Example 7 - Rubidium and Rubidium Chloride Target Solutions

The processing of either rubidium chloride or rubidium metal targets follows a similar procedure once the target has been successfully dissolved. In essence, 82Sr needs to be selectively extracted from a solution of RbCl in a 0.1 M NH_3 / 0.1M NH_4Cl buffer adjusted to a pH of between 9 and 10. Batch experiments were performed in simulated buffer solutions to determine the strontium selectivity in the presence of high concentrations of rubidium ions. Only the ion exchange materials that exhibited high strontium selectivities in the initial scoping studies with NaCl solutions were evaluated. K_d values were obtained as described previously. Two rubidium chloride solutions were selected which represent typical rubidium concentrations obtained during the processing of rubidium metal (1.95 M Rb+) and rubidium chloride targets (0.68 M Rb+). In both cases, Chelex 100 is used in the preliminary step to remove the 82Sr from the buffered rubidium solutions. The K_d values for the ion exchange materials are shown in Figure 1.

In the buffered rubidium solutions, there is little difference between the different nonatitanates evaluated. This is in stark contrast to the sodium molybdate solutions where a large variation in the performance of the titanates was observed. The nonatitanates were clearly the most effective materials at removing strontium from the buffered solutions with strontium K_d values of around 15,000 mL/g in 0.68 M Rb+ solutions and approximately 5,000 mL/g in 1.96 M Rb+ solutions. By contrast, Chelex 100 ion exchange resin gave K_d values of less than 1,000 mL/g in both solutions. Hydrous titanium oxide and hydrous tin oxide also exhibited appreciable K_d values, but they performed less efficiently than the nonatitanates in both solutions. Consequently, this data demonstrates that using sodium nonatitanate in place of Chelex 100 ion exchange resin will greatly increase the amount of strontium extracted from the target solutions.

The ion exchange materials were also evaluated for their rubidium selectivity from 0.1 M NH_3 / 0.1M NH_4Cl buffer solution. The buffer was prepared, spiked with 86Rb and the pH adjusted to approximately 9.25 with concentrated ammonia. 86Rb K_d values were then determined following the method described earlier. All of the sodium nonatitanates had a K_d < 20 mL/g. The very low rubidium selectivity in the pure buffer is almost certainly due to competition from NH_4+ ions for the available ion exchange sites. Consequently, absorption of rubidium during the processing of rubidium and rubidium chloride targets will be minimal, and any rubidium absorbed will be readily removed by washing with additional 0.1 M NH_3 / 0.1M NH_4Cl buffer solution. Thus, a clean separation of 82Sr from these targets can be obtained using sodium nonatitanate.

The performance could also be improved by removing the buffer and increasing the pH to improve the amounts of strontium absorbed. (Buffers were initially utilized to maximize the performance of the organic ion exchange resins currently used and are not essential to the 82Sr recovery process.)

Example 9 - Kinetic Experiments

In order for the sodium nonatitanate materials to find applications in the processing of irradiated target solutions, they must exhibit fast ion exchange kinetics allowing solutions to be passed through an ion exchange column at an acceptable rate. The kinetics of strontium absorption from alkaline molybdate target solutions was evaluated using a simple batch procedure. Ion exchange material, in the amount of 0.05 g, was shaken with 10 mL of molybdate solution spiked with 89Sr to give a total activity of approximately 155,000 cpm/mL. After an allotted time, the material was filtered through a 0.2 m syringe filter and the activity in the aqueous phase determined by LSC. The results are shown below in Figure 2.

From the data in Figure 2, it is clear that the reaction kinetics for the sodium nonatitanate powder is extremely rapid, with over 99 % of the 89Sr removed in only 1 minute. By contrast, the reaction kinetics of the organic ion exchanged resins was much slower and the total amount of 89Sr removed after 1 hour was much less.

The exceedingly rapid kinetics can partly be explained by the fact that the nonatitanate was in the form of a fine powder, whereas the two resins were in the form of beads (see Table 1). As a consequence, a relatively slow reaction rate would be expected for the beads because the uptake of 82Sr will be dependent upon the rate of diffusion of the 82Sr to the internal functional groups. The rate of uptake of a sample of sodium nonatitanate pellets (using hydrous titanium dioxide as a binder) was significantly slower than the powdered form, but the kinetics and amount of 82Sr absorbed was still significantly better than for either of the two organic resins. As the pelletization process is improved, it is expected that the kinetics and selectivity of the pelletized sodium nonatitanate will improve substantially. Other sodium nonatitanate powders of varying crystallinities also showed rapid kinetics. Other potentially suitable binders for forming suitable pellets include titanium isopropoxide or tetraethyl orthosilicate (TEOS) as a binder precursor.

Example 10 - 82Sr Removal from Irradiated Targets Using Pelletized Sodium Nonatitanate

A sample of sodium nonatitanate was mixed with titanium isopropoxide as a binder and the resulting paste dried at 105°C for 12 hours. The material was gently broken up using a mortar and pestle and then sieved to produce particles in the range 40 to 60 mesh. The binder content was approximately 20%. These particles were then used to assess the extraction of 89Sr from simulated target solutions.

1 mL of pelletized sodium nonatitanate was slurried into a column and the target simulant that had been spiked with 89Sr to give an activity of approximately 200,000 cpm/mL was passed through the column at a flow rate of 15 mL per hour. The amount of activity removed from solution was then determined. The results are given below in Table 1.

Table 1. Removal of 82Sr From Irradiated Target Solutions

Target (%)	Solution Composition	Volume (mL)	82Sr Removed
Rubidium Metal	1.95M RbCl in 0.1M NH_3/NH_4Cl Buffer, pH10	20	97.3
Rubidium Chloride	0.68M RbCl in 0.1M NH_3/NH_4Cl Buffer, pH 10	20	98.8
Molybdenum Metal	0.26M Na_2MoO_4, pH 12	20	99.9

This data clearly shows the effectiveness of sodium nonatitanate at removing strontium isotopes from 82Sr target materials. Rubidium absorption under these conditions is minimal.

Example 11 - Elution of Strontium

Strontium was quantitatively eluted from the sodium nonatitanate column of Example 10 using 6M nitric acid. Hydrochloric acid was found to be much less effective and also resulted in breakdown of the sodium nonatitanate particles and blocked the ion exchange column.

While the foregoing is directed to the preferred embodiment of the present invention, other and further embodiments of the invention may be devised without

departing from the basic scope thereof, and the scope thereof is determined by the claims that follow.

What is claimed is:

1. A rubidium-82 generator, comprising:

(a) a strontium-82 support medium comprising sodium nonatitanate.

2. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium selectivity greater than 250,000 mL/g at an alkaline pH.

3. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium selectivity less than 100 mL/g at an alkaline pH.

4. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 1,000.

5. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 100,000.

6. A process for preparing a rubidium-82 generator, comprising:

(a) preparing sodium nonatitanate from titanium isopropoxide and aqueous sodium hydroxide;

(b) heating the sodium nonatitanate at a temperature between 100°C and 250°C for a period between 12 hours and 2 weeks; and

(c) absorbing strontium-82 on the sodium nonatitanate from an aqueous solution comprising strontium-82 and sodium chloride, wherein the sodium chloride concentration is between 0.1 and 1 molar.

7. The process of claim 6, wherein the molar ratio of aqueous sodium hydroxide to titanium isopropoxide is in excess of 0.44.

8. The process of claim 6, wherein the molar ratio of aqueous sodium hydroxide to titanium isopropoxide is between 2 and 6.

9. A method of chemically isolating strontium-82 from a proton-irradiated molybdenum target, comprising:

(a) dissolving the molybdenum metal target containing the strontium-82;

(b) adjusting the pH of the dissolved molybdenum target solution to an alkaline pH;

(c) removing precipitates from the solution; and then

(d) absorbing the strontium-82 from the solution onto a support comprising sodium nonatitanate.

10. A process for preparing a solution containing rubidium-82, comprising:

(a) providing a solution containing strontium-82 at a pH between 10 and 14;

(b) absorbing strontium-82 onto a sodium nonatitanate support medium; and

(c) eluting rubidium-82 from the sodium nonatitanate support medium with a solvent.

11. The process of claim 10, wherein the solvent is selected from the group consisting of water and saline solutions.

12. The process of claim 10, wherein the solvent is an aqueous solution having a sodium chloride concentration between 0.001 molar and 1 molar.

13. The process of claim 10, wherein the solvent is an aqueous solution having a sodium chloride concentration between 0.2 molar and 1 molar.

14. The process of claim 10, wherein the solvent is a pharmaceutical-grade saline and buffer solution.

15. A method of chemically isolating strontium-82 from a proton-irradiated rubidium or rubidium chloride target, comprising:

(a) dissolving the target containing the strontium-82;

(b) adjusting the pH of the dissolved target solution to an alkaline pH;

(c) removing precipitates from the solution; and then

(d) absorbing the strontium-82 from the solution onto a support comprising sodium nonatitanate without absorbing rubidium.

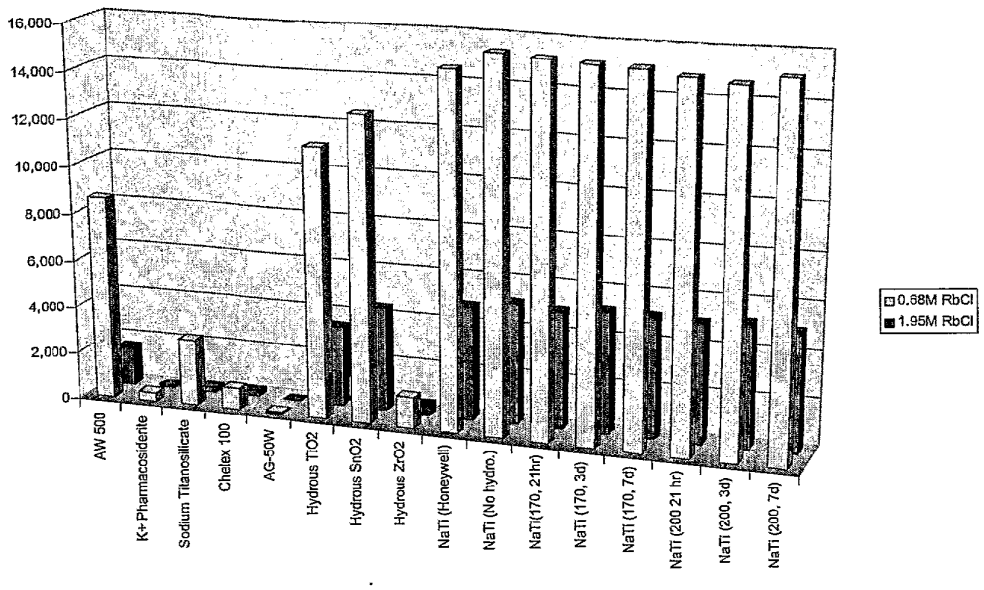

Figure 1. 82Sr K_d Values for the ion exchange materials from simulated rubidium and rubidium chloride target solutions

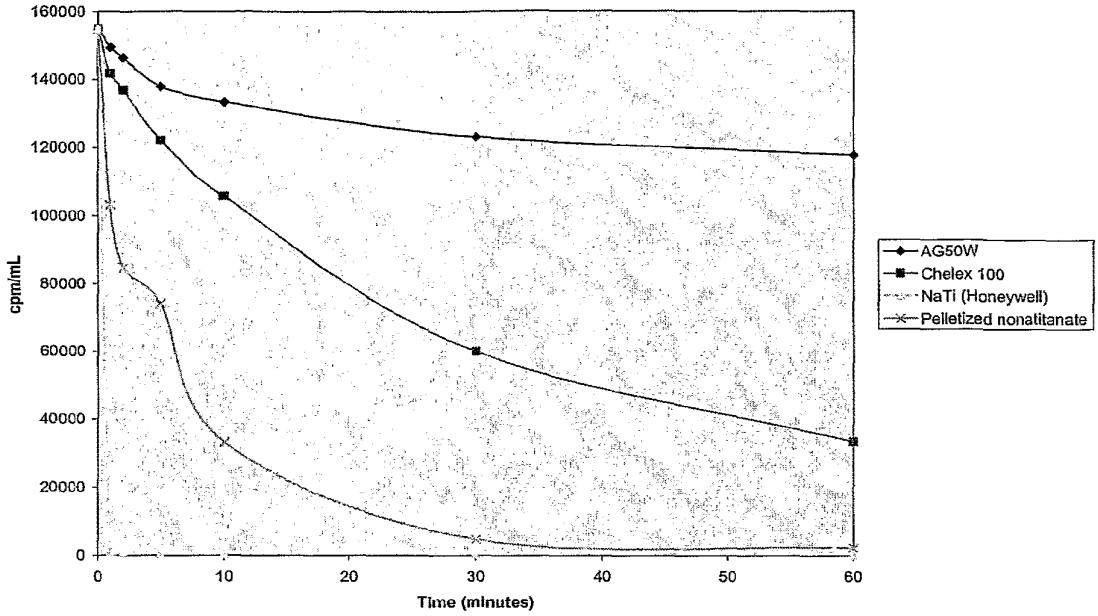

Figure 2. The reduction of 82Sr activity with increasing time.

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G21G4/08

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 7 G21G

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 406 877 A (NEIRINCKX RUDI D ET AL) 27 September 1983 (1983-09-27) the whole document	1-15
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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International Application No
PCT/US 02/41676

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(74) Agents: **SUTTON, Paul, J.** et al.; Greenberg Traurig, LLP, Met Life Building, 200 Park Avenue, New York, NY 10166 (US).

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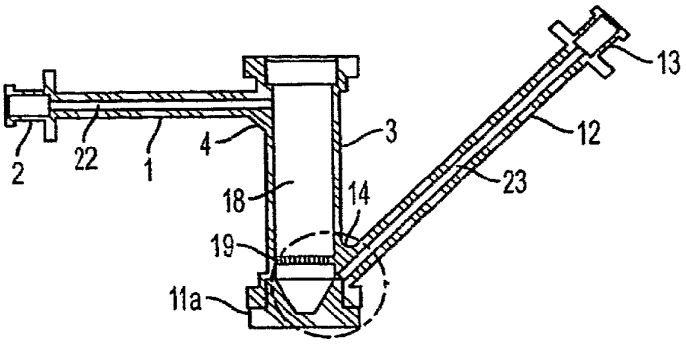
(54) Title: IMPROVED CONTAINERS FOR PHARMACEUTICALS, PARTICULARLY FOR USE IN RADIOISOTOPE GENERATORS



(57) Abstract: The invention is directed to improved containers for pharmaceuticals and any tubing and tubing connectors associated therewith, particularly containers for pharmaceuticals which are irradiated, heated or otherwise subjected to increased pressure. In a preferred embodiment, the invention is directed to an improved container for use in a radioisotope generator, such as a rubidium-82 generator.

WO 2006/026603 A2

IMPROVED CONTAINERS FOR PHARMACEUTICALS, PARTICULARLY FOR USE IN RADIOISOTOPE GENERATORS

TECHNICAL FIELD OF THE INVENTION

The invention is directed to improved containers for pharmaceuticals and the tubing and tubing connectors associated therewith, particularly containers for pharmaceuticals which are heated, irradiated or otherwise subjected to increased pressure. In a preferred embodiment, the invention is directed to an improved container for use in a radioisotope generator. Specifically, the designs and materials of the column container and its closure and associated tubing and tubing connectors have been improved.

SUMMARY OF THE INVENTION

The invention includes improved pharmaceutical containers, particularly improved containers for pharmaceuticals that are subjected to increased pressure (such as by heating or other means) and/or are subjected to radioactivity. In a preferred embodiment, the invention is directed to an improved container, also called a column, for use in a radioisotope generator. In an especially preferred embodiment, the improved column is for use with rubidium-82 generator such as those disclosed in U.S. Patent Nos. 3,953,567; 4,400,358; 4,406,877; 4,562,829; 4,585,009; 4,585,941; and 5,497,951, incorporated herein by reference in their entirety. In a particularly preferred embodiment, the improved column is used in a rubidium-82 generator such as that sold under the trade name CardioGen®.

The improved pharmaceutical container of the invention includes an improved seal and crimping process, as well as changes to the design of the stopper and the container to prevent blockages and improve consistency in packing and closing the container, which improves flow rate and elution from the column.

Further improvements include constructing the container and stopper out of radiation resistant or tolerant materials. In addition, flexible tubing used with the container is made of a radiation resistant or tolerant material, and the Luer locks used to fasten the flexible tubing to the container is made of a radiation resistant or tolerant material and is further improved to insure a tight, secure lock which will not inadvertently loosen or disconnect.

Specifically, the improved container has a new, stronger seal which is used to crimp the stopper in a pharmaceutical container and particularly, which is used to seal a radioisotope generator column/stopper assembly system, such as the CardioGen® system. This improved seal prevents leakage, even at increased pressure, and reduces ballooning of the rubber stopper material. The seal has a configuration similar to one of those shown in Fig. **5**B through Fig. **5**F and Fig. **6** and is made of any suitably strong material including

metal or plastic. A pneumatically operated automatic or semi-automatic crimper, set at optimized pressure, is preferably used to crimp the seal during assembly of a pharmaceutical container such as a radioisotope generator column/stopper assembly system. The invention includes identification of optimized crimping pressure(s) for crimping the seal (regardless of material) to a pharmaceutical container such as a glass or plastic vial or column and thus securing in place a rubber closure(s) when using an automatic crimping system and/or manual crimping.

The stopper which is crimped into place is also improved. Specifically, it is made of a material which is radiation resistant or tolerant, is resistant to ballooning and can withstand at least the pressures at which the container operates. Additionally, the configuration and placement of the stopper are improved. For example, the improved stoppers form tight seals with the column and reduce the "dead volume" at the bottom of the column– space where non-radioactive, decayed eluate could mix with (and dilute) fresh, radioactive eluate, reducing the efficacy of the eluent.

The improved pharmaceutical container also includes improvements to the design which improve its packing/assembly and thus ensure specified flow of eluent through the container.

These improvements are illustrated in the context of a radioisotope generator column container. Flow rate of the eluent through the column could be partially or completely blocked if the stopper blocks the outlet arm of the column. As shown in Figure **1**, the outlet arm of the container of the invention has been repositioned slightly and a small piece of plastic removed from the inside edge of the column to create a recess or notch where the outlet arm enters the column lumen to prevent a stopper from blocking flow. See Figure **4.** A small reinforcement piece of resin is added to the outside of the column between the outlet arm and column body to provide additional strength.

Another improvement in the containers of the invention addresses consistency of assembly and packing of the containers. In prior columns for a radioisotope generator, a plastic basket or spacer was supplied separately and was placed on the top of the column packing before the seal was inserted and the seal crimped into place. In these prior columns, placement of the baskets or spacers, which hold the column packing in place, could vary significantly, potentially creating some problems with consistency in packing. In the improved columns, two small orientation knobs have been added to the outside of the top basket/spacer and the orientation knobs are positioned 180° apart. These knobs fit into two small slots cut into the wall of the column. This combination eliminates the potential variability of manual alignment and depth placement of the basket/spacer into the column and ensures a consistent fit every time. Critical to the function of the column is the alignment of the basket/spacer openings with the column inlet in the top arm. This prevents potential misalignment and consequent restricted flow and possible back pressure and also ensures consistent and timely output of eluent to the patient.

Another improvement is to make the column assembly out of a radiation resistant or tolerant material, such as radiation resistant polypropylene. Likewise, the flexible tubing and Luer connector are made of radiation resistant or tolerant materials, such as radiation resistant polyvinylchloride. Furthermore, the Luer connector on the flexible tube and its counterpart Luer connector on the column assembly are configured to provide for a tight lock which will not leak and which will not loosen or inadvertently disconnect during use.

THE TECHNICAL PROBLEM AND ITS SOLUTION

The invention was designed to solve a number of technical problems experienced with prior art pharmaceutical containers.

1. Leakage From the Stopper/Column Interface

Leakage from the flange (or other area) of the seal of prior pharmaceutical containers such as column/stopper assembly systems was found to occur when the system was exposed to increasing pressure.

The new seal, consisting of a stronger material crimped at optimized crimping pressure, prevents leakage at the flange seal area even at increasing pressure.

2. Ballooning

Ballooning and/or burst of rubber materials (both before and after irradiation) through the center hole of current aluminum seals has been observed when they are subject to repeated pulsations of pressure cycling. The seals of the invention, which are stronger and are crimped at optimized pressure, reduce the likelihood of this problem. However, in a preferred embodiment the seal used in the improved container of the invention has a center hole of reduced size. For example, a seal with the configuration of those in Fig. **5**B, Fig. **5**C, Fig. **5**E or Fig. **6** may preferably be used. Due to the small center hole and strength of these seals, and crimping at optimized pressure, ballooning and/or burst of rubber materials is prevented. Consequently, pharmaceutical containers of the invention, and particularly column/stopper systems of the invention, can be exposed to much higher pressures during use of the system in the field.

In addition, the larger surface area of the crimp resulting from the reduction of the diameter of the center hole serves as additional support for the rubber closure and inhibits possible rupture as it is weakened over time due to the cumulative effect of exposure to radiation from the column or container content.

Also, the stopper is made of a radiation resistant or tolerant material. This also helps prevent ballooning and bursting.

3. Leakage Through Puncture Points

Leakage through puncture points has been observed in prior art pharmaceutical containers. Such leakage may be eliminated in containers of the invention through a combination of the stronger seal material, preferably a smaller center hole, and crimping at optimized pressure.

4. Splitting of the Seal

Splitting or tearing of current aluminum seals has been observed at pressures intended for use with a pharmaceutical container system (or pressures to which the system can potentially be exposed during intended usage in the field).

Due to the strength of the new seal material, no splitting or rupture of seal material is observed at pressures intended for use. For example, the seals on the columns of the invention do not split or rupture when used in, for example, a rubidium generator at intended pressures.

5. Inconsistent Manual Crimping Procedure

The manual crimping procedure commonly used with many prior container systems, including radioisotope column systems, is not always consistent and thus may not result in reproducible crimping pressures. Over-pressuring can result in buckling and collapse of the skirt of the seal material, the closure and/or the container. Under-pressuring can result in a loose overseal. Use of the automatic or semi-automatic crimping procedure of the invention with compressed or pressurized air results in consistent/reproducible crimping pressures, and enables selection of optimized crimping pressures when crimping various seal materials.

6. Maintenance of Consistent Flow/Reduction of Back Pressure

In some prior pharmaceutical columns, flow rate of the eluent through the column could be partially or completely blocked because the stopper blocked the outlet arm of the column. The outlet arm of the container of the invention has been repositioned slightly and a small piece of plastic removed from the inside edge of the column to create a recess or notch where the outlet arm enters the column lumen to prevent a stopper from blocking flow. A small reinforcement piece of resin is added to the outside of the column between the outlet arm and column body to provide additional strength. The recessed outlet arm and notch near the bottom of the column body greatly reduces the chance of back pressure due to a stopper blocking the outlet arm.

7. Inconsistent Positioning Within Column

In a column for a radioisotope generator, a plastic basket or spacer is supplied separately and is placed on the top of the packed column before the seal or closure is inserted and the seal crimped into place. In prior columns, the baskets/spacers, which hold the column packing in place, were not easily positioned consistently both in terms of depth and orientation. In the improved columns of the invention, two small orientation knobs have been added to the outside of the top basket/spacer and these orientation knobs are positioned 180° apart. These knobs fit into two small slots cut into the wall of the column. This combination eliminates the potential variability of manual placement of the basket into the column, ensuring a consistent fit from generator to generator and reducing the variability in packing density associated with this manual process.

8. Degradation Due To Radiation

Many materials degrade when exposed to radiation. Degradation includes possible changes in color, loss of flexibility, increased brittleness and the leaching out of various substances from the materials. To avoid these potential problems, the column assembly,

stopper, flexible tubing and Luer connectors are made out of radiation resistant or tolerant materials.

Frequently, when a material is said to be radiation resistant or tolerant, that means the material can withstand the amount of radiation used for sterilization, which is typically about 25 kGy. For the purposes of the present invention, however, a material is radiation resistant or tolerant when it can be exposed to about 145 kGy radiation and not degrade to the point where the functioning of the column assembly will be adversely affected.

9. Properly Closed Luer Locks

Luer locks are known in the art. However, it can be difficult to determine when a Luer lock has been sufficiently tightened to form a tight, non-leaking lock. Thus, one improvement is to provide for one or more tabs on each Luer connector. When the tabs achieve a certain orientation with respect to each other, for example when the tabs line up, such orientation means that the Luer lock has been sufficiently tightened.

Another potential difficulty with Luer locks is that they can come loose, i.e. disconnect, during use, which has the potential of causing a leak. To overcome this potential difficulty, the Luer connectors screw together and are each provided with one or more tabs. As the Luer connectors approach their fully tightened position, the tabs overlap. Further tightening causes the overlapping tabs to pass by each other, which can cause a clicking sound or sensation. When this occurs, the Luer lock is sufficiently tightened. Also, the Luer locks cannot become loose, e.g. unscrew, because the overlapping tabs will inhibit this action.

BRIEF DESCRIPTION OF THE FIGURES

Figs. **1A** through **1G** illustrate the inventive column assembly from different angles and cross sections.

Figs. **2A** through **2D** illustrate an alternative embodiment of the inventive assembly from different angles and cross sections.

Figs. **3A** throu gh **3D** illustrate a spacer or basket used in the inventive column assembly.

Fig. **4** illustrates a detailed view of the bottom of the inventive column assembly.

Fig. **5A** is a prior art crimp seal.

Figs. **5B** through **5F** illustrate various crimp seals that may be used with the inventive column assembly.

Figs. **6A** and **6B** illustrate a preferred crimp seal.

Figs. **7A** through **7D** illustrate a stopper for use with the inventive column assembly.

Figs. **8A** through **8D** illustrate an improved Luer lock.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to Fig. **1**, Fig. **1A** shows a side view and Fig. **1B** shows a bottom view of the inventive container (e.g., column assembly) of one embodiment of the invention. Fig. **1C** is another side view of the inventive column assembly, cut along line A-A of Fig. **1B**. Fig. **1D** is detail B from Fig. **1C**, at a scale of 3:1 compared to Fig. **1C**. Fig. **1E** is a top view of the inventive column assembly, cut along line E-E of Fig. **1A**. Fig. **1F** is another side view of the inventive column assembly, cut along line C-C of Fig. **1B**. Fig. **1G** is detail D of Fig. **1F**, at a scale of 2:1 compared to Fig. **1F**.

Fig. **1**A has an inlet arm **1** which has an inlet arm female Luer cap **2** at its distal end. The proximal end of the inlet arm **1** attaches to the upper portion of a column **3**. There is also an inlet arm support means **4** to support the inlet arm **1**. The support means is preferably material which is added to support the inlet arm **1**. Preferably, this material is the same material used to construct the column assembly. As shown, the inlet arm support means **4** is a triangular shaped member attached to the inlet arm **1** and the column **3**, although the shape of the support is not limited to a triangle. It can be square, a bar passing from the inlet arm **1** to the column **3**, or any other suitable shape.

The column **3** has a top portion **5** and a bottom portion **6**. The top portion **5** comprises a first top portion **7** and a second top portion **8**. The first top portion **7** is on top of and has a diameter greater then the second top portion **8**, which is on top of and has a greater diameter than the column **3**.

The bottom portion **6** of the column **3** has a similar configuration. It has a first bottom portion **9** and a second bottom portion **10**. The first bottom portion **9** sits below and has a greater diameter than the second bottom portion **10**, which sits below and has a greater diameter than the column **3**. Also shown is a bottom stopper **11**.

An outlet arm **12** is attached to the bottom portion of the column **3**. The distal end of the outlet arm **12** terminates in an outlet arm female Luer cap **13**. There is also an outlet arm support means **14** to support the outlet arm **12**. The support means is preferably material which is added to support the outlet arm **12**. Preferably, this material is the same material used to construct the column assembly. As shown, the outlet arm support means **14** is a triangular shaped member which attaches to the column and the outlet arm **12**, although the shape of the support is not limited to a triangle. It can be a square, a bar passing from the outlet arm **12** to the column **3**, or any other suitable shape.

Fig. **1**C shows a cross section of the inventive column assembly, cut through line A-A of Fig. **1**B. As shown, the inlet arm **1**, column **3** and outlet arm **12** are hollow.

Turning to the hollow interior or lumen of the column **3**, it first defines a top stopper receptacle area **15**. Below that and in communication with it is a top basket receptacle area **16**. As shown in Fig. **1C**, the top basket receptacle area **16** contains a top basket or spacer **17**. Following that is a packing material containing area **18**. Underneath the packing material containing area **18** is a bottom screen **19**, followed by a bottom open area **20**. Underneath the bottom open area **20** is a bottom stopper receptacle area **21**.

Fig. **1**C shows the bottom stopper **11** inserted into the bottom stopper receptacle area **21** of the column **3**. Note that the bottom stopper **11** consumes most of the bottom stopper receptacle area **21**. This minimizes the dead volume in the bottom stopper receptacle area **21**. Minimization of the dead volume minimizes mixing of fresh, radioactive eluent with non-radioactive or decayed eluent, which could dilute the fresh eluent, thereby maintaining a narrow rubidium-82 bolus profile.

The inlet arm **1** and outlet arm **12** are each hollow, the hollow portions being **22** and **23** respectively, and are in communication with the hollow portion of the column **3**. As

shown in Fig. **1C**, the hollow portion **22** of the inlet arm **1** is in communication with the top basket receptacle area **16**.

The intersection of the column **3** and the outflow arm **12** is shown in more detail in Fig. **1D**. As shown therein, no portion of the outflow arm **12** extends into the hollow portion of the column **3**, as was the case with certain prior art column assemblies. Also, the hollow portion **23** of the outflow arm **12** intersects the hollow portion of column **3** at the top of the bottom stopper receptacle area **21** or at about the place the bottom stopper receptacle area **21** and the bottom open area **20** intersect. This configuration, not found in prior art column assemblies, prevents the bottom stopper **11** from blocking the outflow arm **12**.

In a preferred embodiment, an outflow notch **25** is formed where the hollow portion **23** of the outflow arm **12** intersects the hollow interior of the column **3**, thus further preventing any blockage of the outflow arm **12** by the bottom stopper **11**. This embodiment is shown in more detail in Fig. **4**.

Fig. **1E** is a top view of the inventive column assembly. Visible from this perspective are, for example, the top basket or spacer **17** and the top basket receptacle area **16**. Also shown are notches **24a** and **24b**.

The notches **24a** and **24b** are made in the wall of the top basket receptacle area **16**. As shown in Fig. **1E**, they are 180 degrees opposed to each other. They are configured to cooperate with a pair of protrusions which appear on a top basket (discussed below with respect to Fig. **3**) such that the protrusions fit into notches **24a** and **24b**. This configuration insures proper placement of the top basket into the top basket receptacle area **16** so that the top basket is straight and at the correct depth. In prior art column assemblies, which lacked these notches and protrusions, it was possible to insert the top basket in such a manner that it was not straight and/or at the wrong depth, which adversely affected the function of the column assembly.

Fig. **1E** shows two notches **24a** and **24b** 180° opposed to each other. It is understood that the present invention is not limited to this configuration. Rather, there can be 1, 3, 4, 5, 6 or more notches or even a ledge present in the wall of the top basket receptacle area **16** in any configuration, so long as these notches (or ledge) cooperate with protrusions on the top basket to insure its proper fit.

Fig. **1F** shows a side view of the inventive column assembly, cut along line C-C of Fig. **1B**. Fig. **1G** is detail D of Fig. **1E**, showing an alternative embodiment for the first top portion **7a**. As shown in Fig. **1G**, this first top portion **7a** slopes downwardly from its top, whereas the first top portion **7** of Fig. **1F** is squared off, i.e., non-sloping.

Fig. **2** shows an alternative embodiment of the inventive column assembly. As shown in Fig. **2D**, which is detail B from Fig. **2C** at a scale of 3:1, the bottom stopper **11a** is configured to fit into substantially all of the space of the bottom stopper receptacle area **21**. This insures a better fit between the outer wall of the bottom stopper **11a** and the inner wall of the bottom stopper receptacle area **21**, thus further insuring against any leaks. In addition, the stopper **11a** reduces the dead volume in the bottom stopper receptacle area **21**. Minimization of the dead volume minimizes mixing with non-radioactive or decayed eluent, which could dilute the fresh eluent, thereby maintaining a narrow rubidium-82 bolus profile. The bottom stopper **11a** further comprises a bottom stopper hollow space **11b**. This bottom stopper hollow space **11b** helps prevent the bottom stopper **11a** from blocking the outflow arm **12**.

The column assembly is preferably made of polypropylene. Prior art column assemblies were made with H5820 polypropylene. While that product can still be used, in a preferred embodiment the polyproplylene random copolymers PP P5M4R-034 or PP 13R9A (Huntsman Polymers (The Woodlands, TX)) can be used because they are more resistant to radiation than the prior art H5820 polypropylene. See the Prospector X5 data sheets with

ATSM and ISO properties for PP P5M4R-034 and PP 13R9A, which are incorporated herein by reference in their entirety. Of the two Huntsman polypropylenes, PP 13R9A is the more preferred, based upon UV profile, Instron stress testing and appearance after gamma-irradiation.

The manufacturing process for the inventive column assembly has also been improved. A new automatic mold has been designed which improves the quality and appearance of the column assembly, and which increases the efficiency of the manufacturing process. Manufacturing is presently done by Duerr Molding (Union, N.J.).

For example, pins are used to form the hollow portions of the inlet arm **22** and outflow arm **23**. In the prior art molding process, these pins were not fixed, so they floated. As a result, the side wall thickness of the inlet arm **1** and outlet arm **12** varied. In the present process, the pins are fixed. Therefore, the thickness of the side walls is more uniform.

Also, as described above, the position of the outflow arm **12** has been moved, the outflow arm no longer protrudes into the hollow interior or lumen of the column **3**, and the outflow arm resides in a recess or notch. This prevents the outflow arm from being blocked. Furthermore, support means **4, 14** are provided to strengthen the inlet arm **1** and the outflow arm **12**. In addition, notches **24a** and **24b** are provided for the proper placement of the top basket.

Further improvement to the manufacturing process and column assembly are described throughout the instant specification.

The packing material area **18** of the column **3** is designed to receive packing material. The type of packing material used depends upon the intended use of the column arrangement.

When used as, for example, a rubidium-82 generator, such as CardioGen®, the packing material is one which will adhere strontium-82 but will allow for the elution of rubidium-82. Strontium(II)-82 decays into rubidium(I)-82. Elution of strontium-82 is not

desired because it binds to bone and exposes the patient to unnecessary radiation exposure. Presently, stannic oxide is the preferred packing material.

The packing material is loaded into the column **3** in a conventional manner. The column **3** is then loaded with strontium-82 in a conventional manner. For example, the closure is punctured by a needle (or similar device) containing the strontium-82 solution. The strontium-82 solution is slowly added to the top of the packed column and allowed to flow through it by the force of gravity. If necessary, a small vacuum can be used. Also, the packing material is preferably wetted before the strontium-82 is added. Slow addition of the strontium-82 is preferred because it will result in the strontium-82 being absorbed as close to the top of the column as possible.

Filters, preferably fiberglass filters, can also be used in this conventional loading procedure. For example, two fiberglass filters are first placed in the column **3**, then a portion of the packing material is added, followed by a single fiberglass filter, then the remainder of the packing material, then two more fiberglass filters. Once filled, the top basket or spacer **17** is inserted into the top basket receptacle area **16**. The top basket **17** acts as a retainer to hold the packing material in place.

