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<b>(21) International Application Number:</b> PCT/US97/17984 <b>(22) International Filing Date:</b> 3 October 1997 (03.10.97)  <b>(30) Priority Data:</b> 08/742,572                      28 October 1996 (28.10.96)                      US  <b>(71) Applicant:</b> BAXTER INTERNATIONAL INC. [US/US]; One Baxter Parkway, Deerfield, IL 60015 (US).  <b>(72) Inventors:</b> HERMAN, Robert, E.; 542 Northgate Road, Lindenhurst, IL 60046 (US). CHAPMAN, John; 67 Kevin Avenue, Lake Villa, IL 60046 (US). CHONG-SON, Sun; 1051 Highland, Lake Forest, IL 60045 (US). MATHIAS, Jean, M.; Avenue du Tonnelier 46, B-1428 Lillois (BE). MAYAUDON, Véronique; Rue Pasteur 58, F-59600 Gognies-Chausee (FR). DE GHELDERE, Serge; Waversesteenweg 101, B-1560 Hoeilaart (BE). BISCHOF, Daniel, F.; 4913 Raintree Court, McHenry, IL 60050 (US).  <b>(74) Agents:</b> SEREWICZ, Denise, M. et al.; Baxter Healthcare Corporation, Route 120 & Wilson Road, Round Lake, IL 60073 (US).		<b>(81) Designated States:</b> AU, CA, CN, JP, KR, NO, RU, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SYSTEMS AND METHODS FOR REMOVING VIRAL AGENTS FROM BLOOD		
<b>(57) Abstract</b> <p>Systems and methods treat plasma carrying contaminants and cellular matter that are capable of entraining contaminants. The systems and methods separate cellular matter from the plasma by filtration, thereby removing contaminants entrained within the cellular matter. The system and methods add to the plasma a photoactive material. The systems and methods emit radiation at a selected wavelength into the plasma to activate the photoactive material and thereby eradicate the contaminant that is free of entrainment by cellular matter.</p>		

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**SYSTEMS AND METHODS FOR REMOVING  
VIRAL AGENTS FROM BLOOD**

**Field of the Invention**

The invention generally relates to the  
5 eradication of contaminants using photodynamic  
therapy. The invention also generally relates to the  
processing of whole blood and its components for  
storage and transfusion. In a more specific sense,  
the invention relates to the extracorporeal treatment  
10 of collected whole blood and its components with  
photoactive materials to eradicate viruses and other  
pathogenic contaminants.

**Background of the Invention**

With the coming of blood component therapy,  
15 most whole blood collected today is separated into its  
clinically proven components for storage and  
administration. The clinically proven components of  
whole blood include red blood cells, used to treat  
chronic anemia; platelet-poor plasma, from which Clot-  
20 ting Factor VIII-rich cryoprecipitate can be obtained  
for the treatment of hemophilia; and concentrations of  
platelets, used to control thrombocytopenic bleeding.

It is well known that blood can carry infec-  
tious agents like hepatitis-B virus; the human immuno-  
25 deficiency (AIDS) virus; the Herpes virus; and the  
influenza virus. To avoid the transmission of these  
infectious agents during blood transfusions, donors of  
blood are routinely screened and also undergo serolog-  
ic testing to detect the presence of these agents.  
30 Still, it is difficult to always assure that these

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infectious agents are detected.

The use of photodynamic therapy has been suggested as a way to eradicate infectious agents from collected blood and its components. Still, there has  
5 been a general lack of success in economically adapting the benefits of photodynamic therapy to the demands of the blood banking industry. One reason for this is that not all biological contaminants are carried free within the blood where they can be  
10 readily coupled to photoactive agents. Some biological contaminants are entrained on or within white blood cells out of the reach of photoactive agents.

For this and other reasons, the promise of  
15 photodynamic therapy in treating the nation's banked blood supply has gone largely unfulfilled.

#### Summary of the Invention

The invention provides improved systems and methods for treating blood constituents to  
20 adventitious viral agents.

One aspect of the invention provides systems and methods which remove viral agents from plasma. The systems and methods remove from the plasma targeted cellular matter that does or might entrain  
25 viral agents. In a preferred embodiment, the targeted cellular matter includes leukocytes. The system and methods add to the plasma a photoactive material, which binds to viral agents that are free of entrainment by the targeted cellular matter.  
30 Radiation emitted at a selected wavelength into the plasma activates the photoactive material and thereby eradicates the free viral agents.

In a preferred embodiment, a system for treating plasma comprises tubing adapted to be coupled  
35 a plasma source, and a filter in the tubing to

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separate cellular matter from the plasma conveyed from the source. The system includes a transfer container coupled to the tubing to receive cellular matter-reduced plasma from the filter, and a source of photoactive material to be mixed with the plasma. In this embodiment, the tubing includes a path to vent air from the transfer container in a path that bypasses the filter.

In a preferred embodiment, systems and methods remove viral agents entrained within the cellular matter by conveying plasma in a first path through a filter. The systems and methods convey the cellular matter-reduced plasma from the filter in a second path, which includes a connected transfer container. The systems and methods mix the cellular matter-reduced plasma with a photoactive material within the transfer container, forming a plasma mixture.

In this embodiment, the systems and methods convey a portion of the plasma mixture from the transfer container in a flush path, which includes the second path, to thereby expose residual contaminants in the second path to the photoactive material. The systems and methods then separate the transfer container from the filter by severing the second path. After severance from the filter, a remnant of the second path remains attached to the transfer container. However, due to the prior flushing step, all contaminants in the attached second path remnant have been exposed to the photoactive material. Subsequent radiation of the transfer container thereby eradicates contaminants, which are free of entrainment by cellular matter, both within the transfer container and the attached second path remnant.

In a preferred embodiment, the flush path by

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passes the filter and also provides a path to vent air from the transfer container.

Another aspect of the invention provides systems and methods for treating plasma using multi-stage filtration, which targets for removal different species of cellular matter. The systems and methods separate a first species of cellular matter by filtration through a first filter media, thereby removing contaminants entrained within the first species of cellular matter. The systems and methods separating a second species of cellular matter by filtration through a second filter media, thereby removing contaminants entrained within the second species of cellular matter. The systems and methods add to the plasma a photoactive material and emit radiation at a selected wavelength into the plasma to activate the photoactive material, thereby eradicating the contaminant that is free of entrainment by cellular matter. In a preferred embodiment, the first filtration media targets leukocytes for removal, while the second filtration media targets platelets for removal.

Another aspect of the invention provides a kit that envelopes photoactive material in an overwrap that includes a light filtering material. The light filtering material absorbs light that activates the photoactive material. The presence of the light filtering material in the overwrap protects the photoactive material from photo-degradation due to absorption of ambient light during handling and storage prior to use.

In a preferred embodiment, the photoactive material within the kit includes methylene blue. In this embodiment, the light filtering material includes a blue material having phtalocyanine pigments.

In a preferred embodiment, the photoactive material is contained in liquid form within the kit. In this embodiment, the overwrap also includes material that reduces liquid vapor loss from the kit.

5 Other features and advantages of the invention will be pointed out in, or will be apparent from, the drawings, specification and claims that follow.

**Description of the Drawings**

10 Fig. 1 is a plane view of a blood processing and storage kit for reducing the presence of viral agents in plasma;

Fig. 2 is an exploded, perspective view of the laminated walls of the overwrap envelope shown in phantom lines in Fig. 1;

15 Fig. 3 is a side view of the laminated walls of the overwrap envelope shown in Fig. 2;

Fig. 4 is a top perspective view of the laminated walls of the overwrap envelope, after having been joined by a peripheral heat seal;

20 Fig. 5 is an exploded side view of the leukocyte reduction filter that forms a part of the kit shown in Fig. 1;

25 Fig. 6 is a top perspective view of the interior of the outlet housing part for the filter shown in Fig. 5;

Fig. 7 is a plane view the kit shown in Fig. 1 being used to convey plasma from a source container, through the leukocyte reduction filter, and into the processing and storage container;

30 Fig. 8A is a plane view the kit shown in Fig. 7 being used to vent air and residual plasma from the processing and storage container in a bypass path around the leukocyte reduction filter;

35 Fig. 8B is a plane view of the kit shown in Fig. 8A being used to flush the tubing section next to

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the container with photoactive material, to assure exposure of residual viruses occupying the tubing section with photoactive material;

5 Fig. 9 is a perspective view of the kit shown in Figs. 8A and 8B, after separation of the processing and storage container and placement of the processing and storage container in an irradiation chamber;

10 Fig. 10 is a plane view of an alternative embodiment of a blood processing and storage kit for reducing the presence of viral agents in plasma, in which the photoactive material is stored within an auxiliary container whose walls include a light filtering material;

15 Fig. 11 is a plane view of an alternative embodiment of a blood processing and storage kit for reducing the presence of viral agents in plasma, which includes an integrally attached air reservoir;

20 Fig. 12A is a plane view of the kit shown in Fig. 11 being use to vent air and residual plasma from the processing and storage container into the air reservoir;

25 Fig. 12B is a plane view of the kit shown in Fig. 12A being used to flush the tubing section next to the container with photoactive material, to assure exposure of residual viruses occupying the tubing section with photoactive material; and

30 Fig. 13 is a plane view of another alternative embodiment of a blood processing and storage kit for reducing the presence of viral agents in plasma, which reduces the presence of viral agents in plasma by the removal by filtration of least two different cellular blood species which actually do or potentially can entrain viral agents.

35 The invention is not limited to the details



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of the construction and the arrangements of parts set forth in the following description or shown in the drawings. The invention can be practiced in other embodiments and in various other ways. The terminology and phrases are used for description and should not be regarded as limiting.

#### **Description of the Preferred Embodiments**

Fig. 1 shows a blood constituent processing and storage set or kit 300. The kit 300 is intended, during use, to assist in the removal of viral agents from plasma. The viral agents are either carried free within the plasma or are entrained on or within cellular matter (e.g., red blood cells, platelets, and leukocytes) that the plasma carries. The kit 300 shown in Fig. 1 will be described in the context of reducing the presence of viral agents in single donor units of plasma, because it is particularly well suited for this purpose.

The kit 300 includes a processing and storage container 302, which carries an integrally attached length of flexible transfer tubing 304. In the illustrated embodiment, the transfer tubing 304 is made from medical grade plasticized polyvinyl chloride plastic. However, other flexible medical grade plastic materials can be used.

The transfer tubing 304 includes an integrally attached in-line filter 306. The filter 306 includes a filter media 307 (see Fig. 5) that removes from plasma cellular matter that does actually or potentially entrain viral agents.

As Fig. 5 shows, the filter media 307 is encased within a two part housing 348A and 348 B made, for example, from polycarbonate, although any engineering medical grade plastic with appropriate toxicology characteristics can be used. The housing

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348A/348B is sealed about the filter media 307 by, for example, sonic welding.

5 The pore size of the filter media 307 can be tailored to remove by exclusion all or some species of cellular matter found in plasma, depending upon the extent to which viral agents sought to be eliminated are entrained by the different cellular species. In the illustrated embodiment, the principal cellular species targets of the filter 306 are leukocytes, for  
10 it is known that leukocytes entrain many viral agents. With this objective in mind, the filter media 307 comprises a non-fibrous membrane having a pore size smaller than the size of leukocytes, to thereby remove leukocytes by exclusion. In the illustrated  
15 embodiment, the media 307 also includes a prefilter material, which removes fibrin clots and other large size aggregates from the plasma.

