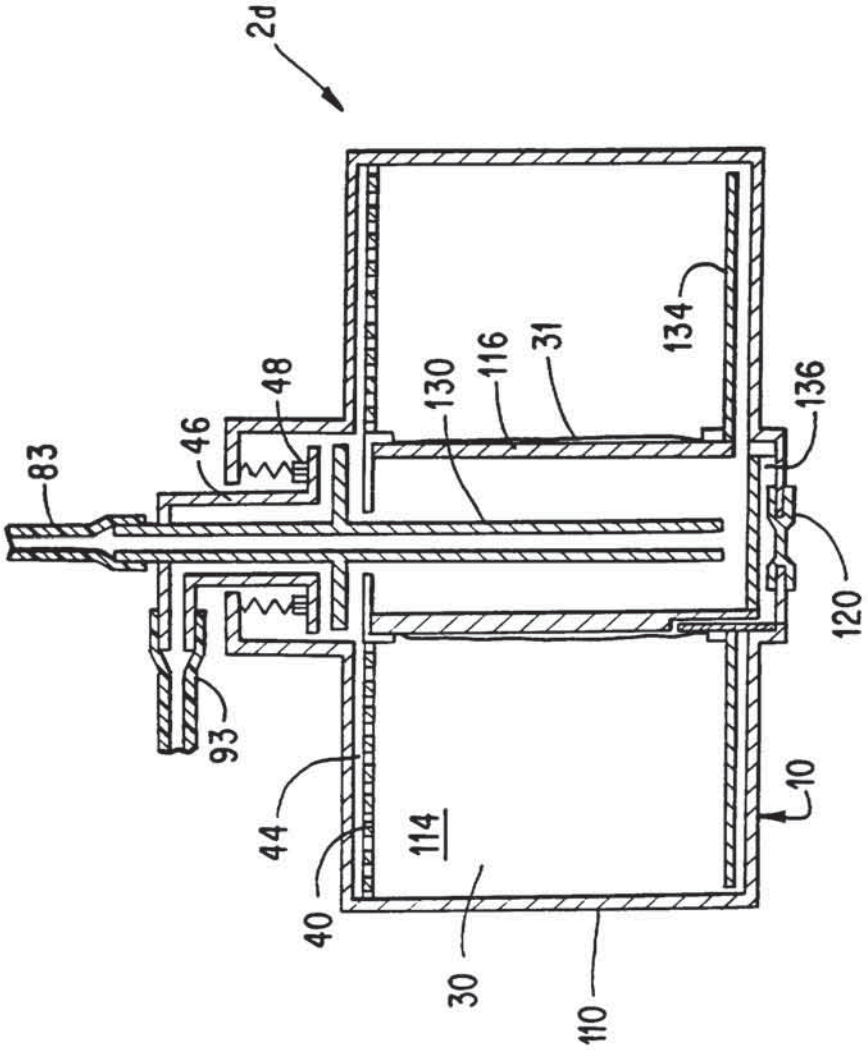


FIG.23

Haemonetics Corporation
Exhibit 2015
Page #901

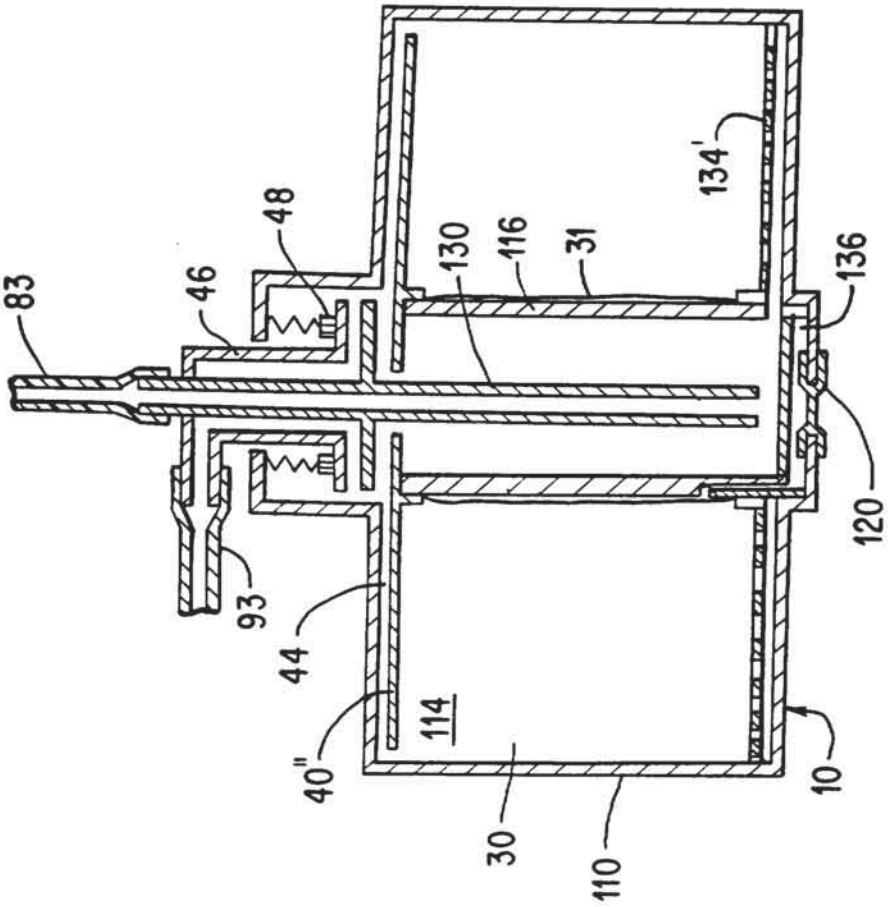


FIG. 24

Haemonetics Corporation
Exhibit 2015
Page #902

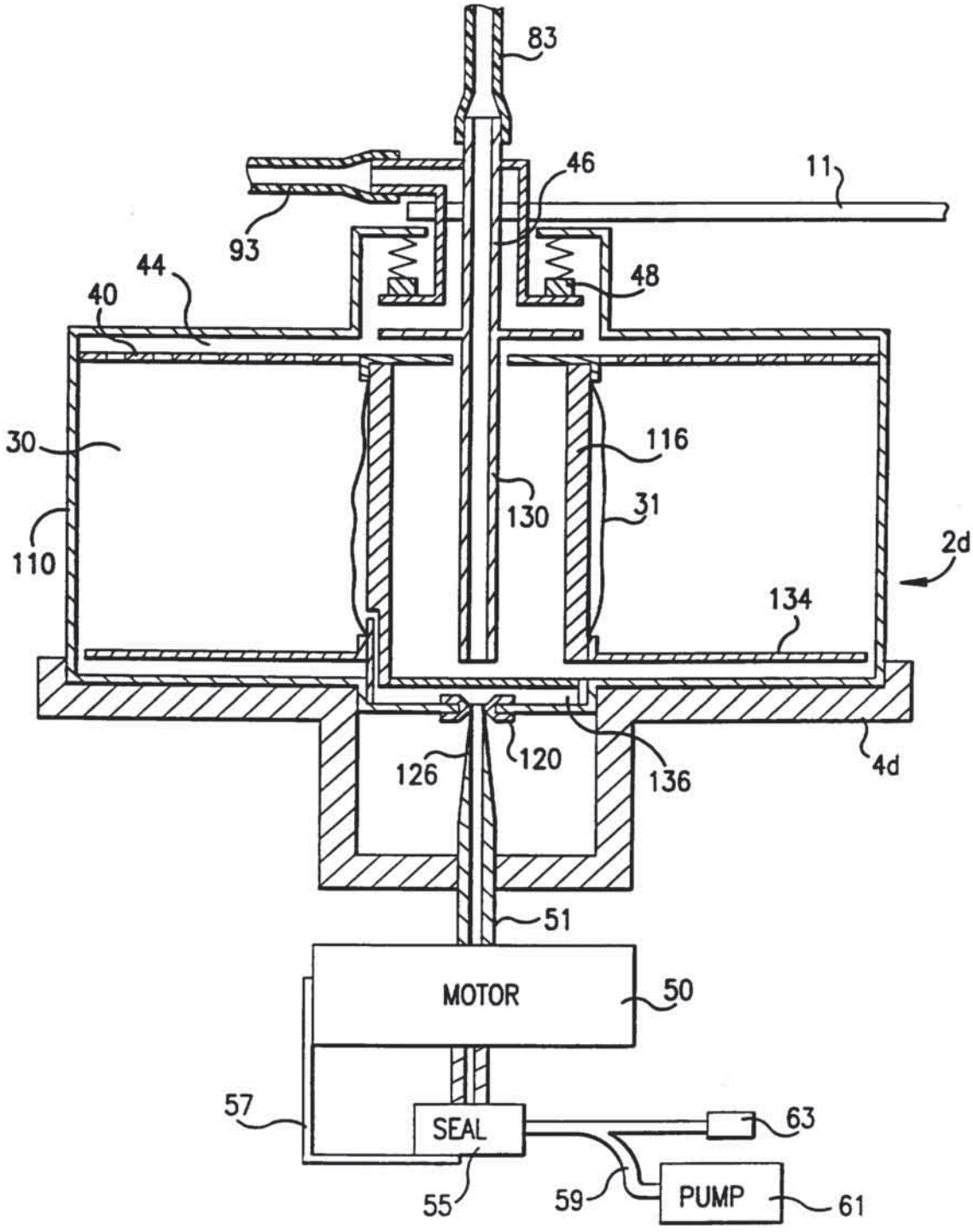

83
46
11
93
44
48
40
30
116
130
31
110
2d
134
126
120
136
4d
51
MOTOR
50
57
SEAL
63
55
59
PUMP
61

FIG.25

25/36

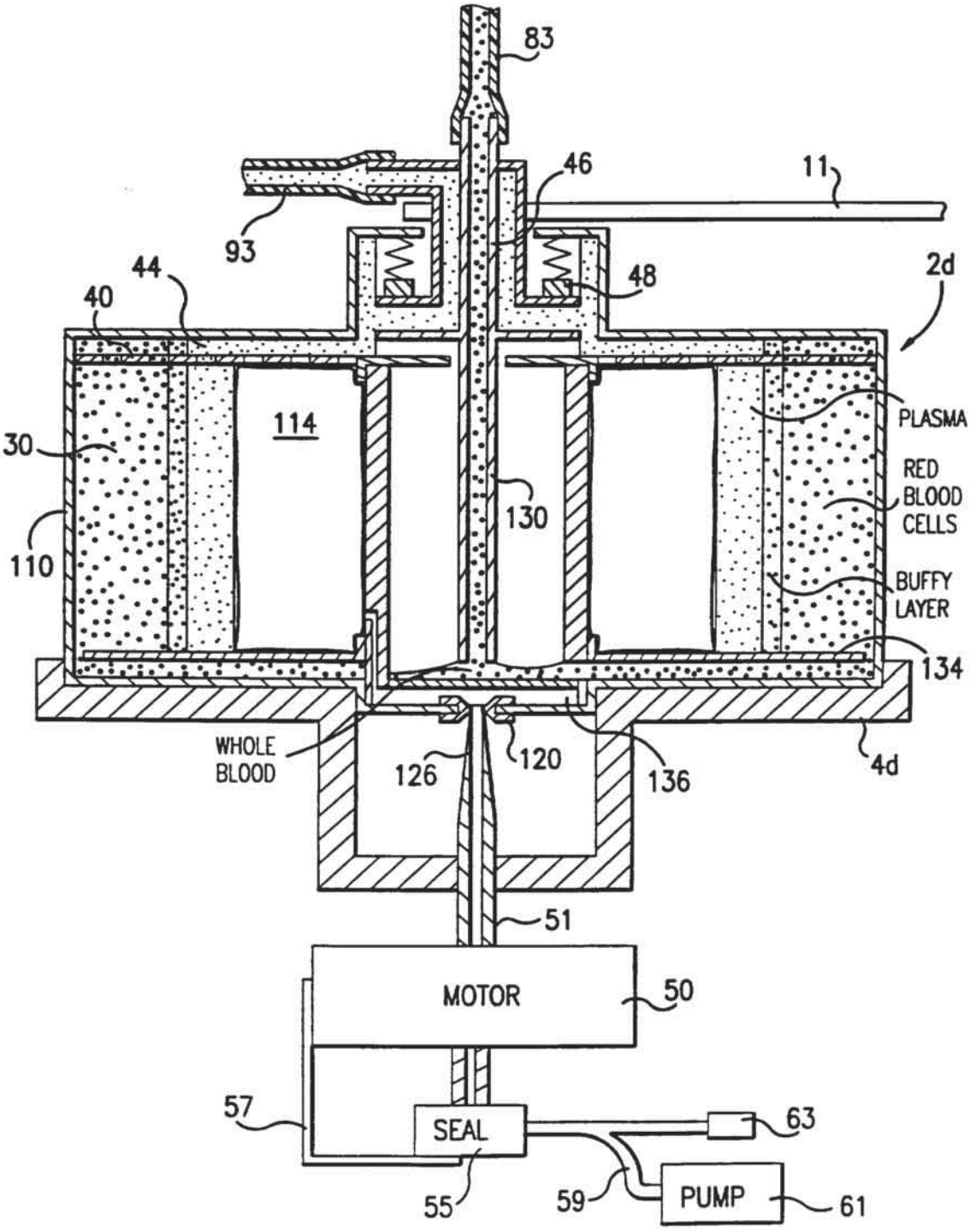


FIG.26

Haemonetics Corporation
Exhibit 2015
Page #904

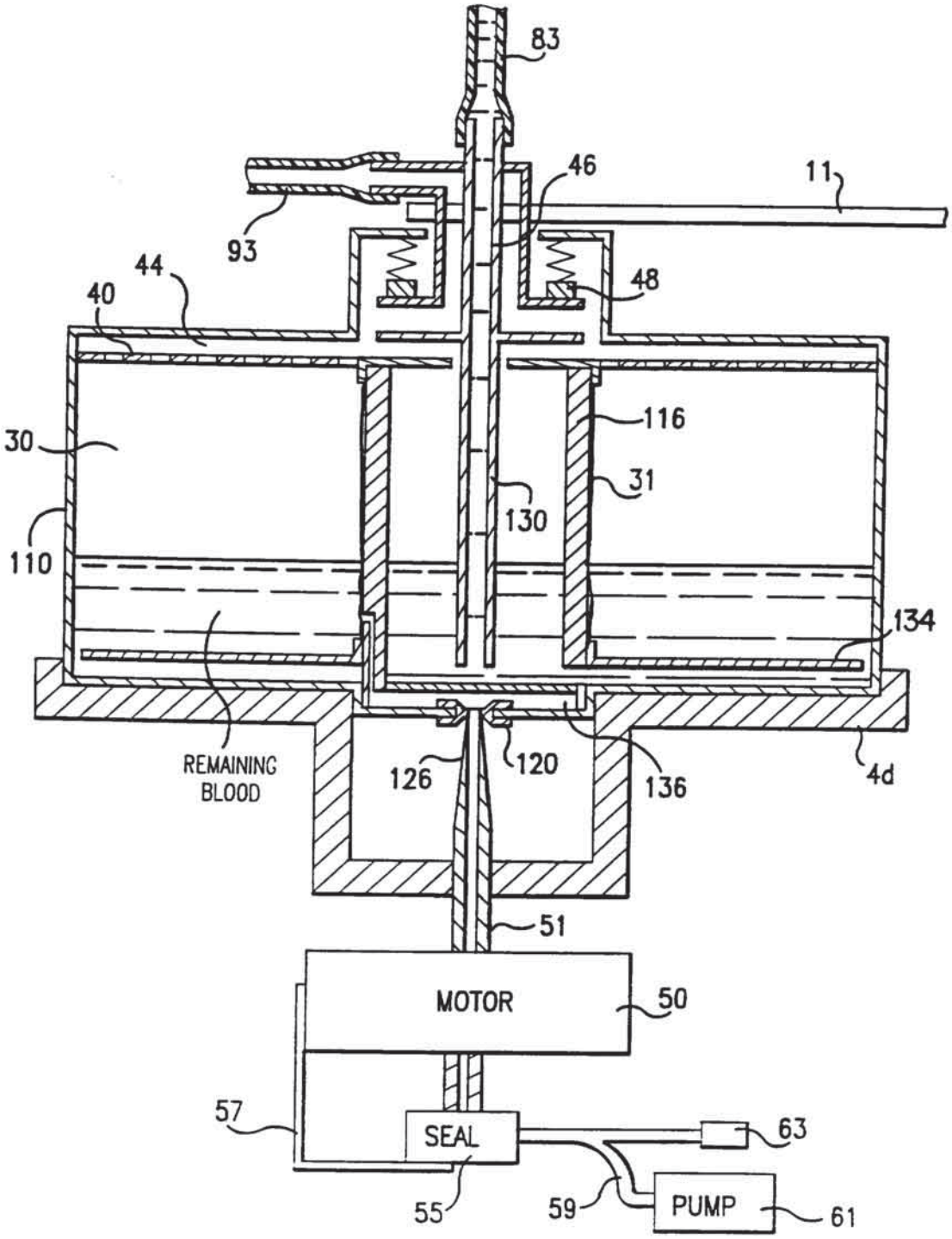


FIG.27

27/36

Haemonetics Corporation
Exhibit 2015
Page #905

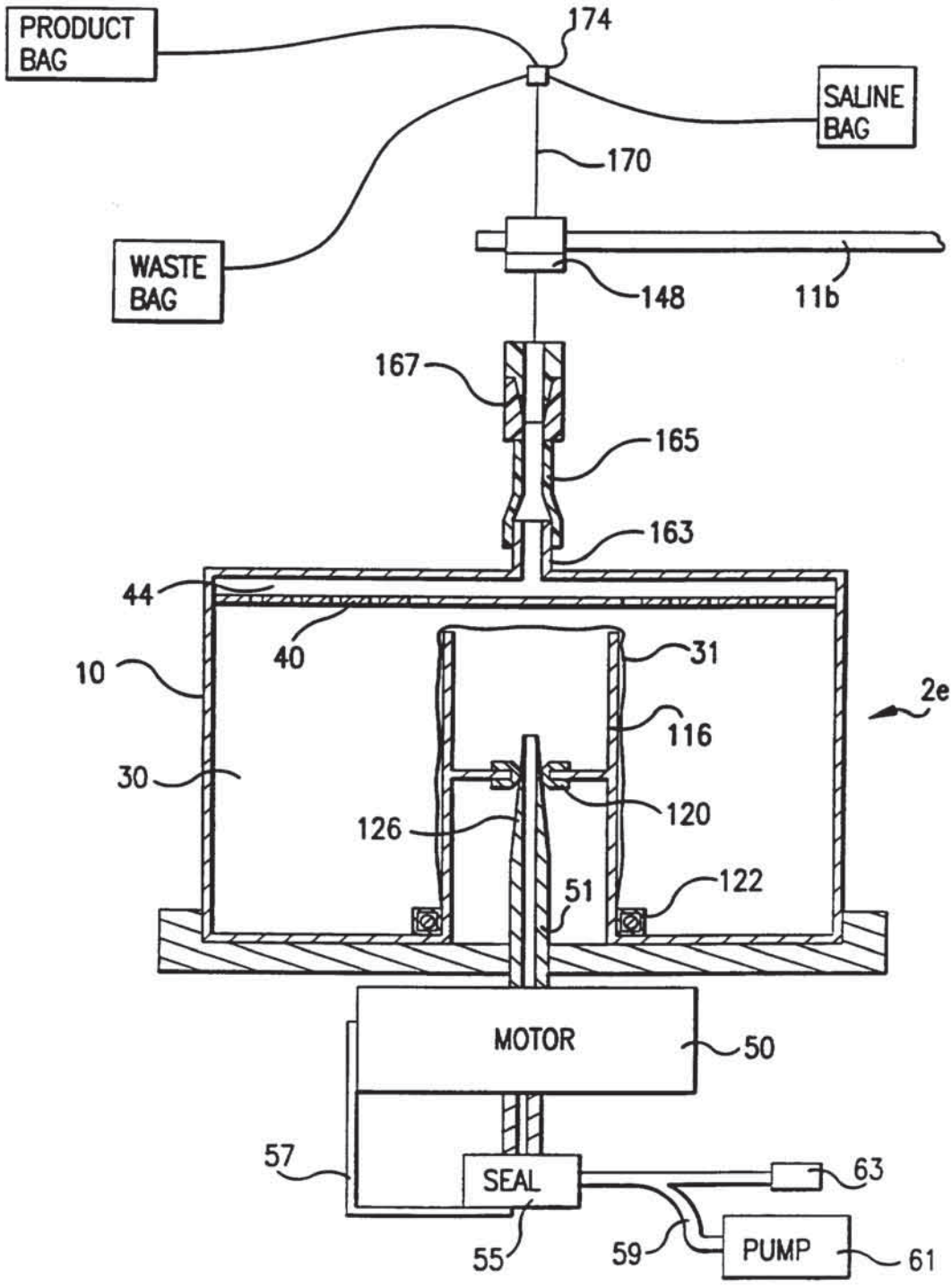

PRODUCT BAG
174
SALINE BAG
170
WASTE BAG
148
11b
167
165
163
44
40
10
31
2e
116
30
120
126
51
122
MOTOR
50
57
SEAL
63
55
59
PUMP
61

FIG.28

28/136

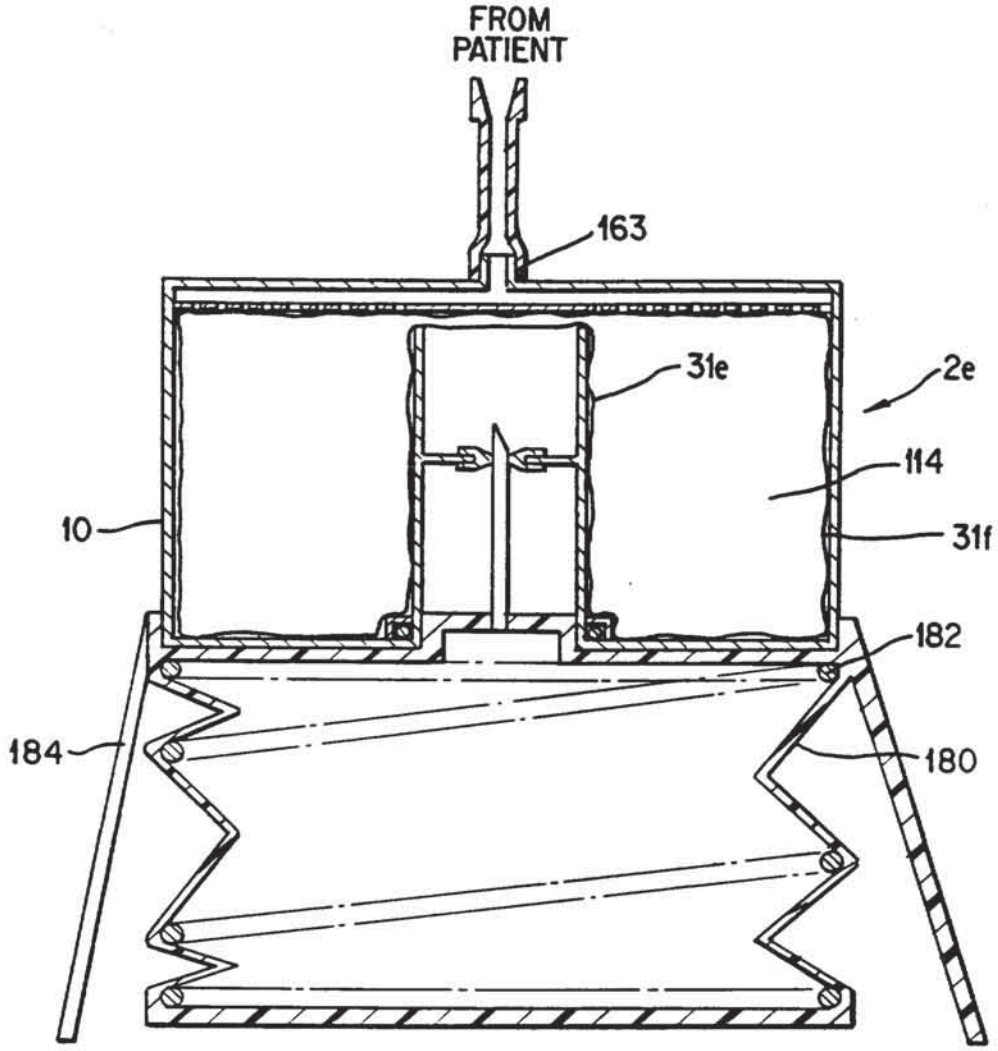


FIG. 29

25/36

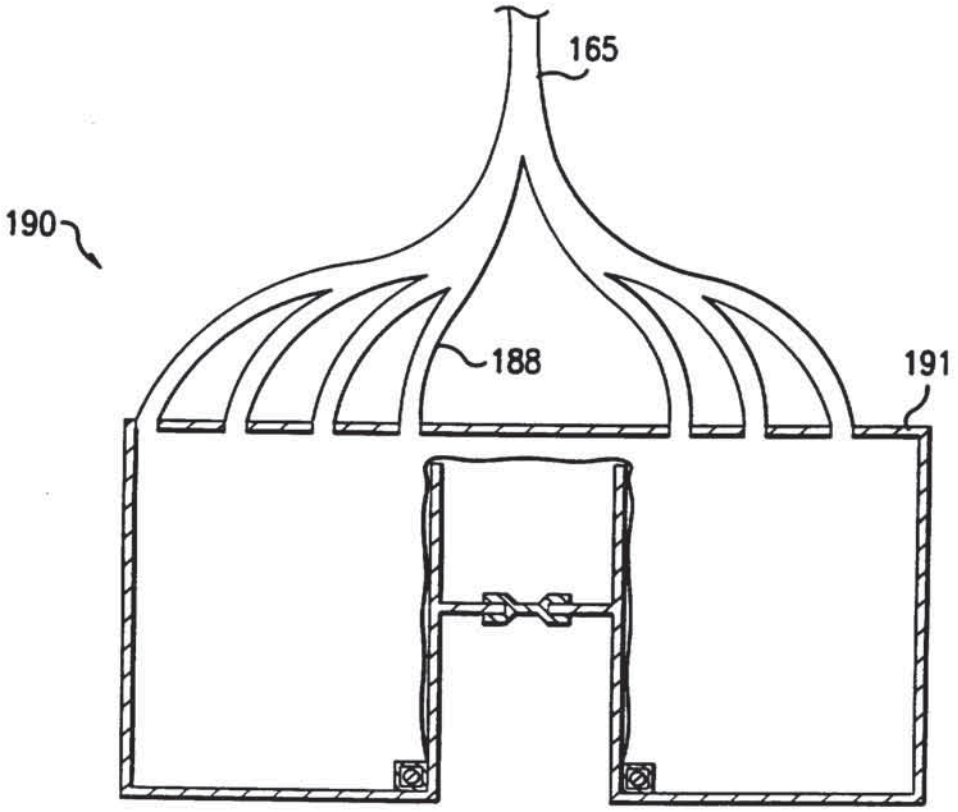


FIG.30

Haemonetics Corporation
Exhibit 2015
Page #908

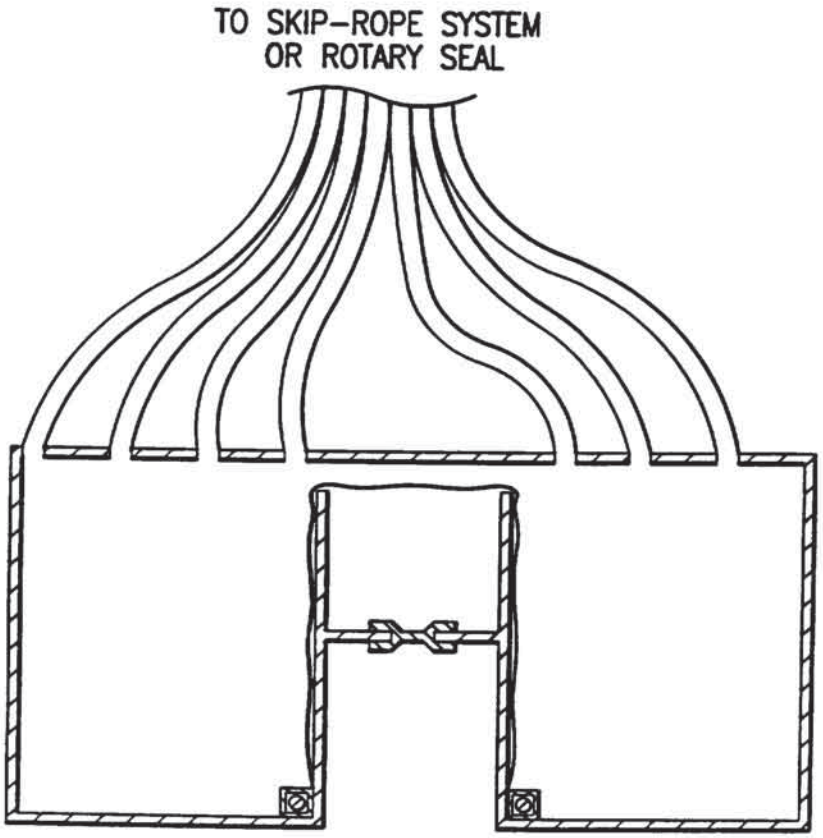


FIG.31

Haemonetics Corporation
Exhibit 2015
Page #909

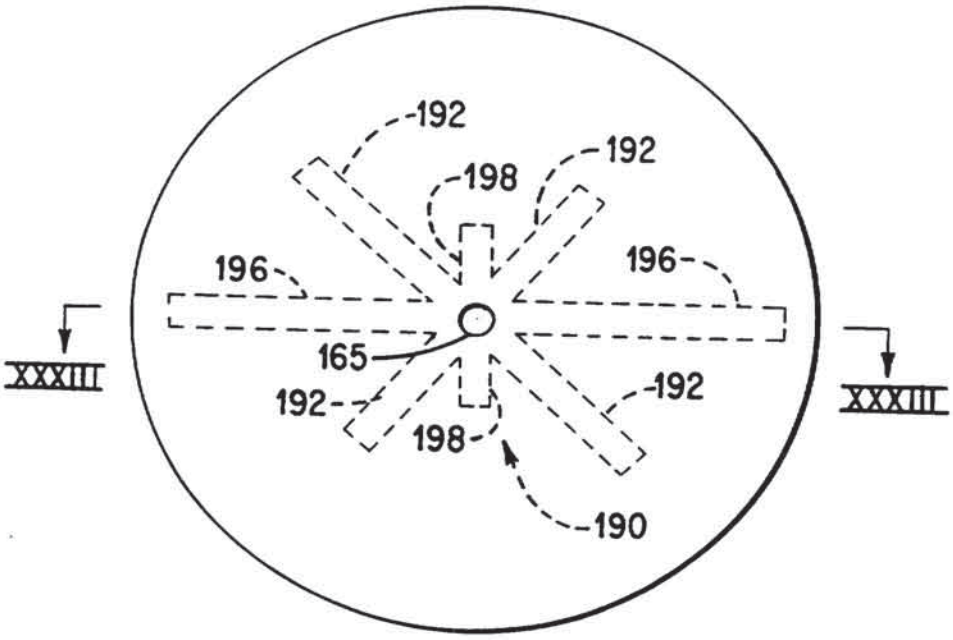


FIG.32

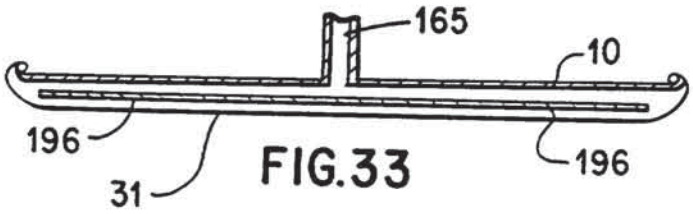


FIG.33

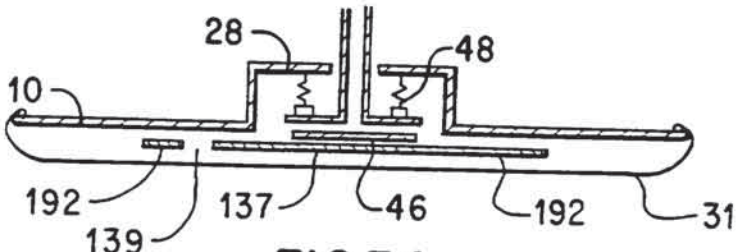


FIG.34

Haemonetics Corporation
Exhibit 2015
Page #910

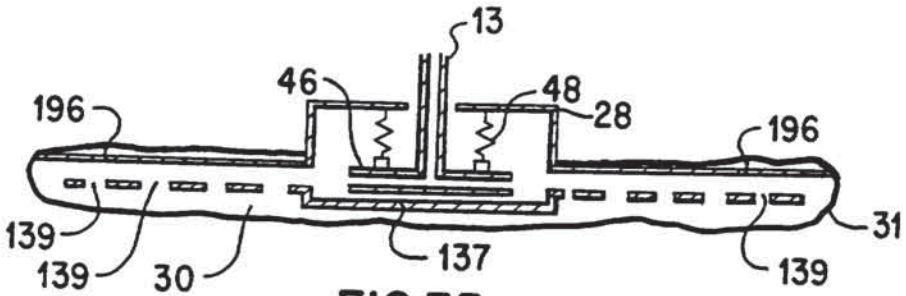


FIG.35

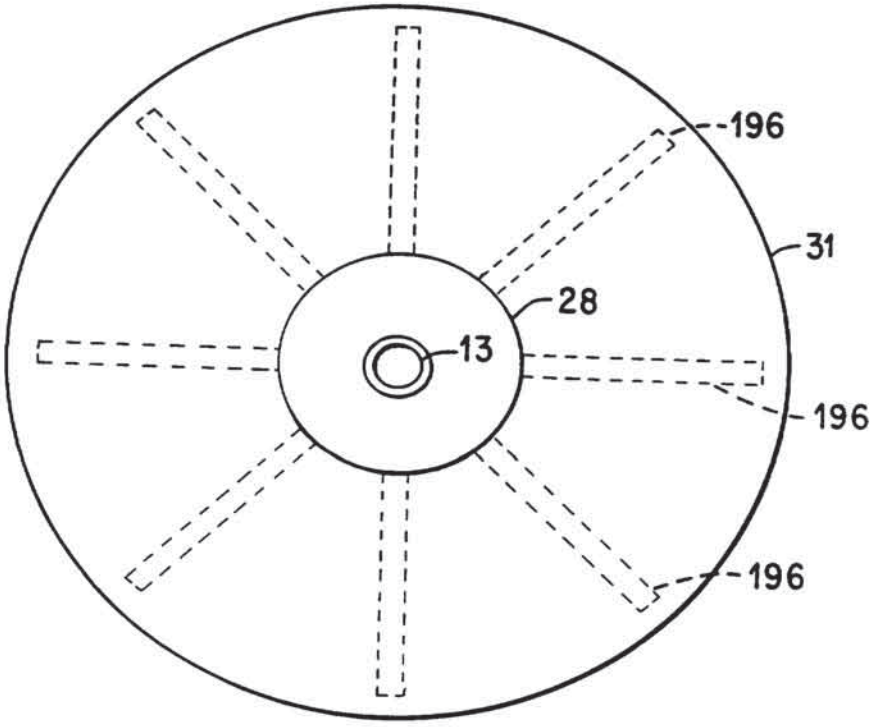


FIG.36

Haemonetics Corporation
Exhibit 2015
Page #911

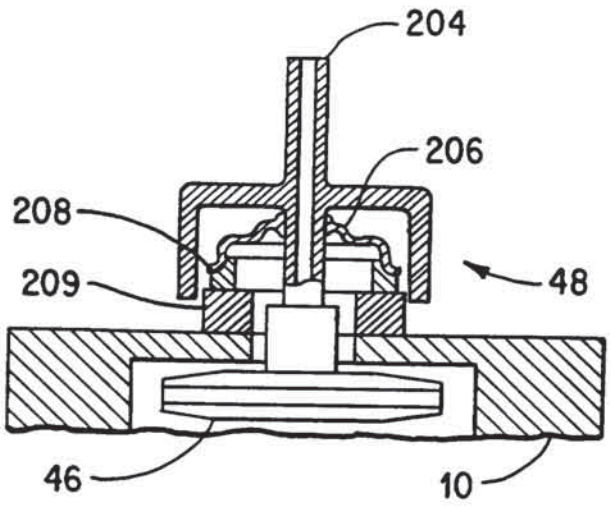


FIG.37

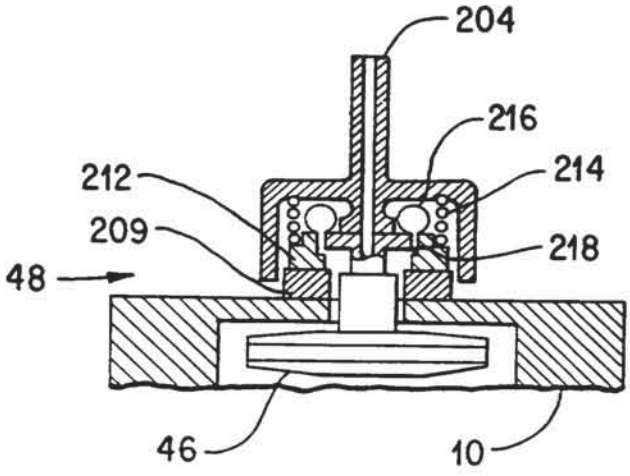


FIG.38

Haemonetics Corporation
Exhibit 2015
Page #912

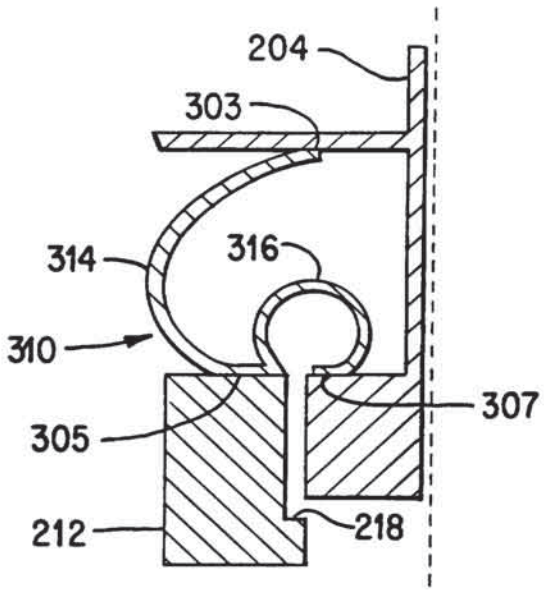


FIG. 39

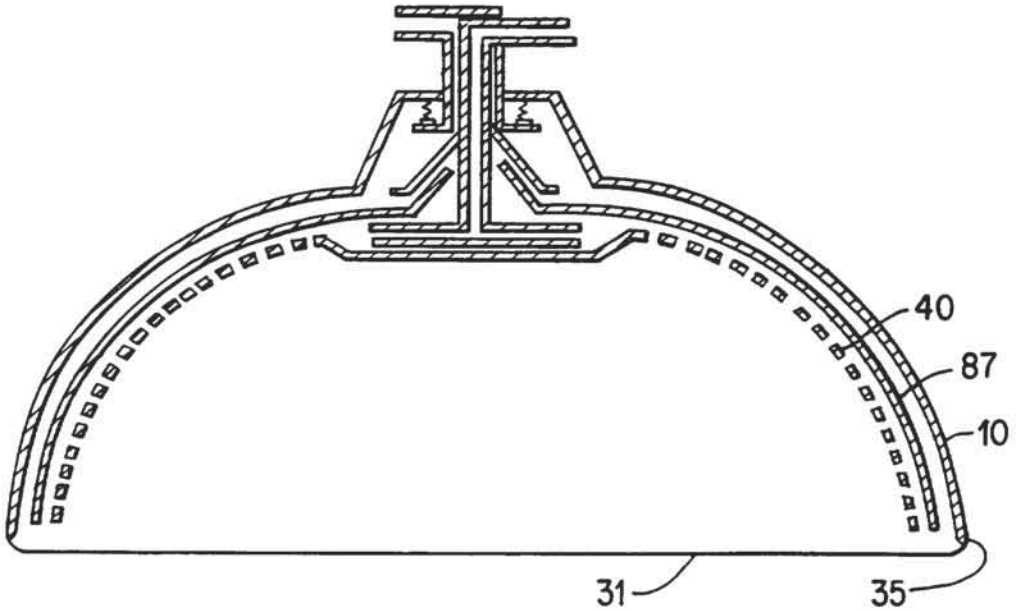


FIG. 40

Haemonetics Corporation
Exhibit 2015
Page #913

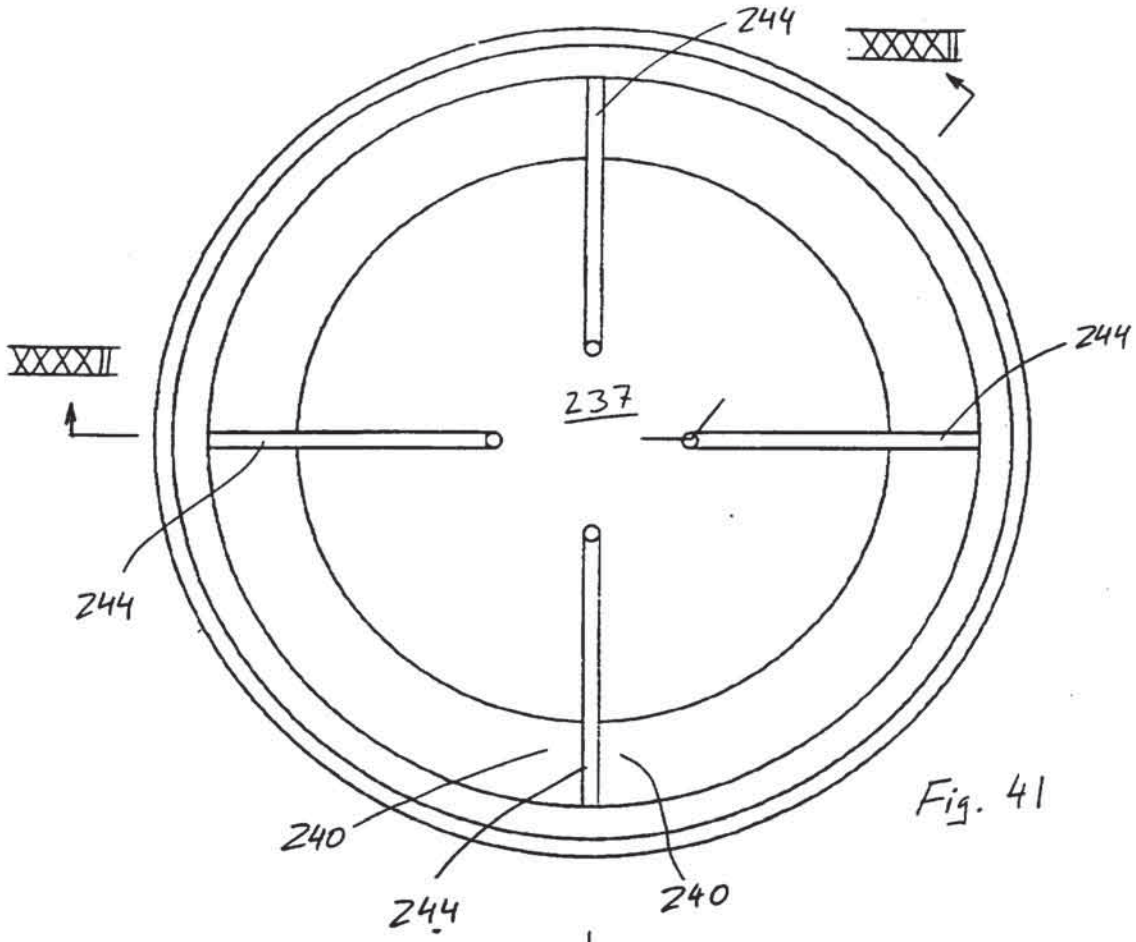


Fig. 41

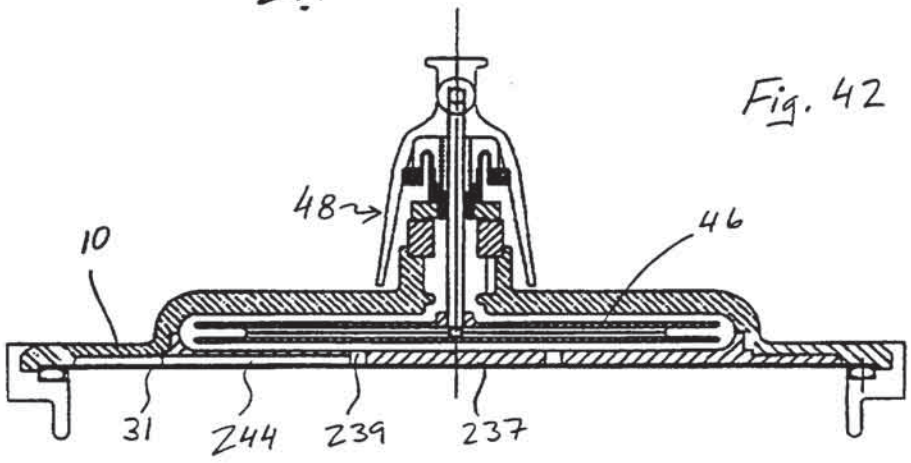


Fig. 42

Haemonetics Corporation
Exhibit 2015
Page #914

Espacenet

Bibliographic data: WO9633023 (A1) — 1996-10-24

PARTICLE SEPARATION APPARATUS AND METHOD

Inventor(s): HLAVINKA DENNIS [US]; CORBIN FRANK [US]; LANGLEY ROBERT [US]; TAYLOR LINDA A [US]; WALKER JOHN C [US] ± (HLAVINKA, DENNIS, ; CORBIN, FRANK, ; LANGLEY, ROBERT, ; TAYLOR, LINDA, A, ; WALKER, JOHN, C)

Applicant(s): COBE LAB [US] ± (COBE LABORATORIES, INC)

Classification: **- international:** ***A61M1/02; A61M1/36; B04B11/04; B04B5/04;*** (IPC1-7): A61M1/36; B04B5/04
- cooperative: **A61M1/0227**; **A61M1/0236**; **A61M1/3618**; **A61M1/362**; **A61M1/3693**; **A61M1/3696**; **B04B5/0428**; **B04B5/0442**; B04B2005/0471

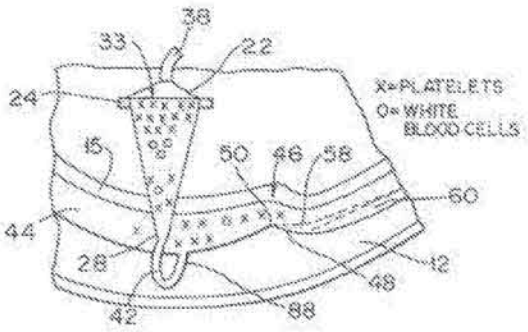
Application number: WO1996US05505 19960418 Global Dossier

Priority number(s): US19950423578 19950418 ; US19950423583 19950418

Also published as: AU5560896 (A) AU702151 (B2) BR9608031 (A) DE69618453 (T2) DE69634860 (T2) more

Abstract of WO9633023 (A1)

An apparatus and method are disclosed for filtering or separating particles. The apparatus has a centrifuge rotor (12) rotatable about an axis of rotation. A fluid chamber (22) rotates with the rotor. A substance is supplied to the inlet (28) of the chamber. A saturated fluidized bed of first particles forms within the fluid chamber and obstructs flow of second particles through the chamber. In an embodiment of the invention, additives substances alter sedimentation velocity of the first particles to modify the filtration characteristics of the saturated fluidized bed. The fluid chamber includes a wall extending between an inlet (28) and outlet (32) to form a fluid chamber interior. The



Haemonetics Corporation
Exhibit 2015
Page #915

interior converges from a position of maximum cross-sectional area toward the inlet. A groove or a step may be formed on an inner surface of the fluid chamber wall to improve particle separation within the fluid chamber.

Haemonetics Corporation
Exhibit 2015
Page #916

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : B04B 5/04, A61M 1/36 — A1

(11) International Publication Number: **WO 96/33023**

(43) International Publication Date: 24 October 1996 (24.10.96)

(21) International Application Number: PCT/US96/05505

(22) International Filing Date: 18 April 1996 (18.04.96)

(30) Priority Data:
08/423,578 18 April 1995 (18.04.95) US
08/423,583 18 April 1995 (18.04.95) US

(71) Applicant: COBE LABORATORIES, INC. [US/US]; 1185 Oak Street, Lakewood, CO 80215 (US).

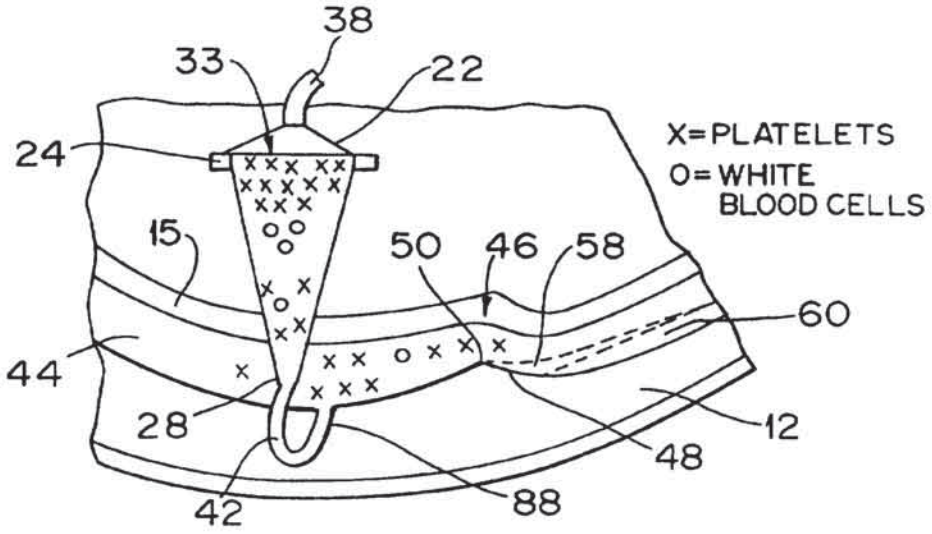
(72) Inventors: HLAVINKA, Dennis; 7365 N. Salvia Court, Golden, CO 80419 (US). CORBIN, Frank; 9703 West Arlington Avenue, Littleton, CO 80123 (US). LANGLEY, Robert; 10160 Xavier Court, Westminster, CO 80030 (US). TAYLOR, Linda, A.; 6159 S. Sheridan Boulevard, Littleton, CO 80123 (US). WALKER, John, C.; 405 S. 42nd Street, Boulder, CO 80303 (US).

(74) Agents: GARRETT, Arthur, S. et al.; Finnegan, Henderson, Farabow, Garrett & Dunner, L.P.P., 1300 I Street, N.W., Washington, DC 20005-3315 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PARTICLE SEPARATION APPARATUS AND METHOD



(57) Abstract

An apparatus and method are disclosed for filtering or separating particles. The apparatus has a centrifuge rotor (12) rotatable about an axis of rotation. A fluid chamber (22) rotates with the rotor. A substance is supplied to the inlet (28) of the chamber. A saturated fluidized bed of first particles forms within the fluid chamber and obstructs flow of second particles through the chamber. In an embodiment of the invention, additives substances alter sedimentation velocity of the first particles to modify the filtration characteristics of the saturated fluidized bed. The fluid chamber includes a wall extending between an inlet (28) and outlet (32) to form a fluid chamber interior. The interior converges from a position of maximum cross-sectional area toward the inlet. A groove or a step may be formed on an inner surface of the fluid chamber wall to improve particle separation within the fluid chamber.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

Description

Particle Separation Apparatus and Method

The entire disclosures of U.S. patent application Serial Nos. 08/423,578 and 08/423,583 are incorporated herein by reference.

Background of the Invention

Field of the Invention

The present invention relates to a method and apparatus for separating first particles from second particles and for separating particles and liquid. The invention has particular advantages in connection with separating blood components.

Description of the Related Art

In many different fields, liquids carrying particle substances must be filtered or processed to obtain either a purified liquid or purified particle end product. In its broadest sense, a filter is any device capable of removing or separating particles from a substance. Thus, the term "filter" as used herein is not limited to a porous media material but includes many different types of processes where particles are either separated from one another or from liquid.

In the medical field, it is often necessary to filter blood. Whole blood consists of various liquid constituents and particle constituents. Sometimes, the particle constituents are referred to as "formed elements". The liquid portion of blood is largely made up of plasma, and the particle constituents include red blood cells (erythrocytes), white blood cells (including leukocytes), and platelets (thrombocytes). While these constituents have similar densities, their average density relationship, in order of decreasing density, is as follows: red blood cells, white blood cells, platelets, and plasma. In addition, the particle constituents are related according to size, in order of decreasing size, as follows: white blood cells, red blood cells, and platelets. The size of red blood cells, however, may vary because red blood cells osmotically change size depending on the hypotonicity or hypertonicity of a liquid,

such as plasma, in which the red blood cells are disbursed. When hypotonicity of plasma increases, the red blood cells osmotically become larger. Conversely, when hypertonicity of plasma increases, the red blood cells osmotically become smaller. Most current purification devices rely on density and size differences or surface chemistry characteristics to separate and/or filter the blood components.

Numerous therapeutic treatments require groups of particles to be removed from whole blood before either liquid or particle components can be infused into a patient. For example, cancer patients often require platelet transfusions after undergoing ablative, chemical, or radiation therapy. In this procedure, donated whole blood is processed to remove platelets and these platelets are then infused into the patient. However, if a patient receives an excessive number of foreign white blood cells as contamination in a platelet transfusion, the patient's body may reject the platelet transfusion, leading to a host of serious health risks.

Typically, donated platelets are separated or harvested from other blood components using a centrifuge. The centrifuge rotates a blood reservoir to separate components within the reservoir using centrifugal force. In use, blood enters the reservoir while it is rotating at a very rapid speed and centrifugal force stratifies the blood components, so that particular components may be separately removed. Centrifuges are effective at separating platelets from whole blood, however they typically are unable to separate all of the white blood cells from the platelets. Historically, blood separation and centrifugation devices are typically unable to consistently (99% of the time) produce platelet product that meets the "leukopoor" standard of less than 5×10^6 white blood cells for at least 3×10^{11} platelets collected.

Because typical centrifuge platelet collection processes are unable to consistently and satisfactorily separate white blood cells from platelets, other processes have been added to improve results. In one procedure, after centrifuging, platelets are passed through a porous woven or non-woven media

filter, which may have a modified surface, to remove white blood cells. However, use of the porous filter introduces its own set of problems. Conventional porous filters may be inefficient because they may permanently remove or trap approximately 5-20% of the platelets. These conventional filters may also reduce "platelet viability," meaning that once passed through a filter a percentage of the platelets cease to function properly and may be partially or fully activated. In addition, porous filters may cause the release of brandykinin, which may lead to hypotensive episodes in a patient. Porous filters are also expensive and often require additional time consuming manual labor to perform a filtration process.

Although porous filters are effective in removing a substantial number of white blood cells, they have drawbacks. For example, after centrifuging and before porous filtering, a period of time must pass to give activated platelets time to transform to a deactivated state. Otherwise, the activated platelets are likely to clog the filter. Therefore, the use of porous filters is not feasible in on-line processes.

Another separation process is one known as centrifugal elutriation. This process separates cells suspended in a liquid medium without the use of a membrane filter. In one common form of elutriation, a cell batch is introduced into a flow of liquid elutriation buffer. This liquid which carries the cell batch in suspension, is then introduced into a funnel-shaped chamber located in a spinning centrifuge. As additional liquid buffer solution flows through the chamber, the liquid sweeps smaller sized, slower-sedimenting cells toward an elutriation boundary within the chamber, while larger, faster-sedimenting cells migrate to an area of the chamber having the greatest centrifugal force.

When the centrifugal force and force generated by the fluid flow are balanced, the fluid flow is increased to force slower-sedimenting cells from an exit port in the chamber, while faster-sedimenting cells are retained in the chamber.

If fluid flow through the chamber is increased, progressively larger, faster-sedimenting cells may be removed from the chamber.

Thus, centrifugal elutriation separates particles having different sedimentation velocities. Stoke's law describes sedimentation velocity (SV) of a spherical particle as follows:

$$SV = \frac{2}{9} \frac{r^2 (\rho_p - \rho_m) g}{\eta}$$

where, r is the radius of the particle, ρ_p is the density of the particle, ρ_m is the density of the liquid medium, η is the viscosity of the medium, and g is the gravitational or centrifugal acceleration. Because the radius of a particle is raised to the second power in the Stoke's equation and the density of the particle is not, the size of a cell, rather than its density, greatly influences its sedimentation rate. This explains why larger particles generally remain in a chamber during centrifugal elutriation, while smaller particles are released, if the particles have similar densities.

As described in U.S. Patent No. 3,825,175 to Sartory, centrifugal elutriation has a number of limitations. In most of these processes, particles must be introduced within a flow of fluid medium in separate discontinuous batches to allow for sufficient particle separation. Thus, some elutriation processes only permit separation in particle batches and require an additional fluid medium to transport particles. In addition, flow forces must be precisely balanced against centrifugal force to allow for proper particle segregation.

Further, a Coriolis jetting effect takes place when particles flow into an elutriation chamber from a high centrifugal field toward a lower centrifugal field. The fluid and particles turbulently collide with an inner wall of the chamber facing the rotational direction of the centrifuge. This phenomenon mixes particles within the chamber and reduces

the effectiveness of the separation process. Further, Coriolis jetting shunts flow along the inner wall from the inlet directly to the outlet. Thus, particles pass around the elutriative field to contaminate the end product.

Particle mixing by particle density inversion is an additional problem encountered in some prior elutriation processes. Fluid flowing within the elutriation chamber has a decreasing velocity as it flows in the centripetal direction from an entrance port toward an increased cross sectional portion of the chamber. Because particles tend to concentrate within a flowing liquid in areas of lower flow velocity, rather than in areas of high flow velocity, the particles concentrate near the increased cross-sectional area of the chamber. Correspondingly, since flow velocity is greatest adjacent the entrance port, the particle concentration is reduced in this area. Density inversion of particles takes place when the centrifugal force urges the particles from the high particle concentration at the portion of increased cross-section toward the entrance port. This particle turnover reduces the effectiveness of particle separation by elutriation.

In addition to red and white blood cells, plasma, and platelets, human blood also includes other particle components, such as T cells, stem cells, and, in some cases, tumor cells. These cells have substantially similar densities, but different sedimentation velocities and sizes. Generally, stem cells are larger than T cells and smaller than tumor cells. Some tumor cells (approximately 30%), however, are smaller than stem cells.

Existing purification devices are capable of purifying peripheral blood to isolate what is known as a peripheral cell collection for transfusion or reinfusion purposes. The peripheral cell collection typically includes primarily plasma, red blood cells, stem cells, and T cells, and may also include tumor cells if the donor's blood included such cells. Although transfusion of a peripheral cell collection is a common medical treatment, transfusion of a large number of T

cells or tumor cells into a patient may have adverse consequences. Removal of T cells and tumor cells from a peripheral cell collection or whole blood before transfusion, however, is extremely difficult.

After undergoing a therapeutic treatment, such as chemotherapy or radiation therapy to eliminate cancerous tumor cells, cancer patients often receive a peripheral cell or bone marrow transfusion to replace stem cells destroyed as a side effect of the treatment. To reduce risks associated with infusing blood components from a foreign donor, some of these transfusions are autologous, where blood components collected from the patient are later reinfused back to the patient.

Blood components initially collected from cancer patients may include cancerous tumor cells, which are then infused back into the cancer patient during reinfusion. This reinfusion of tumor cells may diminish the effectiveness of therapeutic treatments aimed at reducing cancerous tumors in a patient's body.

Another type of transfusion, known as allogenic transfusion, involves collecting blood components from a donor and then infusing the collected blood components into a recipient who is different from the donor. Sometimes, however, the recipient of an allogenic transfusion experiences a disease commonly known as graft versus host disease. In graft versus host disease, T cells, which may accompany the blood components, are infused into the recipient and "recognize" that the recipient's body is "foreign" from that of the donor's. These T cells "attack" healthy cells in the recipient's body, rather than performing a normal immunological protective function.

Prior attempts to separate stem cells from tumor cells or separate stem cells from T cells prior to reinfusion have had limited success. In one separation method, a selective antibody is introduced into a collected blood component sample. The selective antibody chemically attaches to stem cells in the collection to "mark" them. To separate the marked stem cells from the remaining blood components, the

collected blood components are passed between stationary beads coated with a material which chemically bonds with the selective antibody. These chemical bonds retain the marked stem cells on the beads to filter them from the remaining blood components. To remove the marked stem cells from the beads, a chemical solution is flushed through the beads to break the chemical bonds between the material and selective antibody. This separation process, however, is extremely expensive, tedious, and time consuming.

Centrifugal elutriation has been used to separate tumor cells from stem cells or to separate T cells from stem cells. With existing elutriation devices, however, this is time consuming, difficult, and of limited effectiveness.

For these and other reasons, there is a need to improve particle separation.

Summary of the Invention

The present invention is directed to an apparatus and method that substantially obviate one or more of the limitations and disadvantages of the related art. To achieve these and other advantages and in accordance with the purpose of the invention, as embodied and broadly described herein, the invention comprises an apparatus for filtering first particles from a liquid. The apparatus includes a motor, and a centrifuge rotor coupled to the motor for rotation about an axis of rotation. A holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. Means are provided for supplying a substance to the inlet of the fluid chamber, and means are also provided for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained within the fluid chamber.

In another aspect, the invention includes a method of separating first particles from second particles. The method comprises the steps of rotating a centrifuge rotor about an axis of rotation, the rotor having a fluid chamber. With the

method of the invention, rotation of the rotor is controlled and second particles are passed into an inlet of the fluid chamber. A saturated fluidized bed is formed within the chamber with the second particles. Liquid having at least first particles is flowed into the chamber inlet while maintaining the bed in the fluid chamber so that the bed substantially prevents flow of first particles from the inlet to the outlet while substantially permitting flow of liquid to the outlet.

When the method of the invention is used in connection with blood filtering, the liquid may include plasma and the first particles may be white blood cells, while the second particles may be platelets or red cells. Thus, the bed may filter and obstruct the passage of white blood cells.

Further, the invention may include an apparatus for separating constituent components of a fluid. This apparatus comprises a conduit configured to be received by a centrifuge rotor. The conduit has an inlet connected to an inlet line and an outlet fluidly coupled to a fluid chamber.

In another aspect, the invention includes a tubing set having a generally annularly configured channel, a plurality of lines, and a fluid chamber.

In another aspect the invention includes a fluid chamber for separating particle constituents from a liquid. The fluid chamber has at least one groove formed on an inner surface of a wall.

In another aspect, a fluid chamber includes at least one step formed on an inner surface of a wall.

In another aspect, the invention includes an apparatus having a holder for holding a fluid chamber on a rotor. Means are provided on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

In another aspect, the invention includes a method of separating white blood cells from a liquid by forming a substantial barrier to white blood cell flow through the fluid chamber, where the barrier includes a saturated fluidized bed of particles.

In an additional aspect, the invention includes a method of separating first particles from second particles by forming a saturated fluidized bed of third particles.