Fig. **3** shows schematics of the spacer or top basket **26** of the inventive column assembly. The spacer or top basket **26** is cylindrical in shape with an open top portion **27** and a screen **28** at the bottom portion **29**. Another top basket or spacer **17** of similar configuration is shown in Fig. **1**, placed in the top basket receptacle area **16**.

As shown in the embodiment of Figs. **3B** and **3D**, the top basket **26** actually has three cylindrical areas, a top cylindrical area **30**, a middle cylindrical area **31** and a lower cylindrical area **32**. The top **30** and bottom **32** cylindrical areas have diameters about equal to each other, and their diameters are greater than the diameter of the middle cylindrical area **31**.

The top basket **26** also contains protrusions **33a**, **33b** which are designed to cooperate with notches **24a**, **24b** in the top basket receptacle area **16**. In operation, the protrusions **33a**, **33b** fit into the notches **24a**, **24b** to insure proper alignment of the top basket **26** in the top basket receptacle area **16**. When so positioned, the top basket **26** acts as a retainer to hold the packing material in place.

As shown in Figs. **3A** and **3C**, the two protrusions **33a**, **33b** are 180° opposed to each other. They are located at the top cylindrical area **30**. As was the case with the notches **24a**, **24b**, the present invention is not limited to this configuration. Rather, there can be 1, 3, 4, 5, 6 or more protrusions, in any orientation, so long as they cooperate with the notches to help insure a proper fit for the top basket **26** .

The top basket **26** also contains a side opening **34**. As shown in Figs. **3B** and **3D**, the side opening is in the middle cylindrical area **31** of the top basket **26**. The purpose of the side opening is to line up with the inlet arm **1** when the top basket **26** is placed in the top basket receptacle area **16**. In this arrangement, when a liquid is introduced into the inlet arm **1**, it will pass through the side opening **34** into the top basket **26**.

The top basket **26** can be made of any suitable material, such as polypropylene. Preferably, the material will be radiation resistant, i.e. resistant to degradation in the presence of a radioactive material. More preferably, the top basket **26** is made of the same material used to construct the column assembly. In a preferred embodiment, that material is PP P5M4-R-034 or PP 13R9A polypropylene (Huntsman Polymers (The Woodlands, TX). Even more preferably, the material is the PP 13R9A polypropylene. In a yet further preferred embodiment, the top basket **26** is molded at the same time the rest of the column assembly is molded.

As discussed above, Fig. **4** shows a detailed view of the bottom **6** portion of the column **3**. Fig. **4** shows the outflow notch **25** where the hollow portion **23** of the outflow arm

12 intersects the hollow interior of the column **3**. The outlet notch **25** prevents blockage of the hollow portion **23** of the outflow arm **12** by the bottom stopper **11** (not shown in Fig. **4**).

Fig. **5** shows various types of crimp seals to use with the present invention. Fig. **5A** shows the current, prior art crimp seal. Figs **5B-5F** show various alternate embodiments of the crimp seal.

The function of the crimp seal is to form a tight, crimped seal between the stoppers (described below) and the pharmaceutical container to prevent leakage. Also, a central hole is provided in the crimp seal to allow for the insertion of a needle or similar device. In one preferred embodiment the pharmaceutical container is a column, or column assembly, such as one used in a rubidium generator.

The crimp seal can be made of any material, such as plastic or metal. The material should preferably be radiation resistant, and of sufficient strength to withstand pressures of at least 90 psi and preferably up to 160 psi. More preferably, the material should be metal. Preferred metals comprise aluminum, steel and tin, or suitable alloys or mixtures thereof. The metal can be optionally coated. For example, tin coated steel can be used.

The diameter of the crimp seal will vary according to use, for example, vary according to the diameter of the pharmaceutical container which is to be crimped. With respect to a column assembly to be used as a rubidium–82 generator, such as CardioGen®, the diameter of the crimp seal is preferably about 20 mm across its top.

Fig. **5A** shows a conventional prior art crimp seal **35**. It is made out of aluminum which is about 0.2 mm thick, has a flat top portion **36** with a diameter of about 20 mm with central hole **37** of about 9.5mm in diameter and a skirt **38** about 7.5mm high.

There are several potential problems with this prior art crimp seal. First, because aluminum with a thickness of only about 0.2 mm is used, the crimp seal might not be strong enough to insure a strong, leakproof seal. Second, the central hole **37** is large, and therefore

the stopper might not be properly supported. Also, the larger central hole **37** may allow for ballooning of the stopper. Third, this crimp seal is manually crimped to the column **3**. Manual crimping can result in undesirable variability of crimping pressure and, accordingly, can affect how well the crimp seal **35** seals the column **3** to prevent leakage.

Fig. **5B** shows one type of useful crimp seal **39**. This crimp seal **39** comprises two parts, a top crimp member **40** and a bottom washer **41**. Both the top crimp member **40** and the bottom washer **41** are made of aluminum (vendor –West). The thickness of the aluminum for each part can vary depending upon the intended use, but the aluminum used for each member is generally about 0.2 mm thick.

The top crimp member **40** has a central hole **42** and a skirt **43**. The size of each, and the diameter of the crimp seal, can vary depending upon use. As shown in Fig. **5B**, the central hole **42** has a diameter of about 6.4mm and the skirt **43** is about 7.6mm high. The diameter of the top crimp member **40** is about 20 mm. The top crimp member **40** also has a cover **44**, which covers the central hole **42** when not in use but can be pulled or pealed back when in use. Also, while none of Figs. **5C** through **5F** or Fig. **6** show a cover, it is understood that each of these embodiments can employ a cover if desired.

Fig. **5B** also employs a bottom washer **41**. The bottom washer **41** contains a central hole **45**. The bottom washer central hole **45** can have a diameter greater than, the same as or smaller than the diameter of the central hole **42** in the top crimp member **40**. As shown in Fig. **5B**, both central holes **45**, **42** have about the same diameter, i.e. about 6.4mm. The bottom washer **41** does not have a skirt. The diameter of the bottom washer **41** is about 20 mm.

When used, the bottom washer **41** is placed below the top crimp member **40** and both are crimped into place. Crimping is preferably performed via an automatic or semi-automatic

crimper, which is discussed in more detail below. In the alternative, other processes which control the crimping pressure applied can be used.

Fig. **5C** shows another embodiment of the inventive crimp seals. This crimp seal **46** comprises a single member. It is made out of steel (vendor – Microliter). The thickness of the steel can vary according to the intended use, but is generally about 0.2 mm thick. This crimp seal **46** is about 20 mm in diameter, contains a central hole **47** of about 5.0mm in diameter and has a skirt **48** about 7.2mm high. The crimp seal **46** is preferably crimped into place using an automatic or semi-automatic crimper, although other processes which control the pressure applied can be used.

Fig **5D** shows yet another embodiment of the inventive crimp seals. This crimp seal **49** comprises a single member. It is made out of steel (vendor – Microliter). The thickness of the steel can vary according to the intended use, but is generally about 0.2 mm thick. This crimp seal **49** has a diameter of about 20mm, contains a central hole **50** of about 8.0mm in diameter and a skirt **51** about 7.2mm high. The crimp seal **49** is preferably crimped into place using an automatic crimper, although other processes which control the pressure applied can be used.

Fig. **5E** is yet still another embodiment of the inventive crimp seals. This embodiment comprises two parts, a top crimp member **52** and a bottom washer **53**. Both the top crimp member **52** and the bottom washer **53** are made of aluminum (vendor – Microliter). The thickness of the aluminum can vary depending upon the intended use, but the aluminum used for each member is generally about 0.2 mm thick.

The top crimp member **52** has a central hole **54** and a skirt **55**. The central hole **54** has a diameter of about 9.6 mm and the skirt **55** is about 7.6 mm high. The top crimp member **52** has a diameter of about 20mm.

The top crimp member **52** also contains an insert **56**, which is seated in or under the central hole **54**. The insert **56** can be made of any suitable substance, but is preferable made of metal, such as steel, aluminum or tin, or plastic. The insert **56** also contains an insert central hole **57,** which has a diameter of about 5 mm.

The bottom washer **53** also has a central hole **58**, which has a diameter of about 5 mm. The bottom washer **53** is about 20 mm in diameter and it does not have a skirt.

When used, the bottom washer **53** is placed below the top crimp member **52** and the insert **56** and then all are crimped into place. Crimping is preferably performed using an automatic or semi-automatic crimper, although other processes which control the pressure applied can be used.

Fig. **5F** shows yet another embodiment of the inventive crimp seals. Like Fig. **5E**, Fig. **5F** employs two members, a top crimp member **59** and a bottom washer **60**. Both members are made of aluminum (vendor-Microliter). While the thickness of the aluminum can vary with the intended use, generally each member is about 0.2 mm thick.

The top crimp member **59** contains a central hole **61** and a skirt **62**. The central hole **61** has a diameter of about 9.6 mm and the skirt **62** is about 7.6 mm high. The top crimp member **59** has a diameter of about 20mm.

The bottom washer **60** also has a central hole **63**. The bottom washer central hole **63** has a diameter of about 11.4 mm. The diameter of the entire bottom washer **60** is about 20mm. The bottom washer **60** does not have a skirt.

When used, the bottom washer **60** is placed below the top crimp member **59**. Both are then crimped into place. Preferably, an automatic crimper is employed, although other processes which control the pressure applied can be used.

Fig. **6** is an alternate and preferred embodiment of the inventive crimp seals. This crimp seal **64** comprises a single member. It is made out of steel (vendor – Microliter), code

#20-000 M. See the Microliter Product Catalog, which is incorporated herein by reference in its entirety. The thickness of the steel is about 0.20 mm.

The crimp seal **64** contains a central hole **65** and a skirt **66**. The central hole **65** is about 5.00 mm $\pm$ 0.25 mm in diameter and the skirt **66** is about 7.00 mm $\pm$ 0.25 mm high. The entire crimp seal **64** has a diameter of about 20.75 mm $\pm$ 0.25 mm. The crimp seal **64** is preferably crimped into place using an automatic or semi-automatic crimper.

Fig. **7** shows an improved stopper **67** to be used with the inventive column assembly. The stopper **67** is preferably made from a material which will form a tight seal with the column assembly. In a preferred embodiment the stopper **67** is made of a material which is also resistant to radiation.

Prior art stoppers were made of materials such as Itran-Tompkins PT-29 green neoprene rubber. This material had two potential disadvantages. First, it could degrade when exposed to radiation. Second, it contained latex, which could cause allergic reactions.

Various materials were compared to the PT-29 green neoprene used in the prior art. These materials included neoprene, isoprene, bromobutyl, chlorobutyl, nitrile, isoprene/chlorobutyl, EPDM (ethylene propylene diene monomer) and Viton®. These materials were coated, uncoated, siliconized and non-siliconized.

These materials were made into column assembly stoppers and were irradiated simulating the exposure from a 100mCi generator over a time period of 45 days (about 145 kGy). Irradiated stoppers were compared to non-irradiated controls by integrity (pressure) testing of the column/stopper assemblies. Assemblies were pressurized to determine load pressure required to cause ballooning of rubber materials or leaks/burst at the seal closure (up to about 200 psi). In addition, for the purpose of determining potential rubber extractables and/or leechables, additional column/stopper assemblies were irradiated in the presence of

0.9% saline solution. The saline solution was then scanned at 250mm for UV absorbing extractables.

Three elastomeric compositions were identified as suitable to use in the stoppers of the invention: West Pharmaceutical Services (Lionville, PA) 4588/40 isoprene/chlorobutyl; American Stelmi (Princeton, NJ) 6720 bromobutyl; and Helvoet-Pharma (Pennsauken, NJ) Helvoet FM 140/0 chlorobutyl. Of these materials, the most preferred product to use is the West 4588/40 isoprene/chlorobutyl. Other materials may be used as long as they provide the stopper characteristics specified herein.

The stopper **67** should be configured so that it forms a tight seal with the column assembly and minimizes the dead volume (mixing), thus maintaining a narrow rubidium-82 bolus profile and maximizing efficiency. One preferred structure for the stopper is shown in Fig **7**.

Referring to Fig **7B**, the stopper **67** comprises a generally cylindrical top section **68** and a generally cylindrical bottom section **69**. The diameter of the stopper bottom section **69** is about the same as or slightly larger than the inside diameter of the first top portion **7** and first bottom portion **9** of the cylinder **3**, assuming both of these portions **7, 9** have the same diameter. If these portions have different diameters, then the cylindrical bottom section **69** of the stopper **67** will have about the same or slightly larger inside diameter as the portion **7, 9** it is intended to be inserted into. The reason for this configuration is to insure a tight fit between the stopper **67** and the first top **7** and first bottom **9** portions of the cylinder **3**. A tight cylinder **3**/ stopper **67** interface helps prevent leakage.

The stopper top section **68** has a greater diameter than the stopper bottom section **69** to prevent the stopper **67** from being inserted too far into the cylinder **3**. In addition, optionally the stopper top section **68** can have a curved upper edge **70**.

The stopper bottom section **69**, in one preferred embodiment, contains a U-shaped groove **71** in its base. See Fig **7A**. The U-shaped groove **71** traverses greater than half the length of the stopper bottom section **69**, and it terminates in a semi-circular section **72**. Preferably, the center point **73** of the semicircular section **72** should be about at the center point of the stopper bottom section **69**.

The stopper top section **68** contains a central circular indentation **74** in its top surface. See Fig **7C**. Preferably, the diameter of the central circular indentation **74** has a diameter about equal to the width of the U-shape groove **71**. As shown in Figs **7B** and **7D**, the central circular indentation **74** and the U-shaped groove **71** should preferably line up with each other when the stopper is viewed through its cross-section. The central circular indentation **74** and U-shaped groove **71** allow for easy insertion of a needle or similar device into the stopper **67**.

The surface of the stopper top section **68** also contains three spherical dots **75a**, **75b**, **75c** and an indicia, such as a spherical lug **76**. They are spaced equidistant from each other around the central circular indentation **74**. Also, the spherical lug **76** is placed so that it is above the U-shaped grove **71**. In this configuration, when the stopper **67** is inserted into the first top portion **7** of the column **3**, the spherical lug **76** can be lined up with the inlet arm **1**. Thus, the open end of the U-shaped groove **71** will face the inlet arm **1**, thus preventing its blockage.

The same holds true for the first bottom portion **9** of the column **3**. When the stopper **67** (stopper **11** shown in Fig. **1** and stopper **11b** in Fig. **2** can have the same or different configurations from stopper **67**) is inserted therein, the spherical lug **76** is lined up with the outlet arm **12**. The open end of the U-shaped groove **71** will then face the outlet arm **12** and prevent its blockage.

It is understood that the present invention is not limited to a U-shaped groove **71**. Any other configuration, such as a notch, can be used so long as any potential blockage is

avoided. In fact, if there is no potential for blockage, the U-shaped groove **71** or alternative structure can be eliminated.

The stopper **67** is affixed to the column **3** via crimping, using the crimping seals described above in Figs. **5** and **6**. In the prior art, crimping was performed manually. The disadvantage of manual crimping is that it is not always uniform. One problem this can cause is leakage. To overcome this potential problem, the present invention preferably uses automatic or semi-automatic crimping.

Any automatic or semi-automatic crimper can be used for the present invention, so long as it can consistently crimp seals at a specified, controlled pressure. One preferred type of automatic crimper is a pneumatic crimper, which is powered by gas. One example of a pneumatic crimper suitable for the present invention as an AP/CP2000 Lightweight Air Crimper/Decapper (Laboratory Precision Limited, UK). See Laboratory Precision Limited brochure copyrighted April 4, 2001, which is incorporated herein by reference in its entirety.

In the crimping process, a stopper **67** is inserted into the top portion **5** or bottom portion **6** of the column **3**, so that it is seated in the first top portion **7** or first bottom portion **9**, respectively. A crimp seal or a crimp seal and washer (see Figs. **5** and **6**) is/are placed over the stopper **67**. The crimp seal or crimp seal and washer are then crimped into place, either manually or, preferably, automatically or semi-automatically. While the crimping pressure used is optimized based upon the configuration and material of the crimp seal and stopper, generally about 117 ± 3 psi pressure is used.

The resulting crimped crimp seal/stopper configuration can withstand the operative pressures of the system and can further withstand pressures of at least 90 psi and preferably up to 200 psi.

When in operation, connector tubes (not shown) are connected to the column assembly. Referring to Fig **1A**, both the inlet arm **1** and the outlet arm **12** have a female Luer

cap **2**, **13** at their distal ends. These female Luer caps **2**, **13** engage male Luer caps at the proximal ends of the connector tubes.

Prior art connector tubes can discolor from clear to brown and harden upon prolonged exposure to radiation. Also, the Luer connector can discolor and become brittle. In addition, the Luer connectors can loosen or become unintentionally disconnected during shipping or use.

Accordingly, the present invention includes constructing connector tubing out of radiation resistant materials. Preferably, the tubing is made from a flexible radiation resistant polyvinyl chloride (PVC) and the Luer connector is made from a rigid radiation resistant PVC. For example, a preferred material for constructing the tubing is AlphaGary PVC 2232 A/R-78S Clear 030X. See AlphaGary Test Result Certificate, Report Date 8/20/99; Technical Data, Date of Origin 8/99; and Material Safety Data Sheet printed 04/05/00; which are incorporated herein by reference in their entirety. A preferred material for constructing the Luer connector is AlphaGary PVC 2212 RHT/1-118 Clear 080X. See AlphaGary Data Sheet, Revision Date 4/02, which is incorporated herein by reference in its entirety. Also, using this AlphaGary rigid PVC for the Luer connector allows the heat bonding of tubing to the Luer connector.

The present invention further includes an improved Luer lock. The improvements are described below. An embodiment of this improved Luer lock is set forth in Fig. **8**. These improved Luer locks can be used with the pharmaceutical containers of the present invention, or in any other indication where it is desirable to have a connection that will not inadvertently loosen or disconnect.

In the embodiment of Fig. **8**, Fig **8A** show a side view of the inventive column assembly with the inlet arm **1** projecting forward. Also shown is the female Luer cap **2** at the distal end of the inlet arm **1**.

As shown in Fig. **8C**, the female Luer cap **2** terminates in a flange **77**. The flange **77** can be flat or, as shown, contain a groove **78**. Other configurations, known in the art, can also be used.

The flange **77** is configured to engage and mate with threads **78** in a male Luer cap **79**. When the two caps **2, 79** are screwed together, they form a tight Luer lock which will be leak resistant. This configuration is shown in Fig. **8D**.

One difficulty with a Luer lock is to know when the male and female caps **79, 2** have been connected sufficiently to form a tight lock. To overcome this problem, one or more tabs are provided on each of the male **79** and female Luer caps **2.** As shown for example in Figs. **8C** and **8D**, two tabs are provided on each cap **80a, 80b, 81a** and **81b**, although it is understood that the invention is not limited to this configuration only. For example, each of the Luer caps can also contain 1, 3, 4, 5, 6 or more tabs.

In one embodiment, the female Luer cap tabs **80a, 80b** and the male Luer cap tabs **81a, 81b** are so positioned that when the Luer locks is sufficiently tight, the tabs line up with each other. This way, a user knows when tightening is completed. The present invention, however, is not limited to this one configuration, so long as the tab or tabs on each of the Luer connectors **79, 2** are arranged in a desired configuration to demonstrate that the Luer connectors **79, 2** are sufficiently tightened. In another preferred embodiment, as shown in Fig **8D**, the male Luer cap tabs **81a, 81b** overlap with the female Luer cap tabs **80a, 80b**. The tabs are so positioned that this overlap occurs when the tightening is complete. At the point of desired tightening, the tabs **80a, 80b, 81a, 81b** pass by or click past each other. That way, the Luer locks cannot be over- or under-tightened. Also, inadvertent loosening or disconnection of the Luer lock during use or shipping is prevented by the overlapping of the tabs, preventing the Luer connectors **79, 2** from turning in a loosening direction.

When the inventive column assembly is used as, for example, a rubidium-82 generator, it is pre-packaged with strontium-82 in the factory. That is, the product shipped to the customer is radioactive. Therefore, the radioactive column assembly is shipped in a shielded (e.g. lead) container.

Nevertheless, leakage is still a concern upon shipping. Thus, to improve safety when the radioactive column assembly is shipped, an inventive improvement is to ship the product with a liquid absorbent pad. Preferably, the shipping pad is a GP100 absorbent pad (Shell Packaging Corporation, Springfield, NJ). GP100 is a 100% polypropylene non-woven mat of randomly oriented micro-fibers (2-10 micron diameters). See SPC General Product Specifications for GP100 dated May 26, 2003, which is incorporated herein by reference in its entirety. This type of shipping pad, which may have various configurations, thicknesses or absorbent capacities, is useful in absorbing any leaks which may occur.

SUMMARY OF THE PREFERRED EMBODIMENTS

Improved Seal

The new seal, which is used to crimp the rubber stopper in place in a pharmaceutical container and particularly, which is used to seal a radioisotope generator column/stopper assembly system, such as CardioGen®, is preferably made of a sufficiently strong material to eliminate the problems discussed above. Figs. **5B** through **5F** and Fig. **6** illustrate various method of reinforcing the top portion of the seal by use of a second layer (washer) or use of a stronger material such as steel/tin in addition to reducing the size of the center hole. The material may include metal or plastic, but is preferably metal. The metal may include heavy gauge aluminum, steel or tin, but is preferably steel or tin. The seal generally has the configuration shown in Fig. **5B** through **5F** and Fig. **6** and may have a small or large central hole, a shorter or longer skirt and optionally, a cover (e.g., plastic or aluminum over the central hole). The dimensions of the seal will vary, and one skilled in the art will understand that they should be appropriate to the container which is being sealed. Approximate dimensions for seals for a radioisotope generator column are shown in the various examples in Figure **5** and in Fig. **6**. These dimensions are approximate and are not intended to be limiting.

The central hole of the seals of the invention may vary in size. In a preferred embodiment the seal has a smaller central hole such as, for example, those proportional to the central holes shown in Fig. **5B**, Fig. **5C**, Fig. **5E** and Fig **6**.

In one embodiment, seals of Fig. **5B** through Fig **5F** and Fig. **6** are used to seal a radioisotope generator column. These seals are available from the vendors West Pharmaceutical Services (Lionville, PA) and Microliter Analytical Supplies Inc. (Suwannee, GA). In a particularly preferred embodiment, the central hole of the seal is reduced in size such as in the seals in Fig. **5B**, Fig. **5C**, Fig. **5E** and Fig. **6**. The preferred configuration for

this application is a 1-piece steel/tin crimp with a center hole of approximately 4-5 mm diameter and a skirt length of approximately 7.2 to 7.5mm as shown in Fig. **6**.

The combination of using a stronger material such as steel/tin or heavier gauge aluminum and reduction of the center hole results in optimum performance in maintaining a secure leakage free seal under high pressure and particularly repeated exposure (pulsing or cycling) to high pressure as occurs with the use of the rubidium-82 generator as the enlarged surface area of the crimp limits excessive expansion of the rubber closure under pressure.

The use of a stronger material such as steel/tin or heavy gauge aluminum further improves the performance of the crimp by reducing the likelihood of failure due to relaxation or fatigue of the seal flange which is formed at the point where the crimp skirt is folded under the column or container flange when exposed to high or pulsating pressures. It is understood that the skirt length can be varied to provide a proper fit with the container/rubber seal combination to which it is applied.

Improved Seal

In a preferred embodiment improved stoppers are used. Such stoppers are made of a radiation resistant material, preferably isoprene/chlorobutyl and most preferably West 4588/40 isoprene/chlorobutyl. Additionally, the configuration and placement of the stoppers are improved so that they form tight seals with the column, do not block the inlet or outlet arms and reduce the "dead volume" at the bottom of the column. In a preferred embodiment the stoppers are designed to facilitate insertion of a needle or similar device and contain indicia indicating proper insertion orientation. In the most preferred embodiment, the stoppers have the configuration shown in Fig 7A, Fig 7B and Fig. 7C.

Automatic Crimper and Improved Crimping Process

In a preferred embodiment, an automatic or semi-automatic crimper is used to crimp the seals of the invention. The automatic or semi-automatic crimper is set at an optimized

pressure and is able to crimp seals of any material during assembly of a pharmaceutical container such as a radioisotope generator column/stopper assembly system. Suitable automatic crimpers include pressurized and/or compressed air crimpers such as those available from Laboratory Precision Limited under the trade name/model number AP/CP2000. Use of the automatic or semi-automatic crimping procedure of the invention with compressed or pressurized air results in consistent/reproducible crimping pressures, and enables selection of optimized crimping pressures when crimping various seal materials.

Use of optimized pressures improves the performance of the seals of the invention and also improves performance of seals of only moderate strength, such as lighter gauge aluminum and some plastics.

The automatic or semi-automatic, pneumatically powered crimper used to apply the seal is preferably operated at an optimized pressure of between 60 – 140 psi. However, although automatic or semi-automatic crimpers are preferred, it should be noted that application of the seal is not limited to automated equipment, and systems ranging from manual to fully automatic may be used, provided their operation can be optimized to produce repeatable and consistent predetermined pressures in applying the seals.

Column Design Improvements

Manufacturing Process: To create the new column design, a new automatic mold has been designed. The mold and the new columns produced therein exhibit improved column quality and appearance. The new mold also increases the efficiency of the manufacturing process. The increased speed of the new automated mold enables one operator to run the process efficiently.

Column Design: The improved pharmaceutical container also includes improvements to the design which ensure specified flow of eluent through the container and improve its packing and consistency. In one embodiment the improved container comprises a column

used in a radioisotope generator. The improved column includes a repositioned outlet arm, and the column outlet resides in a recess or notch in the inside ledge of the column where the outlet arm enters the column lumen, to prevent a stopper from blocking the flow. These improvements further include introducing small reinforcement pieces of resin to the outside of the column between the outlet arm and column body and between the inlet arm and column body to provide additional strength. Additionally, the seam of the inlet and outlet arms has been eliminated by changing the mold runners. This change has improved the consistency of the inlet and outlet arm diameters and made the arms stronger.

Furthermore, to address consistency of packing of the containers, two small alignment slots have been cut into the wall of the column to receive the orientation knobs on the baskets that properly align and seat the basket in the column and limit the insertion depth into the column. This improves the consistency of packing density and eliminates potential blockage of the inlet arm. Additionally, in one embodiment, the improved column has stopper flanges and Luer flanges with much smoother surfaces with sharper edges to improve the sealing ability of the crimp. These attributes improve stopper and Luer contact to the column and greatly reduce the chance of leakage. Also, the flashing on the column is reduced greatly to enhance the appearance of the part.

Finally, the column assembly is made from a radiation resistant or tolerant material. The most preferred material is Huntsman PP 13R9A polypropylene.

Luer Lock and Connector Tube Improvements

The Luer locks and connector tubes used with the column have also been improved. First, the connector tubes are made from a radiation resistant or tolerant material. Preferably, this material is AlphaGary PVC 2232 A/R-78S clear 030X.

Second, the terminal end of the connector tube which attaches to the column contains a male Luer cap. This male Luer cap is made of a radiation resistant material, preferably AlphaGary PVC 2212RHT/1-118 clear 080X.

Third, the male and female Luer caps screw together and each contains tabs, preferably two tabs each. When the tabs line up with each other in one embodiment or overlap with each other in another embodiment, that indicates that the two Luer caps are sufficiently tightened or screwed together to form a tight seal or lock. Also, in a preferred embodiment the overlapping tabs prevent the Luer caps from becoming loose, ie unscrewing inadvertently.

Shipping Improvements

The columns can be shipped pre-loaded with, for example, strontium-82. Therefore, the columns are shipped in sealed containers containing GP-100 absorbent material to absorb any leakage.

The above description is to be taken as illustrative and not in the limiting sense. Many modifications can be made to the design without deviating from the scope thereof.

What Is Claimed Is:

1. An improved pharmaceutical container for containing a pharmaceutical agent which is heated, subjected to increased pressure or radioactive, comprising:

a. an inlet arm,

b. a hollow column, and

c. an outlet arm,

wherein the improvement comprises configuring the outlet arm so that it does not protrude into the hollow portion of the column, and support means to support the inlet arm and the outlet arm.

2. The improved pharmaceutical container of claim 1, wherein the container is constructed of a material which is resistant to radiation.

3. The improved pharmaceutical container of claim 1 or 2, wherein the container is constructed of a radiation resistant polypropylene.

4. The improved pharmaceutical container of any of claims 1 through 3, wherein the container is constructed of PP 13R9A polypropylene.

5. An improved pharmaceutical container of any one of claims 1 through 4, wherein a notch is provided in the hollow column at the point where the outflow arm intersects the hollow column.

6. The improved pharmaceutical container of any one of claims 1 through 5, further comprising a basket receptacle area inside the column for receiving a basket where the inlet arm intersects the column, said basket receptacle area further comprising one or more notches, said notches configured to cooperate with one or more protrusions on a basket to be inserted into the basket receptacle area in such a way so as to insure that the basket is properly seated in the basket receptacle area.

7. The improved pharmaceutical container of any one of claims 1 through 6, further comprising two stoppers which form tight seals with and prevent leakage from an open top end and an open bottom end of the column, wherein said stoppers are made of a material which is resistant to radiation, optionally further comprising a packing material and/or a pharmaceutical agent.

8. The improved pharmaceutical container of claim 7, wherein the bottom stopper takes up substantially all of the space at the open bottom end of the column, without blocking the outlet arm, so as to reduce the amount of the dead volume at the bottom of the column.

9. The improved pharmaceutical container of claim 7 or 8, wherein said stoppers are made of a material selected from the group consisting of isoprene/chlorobutyl, bromobutyl and FM 140/0 chlorobutyl.

10. The improved pharmaceutical container of claim any one of claims 7 through 9, wherein said stoppers are made of isoprene/chlorobutyl.

11. The improved pharmaceutical container of any one of claims 7 through 10, wherein each of said stoppers comprises a top cylindrical portion and a bottom cylindrical portion, said bottom cylindrical portion having a diameter sufficient to insure a tight seal between the stopper and the cylinder interface, and said top cylindrical portion having a diameter greater than the bottom cylindrical portion.

12. The improved pharmaceutical container of claim 11, wherein the bottom cylindrical portion contains a U-shaped channel at its base.

13. The improved pharmaceutical container of claim 12, wherein the top cylindrical portion has indicia disposed on its surface, said indicia disposed so that it indicates the direction of the open end of the U-shaped channel.

14. The improved pharmaceutical container of any one of claims 8 through 13, further comprising a centrally located indentation at a top end of the stopper.

15. The improved pharmaceutical container of any one of claims 8 through 14, wherein the stoppers are held in place by crimping a crimp seal around the stoppers to affix them to the container.

16. The improved pharmaceutical container of claim 15, wherein the crimping is performed with an automatic or semi-automatic crimper.

17. The improved pharmaceutical container of claim 15 or 16, wherein the automatic crimper is a pneumatic crimper.

18. The improved pharmaceutical container of any one of claims 15 through 17, wherein the crimp seal is crimped at a pressure of about 60-140 psi.

19. The improved pharmaceutical container of any one of claims 15 through 18, wherein the crimp seal is constructed of a material which is resistant to radiation.

20. The improved pharmaceutical container of any one of any one of claims 15 through 19, wherein the crimp seal is constructed of a material selected from the group consisting of aluminum, steel and tin.

21. The improved pharmaceutical container of any one of claims 15 through 20, wherein the crimped stopper is able to withstand a pressure of between 90 psi and 200 psi inside the sealed container.

22. The improved pharmaceutical container of any one of claims 15 through 21, wherein the crimp seal is made of aluminum and comprises a top crimp member and a bottom washer.

23. The improved pharmaceutical container of claims 15 through 21, wherein the crimp seal is made of steel and comprises a single crimp seal member.

24. The improved pharmaceutical container of claim 22, wherein the top crimp member comprises a generally circular surface with a central hole and a skirt, and the bottom washer comprises a generally circular surface with a central hole.

25. The improved pharmaceutical container of claim 23, wherein the crimp seal member comprises a generally circular surface with a central hole and a skirt.

26. The improved pharmaceutical container of claim 22 or 24, wherein the top crimp member further comprises an insert, said insert being seated in or under the central hole, and further wherein said insert contains a central hole whose diameter is less than the diameter of the central hole in the top crimp member.

27. The improved pharmaceutical container of any one of claims 15 through 21, 23 and 25, wherein said crimp seal comprises a single crimp seal member made of steel with a generally circular surface having a diameter of about 20.75 mm ± 0.25 mm and a skirt with a height of about 7.00 mm ± 0.25 mm, and wherein said generally circular surface has a central hole with a diameter of about 5.00 mm ± 0.25 mm.

28. The improved pharmaceutical container of any one of claims 15 through 27, further comprising a removable cover which covers the central hole in the top crimp member.

29. The improved pharmaceutical container of any one of claims 1 through 28, for generating rubidium-82.

30. The improved pharmaceutical container of any one of claims 1 through 29, further comprising a first connector tube which attaches to the inlet arm via a Luer lock, and a second connector tube which attaches to the outlet arm via a Luer lock, wherein a portion of each Luer lock is affixed to each of the connector tubes and another portion of the Luer locks is affixed to each of the inlet arm and outlet arm.

31. The improved pharmaceutical container of claim 30, wherein the connector tubes and the Luer lock portions attached to the connector tubes are made of materials which are resistant to radiation.

32. The improved pharmaceutical container of claim 30 or 31, wherein the connector tubes are made of a flexible, radiation resistant polyvinyl chloride and the Luer lock portions attached to the connector tubes are made of a rigid, radiation resistant polyvinyl chloride.

33. The improved pharmaceutical container of any one of claims 30 through 32, wherein the connector tubes are made of PVC 2232 A/R-78S clear 030X and the Luer lock portions attached to the connector tubes are made of PVC 2212 RHT/1-118 clear 080X.

34. An improved Luer lock comprising a female Luer cap and a male Luer cap, wherein one of said Luer caps contains a flange and the other of said Luer caps contains threads, configured so that the flange and threads cooperate with each other in such a way that the female Luer cap and male Luer cap can be screwed together, wherein the improvement comprises providing for one or a plurality of tabs on each of the male and female Luer caps, wherein the tabs on the male Luer cap and the tabs on the female Luer cap achieve a desired configuration with respect to each other when the tightening of the two Luer caps together is complete.

35. The improved Luer lock of claim 34, wherein the male and female Luer caps each contain two tabs.

36. The improved Luer lock of claim 34 or 35, wherein the desired configuration is where the respective tabs on the male Luer cap and the female Luer cap line up with each other.

37. The improved Luer lock of claim 34 or 35, wherein the desired configuration is where the respective tabs on the male Luer cap and the female Luer cap overlap with each other, thus preventing overtightening or inadvertent loosening of the Luer lock.

38. The improved pharmaceutical container of any one of claims 1 through 33, which is shipped or packed in with an absorbent material.

