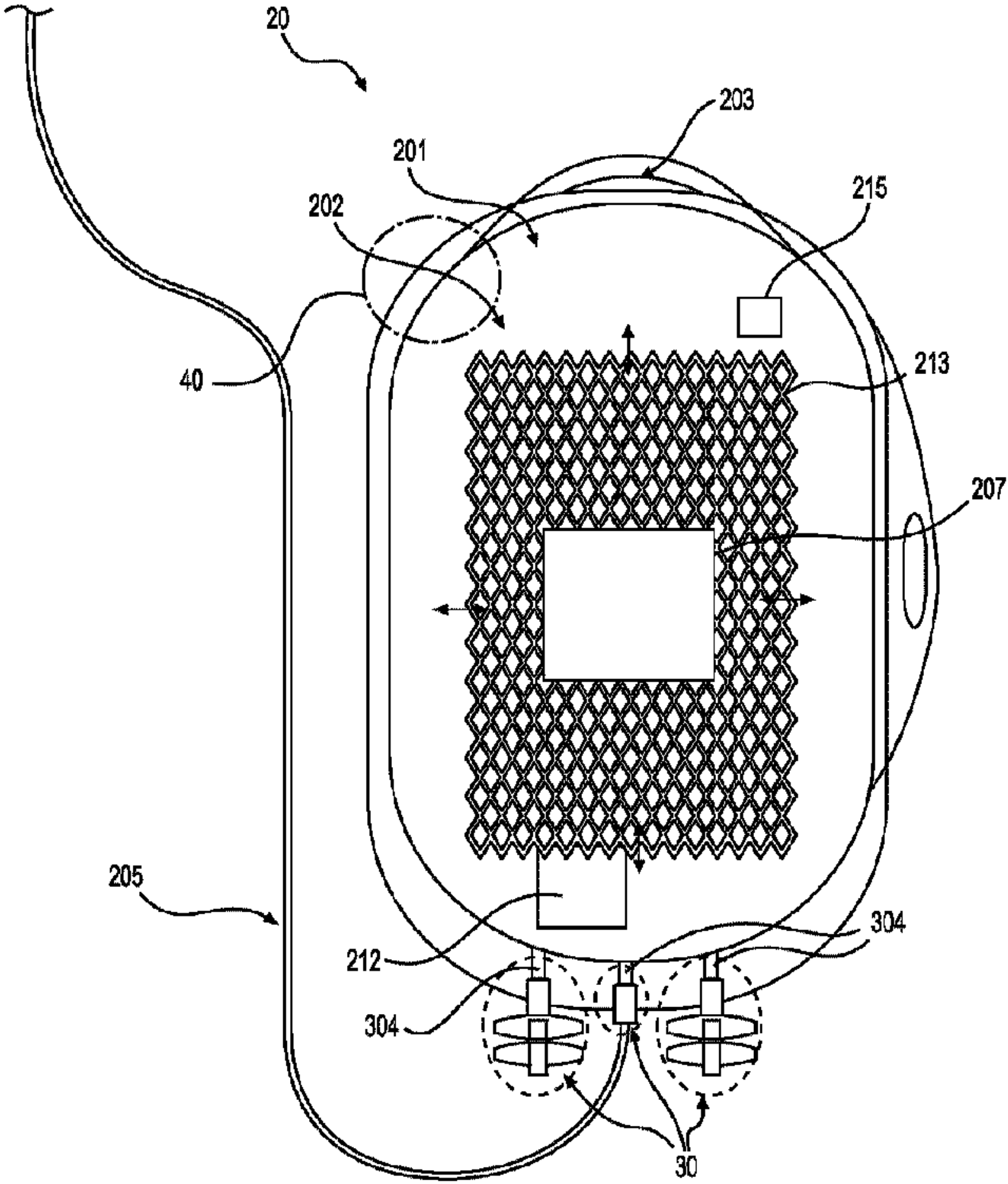

ASB with three inlet/outlets 30 (Headspace measurement)
Partial Pressure of Oxygen (PO_2)
5
4
3
2
1
0
1
5
7
9
13
15
84
Processing Time (days)
ASB 2
ASB 9
ASB 11

FIG. 16


20
203
201
202
215
40
213
207
205
212
304
304
30