In another aspect of the invention, a method is provided for separating smaller first particles from larger second particles. This method includes the steps of adding third particles to a liquid having the first particles and second particles, the third particles being larger than the first particles and smaller than the second particles, and forming a saturated fluidized bed of at least one of the first and third particles.

In another aspect, the invention includes a fluid chamber connected to centrifugal generating means, means for establishing a saturated fluidized bed of particles within the fluid chamber and means for maintaining the saturated fluidized bed in the chamber.

In another aspect, the invention includes an apparatus having a fluid chamber, a separation chamber configured to be received by a centrifuge rotor to centrifugally separate particles within the separation chamber, and means for fluid coupling the fluid chamber to the separation chamber.

In another aspect, the invention includes a method of separating blood components. The method comprises the steps of applying a centrifugal force to blood to separate the blood into components including at least plasma, platelets, and white blood cells, whereby at least a portion of the platelets become activated during the applying step, and filtering the components to remove white blood cells, while a substantial number of platelets remain activated.

In another aspect the invention includes an apparatus and method for separating particles from a liquid by initially separating particles in a liquid according to different

densities and/or different sedimentation velocities, flowing at least a portion of the particles separated in the initial separating step into a fluid chamber, and further separating the particles within the fluid chamber according to different sedimentation velocities.

In another aspect, the invention includes an apparatus and method for separating blood components by directing separated blood components from a separation chamber into a fluid chamber to filter the separated components.

In another aspect, the invention includes a method and apparatus for reducing Coriolis jetting and/or density inversion.

In another aspect, the invention includes a method of separating particles without adding a substantial amount of a diluting fluid.

In another aspect, the invention includes an apparatus and method for separating and/or filtering blood components.

In particular the invention includes a method for continuously separating particles.

In another aspect of the invention, the sedimentation velocity of the bed forming particles is altered.

In an aspect of the invention, the bed forming particles include red blood cells and the obstructed particles include cells chosen from a group consisting of stem cells and tumor cells.

In another aspect, the invention includes a method of separating first particles from second particles having a sedimentation velocity different from that of the first particles. The method comprises the steps of altering sedimentation velocity of third particles, forming within a fluid chamber a saturated fluidized bed of third particles, and obstructing with the saturated fluidized third particle bed movement of the second particles through the fluid chamber while permitting liquid and the first particles to pass through the fluid chamber.

In another aspect, the method of the invention comprises the steps flowing liquid having first, second, and third particles into a fluid chamber and forming a saturated fluidized bed of the third particles within the fluid chamber. The saturated fluidized third particle bed obstructs flow of the second particles through the fluid chamber. The method also includes the step of permitting the liquid, the first particles, and a portion of the third particles to pass through the fluid chamber.

In another aspect, the method includes an additional step of separating particles flowing from the outlet of the fluid chamber from the liquid flowing from the outlet of the fluid chamber.

The invention also includes an apparatus for separating first particles from second particles. The apparatus comprises a motor and a centrifuge rotor coupled to the motor for rotation about an axis of rotation. A holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. First and second particles are supplied to the inlet of the fluid chamber, as are substances that alter sedimentation velocity of the second particles. In addition, the apparatus includes structure for controlling at least one of the motor and substances supplied to the fluid chamber in order to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber.

In another variation of the apparatus, structure is provided for separating particles and liquid flowing from the outlet of the fluid chamber.

According to another aspect of the present invention, the bed forming particles may comprise particles osmotically responsive to the concentration of a solute dissolved in a liquid in which the second particles are dispersed. In accordance with this aspect of the invention, the size, and thus the settling velocity, of the bed forming particles are

adjusted by adjusting the solute concentration thereby adjusting the separation characteristics of the particles in the fluid chamber.

It is to be understood that both the foregoing general description and the following detailed description are exemplary, and are intended to provide further explanation of the invention as claimed. The accompanying drawings are included to provide a further understanding of the invention and are incorporated in and constitute a part of this specification. The drawings illustrate embodiments of the invention and, together with the description, serve to explain the principles of the invention.

Brief Description of the Drawings

Fig. 1 is a perspective view of a centrifuge apparatus in accordance with a embodiment of the invention;

Fig. 2 is an exploded side view of a fluid chamber shown in Fig. 1;

Fig. 3 is a partial schematic view of the apparatus of Fig. 1 illustrating a detailed view of components of the apparatus;

Fig. 4 depicts a portion of a tubing set in accordance with the invention;

Fig. 5 schematically illustrates a saturated fluidized bed formed within a fluid chamber, where the fluid chamber is a component of the tubing set of Fig. 4 mounted to the centrifuge apparatus of Fig. 1;

Fig. 6 is a cross-sectional view of a first alternate embodiment of the fluid chamber of Fig. 2;

Fig. 7 is a cross-sectional view of a second alternative embodiment of the fluid chamber of Fig. 2;

Fig. 8 is a cross-sectional view of a third alternative embodiment of the fluid chamber of Fig. 2;

Fig. 9 is a cross-sectional view of a fourth alternative embodiment of the fluid chamber of Fig. 2;

Fig. 10 is a perspective view of an alternate embodiment of a centrifuge apparatus of the invention;

Fig. 11 is a cross-sectional schematic view of another embodiment of the centrifuge apparatus of the invention;

Fig. 12 is a partial perspective view of the centrifuge apparatus of Fig. 11;

Fig. 13 illustrates a separation chamber and fluid chamber in another embodiment of the invention;

Fig. 14 is a partial view of a centrifuge apparatus including a separation chamber and multiple fluid chambers in a further embodiment of the invention;

Fig. 15 is a schematic diagram illustrating a tubing set in accordance with the present invention, including the portion depicted in Fig. 4;

Fig. 16 is a cross-sectional view of a fifth alternative embodiment of the fluid chamber of Fig. 2;

Fig. 17 is a cross-sectional view of a sixth alternative embodiment of the fluid chamber of Fig. 16;

Fig. 18 is a schematic diagram of an embodiment of the invention including a fluid supply line coupled to a primary substance container and additive containers;

Fig. 19 is a partial schematic diagram of a centrifuge apparatus including a fluid chamber and supplemental fluid chamber in accordance with an embodiment of the invention; and

Fig. 20 is a partial schematic diagram of a centrifuge apparatus including a fluid chamber and separation channel in accordance with the invention.

Description of the Preferred Embodiments

Reference will now be made in detail to the present preferred embodiments of the invention illustrated in the accompanying drawings.

An embodiment of the present invention is described by referring to its use with a COBE® SPECTRA™ two stage sealless blood component centrifuge manufactured by the assignee of the invention. The COBE® SPECTRA™ centrifuge incorporates a one-omega/two-omega sealless tubing connection as disclosed in U.S. Patent No. 4,425,112 to Ito, the entire disclosure of which is incorporated herein by reference. The COBE® SPECTRA™ centrifuge also uses a two-stage blood component separation

channel substantially as disclosed in U.S. Patent No. 4,708,712 to Mulzet, the entire disclosure of which is also incorporated herein by reference. Although the embodiment of the invention is described in combination with the COBE® SPECTRA™ centrifuge, this description is not intended to limit the invention in any sense.

As will be apparent to one having skill in the art, the present invention may be advantageously used in a variety of centrifuge devices commonly used to separate blood into its components. In particular, the present invention may be used with any centrifugal apparatus that employs a component collect line such as a platelet collect line or a platelet rich plasma line, whether or not the apparatus employs a two stage channel or a one-omega/two-omega sealless tubing connection.

In accordance with the invention there is provided an apparatus for filtering first particles from a liquid, comprising a centrifuge rotor coupled to a motor for rotating the centrifuge rotor about an axis of rotation. As embodied herein and illustrated in Fig. 1, centrifuge 10 includes a rotor 12. The rotor 12 has an annular groove or passageway 14 having an open upper surface adapted to receive a conduit or channel 44 of a tubing set 70 shown in Fig. 4. The passageway 14 completely surrounds the rotor's axis of rotation 13 and is bounded on an inner surface by wall 15 positioned on a top surface 17 of rotor 12. A motor 16 is coupled to rotor 12 to rotate the rotor 12 about the axis of rotation 13. This coupling is accomplished directly or indirectly through a shaft 18 connected to an arm 19 that mounts to the rotor 12. Alternately, the shaft 18 may be coupled to the motor 16 through a gearing transmission (not shown). A shroud 20 is positioned on the rotor 12 to protect the motor 16 and shaft 18.

In accordance with the present invention, a holder is provided for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber. As embodied

herein and as illustrated in Fig. 1, the holder may include a mounting bracket 24 for maintaining a fluid chamber 22 on rotor 12 with an outlet 32 generally positioned closer to the rotation axis 13 than an inlet 28. The fluid chamber 22 fits within the mounting bracket 24 as illustrated in Fig. 1. The fluid chamber 22 may also be secured to the rotor 12 at alternate locations, such as beneath passageway 14. The fluid chamber 22 may be constructed of a transparent or translucent copolyester plastic, such as PETG, to allow viewing of the contents within the chamber interior with the aid of an optional strobe (not shown) during a centrifuge procedure.

As illustrated in Fig. 2, the fluid chamber 22 is formed by joining a first chamber section 26 having the inlet 28 to a second chamber section 30 having the outlet 32. The inlet 28 and outlet 32 are arranged along a longitudinal axis A-A.

In an embodiment of the invention the fluid chamber 22 has an interior volume of about 14.5 ml., although this parameter may be increased or decreased depending on the particular application. The interior of the first chamber section 26 has a frustoconical shape with a conical angle 34a of approximately 30 degrees. The interior of the second chamber section 30 also has a frustoconical shape having a conical angle 34b of approximately 120 degrees. These angles may be varied. For example, the conical angle 34b may range from approximately 90 to 120 degrees and the conical angle 34a may range from approximately 30 to 90 degrees.

The volume of the fluid chamber 22 should be at least large enough to accommodate enough platelets to provide a saturated fluidized particle bed (described below) for a particular range of flow rates, particle sizes, and centrifuge rotor 12 speeds.

Preferably, the fluid chamber interior has a maximum cross- sectional area 33 located at a position intermediate the inlet 28 and outlet 32 where sections 26, 30 join. The cross sectional area of the fluid chamber interior decreases or tapers from the maximum cross-sectional area 33 in both directions along axis A-A. Although the fluid chamber 22 is

depicted with two sections 26, 30 having frustoconical interior shapes, the interior shapes may be paraboloidal, or of any other shape having a major cross-sectional area greater than the inlet or outlet area. The fluid chamber 22 may be constructed from a unitary piece of plastic rather than from separate sections.

In accordance with the present invention, there is also provided means for supplying a substance to the inlet of the fluid chamber. As embodied herein and as schematically illustrated in Fig. 3, a pump 36 is fluidly connected to the fluid chamber 22 through outflow tubing 38. The pump 36 draws fluid and particles from the outlet 32 of the fluid chamber 22. The pump 36 is preferably a peristaltic pump or impeller pump configured to prevent significant damage to blood components, but any fluid pumping or drawing device may be provided. In an alternative embodiment (not shown), the pump 36 may be fluidly connected to the inlet of the fluid chamber 22 to directly move substances into and through the fluid chamber 22. The pump 22 may be mounted at any convenient location.

In accordance with the invention there is also provided means for controlling the motor and/or the supply means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained in the chamber. As embodied herein and illustrated in Fig. 3, the controlling means may include a controller 40 connected to both the centrifuge motor 16 and the pump 36. As explained in detail below, during a centrifuge operation, controller 40 maintains a saturated fluidized particle bed within the fluid chamber 22 to separate particles. Controller 40 may include a computer having programmed instructions provided by a ROM or RAM as is commonly known in the art.

The controller 40 may vary the rotational speed of the centrifuge rotor 12 by regulating frequency, current, or voltage of the electricity applied to the motor 16. Alternatively, the rotor speed can be varied by shifting the arrangement of a transmission (not shown), such as by changing

gearing to alter a rotational coupling between the motor 16 and rotor 12. The controller 40 may receive input from a rotational speed detector (not shown) to constantly monitor the rotor speed.

The controller 40 may also regulate the pump 36 to vary the flow rate of the substance supplied to the fluid chamber 22. For example, the controller 40 may vary the electricity provided to the pump 36. Alternatively the controller 40 may vary the flow rate to the chamber 22 by regulating a valving structure (not shown) positioned either within an inflow tubing 42 connected to the inlet 28 or within outflow tubing 38. The controller 40 may receive an input from a flow detector (not shown) positioned within the inflow tubing 42 to monitor the flow rate of substances entering the fluid chamber 22. Although a single controller 40 having multiple operations is schematically depicted in the embodiment shown in Fig. 3, the control means of the invention may include any number of individual controllers, each for performing a single function or a number of functions. The controller 40 may control flow rates in many other ways as is known in the art.

As described above, the rotor 12 is configured with an annular passageway 14 that is open along a top surface as illustrated in Fig. 1. This passageway 14 is provided to receive a channel 44 of tubing set 70, as partially shown in Fig. 5. As best illustrated in Fig. 4, tubing set 70 preferably includes a semi-rigid conduit formed into a channel 44 having a generally rectangular cross-section. A connector 71 joins ends of the channel 44 to form an annular or loop shape that fits within passageway 14. A supply line 78 provides whole blood to an inlet of the semi-rigid channel 44, while a tubing segment 42, outlet lines 72, 74, and a control line 76 allow for removal of blood components during a centrifuge operation and flow control within the channel 44. Further details of the general configuration and functioning of the channel 44, tubing segment 42, and lines 72, 74, 76 and 78 are described in U.S. Patent 4,708,712.

A protective sheath 80 surrounds the lines 72, 74, 76, 78 and outflow tubing 38. When the channel 44 of the tubing set 70 is removably positioned within the passageway 14, the lines 72, 74, 76 and 78 extend through slots 82, 84, 86, respectively, formed in wall 15, while the inflow tubing 42 rests in a slot 88 formed by passageway 14 (See Figs. 1 and 5).

Fig. 15 is a more complete view of a second embodiment of the tubing set 70. The tubing set 70 may further include a plurality of additional elements for collecting blood components including, but not limited to one or more donor access lines 902, sample devices 904, spikes 906, filled solution bags (not shown) for the addition of fluids to the tubing set 70, wastes bags 908, accumulator bags 910, blood component bags 912, pump cartridges 914 for interfitting with various fluid pumps such as the pump 36, air chambers 916, monitoring device interfaces 918, inter-connecting tubing and fittings 920, and various miscellaneous elements and accessories.

As shown in Figs. 3 and 5, a separation chamber 46 is positioned within a flow passage of the channel 44. Particles initially separate within the separation chamber 46 according to density and/or sedimentation velocity in response to centrifugal force. The separation chamber 46 includes a ridge 48 positioned on an outer wall of the passageway 14 for deforming a portion of the channel 44 to create a dam 50 within the channel 44. Alternatively, the dam 50 may be a permanent structure mounted within the flow passage of the channel 44. Although only a single separation chamber 46 and dam 50 are depicted in the figures, the flow passage may have multiple separation chambers or dams depending upon desired use.

When channel 44 is positioned in passageway 14, a collect well 54 forms in channel 44 adjacent dam 50. A tubing segment 42 connecting an outlet 56 of the well 54 to the inlet 28 of the fluid chamber 22 allows for separated substances in the collect well 54 to be conveyed to the fluid chamber 22.

Although the embodiment shown in Figs. 3-5 includes a tubing segment 42, any fluid coupling may be used between the separation chamber 46 and fluid chamber 22. For example, the inlet 28 of fluid chamber 22 may be directly connected to channel 44.

A method of separating particles of blood is discussed below with reference to Figs. 3 and 5. Although the invention is described in connection with a blood component separation process, it should be understood that the invention in its broadest sense is not so limited. The invention may be used to separate a number of different particles. In addition the invention is applicable to both double needle and single needle blood purification or filtration applications. For example, the invention of the present application may be practiced with the SINGLE NEEDLE RECIRCULATION SYSTEM FOR HARVESTING BLOOD COMPONENTS of U.S. Patent No. 5,437,624, issued August 1, 1995, the disclosure of which is incorporated herein by reference.

Preferably the fluid chamber 22 is initially primed with a low density fluid medium, such as air, saline solution, or plasma, having a density less than or equal to the density of liquid plasma. This priming fluid allows for efficient establishment of a saturated fluidized bed of platelets within the fluid chamber 22. When a saline solution is used, this liquid enters the channel 44 through supply line 78. The saline then flows into the outlet 56 and through the chamber 22 when controller 40 activates pump 36. Controller 40 also initiates operation of the motor 16 to rotate the centrifuge rotor 12 and fluid chamber 22 in the direction of arrow "B" in Fig. 3. During rotation, twisting of fluid lines 72, 74, 76, 78 and outflow tubing 38 connected to the centrifuge rotor 12 and fluid chamber 22 is prevented by a sealless one-omega/two-omega tubing connection as is known in the art and described in U.S. Patent No. 4,425,112.

After the apparatus is primed, and as the centrifuge rotates, whole blood or blood components are introduced through supply line 78 into the semi-rigid channel 44. When

whole blood is used, the whole blood can be added to the semi-rigid channel 44 by transferring the blood directly from a donor through supply line 78. In the alternative, the blood may be transferred from a container, such as a blood bag, to supply line 78.

The blood within the channel 44 is subjected to a centrifugal force as the centrifuge rotor 12 continues to rotate in the direction of arrow "B" in Fig. 3. This centrifugal force acts in a radial direction away from the axis of rotation 13 of the rotor 12 as indicated by arrow "C" in Fig. 3.

The blood components undergo an initial separation within the channel 44. The components of whole blood stratify in order of decreasing density as follows: 1. red blood cells, 2. white blood cells, 3. platelets, and 4. plasma. The controller 40 regulates the rotational speed of the centrifuge rotor 12 to ensure that this particle stratification takes place. The blood particles form a buffy coat layer 58 and an outer layer 60 along an outer wall surface of the channel 44 within the separation chamber 46. The outer layer 60 includes particles having a density greater than the density of the particles in the buffy coat layer 58. Typically, the outer layer 60 includes red blood cells and white blood cells, while the buffy coat layer 58 includes platelets and white blood cells.

Plasma, the least dense blood component, flows within the channel 44 along the top surface of the buffy coat layer 58. When the height of the buffy coat layer 58 approaches the top of dam 50, the flowing plasma washes the platelets and some white blood cells of the buffy layer 58 over the dam 50. After these particles are washed over the dam 50, they enter the collect well 54. Some of the platelets may also flow past the collect well 54 and then reverse direction to settle back into the collect well 54, as described in U.S. Patent Application 08/422,598 entitled SPILLOVER COLLECTION OF SPARSE

BAD ORIGINAL

COMPONENTS SUCH AS MONONUCLEAR COMPONENTS OF WHOLE BLOOD, filed April 14, 1995, the disclosure of which is incorporated herein by reference.

The white blood cells and red blood cells within the outer layer 60 are removed through outlet line 74, while platelet poor plasma is removed through outlet line 72. The controller 40 may control optional pumps (not shown) connected to lines 72, 74, or 76 to remove these blood components, as is known in the art. After the red blood cells, white blood cells, and plasma are thus removed, they are collected and recombined with other blood components or further separated. Alternately, these removed blood components may be reinfused into a donor.

Plasma carries platelets and white blood cells from the collect well 54 into the fluid chamber 22, filled with the priming fluid, so that a saturated fluidized particle bed may be formed. The controller 40 maintains the rotation speed of the rotor 12 within a predetermined rotational speed range to facilitate formation of this saturated fluidized bed. In addition, the controller 40 regulates the pump 36 to convey plasma, platelets, and white blood cells at a predetermined flow rate through the tubing segment 42 and into inlet 28 of the fluid chamber 22. These flowing blood components displace the priming fluid from the fluid chamber 22.

When the platelet and white blood cell particles enter the fluid chamber 22, they are subjected to two opposing forces. Plasma flowing through the fluid chamber with the aid of pump 36 establishes a first viscous drag force when plasma flowing through the fluid chamber 22 urges the particles toward the outlet 32 in the direction "D", shown in Fig. 3. A second centrifugal force created by rotation of the rotor 12 and fluid chamber 22 acts in the direction "C" to urge the particles toward the inlet 28.

The controller 40 regulates the rotational speed of the rotor 12 and the flow rate of the pump 36 to collect platelets and white blood cells in the fluid chamber 22. As plasma flows through the fluid chamber 22, the flow velocity of the

BAD ORIGINAL

plasma decreases as the plasma flow approaches the maximum cross-sectional area 33. This flow reaches a minimum velocity at this maximum cross-sectional area 33. Because the rotating centrifuge rotor 12 creates a sufficient gravitational field in the fluid chamber 22, the platelets accumulate near the maximum cross-sectional area 33 rather than flowing from the fluid chamber 22 with the plasma. The white blood cells accumulate somewhat below the maximum cross- sectional area 33. However, density inversion tends to mix these particles slightly during this initial establishment of the saturated fluidized particle bed.

The larger white blood cells accumulate closer to inlet 28 than the smaller platelet cells, because of their different sedimentation velocities. Preferably, the rotational speed and flow rate are controlled so that very few platelets and white blood cells flow from the fluid chamber 22 during formation of the saturated fluidized particle bed.

The platelets and white blood cells continue to accumulate in the fluid chamber 22 while plasma flows through the fluid chamber 22. As the concentration of platelets increases, the interstices between the particles become reduced and the viscous drag force from the plasma flow gradually increases. Eventually the platelet bed becomes a saturated fluidized particle bed within the fluid chamber 22. Since the bed is now saturated with platelets, for each new platelet that enters the saturated bed in the fluid chamber 22, a single platelet must exit the bed. Thus, the bed operates at a steady state condition with platelets exiting the bed at a rate equal to the rate additional platelets enter the bed after flowing through inlet 28. This bed is depicted schematically in Fig. 5, where the "X" symbol represents platelets and the "O" symbol represents white blood cells. As explained below, and depicted in Fig. 5, the saturated fluidized particle bed substantially obstructs or prevents white blood cells, "O", from passing through the fluid chamber 22.

The saturated bed establishes itself automatically, independent of the concentration of particles flowing into the fluid chamber 22. Plasma flowing into the fluid chamber 22 passes through the platelet bed both before and after the platelet saturation point.

The saturated bed of platelets occupies a varying volume in the fluid chamber 22 near the maximum cross-sectional area 33, depending on the flow rate and centrifugal field. The number of platelets in the saturated bed depends on a number of factors, such as the flow rate into the fluid chamber 22, the volume of the fluid chamber 22 and rotational speed. If these variables remain constant, the number of platelets in the saturated fluidized bed remains substantially constant. When the flow rate of blood components into the fluid chamber 22 changes, the bed self adjusts to maintain itself by either releasing excess platelets or accepting additional platelets flowing into the fluid chamber 22. For example, when the plasma flow rate into the fluid chamber 22 increases, this additional plasma flow sweeps excess platelets out of the now super-saturated bed, and the bed reestablishes itself in the saturated condition at the increased flow rate. Therefore, the concentration of platelets in the bed is lower due to the release of bed platelets.

After the saturated fluidized bed of platelets forms, flowing plasma carries additional platelets into the fluid chamber 22 and the bed. These additional platelets add to the bed and increase the viscous drag of the plasma flow through the bed. At some point the viscous drag is sufficient to cause platelets near the maximum cross-section area 33 to exit the saturated bed and fluid chamber 22. Thus, if the rotational speed and flow rate into the fluid chamber 22 remain constant, the number and concentration of platelets flowing into the saturated fluidized bed of platelets substantially equals the number and concentration of platelets released from the bed. This is in sharp contrast from the prior art.

Although the bed is saturated with platelets, a small number of white blood cells may be interspersed in the platelet bed. These white blood cells, however will tend to "fall" or settle out of the platelet bed toward inlet 28 due to their higher sedimentation velocity. Most white blood cells generally collect within the fluid chamber 22 between the saturated platelet bed and the inlet 28, as depicted in Fig. 5 and described below.

The saturated fluidized bed of platelet particles functions as a filter or barrier to white blood cells flowing into the fluid chamber 22. When blood components flow into the fluid chamber 22, plasma freely passes through the bed. However, the saturated fluidized platelet bed creates a substantial barrier to white blood cells entering the fluid chamber 22 and retains these white blood cells within the fluid chamber 22. Thus, the bed effectively filters white blood cells from the blood components continuously entering the fluid chamber 22, while allowing plasma and platelets released from the saturated bed to exit the chamber 22. This replenishment and release of platelets is referred to as the bed's self-selecting quality. Substantially all of these filtered white blood cells accumulate within the fluid chamber 22 between the saturated fluidized platelet bed and the inlet 28.

The particle separation or filtration of the saturated fluidized particle bed obviates a number of limitations associated with prior art elutriation. For example, particles may be separated or filtered in a continuous steady state manner without batch processing. In addition, an additional elutriating fluid medium is not required. Furthermore, after the saturated fluidized particle bed is established, flow rates may be varied over a range without changing the size of the particles leaving the fluid chamber 22. Unlike prior art elutriation, the present invention establishes a saturated particle bed consisting of numerically predominant particles. This bed automatically passes the predominant particles while rejecting larger particles.

The apparatus and method of the invention separate substantially all of the white blood cells from the platelets and plasma flowing through the fluid chamber 22. The barrier to white blood cells is created, at least in part, because white blood cells have a size and sedimentation velocity greater than that of the platelets forming the saturated fluidized particle bed. Therefore, particles of similar densities are separated according to different sizes or sedimentation velocities.

Because the initial separation at dam 50 and the saturated fluidized bed remove a majority of the red blood cells and white blood cells, the fluid exiting the fluid chamber 22 consists mainly of plasma and platelets. A device as described herein was operated 30 times using whole human blood. Each operation resulted in a leukopoor product having less than $3x10^6$ white blood cells per $3x10^{11}$ platelets. Based on these results it is expected that platelet product exiting the fluid chamber 22 will consistently (at least 99% of the time) meet the leukopoor standard of less than 5×10^6 white blood cells when at least 3×10^{11} platelets flow from the fluid chamber 22.

Unlike a conventional porous filter, where the filtered white blood cells are retained in the filter, the present invention allows a substantial fraction of white blood cells to be recovered and returned to the donor.

Preferably, 80% to 99% of the platelets initially entering the channel 44 may be recovered in a viable state. More preferably, at least 95% or at least 98% of the platelets initially entering the channel 44 are recovered from both the channel 44 and the fluid chamber 22.

When the blood components are initially separated with the separation chamber 46, a substantial number of platelets may become slightly activated. The saturated fluidized platelet bed allows white blood cells to be filtered from plasma and platelets despite this slight activation. Thus, the present invention does not require a waiting period to

filter white blood cells after blood components undergo initial separation in a separation chamber 46. This is in contrast to methods using conventional filters.

After separation, the platelets and plasma exiting the fluid chamber 22 are collected in appropriate containers and stored for later use. The red blood cells and white blood cells removed from the semi-rigid channel 44 may be combined with the remainder of the plasma in the system for donor reinfusion or storage. Alternatively, these components may be further separated by the apparatus 10.

In an embodiment of the invention, the controller 40 regulates the rotational speed of the rotor 12 within a preferred range of 1,800 to 2,400 RPM. Preferably the rotation is controlled at 2,400 RPM to create a gravitational field within the fluid chamber 22 ranging from approximately 800G adjacent to the inlet 28 to approximately 500G adjacent to the outlet 32. The controller 40 maintains the flow rate into the fluid chamber 22 within a range of 1 ml/min to 15 ml/min. The preferred flow rate ranges from 2 ml/min to 8 ml/min. The specific flow rate is selected according to an initial platelet count and the total volume of whole blood being processed, among other things.

In an embodiment of the invention, filtering may take place at the same flow rate used to form the saturated fluidized bed. Optionally the flow rate during filtering may be greater than the flow rate used during the bed formation to increase the rate of particle filtration. For this optional arrangement, the controller 40 may increase the flow rate of the blood components entering the fluid chamber 22 while maintaining the saturated fluidized bed. The controller 40 increases flow rate by increasing the rate of pump 36.

The controller 40 maintains the saturated fluidized bed throughout the filtering process as blood components flow into the fluid chamber 22. The controller 40 ensures that the flow through the fluid chamber 22 is smooth and steady by regulating the supply of fluid and rotation of the centrifuge rotor 12. This regulation properly balances the forces in the

fluid chamber 22 to maintain the saturated fluidized bed. As described in more detail below, the controller 40 may increase flow into the fluid chamber 22 while maintaining the saturated fluidized bed.

At the end of a blood component separation session, the controller 40 may recover platelets retained both in the buffy coat layer 58 of channel 44 and within the saturated fluidized bed of fluid chamber 22. The controller 40 recovers platelets in the buffy coat layer 58 by either decreasing rotational speed of the rotor 12 or increasing the amount of plasma exiting the channel 44. For example, in a preferred manner of recovering platelets in the buffy coat layer, the rotor speed is suddenly decreased from 2,400 RPM to 1,800 RPM, and then increased back to 2,400 RPM. This spills platelets and white blood cells retained in the buffy coat layer 58 over the dam 50 and into the fluid chamber 22. Within the fluid chamber 22 the saturated fluidized platelet bed blocks passage of the white blood cells from the buffy coat layer 58, while buffy coat layer 58 platelets simultaneously add to the bed and release platelets from the saturated bed. Thus, the apparatus may filter substantially all of the white blood cells from the buffy coat layer 58. This increases platelet yield significantly.

The buffy coat layer 58 may spill over the dam in the manner described in above-mentioned U.S. Patent Application 08/422,598. This is particularly effective in a mononuclear cell collection procedure, because the fluid chamber 22 may allow for separation of red blood cells from mononuclear cells.

In addition, platelets in the saturated fluidized bed are harvested to recover a substantial number of platelets from the fluid chamber 22. During bed harvest, the controller 40 increases the flow rate and/or decreases the centrifuge rotator 12 speed to release platelets from the bed. This flushes from the fluid chamber 22 most of the platelets that made up the saturated fluidized bed to substantially increase platelet yield. The harvesting continues until substantially

all of the platelets are removed, just before an unacceptable number of white blood cells begin to flow from the fluid chamber 22.

The harvested platelets that made up the bed may be combined with the platelets previously collected. In addition, the remainder of contents of the fluid chamber 22, having a high concentration of white blood cells, can be separately collected for later use or recombined with the blood components removed from channel 44 for return to a donor.

The invention particularly allows trace or contaminating first particles to be separated from a liquid having a larger number of second particles. Preferably the first particles to be filtered, such as white blood cells, have a concentration insufficient to form a saturated fluidized particle bed. However, the invention in its broadest application is directed to either separating first particles from liquid or separating first from second particles without concern for particular particle concentrations.

Although the inventive device and method have been described in terms of removing white blood cells and collecting platelets, this description is not to be construed as a limitation on the scope of the invention. The invention may be used to separate any of the particle components of blood from one another. For example, the saturated fluidized bed may be formed from red blood cells to prevent flow of white blood cells through the fluid chamber 22, so long as the red blood cells do not rouleau (clump). Alternatively, the liquid for carrying the particles may be saline or another substitute for plasma. In addition, the invention may be practiced to remove white blood cells or other components from whole blood removed from an umbilical cord to collect stem cells. Further, one could practice the invention by filtering or separating particles from fluids unrelated to either blood or biologically related substances.

The apparatus and method of the invention may separate white blood cells, including stem cells, and tumor cells by forming a saturated fluidized particle bed of stem cells to substantially prevent tumor cells from flowing through the fluid chamber 22. In the alternative, the tumor cells may form a saturated fluidized particle bed to substantially obstruct flow of stem cells through the fluid chamber 22.

In another aspect of the invention, smaller first particles, such as tumor cells, may be separated from larger second particles, such as stem cells, by forming a saturated fluidized particle bed with intermediate sized third particles. Initially, intermediate sized third particles are added to a liquid carrying the first and second particles. Preferably, the concentration of added third particles exceeds the concentration of both the first and second particles. These third particles are preferably magnetic micro-beads or some other substance readily separable from the other particles.

The liquid carrying the first, second, and third particles then passes into the fluid chamber 22. Eventually, the third particles form a saturated fluidized particle bed, in the same manner as described above. As more of the liquid and particles flow into the fluid chamber 22, the liquid and smaller first particles pass through the saturated third particle bed, while the bed and particle sedimentation characteristics obstruct movement of the second particles through the bed. Thus, the first and second particles separate within the fluid chamber 22.

The saturated fluidized bed may release third particles as more third particles flow into the bed or when flow rate into the fluid chamber 22 changes. These third particles may be removed from the liquid and first particles exiting the fluid chamber 22. In a preferred embodiment, a particle remover (not shown) having a magnet, magnetically attracts magnetic third particles to remove them from the liquid. Thus, a substantially purified concentration of first particles is obtained.

This alternate method is useful to separate first and second particles both being present in low concentrations and having similar densities, but different sizes. Although the third particles for forming the bed are preferably added along with the first and second particles, they may also be introduced into the fluid chamber 22 in separate steps. This aspect of the invention may be particularly useful in separating tumor cells from stem cells or other blood components, as mentioned above. Alternatively, the first particles may be T cells and the second particles may be stem cells. However, this variant of the inventive method may be practiced to separate many different types of particles. For example, T cells can be separated from stem cells so as to reduce graft versus host disease after stem cell transfusion.

Additional embodiments of the invention will now be described where like or similar elements are identified throughout the drawings by reference characters having the same final two digits.

As shown in Fig. 6, another embodiment of the invention includes a fluid chamber 122 having an inlet 128 and an outlet 132. A groove 190 is formed on an inner surface of the fluid chamber 122 at a position of the maximum cross-sectional area 133. Top and bottom portions 191, 192, oriented substantially perpendicular to a longitudinal axis A-A of the fluid chamber 122, are joined by a side 193. Preferably, the side 193 is parallel to the axis A-A and surrounds this axis to form the substantially annular groove 190.

In an embodiment of the invention, the side 193 is 0.1 inches, while the top and bottom portions 191, 192 are each 0.08 inches. However, the groove 190 may be configured in many different shapes and sizes without departing from the invention.

The groove 190 helps to disperse Coriolis jetting within the fluid chamber 122. Thus, groove 190 improves the particle barrier capability of the saturated fluidized particle bed. Sudden increases in liquid flow rate during a particle separation procedure may limit the ability of the saturated

fluidized particle bed to obstruct particle passage. Liquid flowing into the fluid chamber 22 undergoes a Coriolis jetting effect. This jetting flow reduces the filtration effectiveness of the saturated fluidized particle bed because liquid and particles may pass between the saturated fluidized particle bed and an interior wall surface of the fluid chamber 22 rather than into the bed itself. The fluid chamber 122 including groove 190 counteracts these effects by channeling Coriolis jetting flow in a circumferential direction partially around the axis A-A of fluid chamber 122. Therefore, the groove 190 improves the particle obstruction capability of the saturated bed, especially when liquid flow rates increase.

Figs. 16 and 17 depict fluid chambers 1022 and 1022', respectively, having alternate embodiments of grooves 1090, 1090'. As illustrated in Fig. 16, fluid chamber 1022 includes a groove 1090 having a side 1093 and top and bottom portions 1091 and 1092 formed circumferentially on the inner surface of the fluid chamber 1022 at a position of a maximum cross-sectional area 1033. These top and bottom portions 1091 and 1092 may be perpendicular to a longitudinal axis A-A, while the side 1093 may be parallel to the axis A-A to form a substantially annular groove 1090.

As shown in Fig. 16, a circumferential lip 1094, located closer to the axis A-A than the side 1093, extends from the top portion 1091. The bottom portion 1092 and lip 1094 define a groove entrance 1096. As shown in Fig. 16, this groove entrance 1096 may completely surround axis A-A.

Alternatively, as shown in Fig. 17, the groove entrance may include a plurality of slot-shaped entrances 1095' spaced about the circumference of the fluid chamber 1022' at the position of maximum cross-sectional area 1033'. In this embodiment, the lip 1094' extends to the bottom portion 1092' to form an inner groove wall 1097' located between the slot-shaped entrances 1095.

Preferably, a first entrance 1095' may be provided at a location corresponding to the location of Coriolis jetting, and a second entrance (not shown) may be provided at a

BAD ORIGINAL

diametrically opposite location. The Coriolis jet flow enters the groove 1090' at a first slot-shaped entrance 1095', travels circumferentially around the groove 1090' in both clockwise and counter-clockwise directions, and then exits at another slot-shaped opening.

The configurations of Figs. 16 and 17 are believed to improve direction of Coriolis jetting momentum and further improve performance. The groove configurations of Figs. 16 and 17 may be optionally employed in conjunction with any of the fluid chamber embodiments described herein.

Fig. 7 depicts another embodiment of a fluid chamber 222. A plurality of steps 294 are formed on an inner surface of the fluid chamber 222 between the position of the maximum cross section 233 and the inlet 228. Although only four steps 294 are illustrated, any number of steps 294 may be provided in the fluid chamber 222.

Each step 294 has a base surface 295 oriented substantially perpendicular to a longitudinal fluid chamber axis A-A. In addition, a side surface 296 is positioned orthogonal to the base surface 295. Although Fig. 7 depicts a corner where side surface 295 and base surface 295 intersect, a concave groove may replace this corner. In a preferred embodiment each step 294 surrounds the axis A-A to bound a cylindrical shaped area. Further, the fluid chamber 222 optionally includes a groove 290.

The base surface 295 is 0.05 inches and the side surface 296 is 0.02 inches in a preferred embodiment. However, the sizes for these surfaces and the configuration of each step 294 may be modified without departing from the scope or spirit of the invention.

Adding steps 294 to the fluid chamber 222, also improves the particle obstruction characteristics of the saturated fluidized particles bed, in particular during increases in the rate of fluid flow. The steps 294 provide this improvement by providing momentum deflecting and redirecting surfaces to reduce Coriolis jetting in fluid chamber 222. When Coriolis jetting takes place, the liquid and particles of the jet

travel along an interior surface of the fluid chamber 222 that faces the direction of centrifuge rotation. Therefore, the jet may transport particles between the fluid chamber interior surface and either a saturated fluidized particle bed or an elutriation field positioned in the fluid chamber 222. Thus, particles traveling in the jet may exit the fluid chamber 222 without being separated.

Steps 294 direct or alter the momentum of the Coriolis jet flow of liquid and particles generally in a circumferential direction about axis A-A. Thus, a substantial number of particles originally flowing in the jet must enter the saturated fluidized bed or elutriation field to be separated.

As shown in Fig. 7, the fluid chamber 222 may include additional steps 225 shaped similar to steps 294. The additional steps 225 are located between the position of the maximum cross- section 233 and a fluid chamber outlet 232. In a fashion similar to that described above, these steps 225 tend to redirect the Coriolis jet flow in a circumferential direction surrounding axis A-A.

In addition to adding steps 294 and 225, the conical angle 234b of the second chamber section 230 may be decreased from 120° to 45° to reduce particle contamination caused by density inversion. If faster sedimenting particles should migrate past the maximum cross section 233, the smaller angled walls partially limit some of these particles from flowing directly to outlet 232 because density inversion does not exist in the section 230. Thus, the faster sedimenting particles will "fall" or migrate back between area 233 and inlet 228 under the influence of the gravity centrifugal field, rather than flowing from outlet 232. Optionally, any of the fluid chambers disclosed herein may include a second chamber section 230 with a conical angle 234b less than 120°.

Fig. 8 illustrates an additional embodiment of a fluid chamber 322 having steps 394 and an optional groove 390 similar to groove 190. As shown in Fig. 8, each step 394

includes a base surface 395 substantially perpendicular to axis A-A. This embodiment also includes a side surface 396 oriented at an acute angle to the base surface 395.

In Fig. 9 a further embodiment of a fluid chamber 422 including flow limiting steps 494 and an optional groove 490 is depicted. A side surface 496 of each step 494 is substantially parallel to an axis A-A and forms an obtuse angle with base surface 495.

In Figs. 6-9, the grooves 190, 290, 390, 490 and steps 294, 394, 494 may either completely or only partially surround the chamber axis A-A. These features are provided to facilitate fluid flow rate increases, as described below, as well as to improve steady state performance of the fluid chamber. During blood component separation, the grooves 190, 290, 390, 490 and steps 294, 394, 494 greatly reduce the number of white blood cells that would otherwise bypass the saturated fluidized platelet bed.

The grooves 190, 290, 390, 490, steps 294, 394, 494, and additional steps 225 may be formed in many different configurations without departing from the scope, or spirit of the invention. For example, the base surface and/or side surface of one or more of the steps 294, 394, 494 may have a concave shape. In addition the steps 294, 394, 494 may be arranged in a spiral surrounding axis A-A. Further, a portion of the base surface 295, 395, 495 extending around axis A-A may be positioned lower than a remainder of this surface to form a concavity.

Although the fluid chambers 122, 222, 322, 422, 1022, 1022' are described for use in forming a saturated fluidized particle bed, this description is not intended to limit the scope of the invention in its broadest sense. Because particle separation difficulties, such as those discussed in Sartory, may be reduced or eliminated, a significant advancement from the prior art has been made. These fluid chambers 122, 222, 322, 422 may be used in any particle separation process. In particular, a fluid chamber having a channel, step, or additional step may be used in elutriation.

The grooves 190, 290, 390, 490, steps 294, 394, 494, and additional step 225 may be formed in an injection molding process. Preferably, the fluid chambers 22, 122, 222, 322, 422, 1022, 1022' are initially formed by injection molding in multiple pieces, preferably two, and bonded together by any of several well known processes, such as RF welding, ultrasonic welding, hot plate welding, solvent bonding, or adhesive bonding. Alternatively, these fluid chambers may be formed from a unitary plastic material, as by blow molding. However, any known manufacturing process may be practiced to fabricate the chambers.

When one of the fluid chambers 122, 222, 322, 422, 1022, 1022' is substituted for the fluid chamber 22, the controller 40 may regulate flow of the liquid having first particles in number of preferred ways. Because these fluid chamber designs reduce Coriolis jetting and/or density inversion, the controller 40 may increase flow rate without disrupting the saturated fluidized particle bed.

While maintaining rotational speed of the rotor 12 at a substantially constant rate, the controller 40 may increase flow through the fluid chamber 122, 222, 322, 422, 1022, 1022' with one of, or a combination of, the following different routines. In one routine the controller 40 increases flow rate by rapidly or instantaneously increasing flow through the fluid chamber 122, 222, 322, 422, 1022, 1022'. In another routine, flow rate is increased gradually over time. In yet a further routine, the controller 40 increases flow rate in a sequential manner by gradually increasing the flow rate, maintaining this increased flow rate, and then gradually increasing flow rate again.

However, if the apparatus 10 includes the fluid chamber 22, shown in Figs 1-5, the flow rate control may be more limited. The flow velocity of the liquid and particles entering the fluid chamber 22 should not undergo rapid or extreme fluctuation, otherwise temporary disruption of the effectiveness of the bed may result. The flow velocity can drop suddenly without affecting the bed, however sudden

increases in velocity, if large enough, may disrupt the bed to allow particles, such as white blood cells, to exit the fluid chamber 22.

The controller 40 increases flow into the fluid chamber 22 while maintaining the saturated fluidized bed. The controller 40 may perform this flow rate increase by gradually increasing flow in a continuous fashion until a final flow rate is achieved. In a preferred embodiment, including the fluid chamber 22 shown in Fig. 2, the controller 40 increases the flow rate into the fluid chamber 22 by a ratcheting process.

The controller 40 maintains the bed and increases the flow rate in the ratcheting process by initially reducing the rotational speed of the rotor 12. However, the rotational speed of the rotor 12 is not reduced to a level that allows red blood cells in outer layer 60 to spill over dam 50, otherwise a significant number of both red blood cells and white blood cells will flow into the fluid chamber 22. In an embodiment of the invention, the controller 40 lowers the rotational speed of the rotor 12 so that a centrifugal force at dam 50 remains above 850G. Then, the controller calculates a value for $K = Q_i/N_i^2$, where K is a constant, Q_i is the current flow rate into the fluid chamber 22, and N_i is the current rotational speed of the centrifuge rotor 12.

After the controller 40 reduces the rotational speed of the rotor 12 and calculates K, the controller 40 simultaneously increases both the flow rate into the fluid chamber 22 and the rotational speed of the rotor 12. Thus, an increasing centrifugal force in the fluid chamber 22 counteracts with increasing fluid flow forces in the fluid chamber 22 to maintain the saturated fluidized particle bed as a barrier to other particles. The new flow rate into the chamber, Q, and the new rotational speed N satisfy the equation: $Q/N^2 = K$. Therefore, Q/N^2 equals Q_i/N_i^2.

To increase the flow rate even further, the controller 40 may continue to simultaneously increase both flow rate and rotational speed. Also, if necessary, the controller 40 may

repeat the ratcheting process to further increase flow rate. This is accomplished by repeating the steps of reducing rotational speed and simultaneously increasing both flow rate and rotational speed.

In addition, the controller 40 preferably returns the saturated fluidized particle bed to its original state if a pause in fluid flow to the fluid chamber 22 causes the bed to collapse. The controller 40 may constantly monitor both flow rate, Q, and rotational speed, N, to calculate a value for $K = Q/N^2$. If the flow into the fluid chamber 22 momentarily pauses to collapse the saturated fluidized bed, the particles that made up the bed temporarily remain in the fluid chamber 22. When fluid flow to the fluid chamber 22 is reinitiated, the controller 40 controls both the flow rate, Q, and rotational speed, N, so that these parameters satisfy the $K = Q/N^2$ relationship existing immediately before fluid flow to the fluid chamber 22 was interrupted. This automatically returns the particles of the collapsed bed back into a saturated fluidized bed form.

After a bed collapses the saturated fluidized particle bed may recover in many other different ways. For example, after a pause in fluid flow the flow rate may be increased in a stepwise or gradual fashion to provide bed recovery.

Fig. 10 illustrates another embodiment of the invention. In this embodiment a fluid chamber 522 is mounted on a centrifuge rotor 512. The rotor 512 includes an outer bowl 521 and a clip 523 for holding a separation chamber 546 formed in an elongated flexible tubular or belt shape from plastic material. The device depicted in Fig. 10 separates particles, in particular blood components, within the separation chamber 546 by generating centrifugal force. For further details concerning the configuration and operation of this device, refer to U.S. Patent 5,362,291 to Williamson, IV, U.S. Patent 5,360,542 to Brown et al., and U.S. Patent 5,078,671 to Dennehey et al., the disclosures of which are incorporated herein by reference.

The fluid chamber 522 is mounted or held on the centrifuge rotor 512 with an outlet 532 facing substantially toward an axis of rotation 513 of the centrifuge rotor 512. Inflow tubing 542 supplies liquid and particles to the fluid chamber 522 after the particles undergo an initial separation within a portion of the separation chamber 546. In a similar fashion, outflow tubing 538 conveys substances from the fluid chamber 522 to another portion of the separation chamber 546.

In using the embodiment shown in Fig. 10, particles carried by a liquid are separated in the separation chamber 546 according to density and size differences of the particles. After being initially separated, the liquid and particles, for example plasma carrying platelets and white blood cells, flow into the fluid chamber 522. Within fluid chamber 522, a saturated fluidized particle bed forms to further separate particular particles from the flowing liquid.

Yet another embodiment of the invention is illustrated in Figs. 11 and 12. This embodiment includes both a separation chamber 646 shaped as a container and a collection container 627. Holders 629, 631 hold separation chamber 646 and container 627, respectively, on a centrifuge rotor 612. Flow lines 635, 638 provide fluid flow to and from the separation chamber 646 and container 627 as indicated by the arrows labelled with the symbol "E" shown in Fig. 11. Further components include a restraining collar 637 and container holder clamp assemblies 639. Particles are separated according to density and size differences within the separation chamber 646 in response to centrifugal force. For further details of how this device is configured and operates, refer to Baxter Heathcare Corporation's CS-3000® Plus Blood Separator Operator's Manual (7-19-3-136), the disclosure of which is incorporated herein by reference.

As depicted in Figs. 11 and 12, a holder 624 holds a fluid chamber 622 on the rotor 612. Inflow tubing 642 conveys liquid and particles initially separated in separation chamber 646 into the fluid chamber 622. In addition, an outflow tubing 638 fluidly couples the fluid chamber 622 to the

BAD ORIGINAL

collection container 627. With this configuration, a saturated fluidized particle bed may be formed in the fluid chamber 622, as explained with respect to the above embodiments, to filter particles.

Fig. 13 illustrates a further embodiment of the invention. This embodiment includes a separation chamber 746, preferably formed from rigid transparent plastic conduit, capable of being inserted into a centrifuge. An inlet 741 allows whole blood to flow into a first stage 743 of the separation chamber 746, so that red blood cells may be removed from a conduit 745, while platelet rich plasma flows through conduit 742. In addition, a conduit 747 and outlet 749 enable removal of platelet poor plasma and platelets, respectively, in a second stage 751. For further details regarding the structural configuration and operation of this embodiment, refer to the Brief Operating Instructions of the Fresenius MT AS 104 blood cell separator (4/6.90(OP)), the disclosure of which is incorporated herein by reference.

As shown in Fig. 13, a fluid chamber 722 may be coupled to the separation chamber 746. A saturated fluidized particle bed may be formed in the fluid chamber 722 to separate particles after initial particle separation in the separation chamber 746, in the manner described above.

In an alternate embodiment (not shown), the fluid chamber 722 may be coupled to outlet 749 of second stage 751. This alternate embodiment would allow for particles to be separated in a manner similar to the particle separation described for the embodiment shown in Figs. 1-5.

Fig. 14 illustrates yet another embodiment of the invention. As shown, a separation chamber 846 and a first fluid chamber 822a are provided on a centrifuge rotor 812 in a manner similar to that of the embodiment of Figs. 1-5. In addition, an outflow tubing 838 fluidly couples an outlet 832a of the fluid chamber 822a to an inlet 828b of an auxiliary fluid chamber 822b. Mounting brackets (holders) 824a, 824b

maintain the fluid chamber and the auxiliary chamber 822a, 822b, respectively, at substantially the same radial distance from a rotation axis of the centrifuge rotor 812.

In using the embodiment shown in Fig. 14, centrifuge rotor 812 rotates to initially separate particles within separation chamber 846 according to density and/or sedimentation velocity. Liquid carries separated particles into the first fluid chamber 822a where particles further separate after formation of a saturated fluidized bed of particles or an elutriation field. Thereafter, the separated particles and liquid flow through tubing 838 into auxiliary fluid chamber 822b where particles are further separated by either a saturated fluidized bed of particles or an elutriation field. Thus, particles separate within chambers 822a, 822b by forming a saturated fluidized particle bed in one of the chambers 822a, 822b and an elutriation boundary in another of the chambers 822a, 822b, or, in the alternative, by forming either a saturated fluidized particle bed or an elutriation boundary in both of the chambers 822a, 822b.

Optionally the chambers 822a, 822b may have different dimensions, such as differing volumes, lengths or maximum diameters. For example, fluid chamber 822a may have a greater volume than that of auxiliary chamber 822b. These different dimensions allow for two different particle separations to take place within each of the chambers 822a, 822b.

The embodiment of Fig. 14 allows for multiple particle separations to take place simultaneously. Additionally, different types of particles may be harvested in one single procedure. Of course, one or more further fluid chambers may be added without departing from the scope of the invention. Furthermore, both of the chambers 822a and 822b may be cylindrical.

It will be apparent to those skilled in the art that various modifications and variations can be made to the structure and methodology of the present invention without departing from the scope or spirit of the invention.

The fluid chambers 122, 222, 322, 422, 1022, or 1022' depicted in the embodiments of Figs. 6-9, 16 and 17, may be substituted for the fluid chambers 22, 522, 622, 722, 822a or 822b. Further, the invention can be modified by including supplemental fluid chambers or separation chambers. Although the invention has been described as having a separation chamber to initially separate particles from the liquid, the invention can be practiced without this initial separation taking place.

Although the controller 40 is described above as controlling rotor speed and flow rate, the controller 40 may also regulate other parameters. For example the controller may control the density or some other characteristic of the liquid used to carry particles into the fluid chamber.

In addition, while the invention is described herein in connection with blood component separation, the invention in its broadest sense is not so limited. The invention is applicable to other medical and non-medical uses.

The particles used to form the saturated fluidized bed in the fluid chamber can differ from the particles within the fluid passing through the fluid chamber for filtration. Additionally, it is possible to initially form the saturated fluidized bed with an extremely high concentration of platelets having very few white blood cells.

Further, the fluid chamber of the invention may be used in a separation process involving elutriation or any other particle separation means without departing from the scope of the invention.

In accordance with the invention there is also provided means for altering sedimentation velocity of particles used to form the saturated bed. Figs. 18-20 illustrate embodiments of the invention including examples of such means. As illustrated in Fig. 18, a portion of a tubing set 1100 preferably includes a primary container 1102 for containing a primary substance including liquid and particles to be separated.

In a preferred embodiment of the invention, the primary substance in primary container 1102 is a peripheral cell collection including, for example, plasma, red blood cells, stem cells, T cells and optionally tumor cells. As mentioned above, devices for purifying blood to obtain a peripheral cell collection are known in the art. As described in more detail below, particular particles, such as red blood cells, in the primary substance are used to form a saturated fluidized particle bed in a fluid chamber 1122 or 1122' shown respectively in Figs 19 and 20. Fluid chambers 1122 and 1122' are preferably constructed in a manner similar to one of the fluid chambers 22, 122, 222, 322, 422, 522, 622, 722, 822a, 822b, 1022, or 1022' described above.

As shown in Fig. 18, the tubing set 1100 also preferably includes a series of additive containers 1104 containing additives for altering sedimentation velocity of the particles in the primary substance forming the saturated fluidized bed in the fluid chamber 1122, 1122'. A series of outflow tubes 1112 and 1114 respectively couple the primary container 1102 and each of the additive containers 1104 to a supply line 1121 of the tubing set 1100 so that the primary substance and additives flowing in the outflow tubes 1112 and 1114 mix in the supply line 1121. As shown respectively in Figs. 19 and 20, the supply line 1121 is coupled to an inlet 1140, 1140' of the fluid chamber 1222, 1222' (respectively).

A series of pumps 1124 and 1126, shown schematically in Fig. 18, regulate flow in the outflow tubes 1112 and 1114 from the primary container 1102 and additive containers 1104 to the supply line 1121. Preferably, the pumps 1124 and 1126 are peristaltic pumps connected to a controller 1106, similar to the controller 40 described above in connection with Fig. 3. Controller 1106 meters the amount of primary substance and additives flowing and mixing in the supply line 1121.

As will be recognized by those skilled in the art, other types of flow regulating devices, such as, for example, valves or impeller pumps, could be used in place of the peristaltic pumps 1124 and 1126. In its broadest sense, the invention

does not require all of the above-described structure. For example, the additive substances could be introduced directly into the primary container 1102 without the use additive containers 1104, pumps 1126, and outflow tubes 1114. When the particles forming the saturated fluidized bed are magnetic, a variable magnetic field adjacent to the fluid chamber 1122, 1122' could alter sedimentation velocity of the bed forming particles.

With the structure described above, it is possible to alter the sedimentation velocity of particles forming a saturated fluidized bed in chamber 1122, 1122'. By changing sedimentation velocity, as described below, filtration characteristics of the saturated fluidized bed may be altered.

In use, one or more of the additive substances in containers 1104 are chosen because of their ability to change the sedimentation velocity of the bed forming particles to a sedimentation velocity greater than that of first particles in the primary substance and less than that of second particles in the primary substance. Controller 1106 regulates pumps 1126 to precisely control the sedimentation velocity of the particles in the saturated fluidized bed. After the sedimentation velocity of the bed forming particles is properly adjusted, the bed allows certain particles to pass through the fluid chamber 1122, 1122' while other particles are retained by the bed in fluid chamber 1122, 1122'.

When sedimentation velocity of the bed forming particles is increased, the saturated fluidized bed retains particles in the fluid chamber 1122 or 1122' that would normally pass through the bed if the sedimentation velocity of the bed forming particles was not altered. Conversely, when sedimentation velocity of the bed forming particles is decreased, the saturated fluidized bed allows particles to pass through the bed that would normally be retained in the fluid chamber 1122 or 1122' if the sedimentation velocity of the bed forming particles was not altered.

In a preferred embodiment of the invention, red blood cells may be used to form the saturated fluidized bed, and one of the additive containers 1104 may contain an additive substance such as water or saline having a weak concentration of salt. For example, the additive substance in one of the additive containers 1104 may be a saline solution having about 0.4% sodium chloride by weight. Such additive substances are hypotonic as compared to red blood cells. Another of the additive containers 1104, preferably contains an additive substance, such as saline having a strong concentration of salt, which is hypertonic as compared to red blood cells. For example, the hypertonic additive solution in one of the additive containers 1104 may be a saline solution having about 7% sodium chloride by weight.

The hypotonic or hypotonic additive substances may be many different types of solutions containing a predetermined concentration of a particular solute. For example, these substances may include albumin as a solute.

As described in more detail below, hypotonic additive solutions tend to osmotically increase the size of red blood cells. Conversely, hypertonic solutions tend to osmotically decrease red blood cell size. Particle sedimentation velocity, as previously discussed, is directly related to the size of the particle according to Stokes law. Therefore, an increase in particle size increases sedimentation velocity, while a decrease in particle size decreases sedimentation velocity.

Another of the additive containers 1104 preferably holds a solution containing albumin or sucrose. Such solutions change the density and/or viscosity of liquid, such as plasma, flowing from the primary container 1102. As mentioned above, sedimentation velocity of a particle is also related to the density and viscosity of a fluid according to Stoke's law. Therefore, by adding density/viscosity altering components into supply line 1121, sedimentation velocity of the saturated fluidized bed particles may be altered.

At least one of the additive containers 1104 preferably contains a substance that links a number of the saturated fluidized bed forming particles in the primary solution together to form a series of saturated bed forming particle groups having a size larger than that of the individual particles. Because the particles groups are larger than the individual particles, sedimentation velocity of the saturated bed forming particle groups is greater than that of the individual particles according to Stoke's law. In a preferred embodiment, such a particle group forming substance contains macromolecules of dextran or fibrogen. These substances cause red blood cells to rouleau -that is the red blood cells link together and form separate red blood cell groups.

In an embodiment of the invention shown in Fig. 19, the supply line 1121 is coupled to the inlet 1140 of fluid chamber 1122. The fluid chamber 1122 is mounted to a centrifuge rotor 1134 of a centrifuge device 1136 preferably including a motor, shaft, arm, holder, pump, and controller 1106 respectively similar or identical to the motor 16, shaft 18, arm 19, holder 24, pump 36, and controller 40 shown in Figs. 1 and 3.

In an alternate embodiment of the invention shown in Fig. 20, the supply line 1121 is coupled to an inlet 1140' of fluid chamber 1122'. The fluid chamber 1122' is mounted to a centrifuge rotor 1134' of a centrifuge device 1136' configured like the centrifuge device 1136 shown in Fig. 19.

In accordance with the invention there is also provided means for separating particles from liquid after the particles and liquid flow from the fluid chamber. As illustrated in Fig. 19, intermediate tubing 1138 couples an outlet 1142 of fluid chamber 1122 to an inlet 1144 of a supplemental chamber 1146. Supplemental chamber 1146 is removably mounted on the centrifuge rotor 1134.

As shown in Fig. 19, the fluid chamber 1122 and supplemental chamber 1146 are spaced at approximately the same distance from an axis of rotation of rotor 1134. A maximum cross-sectional area of the supplemental chamber 1146 is preferably larger than that of the fluid chamber 1122 so that

the supplemental chamber 1146 retains particles without forming a saturated fluidized particle bed. In an alternate embodiment (not shown), the supplemental chamber 1146 is further than fluid chamber 1122 from an axis of rotation of rotor 1134. During rotation of rotor 1134, this spacing allows particles in the supplemental chamber 1146 to encounter a stronger centrifugal force than particles in fluid chamber 1122, thus allowing the supplemental chamber 1146 to have a maximum cross sectional area similar to that of fluid chamber 1122.

As described in more detail below, by controlling flow rate and rotation of rotor 1134, centrifugal force in the supplemental chamber 1146 causes particles passing from fluid chamber 1122 to be retained in chamber 1146 while permitting liquid to pass through an outlet 1148 and into an outlet line 1150.

As shown in Fig. 19, the supplemental chamber 1146 is preferably larger than the fluid chamber 1122, permitting the supplemental chamber 1146 to retain a substantial number of particles. Preferably, an interior of the supplemental chamber 1146 is shaped like that of the fluid chamber 1122.

In an alternative embodiment shown in Fig. 20, intermediate tubing 1138' couples an outlet 1142' of fluid chamber 1122' to an inlet 1152 of a separation channel 1154 mounted to centrifuge rotor 1134'. Adjacent to an outer portion of the centrifuge rotor 1134', the separation channel 1154 has a collection well 1156 for collecting particles flowing into the separation channel 1154. Rotation of centrifuge rotor 1134' sediments particles into the collection well 1156 while slower sedimenting liquid and possibly some slower sedimenting particles remain above a top boundary 1158 of the collection well.

As shown in Fig. 20, collection well 1156 has a particle concentrate outlet 1164 connected to a particle concentrate line 1160. The particle concentrate line 1160 removes particles retained in the collection well 1156. A liquid outlet 1166 is provided above top boundary 1158 and is

connected to liquid outlet line 1162. The liquid outlet line 1162 removes liquid above the top boundary 1158. In addition, the liquid outlet line 1162 may remove slower sedimenting particles above the top boundary 1158.

Preferably, the particle collection well 1156, particle concentrate outlet 1164 and liquid outlet 1166 are located at or adjacent to one end of the separation channel 1154, and the inlet 1152 is located at or adjacent to an opposite end of the separation channel 1154. This spacing ensures ample time for separation of particles from liquid, collection of a substantial number of particles in the collection well 1156, and corresponding removal of a substantial number of particles through the concentrate line 1160.

Methods for separating T cells, tumor cells, stem cells, and/or plasma from a peripheral cell collection are discussed below with reference to Figs. 18-20. Although the invention is described in connection with separating these substances from a peripheral cell collection, it should be understood that the invention in its broadest sense is not so limited. For example, the invention may be readily practiced to separate substances in a bone marrow harvest collection or an umbilical cord cell collection harvested following birth. In addition, the method of the invention in its broadest sense could be practiced with structure different from that described in connection the embodiments shown in Figs, 18-20.

After a donation procedure in which a peripheral cell collection is obtained, the peripheral cell collection is placed in the primary container 1102. A substantial portion of the peripheral cell collection includes plasma, red blood cells, stem cells, and T cells. If the donor's blood included tumor cells, these cells are also present in the peripheral cell collection.

Ultimately, the red blood cells from the peripheral cell collection will be used to form a saturated fluidized bed in the fluid chamber 1122, 1122'. If the number of red blood cells in the peripheral cell collection is insufficient to form the saturated bed, additional red blood cells are

preferably added to the primary container 1102 so that the number of red blood cells exceeds the number of stem cells, T cells, and any tumor cells in the primary container 1102.

At the beginning of a particle separation procedure, the pump 1124 associated with container 1102 is activated to convey the peripheral cell collection from the primary container 1102 to the supply line 1121. In addition, one or more of pumps 1126 associated with the additive substances from additive containers 1104 are used to supply additives to supply line 1121. In the supply line 1121, the peripheral cell collection and one or more of the additive substances mix to increase or decrease the sedimentation velocity of the red blood cells.