39. The improved pharmaceutical container of claim 38, wherein the absorbent material is GP-100.

40. An improved rubiduim -82 generator comprising:

a. a hollow column with a top portion, a middle portion and a bottom portion, said top portion including one or more notches, and a screen separating the middle portion and the bottom portion;

b. a top basket with one or more protrusions, said one or more protrusions configured to cooperate with the one or more notches in the top portion of the hollow column so as to cause the proper seating of the top basket in the top portion of the hollow column, said top basket further comprising a screen at its base and a side opening;

c. an inlet arm which intersects the hollow column at its top portion at a point where the inlet arm is aligned with the side opening in the top basket, and further wherein the inlet arm has a female Luer cap at its distal end, said female Luer cap containing one or more tabs on its outer surface;

d. an outlet arm which intersects but does not protrude into the hollow column at its bottom portion, wherein a notch is provided at the point of intersection on the bottom portion's inner surface, and further

wherein the outlet arm has a female Luer cap at its distal end, said female Luer cap containing one or more tabs on its outer surface;

e. support means to support the inlet arm and the outlet arm to the hollow column

wherein said hollow column, top basket, inlet arm, outlet arm and support means are constructed of a radiation resistant polypropylene;

f. a packing material comprising stannic oxide with strontium-82 adhered to it, said packing material placed in the middle portion of the hollow column above the bottom screen and below the screen of the top basket;

g. a top stopper comprising a radiation resistant material, said top stopper configured to form a tight seal with the top portion of the hollow column but which does not block the inlet arm;

h. a bottom stopper comprising a radiation resistant material, said bottom stopper configured to form a tight seal with the bottom portion of the hollow column and minimizing the dead space in the bottom portion of the hollow column, without blocking the outlet arm;

i. first a crimp seal to crimp the top stopper to the top portion of the hollow column and a second crimp seal to crimp the bottom stopper to the bottom portion of the hollow column, wherein each crimp seal comprises steel with a thickness of about 0.2mm and a central hole about 5.0mm in diameter, wherein each crimp seal is crimped to a pressure of about 117 psi;

j. a first flexible tube comprising a flexible, radiation resistant polyvinyl chloride with a first male Luer cap comprising a rigid, radiation

resistant polyvinyl chloride at one end of said first flexible tube, said first male Luer cap being configured to cooperate with the female Luer cap at the distal end of the inlet arm so that the two Luer caps can be screwed together to form a tight Luer lock, and wherein said first male Luer cap contains one or more tabs on its outer surface which will align with the one or more tabs on the outer surface of the female Luer cap at the distal end of the inlet arm, such that when the two Luer caps are screwed together these tabs achieve a desired configuration with respect to each other when the tightening of the Luer caps is complete; and

k. a second flexible tube comprising a flexible, radiation resistant polyvinyl chloride with a second male Luer cap comprising a rigid, radiation resistant polyvinyl chloride at one end of said second flexible tube, said second male Luer cap being configured to cooperate with the female Luer cap at the distal end of the outlet arm so that the two of them can be screwed together to form a tight Luer lock, and wherein said second male Luer cap contains one or more tabs which will align with the one or more tabs on the female Luer cap at the distal end of the outlet arm, such that when the two Luer caps are screwed together these tabs achieve a desired configuration with respect to each other when the tightening of the Luer caps is complete.

41. An improved rubiduim-82 generator comprising:

a. a hollow column with a top portion, a middle portion and a bottom portion, said top portion including one or more notches, and a screen separating the middle portion and the bottom portion;

b. a top basket with one or more protrusions, said one or more protrusions configured to cooperate with the one or more notches in the top portion of the hollow column so as to cause the proper seating of the top basket in the top portion of the hollow column, said top basket further comprising a screen at its base and a side opening;

c. an inlet arm which intersects the hollow column at its top portion at a point where the inlet arm is aligned with the side opening in the top basket, and further wherein the inlet arm has a female Luer cap at its distal end, said female Luer cap containing one or more tabs on its outer surface;

d. an outlet arm which intersects but does not protrude into the hollow column at its bottom portion, wherein a notch is provided at the point of intersection on the bottom portion's inner surface, and further wherein the outlet arm has a female Luer cap at its distal end, said female Luer cap containing one or more tabs on its outer surface;

e. support means to support the inlet arm and the outlet arm to the hollow column

wherein said hollow column, top basket, inlet arm, outlet arm and support means are constructed of a radiation resistant polypropylene;

f. a packing material comprising stannic oxide with strontium-82 adhered to it, said packing material placed in the middle portion of the hollow column above the bottom screen and below the screen of the top basket;

g. a top stopper comprising a radiation resistant material, said top stopper configured to form a tight seal with the top portion of the hollow column but which does not block the inlet arm;

h. a bottom stopper comprising a radiation resistant material, said bottom stopper configured to form a tight seal with the bottom portion of the hollow column and minimizing the dead space in the bottom portion of the hollow column, without blocking the outlet arm;

i. first a crimp seal to crimp the top stopper to the top portion of the hollow column and a second crimp seal to crimp the bottom stopper to the bottom portion of the hollow column, wherein each crimp seal comprises steel with a thickness of about 0.2mm and a central hole about 5.0mm in diameter, wherein each crimp seal is crimped to a pressure of about 117 psi;

j. a first flexible tube comprising a flexible, radiation resistant polyvinyl chloride with a first male Luer cap comprising a rigid, radiation resistant polyvinyl chloride at one end of said first flexible tube, said first male Luer cap being configured to cooperate with the female Luer cap at the distal end of the inlet arm so that the two Luer caps can be screwed together to form a tight Luer lock and where said first male Luer cap contains one or more tabs on its outer surface which will overlap with the one or more tabs on the outer surface of the female Luer cap at the distal end of the inlet arm, such that when the two Luer caps are screwed together these tabs overlap and are pushed past each other, and a tight Luer lock which is resistant to inadvertent loosening is formed; and

k. a second flexible tube comprising a flexible, radiation resistant polyvinyl chloride with a second male Luer cap comprising a rigid, radiation resistant polyvinyl chloride at one end of said second flexible tube, said second male Luer cap being configured to cooperate with the female Luer cap at the distal end of the outlet arm so that the two of them can be screwed together to form a tight Luer lock, and wherein said second male Luer cap contains one or more tabs which will overlap with the one or more tabs on the female Luer cap at the distal end of the outlet arm, such that when the two Luer caps are screwed together these tabs overlap and are pushed past each other, and a tight Luer lock which is resistant to inadvertent loosening is formed.

42. The improved pharmaceutical container of any one of claims 30 through 33 wherein the Luer locks comprise a female Luer cap and a male Luer cap, wherein one of said Luer caps contains a flange and the other of said Luer caps contains threads, configured so that the flange and threads cooperate with each other in such a way that the female Luer cap and male Luer cap can be screwed together, wherein the improvement comprises providing for one or a plurality of tabs on each of the male and female Luer caps, wherein the tabs on the male Luer cap and the tabs on the female Luer cap achieve a desired configuration with respect to each other when the tightening of the two Luer caps together is complete.

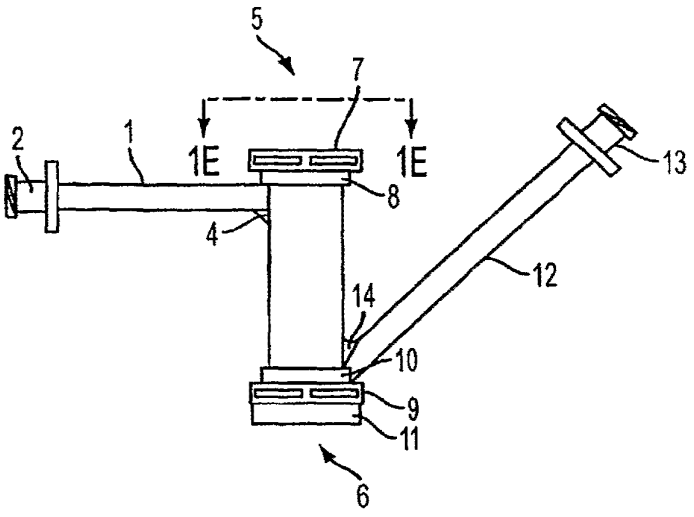


FIG. 1A

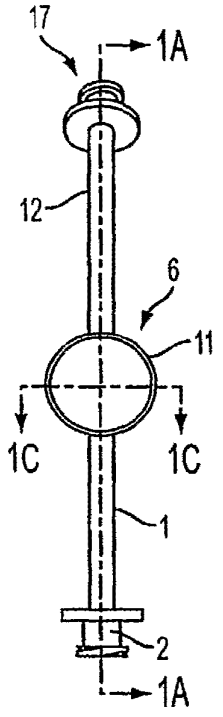
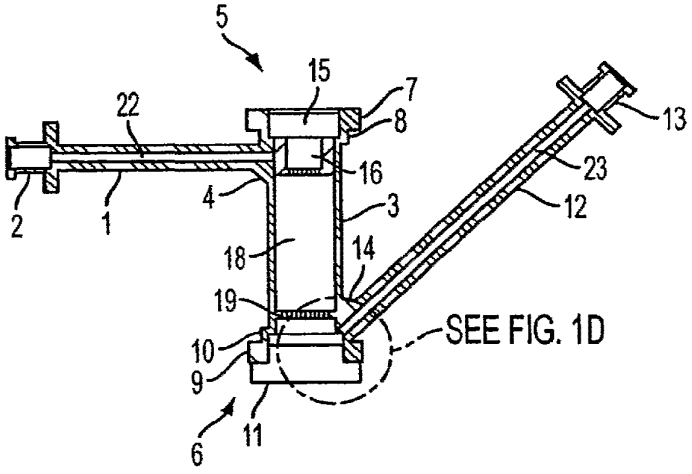


FIG. 1B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SEE FIG. 1D
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FIG. 1C

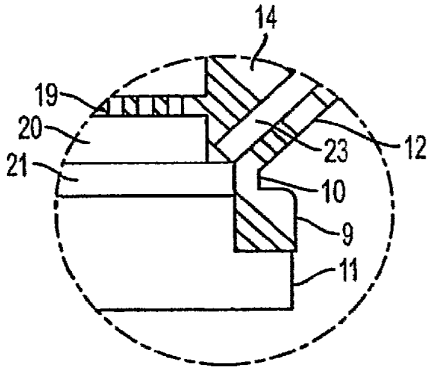
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FIG. 1D

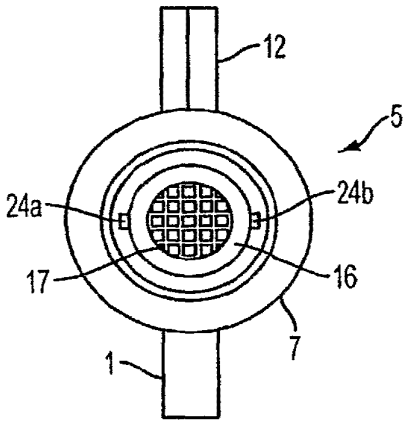

FIG. 1E

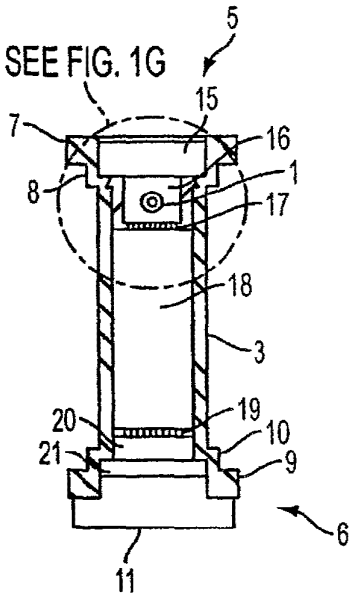

FIG. 1F

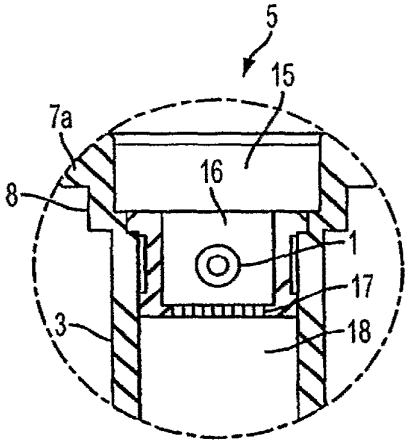

FIG. 1G

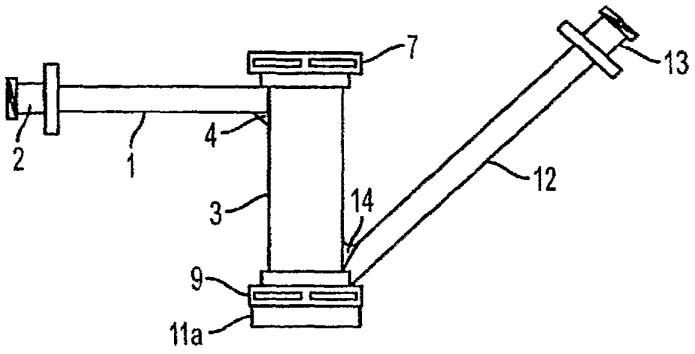

FIG. 2A

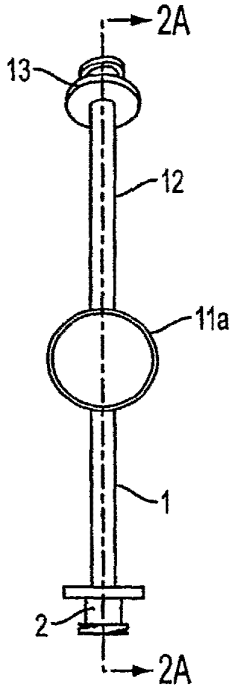

FIG. 2B

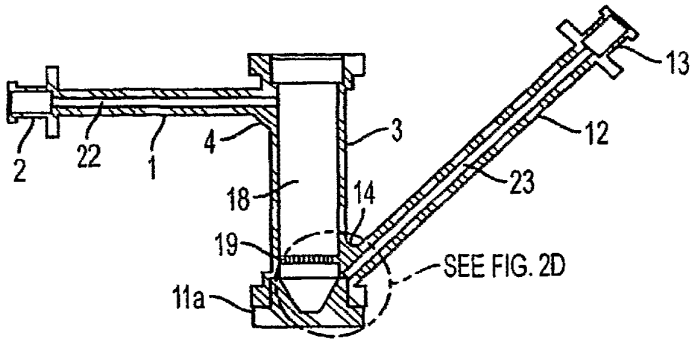

FIG. 2C

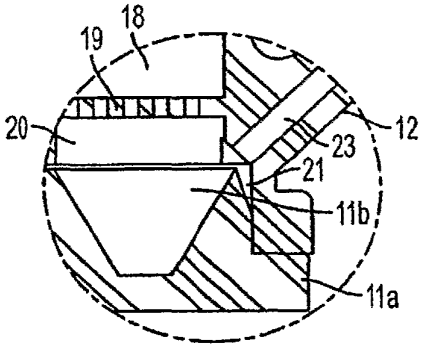

FIG. 2D

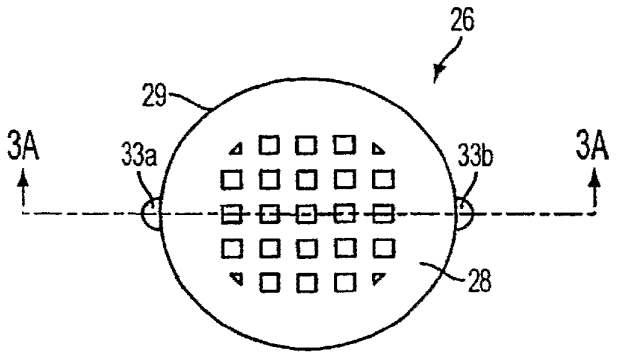

FIG. 3A

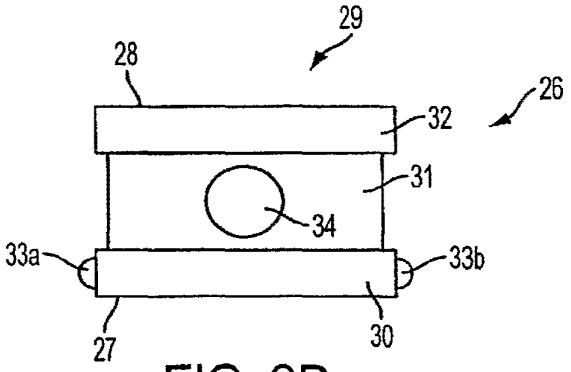

FIG. 3B

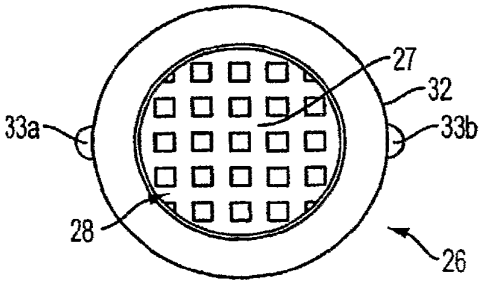

FIG. 3C

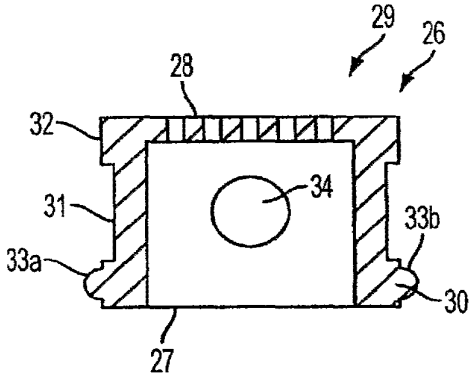

FIG. 3D

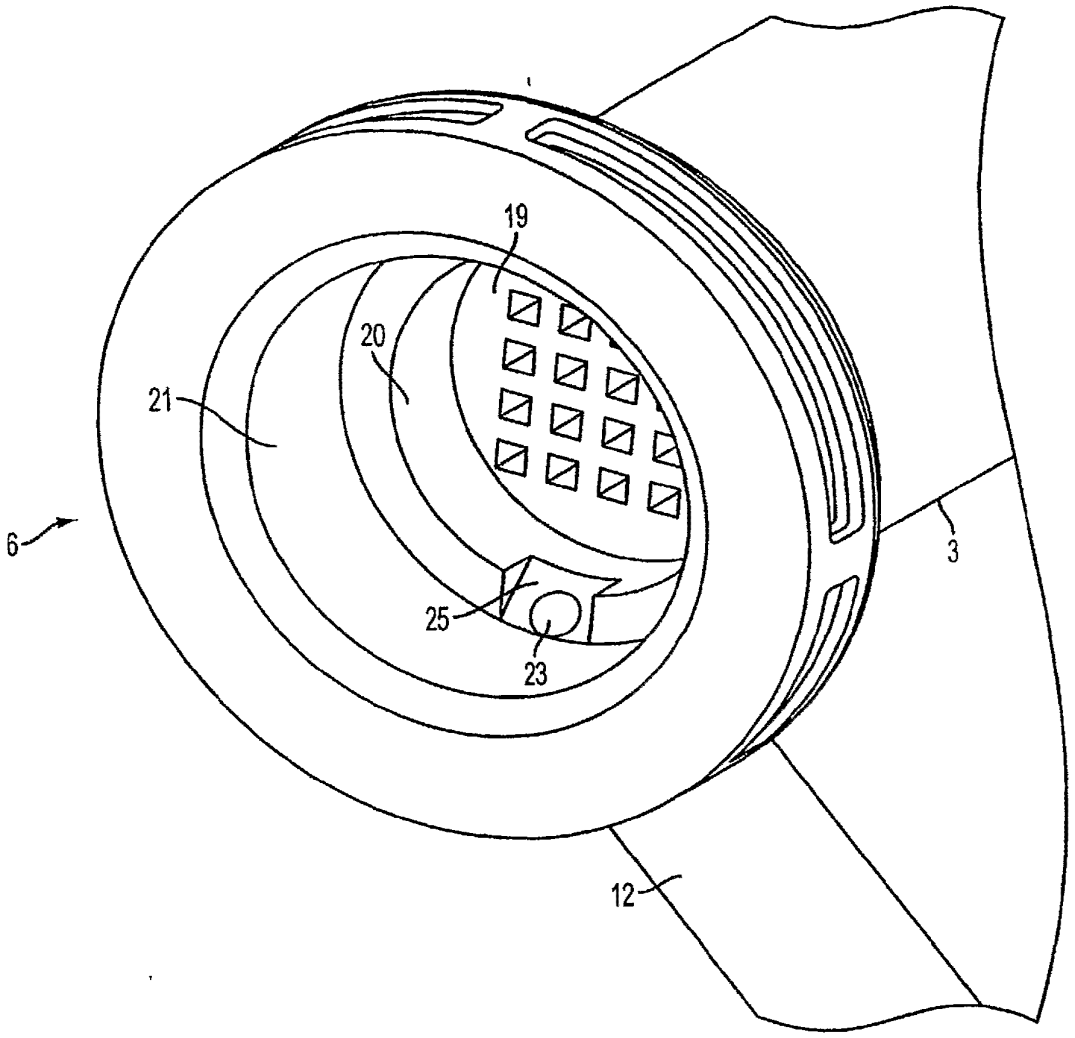

FIG. 4

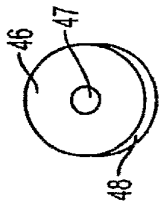

FIG. 5C

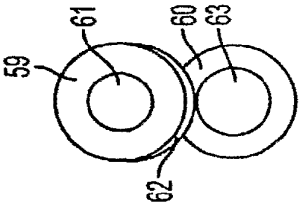

FIG. 5F

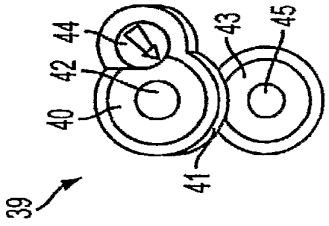

FIG. 5B

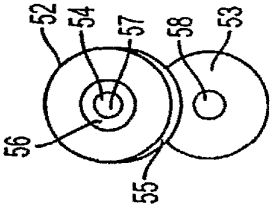

FIG. 5E

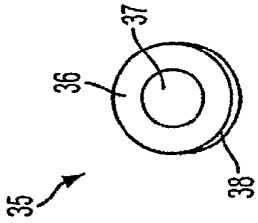

FIG. 5A
PRIOR ART

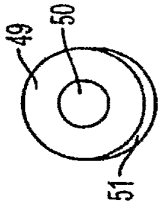

FIG. 5D

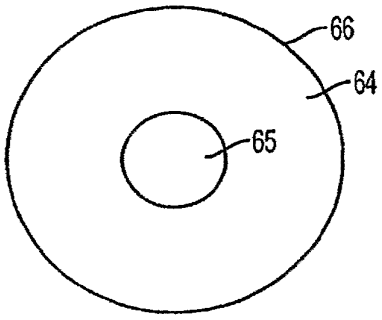

FIG.6A

FIG.6B

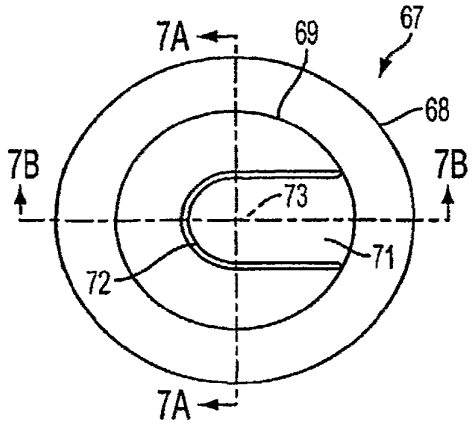

FIG. 7A

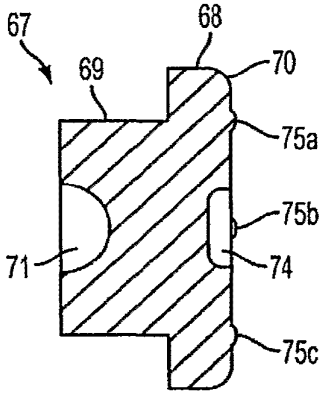

FIG. 7B

1214

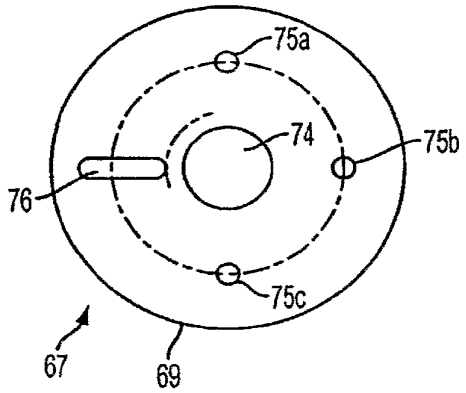

FIG. 7C

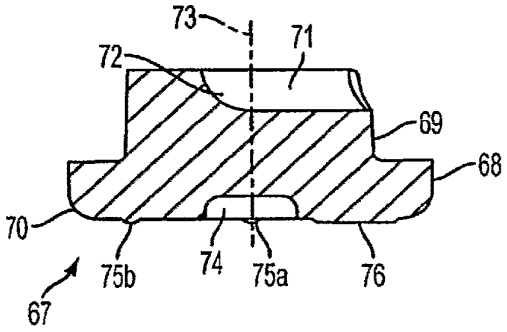

FIG. 7D

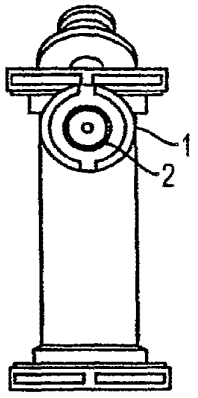

FIG. 8A

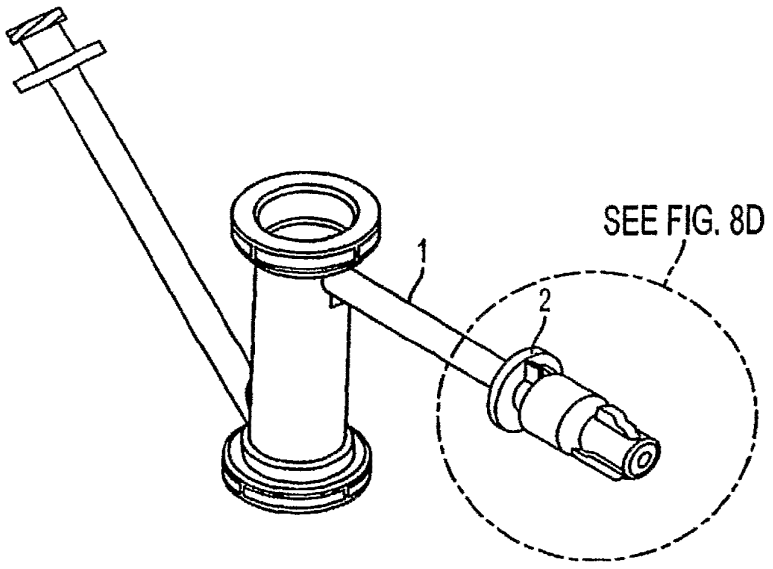

FIG. 8B

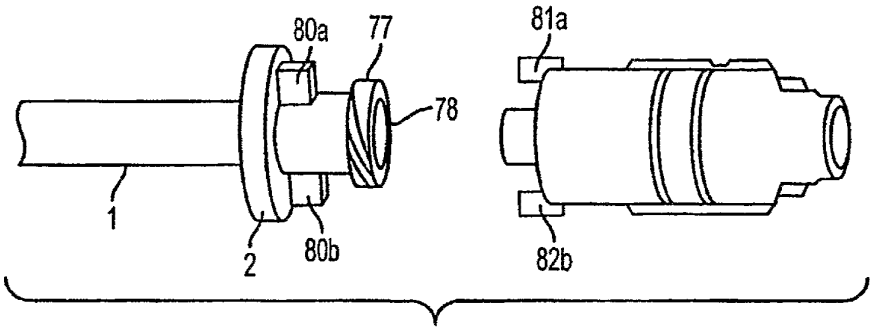

FIG. 8C

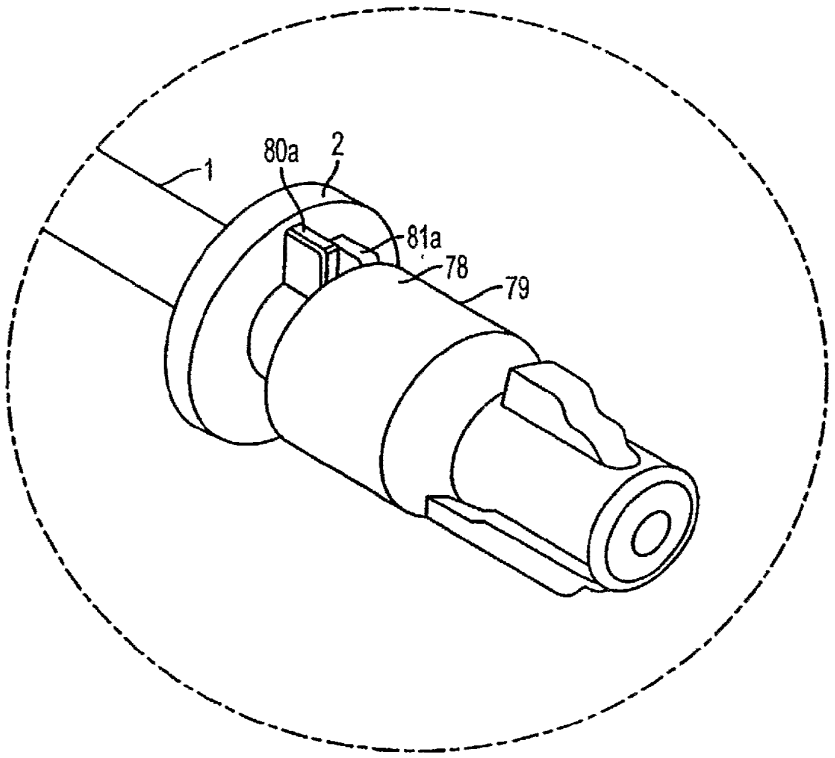

FIG. 8D

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(54) Title: RUBIDIUM-82 GENERATOR BASED ON SODIUM NONATITANATE SUPPORT, AND IMPROVED SEPARATION METHODS FOR THE RECOVERY OF STRONTIUM-82 FROM IRRADIATED TARGETS

(57) Abstract: Sodium nonatitanate compositions, a method using the composition for recovery of ^{82}Sr from irradiated targets, and a method using the composition for generating ^{82}Rb. The sodium nonatitanate materials of the invention are highly selective at separating strontium from solutions derived from the dissolution of irradiated target materials, thus reducing target processing times. The compositions also have a very low affinity for rubidium, making it an ideal material for use as a ^{82}Rb generator. Sodium nonatitanate materials of this type both improve the recovery of ^{82}Sr and provide a safer, more effective ^{82}Rb generator system.

RUBIDIUM-82 GENERATOR BASED ON SODIUM NONATITANATE SUPPORT, AND IMPROVED SEPARATION METHODS FOR THE RECOVERY OF STRONTIUM-82 FROM IRRADIATED TARGETS

BACKGROUND OF THE INVENTION

Field of the Invention

[001] This invention relates to the selective separation of strontium-82 from other radioisotopes, such as those resulting from irradiated molybdenum or rubidium targets, and in the manufacture of a rubidium-82 generator.

Background of the Related Art

[002] The use of radioisotopes as diagnostic and imaging agents in medicine has expanded rapidly in recent years. Positron (β+) emitters are particularly useful in the study of metabolic processes because the positron-electron annihilation reaction produces a pair of gamma rays with an energy level of 511 keV travelling in opposite directions. By placing a series of detectors around a patient who has been administered a positron emitter, both the location and amount of radioactivity can be accurately determined. This property is utilized in Positron Emission Tomography (PET) to image metabolic processes *in vivo*. Rubidium-82 (^{82}Rb) is a short-lived positron-emitting isotope ($T_{½}$ = 76 seconds) that is increasingly being used to study blood flow through the heart and brain. Physiologically, rubidium is an analogue of potassium, and consequently enters the body's large potassium pool, which has a comparatively slow turnover. Thus, after ^{82}Rb is injected intravenously, the tracer's uptake in tissue reflects the rate of delivery, *i.e.*, blood flow, and thus ^{82}Rb rapidly builds up in the heart. This can be used, for example, to study blood-brain barrier leakage and heart muscle perfusion.

[003] The short half-life of ^{82}Rb means that it must be supplied to physicians in the form of a generator, where the parent ^{82}Sr ($T_{½}$ = 25 days) is immobilized on a solid substrate or support and ^{82}Rb eluted as required. The generators that are currently available use hydrous tin oxide to immobilize the ^{82}Sr and allow the elution of ^{82}Rb by saline or other appropriate eluant. The ^{82}Sr ($T_{½}$ = 25 days) is accompanied by unwanted ^{85}Sr ($T_{½}$ = 64 days), generated as a by-product during the manufacture of ^{82}Sr, wherein both isotopes have a relatively long half-life and

a high radiotoxicity due to their tendency to accumulate in bone. Thus, it is essential to minimize or eliminate the introduction of ^{82}Sr and ^{85}Sr into a patient during the administration of ^{82}Rb. Although hydrous tin oxide has proved acceptable to date for use in generators, new materials exhibiting far higher strontium affinities, improved strontium/rubidium separation factors and greater radiolytic stability are needed in order to lower the amount of ^{82}Sr and ^{85}Sr released during elution of the ^{82}Rb.

[004] The parent ^{82}Sr is generated by the proton irradiation of rubidium, rubidium chloride or molybdenum targets followed by dissolution and processing to isolate the ^{82}Sr. The demand for ^{82}Rb generators has grown so great that there is a need to reduce processing times and to increase the yield of ^{82}Sr from processed targets. One method of improving the supply of ^{82}Sr is to improve the processes used to extract ^{82}Sr from irradiated targets. Current methods utilize organic ion exchange or chelating resins to extract very low levels of strontium from dissolved targets containing molar concentrations of inert ions. However, a satisfactory separation of ^{82}Sr from the target materials and other radioisotopes generated during the irradiation procedure requires multiple treatment steps due to the relatively low affinity and low selectivity of the organic ion exchange resins for ^{82}Sr.

[005] ^{82}Sr is produced by the proton irradiation of molybdenum metal, rubidium metal and rubidium chloride targets. The irradiation process also produces a range of other radioactive isotopes (*e.g.*, ^{88}Y, ^{88}Zr, ^{85}Sr) and as a consequence, a series of carefully designed separation procedures have been designed to separate the desired ^{82}Sr from other radioisotopes and inactive species present. The primary method used to separate ^{82}Sr is by a series of ion exchange and selective elution steps. Typically, AG 50 W-X8 ion exchange resin is used to separate ^{82}Sr from dissolved targets. However, this resin is relatively non-selective and will absorb numerous polyvalent cations (*e.g.*, ^{88}Y) in addition to the desired ^{82}Sr. Consequently, multiple separation steps are required to isolate ^{82}Sr from the other isotopes present.

[006] ^{82}Rb can be conveniently supplied to physicians in the form of a generator in which the parent ^{82}Sr is immobilized on an ion exchange material and the ^{82}Rb eluted when required. This means that ^{82}Rb PET can be performed at clinical facilities where a typical generator lasts about a month before the yield of ^{82}Rb diminishes below a usable level.

[007] To be suitable for use in a ^{82}Rb generator, an ion exchange material must exhibit a high affinity for strontium but a low affinity for rubidium, allowing the ^{82}Rb daughter to be eluted from a column containing immobilized ^{82}Sr. Generators have been proposed that were

based on a number of separation media including Chelex 100, Al_2O_3, Sb(V) hexacyanoferrate, polyantimonic acid, titanium vanadate and hydrated tin(IV) oxide, with the hydrated tin(IV) oxide being the most widely used.

[008] However, the crucial component of any system is the actual ion exchange material containing the immobilized ^{82}Sr parent. Current systems using hydrous tin oxide have a limited life due to the breakdown of the hydrous tin dioxide, necessitating frequent replacement.