The composition of the membrane for the media 307 can vary. For examples, hydrophilic  
20 membranes made from nylon, acrylic copolymers, polysulfone, polyvinylidene fluoride, mixed cellulose esters, and cellulose ester can be used to remove leukocytes by exclusion. Non-hydrophilic membranes can also be treated to serve as a membrane for the filter  
25 media 307. Likewise, the composition of the prefilter for the media 307 can vary. For example, the prefilter can comprise fibers of glass or polyester. Material selection takes into account customer preferences, performance objectives, and manufacturing  
30 requirements, including sterilization techniques.

In the illustrated and preferred embodiment, (see Fig. 5), the filter media 307 includes three filter media layers 342, 344, and 346. The first filter media layer 342 comprises USP Grade VI glass  
35 fiber or the equivalent. The second and third filter

media layers 344 and 346 comprise polyethersulfone (PES) membranes, which remove leukocytes by exclusion. The second and third filter media layers 344 and 346 possess pore sizes which are approximately 10 fold  
5 smaller than the size of leukocytes and which decrease in the direction of flow. The second filter media layer 344 has a pore size in the range of about 0.9  $\mu\text{m}$  to about 2.0  $\mu\text{m}$ , with an average pore size of about 1.2  $\mu\text{m}$ . The third filter media layer 346 has a  
10 smaller pore size in the range of about 0.3  $\mu\text{m}$  to about 1.5  $\mu\text{m}$ , with an average pores size of about 0.8  $\mu\text{m}$ . The second and third filter media layers 344 and 346 also incidently remove red blood cells by exclusion.

15 The filter media 307 should preferably be capable of filtering 310 ml of plasma, suspended at a head height of 3 feet, in 20 minutes.

The housing part 348A includes an inlet 350, which, in use, conveys plasma and leukocytes into  
20 contact with the prefilter layer 342. The axis 351 of the inlet 350 is generally parallel to the plane of the layer 342 to uniformly perfuse plasma across the entire prefilter layer 342.

The housing part 348B includes an outlet  
25 352, which conveys leukocyte-reduced plasma from the second and third PES filter layers 344 and 346. As Fig. 6 shows, the interior surface of the housing part 348B is grooved, creating a fluid manifold 354 that uniformly distributes leukocyte-reduced plasma to the  
30 outlet 352.

Referring back to Fig. 1, a length of branch tubing 308 is integrally attached to the transfer tubing 304 by conventional Y-connectors 316. The branch tubing 308 forms a fluid path bypassing the  
35 filter 306. As will be described in greater detail

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later, the branch tubing 308 serves to vent air.

The far end of the transfer tubing 304 carries an air pillow 310. The air pillow 310 prevents collapse of the tubing 304 and 308 caused by pressure differentials during steam sterilization of the kit 300.

The transfer tubing 304 further includes a conventional in-line frangible cannula 312 between the filter outlet 352 and the processing and storage container 302. The cannula 312 normally closes fluid the transfer tubing 304 to fluid flow.

The cannula 312 can be constructed in various ways. U.S. Patents 4,181,140 and 4,294,247 disclose representative constructions for the cannula 312, which are incorporated herein by reference. Alternatively, an external roller clamp or C-clamp of conventional construction could be used for the same purpose.

The branch tubing 308 includes a conventional in-line one-way valve 314. The valve 314 prevents fluid flow through the branch tubing 308 in the direction of the processing and storage container 302, while permitting fluid flow in the opposite direction away from the processing and storage container 302. For redundancy, the branch tubing 308 also includes an external roller clamp or C-clamp 318. The C-clamp 318 normally closes the tubing 308 between the one-way valve 314 and the processing and storage container 302.

The processing and storage container 302 can be constructed in various ways. In the illustrated and preferred embodiment, the container 302 includes an interior chamber 320. The transfer tubing 304 communicates with the chamber 320 for conveying plasma into the chamber 320. In a preferred implementation,

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the chamber 320 is capable of holding between 235 to 310 mL of plasma. A normally sealed outlet port 360 also communicates with the chamber 320. The port 360 is opened when it is time to remove plasma from the chamber 320.

The chamber 320 holds a photoactive material 326. The photoactive material 326 mixes with the plasma introduced into the chamber 320. The photoactive material 320 binds to extracellular viruses that plasma introduced into the chamber 326 may carry. When exposed to light energy in a particular spectrum, the photoactive material 326 inactivates the nucleic acids of the bound viruses, rendering them nonviable.

In the illustrated and preferred embodiment, the photoactive material 326 comprises 10 mL of liquid solution containing 83 micrograms of methylene blue in water at pH 3.1, without buffers or other additives. Methylene blue, a thiazine dye, possesses the ability to bind to nucleic acids with high affinity, targeting the viruses for destruction upon exposure to a particular spectrum of light energy. Methylene blue absorbs light in the 660 nm region of the visible spectrum, which is the spectrum region where plasma is most transparent. Methylene blue inactivates a broad range of viruses, such as HIV, human hepatitis B (HBV), human hepatitis C (HCV), and Parvo virus B19, with minimal loss of therapeutic plasma proteins.

The mixture of plasma and photoactive material 326 is irradiation by light within the chamber 320 as part of a viral inactivation process. The container 302 is therefore made of a material that is substantially transparent to the applied light energy. The material for the container 302 is also adapted to withstand contemplated storage conditions

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for the plasma.

In the illustrated and preferred embodiment, the applied light energy is in the white light spectrum (400 to 700 nm). The container 302 is therefore made of a plastic, poly(ethylene vinyl acetate) material. This material is transparent to white light and is also resistant to the cold temperatures at which frozen plasma is stored. This material is commercially available and is made and sold, for example, by Baxter Healthcare Corporation under the trademark PL-732® Plastic.

The container 302 also includes a flap 322, which extends below the chamber 320. The flap 322 carries a printed label 324 having identifying indicia. The flap 322 keeps the label 324 away from the chamber 320, where it could block or impede the irradiating light.

The container 302 also serves after the viral inactivation process to store the viral inactivated plasma at temperatures below - 30° C, following standard blood banking procedures.

Further details of container 302 are found in copending U.S. Patent Application, Serial No. 08/121,820, filed September 15, 1993, and entitled "Container for Irradiation of Blood Products."

As Fig. 4 shows, the kit 300 is preferably enclosed for storage and handling before use in an overwrap envelope 328 (Fig. 1 diagrammatically shows the envelope 328 in phantom lines). The overwrap envelope 328 serves multiple functions.

To minimize evaporation of the liquid photoactive material 326 from the container 302 prior to use, the envelope 328 includes a material 332 possessing a relatively low water vapor transmission rate (WVTR). In the illustrated and preferred

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embodiment, the targeted WVTR is about  $0.020 \text{ gh}^{-1}$  at  $25^{\circ} \text{C}$  and 60% relative humidity.

5 The particular composition of the water vapor barrier material 332 can vary. In the illustrated and preferred embodiment, the water vapor barrier material 332 comprises an oriented polypropylene material having a thickness of  $25 \text{ }\mu\text{m}$ .

10 To prevent degradation of the photoactive material 326 prior to use, the envelope also includes a light filtering material 330 possessing the ability to absorb ambient light energy in the spectrum that activates the photoactive material 326. It has been discovered that, during storage and handling prior to use, the photoactive material 326 absorbs from ambient  
15 visible light (400 nm to 700 nm) the spectrum that initiates photoactivation. The incidental absorption of ambient visible light by photoactive material 326 initiates a photoreduction process, creating byproducts that are either partially or completely  
20 ineffective for viral inactivation.

For example, exposure of methylene blue to visible ambient light (whose emission spectrum includes the 660 nm region) converts the methylene blue into colorless leucomethylene blue. The  
25 leucomethylene blue photoreduction byproduct is not effective in inactivating viruses.

The particular composition of the light filtering material 330 will vary according to the light sensitivity spectrum of the particular  
30 photoactive material 326 used. In the illustrated and preferred embodiment, the light filtering material 330 comprises a blue dye of phthalocyanine pigments. The blue dye material 326 transmits not more than 1% of light in the range of 600 nm to 700 nm, which is the  
35 spectrum in which methylene blue is activated.

As Figs. 2 and 3 show, in the illustrated and preferred embodiment, the overwrap envelope 328 comprises sheets S1 and S2, each of which comprises a multiple layer laminate L1 and L2. The water vapor barrier material 332 constitutes one of the exterior layers of each laminated sheet S1 and S2. The blue die comprising the light filtering material 330 is printed on the interior face of the water vapor barrier material 332.

Each laminated sheet S1 and S2 also preferably includes as another exterior layer a material 334 that flows in response to heat. The presence of the material 334 makes it possible to heat seal the two sheets S1 and S2 together, forming the envelope 328.

The particular composition of the heat flowing material 334 can vary. In the illustrated and preferred embodiment, the material 334 comprises a cast polypropylene material having a thickness of about 25  $\mu\text{m}$ . The heat flowing material 334 can be attached to the layer 332, for example, by a polyurethane-polyester resin-epoxy.

Laminated sheets S1 and S2 as described, with the layers 330, 332, and 334 and suited for use as the overwrap envelope 328, can be purchased from Hosokawa Yoko Co., LTD. (Japan). The sheet material from this company has a weight of 50  $\text{g/m}^2$  and density 1.0  $\text{g/cm}^3$ .

The envelope 328 is created by laying the sheets S1 and S2 of the overwrap laminate together (as Fig. 3 shows) and applying pressure and heat H along the sheet edges in a heat sealing die. The pressure and heat H form a peripheral heat seal 336, which joins the sheets S1 and S2 together, forming the envelope 328 (as Fig. 4 shows).



Despite the presence of the light filtering material 330, the overwrap envelope 328 as above described nevertheless retains sufficient transparency to other visible light spectrums to allow visual inspection of the contents of the overwrap envelope 328, for quality control or customer inspection purposes.

The overwrap envelope 328, including an appropriate light filtering material 330 as just described, can be used in association with other containers or in other systems which hold liquids or other materials sensitive to ambient light degradation. For example, photoactive materials 326 activated in different spectrum regions will require accordingly different light filtering material 328. For example, 4'-(4-Amino-2-oxa)butyl-4,5'8-trimethylpsoralen (S-59) is a photoactive material usable in conjunction with platelet-containing blood suspensions. S-59 is activated by ultraviolet-A light and can undergo intramolecular reactions when exposed to ambient UV-A and short wavelength regions of visible light. To protect against such degradation of S-59 material, the light filtering material 330 can comprise a UV-A absorbent red die.