When hypotonic solution is added to supply line 1121, the red blood cells osmotically increase in size thereby increasing the sedimentation velocity of the red blood cells. Conversely, when the hypertonic solution is added to supply line 1121, the red blood cells decrease in size thereby reducing the sedimentation velocity of the red blood cells. When saline is used as the hypotonic or hypertonic solution, the mixture of the peripheral cell collection and additive substances in supply line 1121 may include about 0.6% to about 5% sodium chloride by weight. Preferably, the amount of sodium chloride or other solutes in the supply line 1121 is sufficient to prevent hemolysis (bursting) of the red blood cells if the red blood cells increase in size. For example, when saline is used, the amount of sodium chloride in the supply line 1121 is preferably above about 0.4% by weight.

When a solution containing albumin or sucrose is added to supply line 1121, the solution increases the density and/or viscosity of plasma in the supply line 1121, thereby reducing sedimentation velocity of the red blood cells. When a medium including macromolecules of dextran or fibrogen are added to the supply line 1121, the medium causes red blood cells in the supply line 1121 to rouleau, thereby increasing the sedimentation velocity of the red blood cells.

BAD ORIGINAL

Haemonetics Corporation
Exhibit 2015
Page #966

The controller 1106 activates one or more of the pumps 1126 depending on the sedimentation velocity of the red blood cells and the sedimentation velocities of cells that will be separated. For example, to separate faster sedimenting stem cells from slower sedimenting T cells, additive introduction is controlled so that the sedimentation velocity of the red blood cells falls between the sedimentation velocity of the stem cells and the sedimentation velocity of the T cells.

The peripheral cell collection and additive substances flow through the supply line 1121 into the inlet 1140, 1140' of the fluid chamber 1122, 1122'. The controller 1106 controls the rotational speed of the rotor 1136, 1136' and the rate of flow into the fluid chamber 1122, 1122' to establish a saturated fluidized bed of red blood cells in the fluid chamber 1122, 1122'.

The saturated fluidized bed of red blood cells behaves like the earlier-described saturated fluidized bed of platelets. Plasma, additive substances, and slower sedimenting T cells pass through the saturated fluidized red blood cell bed and outlet 1142, 1142', while the bed retains faster sedimenting stem cells in the fluid chamber 1122, 1122'. As red blood cells continue to flow into the fluid chamber 1122, 1122' and enter the saturated fluidized bed, red blood cells flow from the outlet 1142, 1142'. Because the fluidized bed is saturated, the rate at which red blood cells enter the inlet 1140, 1140' equals the rate at which red blood cells pass through the outlet 1142, 1142'.

As the saturated fluidized red blood cell bed continues to filter faster sedimenting particles, the pump 1124 and one or more of additive pumps 1126 continue to mix the peripheral cell collection and additives in the supply line 1121. This ensures that red blood cells entering the saturated fluidized bed and red blood cells in the bed have a sedimentation velocity between that of the first and second particles being separated.

BAD ORIGINAL

In the embodiment of Fig. 19, plasma, additive substances, T cells, and the portion of red blood cells leaving the saturated fluidized bed flow through the outlet 1142 and intermediate tubing 1138 into the inlet 1144 of supplemental chamber 1146. In the supplemental chamber 1146, centrifugal force caused by rotation of the rotor 1134 retains the T cells and red blood cells. Meanwhile, the plasma and additive substances flow from the outlet 1148 into the outlet line 1150. This separates the T cells and red blood cells from the plasma and additive substances.

The stem cells and red blood cells in the fluid chamber 1122 and the T cells and red blood cells in the supplemental chamber 1146 may retain a residue of some of the additive substances, such as albumin, sucrose, dextran, or fibrogen. To wash this residue from these cells, one of pumps 1126 preferably pumps a washing medium such as saline from a corresponding additive container 1104 through the fluid chamber 1122 and supplemental fluid chamber 1146 before completion of the separation procedure. If necessary, rotational speed of the rotor 1134 may be altered to retain particles in the fluid chamber 1122 and supplemental fluid chamber 1146 during washing.

When all of the peripheral cell collection flows from primary container 1102, the controller 1106 terminates rotation of the centrifuge rotor 1134. To remove the stem cells and red blood cells from the fluid chamber 1222, a procedurist releases the fluid chamber 1122 from the centrifuge rotor 1134 and separates the supply line 1121 or intermediate tubing 1138 from the fluid chamber 1122. In a similar fashion, the procedurist removes T cells and red blood cells retained in the supplemental fluid chamber 1146.

In the embodiment of Fig. 20, plasma, additive substances, T cells, and the portion of red blood cells leaving the saturated fluidized bed flow through the outlet 1142' and intermediate tubing 1138' into the inlet 1152 of separation channel 1154. Centrifugal force generated by the rotation of centrifuge rotor 1134' sediments the T cells and

red blood cells in the collection well 1156, while plasma and additive substances remain above the top boundary 1158 of the collection well 1156. As the T cells and red blood cells collect in the collection well 1156, the particle concentrate line 1160 removes them through outlet 1164. Simultaneously, the liquid outlet line 1162 removes plasma and additive substances through the liquid outlet 1166.

When the primary container 1102 empties, the controller 1106 terminates rotation of the rotor 1136'. A procedurist then removes the stem cells and red blood cells from the fluid chamber 1222' by releasing the fluid chamber 1122' from the centrifuge rotor 1134' and separating the supply line 1121' or intermediate tubing 1138' from the fluid chamber 1122'.

To separate faster sedimenting tumor cells from slower sedimenting stem cells, one or more of the pumps 1126 add additive substances from one or more of the additive containers 1104 into the supply line 1121. The additive substances adjust the sedimentation velocity of the red blood cells to a sedimentation velocity between the sedimentation velocity of tumor cells and the sedimentation velocity of stem cells.

As described above, a saturated fluidized bed of red blood cells forms in the fluid chamber 1122, 1122'. Because the tumor cells have a sedimentation velocity greater than that of the red blood cells, the saturated fluidized red blood cell bed retains tumor cells in the fluid chamber 1122, 1122'. Stem cells, which now have a sedimentation velocity less than that of the red blood cells, flow from the outlet 1142, 1142' of fluid chamber 1122, 1122' along with the portion of red blood cells leaving the bed.

In the supplemental chamber 1146 or the separation channel 1154, stem cells and red blood cells separate from the plasma and additive substances in the same way the T cells and red blood cells separate from the plasma and additive substances in the method described above. When the embodiment of Fig. 19 is used, washing medium, such as saline from one of

additive containers 1104, preferably washes additive residue from the particles in fluid chamber 1122, and in supplemental fluid chamber 1146, as described above.

When the primary container 1102 is empty, a procedurist removes tumor cells and red blood cells from the fluid chamber 1122 or 1122'. Stem cells and the red blood cells are removed from the supplemental chamber 1146 shown in Fig. 19 or from the particle concentrate outlet shown in Fig. 20.

The invention may be used to separate slower sedimenting tumor cells from faster sedimenting stem cells by retaining stem cells in the saturated fluidized red blood cell bed, while allowing tumor cells to pass through the bed. The invention, in its broadest sense, may also be used to separate many different types of particles from one another. Thus, it should be understood that the invention is not limited to the examples discussed in this specification. Rather the invention is intended to cover modifications and variations provided they come within the scope of the following claims and their equivalents.

Claims

1. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having an associated fluid chamber rotatable therewith, the fluid chamber having an inlet and an outlet;

controlling rotation of the rotor;

altering sedimentation velocity of the first particles;

passing a quantity of the first particles into the inlet of the rotating fluid chamber;

forming, with the first particles, a saturated fluidized bed within the fluid chamber; and

flowing into the fluid chamber inlet liquid having at least a quantity of the second particles dispersed therein while simultaneously maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of the second particles from the fluid chamber inlet to the fluid chamber outlet while substantially permitting flow of the liquid and a portion of the first particles to the outlet.

2. The method of claim 1, wherein the liquid in the step of flowing additionally includes first particles disbursed therein.

3. The method of claim 1, wherein the first particles include red blood cells, and the second particles include cells chosen from a group consisting of stem cells and tumor cells.

4. The method of claim 1, further comprising the step of removing second particles retained in the fluid chamber.

5. The method of claim 1, wherein the altering step includes the substep of changing size of the first particles.

6. The method of claim 1, wherein the altering step includes the substep of contacting the first particles with a solution that is hypertonic as compared to the first particles so that osmosis decreases size of the first particles.

7. The method of claim 1, wherein the altering step includes the substep of contacting the first particles with a solution that is hypotonic as compared to the first particles so that osmosis increases size of the first particles.

8. The method of claim 1, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the first particles.

9. The method of claim 1, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the first particles.

10. The method of claim 1, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.

11. The method of claim 1, wherein the altering step includes the substep of linking a number of the first particles to form a series of first particle groups.

12. The method of claim 1, wherein the first particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance for causing the red blood cells to rouleau.

13. The method of claim 1, wherein the altering step precedes the flowing step.

14. The method of claim 1, wherein at least a portion of the altering step is simultaneously conducted with the flowing step.

15. The method of claim 1, further comprising the step of separating the portion of first particles flowing to the outlet of the fluid chamber from the liquid flowing to the outlet of the fluid chamber.

16. A method of separating first particles from second particles having a sedimentation velocity different from a sedimentation velocity of the first particles, the method comprising the steps of:

passing liquid into a fluid chamber, the liquid carrying at least the first and second particles;

altering sedimentation velocity of third particles;

introducing the third particles into the fluid chamber;

forming within the fluid chamber a saturated fluidized bed of third particles; and

obstructing with the saturated fluidized third particle bed movement of second particles through the fluid chamber while permitting the liquid and the first particles to pass through the fluid chamber.

17. The method of claim 16, further comprising the step of adding the third particles to the liquid before the step of passing so that the steps of passing and introducing are performed substantially simultaneously.

18. The method of claim 16, wherein the first particles include stem cells, the second particles include tumor cells and the third particles include red blood cells.

19. The method of claim 16, wherein the first particles include cells chosen from a group consisting of tumor cells and T cells, the second particles include stem cells, and the third particles include red blood cells.

20. The method of claim 16, further comprising the step of removing second particles retained in the fluid chamber.

21. The method of claim 16, wherein the altering step includes the substep of changing size of the third particles.

22. The method of claim 16, wherein the altering step includes the substep of contacting the third particles with a solution that is hypertonic as compared to the third particles so that osmosis decreases size of the third particles.

23. The method of claim 16, wherein the altering step includes the substep of contacting the third particles with a solution that is hypotonic as compared to the third particles so that osmosis increases size of the third particles.

24. The method of claim 16, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the third particles.

25. The method of claim 16, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the third particles.

26. The method of claim 16, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.

27. The method of claim 16, wherein the altering step includes the substep of linking together third particles to form a series of third particle groups.

28. The method of claim 16, wherein the third particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance that causes the red blood cells to rouleau.

29. The method of claim 16, wherein the altering step precedes the passing step.

30. The method of claim 16, wherein at least a portion of the altering step is performed simultaneously with the passing step.

31. The method of claim 16, wherein the first and second particles are of substantially equal density, and wherein the altering step further includes the substep of changing size of the third particles so that the third particles are larger than the first particles and smaller than the second particles.

32. The method of claim 16, further comprising the step of separating the first particles permitted to pass through the fluid chamber from the liquid permitted to pass through the fluid chamber.

33. A method of separating first particles from second particles, the method comprising the steps of:

flowing a liquid having first, second, and third particles into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of the third particles;

obstructing flow of the second particles through the fluid chamber with the saturated fluidized third particle bed; and

permitting the liquid, the first particles, and a portion of the third particles to pass through the fluid chamber.

34. The method of claim 33, wherein the first particles include stem cells, the second particles include tumor cells, and the third particles include red blood cells.

35. The method of claim 33, wherein the first particles are cells chosen from a group consisting of tumor cells and T cells, the second particles include stem cells, and the third particles include red blood cells.

36. The method of claim 33, further comprising the step of removing second particles retained in the fluid chamber.

37. The method of claim 33, further comprising the step of altering sedimentation velocity of the third particles.

38. The method of claim 37, wherein the altering step includes the substep of changing size of the third particles.

39. The method of claim 37, wherein the altering step includes the substep of contacting the third particles with a solution that is hypertonic as compared to the third particles so that osmosis decreases size of the third particles.

40. The method of claim 37, wherein the altering step includes the substep of contacting the third particles with a solution that is hypotonic as compared to the third particles so that osmosis increases size of the third particles.

41. The method of claim 37, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis decreases size of the third particles.

42. The method of claim 37, wherein the altering step includes the substep of changing tonicity of the liquid so that osmosis increases size of the third particles.

43. The method of claim 37, wherein the altering step includes the substep of changing at least one of density and viscosity of the liquid.

44. The method of claim 37, wherein the altering step includes the substep of linking together third particles to form a series of third particle groups.

45. The method of claim 37, wherein the third particles are red blood cells, and wherein the altering step includes the substep of contacting the red blood cells with a substance that causes the red blood cells to rouleau.

46. The method of claim 37, wherein the altering step precedes the flowing step.

47. The method of claim 37, wherein at least a portion of the altering step is performed simultaneously with the flowing step.

48. The method of claim 37, wherein the first and second particles are of substantially equal density, and wherein the altering step further includes the substep of changing size of the third particles so that the third particles are larger than the first particles and smaller than the second particles.

49. The method of claim 33, further including, after the permitting step, the step of separating the first particles passing through the fluid chamber from the portion of third particles passing through the fluid chamber.

50. The method of claim 49, wherein the separating step includes the substep of magnetically separating the portion of third particles.

51. The method of claim 33, further comprising the step of separating the first particles and portion of second particles passing through the fluid chamber from the liquid passing through the fluid chamber.

52. The method of claim 33, further comprising the step of adding third particles to the liquid so that a number of third particles in the liquid exceeds both a number of first particles and a number of second particles in the liquid.

53. A method of separating first and second particles, comprising the steps of:

introducing red blood cells into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of the red blood cells;

passing liquid into the fluid chamber, the liquid carrying at least the first and second particles; and

obstructing with the saturated fluidized red blood cell bed movement of second particles through the fluid chamber while permitting the liquid, first particles, and a portion of the red blood cells to pass through the fluid chamber.

54. The method of claim 53, wherein the steps of passing and introducing are performed substantially simultaneously.

55. The method of claim 53, wherein the first particles include stem cells and the second particles include tumor cells.

56. The method of claim 53, wherein the first particles include cells chosen from a group consisting of tumor cells and T cells and the second particles include stem cells.

57. The method of claim 53, further comprising the step of altering sedimentation velocity of the red blood cells.

58. The method of claim 57, wherein the step of altering includes the substep of contacting the red blood cell with saline solution to osmotically change size of the red blood cells.

59. The method of claim 57, wherein the step of altering includes the substep of contacting the red blood cells with a substance that causes red blood cells to rouleau.

60. The method of claim 57, wherein the step of altering includes the substep of changing at least one of the density and viscosity of the liquid.

61. The method of claim 53, further including the step of removing second particles retained in the fluid chamber.

62. The method of claim 53, further comprising the step of separating the first particles and portion of red blood cells passing through the fluid chamber from the liquid passing through the fluid chamber.

63. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having an associated fluid chamber rotatable therewith, the fluid chamber having an inlet and an outlet;

controlling rotation of the rotor;

altering sedimentation velocity of the first particles;

passing a quantity of the first particles into the inlet of the rotating fluid chamber;

forming, with the first particles, a saturated fluidized bed within the fluid chamber;

BAD ORIGINAL

flowing into the fluid chamber inlet liquid having at least a quantity of the second particles dispersed therein while simultaneously maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of the second particles from the fluid chamber inlet to the fluid chamber outlet while substantially permitting flow of the liquid and a portion of the first particles from the outlet; and

separating the portion of first particles flowing from the outlet of the fluid chamber from the liquid flowing from the outlet of the fluid chamber.

64. An apparatus for separating first particles from second particles, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber;

means for supplying liquid and first and second particles to the inlet of the fluid chamber;

means for altering sedimentation velocity of the first particles; and

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber.

65. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for adjusting tonicity of the liquid to osmotically change size of the first particles.

66. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for adjusting at least one of density and viscosity of the liquid.

67. The apparatus of claim 64, wherein the means for altering sedimentation velocity of the first particles includes means for linking together first particles to form a series of first particle groups.

68. The apparatus of claim 64, further comprising a fluid chamber in the holder and means for separating particles flowing from the outlet of the fluid chamber from liquid flowing from the outlet of the fluid chamber.

69. The apparatus of claim 68, wherein the means for separating particles includes a supplemental chamber having an inlet in fluid communication with the outlet of the fluid chamber.

70. The apparatus of claim 68, wherein the means for separating particles includes a separation channel having a collection well for retaining particles therein, the separation channel including an inlet, a particle concentrate outlet located in the collection well, and a liquid outlet located in a portion of the separation channel outside of the collection well, the inlet of the separation channel being flow connected to the outlet of the fluid chamber.

71. An apparatus for separating first particles from second particles, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a fluid chamber connected to the rotor, the fluid chamber having an inlet and an outlet;

means for supplying liquid and first and second particles to the inlet of the fluid chamber;

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of first particles within the fluid chamber and to cause second particles to be retained in the fluid chamber; and

means for separating particles flowing from the outlet of the fluid chamber from liquid flowing from the outlet of the fluid chamber.

72. The apparatus of claim 71, wherein the means for separating particles includes a supplemental chamber having an inlet in fluid communication with the outlet of the fluid chamber.

73. The apparatus of claim 71, wherein the means for separating particles includes a separation channel having a collection well for retaining particles therein, the separation channel including an inlet, a particle concentrate outlet located in the collection well, and a liquid outlet located in a portion of the separation channel outside of the collection well, the inlet of the separation channel being flow connected to the outlet of the fluid chamber.

74. An apparatus for filtering first particles from a liquid, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber;

means for supplying a substance to the inlet of the fluid chamber; and

means for controlling at least one of the motor and the supplying means to maintain a saturated fluidized bed of second particles within the fluid chamber and to cause first particles to be retained in the fluid chamber.

75. The apparatus of claim 74, wherein the means for supplying substance to the inlet of the fluid chamber includes a pump for fluid connection to the fluid chamber, and wherein the controlling means regulates the pump.

76. The apparatus of claim 74, further comprising means on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

77. The apparatus of claim 76, wherein the separation chamber includes a conduit and the receiving means includes a passageway on the rotor for receiving the conduit.

78. The apparatus of claim 77, wherein the passageway includes a ridge positioned therein for contacting the conduit to form a dam in the conduit.

79. The apparatus of claim 76, wherein the separation chamber receiving means includes a holder for a container.

80. The apparatus of claim 74, wherein the controlling means increases a supply of substance to the fluid chamber by sequentially decreasing a rotational speed of the rotor, and then increasing both rotational speed of the centrifuge rotor and a flow of substance provided by the supply means.

81. The apparatus of claim 74, further comprising an auxiliary fluid chamber holder for holding an auxiliary fluid chamber on the rotor with an outlet of the auxiliary fluid chamber positioned closer to the axis of rotation than an inlet of the auxiliary fluid chamber.

82. A method of separating first particles from second particles, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having a fluid chamber;

controlling rotation of the rotor;

passing second particles into an inlet of the fluid chamber;

forming, with the second particles, a saturated fluidized bed within the fluid chamber; and

flowing the liquid having at least first particles into the fluid chamber inlet while maintaining the bed within the fluid chamber, so that the bed substantially prevents flow of first particles from the fluid chamber inlet to a fluid chamber outlet while substantially permitting flow of the liquid to the outlet.

83. The method of claim 82 wherein the step of flowing includes flowing liquid and second particles.

84. The method of claim 82, wherein both the step of passing and the step of flowing includes conveying plasma into the fluid chamber.

85. The method of claim 82, wherein the first particles include white blood cells and the second particles include platelets.

86. The method of claim 82, wherein the first particles include white blood cells and the second particles include red blood cells.

87. The method of claim 82, wherein the first particles include stem cells and the second particles include tumor cells.

88. The method of claim 82, wherein the first particles include tumor cells and the second particles include stem cells.

89. The method of claim 82, wherein the step of controlling includes the substeps of sequentially lowering, and then increasing a rotational speed of the rotor, and the step of flowing includes the substep of increasing flow of liquid having first particles simultaneously with the substep of increasing rotational speed of the rotor.

90. The method of claim 82, wherein the step of controlling includes the substeps of sequentially lowering the speed of the rotor to a first speed N_i, and then increasing the rotor speed to a second speed, N, and wherein the step of flowing includes the substeps of sequentially maintaining flow of liquid having first particles at a first flow rate, Q_i, and then, simultaneously with the substep of increasing the rotor speed, increasing the flow rate to a second flow rate, Q, wherein $Q/N^2=Q_i/N_i^2$.

91. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the step of flowing includes the substep of rapidly increasing a flow rate of the liquid having first particles.

92. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the step of flowing includes the substep of gradually increasing a flow rate of the liquid having first particles.

93. The method of claim 82, wherein the step of controlling includes the substep of substantially maintaining rotational speed of the rotor, and the substep of flowing includes the substeps of gradually increasing a flow rate of the liquid having first particles to a first flow rate, maintaining the first flow rate of the liquid, and gradually increasing the flow rate of the liquid.

94. The method of claim 82, wherein a fluid flow rate during the flowing step is within a range of 1 ml/min to 15 ml/min.

95. The method of claim 82, wherein the step of controlling includes the substep of regulating rotation of the rotor in a speed range to maintain a gravitational field in the fluid chamber ranging from approximately 500G to 800G.

96. The method of claim 82, further comprising, after the step of flowing, the step of removing second particles retained in the fluid chamber.

97. The method of claim 96, further comprising the step of removing first particles from the fluid chamber after the step of removing second particles.

98. The method of claim 82, wherein the step of flowing includes the substeps of conveying blood components into a separation chamber, separating the blood components within the separation chamber, and directing at least a portion of the separated components into the fluid chamber inlet.

99. The method of claim 98, wherein the portion of separated components includes at least plasma, platelets, and white blood cells.

100. The method of claim 98, wherein the portion of separated components includes at least plasma, platelets, and red blood cells.

101. The method of claim 98, wherein the portion of separated components includes at least plasma, red blood cells, and white blood cells.

102. The method of claim 98, further comprising the step of directing platelets retained in the separation chamber into the fluid chamber inlet while maintaining the bed within the fluid chamber.

103. The method of claim 82, further comprising the step of flowing the liquid from the fluid chamber outlet into an inlet of an auxiliary fluid chamber.

104. An apparatus for separating constituent components of a fluid, the apparatus comprising:

a conduit configured to be received by a centrifuge rotor, the conduit having at least one inlet and at least one outlet;

at least one inlet line connected to the conduit inlet;

a fluid chamber having an inlet and an outlet;

means for fluidly coupling the conduit outlet with the fluid chamber inlet; and

an outflow line connected to the outlet of the fluid chamber.

105. The apparatus of claim 104, wherein an interior surface of the fluid chamber extends along a longitudinal axis thereof and the interior surface of the fluid chamber has a maximum cross sectional area at a position intermediate the fluid chamber inlet and the fluid chamber outlet.

106. The apparatus of claim 104, wherein the fluid chamber interior converges along the longitudinal axis from the position of the maximum cross sectional area toward the fluid chamber inlet.

107. The apparatus of claim 104, wherein the fluid chamber interior converges along the longitudinal axis from the position of the maximum cross sectional area toward the fluid chamber outlet.

108. A tubing set for use with a centrifuge including a rotor provided with a generally annular groove and a fluid chamber holder, said tubing set comprising:

a channel having a generally annular configuration adapted to interfit with the annular groove of the centrifuge rotor, the channel including a platelet rich plasma outlet;

a plurality of lines being in fluid communication with the channel, the plurality of lines including at least a whole blood inlet line, a red blood cell outlet line, and a platelet poor plasma outlet line; and

BAD ORIGINAL

a fluid chamber including a first section diverging from an inlet of the fluid chamber to a position of maximum cross-sectional area of the fluid chamber and a second section converging from the position of the maximum cross-sectional area to an outlet of the fluid chamber, the inlet of the fluid chamber being in fluid communication with the platelet rich plasma channel outlet.

109. An apparatus for separating particles from a liquid, the apparatus comprising:

a motor;

a centrifuge rotor coupled to the motor for rotation about an axis of rotation;

a holder for holding a fluid chamber on the rotor with an outlet of the fluid chamber positioned closer to the axis of rotation than an inlet of the fluid chamber; and

means on the rotor for receiving a separation chamber capable of separating particles in response to centrifugal force.

110. The apparatus of claim 109, wherein the separation chamber includes a conduit and the receiving means includes a passageway on the rotor for receiving the conduit.

111. The apparatus of claim 110, wherein the passageway includes a ridge positioned therein for contacting the conduit to form a dam in the conduit.

112. The apparatus of claim 109, wherein the separation chamber receiving means includes a holder for a container.

113. The apparatus of claim 109, further comprising a separation chamber mounted within the receiving means and a fluid chamber mounted within the fluid chamber holder, the separation chamber being flow connected to the fluid chamber.

114. A method of separating white blood cells from a liquid, the method comprising the steps of:

passing at least particles into an inlet of a fluid chamber;

forming within the fluid chamber a substantial barrier to white blood cell flow through the fluid chamber, the barrier including a saturated fluidized bed of the particles;

flowing into the fluid chamber a liquid having at least the particles and the white blood cells to be separated;

obstructing with the fluidized bed, while permitting the liquid to pass through the fluid chamber, white blood cell movement through the fluid chamber; and

releasing a portion of the particles from the fluidized bed while maintaining a saturated bed of the particles in the fluid chamber.

115. The method of claim 114, wherein the particles include platelets.

116. The method of claim 115, further comprising the step of separating particle constituents from the white blood cells before the flowing step.

117. The method of claim 114, wherein the particles include red blood cells.

118. The method of claim 114, wherein the liquid includes components of blood removed from an umbilical cord.

119. The method of claim 114, further including the step of priming the fluid chamber with a priming fluid having a density less than a density of the liquid.

120. The method of claim 119, wherein said priming fluid comprises one of saline solution and air.

121. The method of claim 114, further including the step of priming the fluid chamber with the liquid.

122. A method of separating first particles from second particles, the method comprising the steps of:

passing liquid into a fluid chamber, the liquid carrying at least the first and second particles to be separated;

introducing third particles into the fluid chamber;

forming within the fluid chamber a saturated fluidized bed of third particles; and

obstructing with the saturated fluidized third particle bed movement of second particles through the fluid chamber while permitting the liquid and the first particles to pass through the fluid chamber.

123. The method of claim 122, further comprising the step of adding the third particles to the liquid before the step of passing so that the steps of passing and introducing are performed simultaneously.

124. The method of claim 122, wherein the first particles include tumor cells and the second particles include stem cells.

125. The method of claim 122, wherein the first particles include stem cells and the second particles include tumor cells.

126. The method of claim 122, wherein the third particles are magnetic and the method further comprises the step of separating first and third particles by magnetically attracting the third particles.

127. The method of claim 122, wherein the first and second particles have a substantially equal density, and the third particles have a size larger than the first particles and smaller than the second particles.

128. A method of separating smaller first particles from larger second particles, the method comprising the steps of:

adding third particles to a liquid having the first particles and second particles, the third particles being larger than the first particles and smaller than the second particles;

flowing the liquid having the first, second, and third particles into a fluid chamber;

forming within the fluid chamber a saturated fluidized bed of at least one of the first and third particles;

obstructing flow of the second particles through the fluid chamber with the fluidized bed; and

permitting the liquid, first, and third particles to pass through the fluid chamber.

129. The method of claim 128, further including the step of removing the third particles from the liquid after the permitting step.

130. The method of claim 128, wherein the number of third particles added during the adding step exceeds both the number of first particles and the number of second particles in the liquid.

131. The method of claim 128, wherein the first particles include tumor cells and the second particles include stem cells.

132. The method of claim 128, wherein the first particles include stem cells and the second particles include tumor cells.

133. An apparatus for separating portions of a substance, the apparatus comprising:

means for generating a centrifugal field;

a fluid chamber connected to the generating means, the fluid chamber having an inlet and outlet;

means for supplying a substance to the chamber, the substance including at least particles;

means for establishing a saturated fluidized bed of the first particles within the fluid chamber;

means for supplying a substance to be filtered to the fluid chamber; and

means for maintaining the saturated fluidized bed in the chamber so that at least a first portion of the substance to be filtered is retained in the fluid chamber while at least a second portion of the substance to be filtered passes through the fluid chamber.

134. The apparatus of claim 133, further comprising means in fluid communication with the fluid chamber for separating particles from the liquid.

135. An apparatus for separating particles from a liquid, the apparatus comprising:

a fluid chamber having an inlet, an outlet, and a wall extending between and connecting the inlet and the outlet, the wall defining an interior, such that, the interior has a maximum cross- sectional area at a position intermediate the inlet and the outlet, and the wall converges from the position of the maximum cross-sectional area toward the inlet;

a separation chamber configured to be received by a centrifuge rotor to centrifugally separate particles within the separation chamber; and

means for fluid coupling the fluid chamber to the separation chamber, the fluid coupling means being connected to the separation chamber at a location permitting particles in the separation chamber to pass into the fluid chamber, while substantially preventing non-separated particles from passing through the fluid coupling.

136. The apparatus of claim 135, wherein the separation chamber comprises at least a conduit.

137. The apparatus of claim 135, wherein the separation chamber comprises a container.

138. The apparatus of claim 135, further comprising a auxiliary chamber having an inlet and an outlet, the auxiliary chamber inlet being in fluid communication with the fluid chamber outlet, the auxiliary chamber further including an interior diverging from the auxiliary chamber inlet to a position of a maximum cross-sectional area.

139. A method of separating blood components, the method comprising the steps of:

applying a centrifugal force to blood to separate the blood into components including at least plasma, platelets, and white blood cells,

whereby at least a portion of the platelets become at least partially activated during the applying step; and

filtering the components to remove white blood cells, while a substantial number of platelets remain activated.

140. The method of claim 139, further comprising, after the step of filtering, the step of recovering at least 95% of the platelets separated in the applying step.

141. The method of claim 139, further comprising, after the step of filtering, the step of recovering at least 98% of the platelets separated in the applying step.

142. The method of claim 139, wherein the filtering step includes the substep of flowing the components into a saturated fluidized bed of platelets.

143. An apparatus for separating particles from a liquid, the apparatus comprising:

means for initially separating within a separation chamber particles according to at least one of different densities and different sedimentation velocities; and

means, including a fluid chamber fluidly coupled to the initial separating means, for further separating particles according to sedimentation velocity.

144. A method of separating particles in a liquid, the method comprising the steps of:

initially separating particles in a liquid according to at least one of different densities and different sedimentation velocities;

flowing at least a portion of the particles separated in the initial separating step into a fluid chamber; and

further separating the particles within the fluid chamber according to different sedimentation velocities.

145. The method of claim 144, wherein the particles comprises blood components.

146. A method of separating blood components, the method comprising the steps of:

rotating a centrifuge rotor about an axis of rotation, the rotor having a separation chamber and fluid chamber;

controlling rotation of the rotor;

conveying blood components into the separation chamber;

separating the blood components within the separation chamber into at least first blood components and second blood components;

directing second blood components and at least a portion of the first blood components from the separation chamber into the fluid chamber; and

filtering within the fluid chamber the first blood components to remove at least a portion of first particles from the second blood components.

147. The method of claim 146, wherein the step of filtering includes the substep of obstructing passage of first particles using a saturated fluidized bed of second particles.

148. The method of claim 146, wherein the directing step includes the substep of flushing a substantial number of second components retained in the separation chamber into the fluid chamber.

149. A method of separating first and second particles within a fluid chamber provided on a centrifuge rotor, the method comprising the steps of:

rotating the centrifuge rotor about an axis of rotation;

flowing liquid carrying at least first and second particles from a source into an inlet of the fluid chamber without adding a substantial amount of a diluting fluid, the second particles entering the fluid chamber inlet at a first concentration; and

preventing a substantial number of first particles from flowing from the fluid chamber inlet to a fluid chamber outlet while permitting liquid and a concentration of second particles to flow to the outlet, the concentration of second particles being substantially equal to the first concentration.

150. A fluid chamber for separating particle constituents from a liquid, the fluid chamber comprising:

an inlet;

an outlet;

a wall extending between the inlet and outlet to form a fluid chamber interior along a longitudinal axis of the fluid chamber, the interior having a maximum cross sectional area at a position intermediate the inlet and outlet, the interior converging from the position of the maximum cross sectional area toward the inlet; and

at least one groove formed on an inner surface of the wall.

151. The fluid chamber of claim 150, wherein the groove is located in the fluid chamber at the position of the maximum cross sectional area.

152. The fluid chamber of claim 150, wherein the groove includes top and bottom portions orientated substantially perpendicular to the longitudinal axis of the fluid chamber and a side connecting the top and bottom portions.
153. The fluid chamber of claim 152, wherein the side of the groove surrounds the longitudinal axis of the fluid chamber.
154. The fluid chamber of claim 150, wherein the groove extends from an inner position of the wall to an outer position of the wall, the inner position being located closer to the longitudinal axis than the outer position, and wherein the groove has a width extending in a direction parallel to the longitudinal axis, the fluid chamber further including a lip located proximate the inner position for defining at least one entrance into the groove, a dimension of the entrance extending in a direction parallel to the longitudinal axis being less than the width of the groove.
155. The fluid chamber of claim 154, wherein the lip forms an inner groove wall extending between a top and bottom portion of the groove and the entrance includes an opening in the inner groove wall extending along a portion of the groove.
156. The fluid chamber of claim 154, wherein the lip defines first entrance and second entrances extending along portions of the groove, the first entrance being located proximate a Coriolis jetting region.
157. The fluid chamber of claim 154, wherein the entrance is located between the lip and the inlet of the fluid chamber.
158. The fluid chamber of claim 150, further comprising at least one step formed on the inner surface of the wall between the position of the maximum cross sectional area and the inlet.
159. The fluid chamber of claim 150, further comprising at least one step formed on the inner surface of the wall between the position of the maximum cross sectional area and the outlet.

160. A fluid chamber for separating particle constituents from a liquid, the fluid chamber comprising:

an inlet;

an outlet;

a wall extending between the inlet and outlet to form a fluid chamber interior along a longitudinal axis of the fluid chamber, the interior having a maximum cross sectional area at a position intermediate the inlet and outlet, the interior converging from the position of the maximum cross sectional area toward the inlet; and

at least one step formed on an inner surface of the wall.

161. The fluid chamber of claim 160, wherein the step includes a base surface orientated substantially perpendicular to the longitudinal axis of the fluid chamber.

162. The fluid chamber of claim 161, further including a side surface connected to the base surface, the side surface being substantially orthogonal to the base surface.

163. The fluid chamber of claim 161, further including a side surface connected to the base surface, the side surface being orientated at an acute angle with respect to the base surface.

164. The fluid chamber of claim 160, wherein the step includes a side surface orientated substantially parallel to the longitudinal axis.

165. The fluid chamber of claim 160, wherein the step is located between the position of the maximum cross-sectional area and the inlet.

166. The fluid chamber of claim 160, wherein the step is located between the position of the maximum cross-sectional area and the outlet.

167. The fluid chamber of claim 160, wherein the step includes a top surface formed into a concavity.

168. A method of particle separation within a fluid chamber provided on a centrifuge rotor, the method comprising the steps of:

providing at least one flow directing member on an interior wall surface of the fluid chamber, the flow directing member being shaped to reduce Coriolis jetting within the fluid chamber;

rotating the centrifuge rotor about an axis of rotation;

flowing liquid carrying particles into the fluid chamber, such that the flow directing member directs the liquid to substantially prevent the liquid from flowing between a wall of the fluid chamber and a separation area within the chamber; and

separating particles within the fluid chamber at the separation area of the chamber according to differences in sedimentation velocity.

169. The method of claim 168, wherein the separation area comprises one of a fluidized particle bed and an elutriation field.

BAD ORIGINAL

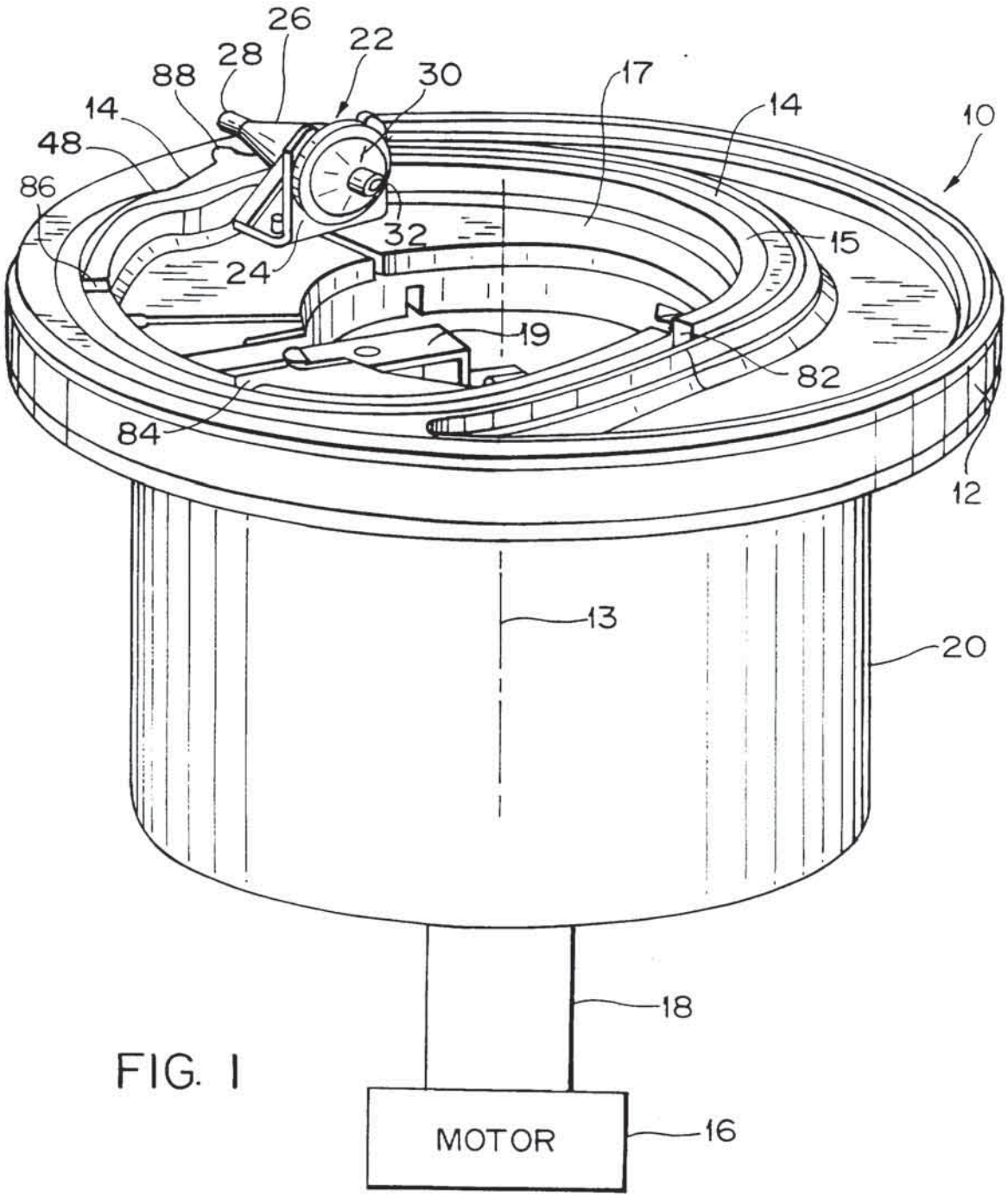


FIG. 1

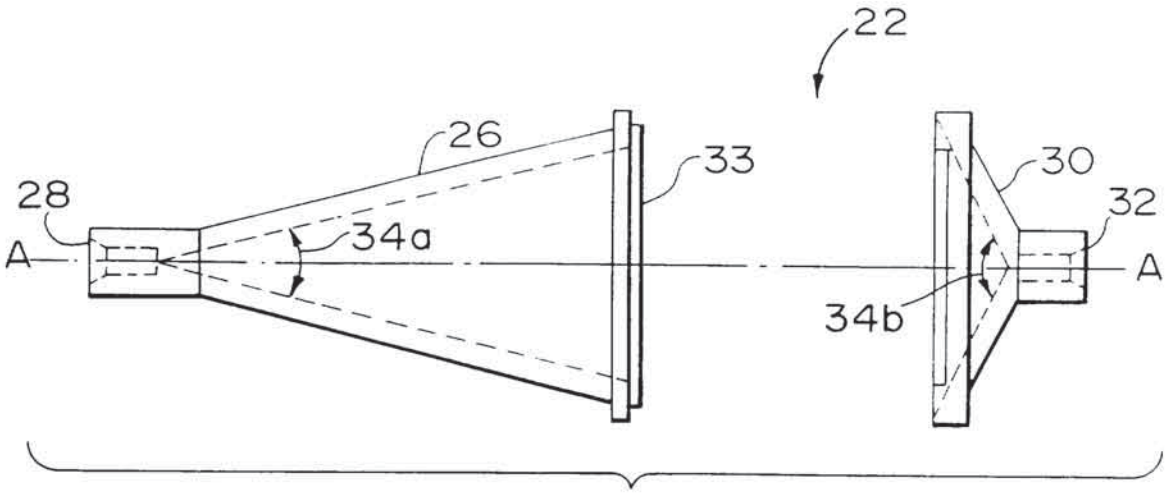

22
26
33
30
28
32
A
34a
A
34b

FIG. 2

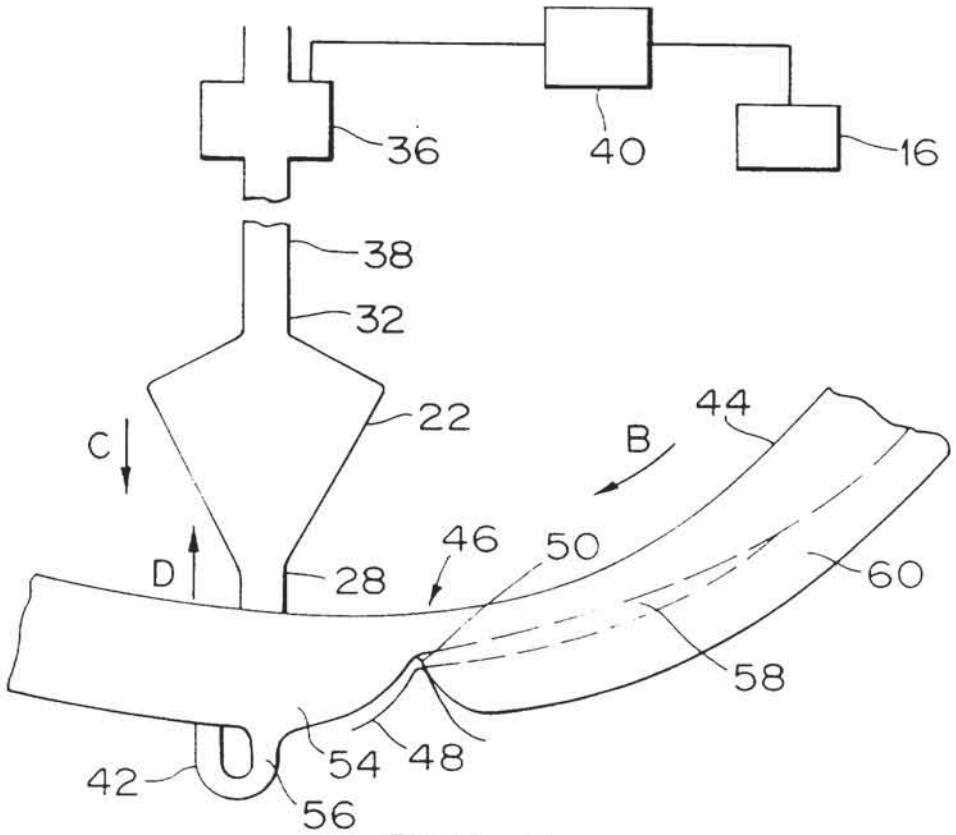

36
40
16
38
32
22
44
C
B
D
46
50
28
60
58
54
48
42
56

FIG. 3

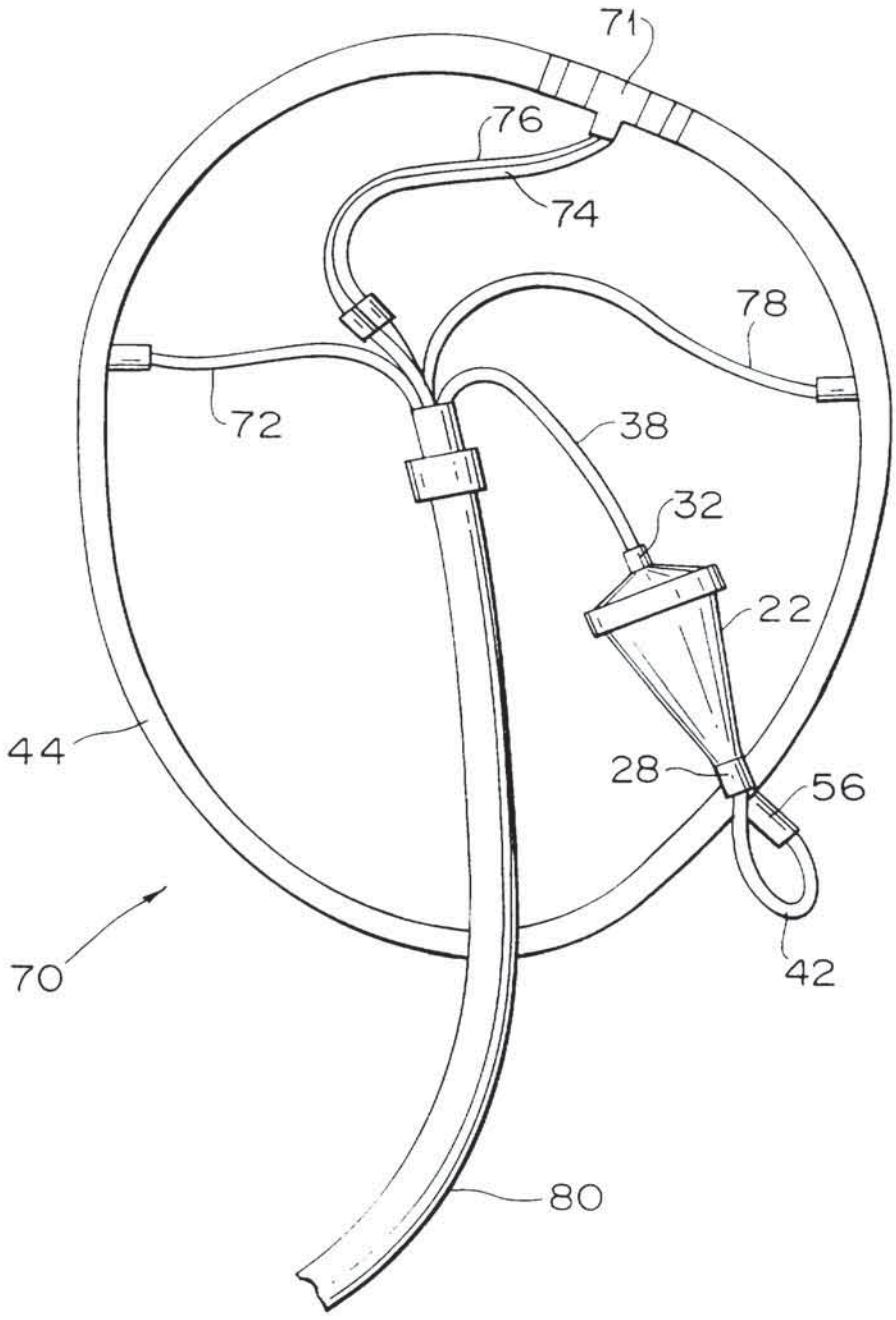


FIG. 4

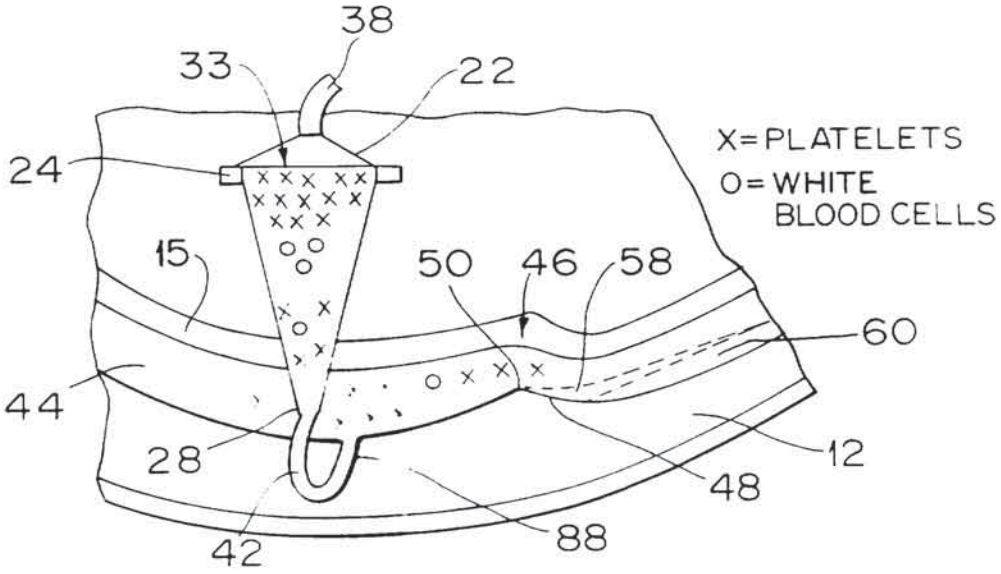


FIG. 5

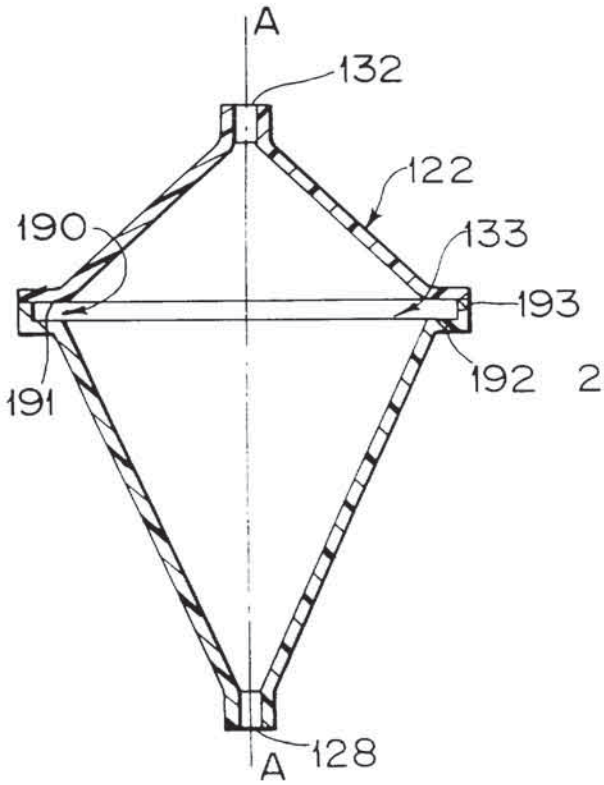


FIG. 6

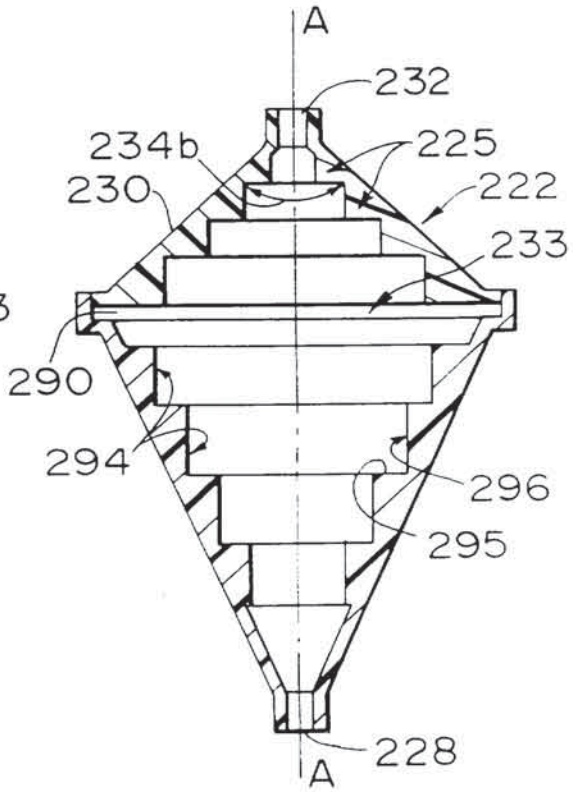


FIG. 7

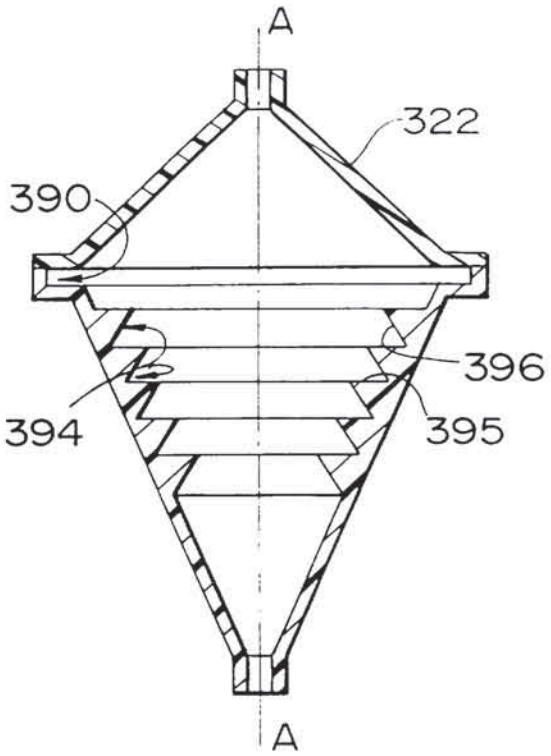


FIG. 8

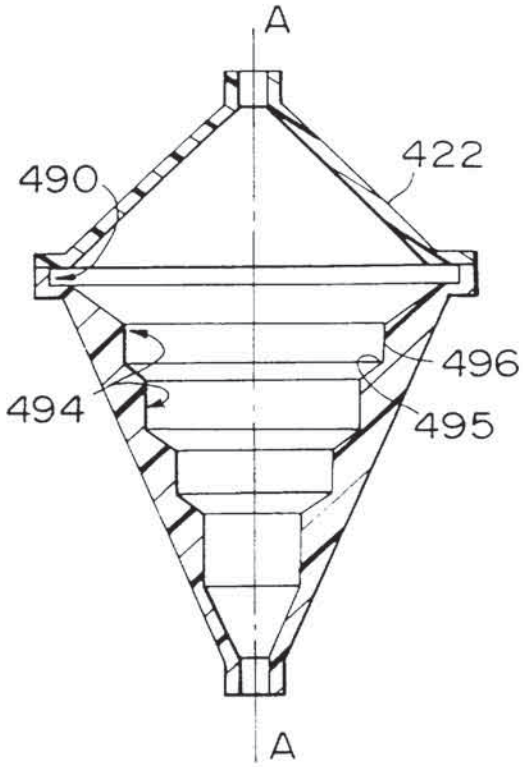


FIG. 9

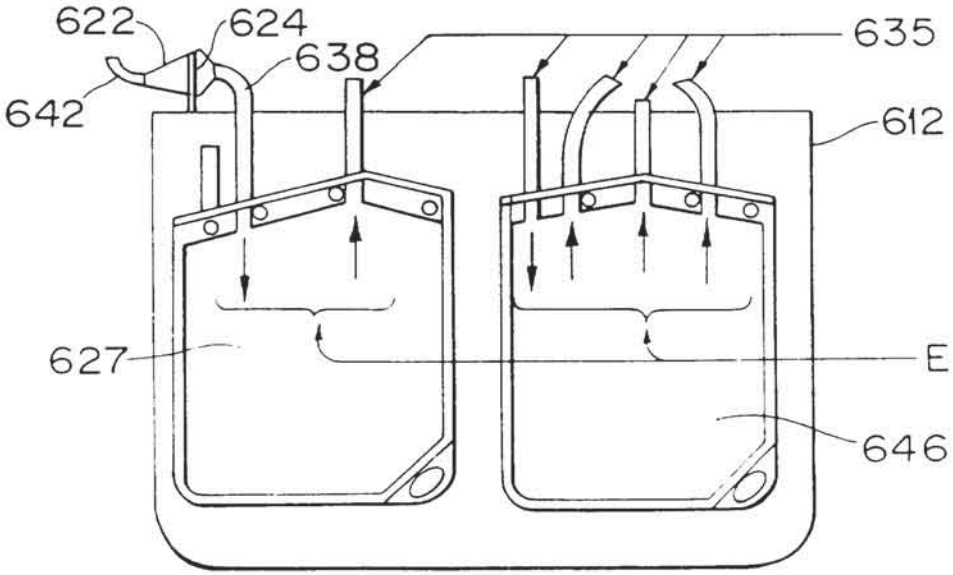


FIG. 11

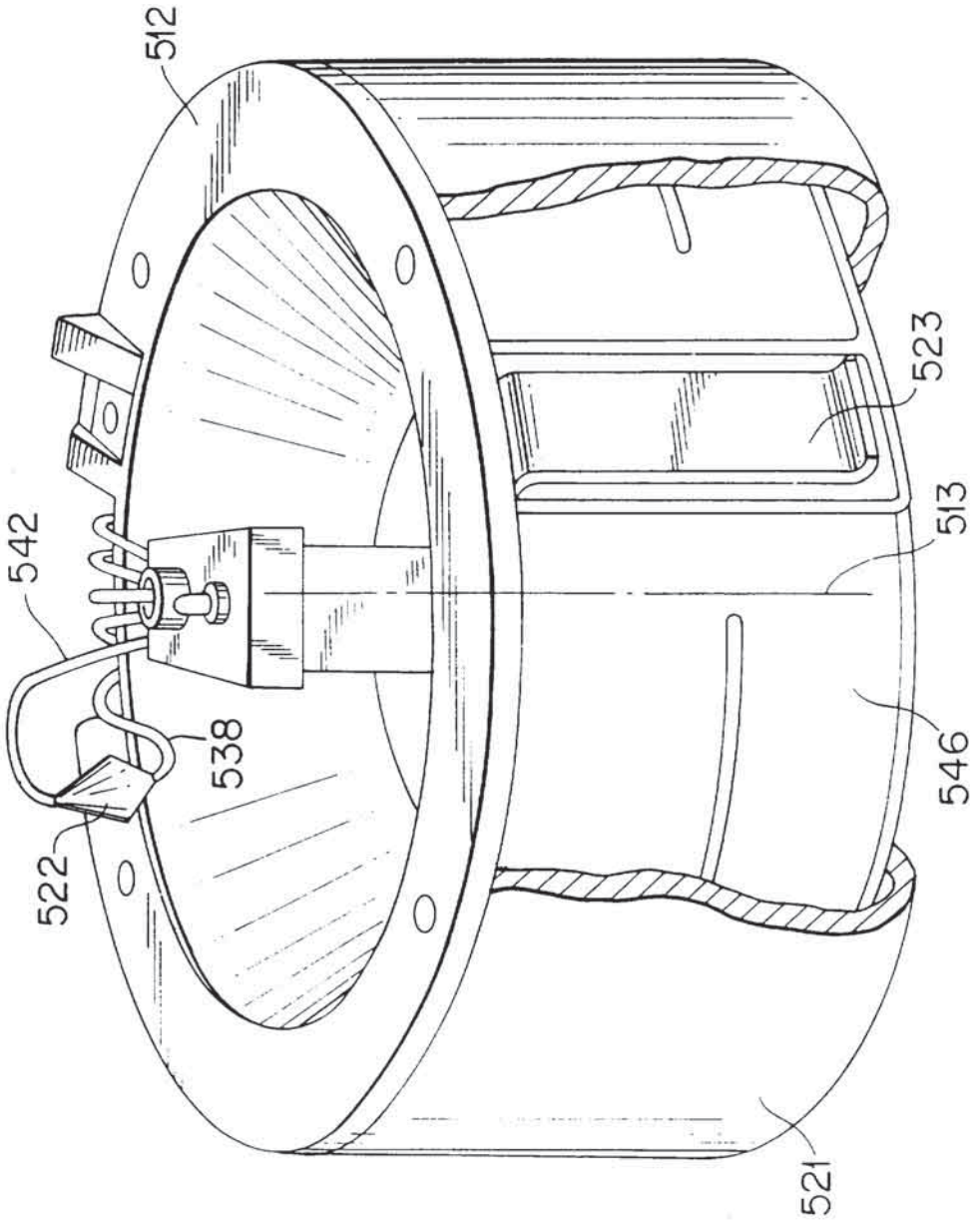


FIG. 10

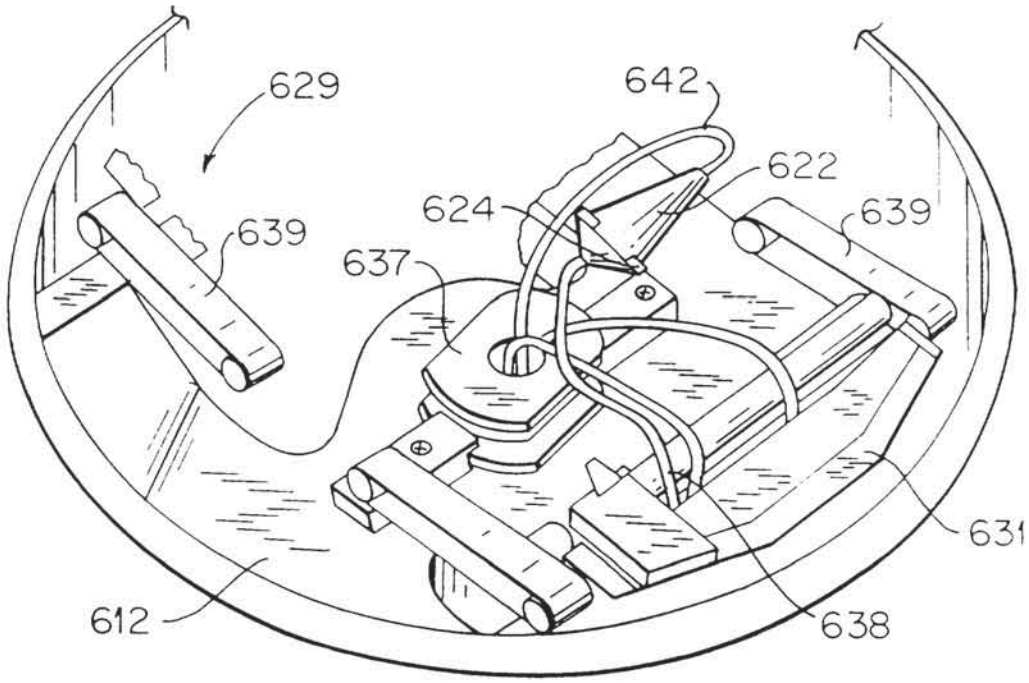


FIG. 12

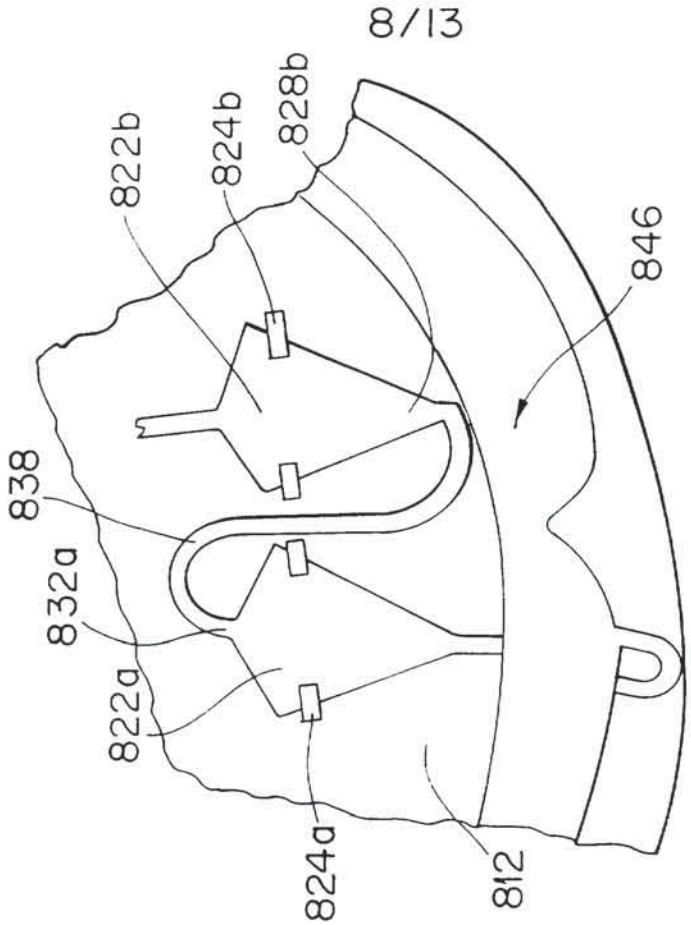

822b
824b
828b
846
838
832a
822a
824a
812

FIG. 14

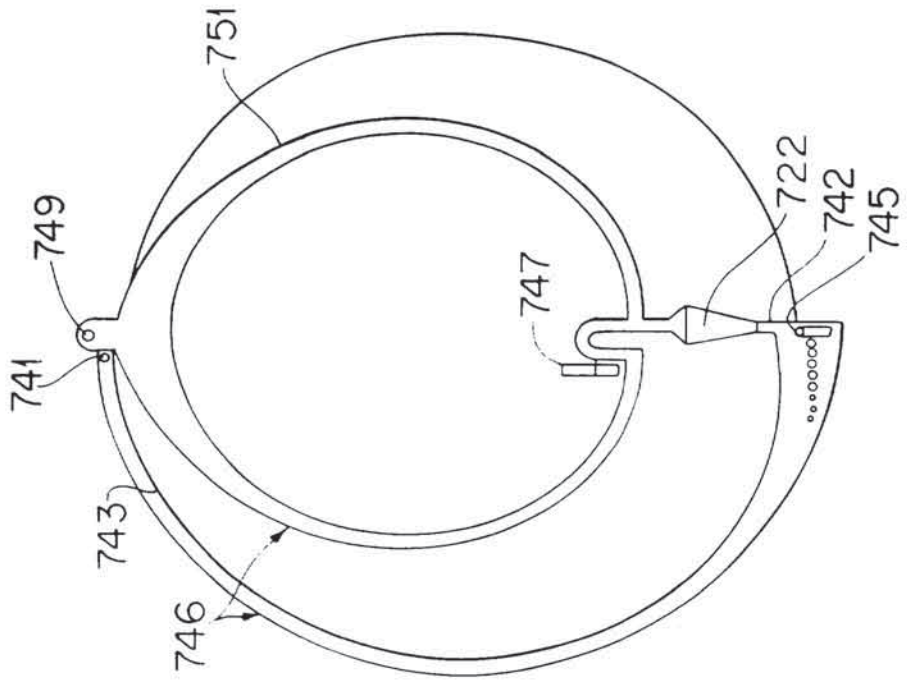

751
749
741
743
746
747
722
742
745

FIG. 13

FIG. 15

WO 96/33023 PCT/US96/05505

Haemonetics Corporation
Exhibit 2015
Page #1003

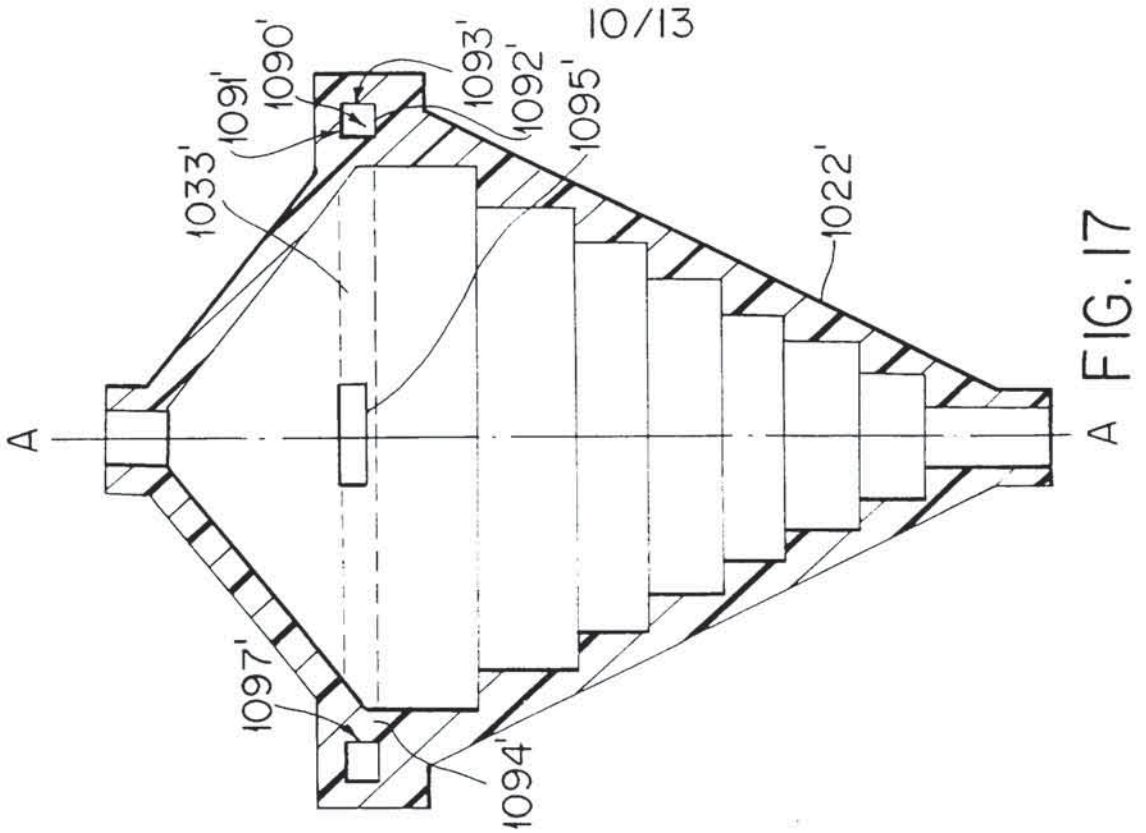

1033'
1091'
1090'
1093'
1092'
1095'
1022'
A
A
1097'
1094'