[009] Therefore, there is a need for a highly strontium selective ion exchange material for use in place of ion exchange resins and hydrated tin(IV) oxide, so that the separation and recovery of ^{82}Sr from Rb, RbCl and Mo targets is greatly facilitated. A replacement for the ion exchange resin will lead to a reduction in processing steps, a decrease in target processing times and thus a decrease in the cost of the ^{82}Sr product. An ion exchange material suitable for use as a ^{82}Rb generator will have a very high selectivity for ^{82}Sr and a very low selectivity for ^{82}Rb to allow elution of the ^{82}Rb by isotonic saline or other solutions and will offer a longer operating life or improved operating conditions compared to hydrated tin(IV) oxide.

SUMMARY OF THE INVENTION

[010] The present invention provides a method of chemically isolating strontium-82 from proton-irradiated molybdenum targets. This comprises dissolving the molybdenum metal target containing the strontium-82, adjusting the pH of the dissolved molybdenum target solution to an alkaline pH, removing precipitates from the solution, and then absorbing the strontium-82 from the solution onto a support comprising sodium nonatitanate. Sodium nonatitanate can also be applied to the efficient recovery of strontium-82 from alkaline RbCl solutions produced during the processing of proton-irradiated rubidium metal and rubidium chloride targets.

[011] The present invention also provides a rubidium-82 generator, comprising a strontium-82 support medium comprising sodium nonatitanate. Preferably, the sodium nonatitanate is characterized by a strontium selectivity greater than 250,000 mL/g at an alkaline pH, and/or the sodium nonatitanate is characterized by a rubidium selectivity less than 100 mL/g at an alkaline pH. More preferably, the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 1,000, and even more preferably greater than 100,000.

[012] The rubidium-82 generator is prepared by a process comprising: preparing sodium nonatitanate from titanium isopropoxide and aqueous sodium hydroxide; heating the sodium

nonatitanate at a temperature between 100°C and 250°C for a period between 12 hours and 2 weeks; and absorbing strontium-82 on the sodium nonatitanate from an aqueous solution comprising strontium-82 and a soluble sodium salt, wherein the sodium salt concentration is between 0.1 and 1 molar. It is also preferred that the titanium isopropoxide and the aqueous sodium hydroxide solution are provided at a sodium hydroxide to titanium isopropoxide molar ratio of greater than 0.44, but preferably providing a large molar excess of sodium hydroxide. The sodium hydroxide to titanium isopropoxide molar ratio is preferably between 1 and 10, more preferably between 2 and 6, and most preferably about 4.

[013] Furthermore, the invention provides a process for preparing a solution containing rubidium-82. The process comprises providing a solution containing strontium-82 at a pH between 10 and 14, absorbing the strontium-82 from the solution onto a sodium nonatitanate support medium, and eluting rubidium-82 from the sodium nonatitanate support medium with a solvent. The solvent is preferably selected from the group consisting of water and saline solutions. More particularly, the solvent may be an aqueous solution having a sodium chloride concentration between 0.001 molar and 1 molar, preferably between 0.1 molar and 1 molar. The solvent may also be a pharmaceutical grade isotonic saline and buffer solution.

BRIEF DESCRIPTION OF THE DRAWINGS

[014] FIG. **1** is a graph showing ^{82}Sr K_d values for the ion exchange materials from simulated rubidium and rubidium chloride target solutions.

[015] FIG. **2** is a graph showing the reduction of ^{82}Sr activity with increasing time.

[016] FIG. **3** is a graph showing the effect of pH on the uptake of ^{85}Sr using normal saline as an eluant.

[017] FIG. **4** is a graph showing ^{85}Sr K_d values in normal saline for NaTi samples of various pellet size.

[018] FIG. **5** is a schematic drawing of a system having a sodium nonatitanate column in accordance with the present invention.

[019] FIGS. **6A-6B** are graphs showing the pH of saline solutions at the inlet and outlet of a $^{82}Sr/^{82}Rb$ column.

DETAILED DESCRIPTION OF THE INVENTION

[020] The present invention provides improved sodium nonatitanate compositions, a method using the composition for recovery of ^{82}Sr from irradiated targets, and a method using the composition for generating ^{82}Rb. The sodium nonatitanate materials of the invention are far more selective at separating strontium from solutions derived from the dissolution of irradiated target materials than current ion exchange resins used in the production of ^{82}Sr. The present invention reduces the number of processing steps required, and thus leads to a decrease in target processing times and a reduction in the cost of the ^{82}Sr product. Waste generation and disposal are also decreased.

[021] According to the present invention, synthetic conditions are adjusted to produce a material with improved properties more applicable to ^{82}Sr processing. The sodium nonatitanate of the present invention has been found to have a very low affinity for rubidium in addition to an exceptionally high affinity for strontium, making it ideal for use as a replacement for the hydrous tin dioxide used in current ^{82}Rb generators. Sodium nonatitanate materials of this type will both improve the retention of ^{82}Sr and lead to a safer, more effective ^{82}Rb generator system for clinical applications.

[022] Sodium nonatitanate, $Na_4Ti_9O_{20}xH_2O$, is an inorganic ion exchange material that has been used for the removal of ^{90}Sr from neutral and alkaline nuclear wastes. The sodium nonatitanate of the present invention has a number of advantages over conventional organic ion exchange resins (*e.g.*, Chelex 100) that include: very high selectivity for trace levels of strontium in the presence of molar concentrations of other ions at alkaline pH; very low affinity for rubidium; excellent radiation, chemical and thermal stability so that there is no release of contaminants (*e.g.*, Ti) into the ^{82}Rb product; rapid reaction kinetics; high cation exchange capacity; absorbed ions are readily stripped by treatment with dilute mineral acid allowing the sodium nonatitanate to be recycled, if desired; scale up of similar synthesis has already been demonstrated; and the sodium nonatitanate powder can be manufactured into pellets appropriate for column operations. Other chemically related sodium titanate materials suitable for use in the same manner as the aforementioned sodium nonatitanate ($Na_4Ti_9O_{20}xH_2O$) include other titanate materials exhibiting high Sr affinity and low Rb affinity, including Sr-Treat (available from Selion Oy) and monosodium titanate (available from Boulder Scientific) It is also anticipated that analogous zirconates may exhibit similar properties.

[023] The invention also provides important improvements in the processing of irradiated targets to recover ^{82}Sr. Sodium nonatitanate has a much greater affinity for ^{82}Sr than currently used ion exchange resins, and a low affinity for other radioactive isotopes. Consequently, the use of sodium nonatitanate greatly simplifies the extraction process by reducing the number of separation steps that are required to produce chemically pure ^{82}Sr. Thus, targets can be processed more rapidly and the recovery of ^{82}Sr improved. Improved isotope selectivity may also facilitate the isolation of other useful isotopes from the targets, leading to greater payback from target processing operations.

[024] Furthermore, less than 1 g of sodium nonatitanate material is needed in a ^{82}Rb generator and 1 kg of this material is expected to be sufficient to process a large number of targets, even if the sodium nonatitanate material is not recycled and is disposed of after one use. Consequently, the additional cost incurred by the use of sodium nonatitanate will be negligible in comparison with the cost savings achieved in the ^{82}Sr production.

[025] It has been determined that replacing hydrous tin dioxide with sodium nonatitanate reduces the amount of ^{82}Sr released during the operation of the ^{82}Rb generator, thereby reducing the exposure of the patient to ^{82}Sr. Sodium nonatitanate is also more chemically stable and less likely to leach non-radioactive contaminants into solution during operation of the generator. The sodium nonatitanate is also more amenable to recycling since the ^{82}Sr can readily be stripped with mineral acid without producing additional impurities. Recycling of ^{82}Sr generators is already being used as a source of additional ^{82}Sr, and improvements to the recycling procedure (obtained by using a superior ion exchange material) will facilitate the recovery of ^{82}Sr from this source.

[026] Although the sodium nonatitanate may be used as a direct replacement for hydrous tin dioxide in the ^{82}Rb generator, it is also possible to use sodium nonatitanate in the form of a disposable add-on filter that could be used to trap any ^{82}Sr that is leached from the generator during the production of ^{82}Rb.

[027] The first step in preparing a ^{82}Rb generator is to load the parent ^{82}Sr onto the sodium nonatitanate material and place the ion exchange material into a suitable column. It is essential that sufficient time be allowed for the ^{82}Sr to be absorbed by the sodium nonatitanate material in order to maximize the loading of the parent radioisotope per gram of ion exchange material.

[028] For an ^{82}Rb generator, the sodium nonatitanate may be loaded into the column and then loaded with ^{82}Sr although this method results in depositing a disproportionate amount of the ^{82}Sr at the top of the column with the remainder of the column remaining as a guard bed to collect any ^{82}Sr that migrates down the column. Alternatively, the sodium nonatitanate may be loaded with ^{82}Sr before being placed in an ion exchange column to avoid preferentially loading the ^{82}Sr on the top of the ion exchange. A high concentration of radioactivity on a very small volume of sodium nonatitante may result in undesirable radiolytic problems. Although sodium nonatitanate has been shown to be highly resistant to radiation damage, it is always considered prudent to avoid any unnecessary radiation exposure.

[029] In the medical field, use of the ^{82}Rb generator preferably provides a saline solution that can be intravenously injected into a patient as an imaging agent at a pH of between about 4.5 and about 7. To achieve the desired pH range of the eluted ^{82}Rb solution, a neutralization step may be performed on the sodium nonatitanate to lower the pH of the sodium nonatitanate. An ^{82}Rb generator having sodium nonatitanate that has not been neutralized to a lower pH produces an ^{82}Rb eluate solution having a higher pH than is desired for an injectable pharmaceutical in the medical field. For example, using a normal saline eluant having an initial pH of about 7.6 to elute ^{82}Rb from an ^{82}Rb generator having sodium nonatitanate that has not been neutralized to a lower pH can produce an eluate with a pH as high as 9.5. Even though over time the pH of the eluate slowly declines as more eluant is run through the generator, it is preferable and more efficient that the ^{82}Rb eluate produced from the generator is immediately suitable for medical use. In one experiment, it was determined that a 2.92 g alkaline nonatitanate column required about 44 L of pH 6.2 saline eluant throughput to lower the pH level of the eluate to within the desired pH range. However, the use of such a high volume of eluant before the ^{82}Rb solution is produced at a desired pH level is unacceptable.

[030] The neutralization step added to the nonatitanate synthesis effectively lowers the pH of the ion exchanger and provides an ^{82}Rb solution having the desired pH range from the first use of the generator. The neutralization step includes adding an acid to the final stage of the nonatitanate synthesis. This neutralization step has no significant effect on the high separation factor that the nonatitanate possesses for strontium and rubidium as required for use in an ^{82}Rb generator. However, using the sodium nonatitanate that has been neutralized to a lower pH results in an ^{82}Rb product having an acceptable pH difference of less than one pH unit between the eluant and the eluate.

[031] The neutralization step includes resuspending the sodium nonatitanate product in a liquid and then adding an acid to lower the pH to between about 7 and about 9, preferably between about 7.2 and about 8.5. The pH is more preferably lowered to between about 7.5 and about 8.3 and most preferably to between about 7.8 and about 8.2. Sodium nonatitanate is partially neutralized by contacting the sodium nonatitanate product with the acidic liquid. The product may be centrifuged, the supernatant poured off, and, if desired, the process repeated to neutralize the sodium nonatitanate product again to obtain the target pH. The liquid may be any suitable liquid such as normal saline, dilute sodium chloride, water or preferably, deionized water. Any strong acid may be added to lower the pH such as, for example, nitric acid, sulfuric acid, or preferably hydrochloric acid.

[032] It is important to maintain the pH of the sodium nonatitanate above a minimum pH during the neutralization step because lowering the pH below neutral also lowers the separation efficiency of Sr/Rb. There is a correlation shown in between pH and the uptake of both ^{85}Sr and ^{82}Rb. At high pH, the uptake of ^{85}Sr is high while the uptake of ^{82}Rb is low. At pH between about 6 and about 7, the uptake of ^{85}Sr starts to decrease while the uptake of ^{82}Rb remains the same or slightly increases. At pH values lower than about 4, the affinity for ^{85}Sr decreases dramatically.

[033] As the pH of the equilibrium saline solution passing through the column increases, the nonatitanate affinity for the strontium increases while the affinity for the rubidium decreases. Therefore, lowering the pH of the produced nonatitanate by performing a neutralizing step at the end of the method of producing the nonatitanate results in generator having a shorter life. To optimize the life time and separation efficiency, either the neutralization step may be omitted or a less complete neutralization step may be performed to achieve a lesser degree of neutralization.

[034] Optionally, an adjustment may be made to the pH of the eluate product obtained from the nonatitanate column that was produced without a neutralization step or was only slightly neutralized during the neutralization step. If the eluate product from the generator has a pH above the desired range, the pH of the eluate product may be decreased to the desired pH range by adding an acid. Acceptable acids include any acid suitable for neutralizing the eluant without rendering the neutralized eluant unsuitable for injection into a patient during a medical procedure as known by those having ordinary skill in the art. Suitable acids would include, for

example, hydrochloric acid (HCl) and acetic acid (CH_3COOH). HCl is preferred because the salt produced by the neutralizing reaction is NaCl, which is already present in the solution.

[035] The acid may be added automatically to adjust the pH or the acid may be added manually. A pH meter preferably measures the pH of the eluate product. Alternatively, other means, such as pH indicating strips, may be used to measure the pH of the eluate. Preferably a pH meter monitors the pH of the eluate as the acid is added to obtain the eluate target pH of between about 4.5 and about 7. The acid may be added using a gravity system to drip or pour the acid into the eluate. Alternatively, a pressure system, such as a syringe, a pump or a gas pressurized system may be used to add the acid to the eluate. When the acid is added automatically, a controller monitors the output signal from a pH meter and adjusts a valve or a pump rate to add the amount of acid necessary to obtain the eluate target pH. If adjusted manually, acid may be added to the eluate by an operator, preferably in pre-packaged amounts, until a pH meter or indicator strip indicates that the target pH has been achieved. Preferably, the acid is added automatically to the eluate as the eluate flows from the column.

[036] The size of the sodium nonatitanate particles used in the generator is an important factor. The use of large particles of sodium nonatitanate in a column provides low flow resistance of the eluant through the column but large particles cannot be packed into a column or elutable container as densely as smaller particles may be packed. Furthermore, large particles create long diffusion paths over which the ^{82}Rb generated by the decay of ^{82}Sr atoms located deep in the particle must travel while diffusing from the centers of the large particles. In contrast, fine particles of sodium nonatitanate permit more material to be packed into a column of a given volume and provide shorter diffusion paths out of the particles, but the fine particles produce greater flow resistance to the eluant during the elution of the ^{82}Rb from the generator.

[037] Therefore, the ^{82}Rb generator preferably includes smaller particles of sodium nonatitanate because the shorter diffusion path allows the particles to equilibrate with the eluant more quickly and because the smaller particles pack more densely into a column of a given size. Both of these factors together promote the elution of ^{82}Rb using a small volume of saline solution as the eluant and obtaining a high concentration of ^{82}Rb in the eluate. Preferably, the particles of sodium nonatitanate are made as small as possible without causing excessive back pressure from the flow of the eluant through the column. Preferably, the size of the particles used in the ^{82}Rb generator range between about 50 μm and about 200 μm. More preferably, the particle size of

the sodium nonatitanate is between about 75 and about 150 μm and most preferably between about 75 and about 100 μm.

[038] Low porosity is a preferred characteristic of the sodium nonatitanate particles for use in the ^{82}Rb generator of the present invention. If the particles are highly porous, much of the parent ^{82}Sr deposits within the pores, which creates a longer diffusion path for the ^{82}Rb to diffuse from the pores into the saline eluant. The ^{82}Rb generated from the ^{82}Sr deposited deep within a pore continues to decay while diffusing from the pore into the eluant stream, which results in a loss of the generated ^{82}Rb and thereby, a lower ^{82}Rb yield.

[039] The column aspect ratio is a factor that contributes to the optimum operation of the ^{82}Rb generator of the present invention. The aspect ratio of a column is the column length over the column diameter. Increasing column length at constant diameter provides for greater retention of ^{82}Sr and thereby minimizes the amount of leached ^{82}Sr in the final eluate product. However, as the column length increases, total pressure drop through the column increases, causing higher back pressure at the inlet to the column. The column aspect ratio affects the properties of the ^{82}Rb generator even at constant column volume and sodium nonatitanate mass.

[040] A long, narrow column having a high aspect ratio offers greater resistance to the flow of the eluant and generates a higher backpressure at the inlet to the column. Because the velocity of a given volume of eluant is higher in a column having a high aspect ratio, the flow through the column having a high aspect ratio is more turbulent, which increases mixing within the eluant stream. Comparatively, a short, wide column having a low aspect ratio operates with a lower velocity of a given volume of eluant through the column and operates at lower pressure drop with less mixing. However, channeling through the bed can occur at low velocities resulting in the eluant bypassing some of the ion exchange material and providing a lower yield. While a wide range of column aspect ratios are acceptable, preferably, without limitation, the aspect ratio may be between about 4 and 50, more preferably between about 6 and about 20.

[041] Preferably, the column or other elutable container is not loaded with uniform material over its entire length. The portion of the column closest to the generator outlet preferably holds sodium nonatitanate containing no ^{82}Sr, serving as a guard bed to intercept any ^{82}Sr or ^{85}Sr released from the generator. By intercepting and capturing any released ^{82}Sr and ^{85}Sr, the product eluant is safe for use as an ^{82}Rb tracer. The guard bed may be formed with sodium nonatitanate that was produced without the neutralization step so that the affinity to capture strontium is at its highest level and the affinity to capture rubidium is at its lowest level.

Optionally, the guard bed may be placed in a second separate container, receiving the eluate from the outlet of the generator, to filter any strontium from the eluant eluted from the ^{82}Rb generator. Alternatively, a guard bed may be installed in the generator as described above coupled with a separate filter containing sodium nonatitanate as an added precaution.

[042] Optionally, the sodium nonatitanate may be supported on the surface of a non-porous support. Placing the sodium nonatitanate in a thin layer on a non-porous support provides the advantage of placing all of the sodium nonatitanate in close contact with the eluant, thereby minimizing the length of the diffusion path of the ^{82}Rb from the nonatitanate to the eluant. Suitable non-porous support materials include inorganic materials that are not damaged in a high radiation field, such as fiberglass, fine glass beads, ceramics, and other similar materials known to those skilled in the art. It is critical that any material chosen for this function does not release anything into the eluate that could contaminate the product.

[043] The examples that follow disclose the methods and materials for the ^{82}Rb generator. Examples 12-18 further disclose the nonatitanate neutralized to a lower pH for providing an eluate having a pH within the desired range.

EXAMPLES

[044] These Examples investigated the suitability of sodium nonatitanate for the use in separating ^{82}Sr from irradiated targets and in the construction of an ^{82}Sr/^{82}Rb generator. Initial batch experiments compared the rubidium and strontium selectivities of a number of different sodium nonatitanate samples with commercially available ion exchange materials (*e.g.*, AW 500, Chelex 100) and some experimental materials that had also exhibited high strontium selectivities (*e.g.*, sodium titanosilicate). Column experiments were then performed using target simulants and generator simulants on materials that exhibited favorable selectivity characteristics. Some work was also performed to investigate the likely interference from other isotopes present in irradiated targets on the production of ^{82}Sr.

Example **1** - Preparation of Sodium Nonatitanate

[045] Sodium nonatitanate (NaTi) was synthesized hydrothermally as follows. 77.5 g of titanium isopropoxide was added to 84.35 g of a 50 wt% solution of NaOH with vigorous stirring and 60 mL of deionized water was added. The resultant gel was heated at approximately 108 °C

for 3 hours, transferred to a hydrothermal pressure vessel with an additional 90 mL of deionized water, and heated at either 170 °C or 200 °C for times ranging from 21 hours to 1 week. After the allotted time, the materials were filtered, washed with ethanol to remove residual base and dried at 60 °C. The mass of sodium nonatitanate produced was approximately 31 g. Each sample was characterized using x-ray powder diffraction (XRD). The reaction is outlined in Equation 1.

$$9\ Ti(OC_3H_7)_4 + 4\ NaOH(aq) \rightarrow Na_4Ti_9O_{20}xH_2O + 9\ C_3H_7OH \qquad (1)$$

[046] The crystallinity of the material was shown to be dependent upon the reaction time and temperature, with the most crystalline materials being produced after 1 week of hydrothermal treatment (200 °C for 7 days). Samples that received no hydrothermal treatment, or only a few days, were virtually amorphous with only a few very broad reflections visible on the XRD pattern.

[047] The theoretical cation exchange capacity (CEC) of sodium nonatitanate is quite high and has a value of 4.74 meq/g, which compares favorably with organic ion exchange resins.

[048] Alternative titanium salts that could be used to manufacture sodium nonatitanate include titanium tetrachloride, $TiCl_4$, and titanium sulfate, $TiOSO_4.xH_2SO_4.yH_2O$. However, hydrolysis of these salts leads to the generation of hydrochloric acid and sulfuric acid, respectively, and thus additional base is required to neutralize the acids during the hydrothermal process. The final product also needed to be exhaustively washed to remove residual sodium chloride or sodium sulfate. Consequently, titanium isopropoxide (which hydrolyzes to form propanol) or titanium dioxide TiO_2 is the preferred starting material because the final product is free from additional sodium salts.

Example **2** - Determination of Strontium Selectivity

[049] Sodium nonatitanate and a variety of other ion exchange materials were obtained and evaluated for use in the separation of ^{82}Sr from targets and in a ^{82}Rb generator. These materials are described below in Table **1**.

Table 1 - Characteristics of Ion Exchange Materials Evaluated in this Study

Material	Source	Sample Preparation
Na-Clinoptilolite	GSA Resources, AZ	Ground to powder.
AW500	Aldrich (1.6 mm Pellets)	Ground to powder
Hydrous SnO_2	Synthesized in house	NaOH + $SnCl_4$. Washed with acetic acid/sodium acetate buffer
K+ Pharmacosiderite ($K_3H(TiO)_4(SiO_4)_3.4H_2O$)	Synthesized according to literature method	None. Used as synthesized
Sodium Titanosilicate ($Na_2Ti_2O_3SiO_4.2H_2O$)	Synthesized according to literature method	None. Used as synthesized
AG 50W-X8 (Na+) (25 - 50 Mesh)	BioRad. Strong acid ion exchange resin.	Converted to Na+ form (for alkaline solutions only)
Chelex 100 (Na+) (50 - 100 Mesh)	BioRad. Chelating resin with iminodiacetic acid functionality	None. Used as received
Sodium Nonatitanate	Honeywell, IL	None. Used as received
Hydrous SiO_2	Synthesized in house	Acetic acid hydrolysis of tetraethyl orthosilicate. Washed with H_2O
Hydrous TiO_2	Synthesized in house	Hydrolysis of titanium isopropoxide. Washed with H_2O
Hydrous ZrO_2	Synthesized in house	$ZrOCl_2$ + NaOH. Washed with deionized water

[050] The strontium selectivity of the ion exchange materials of Table 1 was evaluated in sodium chloride and rubidium chloride solutions using radiotracer techniques. Samples were evaluated using a simple batch technique to allow the rapid screening of a large number of materials over a range of ionic strengths. Blanks were run for each matrix to check for any loss of strontium during filtration or absorption of strontium onto the scintillation vials. In all solutions evaluated, strontium absorption was negligible.

[051] 0.05 g of each of the ion exchange materials was contacted with 10 mL of a solution, spiked with ^{89}Sr, in a capped scintillation vial. (The total strontium content was approximately 1.6 ppm, thus preventing any loss of strontium in solution due to precipitation of sparingly soluble $Sr(OH)_2$ at alkaline pH values.) The mixtures were shaken for 6 hours, filtered through a 0.2 μm syringe filter and the residual activity determined using liquid scintillation counting (LSC). Distribution Coefficients (K_d values) were then determined according to Equation 2:

$$K_d = (A_i - A_f) / A_f * V/m \qquad (2)$$

where: A_i = initial activity in solution (counts per minute (cpm)/mL)

A_f = final activity in solution (cpm/mL)

V = volume of solution (mL)

m = mass of exchanger (g)

[052] The final pH of the solution was also noted. The period of 6 hours was chosen to allow equilibrium to be reached for each of the ion exchange materials. However, previous work on the titanosilicates and titanates had shown the reaction rates to be rapid with the majority of the uptake occurring in only a few minutes. The concentration of the chloride solutions was varied from 1M to 0.001M to evaluate the effect of increasing Rb^+ and Na^+ concentrations on the uptake of Sr^{2+}. All experiments were performed in duplicate, and if significant variations between duplicate samples occurred, the experiments were repeated until good agreements on the K_d values were obtained. The results are shown in Tables 2 and 3 and represented the average K_d obtained, quoted to 3 significant figures.

Table **2** - Strontium Selectivity Data from Unbuffered Sodium Chloride Solutions

Ion Exchange Material	**K_d mL/g**			
	1M NaCl	**0.1M NaCl**	**0.01M NaCl**	**0.001M NaCl**
Na-Clinoptilolite	8	124	3,260	36,900
AW500	1,860	88,300	1,270,000	1,210,000
Hydrous SnO_2	767	43,000	124,000	51,800
K+ Pharmacosiderite	18,300	251,000	594,000	281,000
Sodium Titanosilicate	556,000	273,000	119,000	42,900
AG 50W (Na+)	32	3,380	365,000	2,510,000
Chelex 100 (Na+)	610	26,400	726,000	1,300,000
NaTi (Honeywell)	80,600	1,030,000	258,000	166,000
NaTi (No hydrothermal)	1,530,000	2,570,000	739,000	372,000
NaTi (170°C, 21hr)	1,030,000	1,240,000	272,000	172,000
NaTi (170°C, 3d)	959,000	633,000	218,000	93,100
NaTi (170°C, 7d)	167,000	834,000	264,000	90,400
NaTi (200°C, 21hr)	439,000	1,390,000	197,000	120,000
NaTi (200°C, 3 d)	261,000	898,000	251,000	158,000
NaTi (200°C, 7d)	195,000	955,000	265,000	214,000
ZrO_2	3,360	52,200	213,000	232,000

Table 3 - Strontium Selectivity Data from Unbuffered Rubidium Chloride Solutions

Material	K_d mL/g 1M RbCl	0.1M RbCl	0.01M RbCl	0.001M RbCl
Na-Clinoptilolite	19	3	88	11,000
AW500	9,750	107,000	1,020,000	1,280,000
Hydrous SnO_2	766	66,100	104,000	51,800
K+ Pharmacosiderite	1,950	40,800	419,000	427,000
Sodium Titanosilicate	12,600	94,700	164,000	179,000
AG-50W (Na+)	44	3,870	237,000	800,000
Chelex 100 (Na+)	1,580	38,400	555,000	977,000
NaTi (Honeywell)	13,900	108,000	279,000	324,000
NaTi (No hydrothermal)	14,220	116,000	345,000	429,000
NaTi (170°C, 21hr)	10,500	71,700	193,000	205,000
NaTi (170°C, 3d)	15,100	39,500	68,000	95,200
NaTi (170°C, 7d)	23,000	55,800	31,200	110,000
NaTi (200°C, 21hr)	11,000	66,400	110,000	103,000
NaTi (200°C, 3 d)	10,600	56,800	146,000	158,000
NaTi (200°C, 7d)	10,500	57,400	146,000	158,000
ZrO_2	3,000	42,400	184,000	221,000

[053] Comparing the selectivity data from sodium and rubidium solutions, it is evident that rubidium ions cause a reduction in affinity for the strontium ion for all of the exchangers indicating that the affinity of these materials for rubidium is significantly higher than the affinity for sodium ions. The pH of the final solutions was generally alkaline for the nonatitanates (NaTi) and titanosilicates, with pH values as high as 12 being measured. This was due to hydrolysis of the exchangers resulting in the absorption of protons and the release of sodium ions, thus increasing the pH of the aqueous phase. This effect can be overcome, if desired, by buffering the solution.

[054] The most distinct trend was observed in 1M NaCl solutions for the sodium nonatitanate samples. The highest K_d was observed for the non-hydrothermal material and the K_d values decreased with increasing reaction time for both the 200 °C and 170 °C materials. Clearly, strontium uptake is facilitated by having a low-crystallinity material. This suggests that as the crystallinity increases and the size of the nonatitanate crystallites also increases, it becomes thermodynamically less favorable for exchange of the sodium ions by strontium. It is also interesting to note that the majority of the sodium nonatitanates exhibit a higher selectivity for strontium in 1M NaCl than in 0.001M NaCl. This indicates that the higher ionic strength facilitates the Na^+/Sr^{2+} exchange reaction and more than compensates for the increased competition for the ion exchange sites from the additional Na^+ ions.

[055] This data shows that sodium nonatitanate is an ideal material for the recovery of ^{82}Sr from irradiated rubidium and rubidium chloride targets and in the manufacture of a ^{82}Rb generator.

Example 3 - Rubidium Selectivity from NaCl Solutions

[056] For an ion exchange material to be suitable for use in a ^{82}Rb generator, it must have a very high selectivity for strontium to prevent any loss of ^{82}Sr from the ion exchange column and release to the patient undergoing a PET scan. This property was clearly demonstrated in Example 2. It must also have a very low selectivity towards rubidium, thus allowing ^{82}Rb to be released into solution as saline is passed through the ^{82}Rb generator. Consequently, the rubidium selectivity of the ion exchange materials was evaluated in sodium chloride media following the procedure described in Example 2. The same procedure was followed using ^{86}Rb to spike the solutions to give an activity of approximately 200,000 cpm/mL. Total rubidium in solution was < 0.05 ppm. The distribution coefficients of the materials are shown below in Table 4.

Table 4 - Rubidium Selectivity Data from Unbuffered Sodium Chloride Solutions

Ion Exchange Material	1M NaCl	0.1M NaCl	0.01M NaCl	0.001M NaCl
AW500	116	620	4920	21900
Hydrous SnO_2	1	6	36	290
K+ Pharmacosiderite	148	475	2030	4020
Sodium Titanosilicate	8,010	194,000	114000	75800
AG 50W (Na+)	7	75	688	6680
Chelex 100 (Na+)	3	8	43	256
NaTi (Honeywell)	9	102	488	817
NaTi (No hydrothermal)	4	59	280	446
NaTi (170°C, 21hr)	9	56	209	297
NaTi (170$_o$C, 3d)	7	46	198	311
NaTi (170°C, 7d)	3	15	47	71
NaTi (200°C, 21hr)	8	79	334	502
NaTi (200°C, 3d)	8	52	207	307
NaTi (200°C, 7d)	4	25	111	178
ZrO_2	1	12	60	154

Table **4A** - Strontium-Rubidium Separation Factor

Ion Exchange Material	1M NaCl	0.1M NaCl	0.01M NaCl	0.001M NaCl
AW500	16.0	142	258	55.3
Hydrous SnO2	767	7,167	3,444	179
K+ Pharmacosiderite	124	528	293	69.9
Sodium Titanosilicate	69.4	1.41	1.04	0.57
AG 50W (Na+)	4.57	45.1	531	376
Chelex 100 (Na+)	203	3,300	16,884	5,078
NaTi (Honeywell)	8,956	10,098	529	203
NaTi (No hydrothermal)	382,500	43,559	2,639	834
NaTi (170 C, 21hr)	114,444	22,143	1,301	579
NaTi (170 C, 3d)	137,000	1,370	1,101	299
NaTi (170 C, 7d)	55,667	55,600	5,617	1,273
NaTi (200 C, 21hr)	54,875	17,595	590	239
NaTi (200 C, 3d)	32,625	17,269	1,213	515
NaTi (200 C, 7d)	48,750	38,200	2,387	1,202
ZrO2	3,360	4,350	3,550	1,506

Table **4B** - Percent Rubidium Retention Generated on 0.1 g of Exchanger in NaCl Solution

Ion Exchange Material	1M NaCl	0.1M NaCl	0.01M NaCl	0.001M NaCl
AW500	18.8	55.4	90.8	97.8
Hydrous SnO2	0.2	1.2	6.7	36.7
K+ Pharmacosiderite	22.8	48.7	80.2	88.9
Sodium Titanosilicate	94.1	99.7	99.6	99.3
AG 50W (Na+)	1.4	13.0	57.9	93.0
Chelex 100 (Na+)	0.6	1.6	7.9	33.9
NaTi (Honeywell)	1.8	16.9	49.4	62.0
NaTi (No hydrothermal)	0.8	10.6	35.9	47.1
NaTi (170 C, 21hr)	1.8	10.1	29.5	37.3
NaTi (170 C, 3d)	1.4	8.4	28.4	38.3
NaTi (170 C, 7d)	0.6	2.9	8.6	12.4
NaTi (200 C, 21hr)	1.6	13.6	40.0	50.1
NaTi (200 C, 3d)	1.6	9.4	29.3	38.0
NaTi (200 C, 7d)	0.8	4.8	18.2	26.3
ZrO2	0.2	2.3	10.7	23.5

[057] From the data in Table **4**, it is clear that the all of the sodium nonatitanate materials have a very low affinity for rubidium, particularly in the presence of relatively high amounts of sodium ions. In general, the rubidium selectivity decreased with increasing reaction time for both series of nonatitanates (170 °C and 200 °C) with the lowest affinity being demonstrated by the sample that was heated hydrothermally at 170 °C for 1 week. Uptake was negligible in 1M NaCl and the very low reduction in activity that was noted could be accounted for by absorption of rubidium during filtration and by pipetting errors during the counting procedure. Consequently, samples with K_d values that were below 10 mL/g can be considered to

have no affinity at all for ^{86}Rb. Some rubidium uptake was evident in very dilute sodium solutions, but the K_d values were low for all of the titanate samples. This suggests that the uptake of rubidium was more likely due to the materials having an exceptionally low affinity for sodium rather than any real affinity for rubidium. All of the sodium nonatitanate materials performed better than the commercially available sample obtained from Honeywell, Inc. The materials are clearly ideal for use in a ^{82}Rb generator.

[058] Hydrous tin dioxide exhibited some of the lowest rubidium affinities and was comparable with Chelex 100, the best of the nonatitanates and the hydrous zirconium dioxide. However, hydrous tin dioxide exhibited much lower strontium K_d values than the nonatitanates. Therefore, nonatitanate materials are preferred because they have higher strontium/rubidium separation factors. Hydrous tin dioxide also has a limited pH stability range and significant dissolution and release of absorbed strontium is likely to occur should any significant pH perturbations occur outside the range of pH 4 to pH 9. Radiation stability of hydrous tin dioxide is also limited, with particle breakdown causing current ^{82}Rb generators to be replaced before decay has reduced the ^{82}Rb below useable levels.

[059] The rubidium selectivity data also indicates that AW500, potassium Pharmacosiderite and the sodium titanosilicate have a strong affinity for rubidium in a range of saline solutions. Consequently, these materials will be unsuitable for use in a 82Rb generator and have only limited applications in the processing of irradiated target materials.

Example 4 - Strontium and Rubidium Selectivity in 0.1M Sodium Acetate/Acetic Acid Buffer

[060] In order to prevent hydrolysis reactions from raising the pH as described above, some strontium and rubidium selectivity experiments were performed in a 0.1M sodium acetate / acetic acid buffer solution. In these tests, the final pH remained between 5.2 and 6.3, which is a more clinically acceptable pH for an ^{82}Rb infusion. Rubidium K_d values remained low, as expected, following the trend observed in Table 5. Strontium K_d values were considerably lower, with a maximum K_d value of 80,000 mL/g being obtained for the sodium nonatitanate sample that was heated hydrothermally at 170 °C for 21 hours. This is considerably lower than the K_d value of over 1,200,000 mL/g that was obtained in unbuffered 0.1M NaCl (pH ~ 12). The K_d values obtained for the other ion exchange materials were also considerably lower. However, the Sr/Rb separation factors remained high and the sodium nonatitanates still outperformed hydrous

tin dioxide and the organic ion exchange resins. The affinity of sodium nonatitanate for strontium is greatest at higher pH values.