For another example, as Fig. 10 shows, instead of using a light filtering overwrap envelope 328, the kit 300 (or another system) can include an auxiliary container 362 to store the light activated material 326 before use. The walls of the container 362 include an appropriate light filtering material 330 to protect the light activated material 326 from ambient light degradation before use. In this arrangement, the photoactivated material 326 is transferred from the auxiliary container 362 to plasma before the light activation process, either before or

during filtration, or after filtration when the plasma occupies the processing and storage container 302. Of course, a container (like the container 302), which is intended to ultimately serve as a light transparent chamber, must remain free or essentially free of a light filtering material. In this arrangement, it is still desirable to provide an overwrap envelope 364 (shown diagrammatically in Fig. 10) to decrease water vapor loss of the liquid photoactive material 326 during storage and handling prior to use.

The overwrap envelope 328 (or 364 in the Fig. 10 embodiment) is torn away when it is time to use the kit 300. As Fig. 7 shows, a container 338 holding the plasma P is connected in a sterile fashion to the transfer tubing 304 near the air pillow 310. The source container 338 can, for example, hold fresh plasma or plasma that has been frozen and thawed. The plasma is harvested by conventional blood banking procedures. These procedures, which are accomplished through centrifugation of whole blood, yield plasma that is essentially free of red blood cells.

Known sterile connection mechanisms (not shown) like that shown in Spencer U.S. Patent 4,412,835 can be used for connecting the container 338 to the transfer tubing 304. These mechanisms form a molten seal between tubing ends, which, once cooled, forms a sterile weld 360. The air pillow 310 is discarded after sterile connection between the source container 338 and the transfer tubing 304 is made.

As Fig. 7 shows, once the sterile connection is made, the source container 338 is suspended above the processing and storage container 302. The operator checks to assure that the clamp 318 is closed on the bypass branch tubing 308. The operator breaks the cannula 312, and the plasma P flows by gravity head

pressure through the filter 306. The leukocyte-reduced plasma exits the filter 306 and drains into the chamber 320 of the container 302.

It has been observed that the triple layer  
5 membrane filter 306 described above provides plasma having a leukocyte level that is below the limit of flow cytometer detection (i.e., less than about one leukocyte per  $\mu\text{L}$ ). The actual residual level of leukocytes in the plasma after filtration by the  
10 filter 306 is estimated not to exceed an average theoretical level of 0.004 leukocyte per  $\mu\text{L}$ . Based upon an initial leukocyte level of  $0.79 \times 10^8$  per L, the leukocyte reduction percentage of the filter 306 is estimated to be about 99.99% (log reduction  $\geq 4.0$ ).

15 The methylene blue photoactive material 326 is mixed with the leukocyte-reduced plasma within the container 302 by manual inversion.

As Fig. 8A shows, after mixing plasma P and photoactive material 326 within the container chamber  
20 320, the clamp 318 is opened and the container 302 squeezed. Air A is vented from the container 302, through the bypass branch tubing 308 back into the source container 338. As Fig. 8A also shows, the venting of air A also displaces residual plasma P, out  
25 of the transfer tubing 304 between the filter 306 and the container 302 and into the bypass branch tubing 308. Viruses in the residual plasma P, having never entered the container chamber 320 have not been exposed to the photoactive material 326 and therefore  
30 should be removed before undertaking the desired photoactivation process.

As Fig. 8B shows, as air venting proceeds, an amount of the mixture M of photoactive material 326 and plasma P will enter the section 305 of the  
35 transfer tubing 304 between the filter 306 and the

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container 302. The mixture M is allowed to drain back into the container 302. The mixture M flushes this section of the transfer tubing 304 with the photoactive material 326 and plasma mixture. The flushing process assures that viruses still occupying this section of the tubing 304 after air venting will become mixed with the photoactive material 326. This assures that all viruses present in the container 302 and adjacent section 305 of tubing 304 are exposed to the material 326, to thereby assure the desired virucidal effect during subsequent exposure to light irradiation.

After air venting and flushing, as just described, the tubing 305 next to the container 302 is sealed closed using, for example, a dielectric tube sealer. As Fig. 9 shows, the remaining portion of the kit 300 containing the filter 306 is removed and discarded. A remnant of the tubing 305 remains connected to the container 302.

The container 302 holding the methylene blue and leukocyte-reduced plasma, and carrying a remnant of the tubing section 305, is placed into a white light chamber 356 (see Fig. 9). The chamber 356 comprises twelve fluorescent lamps 358, which supply output in the visible range (400 to 700 nm) to both sides of the container 306. The chamber 356 monitors the light intensity and adjusts exposure time to control total light dosage delivered to the container 306. The light activates the methylene blue to release singlet oxygen, which inactivates viruses in the plasma. The approximate time of illumination to deliver a targeted dose of 33 J per cm<sup>3</sup> is 30 minutes. Further details of the chamber 356 can be found in copending U.S. Patent Application Serial No. \_\_\_\_\_, filed \_\_\_\_\_, and entitled "A System to Detect and

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Identify Bags That Have Been Processed in the Illuminating Device for Inactivation of Viruses."

After the illumination step, the leukocyte-reduced plasma is frozen within the container 302 at  
5 less than -30°C for storage using conventional blood bank practices. The plasma within the container 302 is thawed when fractionation or transfusion is required.

In the illustrated embodiment (see Fig. 1),  
10 the kit 300 includes written instructions 374 for using the kit for its intended purpose. The instructions 374 direct the technician to handle the kit in a prescribed way to best accomplish the desired therapeutic objectives, as set forth in the preceding  
15 description and shown in Figs. 7 to 9.

The instructions 374 may take various forms. Representative instructions 374 direct the technician, upon removal of the overwrap 328, to convey plasma through the tubing 304 from the source 338 through the  
20 filter 306 to separate leukocytes from the plasma. The representative instructions 374 also direct the technician to convey leukocyte-reduced plasma through the tubing 304 from the filter 306 to the transfer container 302. The representative instructions 374  
25 also instruct the technician to mix the photoactivated material 326 with the plasma and to expose leukocyte-reduced plasma mixed with the photoactive material 326 to light that activates the photoactive material 326. The representative instructions 374 also direct  
30 the technician to store the plasma in the container 302 after the photoactivation process.

The instructions 374 can, of course, include further details based upon the particular  
35 configuration of the kit 300. For example, in the context of the kit 300 shown in Fig. 1, the

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instructions 374 can direct the technician to mix the photoactivated material with leukocyte-reduced plasma within in the container chamber 320. In this context, the instructions 374 can also direct the technician to  
5 expose the container chamber 320 to light that activates the photoactive material 326 mixed within the chamber 320 with the leukocyte-reduced plasma. The instructions 374 can also direct the technician to vent air from the container chamber 320 in a path that  
10 bypasses the filter 306, which in Fig. 1 comprises the branch tubing 308. The instructions 374 can also instruct the technician to flush the tubing 304 downstream of the filter 306 with plasma and photoactive material 326 from the chamber 320.

15 **EXAMPLE**

A study was conducted to demonstrate the ability of the kit 300 when used in accordance with the instructions 374 to inactivate viruses under intended use conditions. In the study, a maximum  
20 plasma volume of 310 mL was employed to provide the lowest concentration of methylene blue and the greatest fluid thickness to be illuminated. In addition, the nominal targeted light dose of  $33 \text{ J/cm}^2$  was reduced to 24 or  $30 \text{ J/cm}^2$  to further stress the  
25 study conditions.

Plasma was collected from CPD anticoagulated whole blood units following routine blood bank procedures, yielding plasma that is essentially free of red blood cells. The plasma was not frozen prior  
30 to treatment during the study.

A panel of viruses was selected to represent the most significant agents that can contaminate fresh frozen plasma and to represent a broad spectrum of physical/chemical forms of viruses (i.e., lipid  
35 enveloped and non-lipid enveloped RNA and DNA viruses,

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as well as intra-cellular viruses). The panel included the following viruses: BVDV (strain Singer); HIV Type 1 (HIV-1, strain III<sub>g</sub>); human herpes simplex virus Type 1 (HSV-1, strain MacIntyre); pseudorabies virus (PRV, strain Aujeszky); simian virus Type 40 (SV-40, strain Pa-57); duck hepatitis B DHBV; and cell associated HIV (H-9/HIV, HIV III<sub>g</sub> chronically infected H-9 cells).

These viruses were added to units of plasma before treatment in physiologically representative concentrations. A process control comprising an aliquot of virus-spiked plasma, was collected from each unit prior to processing in the kit 300. The process control served as the baseline value for the calculation of the virus load reduction, called the log reduction value (LRV). LRV represents either (i) the difference in log virus titers between the process control and the processed sample, or (ii) the difference in log virus titers between the process control and the validated sensitivity limit of the assay, if there was no recoverable virus (indicated by the use of the symbol ">" in the Table 1 below).

The virus panel and the log reduction values (LRV's) obtained by processing the plasma in the kit 300 in accordance with the instructions 374 are summarized in the following Table 1:

**TABLE 1: Results of Study on Viral Inactivation Using the Kit 300**

Virus	Model for	Size (nm)	LRV
HIV	Self	110	>6.6 at 24 J/cm <sup>2</sup>
BVDV	HCV	60-70	>5.93 ± 0.07 at 24 J/cm <sup>2</sup>
DHBV	HBV	40	3.5 at 30 J/cm <sup>2</sup>
PRV	enveloped DNA virus	150-180	5.52 ± 0.38 at 30 J/cm <sup>2</sup>
HSV	enveloped DNA virus	150-180	>6.16 ± 0.06 at 24 J/cm <sup>2</sup>
SV-40	non- enveloped DNA virus	55	4.27 ± 0.30 at 24 J/cm <sup>2</sup>
HIV/H9	virus- infected leukocytes		No Recoverable Viruses after challenge with 1x10 <sup>8</sup> HIV/H9 cells

Table 1 demonstrates that use of the kit 300 is effective against small and large lipid enveloped viruses with either RNA or DNA genomes. Table 1 also demonstrates the capability of the kit 300 to inactivate certain non-enveloped viruses, which are not resistant to the virucidal action of methylene blue (for example, non-enveloped encephalomyocarditis virus (EMC) has demonstrated a resistance to the



virucidal action of methylene blue).

The kit 300 provides more reliability and ease of use than the removal of leukocytes from plasma by lysing using conventional freeze-thaw processes.

5 The kit 300 also provides greater removal of adventitious agents (i.e., viruses) than mere light inactivation (which does not remove intracellular agents) and/or bed-side filtering of plasma (which only removes fibrin clots, and not leukocytes).

10 Fig. 11 shows, as an alternative embodiment, a kit 300' sharing many of the component parts of the kit 300 shown in Fig. 1. The common elements (which are assigned the same reference numbers as in Fig. 1) include the processing and storage container 302, the  
15 transfer tubing 304, the filter 306, the photoactive material 326, and the frangible cannula 312.

However, the kit 300' shown in Fig. 11 does not include the branch tubing 308 and the air pillow 310.

20 Instead, the far end of the tubing 304 in the kit 300' is closed by a plug 372. The kit 300' also includes an air reservoir 370 integrally connected to the tubing 304 by the Y-connector 316 between the filter 306 and the container 302.

25 The air reservoir 370 takes the place of the air pillow 310. Like the pillow 310, the reservoir 370 contains a residual amount of air to prevent collapse of the tubing 304 during steam sterilization. The reservoir 370 also serves as a chamber to receive  
30 vented air and residual plasma from the container 302 at the end of the filtration process.