FIG. 17

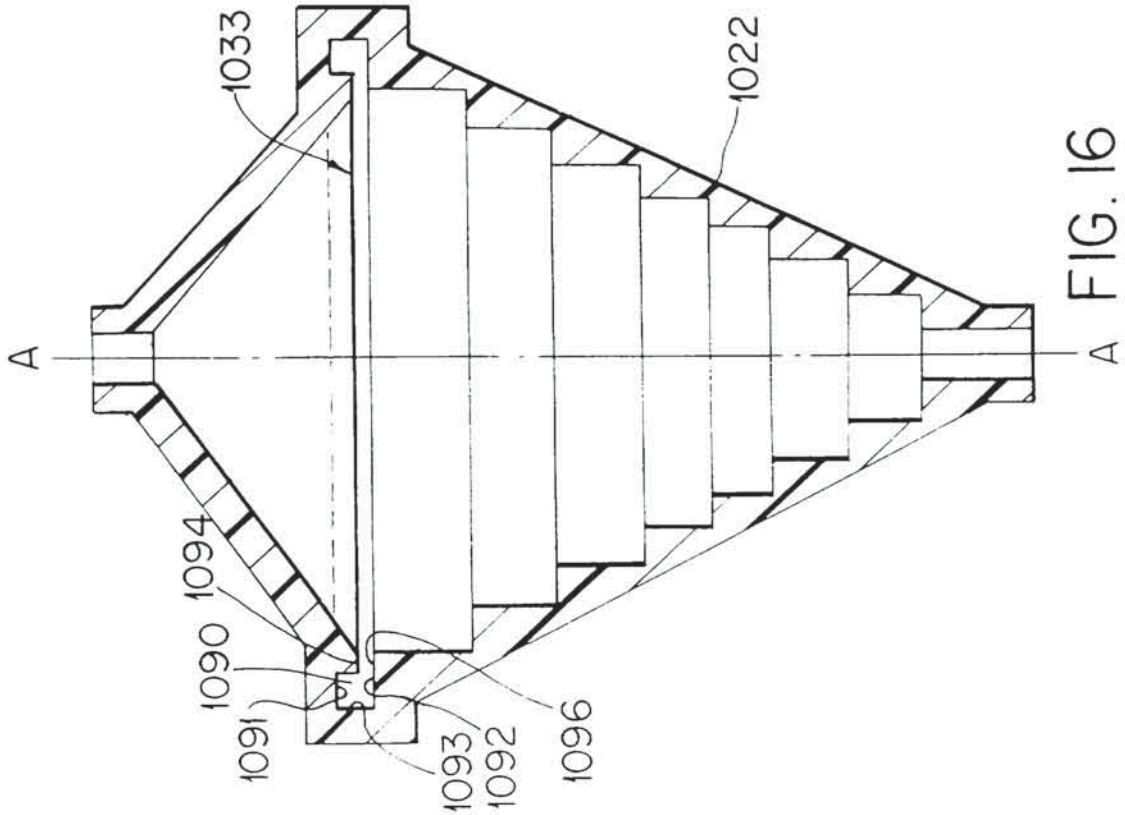

1033
1022
A
A
1094
1090
1091
1093
1092
1096

FIG. 16

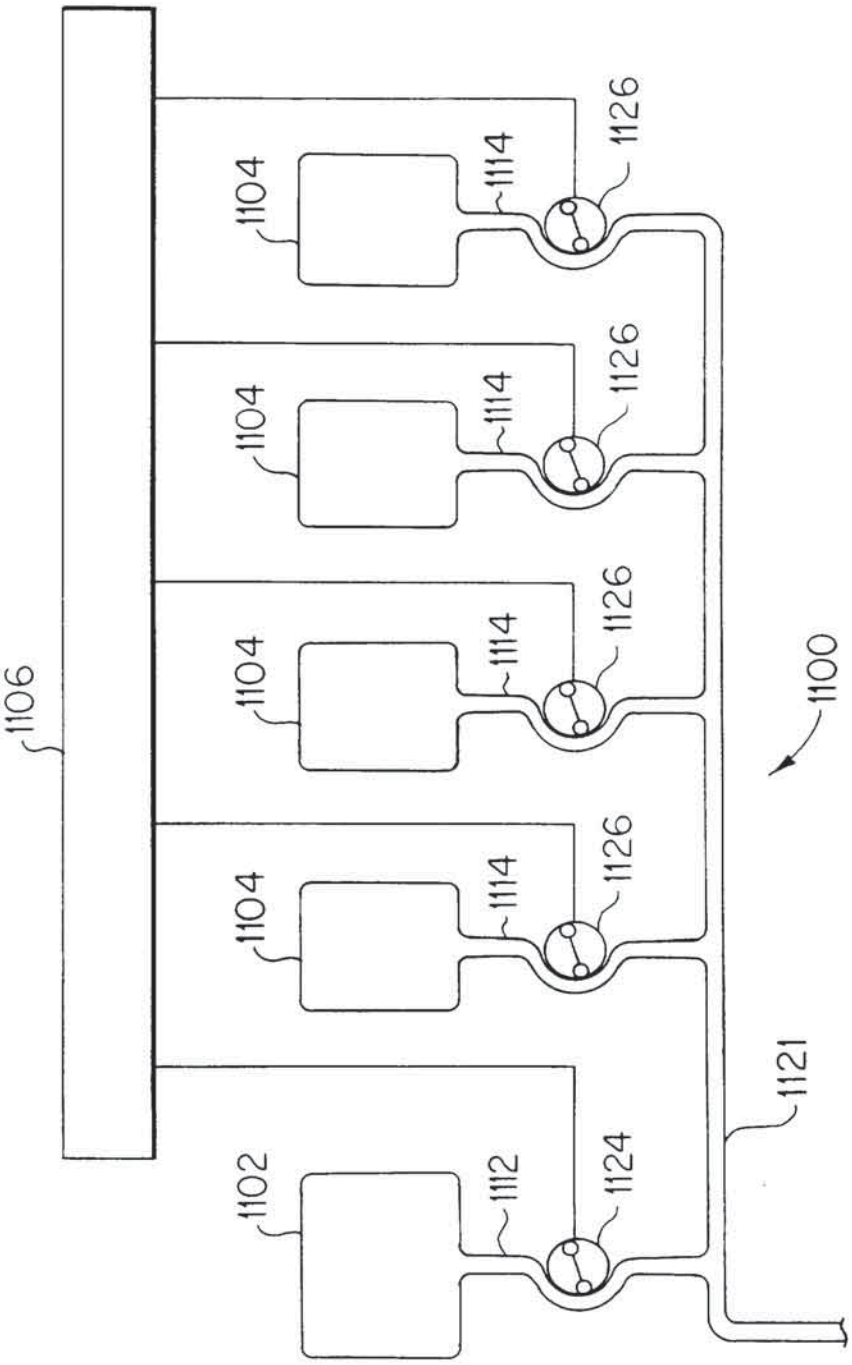


FIG. 18

Haemonetics Corporation
Exhibit 2015
Page #1005

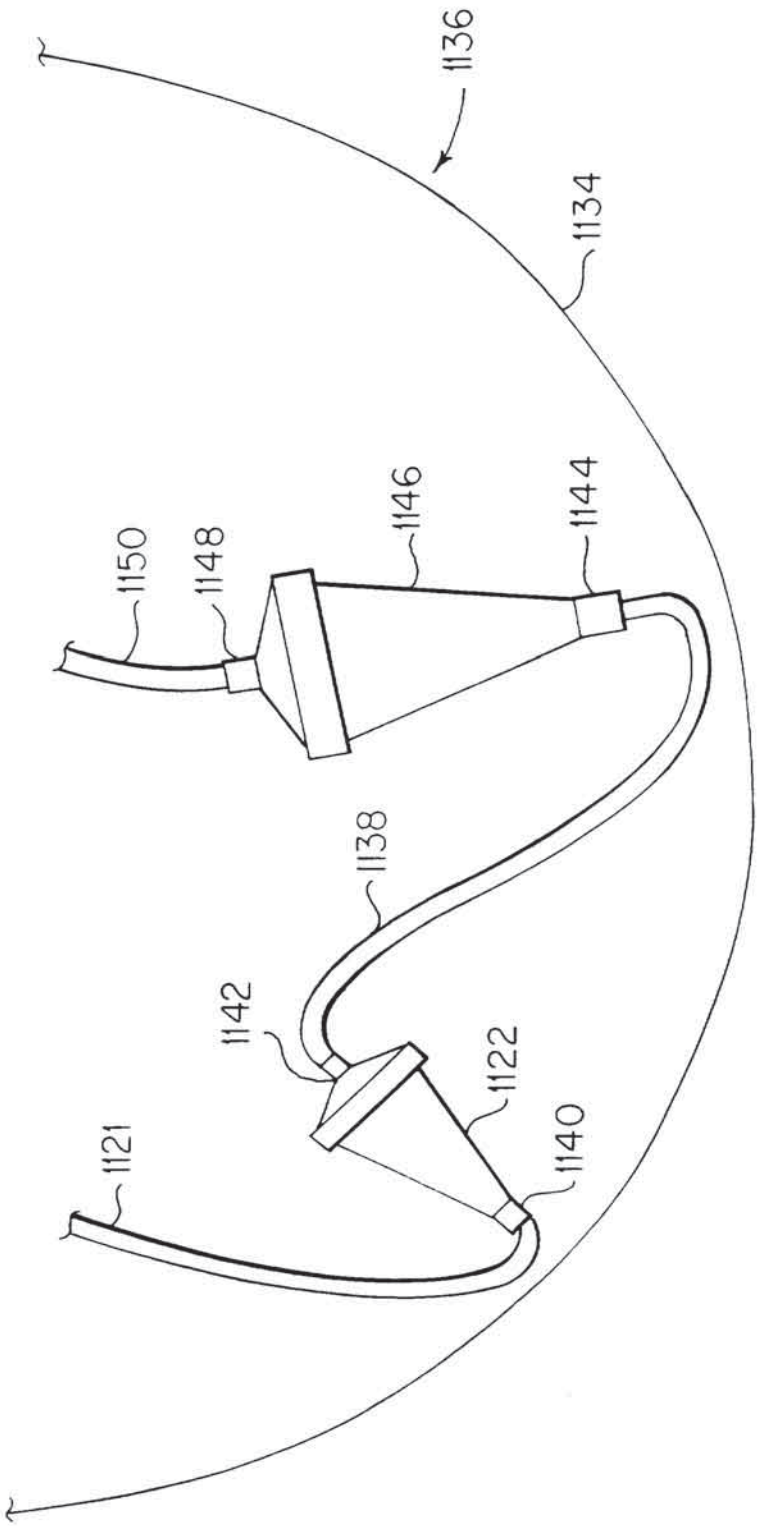


FIG. 19

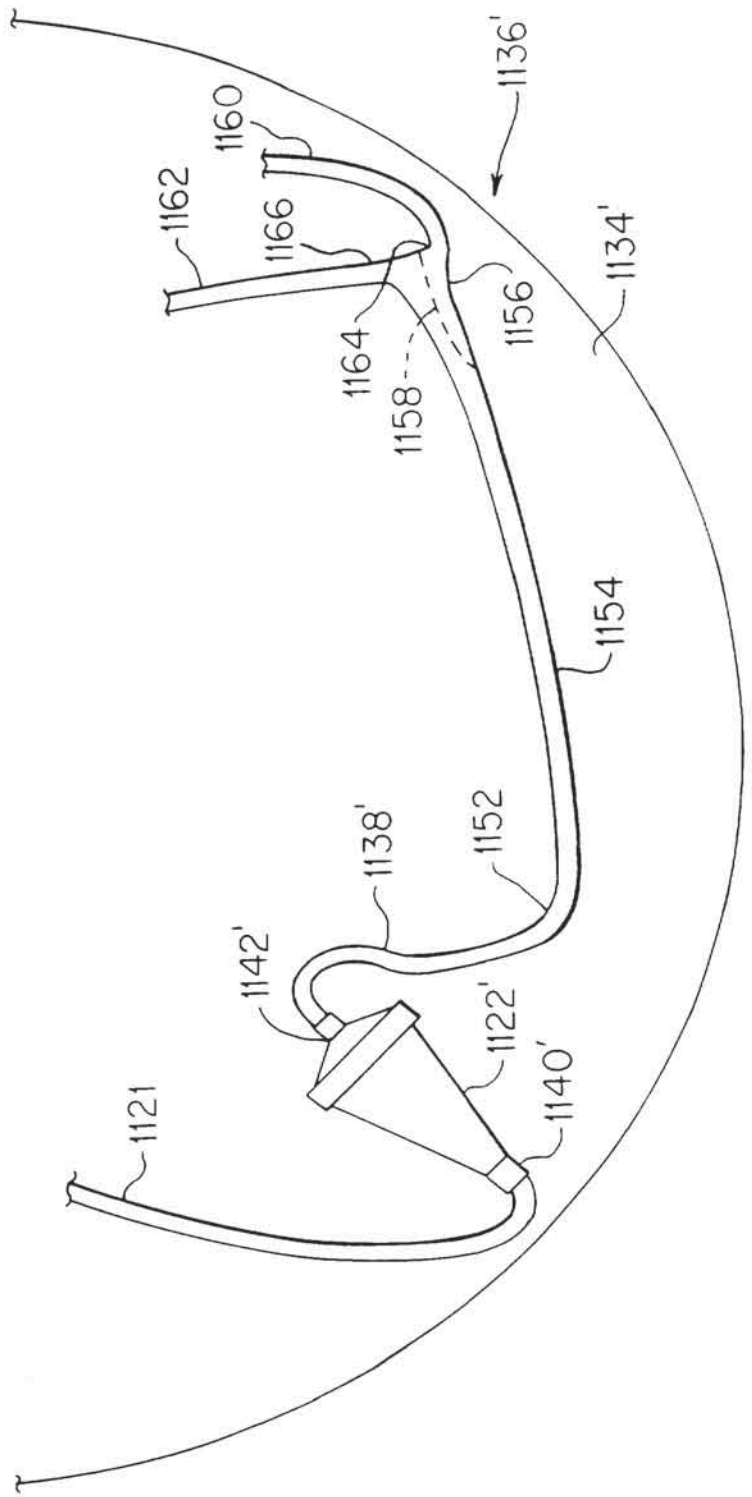

1136'
1160
1162
1166
1134'
1164
1156
1158
1154
1138'
1152
1142'
1122'
1140'
1121

FIG. 20

INTERNATIONAL SEARCH REPORT

Ir itional Application No
PCT/US 96/05505

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B04B5/04 A61M1/36

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B04B A61M

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 27698 (BAXTER INTERNATIONAL INC.) 8 December 1994	143-146
Y	see the whole document	1-70,87, 88, 124-127, 131,132, 139-142, 147,148

-/--

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 1996	26.08.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Leitner, J

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

Haemonetics Corporation
Exhibit 2015
Page #1008

INTERNATIONAL SEARCH REPORT

Ir ıtional Application No
PCT/US 96/05505

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 187 979 (H.M. CULLIS) 12 February 1980	71,72, 74-76, 82-86, 96,97, 103,109, 114-123, 128,130, 133,134, 149
Y		1-70,73, 77-79, 87,88, 104-108, 110-113, 124-127, 131,132, 135-142, 147,148
A	see the whole document	80,81, 98-102, 150,160, 168
Y	US,A,4 708 712 (A.P. MULZET) 24 November 1987 cited in the application see abstract; figures	73, 77-79, 104-108, 110-113, 135-138
A	US,A,4 350 283 (A.L. LEONIAN) 21 September 1982	
A	US,A,4 322 298 (M.D. PERSIDSKY) 30 March 1982	
A	US,A,4 416 654 (D.W. SCHOENDORFER) 22 November 1983	
A	US,A,3 825 175 (W.K. SARTORY) 23 July 1974 cited in the application	
A	US,A,4 269 718 (M.D. PERSIDSKY) 26 May 1981	
A	DE,A,37 00 122 (M. LUTZ) 14 July 1988	
A	US,A,5 282 982 (J.R. WELLS) 1 February 1994	
A	US,A,5 397 479 (L. KASS) 14 March 1995	

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Haemonetics Corporation
Exhibit 2015
Page #1009

INTERNATIONAL SEARCH REPORT

Information on patent family members

i ational Application No
PCT/US 96/05505

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9427698	08-12-94	CA-A-	2140455	08-12-94
		EP-A-	0653062	17-05-95
US-A-4187979	12-02-80	NONE		
US-A-4708712	24-11-87	CA-A-	1298822	14-04-92
		DE-A-	3710217	01-10-87
		FR-A-	2596294	02-10-87
		GB-A,B	2188569	07-10-87
		JP-B-	1044104	26-09-89
		JP-C-	1566923	25-06-90
		JP-A-	62294454	21-12-87
US-A-4350283	21-09-82	NONE		
US-A-4322298	30-03-82	NONE		
US-A-4416654	22-11-83	US-A-	4464167	07-08-84
US-A-3825175	23-07-74	CA-A-	996526	07-09-76
		CH-A-	593715	15-12-77
		DE-A-	2426908	02-01-75
		FR-A,B	2232368	03-01-75
		GB-A-	1455203	10-11-76
		JP-A-	50032562	29-03-75
		SE-A-	7407053	09-12-74
US-A-4269718	26-05-81	CA-A-	1185218	09-04-85
		DE-A-	3117710	08-04-82
		FR-A,B	2481614	06-11-81
		GB-A,B	2075376	18-11-81
		JP-A-	57026619	12-02-82
		SE-A-	8102776	06-11-81
DE-A-3700122	14-07-88	NONE		
US-A-5282982	01-02-94	AU-B-	2324792	11-02-93
		WO-A-	9300937	21-01-93
US-A-5397479	14-03-95	AU-B-	6635894	21-11-94

Haemonetics Corporation
Exhibit 2015
Page #1010

INTERNATIONAL SEARCH REPORT

Information on patent family members

I ıational Application No
PCT/US 96/05505

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5397479		CA-A-	2161408	10-11-94
		EP-A-	0696933	21-02-96
		WO-A-	9425135	10-11-94
		US-A-	5482829	09-01-96

Form PCT/ISA/210 (patent family annex) (July 1992)

Haemonetics Corporation
Exhibit 2015
Page #1011

Espacenet

Bibliographic data: WO0205059 (A2) — 2002-01-17

MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS

Inventor(s): CORK WILLIAM H [US]; ULMES JAMES J [US]; WEST RICHARD L [US]; LO YING-CHEN [US]; WEBER MARK C [US]; MIN KYUNGYOON [KR] ± (CORK, WILLIAM H, ; ULMES, JAMES, J, ; WEST, RICHARD, L, ; LO, YING-CHEN, ; WEBER, MARK, C, ; MIN, KYUNGYOON)

Applicant(s): BAXTER INT [US]; CORK WILLIAM H [US]; ULMES JAMES J [US]; WEST RICHARD L [US]; LO YING CHEN [US]; WEBER MARK C [US]; MIN KYUNGYOON [KR] ± (BAXTER INTERNATIONAL INC, ; CORK, WILLIAM H, ; ULMES, JAMES, J, ; WEST, RICHARD, L, ; LO, YING-CHEN, ; WEBER, MARK, C, ; MIN, KYUNGYOON)

Classification: - international: ***A61B5/00; A61B5/145; A61M1/36; A61M1/38; A61M37/00; B01D17/00; B01D37/00; B01D61/00; B01D61/22; B01L99/00; C02F1/00; C12M1/34; G01N33/48; G01N33/49; G01N33/50; G01N35/08; G06F1/00;*** *A61B19/02; A61M1/02; G01N35/00;* ***G06F;*** (IPC1-7): G06F

- cooperative: **A61B5/14546; A61B5/14557; A61B5/417; A61B50/13; A61M1/3609; A61M1/367; A61M1/3696; A61M1/38; B01D61/22; G01N33/491; G01N33/5005; G01N33/5094; G01N35/08;** A61B2562/028; A61M1/0209; A61M2205/12; A61M2205/33; A61M2205/52; A61M2230/20; G01N2035/00237; Y10T436/117497

Application number: WO2001US21188 20010703 Global Dossier

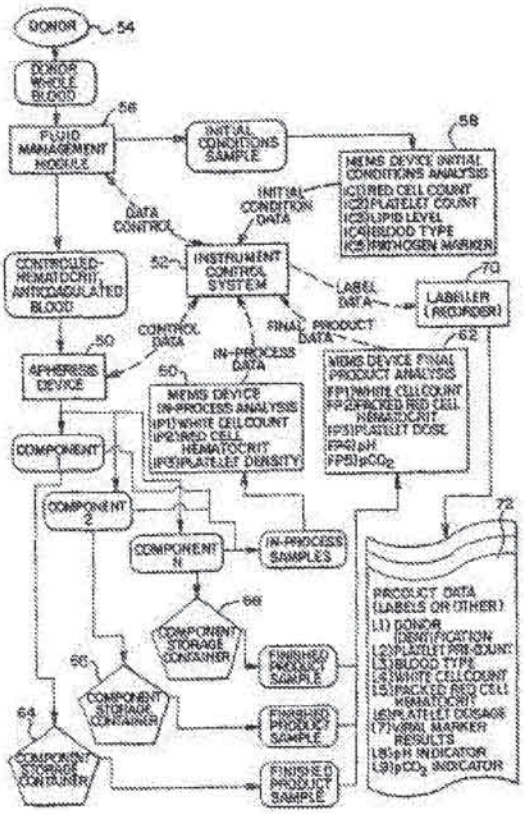
Priority number(s): US20000216640P 20000707

Also published as: WO0205059 (A3) AU7181001 (A) AU777087 (B2) BR0106942 (A) CA2382371 (A1) more

Abstract of WO0205059 (A2)

Haemonetics Corporation
Exhibit 2015
Page #1012

A biological suspension processing system is disclosed that may include a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path for introducing a suspension into the treatment device and a second fluid flow path for withdrawing a constituent of the suspension from the device. At least on microelectromechanical (MEM) sensor communicates with one of the fluid flow paths for sensing a selectedcharacteristic of the fluid therewith. The MEM sensor may be located elsewhere, such as on a container or bag and communicate with the interior for sensing a characteristic of the fluid contained therein. A wide variety of characteristics may be sensed, such as flow rate, pH, cell type, cell antigenicity, DNA, viral or bacterial presence, cholesterol, hematocrit, cell concentration, cell count, partial pressure, pathogen presence, or viscosity.



Haemonetics Corporation
Exhibit 2015
Page #1013

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/05059 A2

(51) International Patent Classification[7]: G06F

(21) International Application Number: PCT/US01/21188

(22) International Filing Date: 3 July 2001 (03.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/216,640 7 July 2000 (07.07.2000) US

(71) Applicant *(for all designated States except US)*: **BAXTER INTERNATIONAL INC.** [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CORK, William H.** [US/US]; ** (**). **ULMES, James, J.** [US/US]; ** (**). **WEST, Richard, L.** [US/US]; 37162 North Lake Shore Drive, Lake Villa, IL 60046 (US). **LO, Ying-Chen** [US/US]; 225 Fox Run Road, Green Oaks, IL 60048 (US). **WEBER, Mark, C.** [US/US]; 800 Birch Street, Algonquin, IL 60102 (US). **MIN, Kyungyoon** [KR/KR]; 7267 Clem Drive, Gurnee, IL 60031 (US).

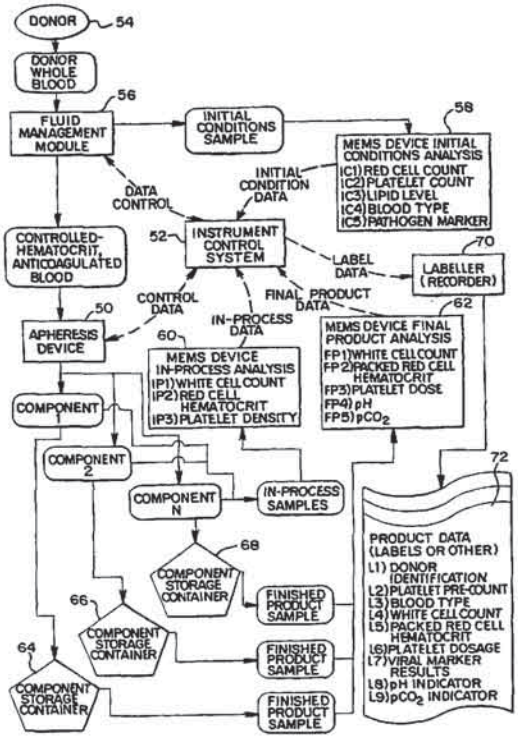
(74) Agents: **PRICE, Bradford, R., L.**; Baxter Healthcare Corporation, Route 120 and Wilson Road, Round Lake, IL 60073 et al. (US).

(81) Designated States *(national)*: AU, BR, CA, CH, CN, DE, ES, GB, IN, JP, MX, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

[Continued on next page]

(54) Title: MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS



(57) Abstract: A biological suspension processing system is disclosed that may include a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path for introducing a suspension into the treatment device and a second fluid flow path for withdrawing a constituent of the suspension from the device. At least on micro-electromechanical (MEM) sensor communicates with one of the fluid flow paths for sensing a selectedcharacteristic of the fluid therewith. The MEM sensor may be located elsewhere, such as on a container or bag and communicate with the interior for sensing a characteristic of the fluid contained therein. A wide variety of characteristics may be sensed, such as flow rate, pH, cell type, cell antigenicity, DNA, viral or bacterial presence, cholesterol, hematocrit, cell concentration, cell count, partial pressure, pathogen presence, or viscosity.

WO 02/05059 A2

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MEDICAL SYSTEM, METHOD AND APPARATUS EMPLOYING MEMS

William H. Cork
James J. Ulmes
Richard L. West
Ying-Cheng Lo, Ph.D.
Mark C. Weber
Kyungyoon Min

The present invention relates generally to medical systems, methods and apparatus for processing biological suspensions including, but not limited to, blood. More specifically, the present invention relates to novel medical systems, methods and apparatus (for processing biological suspensions) that employ microelectromechanical systems ("MEMS") as sensors, detectors or other elements for improving product quality, purity, consistency, characterization, and/or production.

The present invention is described below in connection with the processing of blood and blood components, a field in which it is expected to find substantial application and benefit. However, it should be understood that the present invention is not limited to blood or blood component processing and may be employed in connection with the processing of other biological suspensions, for example, bone marrow or cell growth media.

The processing of blood and blood components has taken on increased significance in recent years due to

the increased demand for blood and blood components for therapeutic application. Blood is a suspension of cells or cell fragments that are suspended in a liquid. The cells include red cells, for carrying oxygen from the lungs to the muscles and returning carbon dioxide from the muscles to the lungs, white cells, for fighting infection, and platelets, for clotting. The cells are suspended in a liquid called plasma, and the plasma itself has constituents that can be separated through a process called fractionation. For purposes of this description, blood "component" and blood "constituent" are used interchangeably.

Red cells are typically needed by patients suffering from significant blood loss. Platelets are required by many patients undergoing chemotherapy or radiation treatment, which reduces the ability of the body to make new bloods cells (and platelets are among the shortest-lived blood cell). Plasma may be administered to patients for a variety of reasons, or may be subjected to further fractionation to isolate and concentrate certain blood proteins.

As the demand for blood components has increased, it has become routine to separate collected blood into its constituent parts so that only the required constituent is given to the patient, and the other components or constituents remain available for other patients, or are returned to the donor. A term commonly used for separation of blood into one or more constituents is "apheresis." Apheresis may be done manually, after whole

blood is collected, or it may be carried out in an automated or semi-automated procedure.

Automated apheresis typically employs a reusable device or instrument and a disposable, single use tubing set through which the blood flows for processing. The collected constituent, such as platelets, red cells or plasma, is typically withdrawn and directed to a storage container, or collected within a container inside the device, and the other blood constituents are either returned to the donor or separately withdrawn and stored for other uses. A variety of devices, based on different principles, have been used in automated apheresis. The most common devices are based on centrifugation principles, and separate the blood components based on their different densities. The CS-3000® and Amicus separators by Baxter Healthcare Corporation of Deerfield, Illinois, and the Trima® and Spectra® separators by Gambro BCT of Lakewood, Colorado, are examples of centrifugal blood separators or apheresis devices. The Autopheresis-C separator by Baxter Healthcare Corporation is another type of apheresis device. It operates on a principle of membrane separation using Taylor vortices, which is much different than the above-identified centrifugation devices. The present invention is not limited to a particular treatment device or principle of operation, and may be of significant benefit in any of these and other blood or suspension treatment devices.

In addition to collection of blood constituents from healthy donors, the same equipment and processes may be used therapeutically, to treat ill patients. For

example, when it is believed that a patient may benefit by depleting the amount of white cells or by removing plasma, the same equipment used with donors may be used to collect those constituents from patients, returning the remainder of the blood to the patient. Blood processing as a therapeutic procedure for a wide variety of conditions has also grown in recent years.

Although blood constituent collection or depletion has been performed for many years, and advances have been made, there remain significant areas where further improvements are needed. One area where there is significant need for improvement is in reducing the potential for human error in the collection and testing of blood components. In a normal platelet collection procedure, for example, a number of tests are conducted on the blood withdrawn from the donor and on the platelet concentrate that is collected. For example, an incoming blood sample may be withdrawn from the tubing set and sent to a laboratory for testing regarding platelet count, the presence of pathogens, blood type, and a variety of other tests.

A sample of the collected blood constituent may also be subjected to similar tests. For platelets, for example, the amount of collected platelets is a particularly important number, because a certain amount of platelets (4×10^{11}) is usually necessary to constitute a standard "dose" or "unit" of platelets. In addition to determining the number (or, alternatively, the density) of platelets collected, the collected platelet product also may be tested for the presence of white cells, which

are a suggested source of adverse reactions in some patients.

Many of these tests either are not conducted at the same place the blood component is collected or require 24-48 hours to complete. Great care must be taken, and numerous administrative steps completed, to assure that the sample is properly traceable to the collected blood product, and that the laboratory results are properly recorded in connection with the particular blood product collected. Notwithstanding such care, because of the number of individuals and steps involved, the risk of human error in this process is real, even if small. Accordingly there is a continuing need for advances that reduce the amount of human handling and intervention required, and thus the potential for error as well as the cost associated with collecting and testing blood constituents. More specifically, there is a need for collection or treatment systems that provide a product, such as blood platelets, red cells or plasma, which is fully or partially characterized, such as by cell count, pathogen presence, white cell count, blood type, et cetera, with minimum human intervention and with minimum need for testing procedures that separate the testing from the treatment process itself and thereby introduce opportunity for human error.

Because the demand for blood components is not constant, it also is not unusual for certain blood constituents to be wasted due to outdating before they are used. Although red cells, which may be refrigerated and stored for lengthier periods of time, blood platelets

are normally stored at room temperature, and have a limited shelf life of about 5-7 days under the best of circumstances. Both, however, have limited shelf life, and, as a result, it is not uncommon for a significant amount of collected blood constituent product to be wasted because it is not used within the allowed shelf life period. Thus, in light of the limited donor pool that is available to contribute platelets and other blood components, there is a need for better efficiencies in collecting and using blood components.

In addition to the above, there is a continuing need for devices that make the collection process itself more efficient. For example, the hematocrit and platelet count of a donor may be of significant value in tailoring or optimizing the collection procedure to obtain the desired amount of the collected product, in the desired amount of time, with the desired amount of purity or freedom from undesirable components, and with minimum adverse effects to the donor or patient. Although the donor's hematocrit may be measured reasonably easily prior to a collection procedure, platelet count is an expensive and time consuming procedure, and typically is not done prior to the procedure. In most platelet collection procedures, the best available information is an estimated platelet count, based on an average of prior donations, which can vary widely. Accordingly, there is a need for more current information that can be used to optimize the collection procedure.

In summary, there is a continuing need for improvement in providing blood constituents regarding (1)

the consistency of the collected product, for example in terms of the yield or amount of constituent collected and available for transfusion or the quality (e.g., viability) of the blood constituent collected, (2) the purity of the collected product, for example the absence of undesirable contaminants and better assurance of completion of all the necessary testing with reduced chance of human error, (3) the efficiency of collection and usage of collected blood constituent, (4) the cost and error potential in the collection and associated testing and administrative burden and (5) the safety afforded to the donor.

Within the past decade significant progress has also been made in the field of microelectromechanical systems (MEMS). MEMS is a class of systems that are physically very, very small. These systems typically, but not exclusively, have both electrical and mechanical or optical components. Modified integrated circuit fabrication techniques and materials were originally used to create these very small devices or systems, but currently many more fabrication techniques and materials are available.

MEMS devices have been conceived for a variety of sensing and actuating functions. MEMS devices have been conceived for typing blood, counting cells, identifying DNA, performing chemical assays, measuring pH, sensing partial pressures, and performing a wide variety of other procedures and tests. Recently, various manufacturers have even claimed to have developed a "lab on a chip" that is suitable for carrying out a variety of blood or

blood constituent assays or tests. However, progress in integrating MEMS devices into pre-existing medical procedures to enhance performance and reduce potential for human error has been limited.

SUMMARY

To achieve one or more of the above objectives, the present invention employs a MEMS sensor in a system for processing a biological suspension, for example blood, in a treatment device, wherein the MEMS sensor is employed to sense one or more fluid characteristics of fluid flowing into or from the treatment device. More specifically, the present invention may be embodied in a biological suspension processing system comprising a suspension treatment device for treating one or more components of a biological suspension, a first fluid flow path communicating with the treatment device for introducing a suspension into the treatment device, and a second fluid flow path communicating with the treatment device for withdrawing a constituent of the suspension from the treatment device. In accordance with the present invention, at least one microelectromechanical (MEMS) sensor communicates with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path. The treatment device may be an apheresis device for separating and collecting one or more blood constituents, but in its broader aspects, the present invention is not necessarily limited to a particular suspension treatment device or to a particular apheresis device or separator.

Turning back to aspects of the present invention, the MEMS sensor may be operable to sense a characteristic such as, for example, one of those selected from the group consisting of flow rate, pH, cell type, cell antigenicity, cell concentration, cell count, viscosity, cholesterol, hematocrit, DNA, viral or bacterial presence, pathogen presence, and/or partial pressure of a selected gas or other characteristics.

To aid in control of the system, the sensor may communicate with the first fluid flow path and generate a signal responsive to one or more selected characteristics of the fluid (e.g. platelet count) in the first fluid flow path. The suspension treatment device may include a controller adapted to receive the sensor signal and to control the treatment device in response to the signal. This system could be used, for example, to optimize the treatment procedure time, to provide a more consistent product, to provide a product that has a certain minimum quantity of suspension constituent, or to better safeguard patient affects. A sensor may also communicate with the second fluid flow path, which conducts the fluid being withdrawn from the treatment device, for example to count desired or non-desired components, such as platelets or white cells, or for other desired purposes.

For even better control the system may include sensor adapted to sense a selected characteristic a plurality of times at discrete intervals. This sensor may generate a signal each time it senses the characteristic, and the suspension treatment device may

include a controller that is adapted to receive the sensor signal and to control the treatment device in response thereto. Thus, periodic sensing may be used to better optimize or improve the treatment procedure over all or part of the treatment procedure. For example, the sensor may communicate with the second fluid flow path and sense the approximate quantity or concentration of a selected cell, with the controller controlling the system to collect a desired quantity of the selected cell, or alternatively, to reduce the collected amount of the selected cell.

The system may further comprise a container communicating with the second fluid flow path for receiving the withdrawn constituent, with the system being adapted to provide tracking information for associating with the container the particular characteristic sensed by at least one sensor. A machine readable or human readable data storage media may be carried by the container to store information regarding the particular characteristics sensed by at least one sensor. The data storage media is not limited to a particular type, and may comprises a graphic indicator such as a bar code label on the container, an electronic data storage device, such as one with a non-volatile semiconductor memory, or an icon or other graphic carried by the container representative of the sensed characteristic. This tracking may be entirely carried out by the system, thereby reducing the possibility of human error in mishandling of the sample or information.

When the suspension includes one or more blood components and the blood component withdrawn is a cellular component, the system may include a container for storing the cellular component withdrawn, and the data storage media may include data regarding, for example, the type, quality, purity, quantity and/or concentration of the cellular component in the container. More specifically, the system may include a first sensor communicating with the first fluid flow path and a second sensor communicating with the second flow path and the treatment device may comprise an apheresis device. When the suspension comprises whole blood, the first sensor may sense inter alia, platelets to determine a platelet count in the suspension introduced into the apheresis device and the second sensor may sense inter alia, platelets withdrawn to determine a platelet count in the second flow path. A container communicating with the second flow path may be provided to store the blood platelets withdrawn, and the system may further comprises machine readable or human readable data storage media carried by the container for storing information regarding platelet count sensed by one or both of said sensors. To reduce the number of human interventions required, the system may itself include a data recording device for receiving a signal from one or more of the sensors and recording the data regarding the sensed characteristic. The data recording device may be a printer for printing a human or machine readable report of the characteristic sensed, such as directly on the container or on a label affixed to the container.

Alternatively, the container may carry a machine readable electronic data storage device, and the data recording device be adapted to transfer data regarding the selected characteristic sensed by the sensor to the electronic data storage device. An electronic data storage device may preferably comprise a non-volatile semiconductor memory, or "write once, reads many times" memory so that the data is not inadvertently lost or destroyed by power loss. In other words, a memory or processing chip may be added to the blood constituent storage container, such as permanently mounted in the tail flap of the container, with a non-volatile memory, for receiving and storing data for later access by the appropriate electronic reading instrument.

The blood component storage container also may include a microelectromechanical sensor carried by the container and communicating with the container compartment for sensing a selected characteristic, for example just before administration to a patient, of the blood component received or stored therein. Such a sensor similarly may include a non-volatile semiconductor memory or so-called "write once, read many times" data storage.

In accordance with another aspect, the present invention may be directed to a blood processing system for providing a characterized blood constituent product in which the system comprises: an apheresis device for separating one or more desired cellular blood constituents from a suspension comprising whole blood, a first fluid flow path communicating with the apheresis

device for introducing a suspension comprising whole blood into the device, a second fluid flow path communicating with the apheresis device for withdrawing at least one desired cellular blood constituent from the device, a container communicating with the second fluid flow path for receiving the blood constituent withdrawn from the apheresis device, machine readable or human readable data storage media carried by the container, at least one microelectromechanical sensor communicating with the first fluid flow path for sensing at least one characteristic of the whole blood and for generating at least one electrical signal responsive to such sensing, at least one microelectromechanical sensor communicating with the second flow path for sensing the quantity of cellular blood constituent withdrawn from the apheresis device and for generating an electrical signal responsive to such sensing, a data recorder adapted to receive the electrical signals from the sensors and to record data regarding the sensed characteristics on the data storage media, whereby a user may readily identify the sensed characteristic regarding the whole blood and the quantity of the desired cellular constituent in the container with a minimum of human intervention.

This system may further include a sensor communicating with the second fluid flow path for sensing the quantity of a non-desired biologic constituent in the flow path and generating an electrical signal responsive to the quantity, the data recorder being adapted to receive such signal and record data regarding the quantity of non-desired cellular constituent in the data

storage media for access by a user of the product in the container. The non-desired biologic component may be a viral constituent, or a cellular constituent, such as white cells.

As before, the system may include a controller adapted to receive the signals from the sensors communicating with the first and second fluid flow paths and to control the apheresis device in response to one or more of such signals to provide a desired cellular blood constituent product characterized by data recorded in the data storage media in accordance with characteristics sensed by the sensors. The data storage media may comprise machine readable graphics carried on the container, for example, a bar code. The system may also, when withdrawing blood from a donor or patient, for example, generate a human-readable report for the donor or patient containing selected data regarding one or more of the sensed characteristics.

In accordance with another aspect of the present invention, a biological suspension processing system may be provided which includes: a blood treatment device for treating one or more components of a biological suspension, a human subject, a first fluid flow path communicating with the vascular system of the human subject and the treatment device for introducing blood from the human subject into the treatment device, a second fluid flow path communicating with the treatment device for withdrawing a constituent of the blood from the treatment device, a third fluid flow path communicating with the treatment device from withdrawing

another constituent of the blood from the treatment device, and at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

The sensor may generate a signal responsive to one or more selected characteristic of the fluid in one of the fluid flow path, with the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto. In the situation where the third fluid flow path communicates with the human subject, and the treatment device is adapted to add anticoagulant to the blood in the first fluid flow path, the selected characteristic may include the hematocrit of blood in the first fluid flow path. In that setting, the controller may control the addition of anticoagulant into the first fluid flow path to prevent too much anticoagulant from being returned to the donor or patient, because, as is well known excess anticoagulant flow to the donor or patient may have deleterious consequences.

The signal from the sensor and the control of the treatment device is not limited, however, to the safety of the human subject. The controller may, for example, in response to the signal control the treatment device to withdraw a constituent of desired quality, to withdraw a constituent of desired quantity, to withdraw a constituent that is depleted of an undesired component, or to withdraw a selected minimum quantity of constituents, such as platelets, red cells or plasma, or

to withdraw a certain amount of constituent in a maximum or minimum procedure time.

In a more specific embodiment of the present invention, the MEMS sensor(s) or other MEMS devices are located on a common disposable carrier or cassette. The carrier includes internally defined fluid flow passageways that may be selectively opened or closed by macro or MEMS scale valves to control flow of fluid to the sensors in response to control signals from the device controller. The carrier is preferably adapted to interfit with a reusable reader/controller which cooperates with the MEMS devices located in the cassette to provide a signal responsive to the sensed characteristic, which signal may be used to optimize the treatment procedure or to identify the sensed characteristic for later association with or labeling of the collected blood product, or to control the flow of fluid through the cassette.

Although the carrier may take several different forms, in one form of a cassette, it is comprised of a rigid plastic base that mounts a plurality of MEMS sensors or other MEMS devices such as valves or pumps, and has preformed passageways defined in the base with fluid flow control valve modules located to control the flow of selected fluid to the desired MEMS sensor. The cassette may include preformed open passageways that are closed by a resilient membrane which overlies one side of the cassette and is sealed to the passageway walls (either temporarily by pressure exerted by the reader or permanently by solvent or sonic bonding) to close the

passageways. The membrane may cooperate, such as by mechanical or pneumatic actuation, with the valve modules to control the flow of fluid through passageways in the MEMS cassette.

The present invention is not limited to a particular type of MEMS sensor or to a particular principle of operation. The MEMS devices useful in the present invention may be static or dynamic, purely mechanical, biomechanical or electro-mechanical. They may also include optical components, and they may be dry or used in combination with liquid reagents or other liquids.

One type of MEMS sensor that holds promise for apheresis procedures is a microcytometer in which particles, for example cells, or cell fragments, are fed through a narrow, microfluidic channel in single file. Other MEMS sensors may be based, for example, on centrifugal microfluidics analysis employing a rotating compact disc that employs, for example, a micro-fluidics manifold and spectrophotometric cuvette formed on the surface of the disc, which may be read by an optical disc reader.

Because certain MEMS devices may require special or separate sterilization procedures as compared to other MEMS devices, the present invention also contemplates that there may be more than one MEMS carrier or cassette. For example, MEMS employing reagents may require a different sterilization technique, such as ethylene oxide sterilization, as compared to purely mechanical or electro/mechanical, optical/mechanical or optical/electrical MEMS devices, which may be suitable

for radiation or heat sterilization. There may also be other reasons for having more than one MEMS cassette, including ease of manufacturing, ease of mounting or assembly on the treatment device, and the like. In such case, the MEMS cassette may be attached to the remainder of the fluid circuit after sterilization, as by sterile docking or other sterile connection procedure.

Fluid may be pumped through the MEMS cassette by the peristaltic pumps that are typically employed on apheresis devices for moving blood and blood components through the tubing set or, alternatively, the MEMS cassette itself may include macro and/or MEMS-scale pumps for circulating fluid through the MEMS cassette and to the desired MEMS sensor. Similarly, liquid flow through the cassette may be controlled by MEMS scale valves, or by macro scale valves such as those employed in the fluid flow control modules of the Amicus apheresis centrifuge marketed by Baxter Healthcare.

Additional aspects and features of the present invention are set forth in the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is schematic flow chart of a suspension treatment system embodying the present invention.

Figure 2 is a software/data flow chart for a control and data flow system that may be employed in the present invention.

Figure 3 is a perspective view of a reusable suspension treatment device, specifically an apheresis device, embodying the present invention.

Figure 4 is an enlarged perspective view of a portion of the device of Figure 3, showing the reader/controller for a MEMS cassette or carrier.

Figure 5 is a plan schematic of a disposable fluid circuit, including a MEMS cassette or carrier, for use with the device of Figure 3 and employing the present invention.

Figure 6 is an exploded perspective view of a MEMS cassette or carrier that may be used in the disposable fluid circuit of Figure 5, embodying the present invention.

Figure 7a is a top view of the assembled MEMS cassette of Figure 6.

Figure 7b is a side view of the MEMS cassette of Figure 7a.

Figure 8 is a perspective view of the reader/controller for the MEMS cassette.

Figure 9 is an enlarged perspective view of the device of Figure 3, embodying an alternative MEMS cassette reader/controller.

Figure 10 is an exploded perspective view of a MEMS cassette that may be used with the reader/controller shown in Figure 9.

Figure 11 is a rear perspective view of the assembled MEMS cassette of Figure 10, illustrating macro-scale valve modules for fluid flow control.

Figure 12 is an enlarged perspective view showing the interfit between the MEMS cassette of Figure 10 and the reader/controller of Figure 9.

Haemonetics Corporation
Exhibit 2015
Page #1034

Figure 13 is a schematic view of MEMS microcytometer that may be used in the present invention.

Figure 14 is a view of the microcytometer of Figure 13, illustrating the focusing of blood cells using sheath flow.

Figures 15a and 15b are cross-section views of a bistable valve that may be used in the MEMS cassette of the present invention.

Figure 16 is a top plan view of an alternative MEMS cassette embodying the present invention, which includes fluid pumping chambers for pumping fluid through the cassette.

Figure 17a is a plan view of a compact disc employing a microfluidic manifold and a spectrophotometric cuvette.

Figure 17b is an elevational view of a reader for the compact disc of Figure 17a.

Figure 18a is a plan view of a blood component storage container having a MEMS sensor mounted in or carried on the container wall for accessing the contents.

Figure 18b is a plan view of the container of Figure 18a with a reader for reading the MEMS sensor.

DETAILED DESCRIPTION OF DRAWINGS

Turning now to a more detailed description of the drawings, Figure 1 is a flow chart illustrating a treatment system embodying the present invention. Although the flow chart in Figure 1 is in the context of a blood apheresis system, the flow chart and the steps indicated therein have application to other suspension treatment systems as well.

Before describing the treatment system in more detail, it should be understood that the flow chart is intended to reflect general system features and functions, and not necessarily the system structure. For example, it should be understood that features shown in a single box or grouping of the flow chart may represent what are actually two or more physical modules or structures in the actual product, and more than one box or grouping in the flow chart may be a single physical module or structure in the final product. The purpose of the flow chart is simply to illustrate one embodiment of an overall system and function, and not to limit the actual physical structure.

As applied to apheresis, the system in Figure 1 includes an apheresis device 50, such as a centrifuge, spinning membrane separator or other apheresis device or instrument, and an instrument or device control system 52. The control system 52, which may comprise a programmable microprocessor, performs a variety of control and monitoring functions for carrying out an apheresis procedure. It receives and sends data regarding various initial, in-process and final product characteristics, it controls the fluid flow through the system, it controls the operation of the apheresis device and it tracks and stores data for labeling the final product or for communicating with data storage media associated with the container in which product is collected during the apheresis procedure.

In the system shown in Figure 1, whole blood is collected from a donor 54, such as a healthy adult human.

The flow of blood (and other liquids such as priming solution and anticoagulant) through the system is controlled by a fluid management module 56. In accordance with the present invention, one or more characteristics of the blood flowing into the system may be sensed by one or more MEMS sensors. For example, an initial sample of the whole blood, before processing, may brought into contact with one or more initial condition MEMS sensors 58 for sensing or measuring red cell count, platelet count, lipid level, blood type or markers representative of pathogen (viral or bacteria) presence. As used here, "sensor" or "sensing" is used broadly and includes detecting, measuring, monitoring, analyzing, characterizing, sampling and any other tests or analysis that may be desired.

Data from the initial conditional sampling, typically in the form of an electrical signal, may be fed back to the control system 52 for purposes, for example, of controlling the fluid management module or the apheresis separation process or for tracking or storing information relating to the sensed characteristic for later association with the collected product. For example, data as to blood type may be saved for recording on a machine readable or human readable data storage media carried by the container for the collected product, such as a descriptive label, bar code or electronic memory device. Data regarding initial platelet count may be used, for example, to optimize the apheresis procedure to minimize procedure time, to maximize the amount of

platelets collected or to better assure collection of a certain minimum number of platelets.

The anticoagulated whole blood is directed by the fluid management module to the apheresis device or instrument 50. There, the blood is separated into one or more components, such as components nos. 1, 2 and up to "n" components. During the apheresis procedure, in-process data may be sensed by one or more of the in-process condition MEMS sensors 60, for detecting characteristics such as white cell count, red cell hematocrit and platelet density. Data from the in-process condition MEMS sensor(s) may be fed back to the control system 52, typically for controlling the apheresis process and/or fluid flow. The in-process condition MEMS sensor may sample fluid one or more times during the procedure, as desired. To provide periodic adjustment of the apheresis device or fluid flow throughout the apheresis procedure, a plurality of MEMS sensors may be employed in the in-process sensing. These MEMS sensors may be activated by the control system to sense one or more selected characteristic at selected time intervals throughout the procedure or upon occurrence of certain triggering events, such as power outage, red cell spill over or other event.

The separated blood components not returned to the donor are directed to storage containers 64, 66 and 68, respectively. It is not necessary, of course, for the storage containers to be outside of the apheresis device. In the Baxter CS-3000® and Amicus® centrifuges, for example, blood components may be collected in containers

that reside inside the rotating centrifuge until the apheresis procedure is completed.

As one or more components are collected, one or more characteristics of the final collected product may be sensed by the MEMS final product condition sensor(s) 62 and data relayed back to the controller 52. The final product condition MEMS sensor 62 may be provided to sense one or more characteristics of the collected product, such as white cell count, packed red cell hematocrit, platelet dose, pH, or gas (e.g., CO_2) partial pressure. The final product condition MEMS may feed data back to the control system 52 for optimizing the apheresis procedure, controlling fluid flow and/or storing/tracking data for association with the final collected product.

One of the benefits of certain aspects of the present invention is the providing of a final product that is fully or partially characterized according to the initial condition, in-process and/or final product condition MEMS sensors, with the characteristics sensed being tracked or stored for association with the final product container, all occurring with reduced human intervention and opportunity for error. For example, having received data from the various MEMS condition sensors 58, 60 and 62, the instrument control system 52 may relay that data to a recorder or labeler 70, which records the data onto data storage media 72 carried by the storage container. The data or storage media may be human readable, or machine readable (e.g., graphic or bar code), or a combination of both or other form. The recorder may, for example, print a label for attachment

to the container, or transfer the data to a machine readable electronic storage device, such as a memory chip, carried by the container. The result is a blood component product characterized as needed, with reduced need for human intervention or opportunity for human error.

Figure 2 is an outline of certain aspects of a programmable operation control system. As shown there, the procedure process master control module 74 may instruct (shown by dashed lines) various elements of the system to perform certain functions, and receive (shown by solid lines) data from one or more of those elements. For example, the master control may direct the sample pre-measurement module 76 to carry out certain initial condition sensing. This may be carried out by opening a macro or MEMS-scale valve that directs incoming whole blood into contact with the desired initial condition MEMS sensor 58. The information or data regarding the sensed characteristic is then relayed back through the pre-measurement module to the master control module for storage or for later association with the collected blood product.

Similar steps may be carried out as between the master control module 74 and the in-process module 78 and in-process MEMS sensor(s) 60, and as between the master control module and the final product configuration module 80 and final product condition sensor(s) 62.

Information from the various MEMS sensors may then be relayed to the recorder/labeler 70 for associating the data with the final product container. In one simple

form, this may be by way of printing a label for attachment to the container or for printing the desired information on a pre-attached label, although the present invention also contemplates that data could be transferred optically or electrically to an electronic data storage device (such as a non-volatile memory chip or "write once, read many times" storage device) attached to the final product container. If the operator desires that only certain information be displayed with the product, the system permits less than all of the characteristics that are sensed to be displayed on or in connection with the collected product.

Figure 3 shows a biological suspension treatment device, and specifically an Amicus® apheresis instrument 82 of the general type made and sold by Baxter Healthcare Corporation of Deerfield, Illinois. The Amicus® separator is described in detail in U.S. Patent No. 5,462,416, which is incorporated by reference, and that description will not be repeated in full here.

Briefly, the Amicus® separator is based on centrifugation principles, and separates blood components by reason of their different densities. The Amicus® separator is intended to work with a disposable, one-time use plastic tubing set, which will be described later, through which blood and blood components flow during the apheresis procedure.

The Amicus® separator includes a base portion, generally at 84, a fluid management and sensor panel area 86, and a display screen and touch control panel 88. The machine base 84 contains the rotating centrifuge chamber

drive hardware and control electronics. The centrifuge chamber is accessible through a drop-down front door 90 for loading and removing the disposable tubing set.

The fluid management and sensor panel includes three pump and valve stations, each of which has a pair of peristaltic pumps 92 and adjacent flow control module 94 for pumping fluid through the system and controlling the direction of fluid flow. User information regarding the apheresis procedure is displayed on the display screen 88, which also includes touch input capability for operator entry of information or control commands prior to and during the apheresis procedure.

In accordance with a preferred version of the present invention, the MEMS sensors and other devices are mounted on a single MEMS carrier or cassette 96 (Figure 5), which is part of the disposable fluid circuit and intended for one-time use only. The apheresis instrument 82 (Figure 3) includes a MEMS cassette reader/controller 98 into which the MEMS cassette is mounted when the disposable fluid circuit is installed on the instrument. The reader/actuator 98 cooperates with the MEMS cassette for reading or transferring data from the MEMS sensors on the cassette and for controlling flow of fluid through the MEMS cassette and to the desired MEMS sensor or other MEMS device.

The MEMS cassette reader/controller shown in Figure 3, and shown in larger view in Figure 4, employs a base 100 adapted to receive the MEMS cassette and a door 102 pivotally mounted on the base for closing over the cassette to block out ambient light and cooperate with

optical, electronic or mechanical devices located in the base portion for reading or interpreting the MEMS sensors or other devices and/or for actuating valves or pumps located in the MEMS cassette.

Figure 5 is a schematic view of a disposable one-time-use processing assembly or fluid circuit 104 embodying the MEMS cassette/carrier 96 of the present invention for use on the apheresis instrument shown in Figure 3. A detailed description of the disposable fluid circuit may be found in U.S. Patent No. 5,462,416, which was previously incorporated by reference, and will not be repeated here.

The processing assembly 104 includes an array of flexible tubing that forms the fluid circuit through which blood and blood components flow. The fluid circuit conveys liquid to and from a processing chamber 106 that is mounted in the rotating centrifuge chamber during use. The fluid circuit includes a number of containers 110a-f that fit on hangers on the centrifuge assembly to dispense and receive liquids during the apheresis process.

The fluid circuit 104 also includes one or more in-line fluid control cassettes 112, which are not to be confused with the MEMS cassette (although the fluid control cassettes could also include MEMS sensors or other MEMS devices and thus incorporate features of the present invention, if desired). Figure 5 shows three such cassettes designated 112a , 112b and 112c. The cassettes serve in association with the pump and valve stations on the centrifuge assembly to direct liquid flow

among the multiple liquid sources and destinations. During a blood processing procedure the cassettes centralize the valving and pumping functions to carry out the selected procedure. Further details of these functions are described in the above mentioned U.S. Patent No. 4,562,416.

A portion of the fluid circuit 108 leading between the cassettes 112a-c and the processing chamber 106 is bundled together to form an umbilicus 114. The umbilicus links the rotating parts of the processing assembly (principally the fluid management processing chamber) with the non-rotating, stationary parts of the processing assembly (principally the cassettes and containers and fluid circuit tubing and MEMS carrier or cassette). The umbilicus links the rotating and stationary parts of the processing assembly without using rotating seals, by employing the well known one-omega two-omega principle, which has long been successfully used in the CS-3000® centrifuge marketed by Baxter Healthcare Corporation.