Example **5** - Molybdenum Targets

[061] The basic steps of a proposed process to obtain ^{82}Sr from irradiated molybdenum targets are as follows:

1. Dissolve the irradiated molybdenum target in 30% hydrogen peroxide, ensuring excess hydrogen peroxide is destroyed.

2. Add sodium hydroxide to bring the pH to approximately 12.

3. Filter the solution to remove any precipitate. It is predicted that the majority of ^{88}Zr and ^{59}Fe will be found in the precipitate, and experiments have confirmed that 99% or more of the ^{88}Y precipitated out of solution on the addition of NaOH.

4. Pass the solution through a column of sodium nonatitanate and wash the column with two bed volumes of 0.1M NaCl, adjusted to pH 12 with NaOH. ^{82}Sr and ^{85}Sr will be absorbed. ^{82}Rb and other Rb isotopes will remain in the aqueous phase. Molybdate anions will also pass through the column.

5. The column can then be stripped using dilute mineral acid to recover the ^{82}Sr and the sodium nonatitanate reused or discarded.

[062] There is a range of other isotopes present in addition to ^{82}Sr, including ^{75}Se, ^{73}As, ^{74}As, ^{7}Be, ^{68}Ge, ^{48}V, ^{60}Co (and other Co isotopes), ^{54}Mn, ^{51}Cr and ^{95m}Tc. In the alkaline target solution, Se, As, V, Ge, Cr, Mn and Tc are expected to be present as anions and thus will not be absorbed onto the sodium nonatitanate. Significant amounts of Co would be expected to precipitate when the target solution is neutralized, and thus little is expected to be available under alkaline conditions to absorb onto the sodium nonatitanate. The most likely isotope to be absorbed is beryllium, because it is a Group II metal with a similar aqueous chemistry to strontium. However, the affinity of sodium nonatitanate for Group II metals decreases in the order Sr > Ca > Mg. No data is available for beryllium, but if the trend continues, the affinity would be expected to be low. Thus, any absorbed ^{7}Be would be readily removed by an alkaline sodium chloride (or similar) wash.

[063] The current process for recovering ^{82}Sr from irradiated rubidium metal and rubidium chloride targets requires minimal modification to facilitate the use of sodium nonatitanate. Both targets are processed following standard processing procedures to generate

rubidium chloride solutions in an ammonia/ammonium chloride buffer solution. These solutions are then passed through a sodium nonatitanate column and washed with additional buffer to remove any weakly held rubidium cations. Strontium and possibly some other cationic species present will be absorbed onto the nonatitanate column, whereas rubidium cations, ammonium cations and anions will rapidly pass through the column. If additional cations are absorbed onto the sodium nonatitanate, they can be selectively removed by washing with an appropriate eluant (*e.g.*, citrate, nitrilotriacetate.) The strontium selectivity of sodium nonatitanate has been shown to be unaffected by a number of common complexants and as a consequence, it should be a relatively simple manner to elute any undesirable cations from the column, leaving pure $^{82/85}Sr$.

[064] FIG. **1** clearly shows the exceptionally high affinity of the sodium nonatitanate materials in comparison with the currently utilized organic resin Chelex 100. All of the sodium nonatitanates performed equally well in the buffered rubidium target solutions indicating that the synthetic conditions are not too important when the material is being used in solutions containing high concentrations of rubidium ions. Thus, by replacing the Chelex 100 with sodium nonatitanate, a more efficient ^{82}Sr isolation can be achieved.

[065] It has also been shown that it is possible to tailor the selectivity of the sodium nonatitanate to achieve the optimum Sr/Rb separation by manipulating the reaction conditions. The differing selectivities were most obvious in sodium solutions, with the less crystalline materials exhibiting the highest strontium distribution coefficients. However, the series of nonatitanates showed little difference in behavior when the predominant cation in solution was Rb^+. The materials synthesized clearly demonstrated superior characteristics to the commercially available sample in almost all matrices evaluated. The majority of the sodium nonatitanate samples also exhibited greater strontium selectivities than hydrous tin dioxide in a range of sodium chloride solutions, from 1M to 0.001M. Rubidium selectivities were low, making the sodium nonatitanate ideal as a replacement for hydrous tin dioxide in a ^{82}Rb generator.

[066] Commercially, one method of ^{82}Sr production is *via* the proton spallation reaction with natural molybdenum metal targets. A simulated molybdate target solution was prepared as follows: 12.5 g of molybdenum powder was carefully dissolved in 30% H_2O_2 solution and made up to a total volume of 500 mL to produce a clear yellow solution of molybdic acid, H_2MoO_4. Solid sodium hydroxide granules totaling 10.9 g were then carefully added to neutralize the solution and bring the pH to approximately 12.3. The colorless solution was then filtered to remove any precipitate. This alkaline molybdate solution was spiked with either ^{86}Rb or ^{89}Sr and

K_d values determined as described previously. Separation factors for the strontium/rubidium selectivity were also calculated by dividing the strontium K_d by the rubidium K_d, thus allowing the relative affinities of the ion exchange materials to be directly compared. The results are illustrated below in Table 5.

Table 5 - Strontium and Rubidium Absorption from Simulated Molybdate Target Solutions

Material	Sr Kd, mL/g	Rb Kd, mL/g	Separation Factor
AW500	7,070	194	36.4
K+ Pharmacosiderite	187,000	142	1320
Sodium Titanosilicate	547,000	6500	84.2
Chelex 100 (Na+)	3,120	5	624
AG 50W-X8 (Na+)	69	18	3.83
NaTi (Honeywell)	337,000	27	12,500
NaTi (No hydrothermal)	1,690,000	12	141,000
NaTi (170°C, 21hr)	1,000,000	12	83,300
NaTi (170°C, 3d)	829,000	14	59,200
NaTi (170°C, 7d)	324,000	3	108,000
NaTi (200°C, 21hr)	954,000	12	79,500
NaTi (200°C, 3 d)	687,000	11	62,500
NaTi (200°C, 7d)	772,000	9	85,800
ZrO_2	168,000	8	21,000

[067] From this data, it is clear that the sodium nonatitanate materials are far superior to Chelex 100 and AG 50W-X8 ion exchange resins for the recovery of ^{82}Sr from irradiated molybdenum targets. High K_d values in excess of 500,000 mL/g indicate that almost 100% strontium removal was achieved by some of the nonatitanate samples, with the residual strontium in solution approaching background levels. In the alkaline conditions used in this test, the Chelex 100 resin had the lowest affinity for strontium of all of the materials evaluated. The selectivity of the sodium nonatitanate for rubidium was lowest for the sodium nonatitanate material that was prepared by heating for 1 week at 170 °C to obtain a relatively crystalline product. However, strontium selectivity also decreased with increasing reaction time.

[068] The best overall strontium/rubidium separation factor was obtained for the material that had not undergone any hydrothermal treatment. All of the materials performed better than the commercially available nonatitanate materials. Thus, it is possible to alter the selectivity of the material by controlling the reaction conditions to produce an improved sodium nonatitanate material for use in ^{82}Sr separations. Rubidium selectivities were very low for all of

the nonatitanates, indicating minimal rubidium absorption would occur in a column process and that any rubidium absorbed would be readily removed by a dilute saline wash.

[069] The sodium titanosilicate, potassium Pharmacosiderite and AW500 exhibit selectivities for rubidium that are too high to allow their use in the selective removal of ^{82}Sr from irradiated molybdenum targets. This high selectivity would result in some rubidium being retained on the column that would not be readily removed by a simple saline wash, thus leading to contamination of the ^{82}Sr product with both radioactive and stable rubidium isotopes. Hydrous tin oxide was not evaluated because, due to the amphoteric nature of tin, significant dissolution would be expected at a pH in excess of 12.

Example **6** - Acid Molybdate Target Solutions

[070] Sodium nonatitanate has a relatively low affinity for strontium at pH values less than 6, and was not expected to exhibit any affinity for strontium from the acidic molybdate target solutions prior to the addition of sodium hydroxide. K_d values were determined to confirm this and to compare it with the K_d values for both Chelex 100 and AG 50W-X8 under identical conditions. The data obtained is shown below in Table **6**.

Table **6** - Affinity of Selected Ion Exchange Materials for Strontium in Acidic Molybdate Target Solutions

Ion Exchange Material	**Sr K_d mL/g**	**Final pH of Solution**
Chelex 100	25	1.43
AG 50W-X8	18,300	1.42
Sodium Nonatitanate (Honeywell)	1,260	1.53

[071] These data clearly indicate that for the processing of acid molybdate solutions, the strong acid ion exchange resin AG 50W-X8 is the preferred medium. However, the Sr K_d value of 18,300 mL/g in the acidic media is nearly two orders of magnitude lower than the K_d value of 1,690,000 mL/g that was obtained for the best of the sodium nonatitanate materials in alkaline molybdate solutions. Consequently, it is evident that ^{82}Sr can be recovered more effectively from alkaline solution using sodium nonatitanate than is currently achieved using AG 50W-X8 from acidic media.

Example 7 - Rubidium and Rubidium Chloride Target Solutions

[072] The processing of either rubidium chloride or rubidium metal targets follows a similar procedure once the target has been successfully dissolved. In essence, ^{82}Sr needs to be selectively extracted from a solution of RbCl in a 0.1 M NH_3 / 0.1M NH_4Cl buffer adjusted to a pH of between 9 and 10. Batch experiments were performed in simulated buffer solutions to determine the strontium selectivity in the presence of high concentrations of rubidium ions. Only the ion exchange materials that exhibited high strontium selectivities in the initial scoping studies with NaCl solutions were evaluated. K_d values were obtained as described previously. Two rubidium chloride solutions were selected which represent typical rubidium concentrations obtained during the processing of rubidium metal (1.95 M Rb^+) and rubidium chloride targets (0.68 M Rb^+). In both cases, Chelex 100 is used in the preliminary step to remove the ^{82}Sr from the buffered rubidium solutions. The K_d values for the ion exchange materials are shown in FIG. 1.

[073] In the buffered rubidium solutions, there is little difference between the different nonatitanates evaluated. This is in stark contrast to the sodium molybdate solutions where a large variation in the performance of the titanates was observed. The nonatitanates were clearly the most effective materials at removing strontium from the buffered solutions with strontium K_d values of around 15,000 mL/g in 0.68 M Rb^+ solutions and approximately 5,000 mL/g in 1.96 M Rb^+ solutions. By contrast, Chelex 100 ion exchange resin gave K_d values of less than 1,000 mL/g in both solutions. Hydrous titanium oxide and hydrous tin oxide also exhibited appreciable K_d values, but they performed less efficiently than the nonatitanates in both solutions. Consequently, this data demonstrates that using sodium nonatitanate in place of Chelex 100 ion exchange resin will greatly increase the amount of strontium extracted from the target solutions.

[074] The ion exchange materials were also evaluated for their rubidium selectivity from 0.1 M NH_3 / 0.1M NH_4Cl buffer solution. The buffer was prepared, spiked with ^{86}Rb and the pH adjusted to approximately 9.25 with concentrated ammonia. ^{86}Rb K_d values were then determined following the method described earlier. All of the sodium nonatitanates had a K_d < 20 mL/g. The very low rubidium selectivity in the pure buffer is almost certainly due to competition from NH_4^+ ions for the available ion exchange sites. Consequently, absorption of rubidium during the processing of rubidium and rubidium chloride targets will be minimal, and any rubidium absorbed will be readily removed by washing with additional 0.1 M NH_3 / 0.1M

NH_4Cl buffer solution. Thus, a clean separation of ^{82}Sr from these targets can be obtained using sodium nonatitanate.

[075] The performance could also be improved by removing the buffer and increasing the pH to improve the amounts of strontium absorbed. (Buffers were initially utilized to maximize the performance of the organic ion exchange resins currently used and are not essential to the ^{82}Sr recovery process.)

Example **8** - Kinetic Experiments

[076] In order for the sodium nonatitanate materials to find applications in the processing of irradiated target solutions, they must exhibit fast ion exchange kinetics allowing solutions to be passed through an ion exchange column at an acceptable rate. The kinetics of strontium absorption from alkaline molybdate target solutions was evaluated using a simple batch procedure. Ion exchange material, in the amount of 0.05 g, was shaken with 10 mL of molybdate solution spiked with ^{89}Sr to give a total activity of approximately 155,000 cpm/mL. After an allotted time, the material was filtered through a 0.2 m syringe filter and the activity in the aqueous phase determined by LSC. The results are shown below in FIG. **2**.

[077] From the data in FIG. **2**, it is clear that the reaction kinetics for the sodium nonatitanate powder is extremely rapid, with over 99 % of the ^{89}Sr removed in only 1 minute. By contrast, the reaction kinetics of the organic ion exchange resins was much slower and the total amount of ^{89}Sr removed after 1 hour was much less.

[078] The exceedingly rapid kinetics can partly be explained by the fact that the nonatitanate was in the form of a fine powder, whereas the two resins were in the form of beads (see Table 1). As a consequence, a relatively slow reaction rate would be expected for the beads because the uptake of ^{82}Sr will be dependent upon the rate of diffusion of the ^{82}Sr to the internal exchange sites. The rate of uptake of a sample of sodium nonatitanate pellets (using hydrous titanium dioxide as a binder) was significantly slower than the powdered form, but the kinetics and amount of ^{82}Sr absorbed was still significantly better than for either of the two organic resins. As the pelletization process is improved, it is expected that the kinetics and selectivity of the pelletized sodium nonatitanate will improve substantially. Other sodium nonatitanate powders of varying crystallinities also showed rapid kinetics. Other potentially suitable binders for forming suitable pellets include titanium isopropoxide or tetraethyl orthosilicate (TEOS) as a binder precursor.

Example **9** - ^{82}Sr Removal from Irradiated Targets Using Pelletized Sodium Nonatitanate

[079] A sample of sodium nonatitanate was mixed with titanium isopropoxide as a binder and the resulting paste dried at 105 °C for 12 hours. The material was gently broken up using a mortar and pestle and then sieved to produce particles in the range 40 to 60 mesh. The binder content was approximately 20%. These particles were then used to assess the extraction of ^{89}Sr from simulated target solutions.

[080] 1 mL of pelletized sodium nonatitanate was slurried into a column and the target simulant that had been spiked with ^{89}Sr to give an activity of approximately 200,000 cpm/mL was passed through the column at a flow rate of 15 mL per hour. The amount of activity removed from solution was then determined. The results are given below in Table 7.

Table **7** - Removal of ^{89}Sr from Irradiated Target Solutions

Target	Solution Composition	Volume (mL)	^{89}Sr Removed (%)
Rubidium Metal	1.95M RbCl in 0.1M NH_3/NH_4Cl Buffer, pH10	20	97.3
Rubidium Chloride	0.68M RbCl in 0.1M NH_3/NH_4Cl Buffer, pH 10	28	98.8
Molybdenum Metal	0.26M Na_2MoO_4, pH 12	20	99.9

[081] This data clearly shows the effectiveness of sodium nonatitanate for removing strontium isotopes from ^{82}Sr target materials. Rubidium absorption under these conditions is minimal.

Example **10** - Elution of Strontium

[082] Strontium was quantitatively eluted from the sodium nonatitanate column of Example **9** using 6M nitric acid. Hydrochloric acid was found to be much less effective and also resulted in breakdown of the sodium nonatitanate particles and blocked the ion exchange column.

Example **11** – Formation of Acid Washed Sodium Nonatitanate Pellets

[083] As described in Example **1**, sodium nonatitanate (NaTi) was synthesized hydrothermally as follows. 77.5 g of titanium isopropoxide was added to 84.35 g of a 50 wt. % solution of NaOH with vigorous stirring and 60 mL of deionized water was added. The resultant gel was heated at approximately 108 °C for 3 hours, transferred to a hydrothermal pressure vessel

with an additional 90 mL of deionized water, and heated at either 170 °C or 200 °C for times ranging from 21 hours to 1 week.

[084] After the hydrothermal treatment disclosed in Example **1**, the vessel was cooled down and the sodium nonatitanate was transferred into a centrifuge tube and separated from solution by centrifugation (3,300 rpm for 14 minutes). The recovered nonatitanate was washed by resuspending it in 500 mL of deionized water (DIW) by mixing it thoroughly and then again separated by centrifugation. These washing steps were repeated twice.

[085] The pH of deionized water was adjusted to 3 by the addition of HCl. The washed nonatitanate was added to the low pH DIW and mixed thoroughly. The nonatitanate was recovered through centrifugation and dried in a 60 °C oven for two nights. The hard acid washed nonatitanate was then ground, sized and sieved to 50x100 mesh and 100x200 mesh using nylon screens. Fines were washed off and the pellets were dried at 60 °C.

Example **12** – Formation of Neutralized Nonatitanate Pellets

[086] Sodium nonatitanate was prepared by treating it hydrothermally for 21 hours at 200 °C. The white product was washed by suspending it in DIW with stirring. 3 M nitric acid was added dropwise to maintain a pH of 8.0 for one hour. After a final DIW wash, the material was dried overnight at 60 °C. The dried material was sized into particles using a series of nylon sieves, and collecting the 100x200 mesh particles for column use. The sized material was rinsed of fines.

[087] Pellet size is a factor that affects the performance of the 82Sr/82Rb generator column because higher Sr uptake is obtained with finer particles due to the faster sorption with the material having the smaller particle size and resulting greater surface area. FIG. **4** is a graph showing the ^{85}Sr K_d values in normal saline for NaTi samples of various pellet size, without a binder.

Example **13** – Packing Column with Sodium Nonatitanate and Loading with Parent ^{82}Sr

[088] To prepare the generator column, the sodium nonatitanate particles were suspended in saline and slurried into the column. First, 1.125 g of exchanger was introduced into the column and sandwiched between two filters (GB003, Schleicher & Schuell blotting paper). This bed provided a guard bed to trap any strontium that was released from the bed above. Next, about 0.375 g of exchanger was equilibrated with inactive strontium ($SrCl_2$) in saline, to simulate

a full loading of ^{82}Sr. This material was placed on top of the guard bed and topped with a third filter.

Example **14** – Balancing pH by the Addition of Acid

[089] Nonatitanate is prepared as described in Example **12** except that the pH is adjusted to 11 instead of 8.0. The material is equilibrated with ^{82}Sr and loaded into a column having a guard bed as described in Example **13**. The column is eluted with normal (0.9 %) saline with 50 mL/min flow. The resulting solution contains a high yield of ^{82}Rb in 49mL of solution at pH 10. This solution is dosed with 1 mL of 0.05 M HCl, neutralizing the basicity of the saline to yield 50 mL of solution at pH 7, suitable for use as a medical pharmaceutical as previously described.

Example **15** – Supported Sodium Nonatitanate

[090] Fine glass helices of the type commonly used to pack a high efficiency distillation column are dipped in a dilute (5 wt. %) solution of sodium metasilicate. The helices are allowed to drain so only a thin film of solution remains on their surfaces. The helices are then gently rolled in finely powdered (<400 mesh, < 38 μm) sodium nonatitanate to coat the surfaces with the powder. The coated helices are dried and the metasilicate solution is rendered insoluble by heating to 175 °C in air for 16 hours. The helices are now ready for use in a generator.

Example **16** – Pelletization of the Ion Exchanger

[091] After hydrothermal treatment and washing the material was then resuspended in DIW that has had the pH adjusted to 3 with HCl, mixed thoroughly after which the solid and liquid phases were separated as before. The wet exchanger was dried in a 60 °C oven for two nights, the hard product ground, sized and sieved to 50x100 mesh and 100x200 mesh using nylon screens. Fines were washed off and the pellets dried at 60 °C. These pellets were ready for further testing.

Example **17** – Elution at Lower pH

[092] The column packed with NaTi (neutralized to pH 8.0 as described in Example **12**) was eluted using the syringe pump system as shown in FIG. **5**. USP saline (purchased in 1 L bottles from Fisher Scientific), was methodically drawn into a 60 mL syringe and pushed through

the column in 50 mL increments at a flow rate of 50 mL/min. The eluates were collected in 50 mL falcon tubes. A 5 mL sample of each eluate was analyzed for ^{85}Sr activity by gamma spectroscopy (Wallac 1480 Wizard 3) and the pHs recorded. Over 20 L of USP saline were pumped through the column during the experiment with no ^{85}Sr breakthrough observed.

[093] The results are shown in FIGS. **6A-6B**, which show that all of the saline was eluted at pH values acceptable for injection into a human. The neutralized material retains its strong strontium binding ability and no breakthrough of $^{82,85}Sr$ was observed in over 20 L of eluted USP saline (after the initial washout in 200 mL).

[094] Table **8** provides reproducibility and quality control data of final batches of sodium nonatitanate described by the synthesis procedure, sizing of pellets and ^{85}Sr and ^{86}Rb K_d values.

			Sizing of pellets						
ID	Treatment	Synthesis Yield (Dry weight, g)	50-100 mesh (% of total)	100-200 mesh (% of total)	>100 mesh (% of total)	>200 mesh (% of total)	Loss to sizing (% of total)	^{85}Sr Kd in saline/ equilibration pH	^{86}Rb Kd in saline/ equilibration pH
TA-A-78	'Acid wash'	28.3	65.6	23.0	x	9.5	1.98	1,970,632.5 / 9.89	56.6 / 9.89
TA-A-80	'Acid wash'	19.3	47.2	27.5	x	21.6	3.77	**10,603,837.65 / 9.44**	**84.65 / 9.39**
TA-A-83	'Acid wash'	21.4	48.9	21.0	x	25.7	4.48	5,866,141.8 / 9.43	x
TA-A-84 1-12	Neutralized (pH 8)	12.3	x	46.9	x	53.1	0.00	520,951.3 / 6.82	188.6 / 6.87
TA-A-84 3-19	Neutralized (pH 8)	13.0	38.4	x	59.7	x	1.85	1,518,239.55 / 6.72	232.75 / 6.79
TA-A-87 3-30	Neutralized (pH 8)	13.2	60.8	x	34.0	x	5.16	1,120,327.3 / 6.72	232.65 / 6.70
TA-A-87 4-1	Neutralized (pH 8)	12.1	52.9	x	42.2	x	4.88	1,007,944.3 / 6.78	245.3 / 6.78
TA-A-88	'Acid wash'	25.0	49.4	x	43.0	x	7.64	4,656,739.8 / 9.67	71.5 / 9.62

designates materials used for Kd determination
equilibration time of several days for Kd determination

[095] While the foregoing is directed to the preferred embodiment of the present invention, other and further embodiments of the invention may be devised without departing from the basic scope thereof, and the scope thereof is determined by the claims that follow.

CLAIMS

What is claimed is:

1. A rubidium-82 generator, comprising:

a strontium-82 support medium comprising partially neutralized sodium nonatitanate characterized by a strontium/rubidium separation factor greater than 12,500.

2. The rubidium-82 generator of claim 1, wherein the separation factor is determined in an aqueous sodium chloride solution.

3. The rubidium-82 generator of claim 2, wherein the aqueous sodium chloride solution has a sodium chloride concentration from 0.001 molar to 1 molar.

4. The rubidium-82 generator of claim 2, wherein the aqueous sodium chloride solution is buffered to control acidity.

5. The rubidium-82 generator of claim 2, wherein the aqueous sodium chloride solution is unbuffered.

6. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium selectivity greater than about 85,000 mL/g in a 0.1 molar or 1 molar aqueous sodium chloride solution.

7. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium selectivity less than 100 mL/g in a 0.1 molar aqueous sodium chloride solution.

8. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 10,000 in a 1 molar aqueous sodium chloride solution.

9. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium retention of less than 1.8 % in a 1 molar aqueous sodium chloride solution.

10. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium retention of less than about 13.6 % in a 0.1 molar aqueous sodium chloride solution.

11. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium retention of less than about 40 % in a 0.01 molar aqueous sodium chloride solution.

12. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium retention of less than about 50 % in a 0.001 molar aqueous sodium chloride solution.

13. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium selectivity greater than 250,000 mL/g at an alkaline pH.

14. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a rubidium selectivity less than 100 mL/g at an alkaline pH.

15. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 100,000.

16. The rubidium-82 generator of claim 1, further comprising strontium-82 absorbed on the sodium nonatitanate.

17. The rubidium-82 generator of claim 1, further comprising a sodium nonatitanate filter medium disposed to receive effluent from the strontium-82 support medium to trap strontium-82 leached from the generator.

18. The rubidium-82 generator of claim 1, further comprising a column, wherein the sodium nonatitanate is disposed in the column.

19. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 59,200.

20. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 79,500.

21. The rubidium-82 generator of claim 1, wherein the partially neutralized sodium nonatitanate is characterized by raising a pH of a normal saline eluant from about 7 to less than about 8 when eluted from the generator, wherein the generator has eluted less than about 1 L of eluate.

22. The rubidium-82 generator of claim 1, wherein the partially neutralized sodium nonatitanate is characterized by raising a pH of a normal saline eluant from about 6.5 to less than about 7.5 when eluted from the generator, wherein the generator has eluted less than about 1 L of eluate.

23. The rubidium-82 generator of claim 1, further comprising:

means for neutralizing an eluate eluted from the partially neutralized sodium nonatitanate.

24. The rubidium-82 generator of claim 1, wherein the sodium nonatitanate is supported on a surface of a substrate.

25. The rubidium-82 generator of claim 13, wherein the substrate is non-porous.

26. The rubidium-82 generator of claim 14, wherein the substrate is selected from glass, fiberglass, ceramics, fine glass beads or combinations thereof.

27. A rubidium-82 generator, comprising:

a strontium-82 support medium comprising sodium nonatitanate characterized by a strontium/rubidium separation factor greater than 12,500 at an alkaline pH; and

means for neutralizing an eluate eluted from the generator.

28. The rubidium-82 generator of claim 27, wherein the eluate is neutralized to a pH of between about 4.5 and about 7.

29. The rubidium-82 generator of claim 27, wherein the eluate is neutralized to a pH suitable for injection into a patient during a medical procedure.

30. The rubidium-82 generator of claim 27, wherein the means for neutralizing an eluate comprise automatic means.

31. The rubidium-82 generator of claim 27, wherein the separation factor is determined in an aqueous sodium chloride solution.

32. The rubidium-82 generator of claim 31, wherein the aqueous sodium chloride solution has a sodium chloride concentration from 0.001 molar to 1 molar.

33. The rubidium-82 generator of claim 31, wherein the aqueous sodium chloride solution is buffered to control acidity.

34. The rubidium-82 generator of claim 31, wherein the aqueous sodium chloride solution is unbuffered.

35. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characterized by a strontium selectivity greater than about 85,000 mL/g in a 0.1 molar or 1 molar aqueous sodium chloride solution.

36. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characterized by a rubidium selectivity less than 100 mL/g in a 0.1 molar aqueous sodium chloride solution.

37. rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 10,000 in a 1 molar aqueous sodium chloride solution.

38. The rubidium-82 generator of claim27, wherein the sodium nonatitanate is characterized by a rubidium retention of less than 1.8 % in a 1 molar aqueous sodium chloride solution.

39. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characte4rized by a rubidium retention of less than about 13.6 % in a 0.1 molar aqueous sodium chloride solution.

40. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characterized by a rubidium retention of less than about 40 % in a 0.01 molar aqueous sodium chloride solution.

41. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is characterized by a rubidium retention of less than about 50 % in a 0.001 molar aqueous sodium chloride solution.

42. The rubidium-82 generator of claim 27, wherein the sodium nonatitanate is supported on a surface of a substrate.

43. The rubidium-82 generator of claim 42, wherein the substrate is non-porous.

44. The rubidium-82 generator of claim 43, wherein the substrate is selected from glass, fiberglass, ceramics, fine glass beads or combinations thereof.

45. A process for preparing a rubidium-82 generator, comprising:

preparing sodium nonatitanate from titanium isopropoxide and aqueous sodium hydroxide;

heating the sodium nonatitanate at a temperature between 100°C and 250°C for a period between 12 hours and 2 weeks;

lowering the pH of the sodium nonatitanate; and

absorbing strontium-82 on the neutralized sodium nonatitanate from an aqueous solution comprising strontium-82 and a soluble sodium salt.

46. The method of claim 45, wherein the soluble sodium salt concentration is between about 0.1 and about 1 molar.

47. The process of claim 45, wherein the soluble sodium salt is sodium chloride.

48. The process of claim 45, wherein the molar ratio of aqueous sodium hydroxide to titanium isopropoxide is in excess of 0.44.

49. The process of claim 45, wherein the molar ratio of aqueous sodium hydroxide to titanium isopropoxide is between 2 and 6.

50. The process of claim 45, wherein the aqueous sodium hydroxide is about 50 wt% sodium hydroxide.

51. The process of claim 45, further comprising:

filtering the sodium nonatitanate from the solution.

52. The process of claim 51, further comprising:

washing the sodium nonatitanate with ethanol.

53. The process of claim 52, further comprising:
drying the sodium nonatitanate.

54. The process of claim 45, wherein the molar ratio of aqueous sodium hydroxide to titanium isopropoxide is between about 1 and 10.

55. The process of claim 45, wherein the sodium nonatitanate is heated in a pressure vessel.

56. The process of claim 45, wherein the sodium nonatitanate is prepared in the absence of titanium chlorides and sulfates.

57. The process of claim 45, wherein the step of neutralizing the sodium nonatitanate further comprises:
suspending the sodium nonatitanate in a liquid; and
adding an acid to the liquid to lower the pH.

58. The process of claim 57, wherein the step of adding an acid lowers the pH to between about 7 and about 9.

59. The process of claim 57, wherein the step of adding and acid lowers the pH to between about 7 and about 8.3.

60. The process of claim 57, wherein the liquid comprises water.

61. The process of claim 57, wherein the acid is a strong mineral acid.

62. The process of claim 45, further comprising:
loading the sodium nonatitanate into a column.

63. The process of claim 45, further comprising:

supporting the sodium nonatitanate on a non-porous substrate.

64. The process of claim 45, wherein the solution containing strontium-82 is an acidic aqueous solution.

65. A method of chemically isolating strontium-82 from a proton-irradiated molybdenum target, comprising:

(a) dissolving the molybdenum target containing the strontium-82;

(b) adjusting the pH of the dissolved molybdenum target solution to an alkaline pH;

(c) removing precipitates from the solution; and then

(d) absorbing the strontium-82 from the solution onto a support comprising sodium nonatitanate.

66. The method of claim 65, wherein the molybdenum target is dissolved in hydrogen peroxide.

67. The method of claim 65, wherein the pH is adjusted with sodium hydroxide.

68. The method of claim 65, wherein the pH is adjusted to about 12.

69. The method of claim 65, further comprising:

stripping the strontium-82 from the sodium nonatitanate.

70. The method of claim 65, wherein the strontium-82 is stripped from the sodium nonatitanate with mineral acid.

71. The method of claim 65, further comprising:

washing the sodium nonatitanate with a buffer solution

72. The method of claim 65, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 12,500.

73. The method of claim 65, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 59,200.

74. The method of claim 65, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 100,000.

75. A process for preparing a solution containing rubidium-82, comprising:
providing a solution containing strontium-82;
absorbing strontium-82 onto a sodium nonatitanate support medium; and
eluting rubidium-82 from the sodium nonatitanate support medium with an eluant:
receiving a rubidium-82 eluate formed from the eluting step; and
adjusting a pH of the eluate.

76. The process of claim 75, wherein the eluant is selected from the group consisting of water and saline solutions.

77. The process of claim 75, wherein the eluant is an aqueous solution having a sodium chloride concentration between 0.001 molar and 1 molar.

78. The process of claim 75, wherein the eluant is an aqueous solution having a sodium chloride concentration between 0.2 molar and 1 molar.

79. The process of claim 75, wherein the eluant is a pharmaceutical-grade saline and buffer solution.

80. The process of claim 75, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 12,500.

81. The process of claim 75, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 59,200.

82. The process of claim 75, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 100,000.

83. The process of claim 75, further comprising:
disposing the sodium nonatitanate support medium into a column.

84. The process of claim 75, wherein the eluate is alkaline.

85. The process of claim 75, further comprising:
buffering the solvent.

86. The process of claim 75, wherein the pH of the eluate is adjusted to between about 4.5 and about 7.

87. The process of claim 75, wherein the pH of the eluate is adjusted to a pH suitable for injecting into a patient during a medical procedure.

88. The process of claim 75, wherein the step of adjusting a pH of the eluate comprises;
adding an acid to the eluate.

89. The process of claim 88, wherein the acid is HCl.

90. The process of claim 75, further comprising:
partially neutralizing the sodium nonatitanate before the step of absorbing strontium-82 onto a sodium nonatitanate support medium.

91. A method of chemically isolating strontium-82 from a proton-irradiated rubidium or rubidium chloride target, comprising:

(a) dissolving the target containing the strontium-82;

(b) adjusting the pH of the dissolved target solution to an alkaline pH;

(c) removing precipitates from the solution; and then

(d) absorbing the strontium-82 from the solution onto a support comprising sodium nonatitanate without absorbing rubidium.

92. The method of claim 91, wherein the dissolved target solution includes a buffer.

93. The method of claim 92, wherein the buffer is an ammonia/ammonium chloride buffer.

94. The method of claim 92, wherein the pH is between 9 and 10.

95. The method of claim 91, wherein the pH is greater than 10.

96. The method of claim 91, further comprising:

stripping the strontium-82 from the sodium nonatitanate.

97. The method of claim 96, wherein the strontium-82 is stripped from the sodium nonatitanate with mineral acid.

98. The method of claim 91, further comprising:

washing the sodium nonatitanate with a buffer solution.

99. The method of claim 91, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than 12,500.

100. The method of claim 91, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 59,200.

101. The method of claim 91, wherein the sodium nonatitanate is characterized by a strontium/rubidium separation factor greater than or equal to 100,000.

102. A process for preparing a rubidium-82 generator, comprising:

preparing sodium nonatitanate from titanium tetrachloride or titanium sulfate and aqueous sodium hydroxide;

heating the sodium nonatitanate at a temperature between 100°C and 250°C for a period between 12 hours and 2 weeks;

lowering the pH of the sodium nonatitanate; and

absorbing strontium-82 on the neutralized sodium nonatitanate from an aqueous solution comprising strontium-82 and a soluble sodium salt.

103. The process of claim 102, wherein the soluble sodium salt concentration is between about 0.1 and about 1 molar.

104. The process of claim 102, wherein the soluble sodium salt is sodium chloride.

105. The process of claim 102, wherein the aqueous sodium hydroxide is about 50 wt% sodium hydroxide.

106. The process of claim 102, wherein the molar ratio of aqueous sodium hydroxide to titanium tetrachloride or titanium sulfate is between about 1 and 12.

107. The process of claim 102, further comprising:

filtering to collect the sodium nonatitanate; and

washing the sodium nonatitanate to remove sodium chloride or sodium sulfate.

108. The process of claim 102, wherein the step of neutralizing the sodium nonatitanate further comprises:

suspending the sodium nonatitanate in a liquid; and

adding an acid to the liquid to lower the pH.