More particularly, using the kit 300', plasma from the source container 338 is passed for leukocyte reduction through the filter 306 and mixed  
35 with the photoactive material 326 in the container 320

in the same manner previously described and shown in Fig. 7.

As Fig. 12A shows, after filtration and mixing, air A is vented from the container 302 into the reservoir 370. Residual plasma P is also displaced out of the tubing section 305 and into the reservoir 370. As Fig. 12 B shows, as air venting proceeds, an amount of the mixture M of photoactive material 326 and plasma P will enter the section 305 of the transfer tubing 304 between the filter 306 and the container 302. The mixture M flushes this section of the transfer tubing 304 with the photoactive material 326 and plasma mixture.

In all other respects the process for handling the kit 300' is the same as previously described with respect to the kit 300.

Fig. 13 shows, as another alternative embodiment, a kit 300'' sharing many of the component parts of the kit 300 shown in Fig. 1. The common elements (which are assigned the same reference numbers as in Fig. 1) include the processing and storage container 302, the transfer tubing 304, the branch tubing 308, the filter 306, the photoactive material 326, the air pillow 310, and the frangible cannula 312. The kit 300'' shown in Fig. 13 includes an additional in-line filter 376 in the transfer tubing 304 downstream of the filter 306. The filter 376 includes a filter media 378 that removes from plasma a second cellular species different than the species removed by the filter media 307, which second cellular species does actually or potentially entrain viral agents. In the illustrated and preferred embodiment, where the principal cellular species targeted by the filter media 307 are leukocytes, the second cellular species targeted by the second filter

media 378 are platelets.

As described above in connection with the filter media 307, the pore size of the filter media 378 can be tailored to remove platelets from plasma by exclusion. It is believed that candidate materials for the media 307 formed with a pore size range of between  $.3\mu\text{m}$  and  $.45\mu\text{m}$  (which is smaller than the pore size range of the media 307) will serve to remove platelets from plasma by exclusion.

The presence of the second, downstream media 378, having a smaller pore size than the first, upstream media 307, also provides added assurance that the cellular species targeted for removal by the first media 307 (i.e., leukocytes) will, in fact, be depleted or essentially depleted from the plasma. In this respect, the smaller pore size media 378 serves both a redundant function of removing leukocytes and an added second step function of removing the smaller platelet species.

It should be appreciated that the second filter media 378 can, instead of being separately housed as the filter 378, be integrated as another layer with the already multi-layer filter media 307.

In all other respects the process for handling the kit 300'' is the same as previously described with respect to the kit 300.

Features and advantages of the invention are set forth in the following claims.

**We Claim:**

1. A system for treating plasma comprising tubing adapted to be coupled to a plasma source,  
a filter coupled to the tubing to separate  
5 cellular matter from the plasma conveyed from the source,  
a transfer container coupled to the tubing to receive cellular matter-reduced plasma from the filter,  
10 a source of photoactive material to be mixed with the plasma, and  
the tubing including a path to vent air from the transfer container in a path that bypasses the filter.
2. A system according to claim 1 wherein the source of photoactive material is contained within the transfer container.
3. A system according to claim 1 wherein the transfer container is made, at least in part, of material that is essentially transparent to light that activates the photoactive  
5 material.
4. A system according to claim 1 and further including an overwrap enveloping the transfer container and including light filtering material that absorbs light that activates the  
5 photoactive material.
5. A system according to claim 4 wherein the overwrap includes a vapor barrier material.
6. A system according to claim 4 wherein the photoactive material comprises methylene blue, and  
wherein the light filtering material

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- 5 includes a blue material on the overwrap.
7. A system according to claim 6  
wherein the blue material includes  
phtalocyanine pigments.
8. A system according to claim 1  
wherein the transfer container is made of  
material that accommodates plasma storage.
9. A system according to claim 1  
wherein the source of photoactive material  
comprises an auxiliary container separate from the  
transfer container.
10. A system according to claim 9  
wherein the auxiliary container is made, at  
least in part, of light filtering material that  
absorbs light that activates the photoactive material.
11. A system according to claim 10  
wherein the photoactive material comprises  
methylene blue, and  
wherein the light filtering material
- 5 includes a blue material on the auxiliary container.
12. A system according to claim 11  
wherein the blue material includes  
phtalocyanine pigments.
13. A system according to claim 1  
wherein the path vents air from the transfer  
container to the plasma source.
14. A system according to claim 1  
wherein the path includes a one way valve  
that blocks fluid flow in a direction toward the  
transfer container while permitting fluid flow in a
- 5 direction away from the transfer container.
15. A system according to claim 1  
and further including an air reservoir, and  
wherein the path communicates with the air  
reservoir.

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16. A system according to claim 1 wherein the photoactive material includes methylene blue.

17. A system according to claim 1 wherein the filter removes leukocytes.

18. A system for treating plasma comprising tubing adapted to be coupled to a plasma source,

a first filtration media coupled to the tubing to separate a first species of cellular matter from the plasma conveyed from the source,

a second filtration media coupled to the tubing in series with the first filtration media to separate a second species of cellular matter from the plasma conveyed from the source, which second species of cellular matter is essentially not removed by the first filtration media,

a transfer container coupled to the tubing to receive cellular matter-reduced plasma from the first and second filtration media, and

a source of photoactive material to be mixed with the plasma.

19. A system according to claim 18 wherein the tubing includes a path to vent air from the transfer container in a path that bypasses the first and second filtration media.

20. A system according to claim 18 wherein the source of photoactive material is contained within the transfer container.

21. A system according to claim 18 wherein the transfer container is made, at least in part, of material that is essentially transparent to light that activates the photoactive material.

5

22. A system according to claim 18

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and further including an overwrap enveloping the transfer container and including light filtering material that absorbs light that activates the photoactive material.

5

23. A system according to claim 22 wherein the overwrap includes a vapor barrier material.

24. A system according to claim 22 wherein the photoactive material comprises methylene blue, and

wherein the light filtering material includes a blue material on the overwrap.

5

25. A system according to claim 24 wherein the blue material includes phtalocyanine pigments.

26. A system according to claim 18 wherein the transfer container is made of material that accommodates plasma storage.

27. A system according to claim 18 wherein the source of photoactive material comprises an auxiliary container separate from the transfer container.

28. A system according to claim 27 wherein the auxiliary container is made, at least in part, of light filtering material that absorbs light that activates the photoactive material.

29. A system according to claim 28 wherein the photoactive material comprises methylene blue, and

wherein the light filtering material includes a blue material on the auxiliary container.

5

30. A system according to claim 29 wherein the blue material includes phtalocyanine pigments.

31. A system according to claim 18

- 30 -

wherein the path vents air from the transfer container to the plasma source.

32. A system according to claim 18

wherein the path includes a one way valve that blocks fluid flow in a direction toward the transfer container while permitting fluid flow in a  
5 direction away from the transfer container.

33. A system according to claim 18

and further including an air reservoir, and wherein the path communicates with the air reservoir.

34. A system according to claim 18

wherein the photoactive material includes methylene blue.

35. A system according to claim 18

wherein the one of the first and second filtration media removes leukocytes.

36. A system according to claim 18

wherein the one of the first and second filtration media removes platelets.

37. A system according to claim 18

wherein the first filtration media removes leukocytes, and

wherein the second filtration media removes platelets.

38. A kit comprising

tubing adapted to be coupled to a blood constituent source to convey blood constituent,  
a transfer container coupled to the tubing,  
5 a source of photoactive material to be mixed with the blood constituent, and

an overwrap enveloping at least a portion of the kit and including light filtering material that absorbs light that activates the photoactive material.

39. A kit according to claim 38



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wherein the photoactive material includes methylene blue.

40. A kit according to claim 39 wherein the light filtering material includes a blue material.

41. A kit according to claim 40 wherein the blue material includes phtalocyanine pigments.

42. A kit according to claim 38 wherein the photoactive material includes psoralen.

43. A kit according to claim 42 wherein the light filtering material includes a red material.

44. A kit comprising tubing adapted to be coupled to a plasma source,

5 a filter coupled to the tubing to remove cellular matter from the plasma,

a transfer container coupled to the tubing to receive cellular matter-reduced plasma from the filter,

10 a source of photoactive material to be mixed with the plasma, and

an overwrap enveloping at least a portion of the kit and including light filtering material that absorbs light that activates the photoactive material.

45. A kit according to claim 44 wherein the photoactive material includes methylene blue.

46. A kit according to claim 45 wherein the light filtering material includes a blue material.

47. A kit according to claim 46 wherein the blue material includes

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phtalocyanine pigments.

48. A kit according to claim 44  
and further including instructions for using  
the kit following removal of the overwrap in  
accordance with a method comprising the steps of  
5                   conveying plasma through the tubing  
from the source through the filter to separate  
cellular matter including leukocytes from the plasma,  
                  conveying cellular matter-reduced  
plasma through the tubing from the filter to the  
10           transfer container,  
                  mixing the photoactivated material with  
the plasma, and  
                  exposing leukocyte-reduced plasma mixed  
with the photoactive material to light that activates  
15           the photoactive material.

49. A kit comprising  
tubing adapted to be coupled to a plasma  
source to convey plasma,  
a filter coupled to the tubing to separate  
5           cellular matter from plasma conveyed from the source,  
a transfer container having a chamber that  
holds a photoactive material, the chamber  
communicating with the tubing to receive cellular  
matter-reduced plasma from the filter, the chamber  
10           having a wall made, at least in part, from material  
that is essentially transparent to light that  
activates the photoactive material, and  
an overwrap enveloping at least a portion of  
the kit and including material that absorbs light that  
15           activates the photoactive material.

50. A kit according to claim 49  
wherein the photoactive material includes  
methylene blue.

51. A kit according to claim 50

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wherein the light filtering material includes a blue material.

52. A kit according to claim 51

wherein the blue material includes phtalocyanine pigments.

53. A kit according to claim 49

and further including instructions for using the kit following removal of the overwrap in accordance with a method comprising the steps of

5                   conveying plasma through the tubing  
from the source through the filter to separate  
cellular matter including leukocytes from the plasma,  
                  conveying cellular matter-reduced  
plasma through the tubing from the filter to the  
10   transfer container chamber,

                  mixing the photoactivated material with  
leukocyte-reduced plasma within in the transfer  
container chamber, and

                  exposing the transfer container chamber  
15   to light that activates the photoactive material mixed  
within the chamber with the leukocyte-reduced plasma.

54. A kit according to claim 53

wherein the instructions include the step of  
storing the plasma in the transfer container chamber  
after the exposing step.

55. A kit comprising

tubing adapted to be coupled to a plasma  
source to convey plasma,

5                   a filter coupled to the tubing to separate  
cellular matter from plasma conveyed from the blood  
source,

                  a transfer container coupled to the tubing  
to receive cellular matter-reduced plasma from the  
filter,

10                  a source of liquid photoactive material to

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be mixed with the plasma, and

an overwrap enveloping at least a portion of the kit and including material that both absorbs light that activates the photoactive material and reduces liquid vapor loss from the kit.