In the illustrated and preferred embodiment, the fluid circuit 104 pre-connects the processing chamber 106, the containers 110, the fluid control cassettes 112 and the MEMS carrier/cassette 96. The assembly thereby preferably forms an integral pre-assembled sterile unit, although it is recognized that if separate sterilization is required for the MEMS cassette, it may require subsequent attachment, such as by sterile connection procedure, to the remainder of the fluid circuit.

During a typical dual needle platelet collection procedure, whole blood is drawn into an inlet needle 116

and combined at a junction 118 with anticoagulant such as ACD, which is pumped from the ACD container 110d, through fluid control cassette 112a and from there into the separation/processing chamber 106. In the separation chamber, platelet rich plasma is separated from packed red cells, and each is withdrawn from the separation chamber. The platelet rich plasma is withdrawn through the umbilicus 114 upwardly through cassette 112c and then, after passing through an optical sensor 120, returned to a collection chamber in the centrifuge. There, platelet concentrate is separated from the platelet rich plasma, and platelet-depleted or platelet-poor plasma is withdrawn from the collection chamber and collected in a platelet-poor plasma storage container 110c and/or returned to the donor, with red cells through fluid control cassette 112a and return needle 117. Although illustrated as a dual needle set, the present invention is equally applicable for a single needle fluid circuit of the type also previously sold by Baxter Healthcare Corporation for use on the Amicus® centrifuge.

In accordance with the present invention, as illustrated in Figure 5, the fluid circuit 104 includes at least one MEMS cassette or carrier 96. As shown in Figure 5 for purposes of illustration and not limitation, the MEMS cassette 96 is shown having five fluid connections. The number of connections, however, depends on the fluid characteristics to be sensed, and fewer fluid connections may suffice for many blood-related applications, as will be discussed later.

As illustrated in Figure 5, the MEMS cassette 98 has a fluid inlet 120 connected to the packed red cell line. Fluid in this line may be monitored by MEMS sensors to determine the packed red cell hematocrit for the purpose, for example, of optimizing the separation procedure.

MEMS cassette fluid inlet 122 is connected to the whole blood inlet line. Fluid from this line may be sensed by MEMS sensors, for example, to determine any of the initial condition data such as red cell count, platelet count, lipid level, blood type or the presence of a pathogen (viral or bacteria) indicator or marker.

The next fluid entry inlet line 124, is shown communicating to the platelet rich plasma line. This may be used to perform in-process analysis of white cell count, red cell hematocrit, platelet density and the like.

Fluid connection 126 is connected to the platelet-depleted plasma line. MEMS sensors associated with this connection may be used to sense any of the desired final product characteristics of the plasma. Similarly, fluid connection 128 is attached to the platelet concentrate collection tubing for MEMS sensing of one or more of the final characteristics of the platelet concentrate, such as platelet dose or density, white cell count, platelet size, and the like.

A MEMS cassette or carrier 98 as presently contemplated is depicted in greater detail in Figure 6. As shown there, the cassette includes a rigid MEMS holder or support 130, a plurality of MEMS sensors or other MEMS devices 132, front cover 134 and membrane backing 136.

The holder or support 130 is preferably made of rigid plastic or other suitable material. A plurality of passageways 138 for fluid flow are provided in the MEMS holder, for communicating the desired fluid to the desired MEMS sensor or other device. As illustrated in Figure 6, three such fluid passageways 138 are shown for initial condition, in-process, and finished product characteristic sensing. The passageways are pre-formed into the MEMS holder, and communicate with three arrays of MEMS device-receiving areas 140, which are adapted to receive the desired MEMS sensors or other devices. The center fluid passageway communicates with two rows of MEMS device receiving areas that flank the passageway. The other two passageways communicate with a single row of MEMS devices. The size of the array and number of MEMS sensors or other devices may be varied as needed for a given treatment procedure to provide the desired sensing capability. For those MEMS sensors or other devices that require an electrical power source, the rigid holder may include a plurality of electrical contacts 142. Embedded or embossed electrical leads in the holder may extend between the contacts and the appropriate areas 140 for mounting MEMS sensors or other devices that require a voltage source.

The MEMS holder and MEMS sensors/devices are contained beneath the clear cover plate 134, which is sealed to the holder 130, as by adhesive, sonic or solvent bonding, to form the passageways 138. The clear cover allows for the transmission of light to or from associated optical light sources or receivers in the MEMS

cassette reader. The flexible membrane 196 attached to the underside of the MEMS holder allows for actuation of valves, pumps or other devices associated with the MEMS cassette, as described in more detail later.

Turning to Figure 7A, which is a plan view of the MEMS cassette or carrier 98, the initial condition analysis sample line 144 communicates with a first fluid passageway 138a in the MEMS cassette that communicates with a plurality of MEMS sensors for sensing viral or pathogen markers (e.g., a DNA analysis that may reveal the presence of an unwanted virus or bacteria), blood type, lipid level, platelet count and red cell count. The inlet to each MEMS sensors may be controlled by a valve 141, which may be macro-scale valve that controls flow of the initial fluid to the MEMS sensor or by MEMS-scale valves, which are available from a variety of sources using various principles, such as surface tension, flexing membranes or the like. It is contemplated that the initial condition line would communicate, in an apheresis procedure, with the whole blood inlet line. Additionally, although the passageways 138 are shown as having closed ends, the passageways may also continue through the cassette and return to the fluid circuit so that, for example, the sample lines are receiving a constant throughput of the fluid to be analyzed.

The next inlet line is the in-process analysis sample line 146, which communicates with the fluid flow passageway 138b in the MEMS cassette for sampling various characteristics of the fluid while the apheresis process

is carried out. For example, the in-process fluid may flow through the center passageway 138b to platelet density MEMS sensors, red cell MEMS sensors and MEMS sensors for counting the number of white cells. The in-process flow line may be attached to the platelet-rich plasma line, the packed red cell line or, if desired, with the processing chamber itself.

The final product analysis sample line 148 communicates with the third passageway 138c in the MEMS cassette for determining final product characteristics, such as partial pressure of CO_2, the pH, the platelet density, hematocrit or white cell count. It is anticipated that this final product sample line would be connected to the flow line communicating with the final product collection container, although other connection sites, such as the processing chamber itself, are within the scope of this invention.

Although the characteristics described above are these that may be determined in the platelet collection procedure, the user may select or the manufacturer may employ different MEMS sensors with different objectives or for sensing different characteristics, as desired.

As shown in Figure 8, in use, the MEMS cassette or carrier 96 is preferably mounted within a recessed area in the base 100 of the MEMS cassette reader/controller 98. For MEMS devices employing optical read-out, the base preferably includes an array of light emitting fibers or diodes 150 in registration with the appropriate MEMS devices, and the door 102 may include an array of light collectors or receivers 152 in registration with

the MEMS devices for the purpose of reading the optical transmission, reflection or refraction by the particular MEMS sensor. The base and/or door also include electrical contacts 153 for connecting with electrical contacts 142 of the cassette for MEMS needing an electrical voltage source. Therefore, it is apparent that the present invention is not limited to a particular type of MEMS sensor or device or to MEMS sensors or devices operating on a particular principle.

One example of a MEMS sensor for use in the present invention is illustrated in Figure 13. The MEMS sensor shown there is a MEMS microcytometer 149, and is believed to have particular promise for cell-related applications. As may be seen there, the microcytometer includes a light source 150 for emitting light, such as coherent laser light, at a single file stream of components, such as cells which may be received from the initial condition, in process or final condition flow lines. Light receivers 152 and 154, receive reflected and refracted light from the particles which, in turn, is used to count or characterize the cells flowing through the line, such as by cell type, cell density or number of cells. Fluorescence detection and light scattering can be used to count and characterize the cells. Such detection may also be combined with immunossays techniques to detect and characterize antibody coated beads and antibody-antigen complexes. This type of MEMS sensor has been previously described by, and may be available from Micronics, Inc., of Redmond, Washington.

As shown in Figure 14, the microcytometer 149 employs a micro-fluidic channel 151 in which fluid flowing in a sheath flow arrangement resulting from liquid flow from the intersecting flow channels 153 forms the cells into single file for analysis. Accordingly, it is within the concept of the present invention that the MEMS cassette may also include additional fluid channels 153, as appropriate, for receiving liquids or gases (such as saline, water, reagents, or other liquids or gases) that may be used in connection with the MEMS sensors.

Another MEMS device that may be suitable for application in the present invention is a MEMS sensor based on centrifugal microfluidics analysis. One or more small rotating compact discs may be mounted in the MEMS cassette, which disc may be read by an optical disc reader. The disc employs, for example, a micro-fluidics manifold and spectrophotometric cuvette formed on the surface of the disc. Figure 17 diagrammatically depicts such a device, which has been proposed by and may be available from Gamera Bioscience of Medford, Massachusetts.

Microfluidic mixing devices, capillary connectors employing microchannels, and membrane micro-valves available from TMP of Enscheda, Netherlands, and thin-walled compliant plastic structures, micro-fluidic circuits, silicone button pneumatic actuators and micro-valves as disclosed by Lawrence Livermore National Laboratory at the July 15-16, 1999 Knowledge Foundation conference on Novel Microfabrication Options for Biomems, in San Francisco, California, are but a few of other MEMS

devices that may be incorporated into the MEMS cassette of the present invention.

As noted earlier, the MEMS cassette may include macro-scale valves, for example, as used in the Baxter Amicus® separator for controlling flow through the fluid circuit module sets. These valves and their operation is described in more detail in previously cited U.S. Patent No. 5,462,416. However, the MEMS cassette may also employ MEMS-scale valves 141, as illustrated in Figure 7a.

A wide variety of MEMS-scale valves are available. For example, Figures 15a and 15b show a bi-stable valve 156 employing a membrane 158 that flexes between a closed position, blocking inlet passageway 160 as shown in Figure 15a and an open position as shown in Figure 15b allowing flow between the inlet passageway and outlet passageway 162. The valve presumably opens when the pressure in the valve chamber exceeds a threshold amount, at which time the membrane moves from the stable closed position to the stable open position. The valve moves to the stable closed position when the pressure in the valve chamber drops below a certain threshold value, causing the membrane to move from the stable open position to the stable closed position. Such a bistable microvalve was described by the Institute for Mikrostukturtechnik, at the July, 1999 "Novel Microfabrication Options for Biomems, Technologies & Commercialization Strategies" conference sponsored by the Knowledge Foundation. This is but one example of a MEMS scale valve that may be used in the MEMS cassette. It is also known to use micro-

channels and surface tension to form MEMS scale valves, with the valve opening when fluid pressure exceeds a certain threshold to overcome the effects of surface tension. Such valves may also find use in a MEMS cassettes of the type disclosed here.

An alternative design for the MEMS carrier or cassette and the cassette reader/controller is shown in Figures 9-11. As shown in Figure 9, a cassette reader/controller 164 comprises a pair of upstanding walls 166 defining a MEMS cassette-receiving slot between them. One wall has a function similar to the base 100 of the prior embodiment and the other wall functions in a manner similar to the door of the prior embodiment. In other words, one wall includes an array of light emitting fibers, diodes or the like, and any appropriate electrical contacts for cooperation with the MEMS devices in the MEMS cassette. The facing wall includes an array of light receivers for cooperating with the MEMS sensors and for reading the characteristics sensed. As before, one of these upstanding walls may also include macro-scale valves for actuating or controlling flow through the MEMS cassette, or the MEMS cassette may include MEMS-scale valves for controlling fluid.

Figure 10-11 depicts an alternative MEMS cassette 168 for use with reader/controller 164. The MEMS cassette 168 includes a base 170 having preformed fluid passageways 172 and pre-formed MEMS receiving or mounting areas 174 that may be connected to the passageways as desired for allowing fluid flow from the passageway to the MEMS sensor. As may be seen in Figure 10, the three

fluid pathways extend fully through the base from inlets 176 to outlets 178. A clear 180 cover is mounted on one side of the base and a flexible membrane 182 on the other side of the base.

As shown in an underside view, in Figure 11, valve module areas 184 are provided in the cassette which may be opened or closed by macro-scale valve members which depress the flexible membrane to contact and close against a valve module to block flow between the passageway and MEMS device or, upon release, to open a particular valve module to fluid flow. The valve opening and closing arrangement is preferably comparable to that already employed in the Baxter Amicus® centrifuge, which is described in detail in the U.S. Patent No. 5,462,416.

As illustrated in Figure 12, this alternative embodiment of the MEMS reader 164 and cassette 168 permits very easy loading of the cassette during installation of the disposable by sliding the cassette downwardly between the upstanding walls 166 of the MEMS cassette reader/controller.

Figure 16 illustrates another embodiment of a MEMS cassette or carrier 186 in accordance with the present invention. The earlier described cassettes rely on pressure within the tubing set (created by peristaltic pumps 92) for moving the selected fluid into and through the MEMS cassette. However, the MEMS cassette may itself have pumping chambers for moving fluid through the cassette and, indeed, through the tubing set, if desired. Figure 16 shows such a MEMS cassette 186.

As illustrated in Figure 16, MEMS cassette 186, comparable to previously described embodiments, includes three internal passageways 188 communicating with inlet flow tubing for sensing initial condition, in-process and final condition characteristics. In the Figure 16 embodiment, however, each passageway also communicates with a respective pumping chamber 190. The pumping chamber preferably has one wall defined a flexible membrane bonded to one side of the cassette. Flexing of the membrane by mechanical or pneumatic pressure alternatively reduces and increases the size of the chamber, resulting in a pumping action. Inlet and outlet valves 192 at each end of the pumping chamber, which are alternatively opened and closed, control the direction of flow through the pump. As pointed out earlier, this pumping may be used only to move the desired fluid through the MEMS cassette or may also be used to move fluid through the entire disposable fluid circuit, if desired.

Figure 18a shows a blood component container 194 with a MEMS sensor 196 carried by or embedded in the wall of the container for sensing a selected characteristic of the blood component in the container. The MEMS sensor may be adapted to access the container contents through a frangible part of the container wall or through a piercing member associated with the sensor, and may be adapted to test for bacterial contamination and/or pH of the stored blood component. This would have particular application in sensing the blood component just before

administration to a patient to assure that the pH and bacteria levels are acceptable.

After a suitable assay period required by the MEMS sensor, the results may be read directly from the MEMS sensor. Alternatively, the MEMS sensor may be read by a reader 198 such as an automated optical, magnetic or electronic device, suitable for the particular MEMS sensor mounted on the bag.

Although described in terms of one or more specific embodiments, the present invention is not limited to the specific structures disclosed for illustrative purposes, and includes such changes or modifications as may be apparent to one skilled in the field upon reading this description.

CLAIMS:

1. A biological suspension processing system comprising:

a suspension treatment device for treating one or more components of a biological suspension;

a first fluid flow path communicating with the treatment device for introducing a suspension into the treatment device;

a second fluid flow path communicating with the treatment device for withdrawing a constituent of the suspension from the treatment device; and

at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

2. The system of claim 1 in which a sensor senses one or more characteristics selected from the group consisting of flow rate, pH, cell type, cell antigenicity, cell concentration, cell count, viscosity, cholesterol, hematocrit, DNA, viral or bacterial presence, pathogen presence, and partial pressure of a selected gas.

3. The system of claim 1 in which a sensor communicates with the first fluid flow path and generates a signal responsive to one or more selected characteristic of the fluid in the first fluid flow path, the suspension treatment device including a controller adapted to

receive the sensor signal and to control the treatment device in response thereto.

4. The system of claim 1 in which a sensor communicates with said second fluid flow path and generates a signal responsive to a selected characteristic of the fluid in the second fluid flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

5. The system of claim 1 in which the sensor is adapted to sense the selected characteristic a plurality of times at discrete intervals.

6. The system of claim 5 in which the sensor generates a signal responsive to a selected characteristic of the fluid in the flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

7. The system of claim 6 in which sensor communicates with the second fluid flow path and senses the approximate quantity or concentration of a selected cell.

8. The system of claim 1 further comprising a container communicating with the second fluid flow path for receiving the withdrawn constituent, the system being adapted to provide tracking information for associating

with the container the particular characteristic sensed by at least one sensor.

9. The system of claim 8 in which the system comprises machine readable or human readable data storage media carried by the container, the data storage media storing information regarding the particular characteristic sensed by at least one sensor.

10. The system of claim 9 in which the data storage media comprises a bar code label on the container.

11. The system of claim 9 in which the data storage media comprises an electronic data storage device.

12. The system of claim 11 in which the electronic data storage device has a non-volatile semiconductor memory.

13. The system of claim 9 in which the data storage media comprises at least one icon carried by the container and representative of the sensed characteristic.

14. The system of claim 9 in which the suspension includes one or more blood components and the blood component withdrawn is a cellular component, and the container is for storing the cellular component withdrawn, and the data storage media includes data regarding the type, quality, purity, quantity or

concentration of the cellular blood component in the container.

15. The system of claim 1 in which the at least one sensor includes a first sensor communicating with the first fluid flow path and a second sensor communicating with the second flow path and the treatment device comprises an apheresis device and the suspension comprises whole blood, the first sensor sensing platelets to determine a platelet count in the suspension introduced into the apheresis device and the second sensor sensing platelets to determine a platelet count in the second flow path, wherein the system includes a container communicating with the second flow path for storing blood platelets withdrawn, and the system further comprises machine readable or human readable data storage media carried by the container, the data storage media storing information regarding platelet count sensed by one or both of said sensors.

16. The system of claim 1 in which a sensor communicates with said second fluid flow path, and said system includes a container for storing the constituent withdrawn, the sensor generating a signal responsive to a characteristic of the constituent withdrawn, and the system includes a data recording device for receiving the signal and recording data regarding the sensed characteristic of the constituent withdrawn.

17. The system of claim 16 in which the data recording device comprises a printer for printing a report of the characteristic sensed.

18. The system of claim 17 in which the report is in machine readable graphic format.

19. The system of claim 16 wherein the container carries a machine readable electronic data storage device, and in which the data recording device is adapted to transfer data regarding the selected characteristic sensed by the sensor to the electronic data storage device.

20. The system of claim 19 in which the electronic storage device comprises a non-volatile semiconductor memory.

21. A disposable plastic blood component storage container defining an interior compartment for receiving a blood component, and at least one microelectromechanical sensor carried by the container and communicating with the compartment for sensing a selected characteristic of the blood component received therein.

22. The container of claim 21 in which the sensor is adapted to sense bacterial presence or pH in the blood component just before it is administered to a patient.

23. The container of claim 21 in which the sensor includes write once, read many times data storage, and is adapted to be read by an automated reading device.

24. A blood processing system for providing a characterized blood constituent product, the system comprising:

an apheresis device for separating one or more desired cellular blood constituents from a suspension comprising whole blood;

a first fluid flow path communicating with the apheresis device for introducing a suspension comprising whole blood into the device;

a second fluid flow path communicating with the apheresis device for withdrawing at least one desired cellular blood constituent from the device;

a container communicating with the second fluid flow path for receiving the blood constituent withdrawn from the apheresis device;

machine readable or human readable data storage media carried by the container;

at least one microelectromechanical sensor communicating with the first fluid flow path for sensing at least one characteristic of the whole blood and for generating at least one electrical signal responsive to said sensing;

at least one microelectromechanical sensor communicating with the second flow path for sensing the quantity of cellular blood constituent withdrawn from the

apheresis device and for generating an electrical signal responsive to said sensing;

a data recorder adapted to receive the electrical signals from the sensors and to record data regarding the sensed characteristics on the data storage media, whereby a user may readily identify the sensed characteristic regarding the whole blood and the quantity of the desired cellular constituent in the container.

25. The system of claim 24 including a sensor communicating with the second fluid flow path for sensing the quantity of a non-desired biologic constituent in the flow path and generating an electrical signal responsive to the amount, the data recorder being adapted to receive such signal and record data regarding the quantity of non-desired cellular constituent in the data storage media for access by a user of the product in the container.

26. The system of claim 25 in which the non-desired biologic component is a viral constituent.

27. The system of claim 25 in which the non-desired biologic component is a cellular constituent.

28. The system of claim 27 wherein the desired cellular blood constituent is platelets or red cells and wherein the non-desired cellular constituent is white cells.

29. The system of claim 24 further comprising a controller adapted to receive the signals from the sensors communicating with the first and second fluid flow paths and to control the apheresis device in response to one or more of such signals to provide a desired cellular blood constituent product characterized by data recorded in the data storage media in accordance with characteristics sensed by the sensors.

30. The system of claim 29 in which the desired cellular blood constituent is platelets, red cells, stem cells or white cells.

31. The system of claim 24 in which the data storage media comprises machine readable graphics carried on the container.

32. The system of claim 31 in which the machine readable graphics comprises a bar code.

33. The system of claim 24 in which the first fluid flow path communicates with the vascular system of a human donor, and the system includes means for generating a human-readable report for the donor containing selected data regarding one or more of the sensed characteristics.

34. A biological suspension processing system comprising:

a blood treatment device for treating one or more components of a biological suspension;

a human subject;

a first fluid flow path communicating with the vascular system of the human subject and the treatment device for introducing blood from the human subject into the treatment device;

a second fluid flow path communicating with the treatment device for withdrawing a constituent of the blood from the treatment device;

a third fluid flow path communicating with the treatment device from withdrawing another constituent of the blood from the treatment device; and

at least one microelectromechanical sensor communicating with one of said fluid flow paths for sensing a selected characteristic of the fluid within the flow path.

35. The system of claim 34 in which the sensor generates a signal responsive to one or more selected characteristic of the fluid in one of the fluid flow path, the suspension treatment device including a controller adapted to receive the sensor signal and to control the treatment device in response thereto.

36. The system of claim 35 in which the third fluid flow path communicates with the human subject, the treatment device is adapted to add anticoagulant to the blood in the first fluid flow path, the selected characteristic includes the hematocrit of blood in the first fluid flow path, and the controller controls the addition of anticoagulant into the first fluid flow path.

37. The system of claim 35 in which the controller controls the treatment device in response to the signal to avoid one or more deleterious consequences to the human subject.

38. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a constituent of desired quality.

39. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a constituent of desired quantity.

40. The system of claim 35 in which the control controls the treatment device in response to the signal to withdraw a constituent that is depleted of an undesired component.

41. The system of claim 40 in which the undesired component is white cells.

42. The system of claim 35 in which the controller controls the treatment device in response to the signal to withdraw a desired constituent.

43. The system of claim 42 in which the desired constituent is platelets.

44. The system of claim 42 in which the desired constituent is red cells or plasma.

45. The system of claim 35 in which the sensor senses platelets and the controller controls the treatment device to withdraw a selected minimum quantity of platelets.

FIG. 1

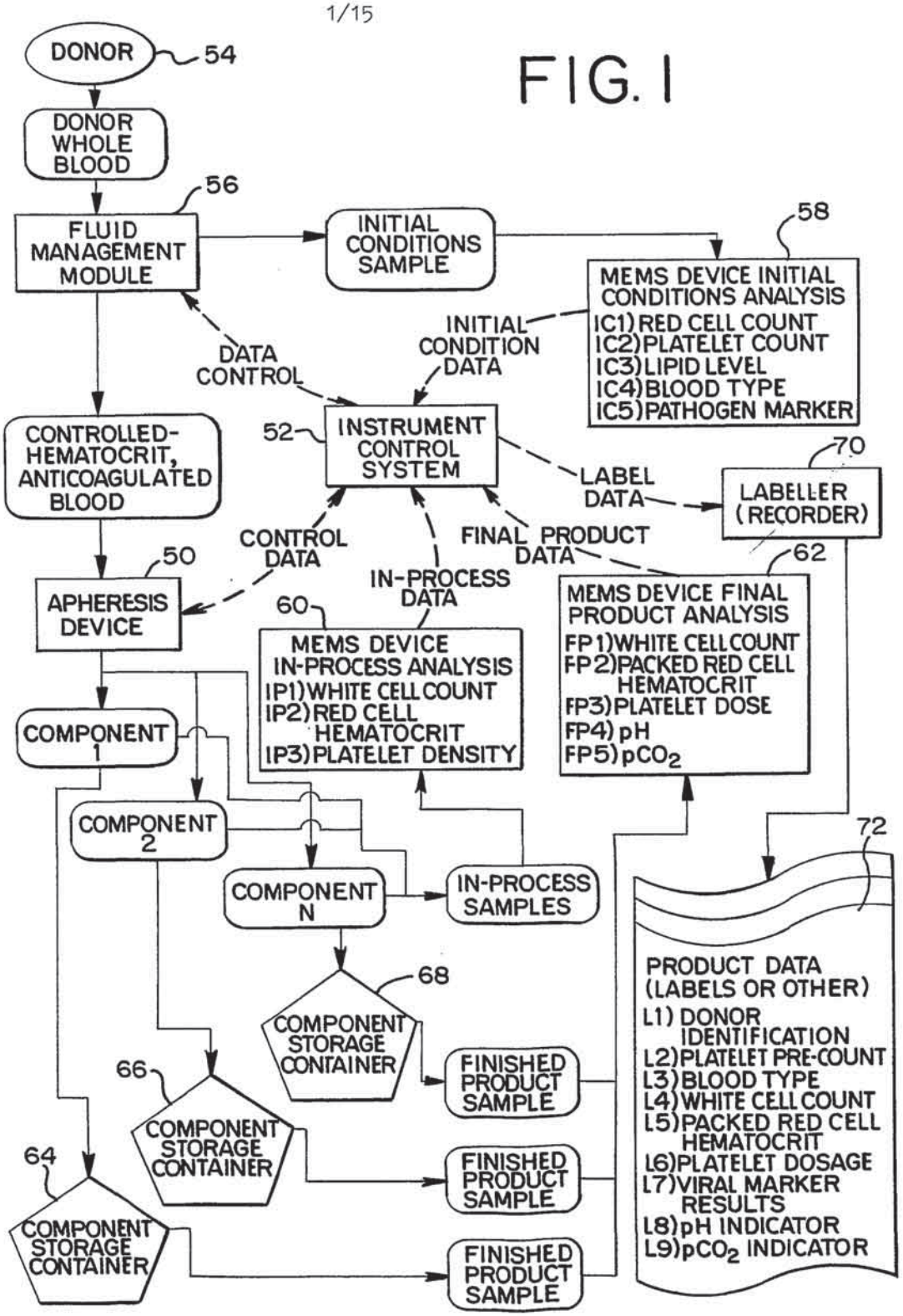

DONOR
54
DONOR WHOLE BLOOD
56
FLUID MANAGEMENT MODULE
INITIAL CONDITIONS SAMPLE
58
MEMS DEVICE INITIAL CONDITIONS ANALYSIS
IC1) RED CELL COUNT
IC2) PLATELET COUNT
IC3) LIPID LEVEL
IC4) BLOOD TYPE
IC5) PATHOGEN MARKER
DATA CONTROL
INITIAL CONDITION DATA
CONTROLLED-HEMATOCRIT, ANTICOAGULATED BLOOD
52
INSTRUMENT CONTROL SYSTEM
LABEL DATA
70
LABELLER (RECORDER)
CONTROL DATA
FINAL PRODUCT DATA
50
APHERESIS DEVICE
IN-PROCESS DATA
60
MEMS DEVICE IN-PROCESS ANALYSIS
IP1) WHITE CELL COUNT
IP2) RED CELL HEMATOCRIT
IP3) PLATELET DENSITY
62
MEMS DEVICE FINAL PRODUCT ANALYSIS
FP1) WHITE CELL COUNT
FP2) PACKED RED CELL HEMATOCRIT
FP3) PLATELET DOSE
FP4) pH
FP5) pCO_2
COMPONENT 1
COMPONENT 2
COMPONENT N
IN-PROCESS SAMPLES
72
PRODUCT DATA (LABELS OR OTHER)
L1) DONOR IDENTIFICATION
L2) PLATELET PRE-COUNT
L3) BLOOD TYPE
L4) WHITE CELL COUNT
L5) PACKED RED CELL HEMATOCRIT
L6) PLATELET DOSAGE
L7) VIRAL MARKER RESULTS
L8) pH INDICATOR
L9) pCO_2 INDICATOR
68
COMPONENT STORAGE CONTAINER
FINISHED PRODUCT SAMPLE
66
COMPONENT STORAGE CONTAINER
FINISHED PRODUCT SAMPLE
64
COMPONENT STORAGE CONTAINER
FINISHED PRODUCT SAMPLE

FIG. 2

Haemonetics Corporation
Exhibit 2015
Page #1069

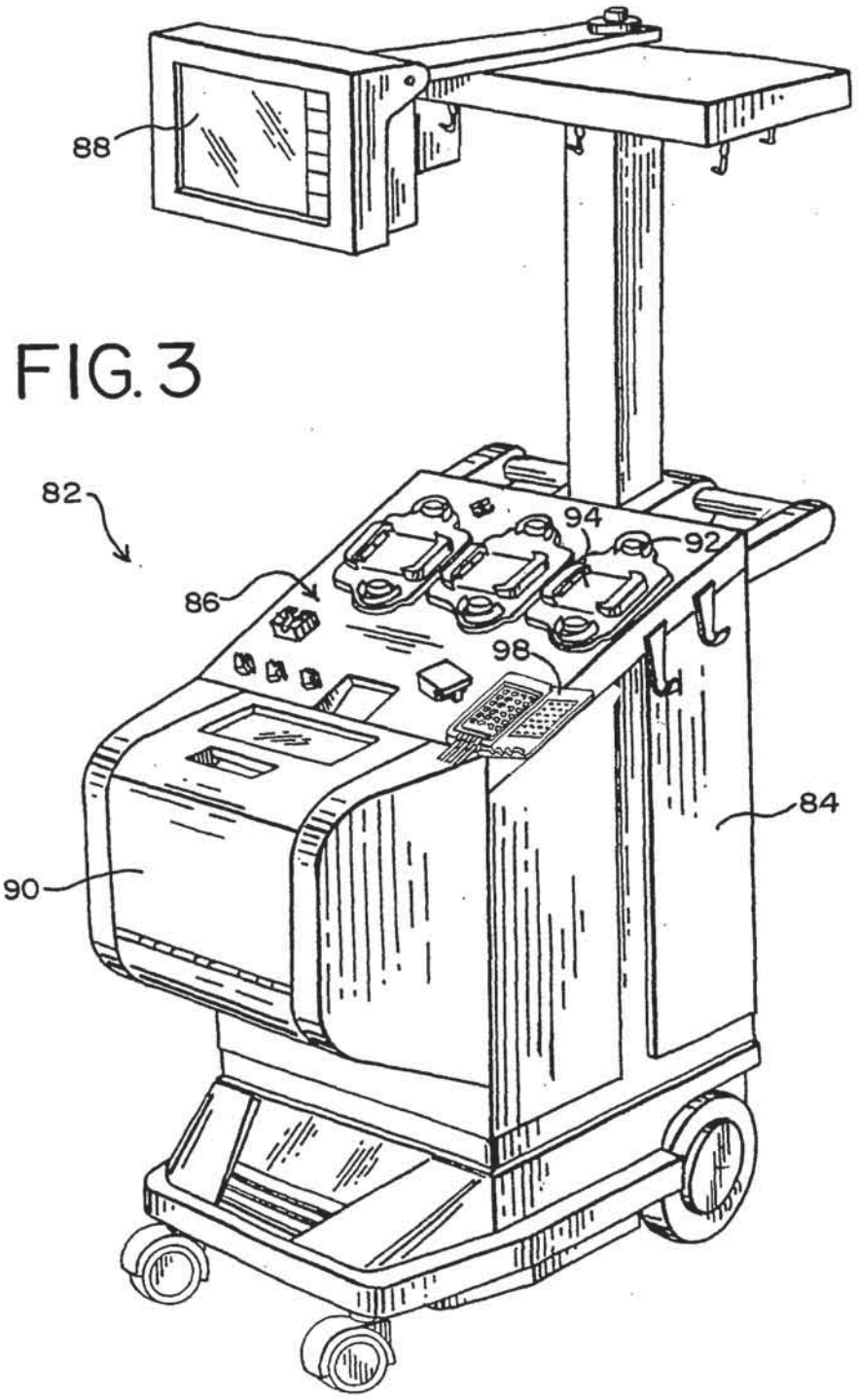


FIG. 3

FIG. 4

Haemonetics Corporation
Exhibit 2015
Page #1071

FIG. 5

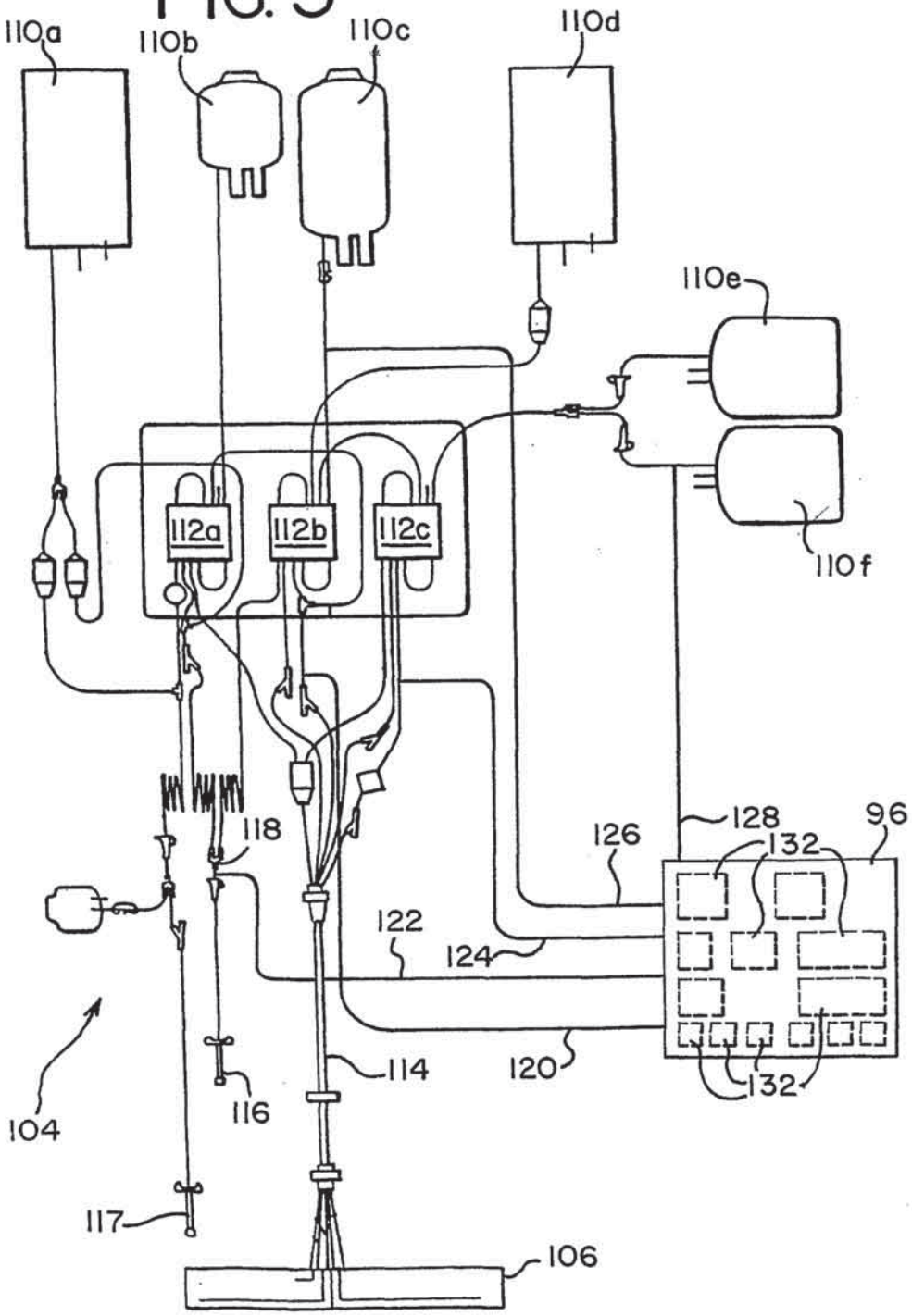
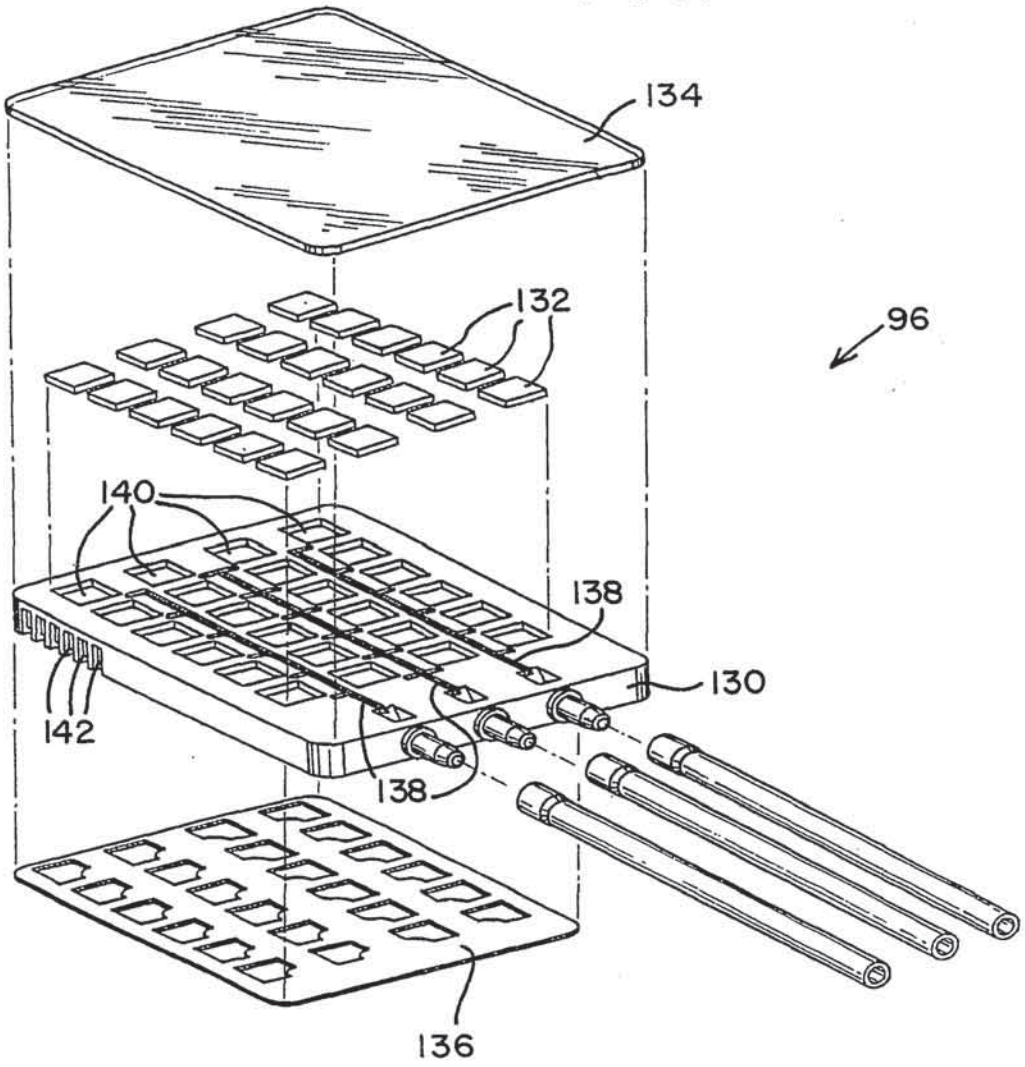

110a
110b
110c
110d
110e
110f
112a
112b
112c
118
126
128
96
132
122
124
120
114
116
104
117
106

FIG. 6



Haemonetics Corporation
Exhibit 2015
Page #1074

FIG. 7A

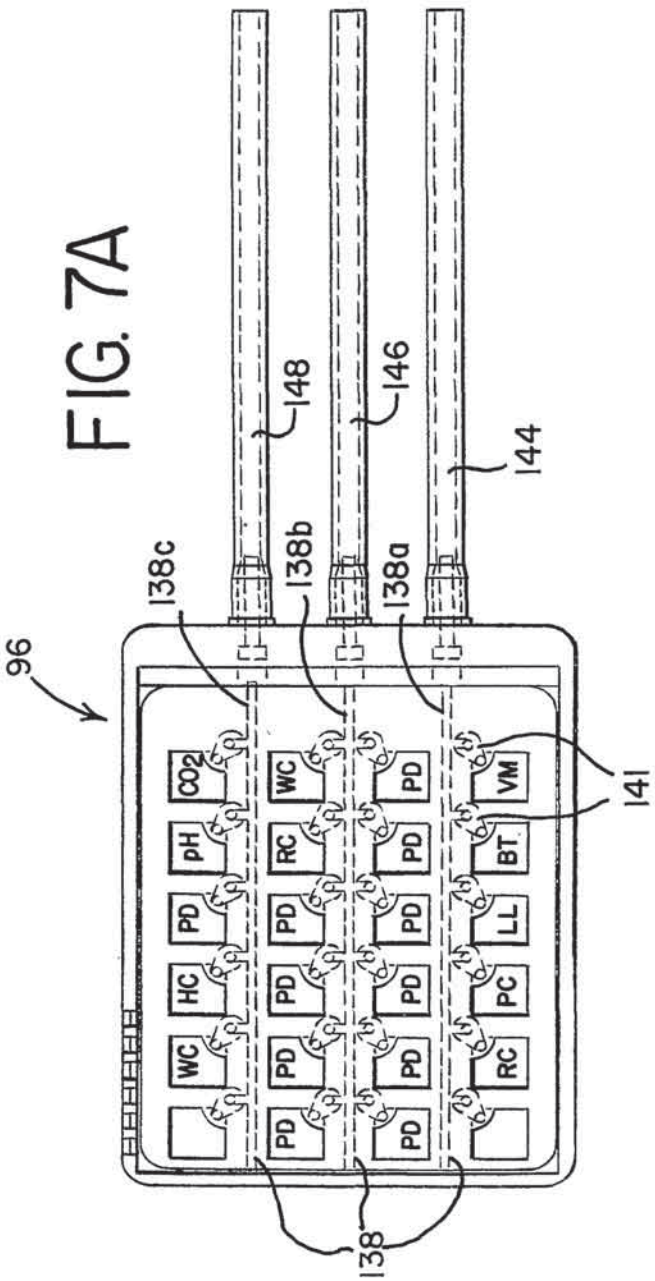


FIG. 7B

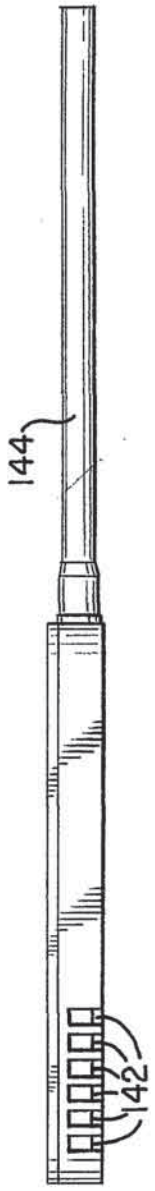


FIG. 8

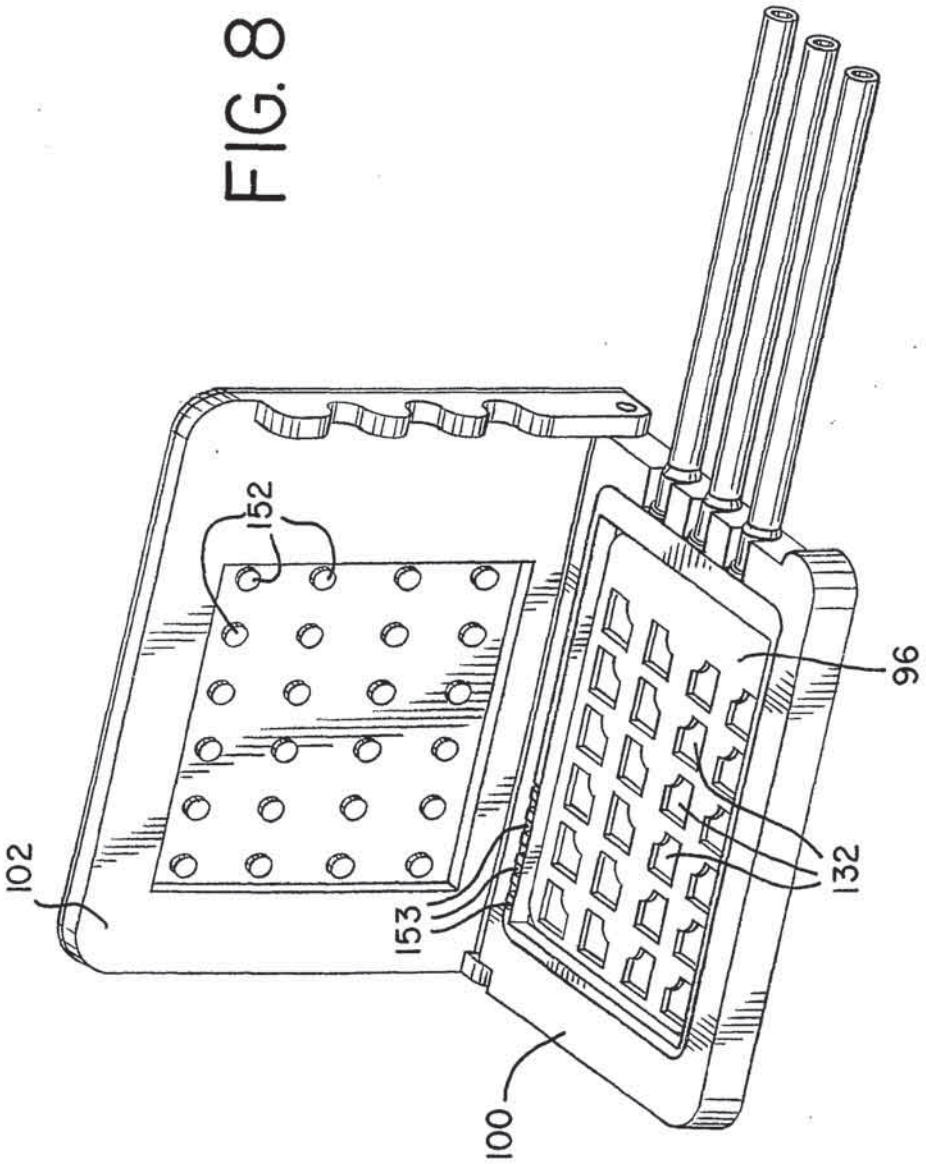
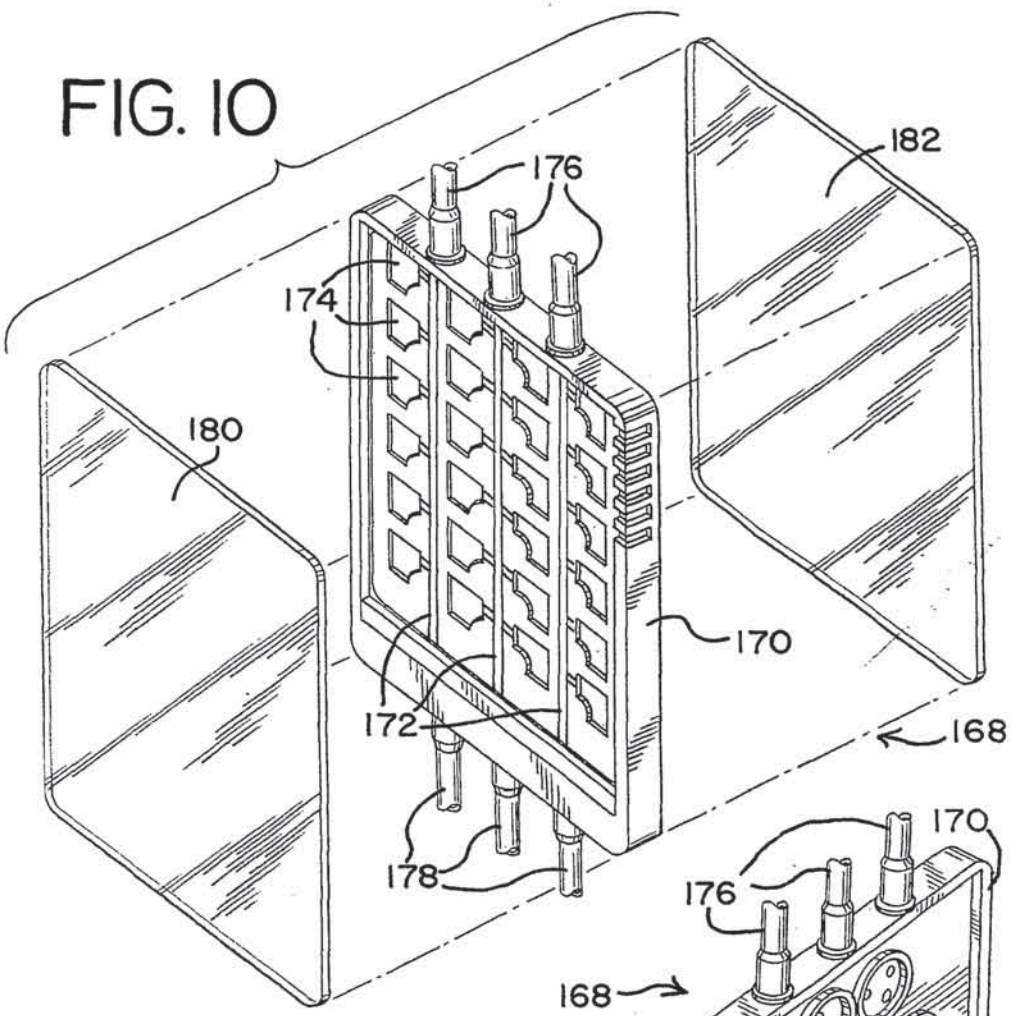


FIG. 9

Haemonetics Corporation
Exhibit 2015
Page #1076

FIG. 10



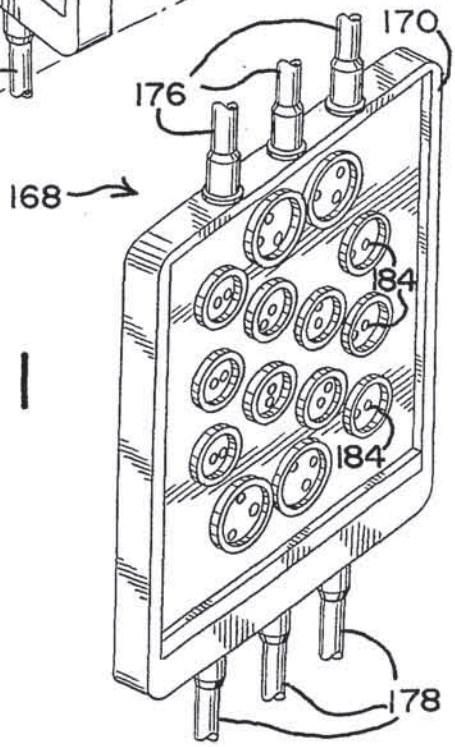


FIG. 11

FIG. 12

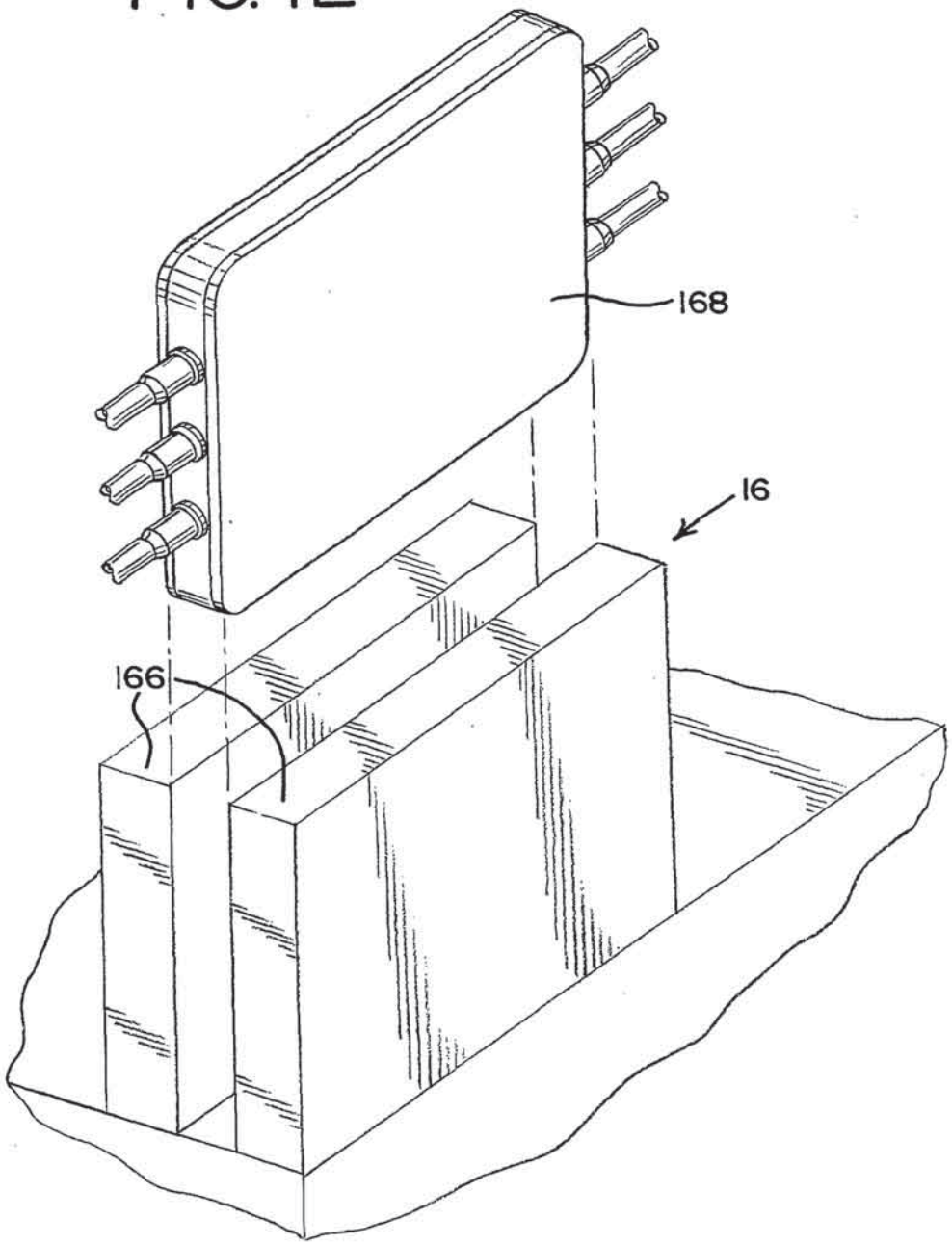


FIG. 13

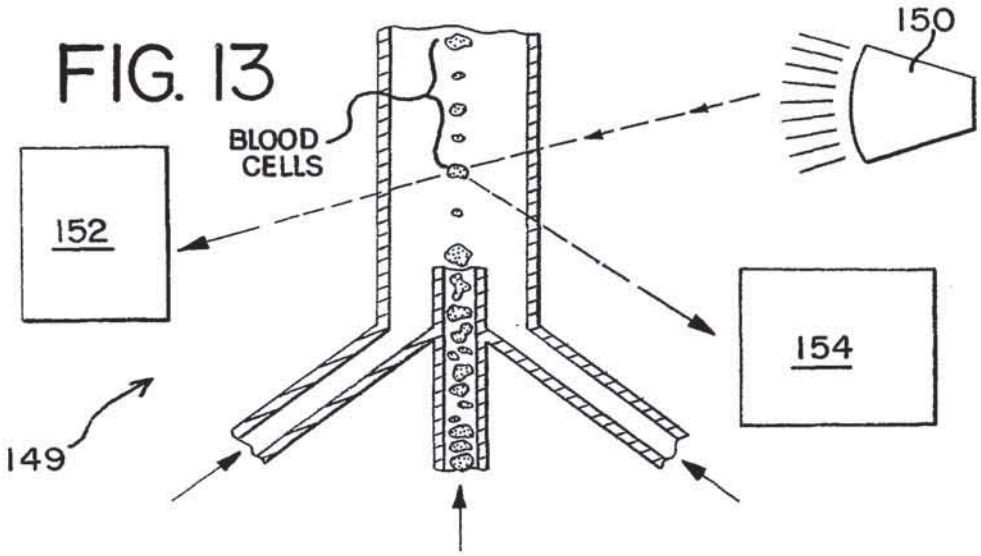


FIG. 14

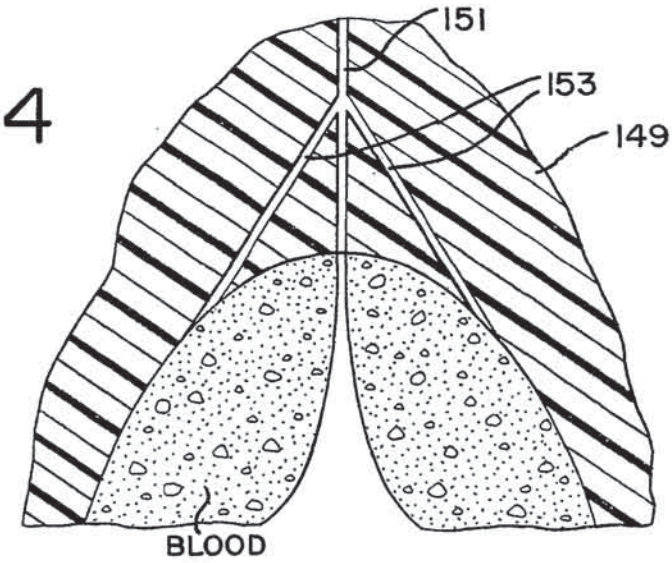


FIG. 15A

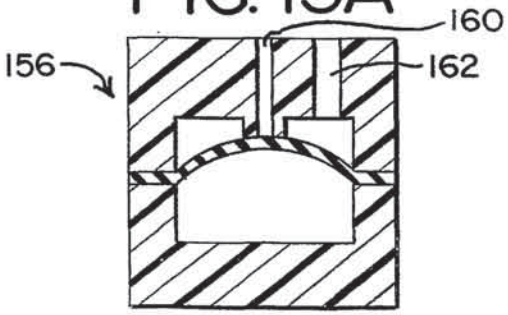


FIG. 15B

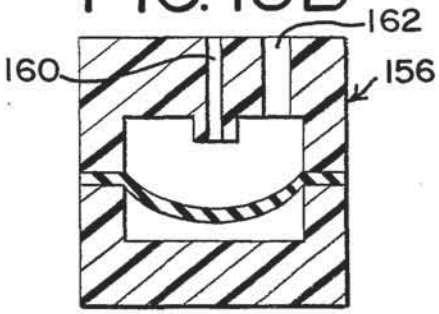


FIG. 16

186
188
WC
HC
PD
pH
CO2
190
PD
PD
PD
PD
RC
WC
190
PD
PD
PD
PD
PD
PD
190
RC
PC
LL
BT
VM
192
192

FIG. 17a

FIG. 17b

FIG. 18A

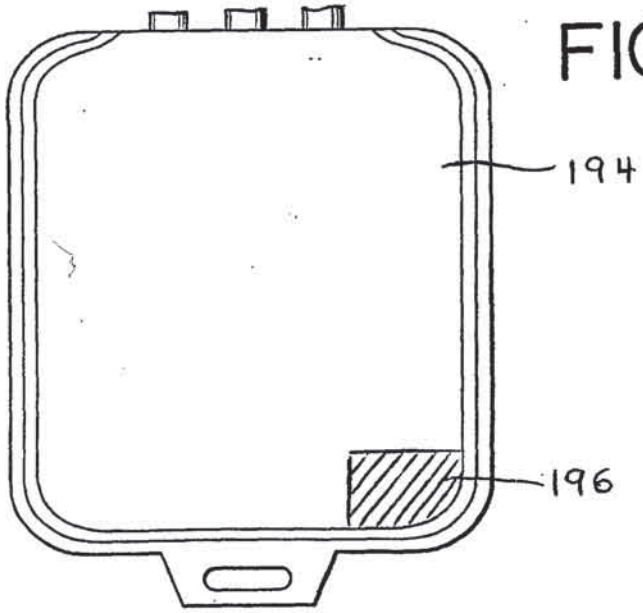
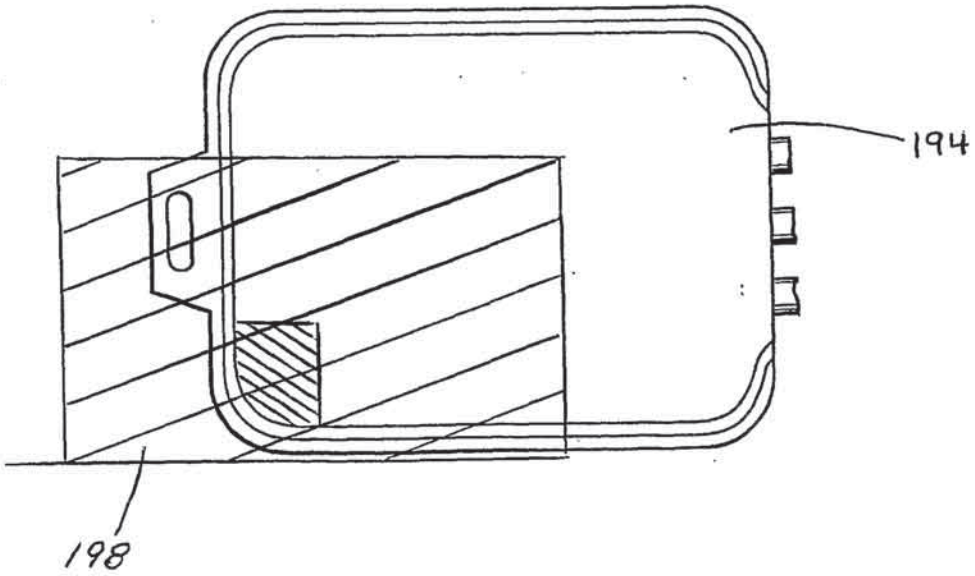


FIG. 18B



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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2007 (12.04.2007)

PCT

(10) International Publication Number
WO 2007/041716 A1

(51) International Patent Classification:
A61M 1/36 (2006.01) *A61M 1/38* (2006.01)

(21) International Application Number:
PCT/US2006/039153

(22) International Filing Date: 5 October 2006 (05.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/596,591 5 October 2005 (05.10.2005) US

(71) Applicant *(for all designated States except US)*: **GAMBRO, INC.** [US/US]; 10810 W. Collins Avenue, Lakewood, Colorado 80215 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **GIBBS, Bruce** [US/US]; 8425 Wright Street, Arvada, Colorado 80005 (US).