109. The process of claim 108, wherein the step of adding an acid lowers the pH to between about 7 and about 9.

110. The process of claim 108, wherein the step of adding and acid lowers the pH to between about 7.2 and about 8.

111. The process of claim 108, wherein the liquid comprises water.

112. The process of claim 108, wherein the acid is a strong mineral acid.

113. The process of claim 102, further comprising:

loading the sodium nonatitanate into a column.

114. The process of claim 102, further comprising:

supporting the sodium nonatitanate on a substrate.

115. The process of claim 102, wherein the solution containing strontium-82 is an acidic aqueous solution.

116. A process, comprising:

eluting a solution of rubidium-82 from a strontium-82 support medium comprising sodium nonatitanate with an aqueous eluant; and

adjusting a pH of the solution.

117. The process of claim 116, wherein the aqueous eluant is selected from the group consisting of water and saline solutions.

118. The process of claim 116, wherein the aqueous eluant has a sodium chloride concentration between 0.001 molar and 1 molar.

119. The process of claim 116, wherein the aqueous eluant has a sodium chloride concentration between 0.2 molar and 1 molar.

120. The process of claim 116, wherein the aqueous eluant is a saline and buffer solution suitable for human injection.

121. The process of claim 116, wherein the sodium nonatitanate is a reaction product of titanium isopropoxide and aqueous sodium hydroxide.

122. The process of claim 116, further comprising passing the rubidium-82 solution through a sodium nonatitanate filter to selectively remove any strontium-82 or strontium-85 from the solution.

123. The process of claim 116, further comprising disposing of the sodium nonatitanate filter.

124. The process of claim 116, further comprising using the rubidium-82 solution as a medical diagnostic agent or medical imaging agent.

125. The process of claim 124, further comprising injecting the rubidium-82 solution intravenously.

126. The process of claim 116, further comprising stripping strontium-82 from the sodium nonatitanate.

127. The process of claim 126, further comprising recovering the stripped strontium-82.

128. The process of claim 127, further comprising recycling the sodium nonatitanate.

129. The process of claim 116, wherein the sodium nonatitanate has not undergone hydrothermal treatment.

130. The process of claim 116 wherein the step of adjusting the pH further comprises:
adding an acid to the solution.

131. The process of claim 116, wherein the pH is adjusted to between about 4 and about 7.5.

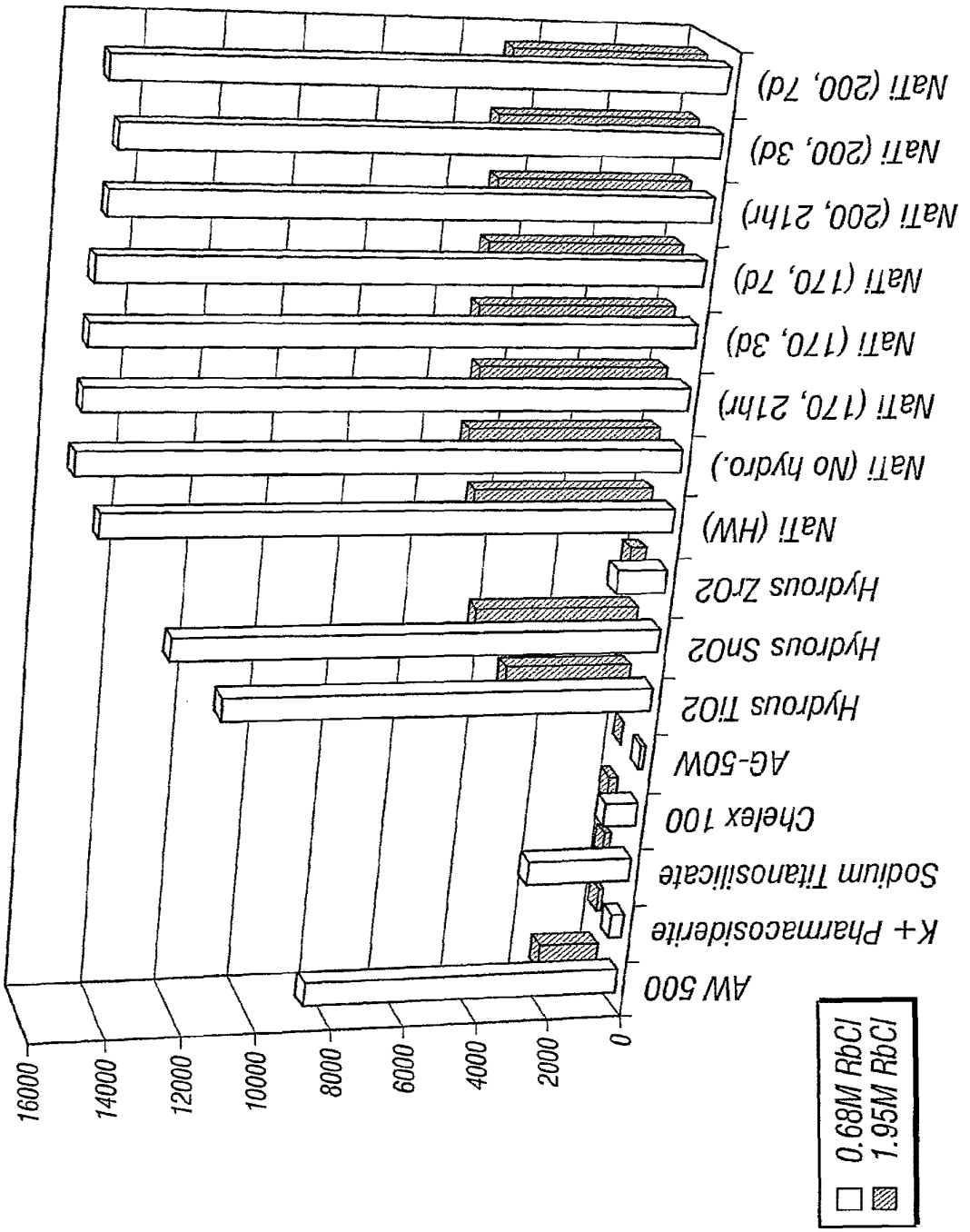
0.68M RbCl
1.95M RbCl
AW 500
K+ Pharmacosiderite
Sodium Titanosilicate
Chelex 100
AG-50W
Hydrous TiO2
Hydrous SnO2
Hydrous ZrO2
NaTi (HW)
NaTi (No hydro.)
NaTi (170, 21hr)
NaTi (170, 3d)
NaTi (170, 7d)
NaTi (200, 21hr)
NaTi (200, 3d)
NaTi (200, 7d)
0
2000
4000
6000
8000
10000
12000
14000
16000

FIG. 1

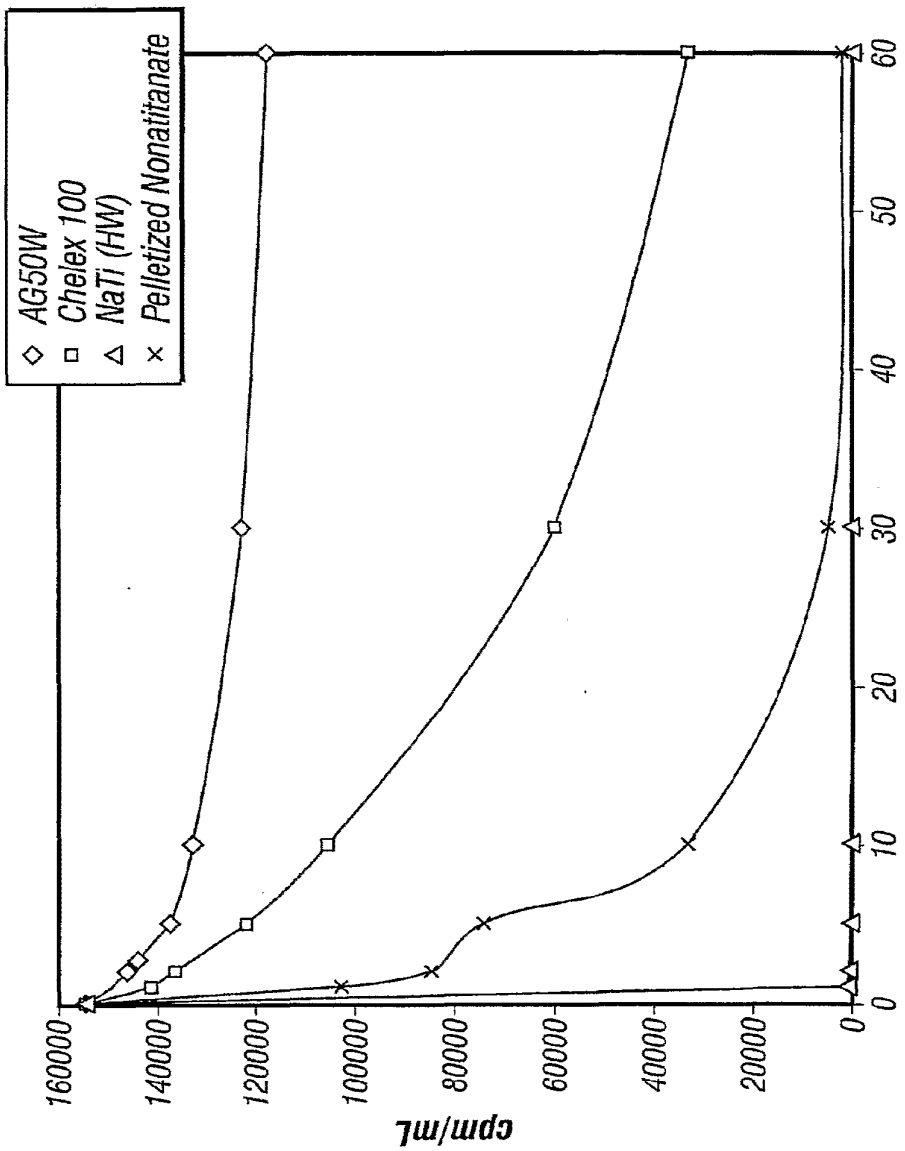
AG50W
Chelex 100
NaTi (HW)
Pelletized Nonatitanate
cpm/mL
160000
140000
120000
100000
80000
60000
40000
20000
0
0
10
20
30
40
50
60
Time (minutes)

FIG. 2

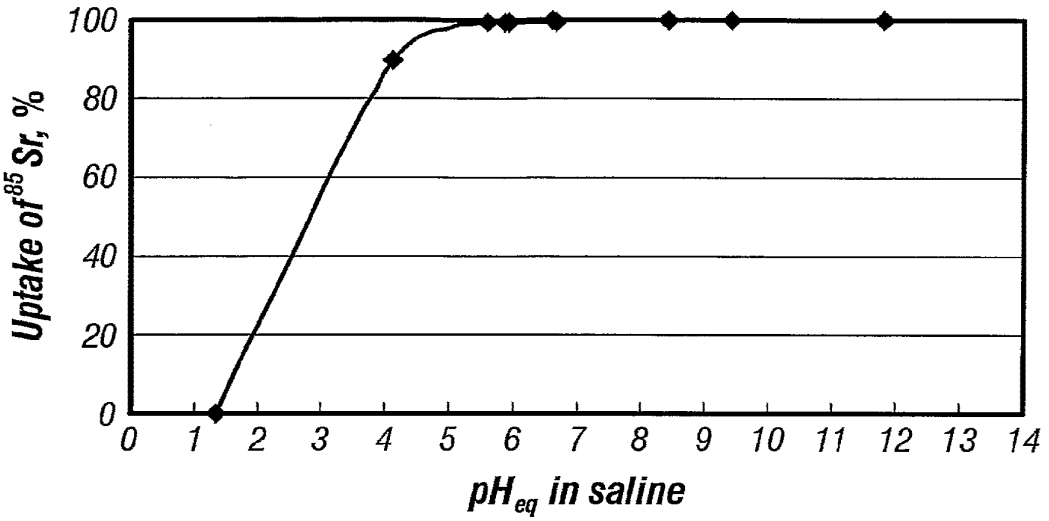
100
80
60
40
20
0
Uptake of ^{85}Sr, %
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
pH_{eq} in saline

FIG. 3

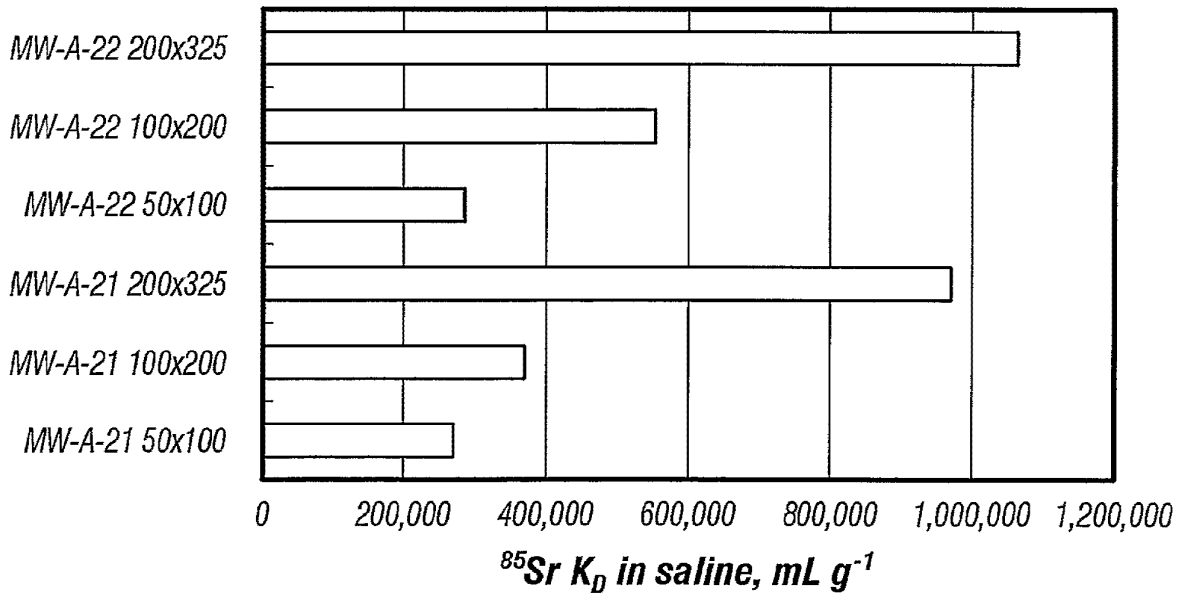
MW-A-22 200x325
MW-A-22 100x200
MW-A-22 50x100
MW-A-21 200x325
MW-A-21 100x200
MW-A-21 50x100
0
200,000
400,000
600,000
800,000
1,000,000
1,200,000
^{85}Sr K_D in saline, mL g^{-1}

FIG. 4

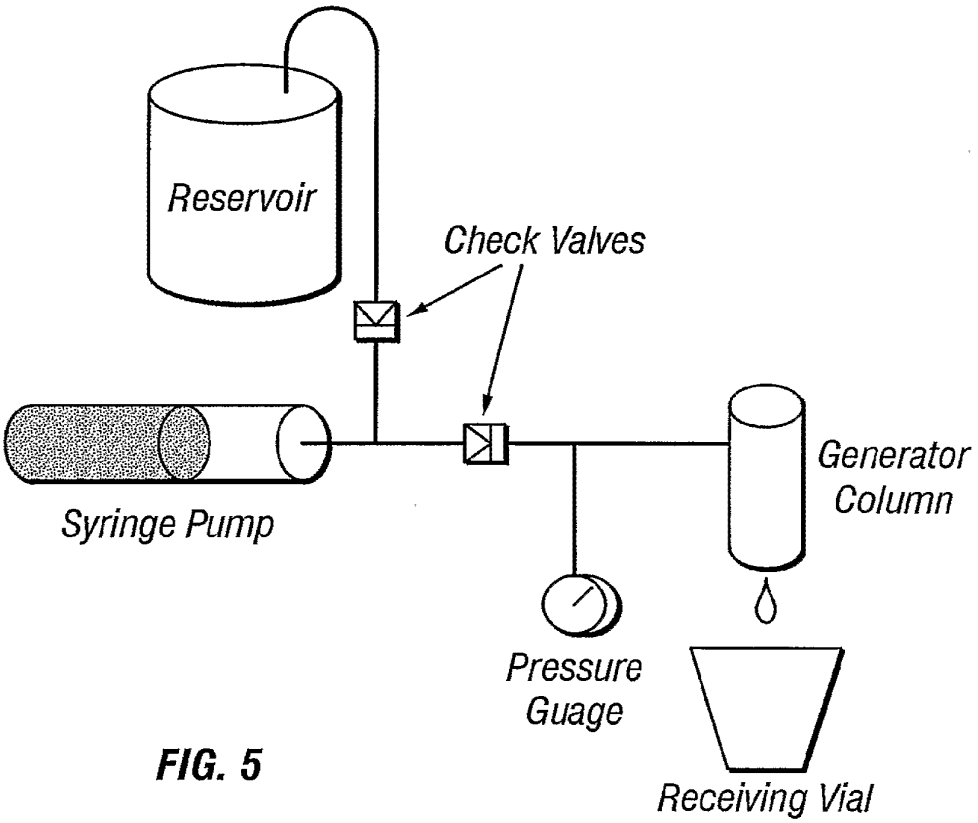
Reservoir
Check Valves
Syringe Pump
Generator Column
Pressure Guage
Receiving Vial

FIG. 5

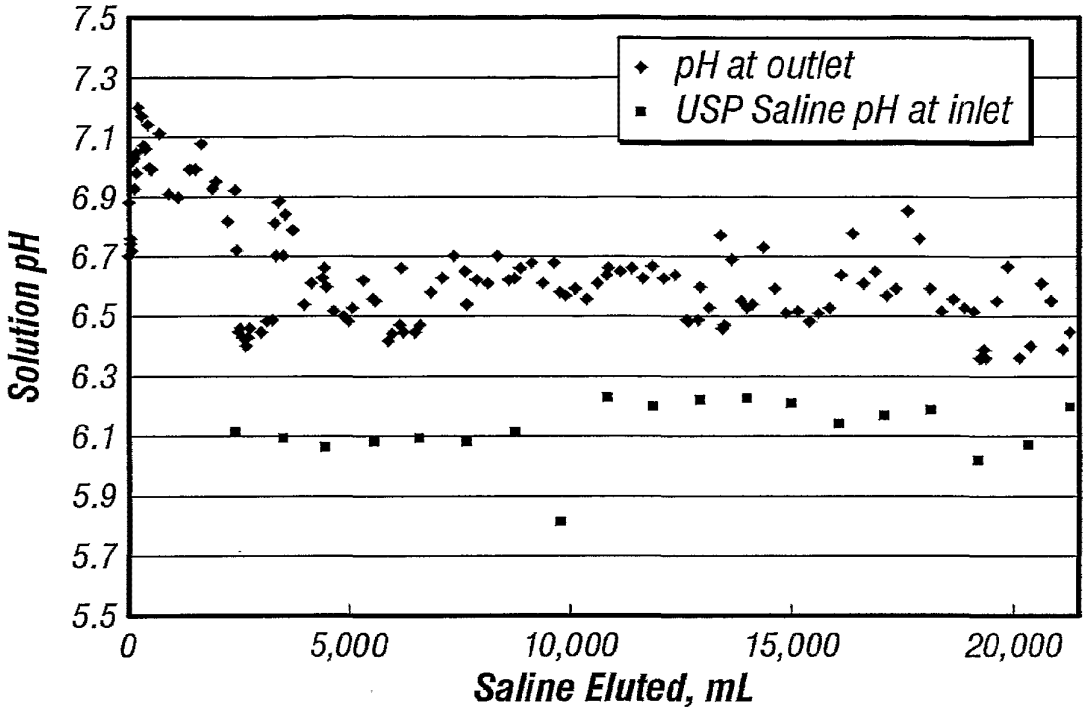
pH at outlet
USP Saline pH at inlet
Solution pH
7.5
7.3
7.1
6.9
6.7
6.5
6.3
6.1
5.9
5.7
5.5
0
5,000
10,000
15,000
20,000
Saline Eluted, mL

FIG. 6A

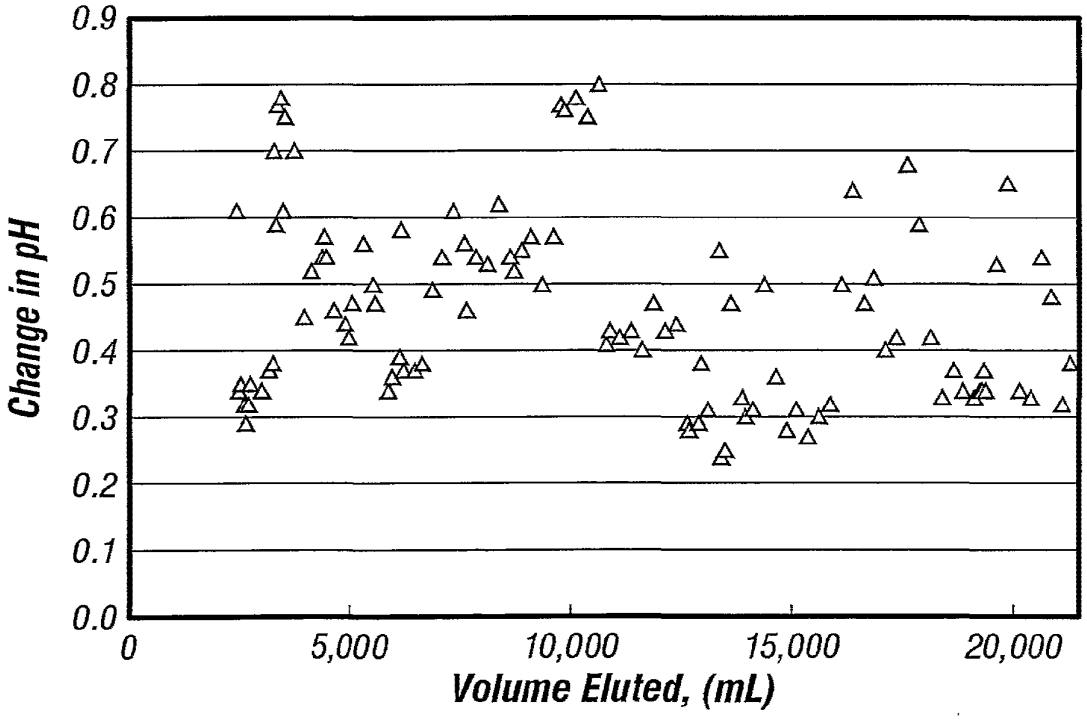
Change in pH
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
5,000
10,000
15,000
20,000
Volume Eluted, (mL)

FIG. 6B

AUTOMATED STRONTIUM-RUBIDIUM INFUSION SYSTEM

The invention relates to medical engineering, and particularly to means for automation of a process for producing a diagnostic solution from a radionuclide strontium-rubidium generator and remote carrying out a checked infusion with automatic checking main process characteristics, such as an introduced activity value, presence of air bubbles as well as a solution weight and activity in a waste container.

One of the most perspective directions in the nuclear diagnostics is the positron emission tomography (PET). Such short and ultra-short living isotopes as C-11, O-15, N-13, and F-18 are used in the PET centers. This obliges to have cyclotrons at the place of diagnostic for making such isotopes. It is possible to widen the functionality of the PET diagnostics in use of generator systems having a parent radionuclide lifetime significantly longer that a lifetime of radionuclides made in cyclotrons of the PET centers. Generator systems ^{82}Sr ($t_{1/2}$ = 25.6 days) → ^{82}Rb ($t_{1/2}$ = 75 seconds) and ^{68}Ge ($t_{1/2}$ = 271 days) → ^{68}Ga ($t_{1/2}$ = 78.3 minutes) are the most promising systems among the PET isotope generators.

Therefore, it is possible to say with respect to generator isotopes that any clinics having PET scanners within a region, a country or a group of countries are to be provided with said isotopes.

Generator systems can find the widest use in so called mobile PET scanners mounted in auto-trailers and called for servicing clinics that have no both own cyclotrons and own PET scanners. Absence of "affixment" of such a mobile PET scanner to an isotope base substantially widens a radius of the territory serviced thereby.

A strontium-rubidium infusion system for producing a diagnostic solution from a radionuclide strontium-rubidium generator and carrying out a checked infusion is known (US 4,562,829, 1986), said system comprising: an eluent tank connected by respective pipes of a transporting system via a first three-way valve to a syringe pump; a strontium-rubidium generator with a first filter and a first pressure sensor at an input; a second three-way valve whose first opening is coupled via a second filter to means for infusing an eluent into a patient and whose second opening is coupled to an eluate surplus storing and collecting means; radioactivity measurement means; and a check and control system. The prior art system is not optimal in a degree of radioactive radiation protection and in a service life of a generator column.

The disclosed invention is directed to elimination of the listed disadvantages. The technical result to be accomplished by using the inventive system consists in enhancement of

effectiveness in carrying out of a diagnostic procedure due to automation of the infusion procedure, reducing undesirable irradiation doses for a patient and maintenance personnel, increasing exploitation lifetimes of a generator column.

The essence of the disclosed invention consists in that an automated strontium-rubidium infusion system comprises: an eluent tank, a strontium-rubidium generator with a filter and a pressure sensor at an input; means for infusing an eluent into a patient, said tank, generator and means being connected by a transporting system to pipes and two three-way valves; radioactivity measuring means; and a check and control unit. At the same time, the eluent tank is connected via first and second openings of the first three-way valve to a syringe pump, a first opening of the second three-way valve is coupled by pipes via a second filter to the means for infusing the eluent into the patient and is coupled by a second opening thereof to a waste receptacle. The system further comprises: third and fourth three-way valves; first and second air bubble detectors coupled to the check and control unit being in communication with a computer, said third three-way valve being connected by first and second openings via pipes to a third opening of the first three-way valve and to an input of the strontium-rubidium generator, respectively, an output of the generator being coupled to a first opening of the fourth three-way valve, wherein the third opening of the third valve and a second opening of the fourth valve are in communication by a pipe, the first air bubble detector is mounted on a pipe between the eluent tank and the first opening of the first valve while the second detector is mounted on a pipe between the third openings of the fourth and second valves.

Further, the radioactivity measurement means include first and second activity sensors. At the same time, the first activity sensor is placed on a pipe between the third openings of the fourth and second valves and is embodied as a beta detector.

A radiation protection of the eluate surplus collecting and storing means may be implemented as a protection box including waste weight check means in the form of a force sensor, while the second activity sensor in the form of a gamma detector may be mounted within an opening of the protective box in order to determine a radioactivity level.

A column of the strontium-rubidium generator has a radiation protection including external main and transportation protective containers, said main protection container being mounted stationary on a shelf of a bogie.

The system is mounted in a closed movable housing. Further, the housing is provided with a shifting tabletop.

The essence of the invention is explained by drawings as follows:

Fig. 1 is a diagram of an infusion system;

Fig. 2 is a general side view of a generator plant;

Fig. 3 is a general top view of the generator plant.

Conditional notation used in drawings is listed below:

1 – Eluent tank

2, 3, 4, 5 – three-way valves

6, 7 – activity sensors

8, 9 – pressure sensors

10 – Syringe pump

11 – strontium-rubidium generator

12 – Check and control unit

13 – Weight sensor

14 – Remote computer

15, 16 – filters

17, 18 – air bubble detectors

19 – Means (needle) for infusing an eluent into a patient

20 – Eluent and eluate waste receptacle

21 – Movable housing

22 – Stand

23 – Protective container of strontium-rubidium generator

24 – Protective container for beta detector

25 – Power supply source

26 – Protective box of waste reservoir

27 – Shifting tabletop

An automated strontium-rubidium infusion system includes means for generating rubidium-82 in a solution which can be infused into a patient, exactly, a rubidium-strontium generator 11 (Fig. 1) of a traditional type in a transporting container. This container is placed in a protective external main container 23 and fulfils a main radiation protection function together with the latter. The assembled system may be mounted in a movable housing 21 (Fig. 2) covered by decorative panels (not shown). There is a stand 22 mounted on a tabletop and having an eluent tank fastened thereon. There are a syringe pump 10 and a computer 14 further mounted here. Components mounted on an upper shelf of the movable housing 21 are as follows:

- the main protective container 23 into which a standard transporting container with the strontium-rubidium generator 11 is placed;

- a protective box 24 with a beta activity detector placed therein and measuring the activity of a solution passed through the strontium-rubidium generator 11;

- a power supply source 25.

A protective box 26 is placed at a lower shelf, said box having an eluent and eluate waste receptacle arranged therein.

A top lid of the container 23 is turned back in Fig. 3, which makes it possible to see a cavity into which the transporting container with the strontium-rubidium generator 11 is placed. In order to make easier the access to the main protective container 23 during recharging a generator system (there are removal of the transporting container with the used column of the strontium-rubidium generator 11 and installation of a transporting container with a fresh column), a tabletop part is made as a shifting tabletop 27 which provides convenience in operation.

Further, the system includes means for infusion, exactly (Fig. 1): a remote-controlled syringe pump 10 whose rod is actuated, for example, by a step motor; means for automated filling the syringe pump with an eluent (a 0.9% NaCl solution); a system for transporting an eluent and an eluate to a patient or an eluent and eluate waste receptacle, said transporting system being provided with multi-way (three-way) valves 2 to 5 (Fig. 1) that ramify the transporting system in accordance with a job making program; antibacterial protection means, exactly, antibacterial filters 15 and 16 at an input and at an output of the transporting system; eluate activity measurement means 6 and 7 for monitoring and dozing in infusion into a patient; pressure measurement means 8 and 9 for measurement a pressure in the transporting system, said means being designed for measuring occlusion as well; an eluent and eluate waste receptacle 20 also capable of measuring a solution activity value and a solution weight in a waste reservoir 13; means 12 for automated check throughout the eluation process and components thereof, implemented by on-board or remote computers 14.

The tank 1 with an eluent (for example, brine) is connected by a plastic fitting to a pipe (for example, an infusion tube that has an outer diameter of 2.5 mm with an inner diameter of 1.5 mm). Lengths of such tubes (pipes) are used further to build the transporting system as a whole for infusion. Other end of the pipe is attached via an air bubble detector 17 that generates a signal to a check and control unit 12 in case of passing an air bubble, and said unit generates a control signal to valves 2, 3, 4, and 5 as a result of which the eluent solution comprising the air bubble is removed into the eluent and eluate waste receptacle 20 and does not passes through the column of the strontium-rubidium generator 11.

The valve 2 switches the infusion system into one of two possible operating modes for: (1) filling the syringe when the syringe pump 10 operates for suction the brine from the eluent tank 1 (via the first and second openings of the valve); or (2) infusing, that is, supplying the brine from the filled syringe of the syringe pump 10 into the infusion system (via the first and third openings of the valve).

Further, the three-way valve 2 is connected by a length of a connecting tube to the first opening of the third three-way valve 4 whose second opening is connected via the first filter 15 to an input of the column of the strontium-rubidium generator 11. The first pressure sensor 8 checks a pressure at the input of the column of the strontium-rubidium generator 11.

The third opening of the valve 4 via a length of a connecting tube is connected to the second opening of the fourth three-way valve 5. This valve (the first opening) also has connections to an output tube of the column of the strontium-rubidium generator 11 and an extension of the infusion system in the third opening.

When the syringe pump operates in the operating "infusion" mode, the pair of three-way valves 4, 5, while operating in synchronism, allows either pumping the brine from the syringe 10 via the column of the strontium-rubidium generator 11 further to the infusion system already in the form of an eluate, that is, a Rb-82-enriched solution, or pumping the brine into the infusion system while by-passing the strontium-rubidium generator 11. Thus operating mode is used when a necessary Rb-82 activity amount has been made and should be delivered to a patient 19 while the infusion system should be filled with the inactive brine at the end of infusion into the patient. When the brine pumping mode is used, practically the entire transporting system, exceptive for a connecting pipe from the strontium-rubidium generator output to the fourth three-way valve, will be filled with the non-radioactive brine and will not be a source of additional undesirable radioactivity for the patient and the maintenance personnel; additionally, a brine volume necessary to after-press the made eluate into the patient will not pass through and deplete the column of the strontium-rubidium generator, because it is known that a potency of the generator depends not only upon a time of using thereof but also upon a volume of the brine passed through the generator.

There are a first radioactivity detector 6 (a beta detector) and a second air bubble detector 18 mounted on a pipe from the third opening of the fourth three-way valve 5 to the third opening of the second three-wave valve 3, said air bubble detector being similar to the first air bubble detector 17.. When an air bubble is detected, the detector 18 generates a signal to the check and control unit that generates a control signal to the second three-way valve 3. As a result, an eluate comprising the air bubble is removed into the eluent and eluate waste

receptacle 20. If an air bubble is not detected, the eluate is directed via the first of said three-way valve 3 and the second filter 16 into the patient, that is, onto a needle 19.

The radioactivity detector 6 operates in real time and measures the Rb-82 activity at a location of the detector 18.

The check for filling said waste receptacle with a liquid is carried out by a force sensor (not shown). To measure a radioactivity present in the eluent and eluate waste receptacle, the second radioactivity sensor 7 (a gamma detector) is used. The radiation protection of the eluate surplus collecting and storing means is implemented as a protection box including a force sensor, while the second activity sensor is mounted within an opening of the protective box.

During infusion into the patient, the second three-way valve 3 is switched for passing the eluent to a pipe connected to the needle 19 via a Millipore filter 16. There is a second pressure sensor 9 mounted in this section which allows measurement of an occlusion pressure when an Rb-82-containing solution in administered into the patient.

The process of operating the strontium-rubidium infusion system takes place under control of a control computer program that registers a status of each of devices included in the infusion system at moments of starting and finishing a step, and also registers actions of said devices under condition of their normal functioning and in case if an emergency situation occurs.

To exclude overfilling the eluent and eluate waste receptacle 20 with a radioactive liquid, a level of said liquid is remotely checked using the force sensor; in doing so, there is monitoring of a total container and liquid weight (volume) and a limit value thereof. Additionally, by fixing a weight of the empty waste collection receptacle, a system for scheduled interrogating the check and control unit receives information that the receptacle is mounted in a container. A maximum waste volume in the receptacle is 250 ml.

The check and control unit 12 is coupled to a remote computer whose display displays a graphical mnemonic diagram of the generator device, said diagram providing observation of parameters to be checked in an automatic mode and parameters for operating control of individual members (the electromagnetic three-way valves 2 to 5 and the pump 10) in a manual mode. The diagram makes it possible to observe a current state of all members (the valves 2 to 5, the air bubble detectors 17, 18) of the disclosed infusion system, and operation of the syringe pump 10. The system also allows reception of information about parameters of a pressure in a line from the pressure sensors 8, 9, and reception of information about an

eluate activity at an output of the generator column 11 and a total activity, a weight of the eluate and eluent waste receptacle 20, an activity in said receptacle from the detectors 6, 7.

The check and control unit 12 of the system is connected to control members of the generator plant, that is, the electromagnetic three-way valves 2, 3, 4, 5 and the pump 10, and also includes members for gathering and processing signals from the sensors 6, 7 (the radioactivity sensors), 8, 9 (the pressure sensors), and 17, 18 (the bubble detectors). The control unit 12 is in communication with a panel personal computer (PPC) or any other remote computer (14) through an Ethernet channel. The control unit receives commands from the PPC or remote computer to execute individual steps of the generator plant operating program and informs said computers about a current state of members controlled thereby and a state of system sensors.