56. A kit according to claim 55 wherein the material of the overwrap includes an oriented polymer.

57. A kit according to claim 56 wherein the oriented polymer includes polypropylene.

58. A kit according to claim 55 wherein the photoactive material includes methylene blue.

59. A kit according to claim 58 wherein the light filtering material includes a blue material.

60. A kit according to claim 59 wherein the blue material includes phtalocyanine pigments.

61. A kit according to claim 55 and further including instructions for using the kit following removal of the overwrap in accordance with a method comprising the steps of

conveying plasma through the tubing from the source through the filter to separate cellular matter including leukocytes from the plasma, conveying cellular matter-reduced plasma through the tubing from the filter to the transfer container,

mixing the photoactivated material with the plasma, and

exposing cellular matter-reduced plasma mixed with the photoactive material to light that activates the photoactive material.

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62. A kit according to claim 38 or 44 or 49  
or 55

wherein the overwrap envelops the entire  
kit.

5

63. A method for treating plasma carrying  
contaminants and at least two species of cellular  
matter capable of entraining contaminants, the method  
comprising the steps of

10 separating a first species of cellular  
matter by filtration through a first filter media,  
thereby removing contaminants entrained within the  
first species of cellular matter,

15 separating a second species of cellular  
matter by filtration through a second filter media,  
thereby removing contaminants entrained within the  
second species of cellular matter,

adding to the plasma a photoactive material,  
and

20 emitting radiation at a selected wavelength  
into the plasma to activate the photoactive material  
and thereby eradicate the contaminant that is free of  
entrainment by cellular matter.

25 64. A method for treating plasma comprising  
the steps of

separating from the plasma leukocytes by  
filtration through a first filter media,

separating from the plasma platelets by  
filtration through a second filter media,

30 adding to the plasma a photoactive material,  
and

emitting radiation at a selected wavelength  
into the plasma to activate the photoactive material.

65. A method for treating a plasma carrying  
contaminants and cellular matter capable of entraining

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contaminants, the method comprising the steps of  
conveying plasma through a first path  
5 through a filter that separates cellular matter from  
the plasma, thereby removing contaminants entrained  
within the cellular matter,  
conveying the plasma from the filter through  
a second path that includes an attached transfer  
10 container,  
mixing within the transfer container the  
plasma with a photoactive material to form a plasma  
mixture,  
conveying a portion of the plasma mixture  
15 from the transfer container through a flush path that  
includes the second path to thereby expose  
contaminants in the second path to the photoactive  
material,  
severing the second path to separate the  
20 transfer container from the filter, the transfer  
container, after severance from the filter, carrying  
a remnant of the second path, and  
emitting radiation into the transfer  
container at a selected wavelength to activate the  
25 photoactive material in the plasma mixture and thereby  
eradicate the contaminant that is free of entrainment  
by cellular matter.

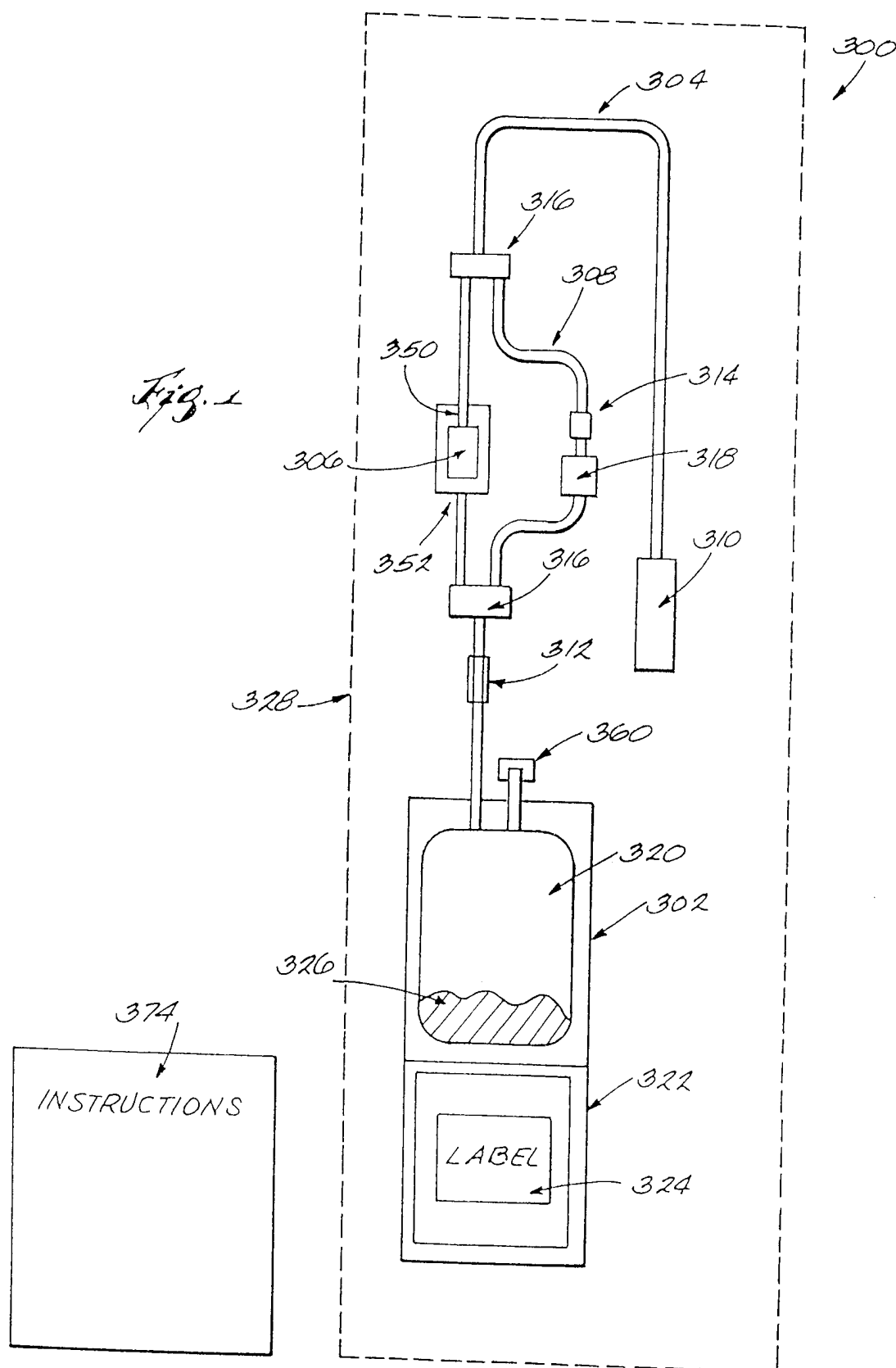
66. A method according to claim 66  
wherein the flush path by passes the filter.

67. A method according to claim 66  
and further including the step of venting  
air from the transfer container through the flush  
path.

68. A method according to claim 67  
wherein the flush path by passes the filter.

69. A method according to claim 66  
and further including the step of storing

the plasma mixture in the transfer container after the radiation emitting step.