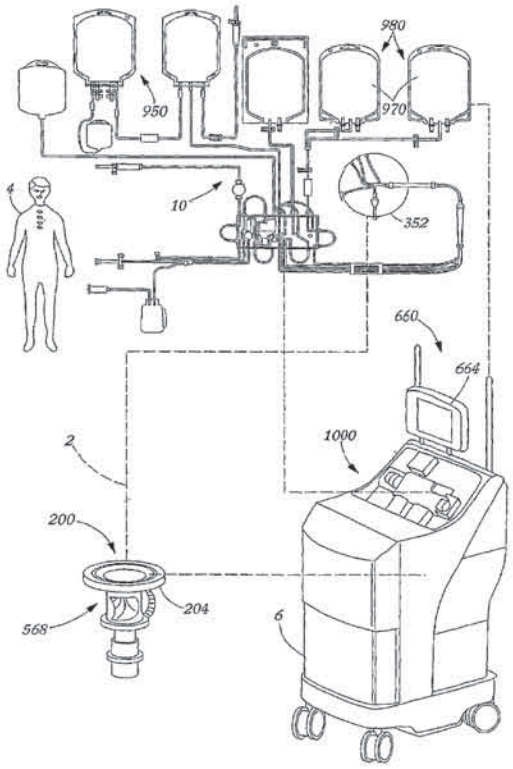
(74) Agent: **ARCINIEGAS, Laura B.**; 10810 W. Collins Avenue, Lakewood, Colorado 80215 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) **Title:** METHOD AND APPARATUS FOR LEUKOREDUCTION OF RED BLOOD CELLS



(57) **Abstract:** This invention relates to a method for the continuous separation of red blood cells from whole blood which includes the steps of removing the whole blood from a donor, continuously separating the whole blood into blood component layers within a separation vessel including at least a plasma layer, a buffy coat layer and a red blood cell layer, removing the plasma layer from the separation vessel, removing the buffy coat layer from the separation vessel, and removing red blood cells from the red blood cell layer which partially overlaps with the buffy coat layer to create a mononuclear cell (MNC)-reduced red blood cell layer in the separation vessel.

WO 2007/041716 A1

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report*

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

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

METHODS AND APPARATUS FOR LEUKOREDUCTION OF RED BLOOD CELLS

PRIORITY CLAIM

This invention claims the benefit of United States provisional application number 60/596,591 filed October 5, 2005.

FIELD OF INVENTION

The present invention relates generally to the field of extracorporeal blood processing methods which are particularly useful in blood component collection, and more particularly, the present invention relates to methods for the leukoreduction of red blood cells collected with an apheresis system.

BACKGROUND OF THE INVENTION

One well-known type of extracorporeal blood processing involves an apheresis system and/or procedure in which blood is removed from a donor or a patient (hereafter cumulatively referred to as a donor), directed to a blood component separation device (*e.g.*, centrifuge), and separated into various blood component types (*e.g.*, red blood cells, white blood cells, platelets, plasma) for collection or therapeutic purposes. One or more or all of these blood component types may be collected, and/or treated for therapeutic purposes before storage or return to a patient, while the remainder may simply be returned to the donor or patient.

A number of factors may affect the commercial viability of an apheresis system. One factor relates to the time and/or expertise required of an individual to prepare and operate the apheresis system. For instance, reducing the time required by the operator to complete an entire collection procedure, as well as reducing the complexity of these actions, can increase productivity and/or lower the potential for operator error. Moreover, reducing the dependency of the system on the operator may further lead to reductions in the credentials desired/required for the operators of these systems.

Donor-related factors may also impact the commercial viability of an apheresis system and include, for example, donor convenience and donor comfort. For instance, donors/patients may have a limited amount of time which may be committed to a donation or therapeutic procedure. Consequently, once at the collection or treatment facility, the amount of time which is actually spent collecting and/or treating blood components is an important consideration. This also relates to donor comfort as the actual collection procedure may be

Haemonetics Corporation
Exhibit 2015
Page #1085

somewhat discomforting because at least one and sometimes two access needles are disposed in the donor throughout the procedure.

Performance-related factors also affect the commercial viability of an apheresis system. Performance may be judged in terms of the collection efficiency of the apheresis system, which may impact or improve product quality and/or may in turn reduce the amount of processing time and thus decrease operator burden and increase donor convenience. The collection efficiency of a system may be gauged in a variety of ways, such as by the amount of a particular blood component type which is collected in relation to the quantity of this blood component type which passes through the apheresis system. Individual characteristics of the donor also contribute to the performance of apheresis systems, for example, some donors have greater percentages of certain blood cell types than other donors.

Performance may also be evaluated based upon the effect which the apheresis procedure has on the various blood component types. For instance, it is desirable to minimize the adverse effects on the blood component types as a result of the apheresis procedure (*e.g.*, reduce platelet activation).

Another performance-related factor is the end quality of the collected blood component. For example, if red blood cells are the component to be collected, it is generally desirable that such red blood cells be leukoreduced by the removal of white blood cells or leukocytes. Contaminating white blood cells can present problems to the ultimate recipient of the collected blood component, by provoking immunogenic reactions and viral diseases.

Conventionally, filters have been used to remove leukocytes from collected blood products or components. For example, U.S. Patent No. 5,954,971 discloses the use of a filter with an apheresis system for filtering a diluted blood component prior to collection. Other distinctive methods have also been used, and these have generally dictated special preliminary steps such as pre-chilling and/or overnight storage of collected components prior to filtration. Another distinct conventional filtration step is the venting or air handling/re-circulation or by-passing at the end of the filtration procedure which had been deemed important for substantial recovery of a remainder portion of the blood component to be processed through a red blood cell filter.

Leukocytes are made up of mononuclear cells and polymorphonuclear cells. Mononuclear cells consist of lymphocytes, monocytes and stem cells. Polymorphonuclear cells consist of granulocytes, eosinophils and basophils. As discussed above, a performance related factor, which may affect apheresis efficiency, is the amount of a particular cell component a donor has. For example, it has been observed that if a donor has a high

Haemonetics Corporation
Exhibit 2015
Page #1086

percentage of lymphocytes as compared to other white blood cell subtypes, (or has a high lymphocyte load), leukofiltration is not as effective as in donors who do not have such high lymphocyte loads. There is often a high residual population of lymphocytes which are not removed via filtration and which contaminate the separated red blood cell component.

The present invention is directed towards removing mononuclear cells in an apheresis procedure before leukoreducing the separated blood components.

SUMMARY OF THE INVENTION

The present invention relates to the extracorporeal separation and collection of red blood cells using an apheresis blood processing system. More particularly, this invention relates to a method for the continuous separation of red blood cells from whole blood wherein the portion of the red blood cells which are closest to the layer containing lymphocytes are collected within the blood processing vessel and are returned to the donor, along with the lymphocytes in the buffy coat, leaving the mononuclear cell reduced red blood cells within the separation vessel.

According to the present invention, before the ultimate collection of the red blood cells in the collection container, the MNC-reduced red blood cells are filtered through a filtration device. This filtration preferably occurs during the overall separation procedure, although it could be initiated soon after and as part of the commencement of the collection procedure. Nevertheless, the separation procedure may be a continuous or batch process, and in either case, the filtration occurs upon or soon after removal of the separated high hematocrit MNC-reduced red blood cells from the processing vessel, yet preferably concurrently with or soon after the overall separation process.

These and still further aspects of the present invention are more particularly described in the following description of the preferred embodiments presented in conjunction with the attached drawings which are described briefly below.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of one embodiment of an apheresis system which can be used in or with the present invention.

Fig. 2 is a partial cross-sectional view of a portion of the separation vessel.

Haemonetics Corporation
Exhibit 2015
Page #1087

Fig. 3 illustrates a tubing and bag set including an extracorporeal tubing circuit, a cassette assembly, and a filter and collection bag assembly for use in or with the system of Fig. 1 pursuant to the present invention.

Fig. 4 illustrates a cassette assembly similar to that shown in the set of Fig. 3.

Fig. 5 illustrates a filter and collection bag assembly similar to that shown in the set of Fig. 3.

Figs. 6A and 6B illustrate alternative filter and collection bag assemblies also usable in a tubing and bag set like that shown in Fig. 3.

Fig. 7 is a schematic view of an apheresis system according to the present invention.

Fig. 8 is a schematic view of an alternative apheresis system also according to the present invention.

Fig. 9 is a schematic view of an alternative apheresis system according to the present invention.

DETAILED DESCRIPTION

The present invention will be described in relation to the accompanying drawings which assist in illustrating the pertinent features hereof. Generally, the primary aspects of the present invention relate to both procedural and structural improvements in or a sub-assembly for use with a blood apheresis system. However, certain of these improvements may be applicable to other extracorporeal blood processing applications whether any blood components are returned directly to the donor or otherwise; and such are within the scope of the present invention as well.

It should be noted that like elements are depicted by like numbers.

A preferred blood apheresis system **2** for use in and/or with the present invention is schematically illustrated in Fig. 1. System **2** provides for a continuous blood component separation process. Generally, whole blood is withdrawn from a donor **4** and is substantially continuously provided to a blood component separation device **6** where the blood is continuously separated into various component types according to density and at least one of these blood component types is preferably continuously collected from the device **6**. One or more of the separated blood components may then either be provided for collection and subsequent use by another through transfusion or may be returned to the donor **4**.

Haemonetics Corporation
Exhibit 2015
Page #1088

Therapeutic treatment and near immediate return of certain separated blood components is a viable alternative use hereof as well. It is also understood that for therapeutic treatment the blood may be separated into components with filtration using the principles of the instant invention and as described below at a patient's bedside for return to such patient.

In the blood apheresis system **2**, blood is withdrawn from the donor **4** and directed through a preconnected extracorporeal tubing circuit **10** and, in one embodiment, a blood processing vessel **352** which together define a closed, sterile and disposable system. The set **10** is preferably disposable and is adapted to be mounted on and/or in the blood component separation device **6**. The separation device **6** preferably includes a pump/valve/sensor assembly **1000** for interfacing with the extracorporeal tubing circuit **10**, and a channel assembly **200** for interfacing with the disposable blood processing vessel **352**.

The channel assembly **200** may include a channel housing **204** which is rotatably interconnected with a rotatable centrifuge rotor assembly **568** which provides the centrifugal forces required to separate blood into its various blood component types by centrifugation. The blood processing vessel **352** may then be interfitted within the channel housing **204**. When connected as described, blood can then be flowed substantially continuously from the donor **4**, through the extracorporeal tubing circuit **10**, and into the rotating blood processing vessel **352**. The blood within the blood processing vessel **352** may then be continuously separated into various blood component types and at least one of these blood component types (platelets, plasma, lymphocytes or red blood cells) is preferably continually removed from the blood processing vessel **352**. Blood components which are not being retained for collection or for therapeutic treatment are preferably also removed from the blood processing vessel **352** and returned to the donor **4** via the extracorporeal tubing circuit **10**. Note, various alternative apheresis systems (not shown) may also make use of the present invention; including batch processing systems (non-continuous inflow of whole blood and/or non-continuous outflow of separated blood components) or smaller scale batch or continuous RBC/plasma separation systems, whether or even if no blood components may be returned to the donor.

Operation of the blood component separation device **6** is preferably controlled by one or more processors included therein, and may advantageously comprise a plurality of embedded computer processors to accommodate interface with ever-increasing PC user facilities (e.g., CD ROM, modem, audio, networking and other capabilities). Relatedly, in order to assist the operator of the apheresis system **2** with various aspects of its operation, the blood component separation device **6** preferably includes a graphical interface **660** with an interactive touch screen **664**.

Haemonetics Corporation
Exhibit 2015
Page #1089

Further details concerning the operation of a preferred apheresis system, such as the Gambro Trima® System and the Trima Accel® System (available from Gambro BCT, Inc., Lakewood, Colorado) may be found in a plurality of publications, including, for example, WO99/11305 and U.S. Patents No. 5,653,887; No. 5,676,644; No. 5,702,357; No. 5,720,716; No. 5,722,946; No. 5,738,644; No. 5,750,025; No. 5,795,317; No. 5,837,150; No. 5,919,154; No. 5,921,950; No. 5,941,842; No. 6,129,656; and No. 6,730,055 among numerous others. The disclosures hereof are incorporated herein as if fully set forth. A plurality of other known apheresis systems may also be useful herewith, as for example, the Baxter CS3000® and/or Amicus® and/or Autopheresis-C® and/or Alyx systems, and/or the Haemonetics MCS® or MCS®+ and/or the Fresenius COM.TEC™ or AS-104™ and/or the system described in Patent No. 6,773,389.

Separation Vessel

Fig. 2 schematically illustrates a portion of the separation vessel **352**. Fig. 2 also illustrates an inflow tube **36** for conveying the whole blood to be separated into the separation vessel **352**; first, second, and third collection lines **64**, **62**, **68** for removing separated substances from the separation vessel **352**; and an interface control line **44** for adjusting the level of an interface between separated substances in the vessel **352**. Preferably, the separation vessel **352** forms what is known as a single stage component separation area rather than forming a plurality of such stages. In other words, each of the components separated in the vessel **352** are collected and removed in only one area of the vessel **352**. In addition, the separation vessel **352** includes a substantially constant radius except in the outlet portion **51** where the outer wall of the outlet portion is preferably positioned further away from the axis of rotation to allow for the ports **56**, **58**, **60**, and **61** be positioned at different radial distances and to create a collection pool with greater depth for the high density red blood cells.

Although the ports **56**, **58**, and **60** and lines **62**, **64**, and **68** are referred to as being "collection" ports and lines the substances removed through these ports and lines can be either collected or reinfused back into a donor.

The separation vessel **352** has a generally annular flow path **46** and includes an inlet portion **48** and outlet portion **51**. A wall **52** prevents substances from passing directly between the inlet and outlet portions **48** and **51** without first flowing around the generally annular flow path **46** (e.g., counterclock-wise as illustrated by arrows in Fig. 2).

Although Fig. 2 shows the inlet portion **48** as having a wide radial cross-section, the outer wall of the inlet portion **48** can be spaced closer to the inner wall of the inlet portion **48**

Haemonetics Corporation
Exhibit 2015
Page #1090

and/or tapered. An inlet port **54** of inflow tube **36** allows for flow of whole blood, into the inlet portion **48** of separation vessel **352**. During a separation procedure, substances entering the inlet portion **48** follow the flow path **46** and stratify according to differences in density in response to rotation of the rotor **568**. Preferably, the flow path **46** between the inlet and outlet portions **48** and **50** is curved and has a substantially constant radius. In addition, the flow path **46** is placed at the maximum distance from the axis of rotation. This shape ensures that components passing through the flow path **46** encounter a relatively constant gravitational field and a maximum possible gravitational field for the rotor **568**.

The separated substances flow into the outlet portion **51** where they are removed via first **56**, second **58**, and third **60** collection ports respectively, of first **62**, second **64**, and third **68** collection lines. Separated substances may also be removed by an interface control port **61** of the interface control line **44**. As shown in Fig. 2, the first **56**, second **58**, and third **60** ports are positioned at varying radial locations on the rotor **568** to remove substances having varying densities. The second collection port **58** is farther from the axis of rotation than the first and third ports **56** and **60** to remove the most dense substances separated in the separation vessel **352**, such as red blood cells. The third port **60** is located closer to the axis of rotation than the first and second ports **56** and **58** to remove the least dense substances separated in the separation vessel **352**, such as plasma. If desired, the first collection port **56** may be used to remove substances having a medium density such as platelets.

The outlet portion **51** includes a barrier **38** for substantially blocking flow of the intermediate density substances, such as the buffy coat, which as discussed above, consists of white blood cells and platelets. Preferably, the barrier **38** extends completely across the outlet portion **51** in a direction generally parallel to the axis of rotation. The first collection port **56** is positioned immediately upstream of barrier **38**, downstream of the inlet portion **48**, to collect the intermediate density substances blocked by the barrier **38**.

Radially inner and outer edges of the barrier **38** are spaced from radially inner and outer walls of the separation vessel **352** to form a first passage **40** for collection of lower density substances if desired, such as plasma, at a radially inner position in the outlet portion **51** and a second passage **66** for higher density substances, such as red blood cells, at a radially outer position in the outlet portion **51**. The second and third collection ports **58** and **60** are positioned downstream of the barrier **38** to collect the respective low and high density substances passing through the first and second passages **40** and **66**.

The interface port **61** is also positioned downstream of the barrier **38**. During a separation procedure, the interface port **61** removes the least dense of the most dense

Haemonetics Corporation
Exhibit 2015
Page #1091

substances in the outlet portion **51** to thereby control the radial position of the interface between the buffy coat layer **82** and the red blood cell layer **86** and plasma layer **84** in the outlet portion **51**.

First port **56** may be used to remove platelets if desired, or may be used to remove the buffy coat layer **82** and a portion of the red blood cell layer next to the buffy coat layer which may contain some contaminating white blood cells. Although the second and third collection ports **58** and **60** and the interface control port **61** are shown downstream of the barrier **38**, one or more of these elements may be upstream of the barrier **38**. In addition, the order of the collection ports **56**, **58**, **60**, and the interface port **61** along the length of the outlet portion **51** could be changed. Further details concerning the structure and operation of the separation vessel **352** is described in U.S. Patent No. 6053856 to Hlavinka, which has been incorporated herein by reference.

Disposable Set: Extracorporeal Tubing Circuit

As illustrated in Figs. 3 and 4, a preconnected extracorporeal tubing circuit **10** is shown which may include a cassette assembly **110** and a number of tubing/collection assemblies **20**, **50**, **60**, **100**, **90**, **950** and **980** interconnected therewith. Preferably, a blood removal/return tubing assembly **20** provides a single needle interface between a donor **4** (see Fig. 1) and the remainder of the tubing circuit **10** (although a two-needle set-up may also be used, not shown). At least two lines **22**, **24** are preferably provided in assembly **20** (see Fig. 4) for removal of blood from and return of components to the donor. This embodiment includes a cassette assembly **110**, which is interconnected between the tubing assembly **20** which connects the donor **4** thereto, and blood inlet/blood component tubing line sub-assembly **60** which provides the interface between cassette assembly **110** and blood processing vessel **352**. Three lines **62**, **64** and **68** are shown in Figs. 3 and 4 for transport of blood and components to and from the processing vessel **352**. An anticoagulant tubing assembly **50**, a plasma collection tubing and bag assembly **90**, a red blood cell collection assembly **950**, a vent bag tubing line sub-assembly **100**, and an additive solution assembly **980** are also interconnected with cassette assembly **110** in this embodiment. As will be appreciated, the extracorporeal tubing circuit **10** and blood processing vessel **352** are pre-interconnected to combinatively yield a closed, pre-sterilized disposable assembly for a single use.

The disclosures of the above-listed patents include numerous further details of an apheresis system for use with the present invention. Such details are not repeated here except generally for certain of those which may relate particularly to red blood cell (hereafter, RBC) collection and/or other RBC processes. Other blood component separation and collection

Haemonetics Corporation
Exhibit 2015
Page #1092

processes are discussed at various points herein where they may be involved in or somewhat related to features of the present disclosure.

For a particular example, emanating from vessel **352** is an RBC outlet tubing line **64** of the blood inlet/blood component tubing assembly **60** which is interconnected with integral RBC passageway **170** of cassette **115** of cassette assembly **110** (see Figs. 3 and 4). The integral RBC passageway **170** includes first and second spurs **170a** and **170b**, respectively. The first spur **170a** is interconnected with RBC return tubing loop **172** to return separated RBCs to a donor **4** as well as the buffy coat and the red blood cells located next to the buffy coat which contain at least some white blood cells. For such purpose, the RBC return tubing loop **172** is preferably interconnected to the top of a blood return reservoir **150** of the cassette assembly **110**. The second spur **170b** may, as preferred herein, be connected with an RBC collection tubing assembly **950** (see Figs. 3 and 4, for example) for collecting RBCs during use. RBC collection tubing and bag assembly **950** preferably includes RBC collector tubing line **951** which communicates with spur 1**70b**, a second collector tubing line **952** communicating with line **951**, an RBC filtration sub-assembly including an RBC leukoreduction filter **960**, an RBC collection reservoir or bag **954**, and an air removal bag **962**. Bag **954** is connected to the filter **960** by tubing line **965**. An optional clamp **966** (see Fig. 5) may be included on line **965**. The air removal bag **962** is attached to the RBC collection bag **954** by a tubing line **961** which may have an optional clamp **963**, (Figure 5), attached thereto. The RBC collection tubing line, filter and container sub-assembly **950** is a preconnected part of the disposable assembly **10**.

An alternative tubing set filter and collection bag assembly **950a** is shown in Fig. 6A and includes a second collection bag **954a** connected via a Y-type of connection **991** to filter **960**, via the branch tubing line **965a**. A further air bag **962a** is preferably connected to the second bag **954a** via a tubing line **961a**. Slide clamps **966a** and **966b** are used to direct flow to the desired bag. More details particularly as to the use hereof will be set forth below.

A further alternative embodiment is shown in Fig. 6B, which embodiment is an assembly **950b** which also includes a second collection bag **954a** with associated componentry (e.g., air bag **962a**, etc.), and a second filter **960a**, in addition to filter **960** described above. Filter 960a is connected via lines **952a** and **965a** between bag **954a** and incoming line **952**. A branch or Y connector 9**91a** allows for split flows between branch **952a** and branch **952b** which leads to the first filter **960**. Also slide clamps **966a** and **966b** may again be used to direct the flow to the respective filters.

Haemonetics Corporation
Exhibit 2015
Page #1093

The embodiment shown in Fig. 1 includes a connected pair of additive solution bags **970**; however the alternative embodiments of Figs. 3 and 4 preferably have an additive fluid tubing assembly **980** for attachment to and delivery of additive fluid(s) such as sterile saline solution(s), or additive plasma or additive storage solution, for example, to the collected or collecting product in bag system **950** as described in further detail below. As shown in Figs. 3 and 4, the additive fluid assembly **980** includes at least an additive fluid inlet tubing line **982** attached to the cassette **110** in fluid communication with an internal additive fluid passageway **140c** which is in turn connected to an additive fluid tubing loop **142** which is connected back to the cassette **110** and an internal additive fluid passageway **140d**. Two further internal passageways or spurs **144c** and **144d** and tubing **145** and **146** are also shown in the alternative embodiment of Figs. 3 and 4. These passageways **140c**, **140d** and **144c**, **144d** and tubing loops/tubing **142**, **145** and **146** are as shown, preferably similar structurally to the platelet passageways described in various of the above-referenced U.S. Patents, though they may take other forms as well. Indeed, the alternative internal passageway **144d** and tubing **145** of the embodiment of Figs. 3 and 4 may as shown, be blocked off to disallow any fluid flow therein or therethrough. Note, although no outlet tubing line is connected thereto in this embodiment, these flow channels could correspond to a platelet or other blood component collection line as shown in Fig. 2. Though similar structurally in many ways, when referring to the embodiment of Figs. 3 and 4, the component elements thereof will be referred to as additive fluid elements as opposed to platelet assembly components. This alternative naming convention will also be used for other component elements which could be referred to in connection with either the platelet assembly or the additive fluid assembly; for example, the platelet or additive fluid inlet pump (described in the art) will hereafter be referred to as an additive solution pump. Note, one further distinction is the connection of tubing line **146** to tubing lines **951** and **952** via connector **979**.

The additive fluid assembly **980** further preferably includes one or more (as shown) spike assemblies **984a**, **984b** with respective spikes **985a**, **985b** and associated sterile barrier devices **986a**, **986b** and tubing connection lines **988a**, **988b** which may be connected to tubing line **982** via a Y-connector **989** as shown. Note, it may be that only one of one or more of the above devices may be necessary; e.g., perhaps only one sterile barrier device may be used even with more than one bag of solution. One or more slide clamp(s) **990** and/or a level sensing or fluid detection apparatus **995** may also be included.

The cassette assembly **110** further includes a pump-engaging, additive fluid inlet tubing loop **142** interconnecting the first respective integral additive fluid passageway **140c** and a second integral additive fluid passageway **140d**. The second integral or additive fluid passageway **140d** includes first and second spurs **144c**, **144d**, respectively. The second spur

Haemonetics Corporation
Exhibit 2015
Page #1094

144d of the second additive fluid passageway **140d** (Figs. 3 and 4) is interconnected with additive fluid tubing **146** to deliver additive fluid through the RBC outlet line **952** for ultimate delivery to the filter **960** and then to the bag **954**. The cassette member **115** also includes an integral frame corner **116** defining a window **118** therethrough. The frame corner **116** includes access openings in window **118** for receiving and orienting the tubing segments including, for example, connector **145** and additive solution tubing **146** in predetermined spaced relationships within window **118** for ultimate engagement with a valve/clamp member on apheresis device **6**. Such a valve/clamp will, when activated, control flow through loop **142**.

In an intervening portion of the cassette **115**, a plasma tubing **68** of blood inlet/blood component tubing assembly **60** (see Figs. 3 and 4) interconnects with a first integral plasma passageway **160a** (see Fig. 4) of cassette assembly **110** (note, this is preferably a plasma collection sub-system; however, other components such as platelets could alternatively be collected here or with a similar arrangement). Cassette assembly **110** further includes a pump-engaging, plasma tubing loop **162** interconnecting the first integral plasma passageway **160a** and a second integral plasma passageway **160b**. The second integral plasma passageway **160b** includes first and second spurs **164a** and **164b**. The first spur **164a** is interconnected to the plasma collection tubing assembly **90** via tubing line **92**. The plasma collection tubing assembly **90** may be employed to collect plasma during use and includes plasma collector tubing **92** and plasma collection bag **94**. A slide clamp **96** (see Fig. 3) may be provided on plasma collector tubing **92**. The second spur **164b** of the second integral plasma passageway **160b** is interconnected to a plasma return tubing loop **166** to return plasma to donor/patient **4**. For such purpose, the plasma return tubing loop **166** is interconnected to the top of the blood return reservoir **150** of the cassette assembly **110**. As is understood, one or more types of uncollected blood components, e.g., plasma and/or platelets, collectively referred to as return blood components, will cyclically accumulate in and be removed from reservoir **150** during use. Here also, valve/clamp access is made through the frame **116** within window **118** of cassette assembly **110** to maintain the plasma collector tubing **92** and plasma return tubing loop **166** in a predetermined spaced relationship within window **118** for flow control therethrough.

Most portions of the tubing assemblies **20, 50, 60, 90, 100, 950, 950a, 950b** and/or **980** and cassette assembly **110** are preferably made from plastic components including, for example, polyvinyl chloride (PVC) tubing lines, that may permit visual observation and monitoring of blood/blood components therewithin during use. It should be noted that thin-walled PVC tubing may be employed for approved, sterile docking (i.e., the direct connection of two pieces of tubing line) for the RBC collector tubing lines **952** and **965**, as may be

Haemonetics Corporation
Exhibit 2015
Page #1095

desired and/or for an RBC storage solution spike assembly **980**. In keeping with one aspect of the invention, all tubing lines are preconnected before sterilization of the total disposable assembly to assure that maximum sterility of the system is maintained. Note, a highly desirable advantage to preconnection of all of the elements of the tubing circuit including the filter and collection bag sub-assembly **950** involves the complete pre-assembly and then sterilization hereof after pre-assembly such that no sterile docking is later necessary (spike addition of storage solution excepted). Thus, the costs and risks of sterile docking are eliminated. Alternatively, thicker-walled PVC tubing may be employed for approved, sterile docking RBC collector tubing lines **952** and/or **965**, *inter alia*.

As mentioned, a cassette assembly **110** in the embodiment of Figure 4, may be mounted upon and operatively interface with the pump/valve/sensor assembly **1000** of a blood component separation device **6** during use. Further details of an apheresis system set-up including the loading and interaction of a disposable assembly **8/10** with a blood component separation device **6**, may be found in the above-listed patents, inter alia, and are not exhaustively repeated here.

Operation of Extracorporeal Tubing Circuit and Blood Component Separation Device

Priming and various other operations of the apheresis process are preferably carried out as set forth in the above-listed patents, inter alia. However, certain basic features are also described generally here with particular reference to the schematic diagrams of Figs. 7, 8, and 9, as well as with continuing reference to Figs. 1-6.

For example, during a blood removal submode, whole blood will be passed from a donor **4** into tubing line **22** of blood removal/return tubing assembly **20** and is then transferred to blood component separation device **6** (see generally Fig. 7). At device **6**, the blood is flowed, preferably pumped via loop **132** (see Fig. 4), to the processing vessel **352** (schematically shown in dashed lines in Fig. 7 or in Fig. 2) via the cassette assembly **110** and line **62** of the blood inlet/blood component tubing assembly **60** (Figs. 3 and 4). Separation processing then occurs preferably on a substantially continuous basis in vessel **352**; i.e., blood substantially continuously flows therein, is continuously separated and continuously flows as separated components therefrom. After separation processing in vessel **352** (though separation is continuously occurring), blood components which are not going to be collected are transferred from the processing vessel **352** to and through cassette assembly **110**, into and may then accumulate in reservoir **150** (Figs. 3 and 4) of cassette **110** up to a predetermined level at which the blood component separation device **6**, in a single needle operation, may (though in a continuous system, need not) pause the blood removal submode and initiate a blood return submode wherein these uncollected and/or treated components may be returned

Haemonetics Corporation
Exhibit 2015
Page #1096

to the donor **4**. As such, these accumulated components may be transferred into the blood return tubing line **24** of blood removal/return tubing assembly **20** and back into the donor **4**. During the single needle blood return mode, when the accumulated return blood components in reservoir **150** are removed down to a predetermined level, blood component separation device **6** will then automatically end the blood return submode. This preferably will also automatically serve to reinitiate or continue the blood removal submode. The cycle between blood removal and blood return submodes will then continue until a predetermined amount of RBCs or other collected blood components have been harvested. In an alternative dual needle scheme, as is known in the art, blood may be continually removed from and blood components continually returned to a donor **4**. Note, the detailed mechanisms for such operations, including controlling the pumps, for example, are not shown or described in detail herein, particularly not in the schematic views of Figs. 7 and 8.

Note also that certain components may be collected simultaneously or consecutively one after the other. In one example, platelets and plasma may be collected prior to collection of RBCs. In the primary example shown in Figs. 1 and 3-4 and 7, 8 and 9, only two components are shown being collected, RBCs in the RBC sub-assembly **950** and plasma (or platelets) in the other collection assembly **90**. When a sufficient quantity of one or the other is collected, further separated portions of such a component are preferably returned to the donor with any other uncollected components, until a sufficient quantity of all components are collected. It is further understood that only RBCs can be collected with all other components including plasma being returned to the donor.

With specific reference to Figs. 3 and 4, in normal operation, whole blood will pass from the donor **4** through the needle and blood removal tubing assembly **20**, cassette assembly **110** and blood inlet tubing line **62** to processing vessel **352**. The whole blood will then be separated in vessel **352**. As shown in Fig. 2, a buffy coat stream containing MNCs (or a stream containing plasma or platelets) may be separated herein and be either collected in a collector assembly (not shown), or diverted to reservoir **150** for ultimate return to the donor. Further, some red blood cells including the red blood cells located at the buffy coat- RBC interface may be separated in and passed, preferably pushed from vessel **352** through RBC outlet tubing line **64**, through cassette assembly **110** and, in return mode, into reservoir **150**. These RBCs containing contaminating MNCs may be returned to the donor **4**, leaving MNC-reduced RBCs in the vessel. In an alternative, during an RBC collection procedure described below, separated MNC-reduced RBCs will be delivered to RBC collector tubing, bag and filter assembly **950** through tubing lines **951** and **952** for collection. The RBC collection protocol may also include a MNC-reduced RBC filtration process using the preconnected

Haemonetics Corporation
Exhibit 2015
Page #1097

leukoreduction filter **960** in line with and prior to RBC collection bag **954**. This procedure will be described further below.

Apheresis Protocol

One protocol, which may be followed for performing an apheresis procedure relative to a donor **4** utilizing the described system **2**, will now be summarized. Initially, an operator loads the disposable plastic assembly **8** in and/or onto the blood component separation device **6**. According hereto, the operator hangs the various bags (e.g., collection bag **954** (and **94**, if used); see Fig. 7, described further below) on the respective hooks (see hook **996** of Fig. 7, e.g.) of the blood component separation device **6**. If one is used, the operator then also loads the cassette assembly **110** on the machine **6** and/or the blood processing vessel **352** within the channel housing **204** as mounted on the centrifuge rotor assembly **568** in the machine **6**.

With the extracorporeal tubing circuit **10** and the blood processing vessel **352** loaded in the described manner, the donor **4** may then be fluidly interconnected with the extracorporeal tubing circuit **10** by inserting an access needle of the needle/tubing assembly **20** into the donor **4** (see, e.g., Fig. 7). In addition, the anticoagulant tubing assembly **50** (see Fig. 3) is primed and the blood removal/return tubing assembly **20** is primed preferably with blood from the donor **4** as described in one or more of the above-listed patents. The blood processing vessel **352** is also primed for the apheresis procedure, preferably also according to processes such as those described in the same above-listed patents. In one embodiment, a blood prime may be used in that blood will be the first liquid introduced into the blood processing vessel **352**. During the priming procedure, as well as throughout the remainder of the apheresis procedure, blood may be continuously flowed into the vessel **352**, blood component types are preferably continuously being separated from each other and one or more of these is also preferably continuously removed from the blood processing vessel **352**, on a blood component type basis. Preferably, at all times during the apheresis procedure, from priming onward, a flow of blood is substantially continuously provided to the blood processing vessel **352** and at least one type of separated component is continuously removed.

It should be noted that when the centrifuge rotor is spinning (as it preferably will be whenever blood is disposed within the blood processing vessel) it will impart centrifugal forces on the blood which will then separate into three primary component layers around the blood processing vessel: a first innermost layer containing at least plasma, a second intermediate layer of "buffy coat" which contains at least platelets and mononuclear cells (MNCs) and a third outermost layer containing primarily red blood cells. It should be noted however, that due to the close sizes of red blood cells and leukocytes, the RBC layer closest

Haemonetics Corporation
Exhibit 2015
Page #1098

to the buffy coat layer interface (at the outermost layer) will contain at least a portion of WBCs. This red blood cell layer partially overlaps with the buffy coat layer.

The buffy coat layer is generally found on the interface between the red blood cell layer and the plasma layer (see element **82** of Fig. 2). Because centrifugal separation will less effectively separate the white blood cells from the red blood cells due to their close size as mentioned above, there is likely to be white blood cell contamination of at least a portion of the the red blood cells closest to the buffy coat layer. As discussed above, this fraction or layer is called the red blood cell layer which partially overlaps with the buffy coat layer (see element **83** of Fig. 2).

Although separation and collection of various components may be performed, RBCs are the component of the most interest in the current invention, and thus the separation and collection protocol will continue with a description of the collection and filtration hereof. It is understood that RBCs may also be the only component collected with all other components being returned to the donor.

In turn, such separated blood components may be selectively collected in corresponding storage reservoirs (not shown) or immediately or after a minor delay returned to the donor **4** during respective blood return submodes (or substantially constantly in a two-needle setup). In this regard, and in one approach where more than one blood component is to be collected, such as plasma and/or platelets, blood apheresis system **2** may be used to collect other components during a time period(s) separate from the collection of red blood cells. These components may also be collected simultaneously. Note, if other components are collected prior to RBCs, then RBCs separated during any such other component phase may be diverted back to the donor and not filtered. Preferably, only collected MNC-reduced RBCs will be filtered in the current embodiment (though therapeutic filtration for a particular donor/patient may also be performed). By removing the other component layers, especially the buffy coat layer and the red blood cell layer which partially overlaps with the buffy coat layer, the remaining MNC-reduced red blood cells will be less contaminated with lymphocytes, and will be able to be filtered more efficiently to remove any remaining white blood cells. The buffy coat layer and the RBC layer containing the at least a portion of MNCs can either be returned to the donor, or collected into a storage reservoir or collection bag and further processed.

In any event, the RBC collection procedure is preferably controlled via control signals provided by blood collection device **6**. Such an RBC collection procedure may include a setup phase and a collection phase. During such a setup phase, the blood apheresis system **2** may be adjusted automatically to establish a predetermined hematocrit in those portions of the

Haemonetics Corporation
Exhibit 2015
Page #1099

blood processing vessel **352** and extracorporeal tubing circuit **10** through which separated RBCs will pass for collection during the RBC collection phase. A desirable resulting hematocrit for RBC collection may be between about 70 and about 90 or even up to 95+, and may be established at about 80. The term high hematocrit refers to those separated, undiluted RBCs leaving the separation vessel **352**. Dilution with storage solution to a different (generally lower) collected hematocrit may follow.

Additionally, blood component device **6** may, during the set-up phase, divert the flow of separated RBCs flowing through RBC tubing line **64** through return tubing loop **172** and into blood return reservoir **150** for return to the donor **4** until the desired hematocrit is established in the separation vessel **352**.

Also during the set up phase, the blood component separation device may divert the flow of the buffy coat layer **82** and the portion of the red blood cells **83** which are closest to the buffy coat layer either back to the donor or into a collection bag for further processing. By removing this portion of the red blood cells and the buffy coat layer from the blood processing vessel, the majority of the mononuclear cells will be removed. The red blood cells remaining in the separation vessel **352** are known as mononuclear cell reduced red blood cells.

The increased efficiency of removing the buffy coat layer and the layer of RBCs next to the buffy coat layer is shown in the table below.

N (= 22)	Contaminating cell count after leukoreduction without removal of buffy coat laver and the RBCs next to buffy coat laver	Contaminating cell count after leukoreduction of MNC-reduced RBCs
1	4.9	0.31
2	2.4	0.02
3	7.8	0.04
4	0.3	0.22
5	0.2	0.05
6	5.9	0.02
7	3.2	0.05
8	0.1	0.09
9	3.0	0.06
10	4.7	0.01
11	2.0	0.04
12	11.3	1.22
13	1.1	.022
14	15.3	4.03
15	1.3	0.37
16	0.4	0.07
17	14.7	0.44
18	0.5	0.03
19	0.3	0.06
20	2.6	0.16

Haemonetics Corporation
Exhibit 2015
Page #1100

21	3.1	2.37
22	2.3	0.04

As can be seen in the table above, the step of removing the buffy coat layer and the RBCs located next to the buffy coat layer produced a final RBC product with much lower WBC contamination as compared to the final RBC product produced without the removal step.

In order to establish the desired packing factor and/or hematocrit for the separated MNC-reduced RBCs, the operating speed of centrifuge rotor assembly **568** (see Fig. 1) may be selectively established via control signals from blood component separation device **6**, and the blood inlet flow rate to vessel **352** may be selectively controlled by blood component separation device **6** controlling the speeds of the respective pump assemblies (not shown or described in detail here). More particularly, increasing the rpms of centrifuge rotor assembly **568** and/or decreasing the inlet flow rate will tend to increase the packing factor and/or hematocrit, while decreasing the rpms and/or increasing the flow rate will tend to decrease the packing factor and/or hematocrit. As can be appreciated, the blood inlet flow rate to vessel **352** may effectively be limited by the desired packing factor or hematocrit.

To establish a desired anticoagulant (AC) ratio, blood component separation device **6** provides appropriate control signals to the anticoagulant pump so as to introduce anticoagulant into the blood inlet flow at a predetermined rate. Relatedly, it should be noted that the inlet flow rate of anticoagulated blood to blood processing vessel **352** may be limited by a predetermined, maximum acceptable anticoagulant infusion rate (ACIR) to the donor **4**. As will be appreciated by those skilled in the art, the predetermined ACIR may be established on a donor-specific basis (e.g. to account for the particular total blood volume of the donor **4**). To establish the desired total uncollected plasma flow rate out of blood processing vessel **352**, blood collection device **6** provides appropriate control signals to the plasma (and platelet) pump assembly(ies). This may also serve to increase the hematocrit in the separated RBCs.

In one embodiment, the desired high hematocrit for the separated RBCs will be between about or approximately 75 and about 85 and will preferably be about or approximately 80; although, again higher hematocrits may be available as well. Then, where a centrifuge rotor assembly **568** may present a defined rotor diameter of about 10 inches, and where a blood processing vessel **352** is utilized, as described hereinabove, it has been determined that in one preferred embodiment channel housing **204** can be typically driven at a rotational velocity of about 3000 rpms to achieve the desired RBC hematocrit during the setup and red blood cell collection phases. Correspondingly, the blood inlet flow rate provided by pumping through loop **132** to vessel **352** may preferably be established at below

Haemonetics Corporation
Exhibit 2015
Page #1101

about 65 ml/min. The desired hematocrit can be reliably stabilized by passing about two whole blood volumes of vessel **352** through vessel **352** before the RBC collection phase is initiated.

To initiate the MNC-reduced RBC collection phase, blood component separation device **6** provides an appropriate control signal to the RBC divert valve assembly (not shown) so as to direct the continuous outflow of the separated MNC-reduced high hematocrit RBCs removed from blood processing vessel **352** via line **64** into the RBC collection system **950** through tubing lines **951** and **952**, and filter **960** into collection container **954** via line **965**.

As may be appreciated, the MNC- reduced, separated RBCs are not pumped out of vessel **352** for collection, but instead are flowed out vessel **352** and through extracorporeal tubing circuit **10** by the pressure of the blood inlet flow to vessel **352**. The inlet blood is pumped into vessel **352** via loop **132** of cassette **110**. The separated MNC-reduced RBCs are pushed or pressed out of the vessel **352**.

During the RBC collection phase, the inlet flow into vessel **352** will likely be limited by the above-noted maximum acceptable ACIR to the donor **4**. The desired inlet flow rate may also be limited by that necessary to maintain the desired packing factor and/or hematocrit, as also discussed. In this regard, it will be appreciated that relative to the setup phase, the inlet flow rate may be adjusted slightly upwards during the RBC collection phase since not all anticoagulant is being returned to the donor **4**. That is, a small portion of the AC may remain with the small amount of plasma that is collected with the high hematocrit RBCs in RBC reservoir **954**.

According to the present invention, the relatively high hematocrit (high-crit) MNC-reduced RBCs optionally may be diluted and then filtered as soon as the blood is separated or very soon after having been separated within vessel **352**. Alternatively, the MNC-reduced RBCs may be filtered without dilution in a high-crit state. The phrase high-crit refers to the state of the separated MNC-reduced RBCs as they emerge from the separation vessel **352**. In the substantially continuous centrifugal separation process as described here, a freshly separated stream of MNC-reduced RBCs is substantially continually flowing out of the vessel **352**, first through tubing line **64**, to and through cassette assembly **110** and then through lines **951** and **952** (where they optionally may be joined by diluting storage solution) to the filter **960** and then through line **965** to bag **954** (see Fig. 7). Preferably, these freshly separated MNC-reduced RBCs will be continuously flowing from vessel **352** through filter **960** and then into collection bag **954** (or also into bag **954a**, see Figs. 6A and 6B). Thus, in the described embodiment, white cell/leukocyte filtration will have begun and is continued

Haemonetics Corporation
Exhibit 2015
Page #1102

simultaneously with or during the overall continuous separation process, prior to collection. More description of this will be set forth in further detail below.

Note, the phrase freshly-separated is intended to describe the newly-separated blood components in and as they emerge from the mechanical separation system such as device **6** and separation vessel **352**. It also includes the state of these same separated components for a reasonable length of time after removal from the mechanical separation device such as from vessel **352**. Thus, for example, a reasonable length of time may include the entire apheresis procedure which may last up to (and perhaps exceed) two (2) or more hours during which filtration may be substantially continuously performed. Two further terms used herein have similar distinctions, namely, "recently removed" and "soon after." Recently removed is referred to herein primarily relative to that blood taken from the donor which may be immediately taken and processed in a mechanical separation system, or which may have been taken and held subject to a reasonable non-long-term-storage type of delay prior to separation processing in a device such as device **6**. Similarly, "soon after" is used in like manners relative to both of these circumstances as well, as, for example, when separated blood components may be removed from the separation vessel, e.g. soon after separation (whether in continuous or batch mode).

In any event, from the standpoint of the donor **4** and machine **6**, following the separation, filtration and collection processes of the desired quantity of red blood cells, blood separation device **6** may then provide a control signal to the RBC divert assembly so as to divert any further RBC flow back to the donor **4** via loop **172**, reservoir **150** and return line **24**. Additionally, if further blood processing, by apheresis centrifugation here, is not desired, rinseback procedures may be completed. Additionally, once the minimum desired RBCs have been diverted into filtration/collection assembly **950** and after filtration completion, the red blood cell collection reservoir **954** (and/or the entire sub-assembly **950**) may then be disconnected from the extracorporeal tubing circuit **10**. Filter **960** may also be removed herewith or separately or remain attached and disposed of with the cassette **110** and other remaining bags or tubes. However, according to the present invention, a storage solution will be, perhaps during and/or after filtration of the RBCs, added to the RBC flow in tubing line **952** to the filter **960** ultimately to the red blood cell reservoir or bag **954**. Preferably, a spike connection to one or more storage solution bag(s) **970** (see Figs. 1 and 7) through a spike **985** is used. This process will also be described further below. Such storage solutions or additive solutions may advantageously facilitate storage of the RBCs for up to about forty-two days at a temperature of about 1 – 6 °C. In this regard, acceptable storage solutions include a storage solution generically referred to in the United States as Additive Solution 3 (AS-3), available from Medsep Corp. located in Covina, California; and/or a storage solution generically

Haemonetics Corporation
Exhibit 2015
Page #1103

referred to in Europe as SAG-M, available from MacoPharma located in Tourcoing, France. It is also possible to use saline before, after or during the filtering process described below which, prior to storage, could be replaced with the desired storage solution. Alternatively saline could be used to flow through the filter **960** to the cassette assembly **110**.

The storage additive solution may be and preferably is contained in a discrete storage solution bag **970** that can be pre-connected, or is separate and may selectively be later interconnected to the tubing circuit **10** via line **982**, preferably through a spike connection **985**. In an alternative embodiment, such selective interconnection may be provided via sterile-docking to tubing line **982** as an example (process not shown) utilizing a sterile connecting device (not shown). By way of example, one such sterile connecting device to interconnect a tubing line **982** to such a storage solution container **970**, is that offered under the trade name "TSCD" or "SCD™ 312" by Terumo Medical Corporation located in Somerset, New Jersey. In the alternative above, the selective interconnection may be established utilizing a sterile barrier filter/spike assembly **980**. The use of such a sterile barrier filter/spike assembly **980** facilitates the maintenance of a closed system, thereby effectively avoiding bacterial contamination. By way of example, the mechanical, sterile barrier filter **986** (Figure 7) or **986a** or **986b** in such an assembly **980** may include a porous membrane having 0.2 micron pores. Pumping via a tubing loop **142** may then provide for selectively flowing solution through tubing line **982** and connecting tubing line **146** for introduction of the storage solution into the RBC line **952** and filter system **950**.

In order to ensure the maintenance of RBC quality, the collection RBC bag **954**, and the storage solution and the anticoagulant used during blood processing should be compatible. For example, the collection RBC reservoir **954** may be a standard PVC DEHP reservoir (i.e. polyvinyl chloride-diethylhexylphthallate) such as those offered by the Medsep Corporation. Alternatively, other PVC reservoirs may be employed. Such a reservoir may utilize a plasticizer offered under the trade name "CITRIFLEX-B6" by Moreflex located in Commerce, California. Further, the anticoagulant utilized in connection with the above-described red blood cell collection procedures may be an acid citrate dextrose-formula A (ACD-A).

Nevertheless, according to an embodiment of the present invention as introduced above, the storage solution may be flowed after and/or added to the flow of separated MNC-reduced red blood cells flowing in lines **951** and **952**, and flow therewith to and through the filter **960.** Filter **960** will remove the majority of the remainder of white blood cells which are left in the MNC-reduced red blood cells. More particularly leukoreduction filtering is desired to establish a white blood cell count of $< 5 \times 10^6$ white blood cells/unit (e.g. about

Haemonetics Corporation
Exhibit 2015
Page #1104

250 ml.) to reduce any likelihood of febrile non-hemolytic transfusion reactions. Moreover, such filtering will more desirably achieve a white blood cell count of $< 1 \times 10^6$ white blood cells/unit to reduce any risk of HLA (i.e. human leukocyte A) sensitization and/or other serious side reactions. Studies have also shown positive effects for pre-storage leukocyte reduction in improving the functional quality of erythrocytes during storage and in decreasing the occurrence of alloimmunization in patients receiving multiple transfusions, as well as being favorable in metabolism reactions such as intra-erythrocyte ATP and/or extracellular potassium levels declining more slowly in filtered products. Perhaps more important is the reduction of transfusion transmitted disease, especially cytomegalovirus (CMV) and/or HIV, *inter alia*.

Accordingly, the red blood cell collection container **954** receives, in one embodiment, RBCs and additive solution from the red cell filter **960** such that high hematocrit (preferably Hct between 70 and 90 and/or approximately equal to 80), freshly separated MNC-reduced red blood cells alone or together with additive solution are preferably pushed through filter **960** and into the ultimate RBC collection bag **954**. Such pushed filtration is shown in Figs. 7, 8 and 9, as will be described further below. The red cell filter **960** and collection bag sub-assembly **950** is preferably preconnected to the tubing circuit **8** as part of the disposable assembly **10** (to avoid the costs and risks of sterile docking) as shown in Figs. 1, 3 and 4 in accordance with the teachings of this invention. The red blood cell filter 960 may also be added to the previously existing disposable systems to form a post-manufacturing-connectable disposable assembly using special new kits or commercially available filter/bag kits such as those available under the trade name "Sepacell" from Asahi Corp and/or Baxter, Inc. and/or "RC100", "RC50" and "BPF4", etc., from Pall Corp., located in Glencove, New York, inter alia. In either event, the red cell filter/bag sub-assembly is preferably connected (pre- or post-) to the tubing circuit **8** through a tubing line **951** and/or **952** as shown.

Referring now primarily to Figs. 3, 4 and 5, the procedure for the filtration of MNC-reduced RBCs freshly separated and collected from the apheresis process is as follows. These freshly separated MNC-reduced RBCs are either in an undiluted, high-hematocrit state (Hct approximately 80) during the preferred filtration process, followed by additive solution or storage solution, or are filtered in a mixed state with additive solution added to the RBC flow in line **952** at the connection **979**. Moreover, storage solution may be flowed through the filter **960** prior to any MNC-reduced RBCs (this may enhance the filtration efficacy) and, as noted above, may optionally be flowed through the filter after leukoreduction of the RBCs to be added to the collected RBCs in bag **954**. In an embodiment, no matter when the additive or storage solution initially flows through the filter, it is preferable to run a sufficient amount

Haemonetics Corporation
Exhibit 2015
Page #1105

of solution through the filter **960** after MNC-reduced RBC filtration to attempt to displace any RBCs remaining in the volume of the filter **960** for collection.

Either simultaneously with the substantially continuous separation and collection process (i.e., as soon as high hematocrit (high-crit) MNC-reduced RBCs are separated from other components and pushed out of vessel **352** to cassette **110** and not diverted back to the donor), or soon after a desired minimum quantity of other blood components have been collected, if desired, the RBC collection/filtration system **950** is activated to filter the MNC-reduced RBCs. This collection process is activated by switching the clamp/valve of device **6** to stop diversion flow through loop **172** and allow flow through line **951** to line **952** and filter **960**.

In either case; simultaneously with the continuous collection in bag **954** from the separation vessel **352**, or soon after completion of any other non-RBC collection process(es), the MNC-reduced RBCs are flowed preferably by intrinsic pressure pushing (non-active pumping) through filter **960**. As such, collection bag **954** may be hung at a level above both the separation vessel **352** and the filter **960** (see Figs. 5-8) so that the continuously flowing MNC-reduced RBCs are allowed to move upwardly from vessel **352** through the filter **960** and into the collection bag **954**. One embodiment of this is shown in Fig. 7, where the collection bag **954** is hung from a hook **996** of the machine **6** in known fashion. Tubing line **965** depends downwardly therefrom and is shown as connected to the filter **960**, out of the top of which extends the next tubing line **952** which ultimately connects downwardly to the cassette **110** via line **951**.

Any air from bag **954**, or air caught between the incoming filtered RBCs and bag **954** is ultimately removed to air removal bag **962** through tubing line connection **961**. The air is evacuated to air removal bag **962** prior to the flow of the incoming RBCs or is evacuated by the flow of the incoming RBCs. It is also understood that air can also be vented prior to even the separation process by initially running the return pump, (not shown) of the apheresis system. It is also understood that removal of air may also be achieved by other known methods, including, for example, hydrophobic vents and/or by-pass lines. It is desirable to perform the filtering of the MNC-reduced RBCs according to the present invention directly on the machine **6** during the apheresis separation process and without pre-cooling or pre-storing the RBCs. In such a case, these procedures are thus performed without the previously conventional steps of intermediate separation/collection and cooling and storing overnight at 4 °C.

Haemonetics Corporation
Exhibit 2015
Page #1106

Then, either after completion of or during and/or even before the filtration in either of these embodiments, namely, the simultaneous collection and filtering, or in the filtering and collection soon after any other component collection processes, storage solution is flowed to and through the filter and/or added to the MNC-reduced RBCs. Again, this may be performed either before and/or during and/or after completion of the filtration of the otherwise high hematocrit MNC-reduced RBCs through filter **960**, although it is preferred that an amount of additional additive or storage solution displace the volume of the filter to recover any residual RBCs therefrom. In particular, a storage solution bag **970** has been connected (by pre-connection or by spike or sterile welding) as depicted in Figs. 1, 7, 8 and 9, the clamp **990** is opened (if any such optional flow-stopping member is used; see Figs. 3 and 4) to allow the introduction of the storage solution into tubing line **982** and pumped via tubing loop **142** through additive solution tubing **146** and into tubing line **952** via connector **979**. The storage solution thus will be pumped from bag **970** through filter **960** and into collection bag **954**. If pumped during collection, the solution may be metered into and mix with and dilute the high-crit MNC-reduced RBCs in line **952** prior to filtration. The rate of mixing can be controlled by pumping via loop **142**. However, the storage solution may be pumped through the filter **960** also before and/or after all of the undiluted MNC-reduced RBCs have been filtered therethrough to assist in the filtration and/or to chase the MNC-reduced RBCs and move any MNC-reduced RBCs caught in the filter out of the filter to the collection bag **954**. Such a storage solution chase may be used also after the metering of storage solution into a pre-filtration MNC-reduced RBC flow (as described above) as well. Again, all of the steps in operating the MNC-reduced RBC filtration system **950** may be performed during the overall apheresis component separation procedure and thus need not be subjected to a cooled, time-delayed environment.

It should be noted that storage solution does not need to be pumped through the filter. Storage solution may also be flushed through the filter manually, using gravity.

One embodiment of the storage solution addition step is shown in Figs. 7, 8 and 9. Note, other component collection processes are not shown here (i.e., whether simultaneous or consecutive collection processes for other components (e.g., plasma and/or platelets) are used is not depicted or described here). In Figs. 7, 8 and 9, the collection bag **954** is shown attached to the upper hook **996** and the air bag **962** hung on another hook **998** (note, air bag **962** may not need to be hung from a hook but could have air bled thereto after the other steps in the process as suggested below). Then, a storage solution bag **970** can be hung from yet another hook **997** so that when connected and hung as shown in Figs. 7 and 8, storage solution can flow down through tubing line **982** and through sterile barrier **986** through pump loop **142**, connecting lines **146** and **952** and then through filter **960** and ultimately into

Haemonetics Corporation
Exhibit 2015
Page #1107

collection bag **954**. Although flow of both storage solution and MNC-reduced RBCs is shown entering the filter **960** in the downward direction in Figs. 7 and 8 and the upward direction in Fig. 9, it is also understood that flow to the filter **960** can be in any direction desired, including, but not limited to sideways. This flow against gravity is possible because the MNC-reduced RBCs are pushed through the filter.

Alternatively, the embodiment shown in Fig. 8 also includes a depiction of the placement of the filter **960** in a substantially fixed position on device **6**. In this embodiment flow will remain in a downward direction to aid in priming the filter **960**. Clips or other restraining devices **901** are shown holding filter **960** in place. The further steps of having collected or simultaneously collecting components other than the RBCs in bag **954** and/or the alternatives of simultaneously pumping solution into the flow of MNC-reduced RBCs and/or having completed filtration thereof through filter **960** prior to the addition of storage solution to filter **960** and bag **954** are not easily separately shown in the Figs.; however, flow control over the storage solution will preferably be made by a pump on device **6** engaging loop **142**.

The embodiment shown in Figure 9 depicts the filter **960** hanging from bag **954** without attachment to device **8**. This embodiment allows flow of both storage solution and MNC-reduced RBCs in the upward direction to and through the filter **960**. Although not shown in Fig. 9, a bracket or clip or other restraining device like that shown as element **901** in Fig. 8 may be used to surround filter **960** to provide mechanical support and to insure the filter is placed in the correct orientation.

In either event, upon completion of filtration and/or chasing with additive solution, the collection bag **954** may be separated from the rest of the set **8**. Optional clamp **966** may be closed prior to such a separation. The separation may be made by RF sealing the tubing line **965** above the filter **960** or line **952** below the filter **960** and then separating in accordance with U.S. Patent Nos. 5,345,070 and 5,520,218, inter alia, along the RF-sealed portion of the tubing line. Other well known methods can also be used to close the tubing line and then also separate the RBC collection system **950** from the remainder of the disposable assembly **8**. An RBC collection system **950** which would be remaining after one such severing, e.g., below the filter **960**, is shown schematically in Figs. 5 and/or 6A or 6B (see below).

With respect to Figure 5 it is noted that tubing line **965** may be a segmented tubing line that is further sealed to provide sample segments as is well known. It is also understood that tubing line **961** in addition to tubing line **965** or alternatively to tubing line **965** may also be segmented to again provide the desired samples for blood tying and other optional purposes.

Haemonetics Corporation
Exhibit 2015
Page #1108

Several advantages can be realized utilizing the preconnected disposable assembly and the above-described procedure for high-crit MNC-reduced red blood cell collection and filtration. Such advantages include: consistency in final RBC product volume and hematocrit; reduced exposure of a recipient if multiple units of blood products are collected from a single donor and transfused to a single recipient; reduced time requirements for RBC collection and filtration, including collection of double units of red blood cells if desired, and reduced risks of leukocyte contamination of the final RBC product due to the filter becoming clogged with MNCs which get pushed through the filter into the previously filtered RBCs, thus causing recontamination of the previously filtered RBCs. Further advantages include a system which is less complicated and requires less human interaction. Less human interaction is advantageous because it decreases the possibilities of human contamination.

In order to assist an operator in performing the various steps of the protocol being used in an apheresis procedure with the apheresis system **2**, the apheresis system **2** preferably includes a computer graphical interface **660** as illustrated generally in Fig. 1. The graphical interface **660** may preferably include a computer display **664** which has "touch screen" capabilities; however, other appropriate input devices (e.g., keyboard) may also be utilized alone or in combination with the touch screen. The graphics interface **660** may provide a number of advantages, but may preferably, at least, assist the operator by providing pictorials of how and/or when the operator may accomplish at least certain steps of the apheresis and/or filtration procedures.

For example, the display screen optionally may sequentially display a number of pictorials to the operator to convey the steps which should be completed to accomplish the filtering procedure described here. More particularly, a pictorial image optionally may be shown on the screen to pictorially convey to the operator when and/or how to hang the respective RBC and solution bags **954** and/or **970** on the machine **6**, initially and/or during use with a storage solution dilution and/or flush (see Figs. 7 and 8, for example). One or more pictorials may also be provided to instruct the operator when to open or close clamps to begin the filtration process, and/or to visually ensure that the filtration process has appropriately begun simultaneously or during RBC collection. One or more pictorials may also be used to instruct the operator when to connect the spike assembly **980** to a storage solution container **970** and/or when to open a clamp or break a frangible connector (if included) after and/or during the MNC-reduced RBCs flow through filter **960**, to thus initiate the flow of the storage solution through the filter **960** and flush any residual MNC-reduced RBCs therethrough. One or more pictorials may also be used to instruct the operator when the tube line **965** leading to the RBC collection bag **954** should be sealed such that the RBC

Haemonetics Corporation
Exhibit 2015
Page #1109

collect bag **954**, and the remaining elements of RBC storage assembly **950** may be separated and/or removed from the disposable assembly **10** and/or from the device **6**. A similar pictorial can instruct when to seal the air tube **961** to isolate the RBC collection bag **954** from the air bag **962** and the rest of the system after the filtration and flushing and air handling procedures may be completed.

Note, a further advantage of the presently described system includes the manner of handling air. More specifically, the present invention eliminates the prior need for the vents and/or by-pass methods and/or apparatuses of conventional red blood cell filters. Moreover, the present invention is capable of delivering this advantage with no reduction in and/or perhaps an increase in the recovery of RBCs that historically have been trapped inside the filtration device.

A means used by the present invention to deliver this advantage is through the provision of a storage solution flush through the filter **960** after the MNC-reduced RBCs have finished filtering therethrough. The storage solution may then be able to wash MNC-reduced RBCs caught therein out of the filter and then into the collection bag **954**. Prior devices relied upon vents or by-pass mechanisms to assist in pushing out any RBCs disposed in the filter. Note, though not preferred or needed, vents or by-passes could still be used with the current pushed filtration process, and also with and/or in lieu of the storage solution flush after filtration. Thus such vents or by-passes may be optional features to the described system if it is desired to purge the filter **960** with air or with a combination of air and fluid.

In any event, elimination of the need for vents or by-passes also reduces other prior difficulties such as inadvertent allowances of excess air into the system. Extra air in the present system will not stop or slow the flow of blood or storage solution through the filter in the present invention. The extra air will then be caught within the collection bag **954** and may thus be removed at the end of the overall process to the air bag **962** (air moved thereto by bag positioning or squeezing, etc.). Then, also, because neither vents nor by-passes are required in this embodiment, failures with respect to the operation of such vents are not of concern since the subsequent storage solution flush recovers the RBCs from the filter without the previously desired use of a vent or by-pass. Consequently, also, the filter may be disposed at any of a plurality of alternative vertical dispositions above or below the vessel **352** and/or the collection bag **954**. Operation of the present invention should not be hindered by such alternative placements. It is understood, however, that air could also be used to chase either the RBCs or additive solution through filter **960** as described above.

Haemonetics Corporation
Exhibit 2015
Page #1110

Although the instant invention eliminates the need for by-passes it is understood that one could be provided in the extracorporeal tubing circuit to by-pass the filter **960** in the event the leukoreduction is terminated or is not desired. Similarly it is understood that an optional pressure relief valve or vent could be added to prevent pressure build up in parts of the system including the filter.

The volume of storage solution to be used may, however, be modified depending upon the relative lengths of tubing lines used and/or the air that gets into the system. For example, if 100 ml of storage solution is desired to be mixed with the end product RBCs in collection bag **954** then some certain volume more than 100 ml of storage solution would preferably be fed into the system to compensate for the tubing lengths and the volume of the filter. The amount of solution may be chosen such that 100 ml would go into the collection bag **954** with the additional amount remaining in the tubing line and filter between the cassette **110** and the collection bag **954**.

Note, a storage solution dilution during RBC filtration and/or flush after filtration completion are the primary alternatives taught here. However it is possible that storage solution flow into bag **954** may be begun at other times as well as, for example, prior to starting the high-crit or diluted MNC-reduced RBC pushed filtration. Pulsed and/or intermittent flows may also be desirable to assist in removing final volumes of RBCs from the filter **960**.

Another alternative introduced hereinabove involves the use of other extracorporeal blood processing systems. Although the preference is for a continuous flow apheresis system, as described here, which includes returning some components back to the donor, batch flow and non-return systems are also useable herewith. For example, a batch mode processor takes in a certain quantity of whole blood which was previously collected from a donor at some point before the separation process is begun. The batch mode processor separates the blood into components (in a centrifuge bowl, e.g.) and then passes the separated components to collection containers. The separated components may also be given back to the donor. The filtration process of the present invention could foreseeably nevertheless operate in substantially the same manner such that the separated MNC-reduced RBCs would nonetheless exist in a substantially high hematocrit state as they are flowed from the separation mechanism, at which point these high-crit separated MNC-reduced RBCs could be flowed to a junction with a storage solution tubing line and from there be passed directly or soon thereafter to and through a filter **960** to be collected ultimately in a collection bag **954**. Though continuity may be reduced (or substantially removed), the principles of firstly removing the buffy coat layer and the RBCs located next to the buffy coat layer before pushed

Haemonetics Corporation
Exhibit 2015
Page #1111

filtration (high-crit or diluted) during or soon after the overall separation and collection remain the same. Note, even if flow through the filter **960** stops at any point, or a plurality of points, this does not appear problematic here where any air entry therein is handled by ultimate capture in the air bag **962**.