The disclosed system improves the safety of use due to the fact that automation of the infusion process has allowed significant reduction in the radioactive irradiation because the system includes additional members that provide ramification of pipes. As a result, it is possible to after-press the made eluate into the patient by the eluent while by-passing the strontium-rubidium generator. At the same time, the pipe is pumped through by the non-radioactive eluent and there is no additional depletion of the strontium-rubidium generator, which makes the life thereof longer. Further, the risk of presence of air bubbles in the eluent delivered into the patient is excluded because of introducing air bubbles into the system of detectors, while detection of said air bubbles immediately results in direction of the eluent and eluate wastes to the eluent and eluate waste receptacle via branches of the pipe without depletion of the strontium-rubidium generator.

CLAIMS

1. An automated strontium-rubidium infusion system comprising:

an eluent tank;

a strontium-rubidium generator with a filter and a pressure sensor at an input;

means for infusing an eluent into a patient, said tank, generator and means being connected by a transporting system to pipes and two three-way valves;

radioactivity measuring means; and

a check and control unit,

wherein the eluent tank is connected via first and second openings of the first three-way valve to a syringe pump, a first opening of the second three-way valve is coupled by pipes via a second filter to the means for infusing the eluent into the patient and is coupled by a second opening thereof to a waste receptacle,

said system being characterized in that it further comprises:

third and fourth three-way valves;

first and second air bubble detectors coupled to the check and control unit being in communication with a computer,

said third three-way valve being connected by first and second openings via pipes to a third opening of the first three-way valve and to an input of the strontium-rubidium generator, respectively, an output of the generator being coupled to a first opening of the fourth three-way valve,

wherein the third opening of the third valve and a second opening of the fourth valve are in communication by a pipe, the first air bubble detector is mounted on a pipe between the eluent tank and the first opening of the first valve while the second detector is mounted on a pipe between the third openings of the fourth and second valves.

2. The system according to claim 2, characterized in that the radioactivity measurement means include first and second activity sensors.

3. The system according to claim 3, characterized in that the first activity sensor is placed on a pipe between the third openings of the fourth and second valves and is embodied as a beta detector.

4. The system according to claim 2, characterized in that the waste receptacle is implemented as a protection box including waste weight check means in the form of a force

sensor, while the second activity sensor in the form of a gamma detector is mounted within an opening of the protective box.

5. The system according to claim 1, characterized in that the strontium-rubidium generator has a radiation protection including external main and transportation protective containers, said main protection container being mounted stationary on a shelf of a bogie.

6. The system according to claim 1, characterized in that it is mounted in a closed movable housing.

7. The system according to claim 6, characterized in that the housing is provided with a shifting tabletop.

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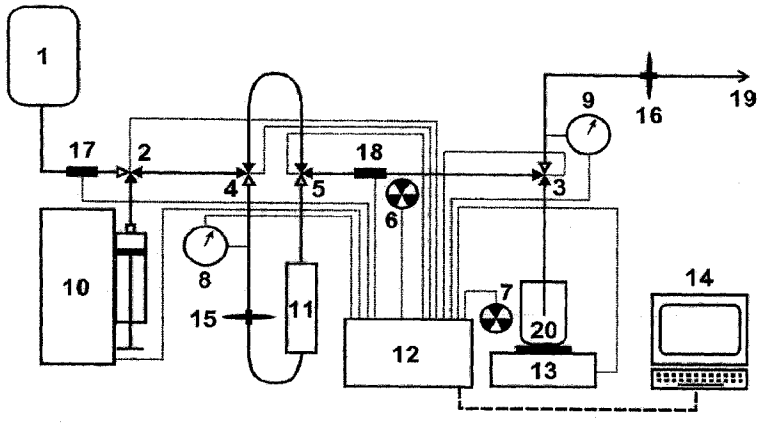
[продолжение на следующей странице]

(54) **Title:** AUTOMATED STRONTIUM-RUBIDIUM INFUSION SYSTEM

(54) **Название изобретения:** АВТОМАТИЗИРОВАННАЯ СТРОНЦИЙ - РУБИДИЕВАЯ ИНФУЗИОННАЯ СИСТЕМА



Фиг. 1

(57) **Abstract:** The invention relates to medical engineering. The inventive automated strontium-rubidium infusion system comprises a container with eluent, a strontium-rubidium generator with a filter and a pressure sensor and an eluate infusion unit, which are connected by means of a transporting system provided with pipes and two three-way valves, radioactivity measuring means and a control and operating unit. An eluent container is connected to a syringe pump via the first valve, the second three-way valve is connected to the eluate infusion unit and a waste receptacle via the second filter. First and second air bubbles detectors are connected to the control and operating unit. The second three-way valve is connected to the first three-way valve and to the input of the strontium-rubidium generator. The generator output is connected to the fourth valve which is connected to the third valve. The first air bubbles detector is placed between the eluent container and the first valve and the second air bubbles detector is placed between the fourth and second valves.

[продолжение на следующей странице]

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(57) Реферат: Изобретение относится к медицинской технике. Автоматизированная стронций - рубидиевая инфузионная система содержит емкость с элюентом, стронций-рубидиевый генератор с фильтром и датчиком давления, средство для инфузии элюата, соединенные системой транспортировки с трубопроводами и двумя трехходовыми клапанами, средства для измерения радиоактивности и блок контроля и управления. Емкость с элюентом через первый клапан соединена со шприцевым насосом, второй трехходовой клапан соединен через второй фильтр со средством для инфузии элюата и со сборником отходов. Первый и второй детекторы воздушных пузырьков подключены к блоку контроля и управления. Второй трехходовой клапан связан с первым трехходовым клапаном и входом стронций-рубидиевого генератора. Выход генератора подключен к четвертому клапану, соединенному с третьим клапаном. Первый детектор воздушных пузырьков установлен между емкостью с элюентом и первым клапаном, а второй детектор - между четвертым и вторым клапанами.

Автоматизированная стронций – рубидиевая инфузионная система

Изобретение относится к медицинской технике, в частности к средствам автоматизации процесса производства диагностического раствора от радионуклидного стронций-рубидиевого генератора и дистанционного проведения контролируемой инфузии, с автоматическим контролем основных характеристик процесса, таких как величина вводимой активности, величина окклюзии, наличие воздушных пузырей, а также вес и активность раствора в контейнере с отходами.

Одним из наиболее перспективных направлений в ядерной диагностике является позитронно-эмиссионная томография (ПЭТ). Для работы в ПЭТ-центрах используют такие коротко и ультра-короткоживущие изотопы как – C-11, O-15, N-13, F-18. Это обязывает иметь на месте проведения диагностики циклотроны для наработки таких изотопов. Возможности ПЭТ-диагностики могут быть существенно расширены при использовании генераторных систем, время жизни материнского радионуклида которых значительно превышает время жизни нарабатываемых на циклотронах ПЭТ-центров радионуклидов. Наиболее перспективными среди изотопных генераторов для ПЭТ стоят генераторные системы ^{82}Sr ($t_{1/2}$=25,6 дней) → ^{82}Rb ($t_{1/2}$=75 сек) и ^{68}Ge ($t_{1/2}$=271 дней) → ^{68}Ga ($t_{1/2}$=68,3 мин).

Поэтому в применении к генераторным изотопам можно говорить о снабжении ими любых клиник, обладающих ПЭТ-сканнерами, в рамках региона, государства или группы государств.

Наибольшее применение генераторные системы могут найти в смонтированных в автотрейлерах так называемых мобильных ПЭТ, вызываемых для обслуживания клиник, не имеющих не только собственных циклотро́нов, но и собственных ПЭТ-сканнеров. При отсутствии «привязки» такого мобильного ПЭТ-сканнера к изотопной базе существенно расширяется радиус обслуживаемой им территории.

Известна стронций-рубидиевая инфузионая система производства диагностического раствора от радионуклидного стронций-рубидиевого генератора и проведения контролируемой инфузии (US 4562829, 1986), включающая емкость с элюентом, соединенную соответствующими трубопроводами системы транспортировки через первый трехходовой клапан с шприцевым насосом, стронций-рубидиевый генератор с первыми фильтром и датчиком давления на входе, второй трехходовой клапан, первое отверстие которого подключено через второй фильтр к средству для инфузии элюата пациенту, а второе – к средству для сбора и хранения излишков элюата, средства для измерения радиоактивности и система контроля и управления. Известная система не является оптимальной по степени защиты от радиоактивного излучения и по сроку службы генераторной колонки.

Предлагаемое изобретение направлено на устранение перечисленных недостатков. Достигаемый при ее использовании технический результат заключается в повышении эффективности проведения диагностической процедуры за счет автоматизации процедуры инфузии, снижении доз нежелательного радиоактивного облучения пациента и обслуживающего персонала, увеличении сроков эксплуатации генераторной колонки.

Сущность предлагаемого изобретения заключается в том, что автоматизированная стронций – рубидиевая инфузионная система, содержит емкость с элюентом, стронций-рубидиевый генератор с фильтром и датчиком давления на входе, средство для инфузии элюата пациенту, соединенные системой транспортировки с трубопроводами и двумя трехходовыми клапанами, средства для измерения радиоактивности и блок контроля и управления. Причем емкость с элюентом через первое и второе отверстия первого трехходового клапана соединена с шприцевым насосом, первое отверстие второго трехходового клапана подключено трубопроводами через второй фильтр к средству для инфузии элюата пациенту, а второе отверстие – к сборнику отходов. В систему

дополнительно введены третий и четвертый трехходовые клапаны, первый и второй детекторы воздушных пузырьков, подключенные к блоку контроля и управления, связанного с компьютером, при этом третий трехходовой клапан связан первым и вторым отверстиями через трубопроводы с третьим отверстием первого трехходового клапана и входом стронций – рубидиевого генератора, соответственно. Выход генератора подключен к первому отверстию четвертого трехходового клапана, причем третье отверстие третьего клапана и второе отверстие четвертого клапана связаны трубопроводом, первый детектор воздушных пузырьков установлен на трубопроводе между емкостью с элюентом и первым отверстием первого клапана, а второй детектор установлен на трубопроводе между третьими отверстиями четвертого и второго клапанов.

Кроме того, средства для измерения радиоактивности включают первый и второй датчики активности. При этом первый датчик активности размещен на трубопроводе между третьими отверстиями четвертого и второго клапанов и выполнен в виде бета-детектора.

Радиационная защита средства для сбора и хранения излишков элюата может быть выполнена в виде защитного бокса, включающего средство контроля веса отходов в виде датчика усилия, а в отверстии защитного бокса установлен второй датчик активности для определения уровня радиоактивности отходов в виде гамма-детектор.

Колонка стронций – рубидиевого генератора имеет радиационную защиту, включающую, предпочтительно, внешний основной и транспортный защитные контейнеры, при этом основной защитный контейнер стационарно установлен на полке тележки.

Система устанавливается в закрытом перемещаемом корпусе. Кроме того, корпус снабжен сдвигающейся столешницей.

Сущность изобретения поясняется следующими чертежами:

Фиг. 1 – схема инфузионной системы;

фиг. 2 – представлен общий вид генераторной установки сбоку;

фиг. 3 – общий вид генераторной установки сверху.

Ниже перечислены условные обозначения, используемые на черетже:

1 – емкость с элюентом

2, 3, 4, 5 – трехходовые клапаны

6, 7 – датчики активности

8, 9 – датчики давления

10 – шприцевой насос

11 – стронций-рубидиевый генератор

12 – блок контроля и управления

13 – датчик веса

14 – удаленный компьютер

15, 16 – фильтры

17, 18 – детекторы воздушных пузырьков

19 – средство для инфузии элюата пациенту (игла)

20 – сборник отходов элюента и элюата

21 – перемещаемый корпус

22 – штатив

23 – защитный контейнер стронций – рубидиевого генератора

24 – защитный контейнер для бета – детектора

25 – источник питания

26 – защитный бокс емкости для отходов

27 – сдвигающаяся столешница.

Автоматизированная стронций – рубидиевая инфузионная система включает в себя средства для генерации рубидия-82 в растворе, который может быть введен пациенту, а именно стронций-рубидиевый генератор 11 (фиг.1), обычного типа в транспортном контейнере. Этот контейнер помещается в защитный внешний основной контейнер 23 и совместно с последним осуществляет функцию основной радиационной защиты. Система в сборе может устанавливаться в перемещаемом корпусе 21 (фиг.

2), закрытым декоративными панелями (не показано). На столешнице установлен штатив 22 с укрепленном на нем емкостью с элюентом 1. Кроме того, здесь установлен шприцевой насос 10 и компьютер 14. На верхней полке перемещаемого корпуса 21 установлены:

- основной защитный контейнер 23, внутрь которого помещен стандартный транспортный контейнер со стронций-рубидиевым генератором 11;
- защитный бокс 24 с размещенным внутри него детектором бета-активности, измеряющим активность раствора, прошедшего через стронций-рубидиевый генератор;
- источник питания 25.

На нижней полке размещен защитный бокс 26, внутри которого располагается сборник отходов элюента и элюата.

На фиг. 3 верхняя крышка контейнера 23 откинута, что позволяет увидеть полость, внутрь которой помещается транспортный контейнер со стронций-рубидиевым генератором 11. Для того, чтобы облегчить доступ к основному защитному контейнеру 23 во время перезарядки генераторной системы (извлекается транспортный контейнер с отработавшей колонкой стронций-рубидиевого генератора 11 и устанавливается транспортный контейнер со свежей генераторной колонкой) – часть столешницы выполнена в виде сдвигающейся столешницы 27, обеспечивающей удобство при работе.

Кроме того, система включает в себя средства для проведения инфузии, а именно (фиг. 1): шприцевой дистанционно управляемый инфузионный насос 10, шток которого приводится в действие, например, шаговым двигателем; средства для автоматизированного заполнения шприцевого насоса элюентом 1 (0.9 % раствором NaCl); систему транспортировки элюента и элюата до пациента или сборника отходов элюента и элюата, снабженную многоходовыми (трехходовыми) клапанами 2 – 5 (фиг.1), осуществляющими ветвление системы транспортировки в

соответствии с программой проведения работ; антибактериальные средства защиты, а именно антибактериальные фильтры 15 и 16 на входе и выходе системы транспортировки; средства измерения активности элюата для текущего контроля и дозирования при инфузии в пациента 6 и 7; средства измерения давления 8 и 9 в транспортной системе, в том числе и для измерения окклюзии; сборник отходов элюента и элюата 20, в том числе с измерением величины активности и веса раствора в емкости для отходов 13 и осуществления защиты от радиоактивности; средства автоматизированного контроля всего процесса элюации и его составных частей 12, осуществляемого с помощью бортового или удаленного компьютеров 14.

В описываемой системе емкость с элюентом 1 (соляным раствором) соединена пластиковым фитингом с трубопроводом (например, трубочкой для инфузий, которая имеет внешний диаметр 2.5 мм при внутреннем диаметре 1.5 мм). Отрезки таких трубочек (трубопроводы) далее используются для построения всей транспортной системы для инфузии. Другой конец трубопровода подсоединен через детектор воздушных пузырьков 17, который, в случае прохождения воздушного пузырька, вырабатывает сигнал на блок контроля и управления 12, который вырабатывает управляющий сигнал на клапаны 2, 3, 4 и 5, в результате чего, раствор элюента, содержащий воздушный пузырек, удаляется в сборник отходов элюента и элюата 20, не проходя колонку стронций-рубидиевого генератора 11.

Клапан 2 осуществляет перевод инфузионной системы в один из двух возможных режимов работы: (1) заполнение шприца при работе шприцевого насоса 10 на всасывание соляного раствора из емкости с элюентом 1 (через первое и второе отверстия клапана) или (2) инфузию, т.е. подачу соляного раствора из заполненного шприца шприцевого насоса 10 в инфузионную систему (через первое и третье отверстия клапана).

Трехходовой клапан 2 далее соединен отрезком соединительной трубки с первым отверстием третьего трехходового клапана 4, второе отверстие которого соединено через первый фильтр 15 с входом колонки стронций-рубидиевого генератора 11. Контроль давления на входе в колонку стронций-рубидиевого генератора 11 осуществляется первым датчиком давления 8.

Третьим отверстием клапан 4, через отрезок соединительной трубки, подсоединен ко второму отверстию четвертого трехходового клапана 5. Этот клапан также имеет соединения с выходной трубкой колонки стронций-рубидиевого генератора 11 (первое отверстие) и продолжением инфузионной системы на третьем отверстии.

В режиме работы шприцевого насоса «инфузия» пара трехходовых клапанов 4, 5, работая синхронно, позволяет либо прокачивать соляной раствор из шприца 10 через колонку стронций-рубидиевого генератора дальше в инфузионную систему уже в виде элюата, т.е. раствора, обогащенного Rb-82, либо прокачивать соляной раствор в инфузионную систему, минуя стронций-рубидиевый генератор 11. Этот режим работы используется тогда, когда необходимое количество активности Rb-82 наработано и оно должно быть доставлено пациенту 19, а инфузионная система должна быть заполнена неактивным соляным раствором на конец инфузии в пациента. При использовании режима прокачки соляного раствора практически вся инфузионная система, за исключением соединительного трубопровода от выхода из стронций-рубидиевого генератора до четвертого трехходового клапана, будет заполнена нерадиоактивным соляным раствором и не будет являться источником дополнительной нежелательной радиоактивности на пациента и обслуживающий персонал; кроме того, объем соляного раствора, необходимый для додавливания наработанного элюата в пациента не будет проходить через колонку стронций-рубидиевого генератора и истощать ее, т.к. известно, что потенция генератора зависит не только от времени его

эксплуатации, но также и от объема пропущенного через него соляного раствора.

На трубопроводе от третьего отверстия четвертого трехходового клапана 5 до третьего отверстия второго трехходового клапана 3 установлены первый детектор радиоактивности 6 (бета-детектор) и второй детектор воздушных пузырьков 18, аналогичный первому детектору пузырьков 17. При обнаружении воздушного пузырька, детектор 18 вырабатывает сигнал на блок контроля и управления, который вырабатывает управляющий сигнал на клапан второго трехходового клапана 3. В результате, элюат содержащий воздушный пузырек, удаляется в сборник отходов элюента и элюата 20. Если воздушный пузырек не обнаружен, элюат направляется через первое отверстие трехходового клапана 3 и второй фильтр 16 в пациента, т.е. на иглу 19

Детектор радиоактивности 6 работает в режиме реального времени и измеряет активность Rb-82 в месте расположения детектора 18.

Контроль за наполнением сборника для отходов жидкостью осуществляется с помощью датчика усилий (не показан). Для измерения радиоактивности, содержащейся в сборнике для отходов элюента и элюата используется второй датчик радиоактивности 7 (гамма-детектор). Радиационная защита средства для сбора и хранения излишков элюата выполнена в виде защитного бокса, в состав которого включен датчик усилия, а в отверстии защитного бокса установлен второй датчик активности.

При осуществлении инфузии в пациента второй трехходовой клапан 3 переключен на пропускание элюата на трубопровод соединенный с иглой 19 через миллипоровский фильтр 16. На этом отрезке установлен второй датчик давления 9, позволяющий измерять давление окклюзии при введении раствора, содержащего Rb-82, в пациента.

Процесс работы стронций-рубидиевой инфузионной системы происходит под управлением управляющей компьютерной программы, в которой прописывается состояние каждого из устройств, входящих в инфузионную систему, на момент начала и окончания выполнения шага, также прописываются действия этих устройств и условия их функционирования в нормальных условиях и в случае возникновения аварийной ситуации.

Для исключения переполнения в сборнике отходов элюента и элюата 20 радиоактивной жидкости, осуществляется дистанционный контроль за предельным значением ее уровня с помощью датчика усилия, при этом контролируется общий вес тары и жидкости, осуществляется текущий контроль за значением веса (объема) жидкости и за предельным его значением. Кроме того, фиксируя вес пустой тары для сбора отходов, система регламентного опроса блока контроля и управления установки получает информацию о том, что тара установлена в контейнере. Максимальный объём отходов в таре составляет 250 мл.

Блок контроля и управления подключен к удаленному компьютеру, на дисплее которого отображается графическая мнемосхема генераторного устройства, обеспечивающая наблюдение контролируемых параметров в автоматическом режиме и оперативного управления отдельными элементами (электромагнитными трехходовыми клапанами 2 - 5, насосом 10) в ручном режиме. Схема позволяет наблюдать за текущим состоянием всех элементов описываемой системы инфузии (клапанов 2-5, детекторов воздушных пузырьков 17, 18) и за работой шприцевого насоса 10. Также она позволяет получать информацию о параметрах давления в магистралях от датчиков давления 8, 9, активности элюата на выходе из генераторной колонки 11 и суммарной активности, веса емкости сборника отходов элюента и элюата 20, активности в емкости с отходами от детекторов 6,7.

Блок контроля и управления 12 системы связан с управляющими элементами генераторной установки – электромагнитными трехходовыми

клапанами 2, 3, 4, 5 и насосом 10, а также включает элементы для сбора и обработки сигналов с датчиков 6, 7 (датчики радиоактивности), 8, 9 (датчики давления), 17, 18 (детекторы воздушных пузырьков). Блок управления 12 связан с панельным персональным компьютером (PPC) или любым другим удаленным компьютером (14) по каналу Ethernet. Он получает команды от PPC или удаленного компьютера на выполнение отдельных шагов программы работы генераторной установки и информирует их о текущем состоянии управляемых им элементов и состоянии датчиков системы.

Описываемая система повышает безопасность эксплуатации, так как автоматизация процесса инфузии позволила значительно сократить радиоактивное облучение за счет введения в систему дополнительных клапанов, обеспечивающих ветвление трубопроводов. В результате, появилась возможность додавливания наработанного элюата в пациента элюентом, минуя стронций – рубидиевый генератор. При этом трубопровод прокачивается нерадиоактивным элюентом и не происходит дополнительного истощения стронций – рубидиевого генератора, что увеличивает срок его эксплуатации. Кроме того, исключается риск содержания воздушных пузырьков в элюанте, доставляемого пациенту, за счет введения в систему детекторов воздушных пузырьков, при обнаружении которых, элюент сразу направляется к сборнику отходов элюента и элюата через ответвления трубопровода, не истощая стронций – рубидиевый генератор.

Формула изобретения

1. Автоматизированная стронций – рубидиевая инфузионная система, содержащая емкость с элюентом, стронций-рубидиевый генератор с фильтром и датчиком давления на входе, средство для инфузии элюата пациенту, соединенные системой транспортировки с трубопроводами и двумя трехходовыми клапанами, средства для измерения радиоактивности и блок контроля и управления, причем емкость с элюентом через первое и второе отверстия первого трехходового клапана соединена с шприцевым насосом, первое отверстие второго трехходового клапана подключено трубопроводами через второй фильтр к средству для инфузии элюата пациенту, а второе отверстие – к сборнику отходов, отличающаяся тем, что дополнительно введены третий и четвертый трехходовые клапаны, первый и второй детекторы воздушных пузырьков, подключенные к блоку контроля и управления, связанного с компьютером, при этом третий трехходовой клапан связан первым и вторым отверстиями через трубопроводы с третьим отверстием первого трехходового клапана и входом стронций – рубидиевого генератора, соответственно, выход генератора подключен к первому отверстию четвертого трехходового клапана, причем третье отверстие третьего клапана и второе отверстие четвертого клапана связаны трубопроводом, первый детектор воздушных пузырьков установлен на трубопроводе между емкостью с элюентом и первым отверстием первого клапана, а второй детектор установлен на трубопроводе между третьими отверстиями четвертого и второго клапанов.

2. Система по п.1, отличающаяся тем, что средства для измерения радиоактивности включают первый и второй датчики активности.

3. Система по п.2, отличающаяся тем, что первый датчик активности размещен на трубопроводе между третьими отверстиями четвертого и второго клапанов и выполнен в виде бета-детектора.

4. Система по п.1, отличающаяся тем, что радиационная защита сборника отходов выполнена в виде защитного бокса, включающего

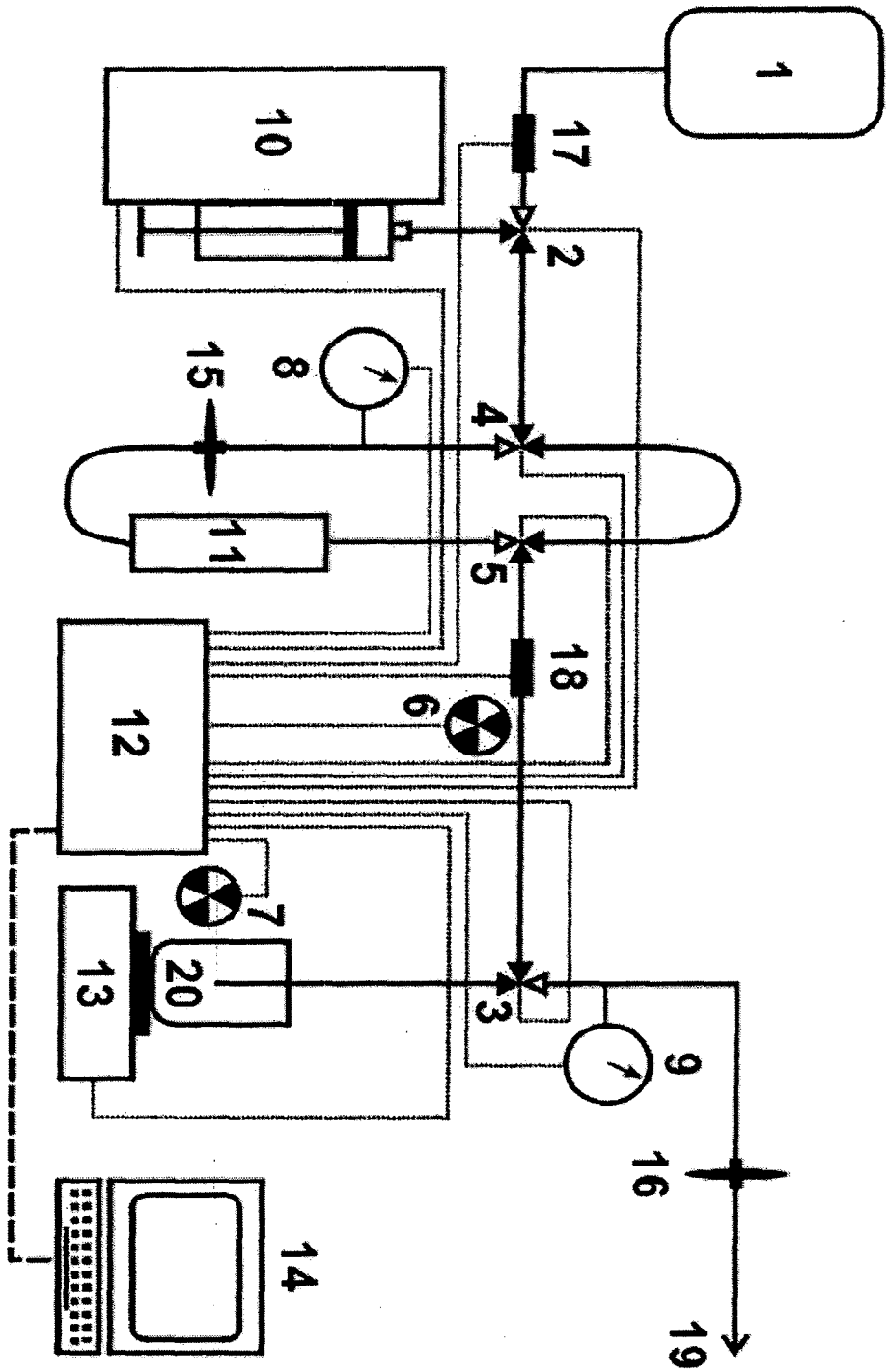
средство контроля веса отходов, выполненного в виде датчика усилия, а в отверстии

защитного бокса установлен второй датчик активности для определения радиоактивности отходов, в виде гамма-детектора.

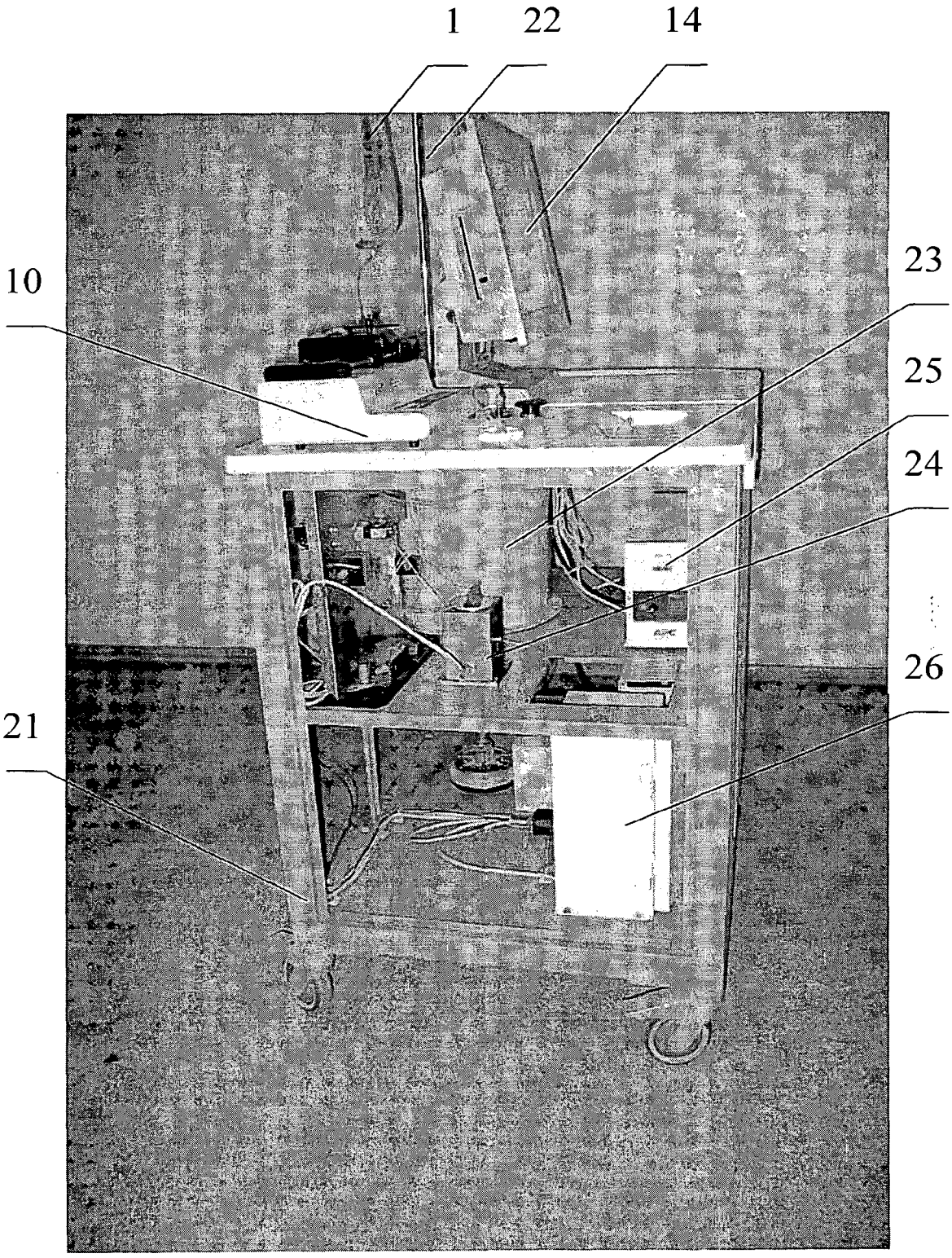
5. Система по п.1, отличающаяся тем, что стронций – рубидиевый генератор имеет радиационную защиту, включающую внешний основной и транспортный защитные контейнеры, при этом основной защитный контейнер стационарно установлен на полке тележки.

6. Система по п.1, отличающаяся тем, что она установлена в закрытом перемещаемом корпусе.

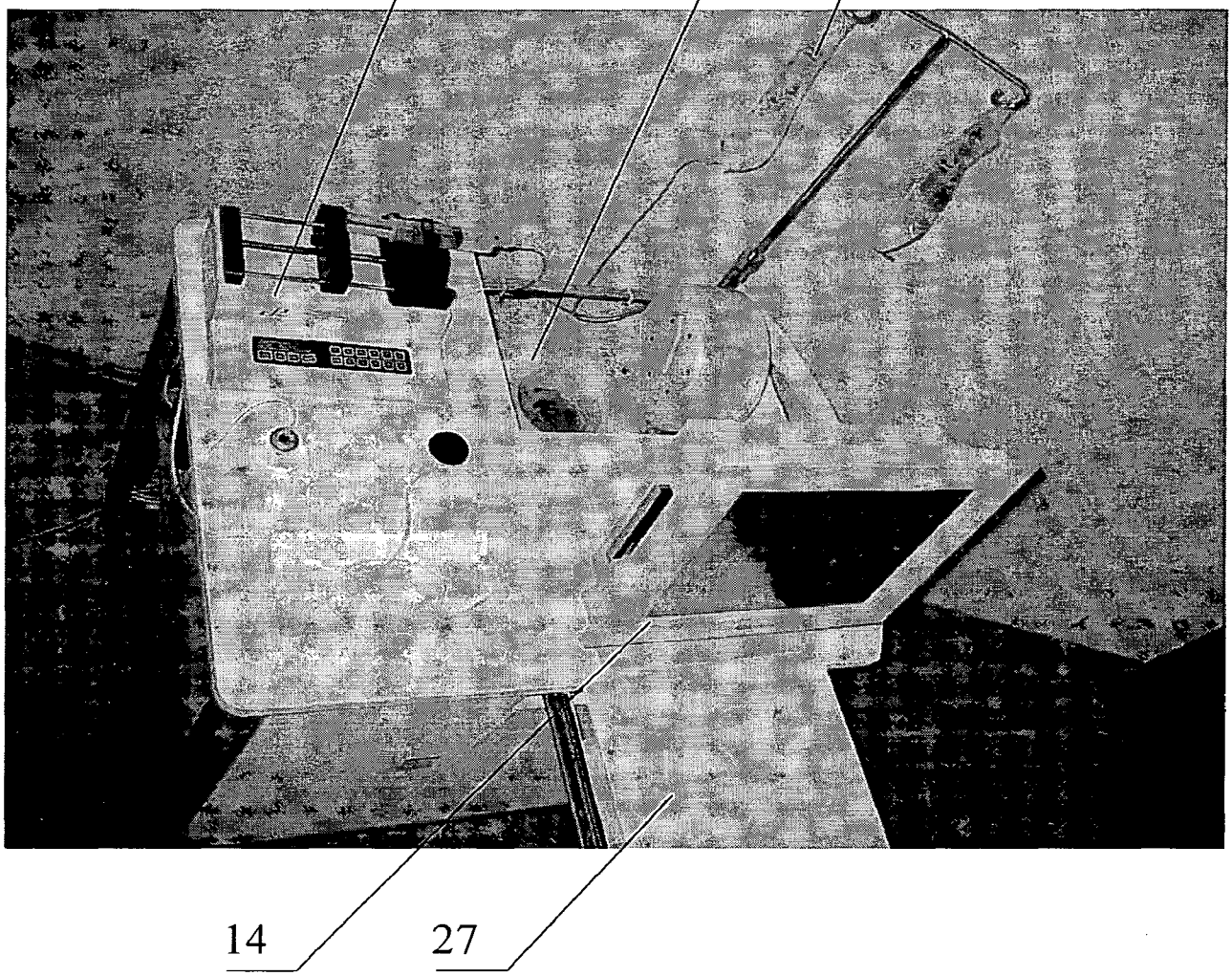
7. Система по п.6, отличающаяся тем, что корпус снабжен сдвигающейся столешницей.