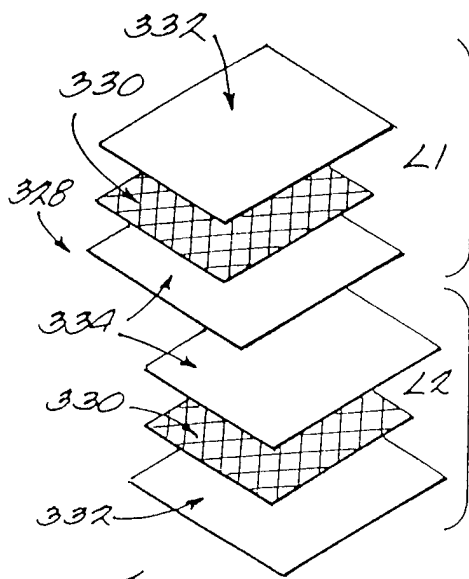


Fig. 2

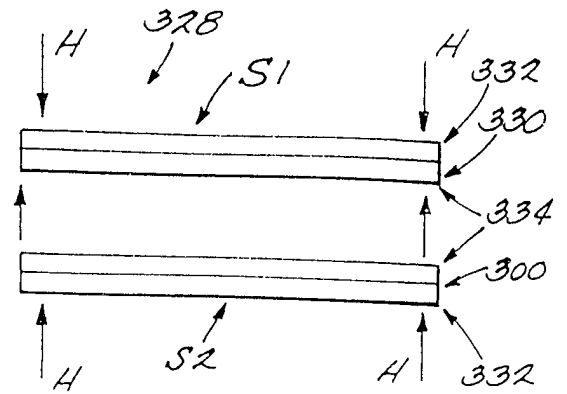


Fig. 3

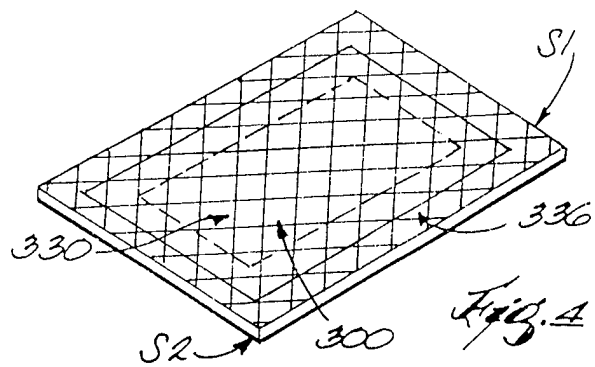


Fig. 4

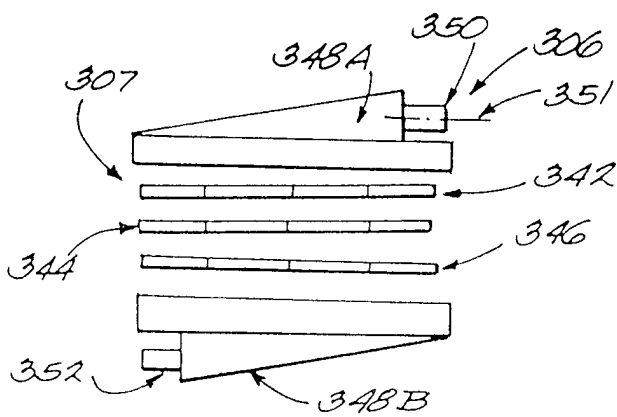


Fig. 5

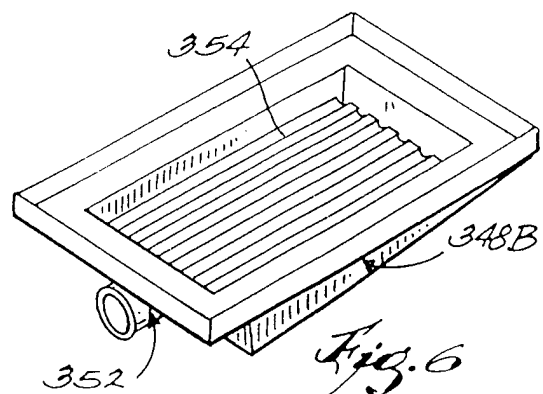
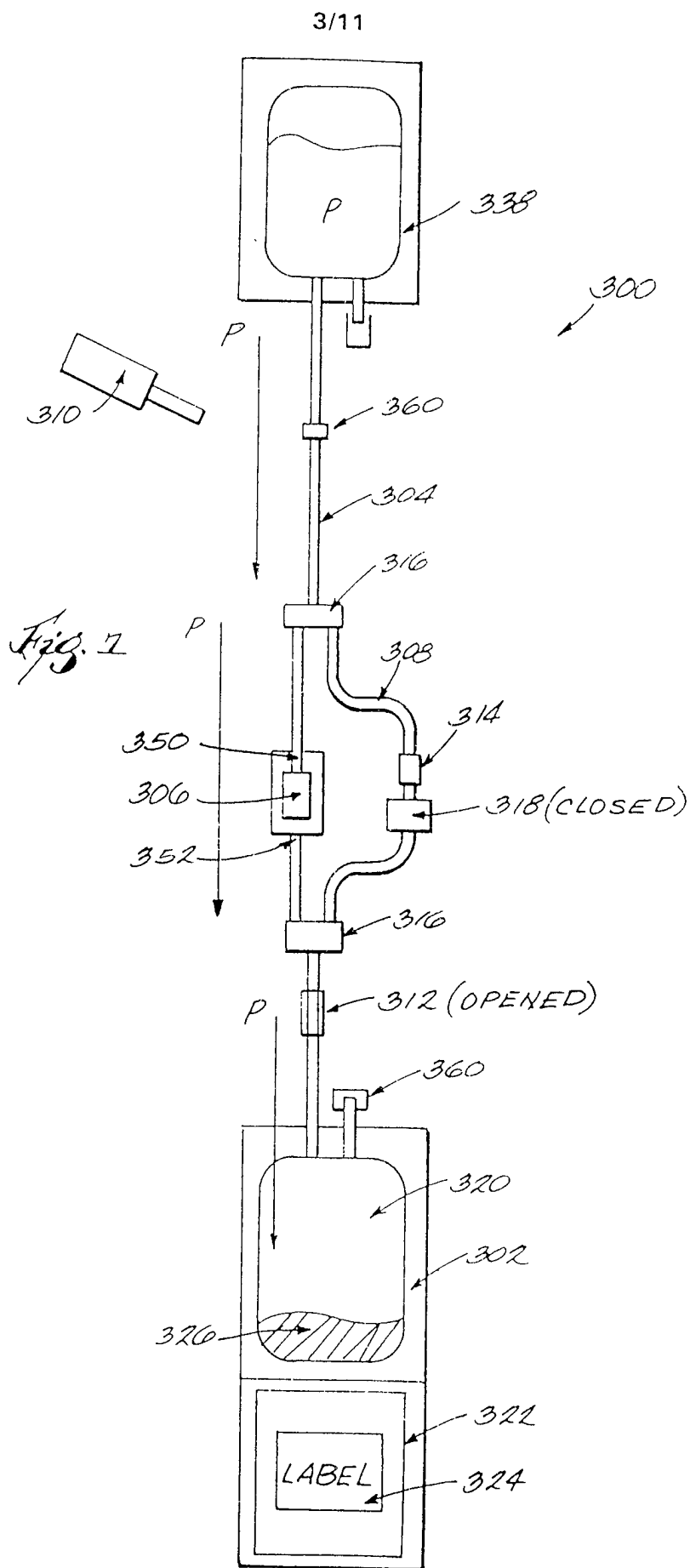
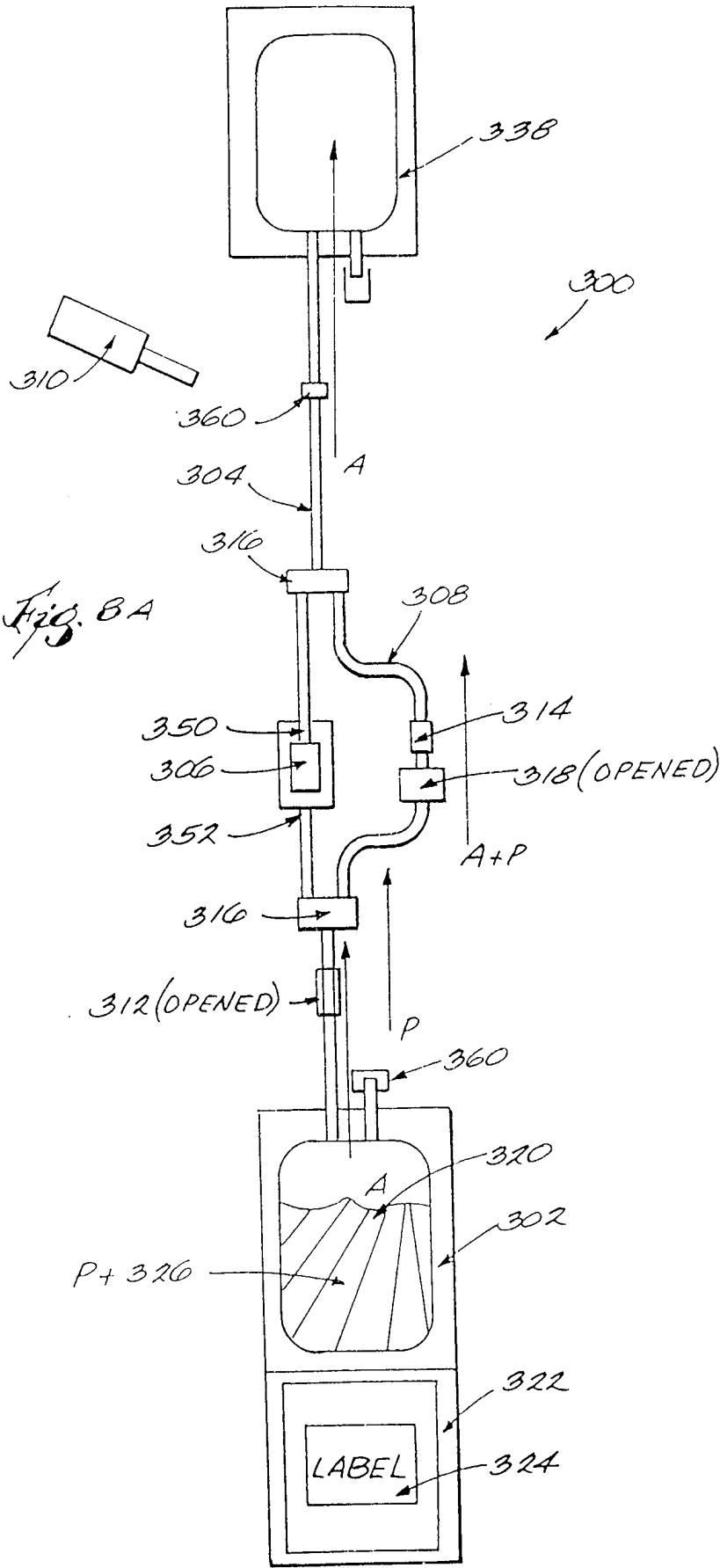
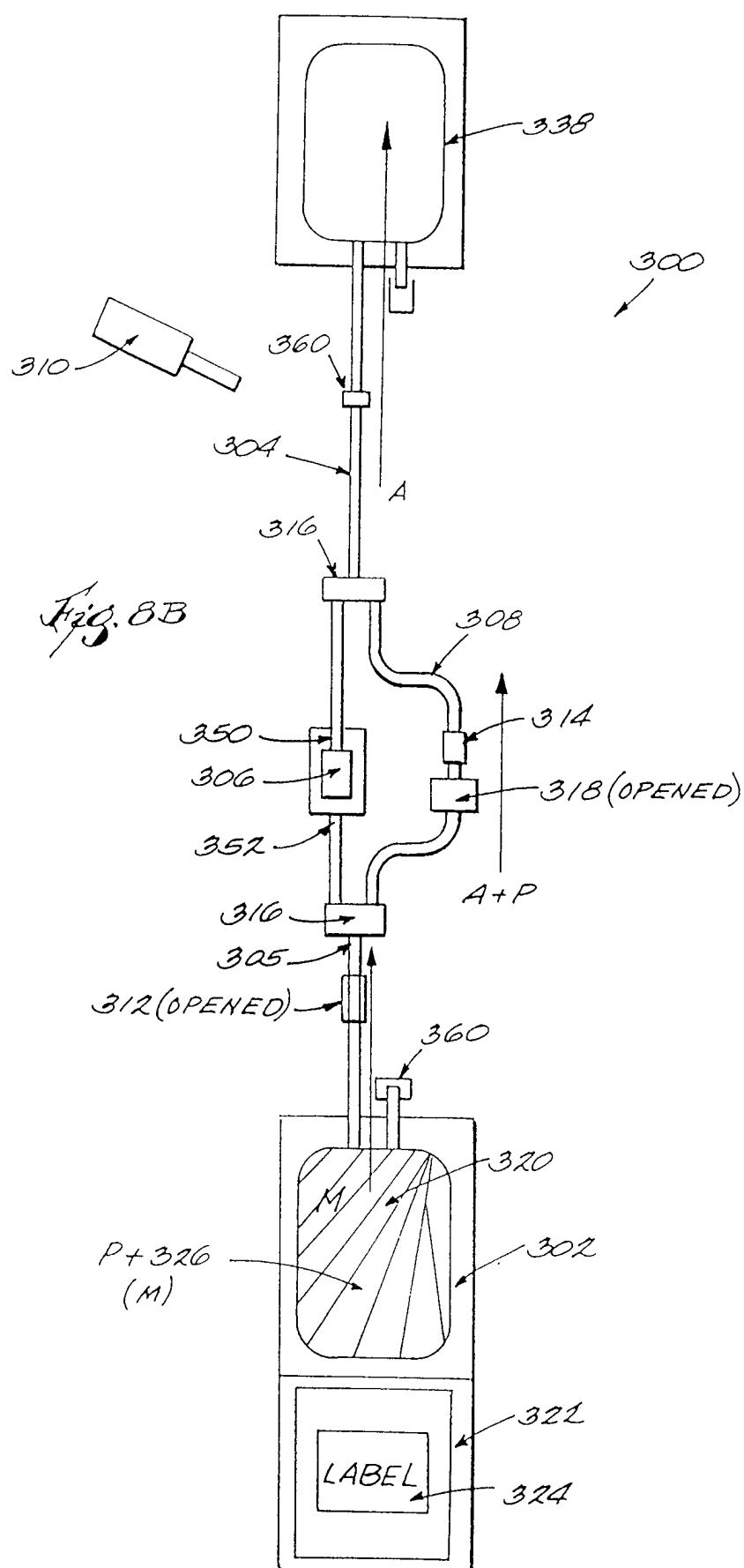