Smaller scale separation and collection devices are also envisioned to be useful herewith. For example, various separation devices (whether centrifugal or membrane or other types) are designed to separate only RBCs and plasma (with the remainder usually remaining in the RBC product), and these can take on smaller scale mechanizations. Nevertheless, the present invention is useful herewith as well in that MNC-reduced RBCs separated hereby may also be freshly push-filtered at high and/or diluted hematocrits. The principle of push-filtering such MNC-reduced RBCs during or soon after the overall separation and collection process remains the same here as well. Thus, whether continuous or in batch mode, a flow of high-crit or diluted, freshly-separated MNC-reduced RBCs can be push-flowed from the separation device immediately or soon after previous processing therein, to and through filter **960** to a collection bag **954**.

The foregoing description of the present invention has been presented for purposes of illustration and description. Furthermore, the description is not intended to limit the invention to the form disclosed herein. Consequently, variations and modifications commensurate with the above teachings, and skill and knowledge of the relevant art, are within the scope of the present invention. The embodiments described hereinabove are further intended to explain best modes known of practicing the invention and to enable others skilled in the art to utilize the invention in such, or other embodiments and with various modifications required by the particular application(s) or use(s) of the present invention. It is intended that the appended claims be construed to include alternative embodiments to the extent permitted by the prior art.

Haemonetics Corporation
Exhibit 2015
Page #1112

CLAIMS

1. A method for providing red blood cells from whole blood using an apheresis system comprising the steps of:

separating the whole blood into blood component layers within a separation vessel wherein the blood component layers comprise at least a plasma layer, a buffy coat layer and a red blood cell layer;

removing the plasma layer from the separation vessel;

removing the buffy coat layer from the separation vessel; and

removing a portion of the red blood cell layer closest to the buffy coat layer to provide a mononuclear cell-reduced red blood cell layer in the separation vessel.

2. The method of claim 1 wherein the whole blood is recently removed from a donor.

3. The method of claim 1 wherein the separating step comprises separating in a continuous manner.

4. The method of claim 1 wherein the separating step comprises separating in a batch wise manner.

5. The method of claim 1 further comprising removing the mononuclear cell-reduced red blood cell layer from the separation vessel.

6. The method of claim 1 further comprising leukoreducing the mononuclear cell-reduced red blood cell layer to create leukoreduced red blood cells.

7. The method of claim 6 wherein the leukoreduced red blood cells are at a high hematocrit.

8. The method of claim 5 wherein the step of removing the mononuclear cell-reduced red blood cell layer further comprises removing the mononuclear cell-reduced red blood cell layer from the separation vessel to a preconnected red blood cell collection bag.

9. The method of claim 8 wherein the step of removing the mononuclear cell-reduced red blood cells from the separation vessel to a preconnected red blood cell collection bag occurs after the mononuclear cell-reduced red blood cells have been leukoreduced.

10. The method of claim 6 wherein the step of leukoreducing the mononuclear cell-reduced red blood cells further comprises pushing the mononuclear cell-reduced red blood cells through a leukoreduction filter preconnected to the separation vessel.

Haemonetics Corporation
Exhibit 2015
Page #1113

11. The method of claim 10 wherein the step of pushing the mononuclear cell-reduced red blood cells through the leukoreduction filter further comprises pushing by non-gravity forces.

12. The method of claim 10 wherein the step of pushing the mononuclear cell-reduced red blood cells through the leukoreduction filter further comprises pushing by indirect pumping forces.

13. The method of claim 2 wherein the step of removing the buffy coat layer further comprises returning the buffy coat layer to the donor.

14. The method of claim 1 wherein the step of removing the buffy coat layer further comprises collecting the buffy coat layer in a preconnected collection container for further processing.

15. The method of claim 2 wherein the step of removing a portion of the red blood cell layer closest to the buffy coat layer further comprises returning the portion of the red blood cell layer closest to the buffy coat layer to the donor.

16. The method of claim 1 wherein the step of removing a portion of the red blood cell layer closest to the buffy coat layer further comprises collecting the portion of the red blood cell layer closest to the buffy coat layer in a preconnected collection container for further processing.

17. The method of claim 10 further comprising flowing a solution through the preconnected leukoreduction filter after the pushing step to displace high hematocrit mononuclear cell-reduced red blood cells from the filter.

18. The method of claim 17 wherein the flowing step comprises flowing a storage solution.

19. The method of claim 6 wherein the separating step comprises separating in a continuous manner and wherein the step of leukoreducing the mononuclear-reduced red blood cells occurs at least partially during the step of separating in a continuous manner.

20. A method for increasing the performance of a leukoreduction filter for leukoreducing cells collected during an apheresis procedure comprising the steps of:

separating in a blood separation vessel whole blood into

an innermost layer containing at least plasma;

an intermediate layer containing at least buffy coat; and

an outermost layer containing at least red blood cells;

Haemonetics Corporation
Exhibit 2015
Page #1114

removing the innermost layer from the blood separation vessel;

removing the intermediate layer from the blood separation vessel; and

removing a portion of the outermost layer closest to the intermediate layer to create a mononuclear cell-reduced red blood cell layer in the blood separation vessel to be further leukoreduced using the leukoreduction filter.

21. The method of claim 20 wherein the step of removing a portion of the outermost layer closest to the intermediate layer increases the performance of the leukoreduction filter by removing mononuclear cells which may clog the leukoreduction filter.

22. The method of claim 20 wherein the step of removing a portion of the outermost layer closest to the intermediate layer increases the performance of the leukoreduction filter by removing mononuclear cells which may be too numerous to be effectively removed by the leukoreduction filter.

Haemonetics Corporation
Exhibit 2015
Page #1115

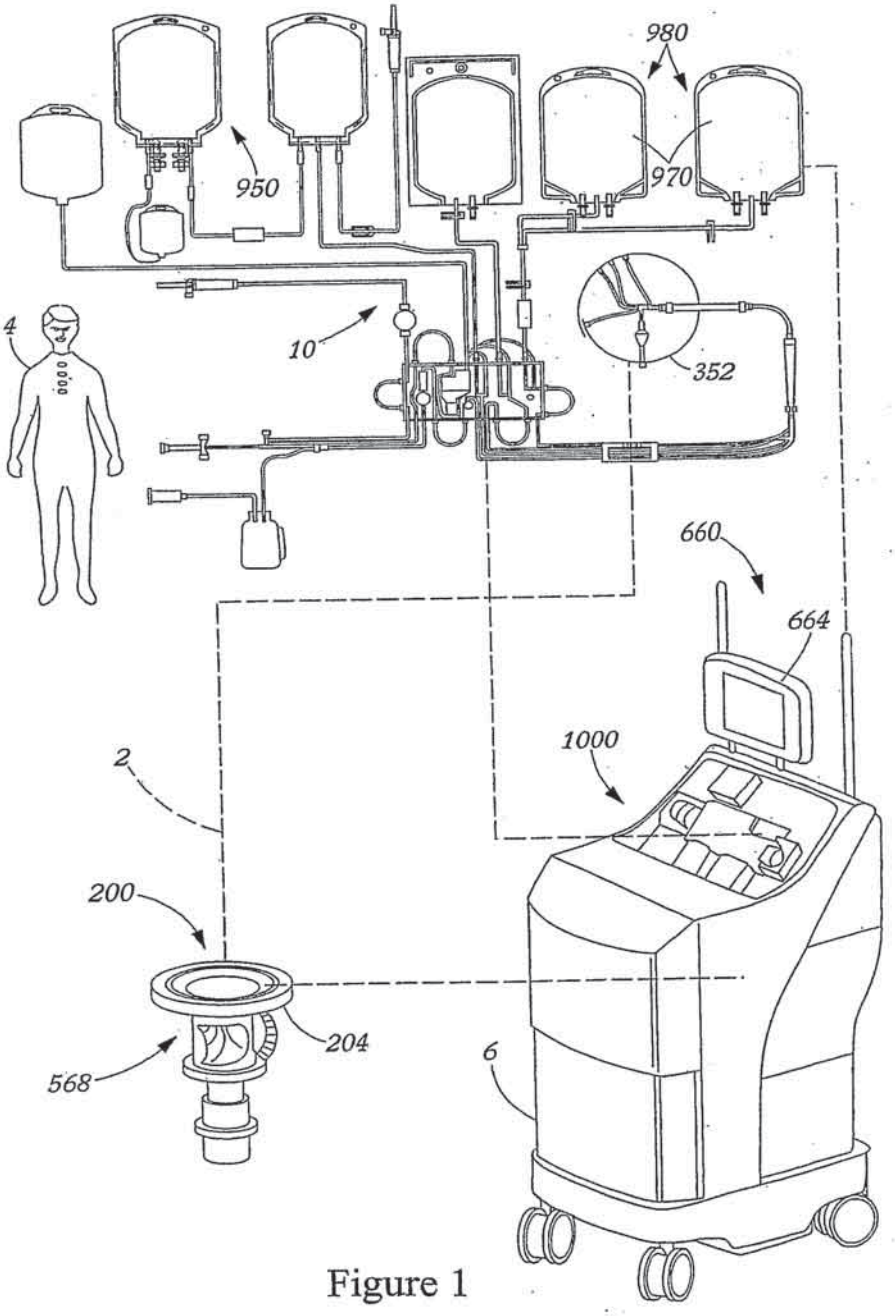


Figure 1

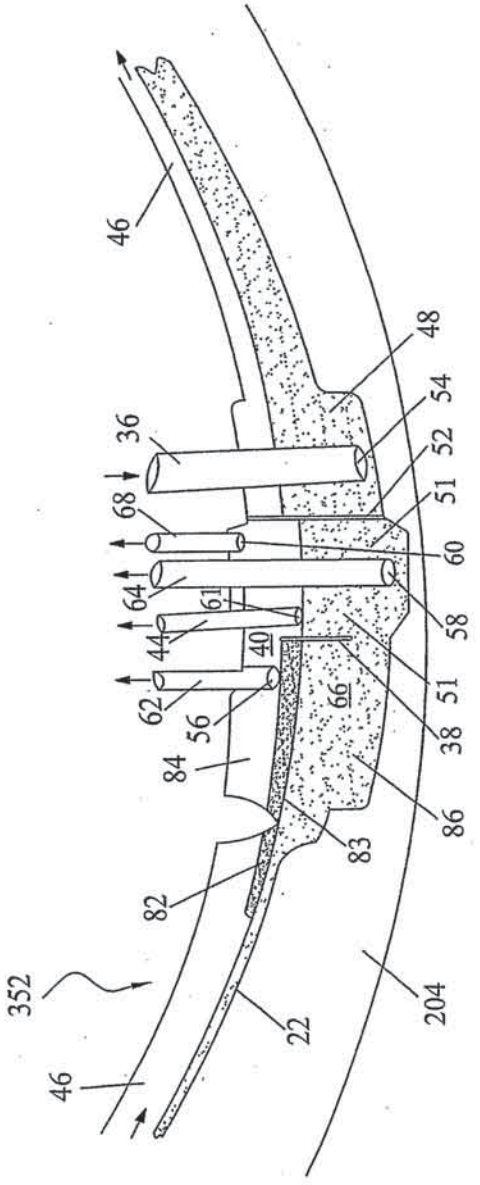

46
48
54
52
51
36
68
60
64
61
58
44
40
62
66
56
38
84
86
83
82
352
22
204
46

Figure 2

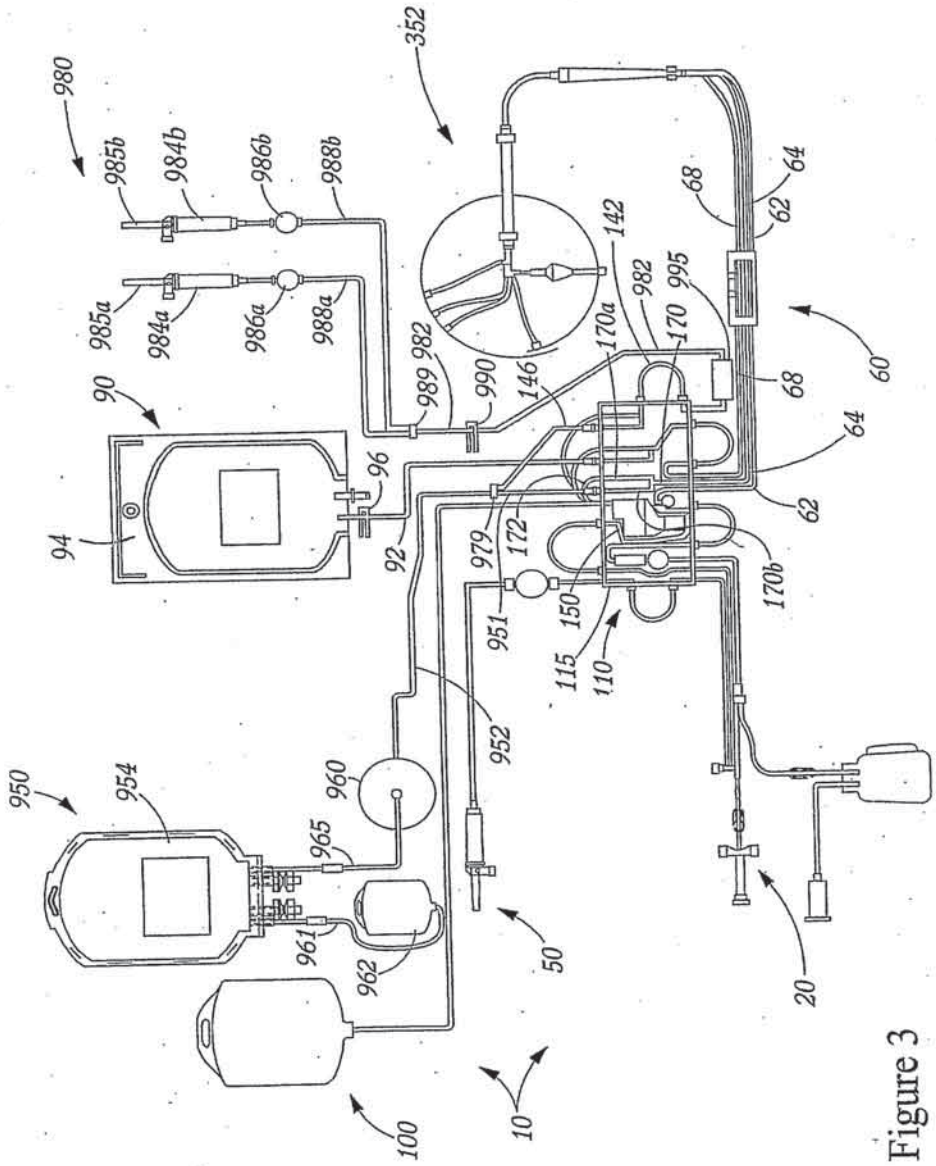

980
985b
984b
986b
988b
352
68
64
62
142
982
995
985a
984a
986a
988a
170a
170
60
982
989
990
146
68
90
64
96
62
94
92
979
172
170b
951
150
115
110
952
950
954
960
965
961
962
50
20
100
10

Figure 3

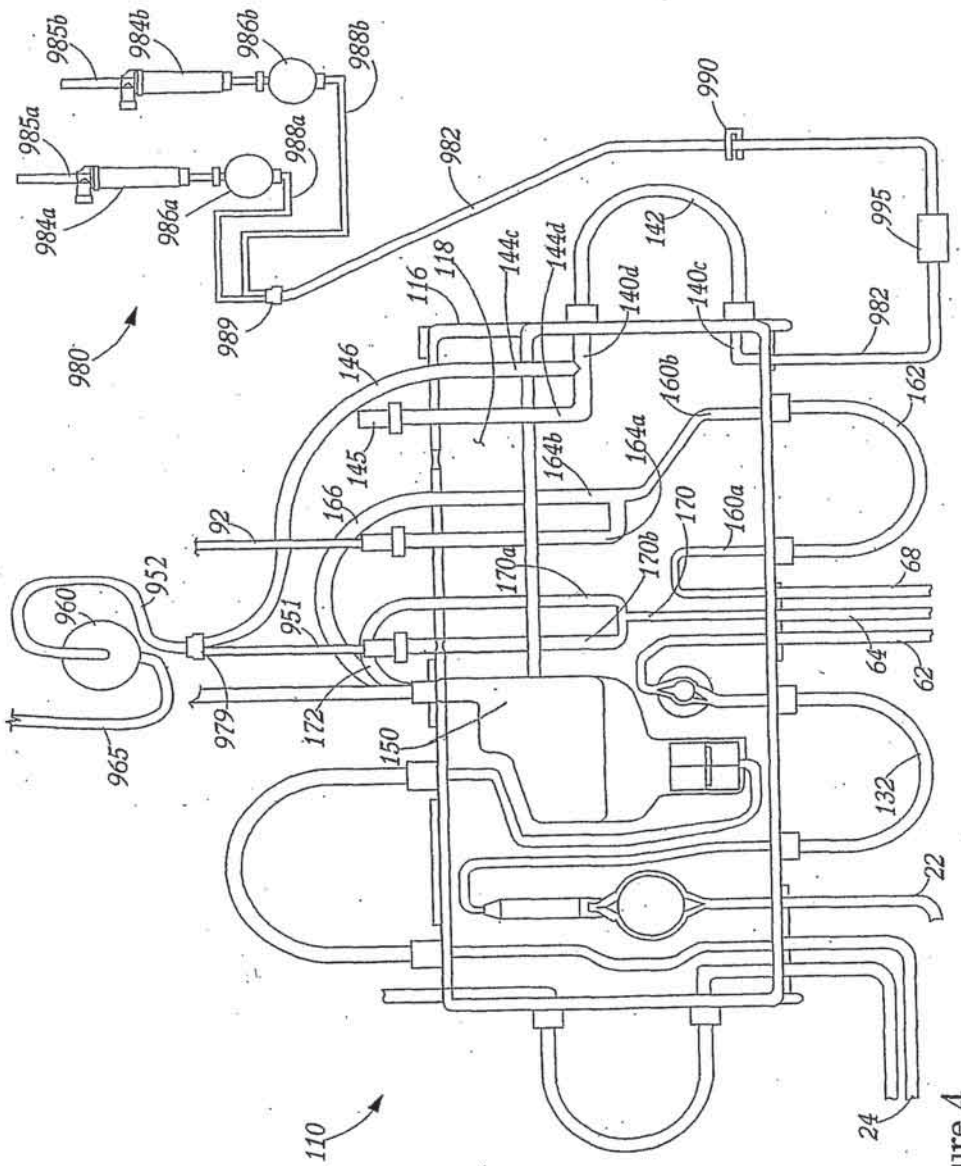

985b
984b
986b
988b
985a
988a
984a
986a
989
980
982
990
995
142
140d
140c
116
118
144c
144d
146
160b
162
145
164b
164a
166
92
170
160a
952
960
951
170a
170b
68
64
62
979
172
150
965
132
22
24
110

Figure 4

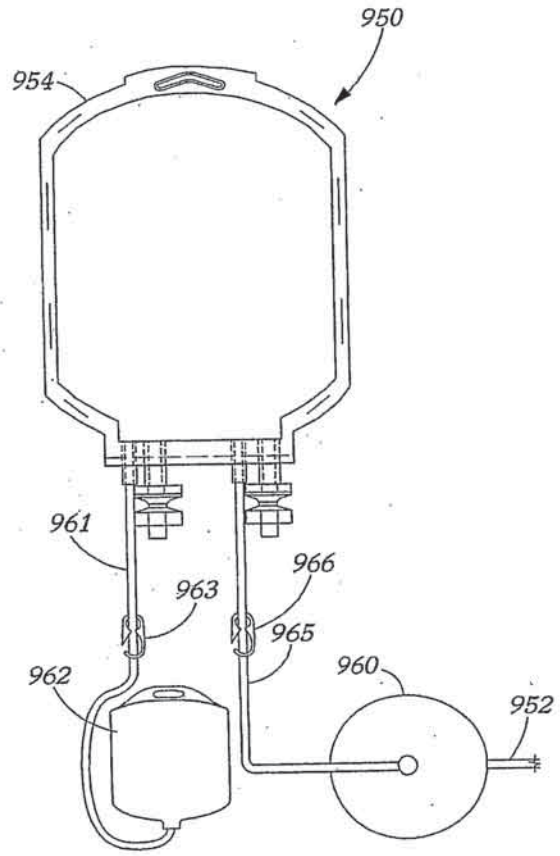


Figure 5

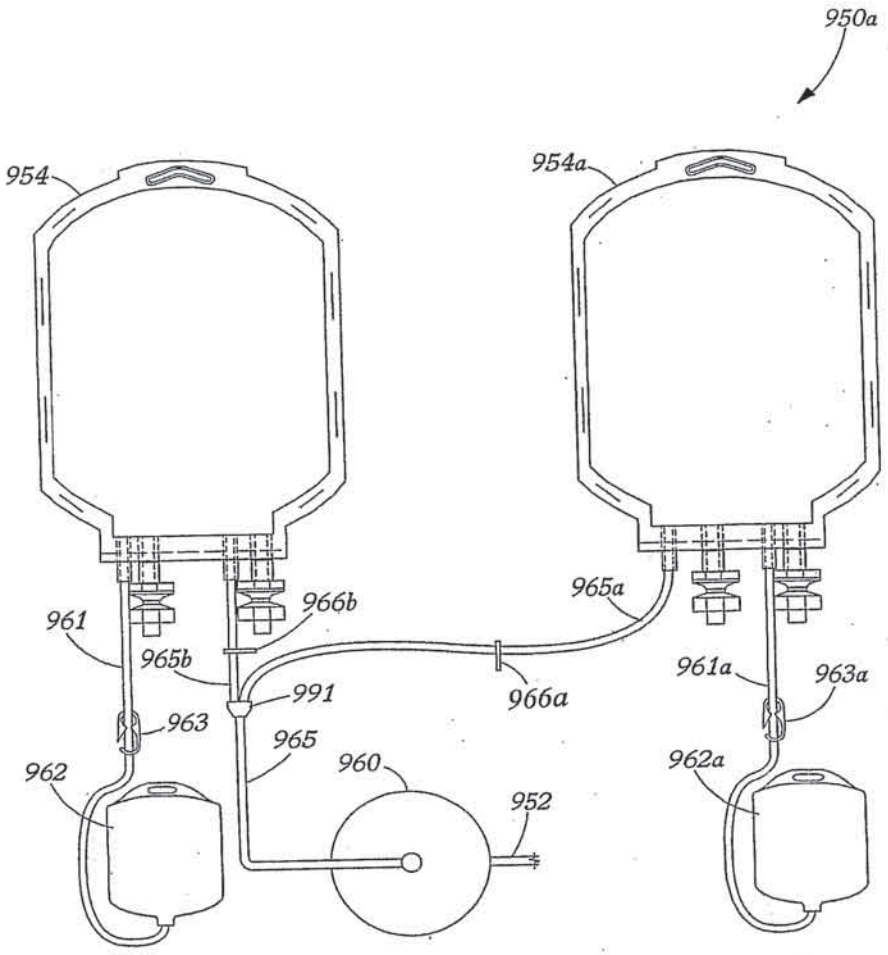

950a
954
954a
961
965b
966b
965a
991
966a
961a
963a
963
965
960
962
952
962a

Figure 6A

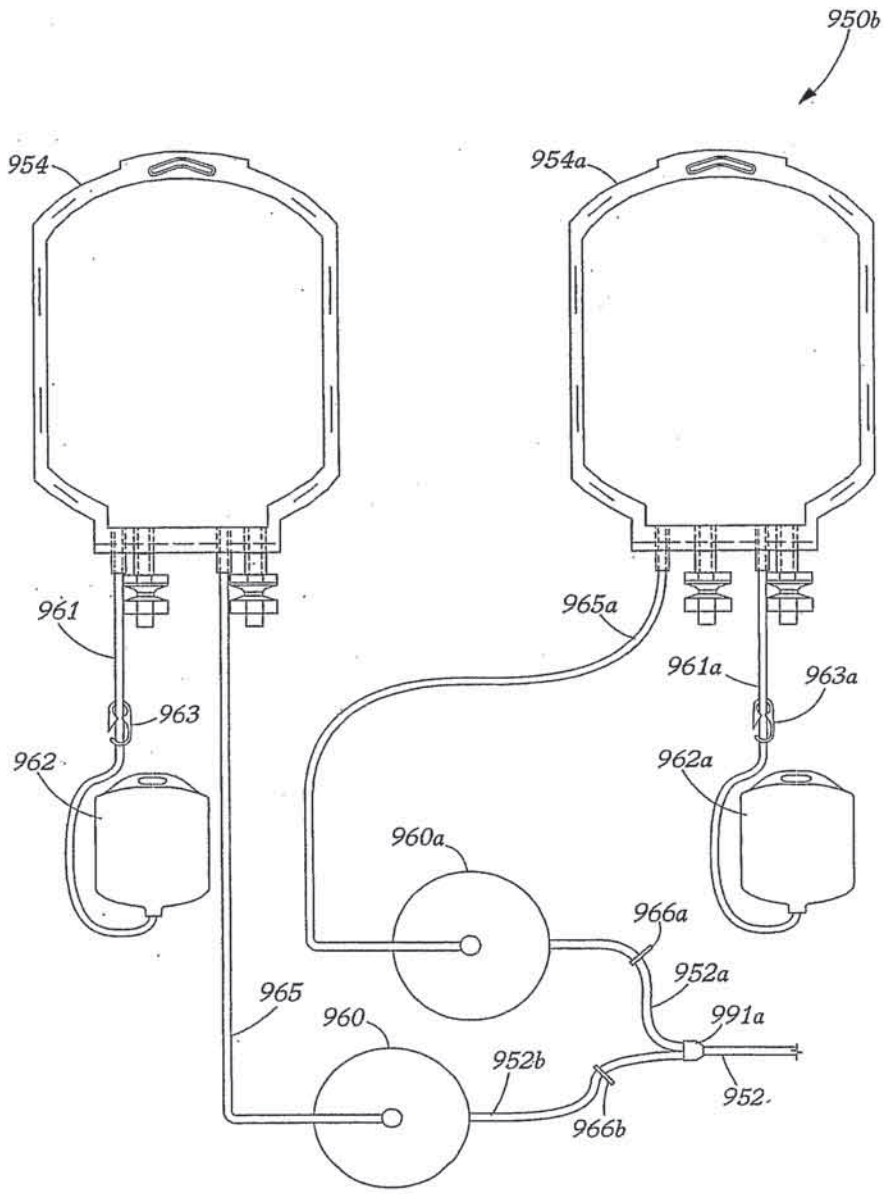

950b
954
954a
961
965a
961a
963a
963
962
962a
960a
966a
952a
965
960
991a
952b
952
966b

Figure 6B

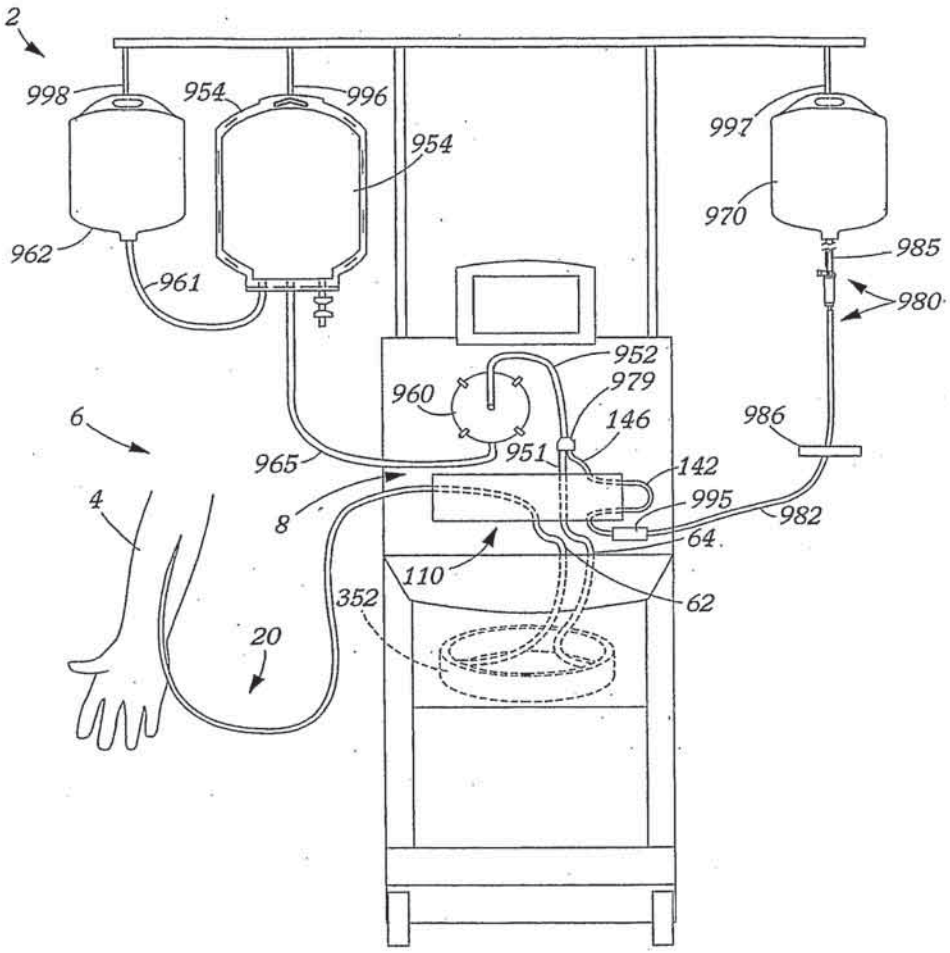

2
998
954
996
954
997
970
962
961
985
980
952
960
979
146
986
6
965
951
142
995
982
4
8
64
110
62
352
20

Figure 7

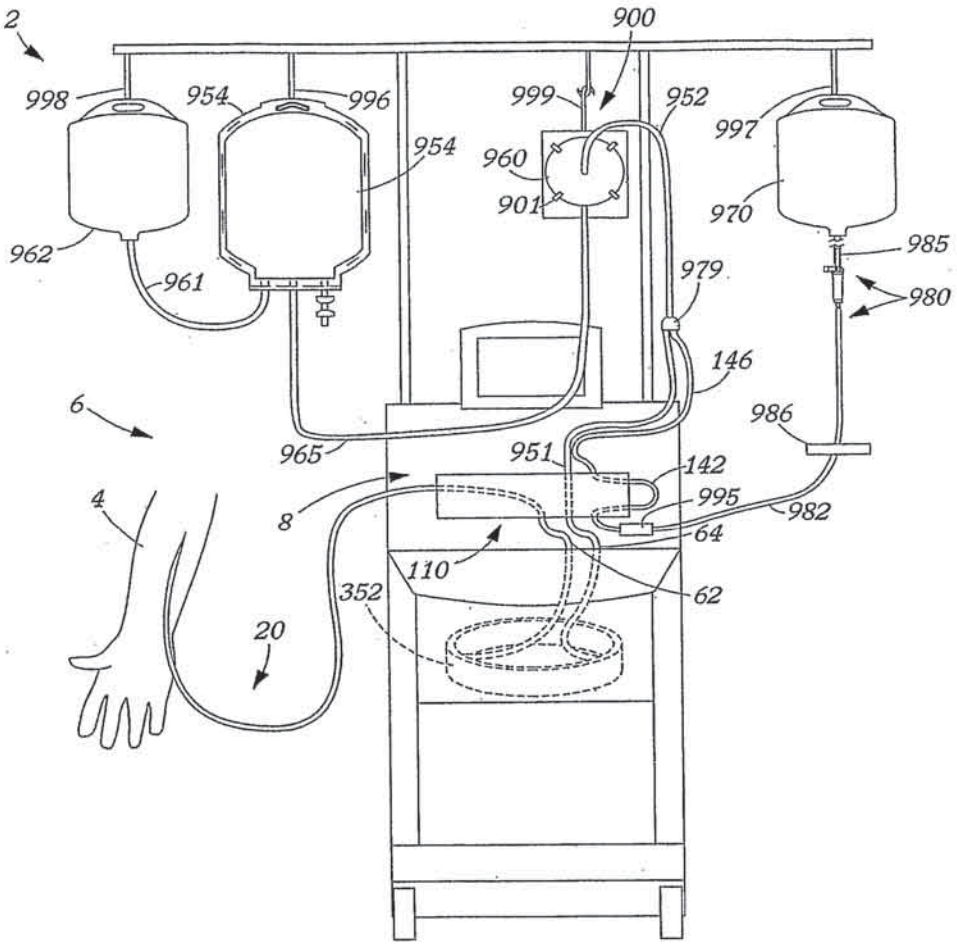

2
900
998
954
996
999
952
997
954
960
901
970
962
961
985
979
980
146
6
986
965
951
142
995
982
4
8
64
110
62
352
20

Figure 8

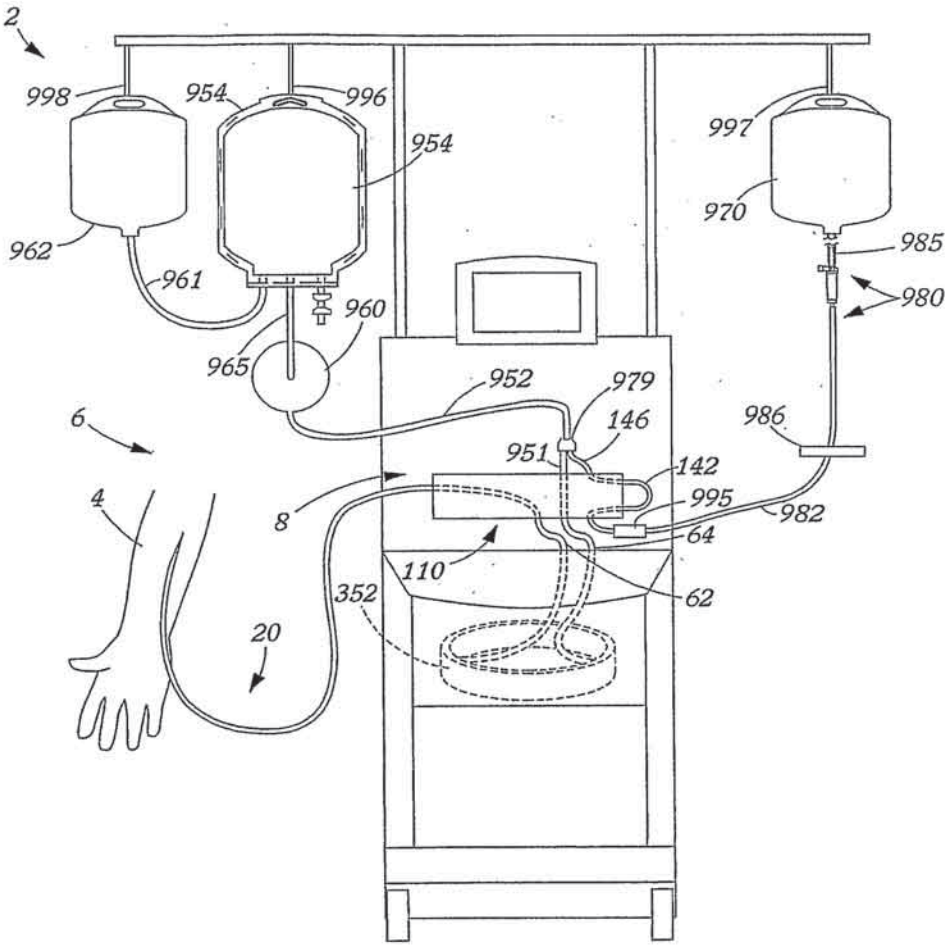

2
998
954
996
954
997
970
962
961
960
985
980
965
952
979
6
146
986
951
142
4
8
995
982
64
110
62
352
20

Figure 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/039153

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M1/36 A61M1/38

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M

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

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/106861 A1 (GIBBS BRUCE M [US] ET AL) 12 June 2003 (2003-06-12) paragraphs [0048] - [0057] paragraph [0071] figures 1-8,10-13	20-22
A	US 6 053 856 A (HLAVINKA DENNIS [US]) 25 April 2000 (2000-04-25) column 6, line 56 - column 8, line 67 column 16, line 49 - column 17, line 37 figure 2	20-22
A	US 2004/079707 A1 (SMITH KELLY B [US] ET AL) 29 April 2004 (2004-04-29) paragraphs [0104] - [0110]	20-22

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2007	01/02/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	BICHLMAYER, K

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/039153

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 464 167 A (SCHOENDORFER DONALD W [US] ET AL) 7 August 1984 (1984-08-07) figure 3	20-22
A	WO 98/46362 A (OMEGA MEDICINTEKNIK AB [SE]; UNGER PETER [SE]; WESTBERG ERIC [SE]) 22 October 1998 (1998-10-22) page 7, lines 4-35	20-22

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/039153

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-19
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Haemonetics Corporation
Exhibit 2015
Page #1128

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2006/039153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003106861 A1	12-06-2003	US 2006184086 A1	17-08-2006
US 6053856 A	25-04-2000	AU 702151 B2	18-02-1999
		AU 5560896 A	07-11-1996
		BR 9608031 A	30-11-1999
		DE 69618453 D1	14-02-2002
		DE 69618453 T2	07-11-2002
		DE 69634860 D1	21-07-2005
		DE 69634860 T2	11-05-2006
		EP 0824380 A1	25-02-1998
		JP 11503966 T	06-04-1999
		WO 9633023 A1	24-10-1996
		US 5939319 A	17-08-1999
US 2004079707 A1	29-04-2004	NONE	
US 4464167 A	07-08-1984	NONE	
WO 9846362 A	22-10-1998	AT 261776 T	15-04-2004
		AU 720556 B2	01-06-2000
		AU 7093098 A	11-11-1998
		DE 69822481 D1	22-04-2004
		EP 1011871 A1	28-06-2000
		JP 2001520570 T	30-10-2001
		US 6261217 B1	17-07-2001

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1611-C80WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2018/033826	International filing date *(day/month/year)* 22 May 2018	(Earliest) Priority Date *(day/month/year)* 30 May 2017
Applicant HAEMONETICS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 1 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. 1

   ☒ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/033826

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61M 1/02; A61M 1/30; A61M 1/34; A61M 1/36; A61M 1/38 (2018.01)

CPC - A61M 1/382; A61M 1/0213; A61M 1/024; A61M 1/304; A61M 1/3424; A61M 1/3441; A61M 1/3609; A61M 1/385 (2018.05)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

USPC - 435/4; 435/7.25; 435/13; 604/4.01; 604/5.01; 604/6.01; 604/6.04; 604/6.09; 604/6.11; 702/19; 702/45 (keyword delimited)

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/0125881 A1 (RYAN) 03 July 2003 (03.07.2003) entire document	1, 3, 5, 6, 8, 10-12, 14, 16, 17, 19
---		---
Y		2, 4, 7, 9, 13, 18, 20
Y	US 2012/0175313 A1 (BARRY, JR. et al) 12 July 2012 (12.07.2012) entire document	2, 4, 13
Y	US 2014/0039373 A1 (HAEMONETICS CORPORATION) 06 February 2014 (06.02.2014) entire document	7, 18
Y	US 2014/0356851 A1 (HAEMONETICS CORPORATION) 04 December 2014 (04.12.2014) entire document	9, 20
A	US 5,970,432 A (ISHIMOTO et al) 19 October 1999 (19.10.1999) entire document	1-20
A	US 7,270,645 B2 (LANGLEY et al) 18 September 2007 (18.09.2007) entire document	1-20
A	US 8,759,094 B2 (RÄNBY) 24 June 2014 (24.06.2014) entire document	1-20

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 July 2018	03 AUG 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JONATHAN C. LOVELY
SUNSTEIN KANN MURPHY & TIMBERS LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	03 AUG 2018
Applicant's or agent's file reference: 1611-C80WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2018/033826	22 May 2018	30 May 2017

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61M 1/02; A61M 1/30; A61M 1/34; A61M 1/36; A61M 1/38 (2018.01)
CPC - A61M 1/382; A61M 1/0213; A61M 1/024; A61M 1/304; A61M 1/3424; A61M 1/3441; A61M 1/3609; A61M 1/385 (2018.05)

Applicant HAEMONETICS CORPORATION

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

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	09 July 2018	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	2, 4, 7, 9, 13, 15, 18, 20	YES
	Claims	1, 3, 5, 6, 8, 10-12, 14, 16, 17, 19	NO
Inventive step (IS)	Claims	15	YES
	Claims	1-14, 16-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1, 3, 5, 6, 8, 10-12, 14, 16, 17, and 19 lack novelty under PCT Article 33(2) as being anticipated by Ryan.

Regarding Claim 1, Ryan discloses a method for collecting plasma (abstract) comprising: (a) determining a weight of a donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation); (b) determining a hematocrit of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation); (c) inserting a venous-access device into the donor (extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011, fig. 1); (d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device (typical plasmapheresis system operating in the collection mode to pump or extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician. The whole blood leaves donor 11 via needle 12 and moved through tube 13, para. 0011; Separator 26 is a conventional plasma separation membrane device, para. 0012, fig. 1); (e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line (In system 10, an anticoagulant, such as sodium citrate is contained in reservoir 18 and is pumped through anticoagulant line 20 by anticoagulant pump 22 to intravenous needle 12 where anticoagulant line 20 is joined with tube 13 by one-way valve 24, mixing of the anticoagulant with the whole blood prior to movement of the whole blood through tube 13, para. 0011, fig. 1); (f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device (Separator 26 is a conventional plasma separation membrane device which comprises a membrane that allows the passage of the plasma component of whole blood therethrough while preventing passage of the cellular components of whole blood through the membrane, separation of the plasma component of blood from the cellular components of blood. After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32. The cellular component of whole blood leaves separator 26 along cellular output line 34, para. 0012); (g) collecting the plasma component from the blood component separation device and into a plasma collection container (After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32, para. 0012); (h) calculating a percentage of anticoagulant in the collected plasma component (paras .0038-0043 regarding the equation for calculation; paras. 0014-0019); calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component (After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019); and continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container (comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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

Regarding Claim 3, Ryan discloses a method according claim 1, further comprising: determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump (After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation; paras. 0014-0019).

Regarding Claim 5, Ryan discloses a method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component (volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32, data from the scale or from the optical sensor is transmitted to controller 46 and to processor 48 which monitor the amount of plasma collected. Controller 46 is responsive to processor 48 which can be any type of conventional microprocessor available for use in calculation and control functions, para. 0031).

Regarding Claim 6, Ryan discloses a method according to claim 1, further comprising: monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

Regarding Claim 8, Ryan discloses a method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation).

Regarding Claim 10, Ryan discloses a method according to claim 1, further comprising: returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line (cellular component of whole blood leaves separator 26 along cellular output line 34, movement of the whole blood cellular component from separator 26 is assisted by cellular component pump 36 whereupon the whole blood cellular component is passed along line 38 until it is deposited in cellular component holding reservoir 40 until it is reinfused into donor 11 along reinfusion line 42 which passes through blood pump 14 and back into donor 11, para. 0012, fig. 1).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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

Regarding Claim 11, Ryan discloses a system for collecting plasma (abstract) comprising: a venous-access device for drawing whole blood from a subject and returning blood components to the subject (extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011, fig. 2); a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container (Separator 26 is a conventional plasma separation membrane device which comprises a membrane that allows the passage of the plasma component of whole blood therethrough while preventing passage of the cellular components of whole blood through the membrane, separation of the plasma component of blood from the cellular components of blood. After separation, the plasma component passes through plasma tube 28 and through plasma valve 30 and is deposited in plasma reservoir 32. The cellular component of whole blood leaves separator 26 along cellular output line 34, para. 0012); a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump (plasmapheresis system operating in the collection mode to pump or extract whole blood from a donor 11 via an intravenous needle 12 which has been positioned in the vein of the donor by a technician, para. 0011; Separator 26 is a conventional plasma separation membrane device, para. 0012, fig. 2; whole blood leaves donor 11 via needle 12 and moves through tube 13 until it contacts whole blood pump 14 which serves to continue to move the whole blood along the preseparator tube 15, para. 0011); an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood (anticoagulant, such as sodium citrate is contained in reservoir 18 and is pumped through anticoagulant line 20 by anticoagulant pump 22 to intravenous needle 12 where anticoagulant line 20 is joined with tube 13, para. 0011); and a controller configured to control the operation of the centrifuge bowl and the blood draw pump, the controller configured to calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation of received products; paras. 0014-0019).

Regarding Claim 12, Ryan discloses a system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; paras .0038-0043 regarding the equation for calculation of received products, equation includes hematocrit and anticoagulant; paras. 0014-0019).

Regarding Claim 14, Ryan discloses a system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump (processor 48 of controller 46 to determine the plasma and anticoagulant volume to be obtained from a donor of a donor-specific body weight, para. 0025, fig. 2; After processor 48 has calculated the volume of plasma which may be removed from donor 11 and has calculated the expected blood volume from which will be obtained from that volume of plasma, controller 46 will operate to initiate the functioning of pump 14 by communicating with pump 14 through communication line 50. The course of pumping by pump 14, rate of actual pumping can be compared with the intended volume of blood that is to be extracted from donor 11. The comparison of expected blood volume to be extracted from donor 11, and the blood volume that is actually extracted from donor 11, is a matter of a continuing calculation based upon the number of revolutions of pump 14 and the amount of blood that is pumped with each revolution of pump 14. This calculation is then continually compared with the volume of blood to be removed from donor 11 as determined by processor 48 at the beginning of the operation. Upon obtaining that goal, controller 46 can shut down pump 14 or notify the operator that the desired volume of blood has been pumped from donor 11, para. 0038; paras .0038-0043 regarding the equation for calculation of received products; paras. 0014-0019).

Regarding Claim 16, Ryan discloses a system according to claim 11, further comprising: a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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

Regarding Claim 17, Ryan discloses a system according to claim 11, further comprising: a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component (control of system 10 is provided by communications link 52 which provides controller 46 with data on the volume of plasma that has arrived in plasma reservoir 32 as a result of the functioning of separator 26 on whole blood received by the pumping of pump 14. It will be appreciated by those skilled in the art that the volume of plasma in reservoir 32 can be determined by weight or by volume using optical sensors which respond to the change in light transmission through plasma reservoir 32 as various portions of plasma reservoir 32 fill with plasma, para. 0031, fig. 1).

Regarding Claim 19, Ryan discloses a system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor (determination of the amount of plasma which can be derived from an individual donor 11 is calculated based on the donor's body weight, hematocrit and the amount of anticoagulant used in the procedure, para. 0014; paras. 0014-0018 regarding the equation).

Claims 2, 4, and 13 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of Barry, Jr. et al. (hereinafter Barry).

Regarding Claim 2, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose further comprising: determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container (e holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. The controller 16 can also diagnose exceptional situations, such as leaks and obstructions in the fluid path. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

Regarding Claim 4, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose further comprising: determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device (holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

Regarding Claim 13, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose further comprising: an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.
Barry is in the field of automatically adjusting the operational parameters of a blood separation procedure (abstract) and teaches an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source (holding trays 144 comprise molded recesses in the base 20 which accommodate selected containers of the flow set 12. and may also include weight sensors, para. 0056; Using the weight sensors, the controller 16 can continuously determine the actual volume of fluid that is moved per pump stroke and correct for any deviations from commanded flow. This measure of monitoring and control is desirable in an automated apheresis application, where it is desirable for anticoagulant to be accurately metered with the whole blood as it is drawn from the donor, and where product quality, plasma purity, may be influenced by the accuracy of the pump flow rates, para. 0057). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Barry for the purpose of continuously monitoring the source fluid container volumes thereby allowing a control measure for product quality (Barry, para. 0057).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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

Claims 7 and 18 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of US 2014/0039373 A1 to Haemonetics Corporation (hereinafter Haemonetics'373).

Regarding Claim 7, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose wherein step (b) includes monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.
Haemonetics'373 is in the field of an apparatus for separating whole blood (abstract) and teaches monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor (controller 190 may also monitor the output signal from the optical sensor 14 to determine when the bowl 120 is full of red blood cells, para. 0038; input device 198 may allow the user to input a target volume of whole blood to withdraw, a target volume of red blood cells to collect, and/or the hematocrit value of the whole blood being drawn into the system 100, controller 190 may control the speed of the centrifuge 110 based, at least in part, upon the hematocrit valve of the whole blood, the controller may increase the speed for high hematocrit donors, controller 190 may also receive outputs from the pressure sensors and a line sensor 14. The line sensor 14 may be an optical sensor that detects the presence of blood components passing through the line sensor 14 from the output port PT2, para. 0031; controller 190 may calculate the total volume of blood drawn from the source based upon the number of revolutions of the draw pump P1, para. 0037, 450, fig. 4). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'373 for the purpose of determining the hematocrit of the patient during removal of blood products thereby allowing greater patient safety and control of the flow through the system (Haemonetics'373, para. 0031).

Regarding Claim 18, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose further comprising: an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.
Haemonetics'373 is in the field of an apparatus for separating whole blood (abstract) and teaches further comprising: an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor (controller 190 may also monitor the output signal from the optical sensor 14 to determine when the bowl 120 is full of red blood cells, para. 0038; input device 198 may allow the user to input a target volume of whole blood to withdraw, a target volume of red blood cells to collect, and/or the hematocrit value of the whole blood being drawn into the system 100, controller 190 may control the speed of the centrifuge 110 based, at least in part, upon the hematocrit valve of the whole blood, the controller may increase the speed for high hematocrit donors, controller 190 may also receive outputs from the pressure sensors and a line sensor 14. The line sensor 14 may be an optical sensor that detects the presence of blood components passing through the line sensor 14 from the output port PT2, para. 0031; controller 190 may calculate the total volume of blood drawn from the source based upon the number of revolutions of the draw pump P1, para. 0037, 450, fig. 4). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'373 for the purpose of determining the hematocrit of the patient during removal of blood products thereby allowing greater patient safety and control of the flow through the system (Haemonetics'373, para. 0031).

Claims 9 and 20 lack an inventive step under PCT Article 33(3) as being obvious over Ryan in view of US 2014/0356851 A1 to Haemonetics Corporation (hereinafter Haemonetics'851).

Regarding Claim 9, Ryan discloses a method according to claim 1, but Ryan fails to explicitly disclose wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.
Haemonetics'851 is in the field of apheresis system that includes priming the blood apheresis system with anticoagulant (abstract) and teaches wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step (pumps P1 and P3 are energized to prime the tube 28 of the apparatus 10 with the anticoagulant, After priming, the venous access device 24 may be inserted into the donor and the draw step is ready to be commenced, para. 0030; FIG. 3 is a flowchart depicting a method for collecting blood components from a subject, During draw step 310, whole blood is drawn from the subject, typically at a rate of about 80 ml/min. and mixed with the anticoagulant using the pumps P1 and P3, pump P3 introduces and mixes the anticoagulant with the whole blood drawn from the subject, para. 0031). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetic'851 for the purpose of monitoring the anticoagulant in the plasma collection system thereby reducng the risk of returning too mush anticoagulant into the patient (Haemonetics'851, para. 0057).

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2018/033826

Supplemental Box

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

Regarding Claim 20, Ryan discloses a system according to claim 11, but Ryan fails to explicitly disclose wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step
Haemonetics'851 is in the field of apheresis system that includes priming the blood apheresis system with anticoagulant (abstract) and teaches wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step (pumps P1 and P3 are energized to prime the tube 28 of the apparatus 10 with the anticoagulant, After priming, the venous access device 24 may be inserted into the donor and the draw step is ready to be commenced, para. 0030; FIG. 3 is a flowchart depicting a method for collecting blood components from a subject, During draw step 310, whole blood is drawn from the subject, typically at a rate of about 80 ml/min. and mixed with the anticoagulant using the pumps P1 and P3, pump P3 introduces and mixes the anticoagulant with the whole blood drawn from the subject, para. 0031). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Ryan with the teaching of Haemonetics'851 for the purpose of monitoring the anticoagulant in the plasma collection system thereby reducng the risk of returning too mush anticoagulant into the patient (Haemonetics'851, para. 0057).

Claim 15 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 15, the prior art of record, individually or in combination, does not teach or fairly suggest a system according to claim 11, further comprising: an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

Claims 1-20 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

PUBLICATION NOTICE

OC000000104263426

Title: System and Method for Collecting Plasma

Publication No.US-2018-0344910-A1
Publication Date:12/06/2018

NOTICE OF PUBLICATION OF APPLICATION

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

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

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

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

86738
MCCARTER & ENGLISH, LLP BOSTON
265 Franklin Street
Boston, MA 02110

POA ACCEPTANCE LETTER

OC000000103659714

Date Mailed: 11/08/2018

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/05/2018.

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

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

Haemonetics Corporation
Exhibit 2015
Page #1141

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

POWER OF ATTORNEY NOTICE

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

OC000000103659686

Date Mailed: 11/08/2018

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/05/2018.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mbeyene/

PTO/SB/81 (01-09)
Approved for use through 1/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	
Filing Date	
First Named Inventor	
Title	
Art Unit	
Examiner Name	
Attorney Docket Number	

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 86738

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

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

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature	John F. Perullo	Date	10/23/18
Name	John F. Perullo	Telephone	
Title and Company	Vice President, Associate General Counsel and Chief Intellectual Property Officer, Haemonetics Corporation		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: Haemonetics Corporation

Application No./Patent No.: 15/608,183 Filed/Issue Date: May 30, 2017

Titled: SYSTEM AND METHOD FOR COLLECTING PLASMA

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

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

1. [x] The assignee of the entire right, title, and interest.

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

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

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

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

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

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

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

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

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 045684, Frame 0875, or for which a copy thereof is attached.

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

   1. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____, Frame _____, or for which a copy thereof is attached.

   2. From: _____ To: _____
      The document was recorded in the United States Patent and Trademark Office at
      Reel _____, Frame _____, or for which a copy thereof is attached.

ME1 28489428v.1

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

4. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

5. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

6. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____ , Frame _____ , or for which a copy thereof is attached.

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

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

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

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

/Jonathan C. Lovely, Reg. No. 60,821/	November 5, 2018
Signature	Date
Jonathan C. Lovely	60,821
Printed or Typed Name	Title or Registration Number

UNITED STATES PATENT AND TRADEMARK OFFICE
UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND
DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MAY 2, 2018

PTAS

JONATHAN C. LOVELY
SUNSTEIN KANN MURPHY & TIMBERS LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

504894417

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 05/01/2018 REEL/FRAME: 045684/0875
NUMBER OF PAGES: 5

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 1611/C80

ASSIGNOR:
RAGUSA, MICHAEL DOC DATE: 05/01/2018

ASSIGNEE:
HAEMONETICS CORPORATION
400 WOOD ROAD
BRAINTREE, MASSACHUSETTS 02184

APPLICATION NUMBER: 15608183 FILING DATE: 05/30/2017
PATENT NUMBER: ISSUE DATE:
TITLE: SYSTEM AND METHOD FOR COLLECTING PLASMA

ASSIGNMENT RECORDATION BRANCH
PUBLIC RECORDS DIVISION

504894417 05/01/2018

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT4941160

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
MICHAEL RAGUSA	05/01/2018

RECEIVING PARTY DATA

Name:	HAEMONETICS CORPORATION
Street Address:	400 WOOD ROAD
City:	BRAINTREE
State/Country:	MASSACHUSETTS
Postal Code:	02184

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	15608183

CORRESPONDENCE DATA

Fax Number: (617)443-0004

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.

Phone: 617-443-9292
Email: rmooney@sunsteinlaw.com
Correspondent Name: JONATHAN C. LOVELY
Address Line 1: SUNSTEIN KANN MURPHY & TIMBERS LLP
Address Line 2: 125 SUMMER STREET
Address Line 4: BOSTON, MASSACHUSETTS 02110-1618

ATTORNEY DOCKET NUMBER:	1611/C80
NAME OF SUBMITTER:	JONATHAN C. LOVELY
SIGNATURE:	/Jonathan C. Lovely, #60,821/
DATE SIGNED:	05/01/2018

Total Attachments: 4
source=ram1611_C80_Assignment#page1.tif
source=ram1611_C80_Assignment#page2.tif
source=ram1611_C80_Assignment#page3.tif
source=ram1611_C80_Assignment#page4.tif

Electronic Acknowledgement Receipt

EFS ID:	34200899
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	05-NOV-2018
Filing Date:	30-MAY-2017
Time Stamp:	14:48:24
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	102318_Haemonetics_Corporation_-_GPOA_PTO_SB_81.PDF	101461 e045cdd3cac0e73279ae6e112673dc3c3c6b312e	no	2

Warnings:

The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
2	Assignee showing of ownership per 37 CFR 3.73	Statement_Under_37_CFR_3.pdf	24797 01c5ba3894abf12191366afc6028add72e3bc479	no	2
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	2916910_1.PDF	103809 946d57cbe62b4160b0dcadc5fe6418b2ffeb8c9e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	230067	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Practitioner's Docket No. 1611/C80 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael Ragusa
Application No.: 15/608,183 Group No.: 3761
Filed: May 30, 2017 Examiner: Not yet assigned
For: System and Method for Collecting Plasma

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

RESPONSE TO INFORMATIONAL NOTICE TO APPLICANT

I. This replies to the Informational Notice to Applicant mailed on June 8, 2017. A copy of the Informational Notice to Applicant is attached.

DECLARATION OR OATH

II. The inventor's executed declaration is attached.

ADDITIONAL FEES

III. If any fees are required, please charge Deposit Account Number 19-4972.

DATE: August 24, 2017

/Jonathan C. Lovely, #60,821/

Jonathan C. Lovely
Registration No. 60,821
SUNSTEIN KANN MURPHY & TIMBERS LLP
Customer Number 02101
125 Summer Street
Boston, MA 02110-1618

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

INFORMAL NOTICE

OC000000091875551

Date Mailed: 06/08/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Michael Ragusa

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/snguyen/

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

(For Application filed on or after September 16, 2012)

Title of Invention: System and Method for Collecting Plasma

This declaration is directed to:

[ ] The attached application, or

[X] United States application or PCT international application number 15/608,183
filed on May 30, 2017
as amended on _____(if applicable).

The application was made or was authorized to be made by me.

I have reviewed and understand the contents of the above-identified application.

I believe myself to be the original inventor or an original joint inventor of a claimed invention in the application.

I acknowledge the duty to disclose to the US Patent and Trademark Office all information known to me to be material to patentability.

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

WARNING:

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

LEGAL NAME OF INVENTOR

Inventor: Michael Ragusa

Date: 6/1/2017

Signature: Michael J Ragusa

Practitioner's Docket No. 1611/C80 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Michael Ragusa
Application No.: 15/608,183 Group No.: 3761
Filed: May 30, 2017 Examiner: Not yet assigned
For: System and Method for Collecting Plasma

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

TRANSMITTAL OF REPLACEMENT DRAWINGS

Attached please find:

(a) Four replacement drawing sheets for figures 1-4.

(b) Please publish this application with these replacement drawings.