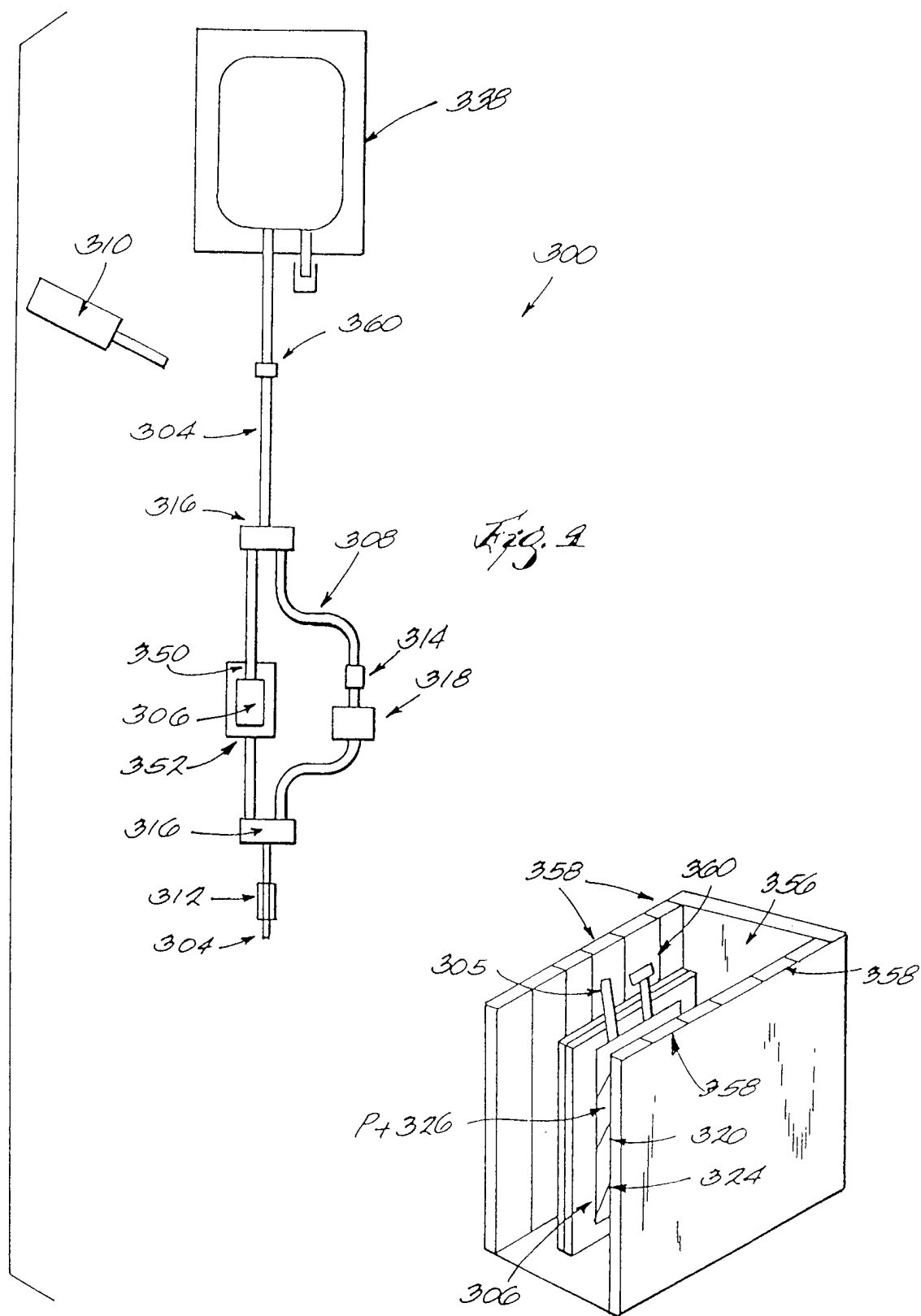
Fig. 6

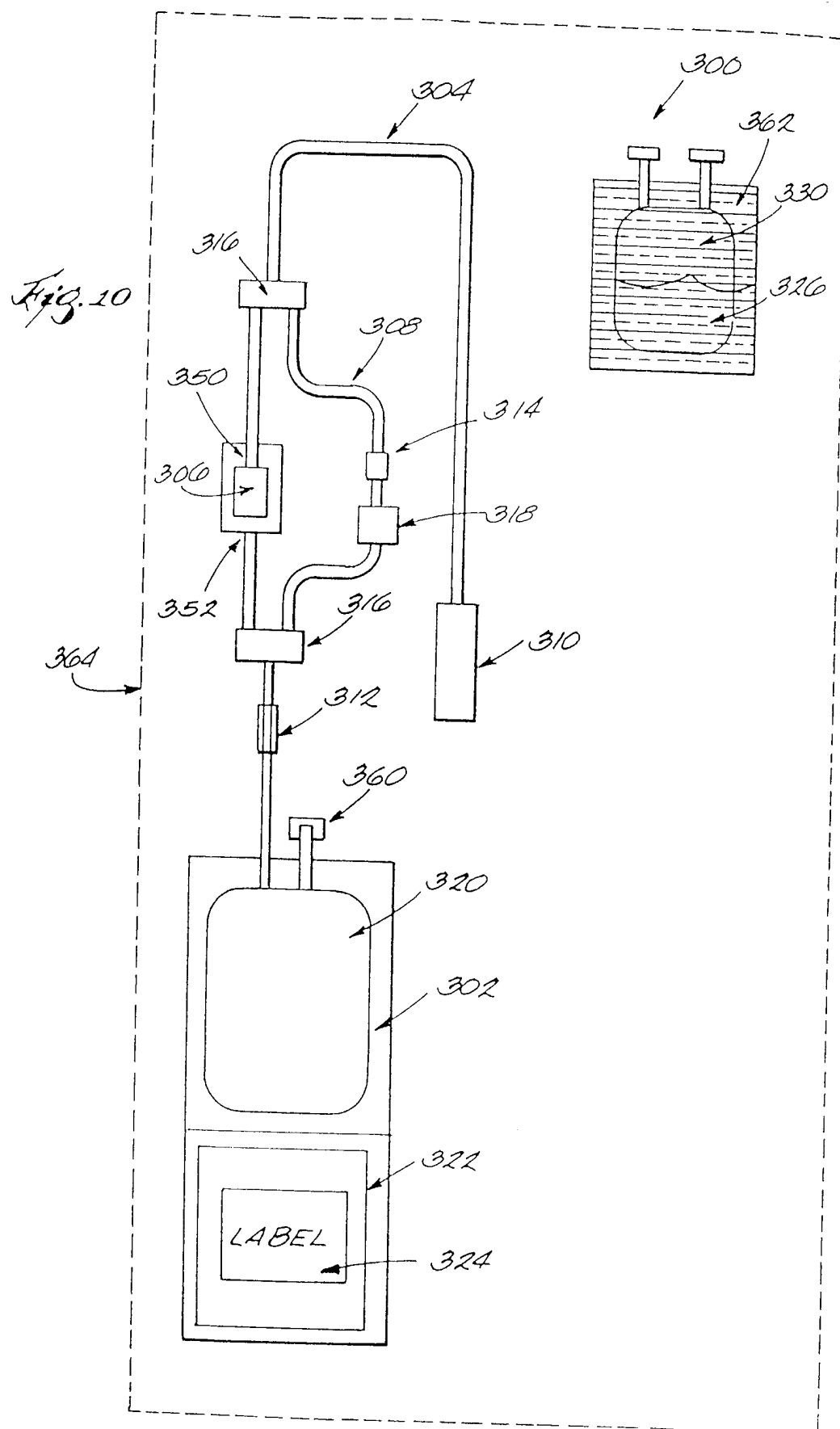


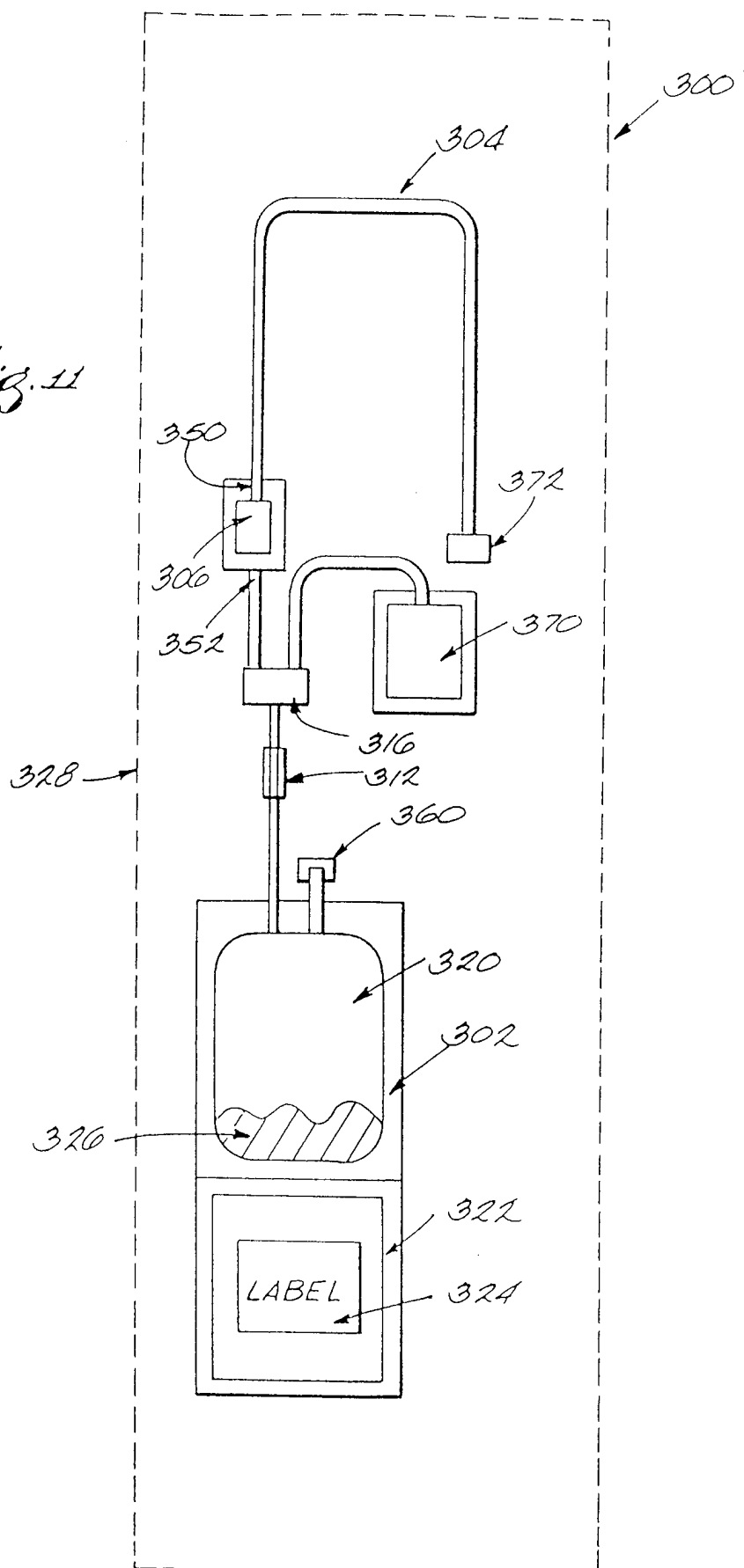


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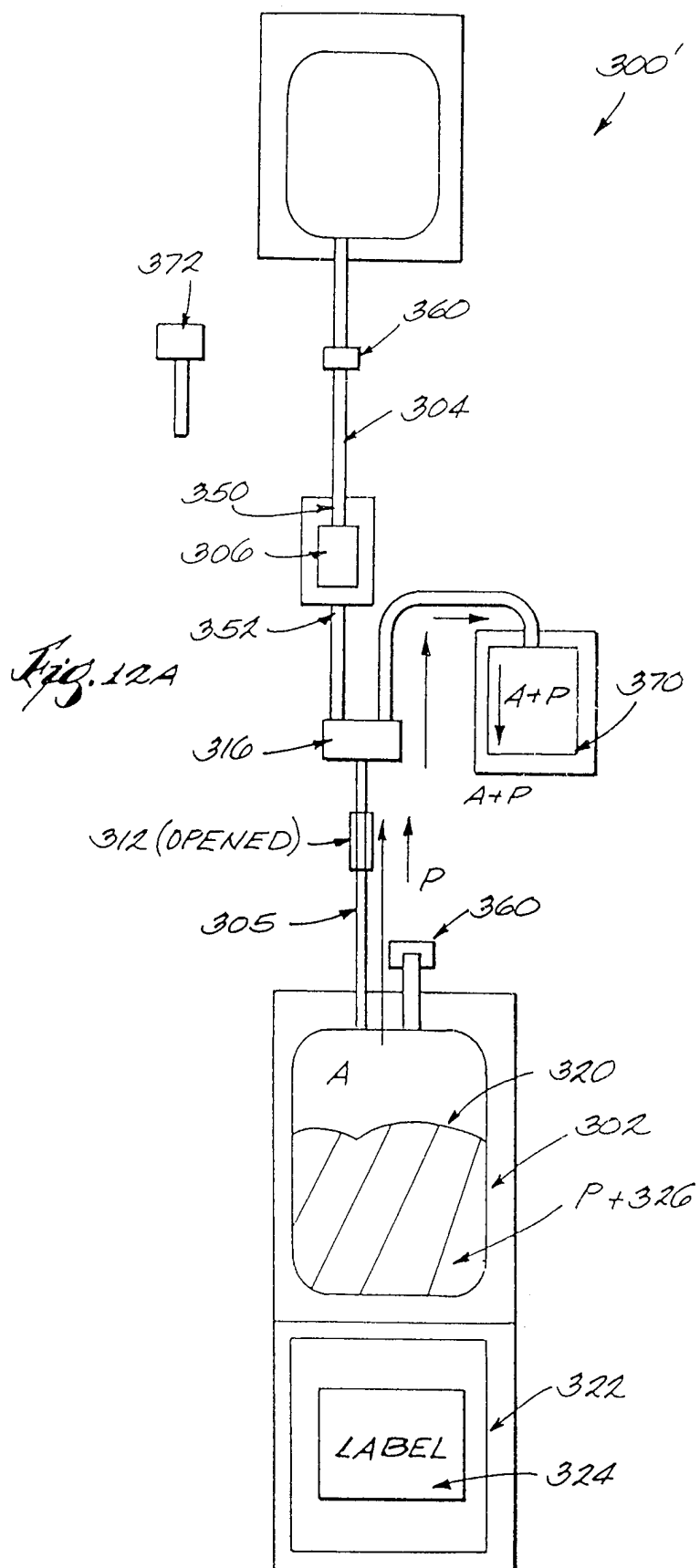






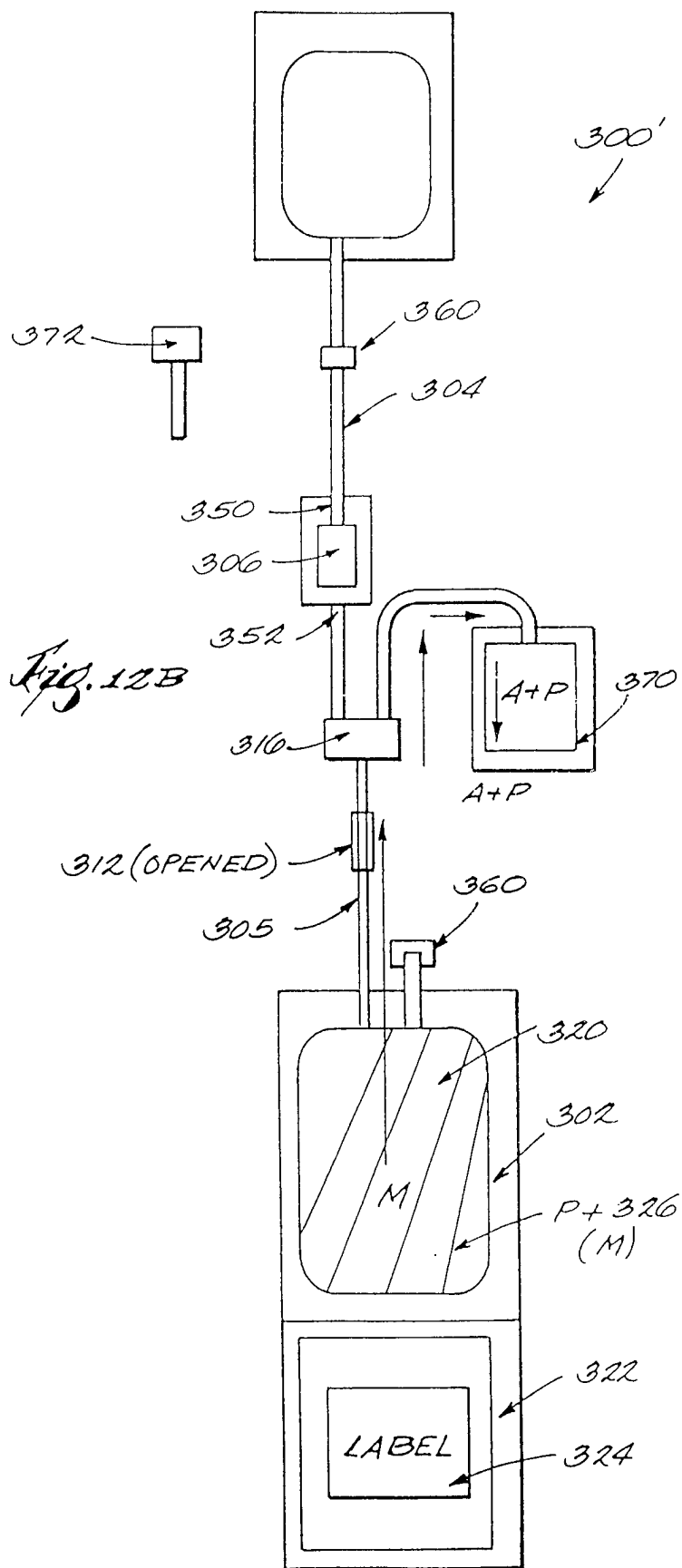
*Fig. 11*

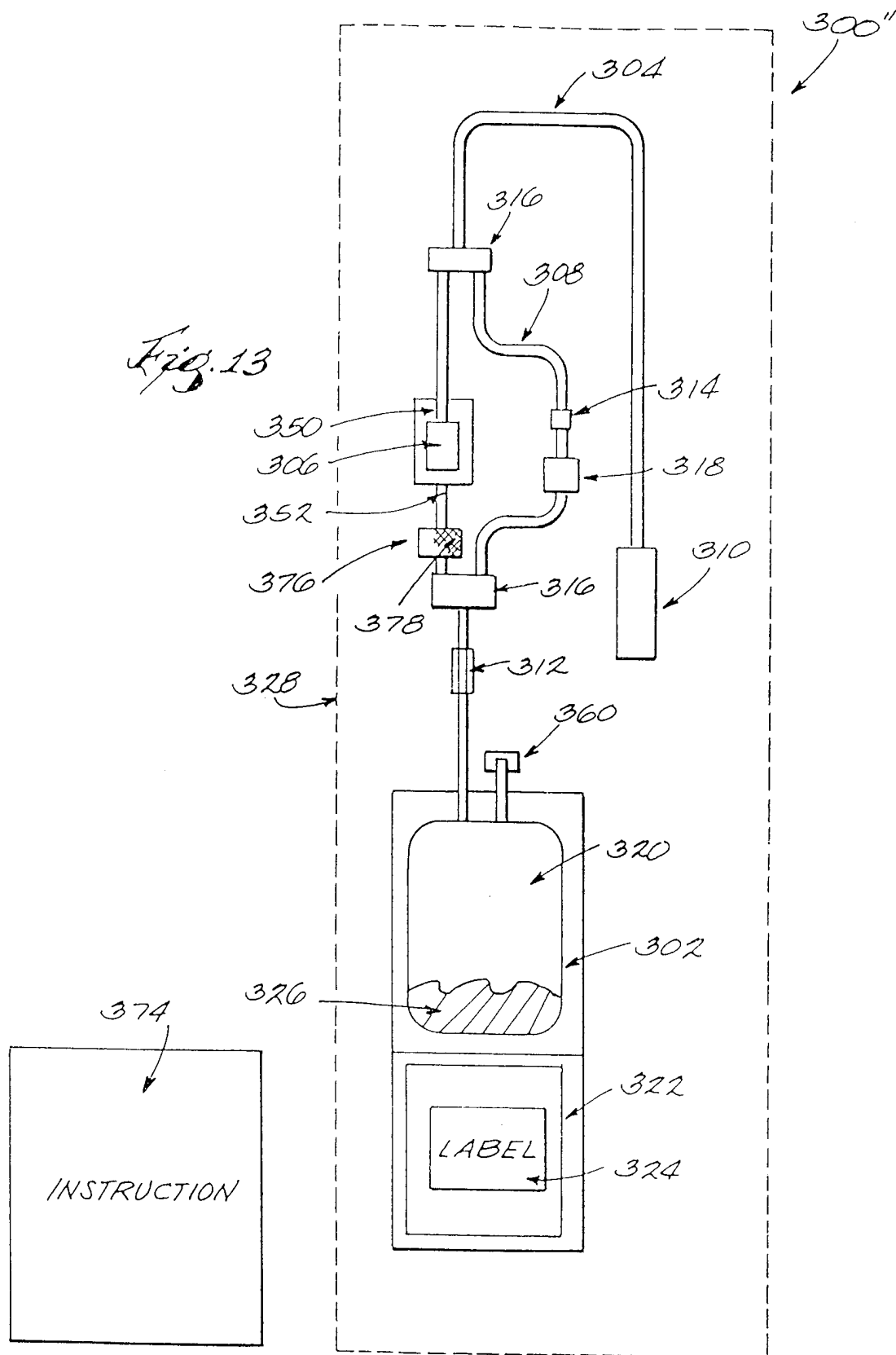
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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/17984

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : C12N 7/04, 7/06

US CL : 435/236, 238

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/236, 238

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

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

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,536,283 A (BISCHOF) 16 July 1996, entire document	1-69
Y	US 5,300,019 A (BISCHOF et al.) 05 April 1994, entire document	1-69
Y	US 5,269,946 A (GOLDHABER et al.) 14 December 1993, entire document	1-69

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

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

Date of the actual completion of the international search

02 DECEMBER 1997

Date of mailing of the international search report

03 FEB 1998

Name and mailing address of the ISA/US  
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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/17984

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, dialog, dialindex

search terms: PHOTODYNAMIC(W)THERAPY AND (VIRAL OR INFECTIOUS AGENT?)