DATE: August 24, 2017

/Jonathan C. Lovely, #60,821/

Jonathan C. Lovely
Registration No. 60,821
SUNSTEIN KANN MURPHY & TIMBERS LLP
Customer Number 02101
125 Summer Street
Boston, MA 02110-1618

01611/00C80 2780488.1

Haemonetics Corporation
Exhibit 2015
Page #1154

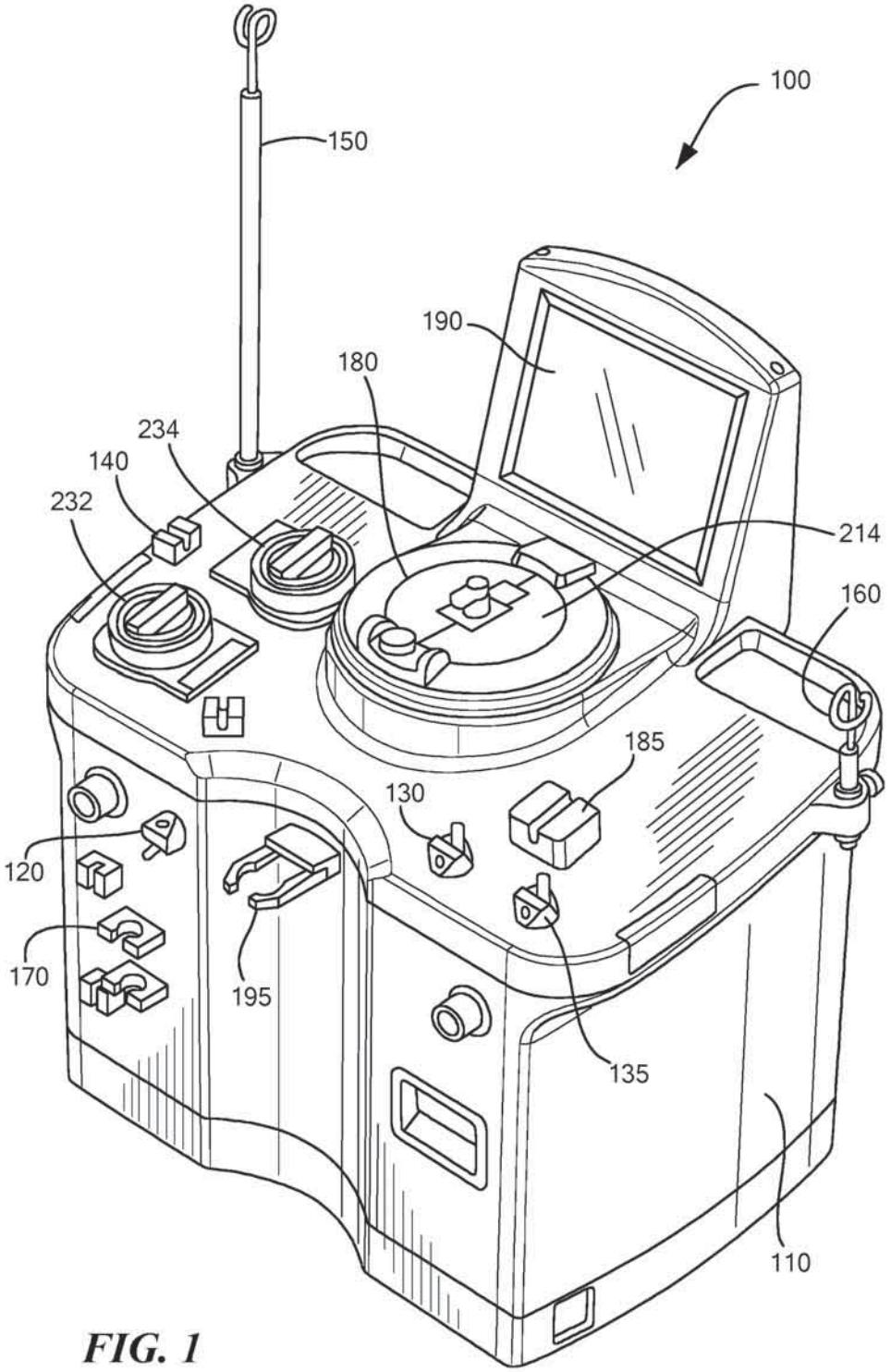


FIG. 1

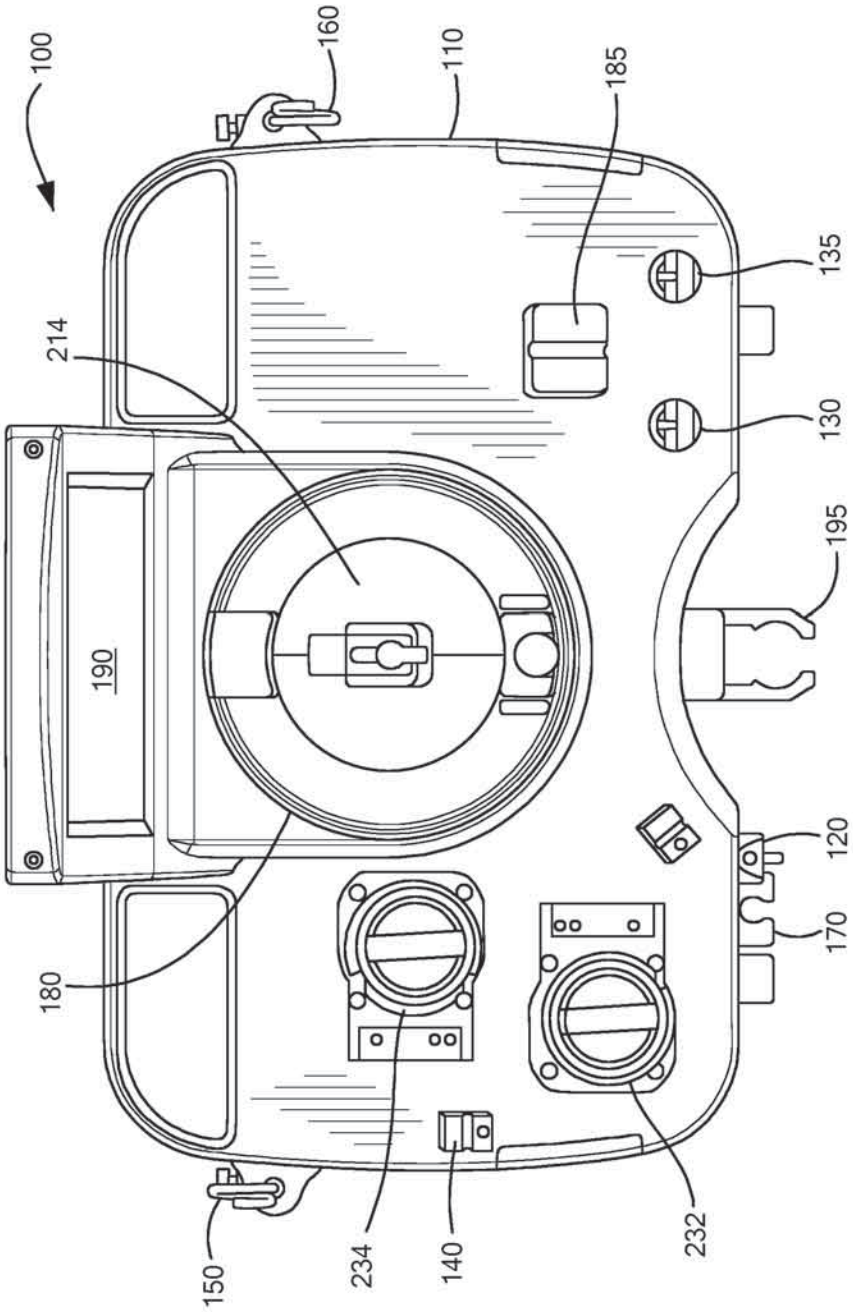


FIG. 2

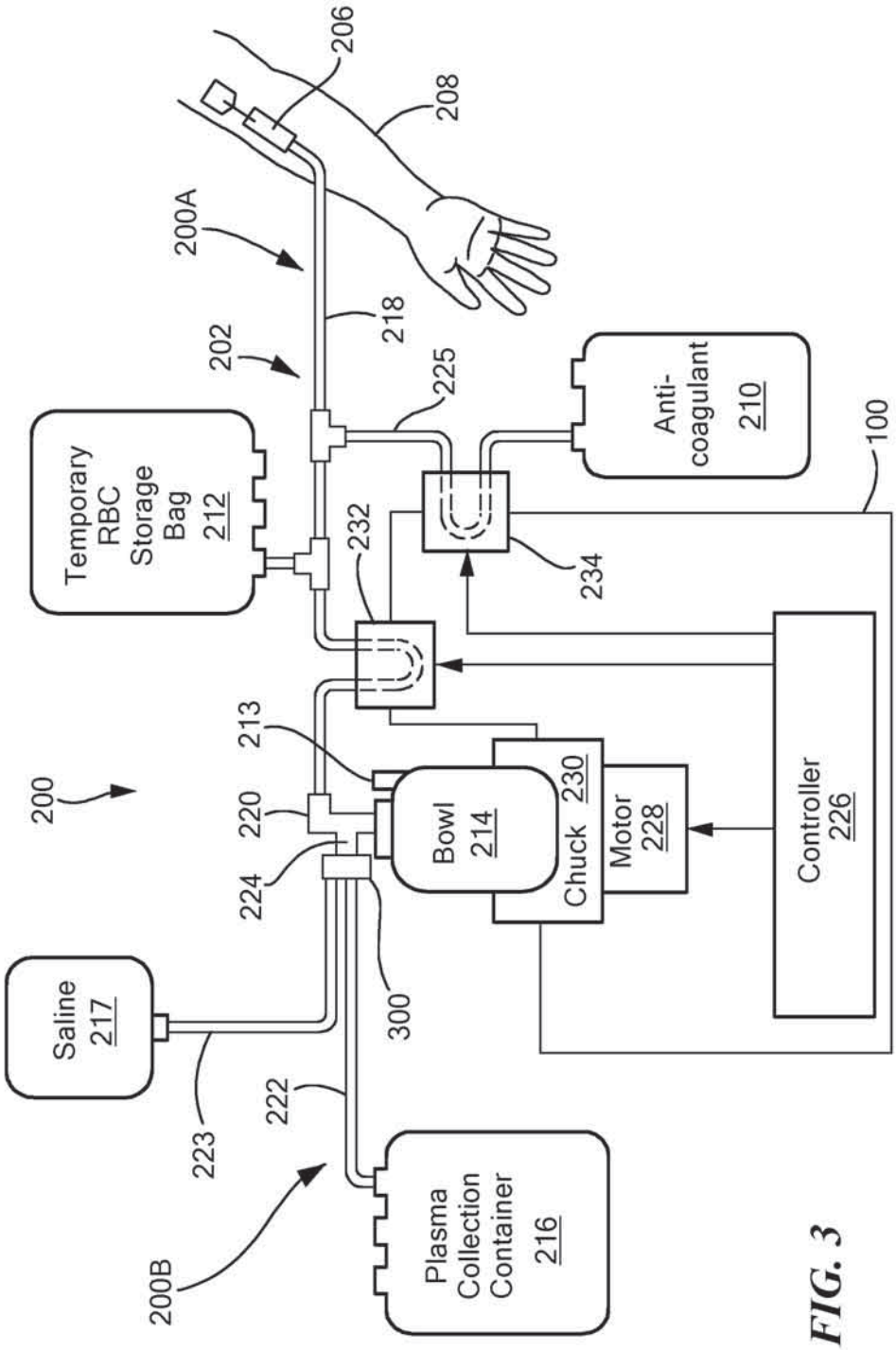

206
208
200A
218
202
225
Anti-coagulant 210
100
Temporary RBC Storage Bag 212
232
234
213
200
220
Bowl 214
Chuck 230
Motor 228
Controller 226
224
300
Saline 217
222
223
200B
Plasma Collection Container 216

FIG. 3

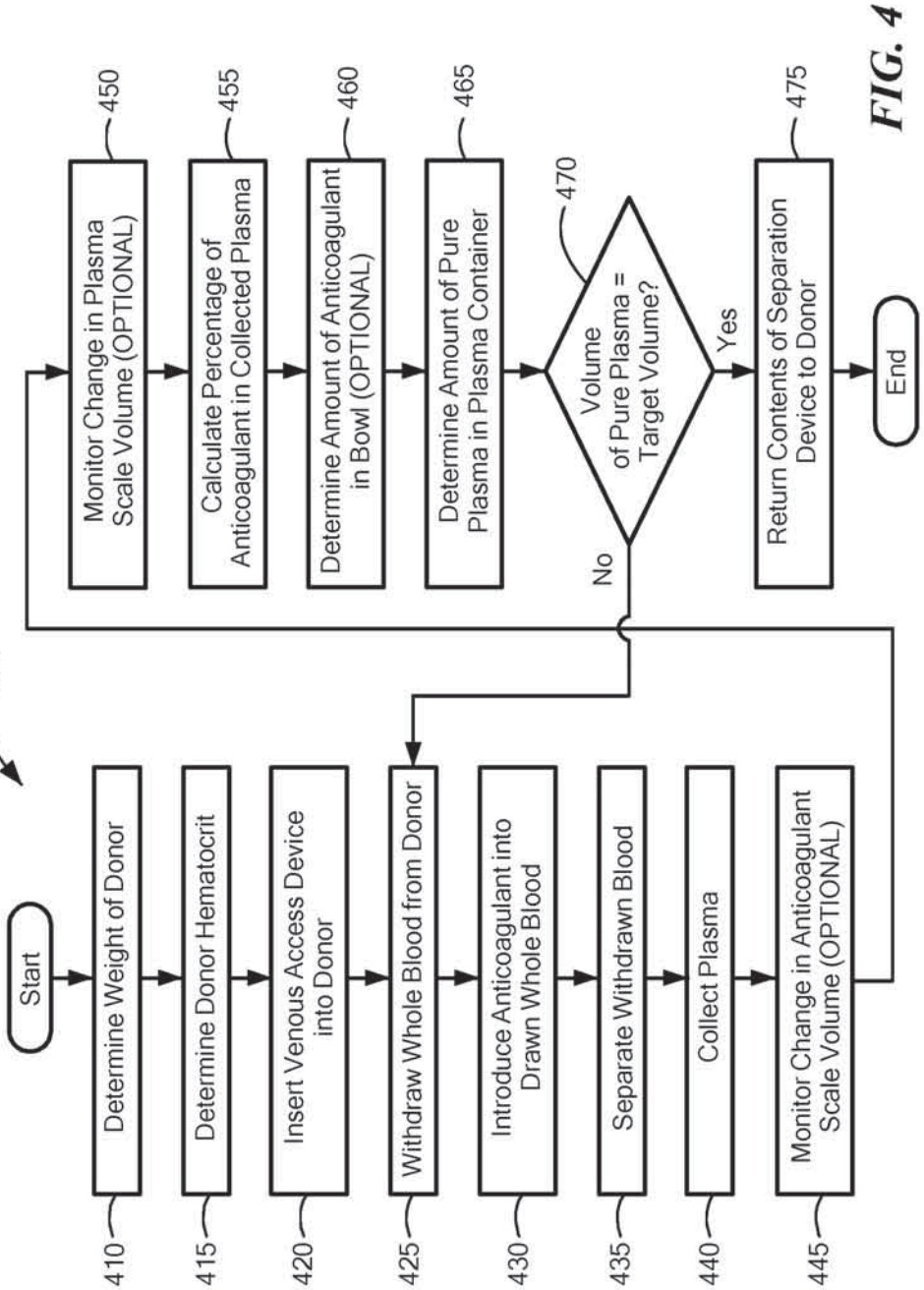

400
Start
Determine Weight of Donor
410
Determine Donor Hematocrit
415
Insert Venous Access Device into Donor
420
Withdraw Whole Blood from Donor
425
Introduce Anticoagulant into Drawn Whole Blood
430
Separate Withdrawn Blood
435
Collect Plasma
440
Monitor Change in Anticoagulant Scale Volume (OPTIONAL)
445
Monitor Change in Plasma Scale Volume (OPTIONAL)
450
Calculate Percentage of Anticoagulant in Collected Plasma
455
Determine Amount of Anticoagulant in Bowl (OPTIONAL)
460
Determine Amount of Pure Plasma in Plasma Container
465
Volume of Pure Plasma = Target Volume?
470
No
Yes
Return Contents of Separation Device to Donor
475
End

FIG. 4

Electronic Acknowledgement Receipt

EFS ID:	30173123
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	24-AUG-2017
Filing Date:	30-MAY-2017
Time Stamp:	15:29:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		ram1611_C80_Declaration.pdf	609558 fa79ebaf9126e0a954169167f1e0e4824830c05b	yes	3

	Multipart Description/PDF files in .zip description			
	Document Description	**Start**	**End**	
	Applicant Response to Pre-Exam Formalities Notice	1	2	
	Oath or Declaration filed	3	3	
Warnings:				
Information:				
2	ram1611_C80_FormalDrawings.pdf	189314 12eb75e21c16aadfc52eb9171ef61108bb881ab1	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	1
	Drawings-only black and white line drawings	2	5
Warnings:			
Information:			
	Total Files Size (in bytes):	798872	

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

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/608,183	05/30/2017	3761	1740	1611/C80	20	2

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

FILING RECEIPT



Date Mailed: 06/08/2017

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Michael Ragusa, Hingham, MA;

Applicant(s)

Haemonetics Corporation, Braintree, MA;

Power of Attorney: The patent practitioners associated with Customer Number 02101

Domestic Applications for which benefit is claimed - None.
A proper domestic benefit claim must be provided in an Application Data Sheet in order to constitute a claim for domestic benefit. See 37 CFR 1.76 and 1.78.

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

If Required, Foreign Filing License Granted: 06/06/2017

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/608,183**

Haemonetics Corporation
Exhibit 2015
Page #1161

Projected Publication Date: 12/06/2018

Non-Publication Request: No

Early Publication Request: No
Title

System and Method for Collecting Plasma

Preliminary Class

604

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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

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

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

Haemonetics Corporation
Exhibit 2015
Page #1162

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
15/608,183	05/30/2017	Michael Ragusa	1611/C80

CONFIRMATION NO. 7286

2101
Sunstein Kann Murphy & Timbers LLP
125 SUMMER STREET
BOSTON, MA 02110-1618

INFORMAL NOTICE

OC000000091875551

Date Mailed: 06/08/2017

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  Michael Ragusa

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/snguyen/

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 15/608,183

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

GENERAL POWER OF ATTORNEY

I/we hereby appoint the practitioners associated with the Customer Number: **02101**

with the firm: SUNSTEIN KANN MURPHY & TIMBERS LLP
125 Summer Street
Boston, MA 02110-1618
United States

As attorneys to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications where the assignee is named as an applicant or where the applications are assigned to the undersigned according to the USPTO assignment records or assignment documents, in which case the details will be listed on an attached form in accordance with 37 CFR 3.73(c).

Address all correspondence to: **Customer Number: 02101**

Direct all telephone calls to: 617-443-9292
Facsimiles to: 617-443-0004

(a) Full name and registered address of Assignee

I/We, (a) Haemonetics Corporation
Assignee

400 Wood Road, Braintree, MA 02184
Address

Dated this 12th day of November, 2012

(b) Signature of Assignee: John F. Perullo

By (c) Signatory's name: JOHN F. PERULLO

(d) Signatory's Title: VP, IP LEGAL AFFAIRS

Attorney Docket: 1611/C80

System and Method for Collecting Plasma

Technical Field

[0001] The present invention relates to systems and methods for blood apheresis, and more particularly system and methods for collecting a plasma product.

Background Art

[0002] Apheresis is a procedure in which individual blood components can be separated and collected from whole blood temporarily withdrawn from a subject. Typically, whole blood is withdrawn through a needle inserted into a vein of the subjects arm and into a cell separator, such as a centrifugal bowl. Once the whole blood is separated into its various components, one or more of the components (e.g., plasma) can be removed from the centrifugal bowl. The remaining components can be returned to the subject along with optional compensation fluid to make up for the volume of the removed component. The process of drawing and returning continues until the quantity of the desired component has been collected, at which point the process is stopped. A central feature of apheresis systems is that the processed but unwanted components are returned to the donor. Separated blood components may include, for example, a high density component such as red blood cells, an intermediate density component such as platelets or white blood cells, and a lower density component such as plasma.

[0003] Many jurisdictions have regulations regarding the amount of whole blood and/or blood components that can be removed from a donor. For example, the U.S. Food and Drug Administration ("the FDA") sets both an upper limit on the volume of plasma that may be collected (e.g., 800 ml for an adult weighing more than 175 pounds) as well as an upper limit on the total collection volume (e.g., 880 ml for an adult weighing more than 175 pounds). Prior art plasma collection systems are unable to determine the total volume of plasma that has been collected (e.g., because the product collected is a mixture of plasma and

Haemonetics Corporation
Exhibit 2015
Page #1167

anticoagulant) and, therefore collect based on the total collection volume, even if the total volume of plasma that has been collected is below the limit prescribed by the FDA.

Summary of the Invention

[0004] In accordance with some embodiments of the present invention, a method for collecting plasma includes determining the weight and hematocrit of a donor, and inserting a venous-access device into the donor. Once the venous access device is inserted, the method may withdraw whole blood from the donor through the venous-access device and a draw line that is connected to a blood component separation device. The method may then introduce anticoagulant into the withdrawn whole blood through an anticoagulant line and separate, using the blood component separation device, the withdrawn whole blood into a plasma component and at least a second blood component. Once separated, the plasma component may be collected from the blood component separation device and into a plasma collection container. During processing, the method may calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma collection container. The volume of pure plasma may be based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component. The method may continue the process (e.g., withdrawing whole blood, introducing anticoagulant into the whole blood, separating the blood, collecting the plasma, and calculating the percentage of anticoagulant and volume of pure plasma) until a target volume of pure plasma is collected within the plasma collection container.

[0005] In some embodiments, the method may determine a change in volume within an anticoagulant container, and the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the change in volume within the anticoagulant container. Additionally or alternatively, the method may determine a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump. In such embodiments, the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the number of rotations of the anticoagulant pump. The method may also determine a volume of anticoagulant within the blood component separation device, and the calculated percentage of anticoagulant in the

Haemonetics Corporation
Exhibit 2015
Page #1168

collected plasma may be based, at least in part, on the volume of anticoagulant within the blood component separation device.

[0006] In further embodiments, the method may monitor the volume and/or weight of the plasma component collected within the plasma collection container (e.g., using a weight sensor), and the calculated volume of pure plasma collected within the plasma collection device may be based, at least in part, on the monitored volume and/or weight of the collected plasma component. Additionally or alternatively, determining the hematocrit of the donor may include monitoring a volume of red blood cells collection within the blood separation device. In such embodiments, the determined hematocrit of the donor may be based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and the volume of whole blood withdrawn from the donor.

[0007] The target volume of pure plasma may be based, at least in part, on the weight of the donor. The percentage of anticoagulant in the collected plasma component may include at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant that is added to the system during a priming step. After collecting at least a portion of the target volume of pure plasma, the method may return the second blood component to the donor through a return line.

[0008] In accordance with additional embodiments, a system for collecting plasma includes a venous-access device for drawing whole blood from a subject and returning blood components to the subject, and a blood component separation device for separating the drawn blood into a plasma component and a second blood component. The blood component separation device has an outlet and is configured to send the plasma component to a plasma container. The system may also include a blood draw line fluidly connected to the venous-access device and an anticoagulant line connected to an anticoagulant source. The blood draw line transports drawn whole blood to the blood component separation device, and the flow through the blood draw line may be controlled by a blood draw pump. The anticoagulant line may introduce anticoagulant into the drawn whole blood.

[0009] Additionally, the system may include a controller that controls the operation of the centrifuge bowl. The controller may also calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container. The volume of pure plasma may be based, at least in part, upon the

Haemonetics Corporation
Exhibit 2015
Page #1169

percentage of anticoagulant in the collected plasma component. The controller may stop the blood draw pump when a target volume of pure plasma (e.g., based, at least in part, on the weight of the donor) is collected within the plasma container. In some embodiments, the percentage of anticoagulant in the collected plasma component may be based, at least in part, on the volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

[0010] The system may also include an anticoagulant source weight sensor that measures the weight of the anticoagulant source. The controller may monitor the change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, and the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the change in volume within the anticoagulant source. Additionally or alternatively, the controller may monitor the number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood. In such embodiments, the calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the number of rotations of the anticoagulant pump.

[0011] In some embodiments, the system may include an optical sensor located on the blood component separation device. The optical sensor may monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device. The calculated percentage of anticoagulant in the collected plasma may be based, at least in part, on the volume of anticoagulant within the blood component separation device.

[0012] In additional embodiments, the system may also include a plasma container weight sensor that monitors a volume and/or weight of the plasma component collected within the plasma collection container. The calculated volume of pure plasma collected within the plasma collection container may be based, at least in part, on the monitored volume and/or weight of collected plasma component. The system may also have an optical sensor located on the blood component separation device. The optical sensor may monitor the volume of red blood cells collected within the blood separation device. The controller may then determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood separation device and the volume of whole blood withdrawn from the donor. The percentage of anticoagulant in the collected plasma component may include at least a portion of the anticoagulant introduced into the

Haemonetics Corporation
Exhibit 2015
Page #1170

withdrawn blood and at least a portion of a volume of anticoagulant added to the system during a priming step.

Brief Description of the Drawings

[0013] The foregoing features of the invention will be more readily understood by reference to the following detailed description, taken with reference to the accompanying drawings, in which:

[0014] Fig. 1 schematically shows a perspective view of a blood processing system in accordance with some embodiments of the present invention.

[0015] Fig. 2 schematically shows a top view of the blood processing system of Figure 1, in accordance with some embodiments of the present invention;

[0016] Fig. 3 schematically shows a disposable set installed within the blood processing system of Figure 1, in accordance with some embodiments of the present invention.

[0017] Fig. 4 is a flowchart depicting a method of collecting plasma, in accordance with embodiments of the present invention.

Detailed Description of Specific Embodiments

[0018] Illustrative embodiments of the present invention provide blood processing systems and methods for collecting a target volume of pure plasma. The system and method calculate a percentage of anticoagulant collected within a plasma collection cotnainer (e.g., in addition to the plasma that is collected within the container) based on the amount of anticoagulant added to the system and the hematocrit of the donor. The system/method may then calculate the volume of pure plasma (e.g., plasma without anticoagulant) that has been collected within the container. Details of the illustrative embodiments are discussed below.

[0019] As shown in Figures 1 and 2, the blood processing system 100 includes a cabinet 110 that houses the main components of the system 100 (e.g., the non-disposable components). Within the cabinet 110, the system 100 may include a first/blood pump 232 that draws whole blood from a subject, and a second/anticoagulant pump 234 that pumps anticoagulant through the system 100 and into the drawn whole blood. Additionally, the

Haemonetics Corporation
Exhibit 2015
Page #1171

system 100 may include a number of valves that may be opened and/or closed to control the fluid flow through the system 100. For example, the system 100 may include a donor valve 120 that may open and close to selectively prevent and allow fluid flow through a donor line 218 (e.g., an inlet line; Fig. 3), and a plasma valve 130 that selectively prevents and allows fluid flow through an outlet/plasma line 222 (Fig. 3). Some embodiments may also include a saline valve 135 that selectively prevents and allows saline to flow through a saline line 223.

[0020] To facilitate the connection and installation of a disposable set and to support the corresponding fluid containers, the system 100 may include an anticoagulant pole 150 on which the anticoagulant solution container 210 (Fig. 3) may be hung, and a saline pole 160 on which a saline solution container 217 (Fig. 3) may be hung (e.g., if the procedure being performed requires the use of saline). Additionally, in some applications, it may be necessary and/or desirable to filter the whole blood drawn from the subject for processing. To that end, the system 100 may include blood filter holder 170 in which the blood filter (located on the disposable set) may be placed.

[0021] As discussed in greater detail below, apheresis systems 100 in accordance with embodiments of the present invention withdraw whole blood from a subject through a venous access device 206 (Fig. 3) using the blood pump 232. As the system 100 withdraws the whole blood from the subject, the whole blood enters a blood component separation device 214, such as a Latham type centrifuge (other type of separation chambers and devices may be used, such as, without limitation, an integral blow-molded centrifuge bowl, as described in U.S. Patent Nos. 4,983,158 and 4,943,273, which are hereby incorporated by reference). The blood component separation device 214 separates the whole blood into its constituent components (e.g., red blood cells, white blood cell, plasma, and platelets). Accordingly, to facilitate operation of the separation device 214, the system 100 may also include a well 180 in which the separation device 214 may be placed and in which the separation device 214 rotates (e.g., to generate the centrifugal forces required to separate the whole blood).

[0022] To allow the user/technician to monitor the system operation and control/set the various parameters of the procedure, the system 100 may include a user interface 190 (e.g., a touch screen device) that displays the operation parameters, any alarm messages, and buttons which the user/technician may depress to control the various parameters. Additional

Haemonetics Corporation
Exhibit 2015
Page #1172

components of the blood processing system 100 are discussed in greater detail below (e.g., in relation to the system operation).

[0023] FIG. 3 is a schematic block diagram of the blood processing system 100 and a disposable collection set 200 (with an inlet disposable set 200A and an outlet disposable set 200B) that may be loaded onto/into the blood processing system 100, in accordance with the present invention. The collection set 200 includes a venous access device 206 (e.g., a phlebotomy needle) for withdrawing blood from a donor's arm 208, a container of anti-coagulant 210, a centrifugation bowl 214 (e.g., a blood component separation device), a saline container 217, and a final plasma collection bag 216. The blood/inlet line 218 couples the venous access device 206 to an inlet port 220 of the bowl 214, the plasma/outlet line 222 couples an outlet port 224 of the bowl 214 to the plasma collection bag 216, and a saline line 223 connects the outlet port 224 of the bowl 214 to the saline container 217. An anticoagulant line 225 connects the anti-coagulant container 210 to the inlet line 218. In addition to the components mentioned above and as shown in Figure 3, the blood processing system 100 includes a controller 226, a motor 228, and a centrifuge chuck 230. The controller 226 is operably coupled to the two pumps 232 and 234, and to the motor 228, which, in turn, drives the chuck 230. The controller 226 may be operably coupled to and in communication with the user interface 190.

[0024] In operation, the disposable collection set 200 (e.g., the inlet disposable set 200A and the outlet disposable set 200B) may be loaded onto/into the blood processing system 100 prior to blood processing. In particular, the blood/inlet line 218 is routed through the blood/first pump 232 and the anticoagulant line 225 from the anti-coagulant container 210 is routed through the anticoagulant/second pump 234. The centrifugation bowl 214 may then be securely loaded into the chuck 230. Once the bowl 214 is secured in place, the technician may install the outlet disposable set 200B. For example the technician may connect a bowl connector 300 to the outlet 224 of the bowl 214, install the plasma container 216 into the weight senor 195, run the saline line 223 through valve 135, and run the plasma/outlet line 222 through valve 130 and the line sensor 185. Once the disposable set 200 is installed and the anticoagulant and saline containers 210/217 are connected, the system 100 is ready to begin blood processing.

Haemonetics Corporation
Exhibit 2015
Page #1173

[0025] Figure 4 is a flowchart depicting an exemplary method of collecting plasma in accordance with various embodiments of the present invention. Prior to connecting the donor to the blood processing device 100, it is beneficial (and perhaps necessary in some instances) to obtain/determine some information regarding the donor, namely, the donor's weight (Step 410) and hematocrit (Step 415). Not only does this information help determine if the individual is a viable donor and the volumes of blood components that may be withdrawn/collected (e.g., per the FDA guidelines), the hematocrit may be used during processing to help collect a target volume of plasma. The technician may obtain/determine the donor's weight by weighing the donor (e.g., on a scale). To obtain/determine the donor's hematocrit, the technician may draw a blood sample from the donor and test the sample of blood. Additionally or alternatively, as discussed in greater detail below, the system may determine the hematocrit during blood processing. For example, the blood processing device 100 may include a hematocrit sensor (not shown) that determines the hematocrit of the blood flowing into the blood processing device 100 and/or the system 100 may determine the hematocrit based on a volume of red blood cells collected within the bowl 214.

[0026] Once the lines 222/223 are in place and the technician has determined the donor's weight and/or hematocrit (if needed), the user/technician may insert the venous access device 206 into the donor's arm 208 (Step 420). Next, the controller 226 activates the two pumps 232, 234 and the motor 228. Operation of the two pumps 232, 234 causes whole blood to be drawn from the donor (step 425), anticoagulant from container 210 to be introduced into the drawn whole blood (step 430), and the now anticoagulated whole blood to be delivered to the inlet port 220 of the bowl 214.

[0027] It should be noted that the anticoagulant line 225 may also include a bacteria filter (not shown) that prevents any bacteria in the anticoagulant source 210, the anticoagulant, or the anticoagulant line 225 from entering the system 100 and/or the subject. Additionally, the anticoagulant line 225 may include an air detector 140 that detects the presence of air within the anticoagulant. The presence of air bubbles within any of the system 100 lines can be problematic for the operation the system 100 and may also be harmful to the subject if the air bubbles enter the blood stream. Therefore, the air detector may be connected to an interlock that stops the flow within the anticoagulant line 225 in the event that an air

Haemonetics Corporation
Exhibit 2015
Page #1174

bubble is detected (e.g., by stopping the anticoagulant pump 234), thereby preventing the air bubbles from entering the subject.

[0028] As the anti-coagulated whole blood is withdrawn from the subject and contained within the blood component separation device 214, the blood component separation device 214 separates the whole blood into several blood components (Step 435). For example, the blood component separation device 214 may separate the whole blood into a first, second, third, and, perhaps, fourth blood component. More specifically, the blood component separation device 214 (and the centrifugal forces created by rotation of the separation device 214) can separate the whole blood into plasma, platelets, red blood cells ("RBC"), and, perhaps, white blood cells ("WBC"). The higher density component, i.e., RBC, is forced to the outer wall of the bowl 214 while the lower density plasma lies nearer the core. A buffy coat is formed between the plasma and the RBC. The buffy coat is made up of an inner layer of platelets, a transitional layer of platelets and WBC and an outer layer of WBC. The plasma is the component closest to the outlet port and is the first fluid component displaced from the bowl 214 via the outlet port 224 as additional anticoagulated whole blood enters the bowl 214 through the inlet port 220.

[0029] As shown in Figure 3, the system 100 may also include an optical sensor 213 that may be applied to a shoulder portion of the bowl 214. The optical sensor monitors each layer of the blood components as they gradually and coaxially advance toward the core from the outer wall of the bowl 214. The optical sensor 213 may be mounted in a position (e.g., within the well 180) at which it can detect the buffy coat and/or the red blood cells reaching a particular radius, and the steps of drawing the whole blood from the subject/donor and introducing the whole blood into the bowl 12 may be altered and/or terminated in response to the detection.

[0030] Additionally, in some embodiments, the optical sensor 213 may be used to determine the hematocrit of the donor during processing. For example, as the bowl 214 fills with red blood cells and the optical sensor 213 detects the layer of red blood cells, the system 100 (e.g., the controller) can determine the volume of red blood cells within bowl 214 based on the location of the red blood cell layer and the fixed/known bowl volume. The system 100 may then calculate the donor hematocrit based on the volume of red blood cells within the bowl and the volume of whole blood that has been processed to that point.

Haemonetics Corporation
Exhibit 2015
Page #1175

[0031] Once the blood component separation device 214 has separated the blood into the various components, one or more of the components can be removed from the blood component separation device 214. For instance, the plasma may be removed to a plasma container 216 (e.g., a plasma bottle) through line 222 (Step 440). As noted above, some embodiments of the system 100 may include a weight sensor 195 (Fig. 1) that measures the amount of plasma collected. The plasma collection process may continue until the a target volume of pure plasma (discussed in greater detail below) is collected within the plasma collection container 216. Although not shown, if the blood processing system 100 and/or the disposable set 200 include platelet, red blood cell, and/or white blood cell bags, each of the bags/containers may include similar weight sensors (e.g., load cells).

[0032] In some embodiments, the system 100 may also include a line sensor 185 (mentioned above) that can determine the type of fluid (e.g., plasma, platelets, red blood cells etc.) exiting the blood component separation device 214. In particular, the line sensor 185 consists of an LED which emits light through the blood components leaving the bowl 214 and a photo detector which receives the light after it passes through the components. The amount of light received by the photo detector is correlated to the density of the fluid passing through the line. For example, if plasma is exiting the bowl 214, the line sensor 185 will be able to detect when the plasma exiting the bowl 214 becomes cloudy with platelets (e.g., the fluid existing the bowl 214 is changing from plasma to platelets). The system 100 may then use this information to either stop the removal of blood components from the bowl 214, stop drawing whole blood from the subject, or redirect the flow by, for example, closing one valve an opening another.

[0033] It is important to note that during processing, the osmolarity of the red blood cells prevents the anticoagulant introduced into the whole blood from entering/remaining with the red blood cells (e.g., within the bowl 214). Rather, the anticoagulant mixes with the plasma component. Therefore, the anticoagulant exits the bowl 214 with the plasma and is collected within collection container 216 along with the plasma. In other words, the weight of the product measured by the weight senor 195 is the weight of the plasma, as well as any anticoagulant that is mixed with the plasma – the weight provided by the weight sensor 195 is not the weight of pure plasma.

Haemonetics Corporation
Exhibit 2015
Page #1176

[0034] Additionally, whole blood contains a variable amount of plasma, as determined by the donor's hematocrit. The hematocrit for typical donors can vary from 38% to 54%, which means that for 100 ml of whole blood, the volume of plasma can vary from 36 to 62 ml. Furthermore, the amount of anticoagulant added to the withdrawn whole blood is fixed (e.g., it does not depend on the hematocrit of the donor), meaning that the percentage of anticoagulant in the collected plasma may vary from 9.7% to 12.7% for donor hematocrits between 38% to 54%, respectively. Therefore, not only does the volume measured by the weight sensor 195 include the volume of anticoagulant, that volume of anticoagulant may vary from donor to donor based on the hematocrit.

[0035] As mentioned above, some embodiments of the present invention continue the blood processing/separation procedure until a target volume of pure plasma (e.g., plasma only – without the volume of any anticoagulant mixed with the plasma included in the target volume) is collected within the plasma collection container 216. To that end, some embodiments of the present invention may calculate the volume of pure plasma within the plasma collection container 216. For example, the technician or the system 100 (e.g., the controller) may calculate the percentage of anticoagulant within the collected plasma (Step 455) (e.g., the plasma contained within the plasma collection container 216) based on the amount of anticoagulant added/metered into the whole blood and the hematocrit of the donor. The technician and/or system can calculate the percentage of anticoagulant according to the following equation, where AC is the amount of anticoagulant added to the system 100. As noted above, because the osmolarity of the red blood cells prevents the anticoagulant from mixing with it, essentially all of the anticoagulant exits the bowl 214 and is collected within the plasma collection container 216 along with the plasma.

$$\%\boldsymbol{AC} = \frac{\mathbf{1}}{\mathbf{1} + (\boldsymbol{AC} - \mathbf{1})(\mathbf{1} - \boldsymbol{Hct_D})}$$

[0036] The amount of anticoagulant that is added to the system 100 can be determined in a number of ways. For example, the system 100 can base the amount of anticoagulant (e.g., the value of "AC" in the above equation) on the predetermined ratio of anticoagulant per unit of anticoagulated whole blood. In some embodiments, the value of "AC" may be the inverse of the predetermined ratio (e.g., "AC" would be 16 if the ratio of

Haemonetics Corporation
Exhibit 2015
Page #1177

anticoagulant to anticoagulated whole blood was 1:16). Additionally or alternatively, the technician/system 100 can monitor the volume of anticoagulant added to the system. In such embodiments, the technician/system can monitor the volume of anticoagulant added to the system 100 based on the number of rotations of the anticoagulant pump (e.g., each rotation of the anticoagulant pump introduces a set volume of anticoagulant into the system 100) and/or based on the change in weight of the anticoagulant container 210 as measured by a weight sensor (discussed in greater detail below).

[0037] Once the technician/system 100 has calculated the percentage of anticoagulant within the plasma collection container 216, the technician/system 100 may then use this information to calculate the volume of pure plasma within the plasma collection container 216 (Step 465). For example, the technician/system 100 may determine the volume of anticoagulant within the container (based on the percentage of anticoagulant within the container 216) and subtract this volume from the total volume of fluid within the container 216 as measured by the weight sensor 195. The system 100 may continue to monitor the volume of pure plasma collected within the container 216 and continue processing whole blood (e.g., continue performing Steps 425, 430, 435, 440, 455, 460 and 465) until a target volume of pure plasma is collected within the plasma collection container 216 (Step 470) (e.g., 800 mL for an adult donor weighing more than 175 pounds or other limit prescribed by the FDA or similar governing body).

[0038] Once the system 100 has collected the target volume of pure plasma within the plasma collection container 216, the system 100 can return the remaining components (e.g., the components remaining within the bowl 214) to the subject (Step 475). For example, when all the plasma has been removed and the bowl 214 is full of RBCs (and any other blood component not collected), the controller 226 stops the draw of whole blood from the subject and reverses the direction of the blood/first pump 232 to draw the RBCs (and other components) from the bowl 214 directly back to the subject. Alternatively, if the system 100 is so equipped, the system may return the components to the subject via a dedicated return line.

[0039] In addition to the non-collected blood components (e.g., the components remaining in the bowl 214), the system 100 may also return saline to the patient/subject. The saline may be used as a compensation fluid to make up for the volume of the blood

Haemonetics Corporation
Exhibit 2015
Page #1178

component (e.g., plasma) that was removed and collected, and is not being returned to the patient. To that end, during the return step (e.g., Step 475), the saline valve 135 may be opened to allow saline from the saline container 217 to flow through the saline line 223 and into the bowl 214 (via outlet 224), where it can be returned to the patient/donor with or after the remaining blood components.

[0040] It should be noted that some embodiments may perform some additional and optional steps to help determine the volume of pure plasma within the plasma collection container 216. For example, as mentioned above, some embodiments may monitor the change in weight of the anticoagulant container 210 (e.g., as measured by a weight sensor/load cell on the anticoagulant container 210) (step 445). This measurement provides an indication of the volume of anticoagulant that has been added to the system 100, and may be used help determine the percentage of anticoagulant within the plasma collection container 216. Additionally or alternatively, some embodiments may similarly, monitor the change in weight and/or volume of the plasma and anticoagulant collected within the plasma collection container 216 (e.g., via weight sensor 195) (step 450). This measurement may be used to calculate of the total volume of pure plasma collected within the plasma collection container 216 (e.g., to obtain the total weight from which to subtract the calculated volume of anticoagulant).

[0041] Some embodiments may also (optionally) monitor the volume of anticoagulant remaining in the bowl 214 (step 460) (e.g., anticoagulant that did not mix with the plasma and/or otherwise remained in the bowl). For example, the system 100 may utilize the optical sensor on the bowl 214 to determine whether any anticoagulant remains within the bowl 214. If it does, the method 400/system 100 may modify the calculation of the amount of pure plasma collected within the plasma collection container (e.g., either increase the calculated amount or decreased the calculated amount), based on the volume of anticoagulant remaining within the bowl 214.

[0042] Various embodiment of the present invention provide numerous benefits over prior art plasma collection systems. In particular, as noted above, prior art plasmapheresis devices end plasma collection based on a total volume of anticoagulated plasma (e.g., pure plasma plus the added anticoagulant). Although this is the easiest method because it requires only that the product collection container be weighed, the amount of true product – the pure

Haemonetics Corporation
Exhibit 2015
Page #1179

plasma – is dependent on the donor's hematocrit. In other words, prior art systems will collect more plasma from low hematocrit donors than from high hematocrit donors because of the variation of the percentage of anticoagulant in the product. Various embodiments of the present invention address the issues of prior art systems by collecting a standard volume (e.g., a target volume) of pure plasma from each donor. As noted above, embodiments of the present invention accomplish this by using knowledge of the donor's hematocrit and the amount of anticoagulant collected within the plasma collection container 216 (e.g., by counting pump rotations and/or using scale/weight sensors, etc.) to determine the percentage of anticoagulant in the product. Additionally, by stopping the plasma collection process based on a volume of pure plasma collected, embodiments of the present invention are able to collect a greater volume of plasma as compared to prior art systems that stop based on a plasma/anticoagulant mixture.

[0043] It is also important to note that, although the various embodiments discussed above are in relation to a blood processing system that collects plasma, the features discussed herein may be applied to any type of blood processing system. For example, the features described herein may be implemented on blood processing systems that collect and/or process red blood cells, platelets and/or white blood cells.

[0044] The embodiments of the invention described above are intended to be merely exemplary; numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in any appended claims.

Haemonetics Corporation
Exhibit 2015
Page #1180

What is claimed is:

1. A method for collecting plasma comprising:

(a) determining a weight of a donor;

(b) determining a hematocrit of the donor;

(c) inserting a venous-access device into the donor;

(d) withdrawing whole blood from the donor through the venous-access device and a draw line, the draw line connected to a blood component separation device;

(e) introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

(f) separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;

(g) collecting the plasma component from the blood component separation device and into a plasma collection container;

(h) calculating a percentage of anticoagulant in the collected plasma component;

(i) calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated percentage of anticoagulant in the collected plasma component; and

(j) continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

2. A method according to claim 1, further comprising:

determining a change in volume within an anticoagulant container, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant container.

3. A method according claim 1, further comprising:

determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated percentage of anticoagulant in

Haemonetics Corporation
Exhibit 2015
Page #1181

the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

4. A method according to claim 1, further comprising:

determining a volume of anticoagulant within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

5. A method according to claim 1, further comprising:

monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

6. A method according to claim 1, further comprising:

monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

7. A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells collection within the blood separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor.

8. A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

9. A method according to claim 1, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

Haemonetics Corporation
Exhibit 2015
Page #1182

10. A method according to claim 1, further comprising:

returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

11. A system for collecting plasma comprising:

a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

a controller configured to control the operation of the centrifuge bowl and the blood draw pump, the controller configured to calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the percentage of anticoagulant in the collected plasma component, the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

12. A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

13. A system according to claim 11, further comprising:

an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant container based on the measured weight of the anticoagulant source, the

Haemonetics Corporation
Exhibit 2015
Page #1183

calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the change in volume within the anticoagulant source.

14. A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the number of rotations of the anticoagulant pump.

15. A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated percentage of anticoagulant in the collected plasma being based, at least in part, on the volume of anticoagulant within the blood component separation device.

16. A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored volume of collected plasma component.

17. A system according to claim 11, further comprising:

a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma collection device based, at least in part, on the monitored weight of collected plasma component.

18. A system according to claim 11, further comprising:

an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the

Haemonetics Corporation
Exhibit 2015
Page #1184

monitored volume of red blood cells collected within the blood separation device and a volume of whole blood withdrawn from the donor

19. A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

20. A system according to claim 11, wherein the percentage of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

Haemonetics Corporation
Exhibit 2015
Page #1185

Attorney Docket: 1611/C80

System and Method for Collecting Plasma

Abstract

A method for collecting plasma includes determining the weight and hematocrit of a donor, and inserting a venous-access device into the donor. The method then withdraws blood from the donor through a draw line connected to a blood component separation device, and introduces anticoagulant into the withdrawn blood. The blood component separation device separates the blood into a plasma component and a second blood component, and the plasma component is collected from the blood component separation device and into a plasma collection container. The method may then calculate (1) a percentage of anticoagulant in the collected plasma component, and (2) a volume of pure plasma collected within the plasma collection container. The volume of pure plasma may be based, at least in part, on the calculated percentage of anticoagulant. The method may continue until a target volume of pure plasma is collected within the plasma collection container.

Haemonetics Corporation
Exhibit 2015
Page #1186

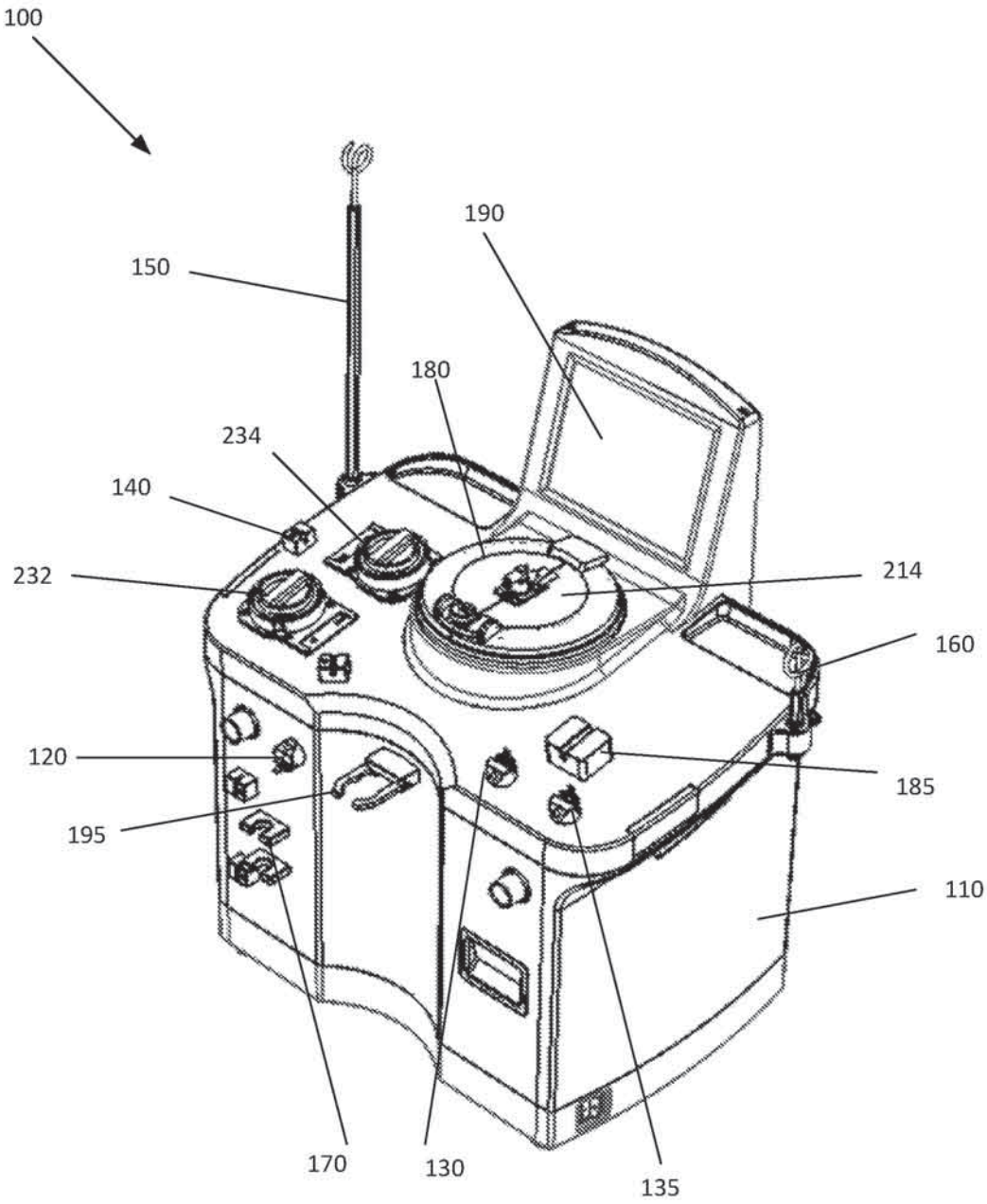


Fig. 1

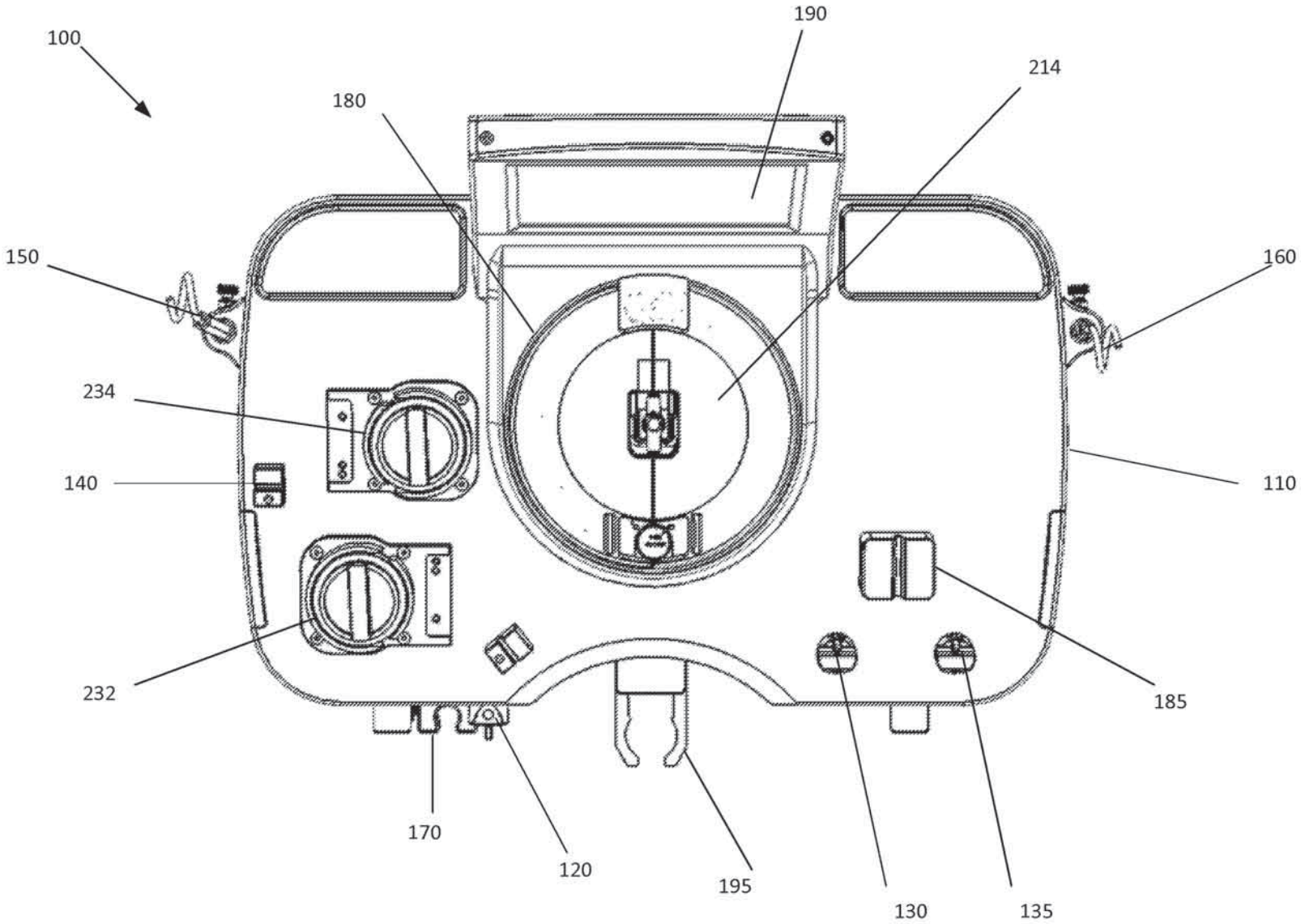


Fig. 2

Haemonetics Corporation
Exhibit 2015
Page #1188

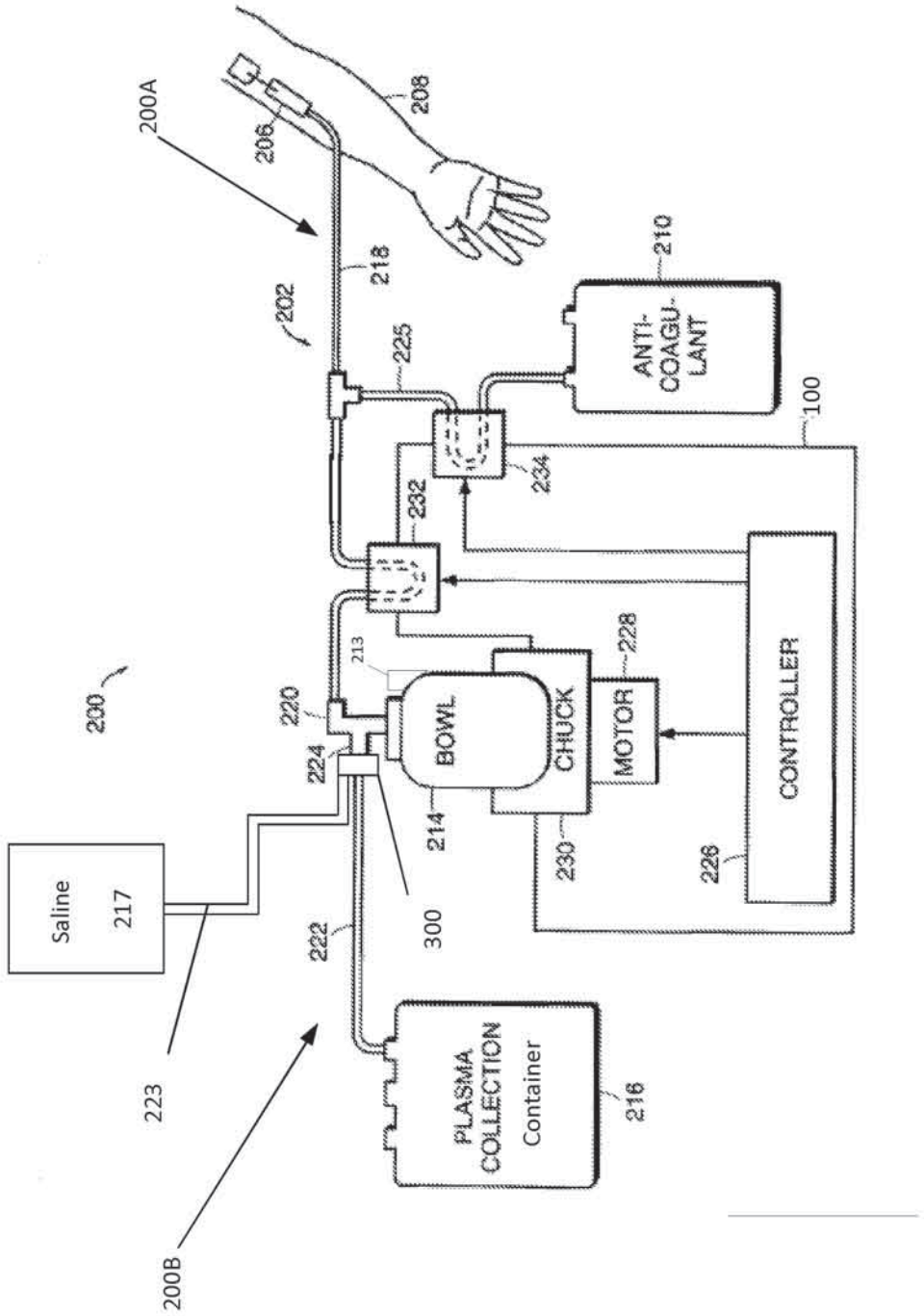

200A
206
208
218
202
225
210
ANTI-
COAGU-
LANT
100
234
232
200
220
213
224
BOWL
CHUCK
MOTOR
228
CONTROLLER
214
230
226
Saline
217
222
300
223
PLASMA
COLLECTION
Container
216
200B

Fig. 3

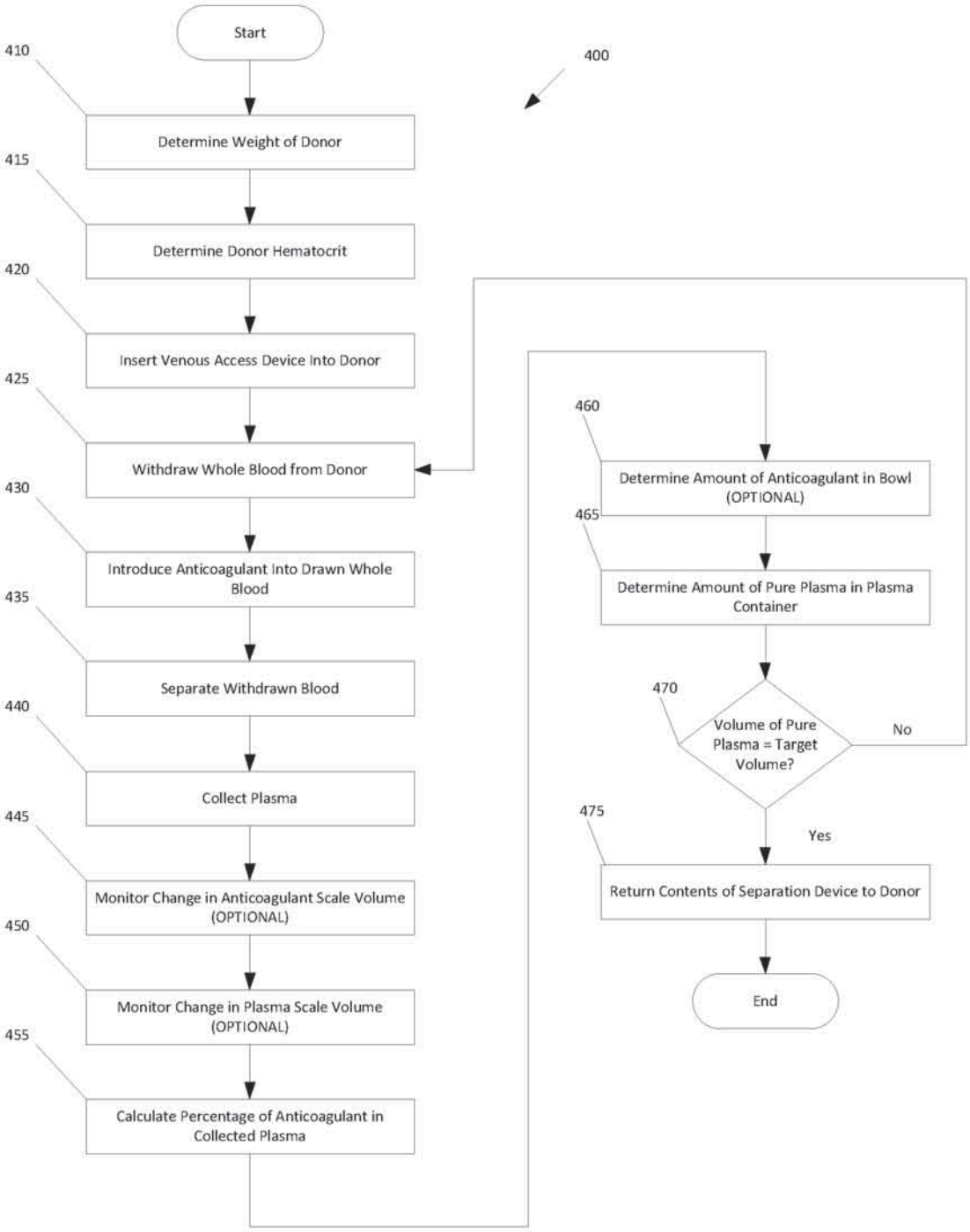

Start
400
410
Determine Weight of Donor
415
Determine Donor Hematocrit
420
Insert Venous Access Device Into Donor
425
Withdraw Whole Blood from Donor
430
Introduce Anticoagulant Into Drawn Whole Blood
435
Separate Withdrawn Blood
440
Collect Plasma
445
Monitor Change in Anticoagulant Scale Volume (OPTIONAL)
450
Monitor Change in Plasma Scale Volume (OPTIONAL)
455
Calculate Percentage of Anticoagulant in Collected Plasma
460
Determine Amount of Anticoagulant in Bowl (OPTIONAL)
465
Determine Amount of Pure Plasma in Plasma Container
470
Volume of Pure Plasma = Target Volume?
No
Yes
475
Return Contents of Separation Device to Donor
End

Fig. 4

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

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

Secrecy Order 37 CFR 5.2:

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

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Michael		Ragusa	

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

City	Hingham	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	4 Willow Circle
Address 2	

City	Hingham	State/Province	MA
Postal Code	02043	Country	US

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

Correspondence Information:

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

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

Customer Number	02101		
Email Address	usptomail@sunsteinlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	System and Method for Collecting Plasma		
Attorney Docket Number	1611/C80	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	4	Suggested Figure for Publication (if any)	

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Filing By Reference:

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

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

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

Publication Information:

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

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

Representative Information:

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

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	02101		

Domestic Benefit/National Stage Information:

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

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Foreign Priority Information:

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

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

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

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Authorization or Opt-Out of Authorization to Permit Access:

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

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

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

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

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

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

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

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

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

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

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Applicant Information:

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

Applicant 1 Remove

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

Clear

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

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

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Haemonetics Corporation		
Mailing Address Information For Applicant:			
Address 1	400 Wood Road		
Address 2			
City	Braintree	**State/Province**	MA
Country	US	Postal Code	02184
Phone Number		Fax Number	
Email Address			

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

Assignee Information including Non-Applicant Assignee Information:

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

Assignee 1

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

Remove

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

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

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

Signature:

Remove

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

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

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

Signature	/Jonathan C. Lovely, #60,821/			Date (YYYY-MM-DD)	2017-05-30
First Name	Jonathan C.	Last Name	Lovely	Registration Number	60,821

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

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1611/C80
	Application Number	
Title of Invention	System and Method for Collecting Plasma	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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

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

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

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

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

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

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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

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

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

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS

Application No.	Not yet assigned
Filing Date	May 30, 2017
First Named Inventor	Michael Ragusa
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Practitioner Docket No.	1611/C80

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

I. To authorize permission for Internet Communications.

☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 60,821.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Jonathan C. Lovely, #60,821/ — Signature

May 30, 2017 — Date

Jonathan C. Lovely — Typed or printed name

617-443-9292 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Filer:	Jonathan Lovely
Attorney Docket Number:	1611/C80

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	280	280
UTILITY SEARCH FEE	1111	1	600	600
UTILITY EXAMINATION FEE	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	140	140
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1740

Electronic Acknowledgement Receipt	
EFS ID:	29321375
Application Number:	15608183
International Application Number:	
Confirmation Number:	7286
Title of Invention:	System and Method for Collecting Plasma
First Named Inventor/Applicant Name:	Michael Ragusa
Customer Number:	2101
Filer:	Jonathan Lovely
Filer Authorized By:	
Attorney Docket Number:	1611/C80
Receipt Date:	30-MAY-2017
Filing Date:	
Time Stamp:	15:14:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1740
RAM confirmation Number	053117INTEFSW00001906194972
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	1611_Haemonetics_General_POA.pdf	64248 24bd3fac30b34fc3e9b648e967ee3fef31199683	no	1
Warnings:					
Information:					
2		ram1611_C80_Application.pdf	365747 6390c738793044b6e554134fc93e6a94994859a7	yes	24

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	14
Claims	15	19
Abstract	20	20
Drawings-only black and white line drawings	21	24

Warnings:					
Information:					
3	Application Data Sheet	ram1611_C80_ADS.pdf	1822879 dcfaafd33bb3e37630561bfa5958be1b79557fa3	no	8
Warnings:					
Information:					
4	Internet Communications Authorized	ram1611_C80_SB439.pdf	88592 770ecf2a65553479cc38e3d587fa9ea1377e4d0a	no	2
Warnings:					
Information:					

5	Fee Worksheet (SB06)	fee-info.pdf	36650 e3cc832ca90411b46a95599126b1df3e21f134a1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2378116		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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