Фиг. 1



Фиг. 2



Фиг. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU2008/000211

A. CLASSIFICATION OF SUBJECT MATTER

A61M 5/168 (2006.01)
A61M 36/06 (2006.01)
A61B 6/00 (2006.01)

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 36/00-36/06, 5/00-5/155, AGIB 6/00-6/10, A61M 5/168

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)
http://www. uspto. gov; http://depatisnet.dpma.de; http://ep.espacenel.com; http://www.fips.ru; http://www.eapatis.com

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4562829 A (E.R. SQUIBB & SONS, INC.), 07.01.1986, the abstract, figure 1	1-7
A	EP 0310148 A (E.R. SQUIBB & SONS, INC), 05.04.1988, the claims, figure	1-7
A	RU 2219959 C2 (FEDERALNOE GOSUDARSTVENNOE UNITARNOE PREDPRIYATIE NAUCHNO-ISSLEDOVATELSKY INSTITUT ELEKTROMEKHANIKI) 27.12.2003, the claims, figure 1	1-7

☐ 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
24 July 2008	04 September 2008
Name and mailing address of the ISA/ RU	Authorized officer
Facsimile No.	Telephone No.

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

ОТЧЕТ О МЕЖДУНАРОДНОМ ПОИСКЕ

Международная заявка № PCT/RU 2008/000211

А. КЛАССИФИКАЦИЯ ПРЕДМЕТА ИЗОБРЕТЕНИЯ: ***A61M 5/168*** *(2006.01)*
A61M 36/06 *(2006.01)*
Согласно Международной патентной классификации МПК ***A61B 6/00*** *(2006.01)*

В. ОБЛАСТИ ПОИСКА:

Проверенный минимум документации (система классификации с индексами классификации):

Другая проверенная документация в той мере, в какой она включена в поисковые подборки:

A61M 36/00-36/06, 5/00-5/155, A61B 6/00-6/10, A61M 5/168

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С. ДОКУМЕНТЫ, СЧИТАЮЩИЕСЯ РЕЛЕВАНТНЫМИ:

Категория*	Цитируемые документы с указанием, где это возможно, релевантных частей	Относится к пункту №
A	US 4562829 A (E.R. SQUIBB & SONS, INC.) 07.01.1986, реферат, фиг. 1	1-7
A	EP 0310148 A (E.R. SQUIBB & SONS, INC) 05.04.1989, формула, фиг.	1-7
A	RU 2219959 C2 (ФЕДЕРАЛЬНОЕ ГОСУДАРСТВЕННОЕ УНИТАРНОЕ ПРЕДПРИЯТИЕ НАУЧНО-ИССЛЕДОВАТЕЛЬСКИЙ ИНСТИТУТ ЭЛЕКТРОМЕХАНИКИ) 27.12.2003, формула, фиг. 1	1-7

☐ последующие документы указаны в продолжении графы С. ☐ данные о патентах-аналогах указаны в приложении

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(54) Title: STRONTIUM-82/RUBIDIUM-82 GENERATOR, METHOD FOR PRODUCING A RUBIDIUM-82 COMPRISING DIAGNOSTIC AGENT, SAID DIAGNOSTIC AGENT AND ITS USE IN MEDICINE

(57) Abstract: The invention relates to a strontium-82/rubidium- 82 generator, comprising a column filled with a cationic exchanger loaded with strontium-82, and having an inlet and an outlet, and a liquid medium, wherein parts of the column, inlet and outlet coming into contact with the liquid medium are iron-free, preferably metal-free, to a method for producing rubidium-82, and to the obtained diagnostic agent.

STRONTIUM-82/RUBIDIUM-82 GENERATOR, METHOD FOR PRODUCING A RUBIDIUM-82 COMPRISING DIAGNOSTIC AGENT, SAID DIAGNOSTIC AGENT AND ITS USE IN MEDICINE

The present invention relates to a strontium-82/rubidium-82 generator, to a method for producing a rubidium-82 comprising diagnostic agent using such strontium-82/rubidium-82 generator, to the diagnostic agent obtainable therewith, and to the use of this diagnostic agent in medicine.

In nuclear medicine conventional diagnostic techniques are applied for coronary artery disease imaging and for the determination of the severity of the disease. Diagnostic agents used for the determination of myocardial perfusion comprise thallium-201 or technetium-99m. However, these diagnostic agents are limited in use by the occurrence of attenuation artefacts and do not permit an accurate estimation of extension and severity of coronary artery disease.

These drawbacks make rubidium a better choice as a potassium-analog. Rubidium-82 is suitable for positron emission tomography, because Rubidium-82 is a positron emitter rendering higher quality images than conventional gamma camera imaging. Moreover Rubidium-82 is a radionuclide with an ultra-short half-life ($t_{1/2}$=75s). This ultra-short half life allows high doses at short imaging times but urges production of rubidium-82 near the patient.

Presently, a strontium-82/rubidium-82 generator comprises a generator column assembly comprising adaptors with nuts and ferrules, a column and two micro filters. The generator column is about 2.6cm in length, 6mm internal diameter and has a 0.5mm wall thickness. All

components are made of stainless steel type 316. The cationic exchanger may be α-hydrous tin oxide loaded with about 50mCi strontium-82. The liquid medium in the strontium-82 loaded cationic exchanger is physiological 0.9% sodium chloride. Sterile and pyrogen free 0.9% sodium chloride is also used as elution medium.

This known strontium-82/rubidium-82 generator may be used for several days to several weeks. However, the known generator is not sufficiently stable for use during an extended period of time. Such stability is determined by a so-called breakthrough of strontium-82 during elution. An early breakthrough of strontium-82 blocks the possibility of reloading the cationic exchanger with strontium-82 for a continued production of the rubidium-82 diagnostic agent. Furthermore, using a generator for an extended period of time requires a method of sterilization of it.

Further research revealed that by using a physiological buffer having a pH of 6-8.5 as an elution medium for rubidium-82, the stability of the strontium-82/rubidium-82 generator can be substantially improved. A substitution of the physiological 0.9% sodium chloride elution medium by a physiological buffer having a pH of 6-8.5 as such is not recommendable in relation to the daily use of the generator. In particular, after use of a sterilization medium in the form of hypochlorite solution it turned out that a gelatinatious material is formed jeopardizing the functionality of the strontium-82/rubidium-82 generator, in particular because the column filters become clogged and ultimately blocked.

The present invention is based on the insight that a strontium-82/rubidium-82 generator having parts coming into contact with the liquid medium, which part has been made of iron-free and preferably of metal-free

material, that such clogging gelatinatious material is not formed and the generator has the desired improved stability and may be reloaded with strontium-82 several times without any significant breakthrough of strontium-82. At the same time, optimal performance and sterility are maintained. The continued use of the strontium-82/rubidium-82 generator and the option of reloading without significant strontium-82 breakthrough results in an extended operation time period before the generator is to be recycled and the cationic exchanger renewed and subsequently loaded again with strontium-82. This results in an extensive reduction in costs.

For instance, a generator according to the invention may be used over an extended period of time such as 2-6 months at substantially constant stability.

Accordingly, the present invention provides a strontium-82/rubidium-82 generator, comprising a column filled with a cationic exchanger loaded with strontium-82, and having an inlet and an outlet, and a liquid medium, wherein parts of the column, inlet and outlet coming into contact with the liquid medium are iron-free, preferably metal-free.

This strontium-82/rubidium-82 generator according to the invention is suitable for elution with a physiological buffer having a pH of 6-8.5 and for sterilization using a hypochlorite solution, without the occurrence of deteriorating clogging and ultimately blocking of the generator due to the formation of gelatinatious material. Without being bound to any theory, it might be that the gelatinatious material formed comprises a water insoluble iron salt. Iron likely originates from the metallic parts of the generator and the counter ions such as phosphate, originate from the elution medium being a physiological buffer, for instance

a phosphate buffer saline solution having a pH of 7.2-7.4.

It is possible that the strontium-82/rubidium-82 generator during storage, transport or out of use for other reasons, may comprise a liquid medium other than the elution medium according to the invention. But, for elution and for maintaining the extended stability, it is required according to the invention that the elution medium for rubidium-82 is a physiological buffer having a pH of 6-8.5. The lower limit for the pH is selected such as to allow to an acceptable extent such as per volume, the elution of rubidium-82 from the cationic exchanger. Accordingly, the lower is the pH, the better is the rubidium-82 elution. However, due to the very short half time of rubidium-82, it is required that the elution medium is almost directly to be administered by for instance intravenous injection into the patient. Preferred is therefore a physiological buffer having a pH in the range of 7-8 and more preferably in the range of 7.2-7.4. A physiological buffer involves that the osmolarity of the buffer is selected such that the injection into a patient will not result in any adverse effects, taking into account a volume to be injected of about 2-30ml at a rate of about 10-80ml/minute.

Suitable physiological buffers comprise citrate/sodium hydroxide buffer, citrate/phosphate buffer, borate/hydrogen chloride buffer, boric acid/sodium hydroxide buffer, Tris buffer, veronal/HCl buffer and piperazine/sodium hydroxide buffer. Preferred physiological buffers are carbonate buffers, phosphate buffers and Tris buffers.

In order to avoid any leaching of metal from the generator, the part of column, inlet and outlet inclusive ferrules, tubings and the like are to be made of iron-

free and preferably metal-free material or coated with metal-free material.

Metal-free means in particular iron-free. Accordingly, it is possible that the column, inlet and outlet or any generator elements may be made of an iron-free metal, such as titanium. However, in the alternative it is preferred that the relevant parts of the column inlet and outlet coming into contact with the liquid medium are made of less expensive metal-free material. A suitable metal-free material is a plastic such as PEEK or Teflon. PEEK material is preferred because PEEK material is already used for columns, inlet and outlet within the HPLC chromatography technique. Such plastic material is of lower costs than iron-free metal material suitable for use in the generator.

In order to guarantee that the rubidium-82 produced as a diagnostic agent with the strontium-82/rubidium-82 generator is suitable for human use intravenously it is mandatory that the generator is frequently, and when needed, sterilized using a sterilization medium. Such sterilization medium is preferably hypochlorite solution of suitable concentration. Hypochlorite has the advantages of a broad anti-bacterial and anti-viral spectrum, relatively easy removal by washing from the generator, and a low detection level. Prior to use this sterilization medium has to be exchanged for either a storage and transportation medium, or directly with the physiologically buffer intended as the elution medium.

A full operation generator assembly for generating and producing the rubidium-82 diagnostic agent in the direct presence of a patient is feasible when the generator comprises

i) a source for the physiological elution buffer;

ii) a source for the sterilisation buffer;

iii) a pump for connecting and transporting the sources to the inlet of the column;

iv) a dose calibrator connected to the outlet of the column; and

v) a patient administration line connected to the dose calibrator.

Such generator is a full service generator for elution, sterilization, and application to the patient and for measuring the radioactive dose generated and a continuous survey of a possible breakthrough of strontium-82. With such full service generator it is preferred that the generator is arranged on a mobile vehicle, such as it is easily transportable between the storage, the radiopharmacy laboratory and the diagnostic room.

It is noted that any cationic exchanger may be used as long as rubidium-82 is selectively eluted. A suitable material is tin oxide, such as α-hydrous tin oxide ($Sn_2O.xH_2O$; x=1-2) or α stannic acid.

Another aspect of the present invention relates to the production of rubidium-82. This method comprises the use of the afore mentioned strontium-82/rubidium-82 generator according to the invention and to elute the generator with the elution buffer being a physiological buffer having in general a pH of 6-8.5, preferably a pH of 7-8 and more preferably of 7.2-7.4. Accordingly, this rubidium-82 diagnostic agent is essentially characterized by the presence of this well defined elution buffer.

As discussed here and above, the methods of the present invention allow the sterilization of the strontium-82/rubidium-82 generator using a sterilization buffer, preferably in the form of a hypochlorite solution. Accordingly, the sterilization of the generator

is guaranteed as well as the sterile and pyrogen free character of the rubidium-82 produced therewith.

A last aspect of the present invention relates in particular to the diagnostic agent being in the form of a solution with the elution buffer being the afore mentioned physiological buffer having a pH of 6-8.5. Such diagnostic agent is suitable for use in medicine such as for myocardial perfusion imaging.

Mentioned and other features and advantages of the generator, its production process and its use as a diagnostic agent will be further illustrated in the description of the drawings and the example which follow and which are given for illustrative purposes without the intention to limit the present invention to any extent.

Figure 1 is a schematic illustration of the rubidium-82 generator in the form of a full surface generator suitable for direct application to a patient;

Figure 2 shows the activity of strontium-82 (Bq) in the eluate per 37MBq rubidium-82, the maximum allowable ratio of Sr-82/Rb-82 is about 750 (ppm); and

Figure 3 shows the activity of strontium-85 (Bq) in the eluate of the generator per 37MBq rubidium-82. The maximum ratio Sr-85/rubidium-82 is about 7500 ppm.

Figure 4 shows the contamination of Sr-82 in the generator's eluate.

Figure 5 shows the contamination of Sr-82 in the eluates expressed as Bq Sr-82 per MBq Rb-82.

Figure 6 shows the contamination of Sr-85 in the eluates expressed as Bq Sr-85 per MBq Rb-82.

Figure 1 shows a strontium-82/rubidium-82 generator 1 according to the invention. The generator 1 comprises a column 2 made of PEEK. The column has the following dimensions (length 5.0 cm, internal diameter 0.75 cm, wall thickness 3.25 mm). The column 2 is loaded

with 4 grams α stannic acid (particle size 75-150µm) in 0.1N ammonium chloride buffer. The column 2 is washed with 0.1N ammonium chloride (pH 10). Subsequently, the column is washed with 2M sodium chloride and with 0.05% hypochlorite solution. The inlet 3 and the outlet 4 are provided with a valve 5 and 6. The inlet 3 is connected to a multi-valve 7 and the outlet 4 to a multi- valve 8. A bypass 9 extends between the multi-valves 7 and 8 which allows transporting liquid medium through the generator 1 while bypassing the column 2.

Strontium-82 (>25mCi Sr-82/mg Sr, Sr-85/Sr-82<5, Rb-83/Sr-82<0.15; Rb-84/Sr-82< 0.15; Sr-83/Sr-82<0.0015; other nuclides/SR-82<0.01) was neutralized with 0.5ml 0.5M Tris buffer (pH 7.5). After the addition of 3.5ml physiological buffered saline, the mixture was applied via a milipore filter (22µm) on the column 2. Subsequently, the column 2 is washed with phosphate buffered saline pH 7.4 (8.2g sodium chloride, 3.1g $Na_2HPO_4.12H_2O$ and 0.3g $NaH_2PO_4.2H_2O$ from the container 15.

The 0.05% hypochlorite solution was applied from a container 11 via a multi-valve 12, an air bubble trap 13, the peristaltic pump 14, the filter 10 and then via the valve 7 and 5 to the column 2. It is noted that the tubings are made of PEEK tubings. The column filters (not shown) are 10 µm titanium filters or metal filter holders coated with PEEK or Teflon coating. The sterile filters are Millex Millipore 0.22 µm membrane filters, diameter 25 mm.

Prior to use for patients, the generator 1 is flushed with physiological buffered saline originating from the container 15 until the eluate does not color a 10% potassium iodide solution. Subsequently, the phosphate elution buffer (pH 7.4) is applied from the source 16 through the column 2. The eluate comprising

rubidium-82 is passed through a dose calibrator 17 calibrated for rubidium-82 measurement.

Figure 2 shows the activity of strontium-82 in the eluate of the column 2 dependent on the elution volume. Clearly, the maximum allowable ratio of SR-82/RB-82 (about 750ppm) was never surpassed except for one occasion which occurred after the third reload of the column 2 with strontium-82. During testing a large amount of air was introduced on the column 2. In an attempt to remove this air the increased leakage of strontium-82 occurred. After normalization the ratio SR-82/RB-82 remained far below the maximum allowable value over several reloads of the same column 2.

The dose calibrator 17 is connected via a multi valve 18 with either a waste container 19 or to a valve 20 for subsequent administration to the patient. However, the tubing 21 could be disconnected at the connection 22 and directly used for administration to the patient.

Filters 23, 24 and 25 guarantee sterile manipulation of the generator 1.

The measuring mode of the dose calibrator 17 is the integral mode. Accordingly, after the desired dose of strontium-82 is eluted from the column 2 the valves towards the column 2 are closed and elution medium is transported via the bypass tube 9 for flushing the system.

After a waiting time of about 5 minutes a subsequent elution and generation of a new strontium-82 diagnostic agent dose is possible.

After use the system is sterilized by flushing from the container 11 the 0.05% hypochlorite solution. The generator 1 may be stored in the hypochlorite solution or in physiological buffered saline or in the elution buffer.

The diagnostic agent comprising rubidium-82 in the physiological buffer having a pH of 6-8.5 showed during myocardial perfusion imaging with positron emission tomography with better imaging quality at lower radiation exposure to patient. The function of the heart could be determined under rest and stress with an in between waiting time of about 6 minutes for applying the adenosine or dobutamine infusion as a stress generating agent.

Figure 3 shows the activity of strontium-85 (Bq) in the eluate of the generator per 37MBq rubidium-82. The maximum ratio SR-85/rubidium-82 is about 7500 ppm. The activity of strontium-85 is well below the maximum of the ratio of Sr-82/Rb-82.

The increased stability of the strontium binding to the carrier material (hydrous stannic oxide) is obtained by increasing the pH to a value of 7.4 by means of a phosphate buffered saline, used as elution fluid. This increased stability allows an extended period of use of the generator of at least 3 supplementary months as compared to commercially available generators which have to be replaced each month. The generator can be refilled every 4 weeks reducing the costs for strontium-82 significantly.

EXAMPLE

In order to illustrate the contamination of generator eluates with Sr-82 and Sr-85 the following experiment was performed.

On day 1 a typical generator column was loaded with 2.3 GBq Sr-82. The generator was eluted repeatedly with phosphate buffered saline (PBS) at pH=7.4. On day 26 and at an elution volume of 3.2 liter the generator was reloaded with 2.2 GBq Sr-82. Again, the generator was

eluted repeatedly with PBS. On day 66 and at a total elution volume of 6.3 liter the generator was reloaded for a second time with 1.2 GBq Sr-82. Again, the generator was eluted repeatedly with PBS (pH=7.4). The total elution volume was 7.9 liter.

Figure 4 represents the contamination of Sr-82 in the generator's eluate. The curve spikes represent the moments of reloading. Figure 5 shows the contamination of Sr-82 in the eluates (lower curve) expressed as Bq Sr-82 per 37 MBq Rb-82 and the maximal contamination of Sr-82(higher curve) acceptable in the currently commercially available Rb-82 generators (Bracco). The level of contamination of Sr-82 is well below the acceptable contamination in the known generators. Figure 6 shows the contamination of Sr-85 in the eluates (lower curve) expressed as Bq Sr-85 per 37 MBq Rb-82 and the maximal contamination of Sr-85 (higher curve) acceptable in currently commercially available Rb-82 generators (Bracco). The level of contamination of Sr-82 is well below the acceptable contamination in the known generators. After three loadings and an elution volume of approximately 8 liters the contaminations of Sr-82 and Sr-85 are still far below the limit. Reloading a Sr-85/Rb-82 generator is of advantage because it reduces costs for Sr-82 by 30% and makes the transport of the generator back to the factory unnecessary.

CLAIMS

1. Strontium-82/rubidium-82 generator, comprising a column filled with a cationic exchanger loaded with strontium-82, and having an inlet and an outlet, and a liquid medium, wherein parts of the column, inlet and outlet coming into contact with the liquid medium are iron-free, preferably metal-free.

2. Generator according to claim 1, wherein the liquid medium is an elution medium for rubidium-82, and is a physiological buffer having a pH of 6 to 8.5, preferably a pH of 7 to 8, more preferably a pH of 7.2 to 7.4.

3. Generator according to claim 1 or 2, wherein the physiological buffer is a carbonate buffer, phosphate buffer or Tris buffer.

4. Generator according to any one of claims 1 to 3, wherein the parts of the column, the inlet and the outlet are coated with a iron-free material and/or are made from a iron-free material, preferably metal free material.

5. Generator according to claim 4, wherein the metal-free material is a plastic, such as PEEK or Teflon.

6. Generator according to any one of claims 1 to 5, wherein the liquid medium is a sterilization medium, preferably a hypochlorite solution.

7. Generator according to any one of claims 1 to 6, comprising:

i) a source for the physiological elution buffer;

ii) a source for the sterilisation buffer;

iii) a pump for connecting and transporting the sources to the inlet of the column;

iv) a dose calibrator connected to the outlet of the column; and

v) a patient administration line connected to the dose calibrator.

8. Generator according to claim 7, arranged on a mobile vehicle.

9. Generator according to any one of claims 1 to 8, wherein the cationic exchanger is reloaded at least one time with strontium-82.

10. Method for producing a rubidium-82 comprising a diagnostic agent, comprising the steps of eluting a strontium-82/rubidium-82 generator according to any one of claims 1 to 9 with the elution buffer defined in any one of claims 2 to 9.

11. Method according to claim 10, comprising the step of sterilizing the strontium-82/rubidium-82 generator using a sterilization buffer, preferably a hypochlorite solution.

12. Method according to claim 10 or 11, comprising the step of storing/transporting the strontium-82/rubidium-82 generator.

13. Diagnostic agent obtainable with the method according to any one of claims 10 to 12.

14. Diagnostic agent according to claim 13, for use in medicine, such as for myocardial perfusion imaging.

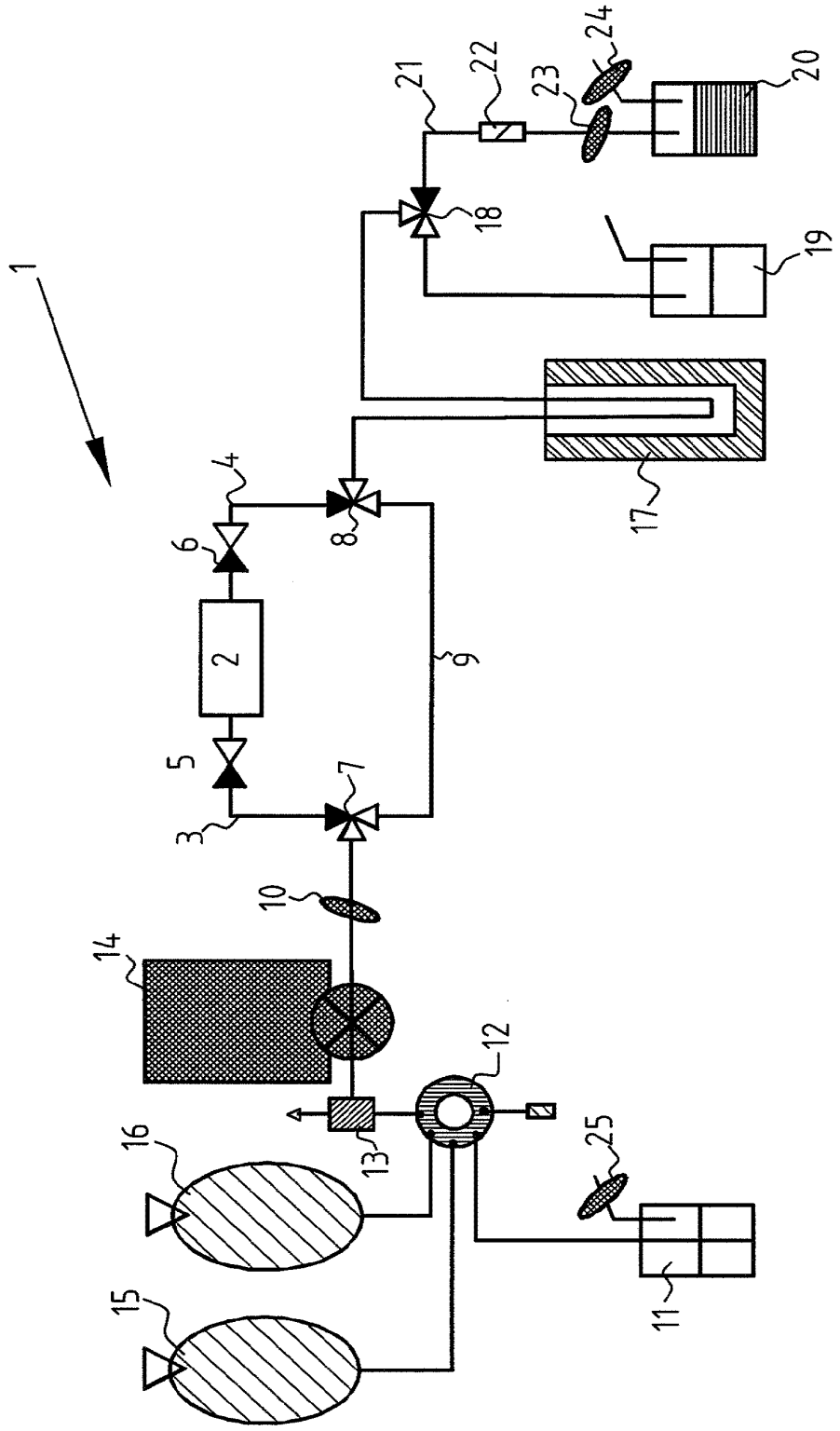


FIG. 1

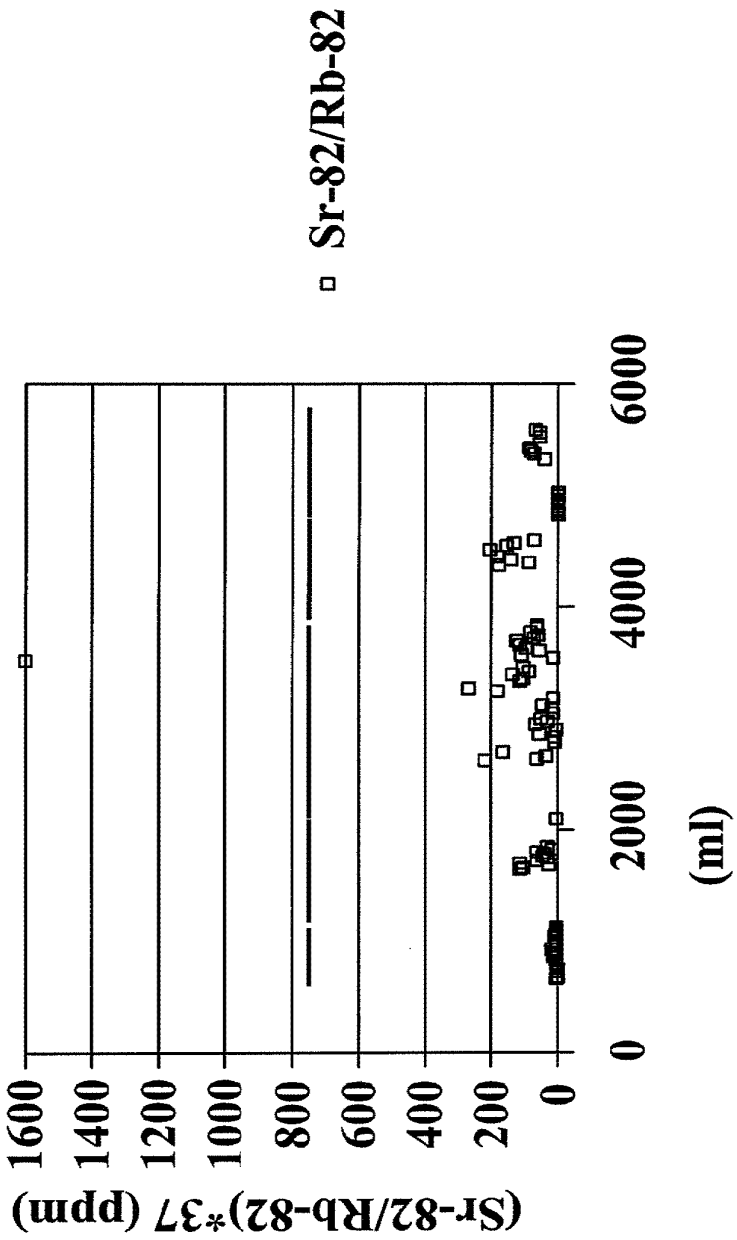

Sr-82/Rb-82
(Sr-82/Rb-82)*37 (ppm)
1600
1400
1200
1000
800
600
400
200
0
0
2000
4000
6000
(ml)

FIG. 2

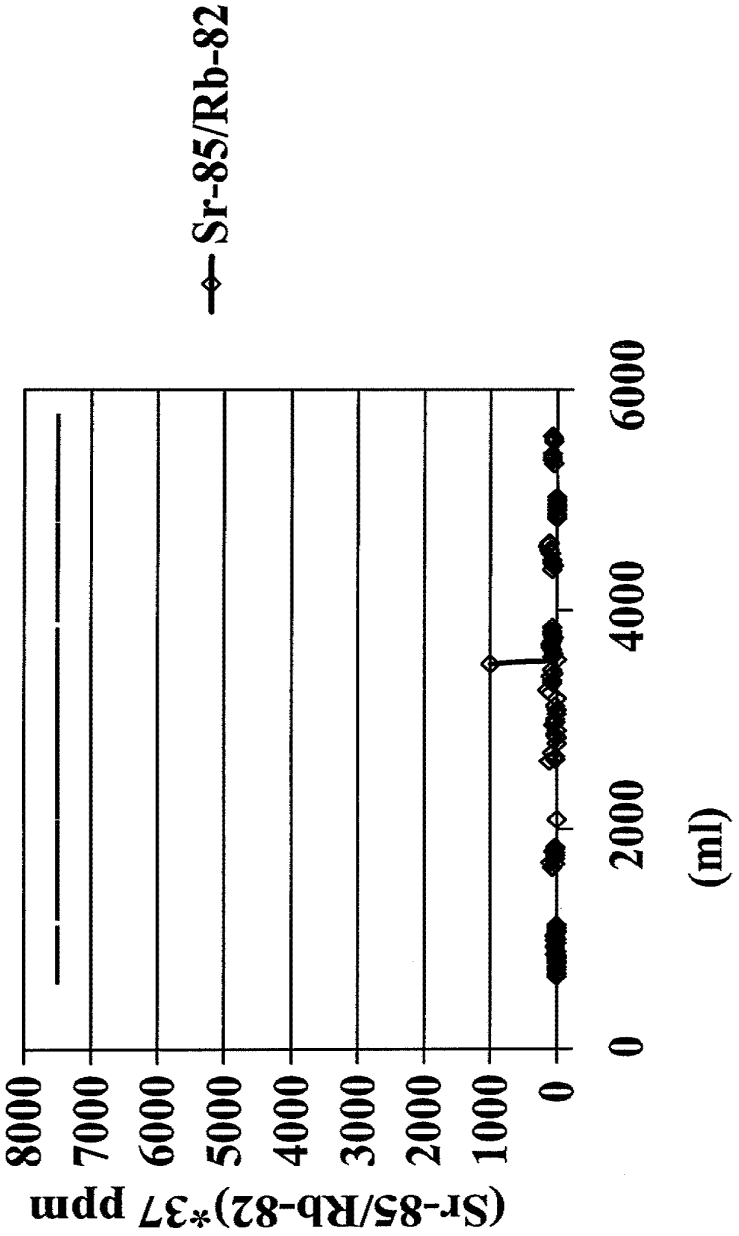
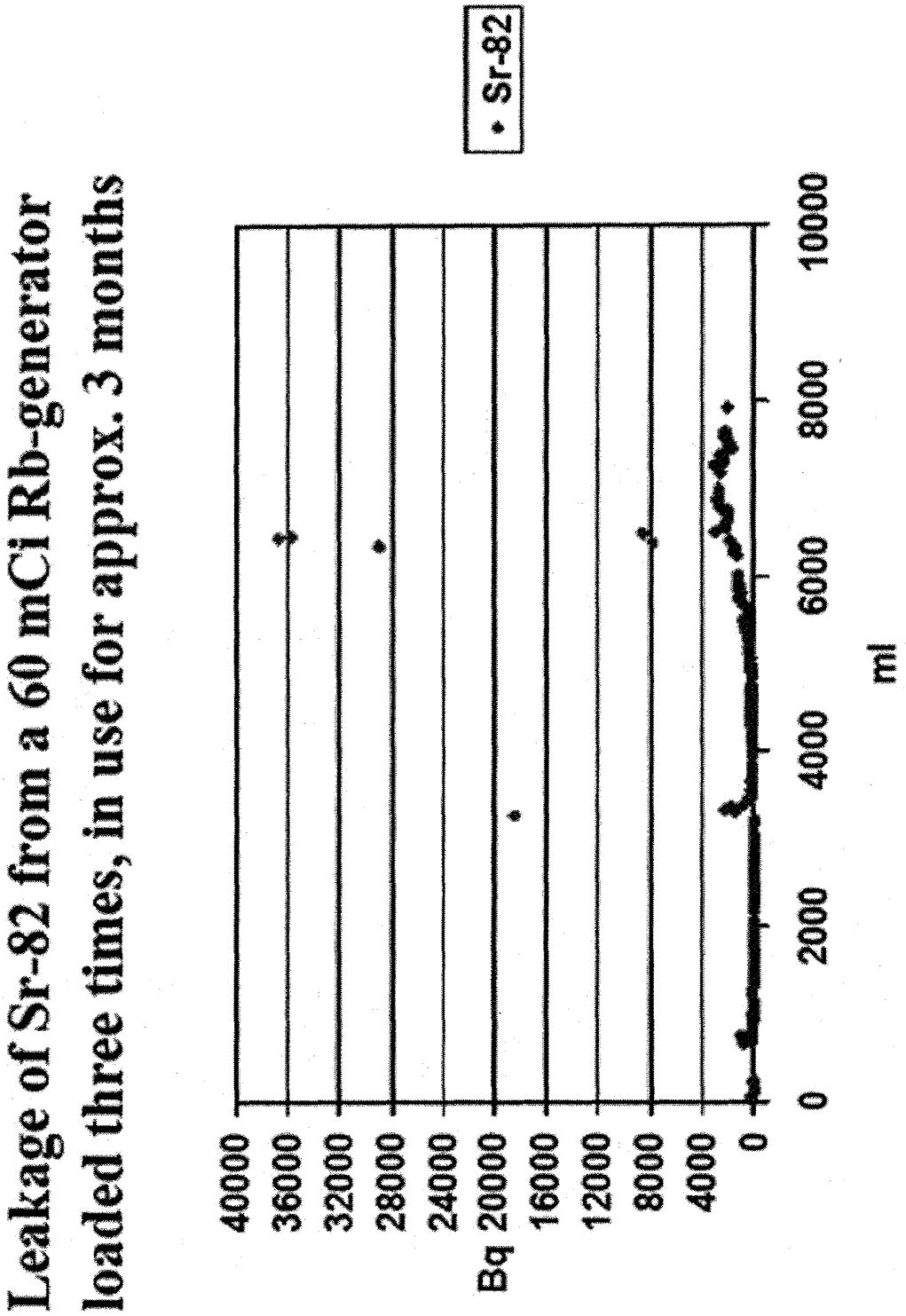

Sr-85/Rb-82
(Sr-85/Rb-82)*37 ppm
8000
7000
6000
5000
4000
3000
2000
1000
0
0
2000
4000
6000
(ml)

FIG. 3


Leakage of Sr-82 from a 60 mCi Rb-generator loaded three times, in use for approx. 3 months
Sr-82
Bq
ml
0
4000
8000
12000
16000
20000
24000
28000
32000
36000
40000
0
2000
4000
6000
8000
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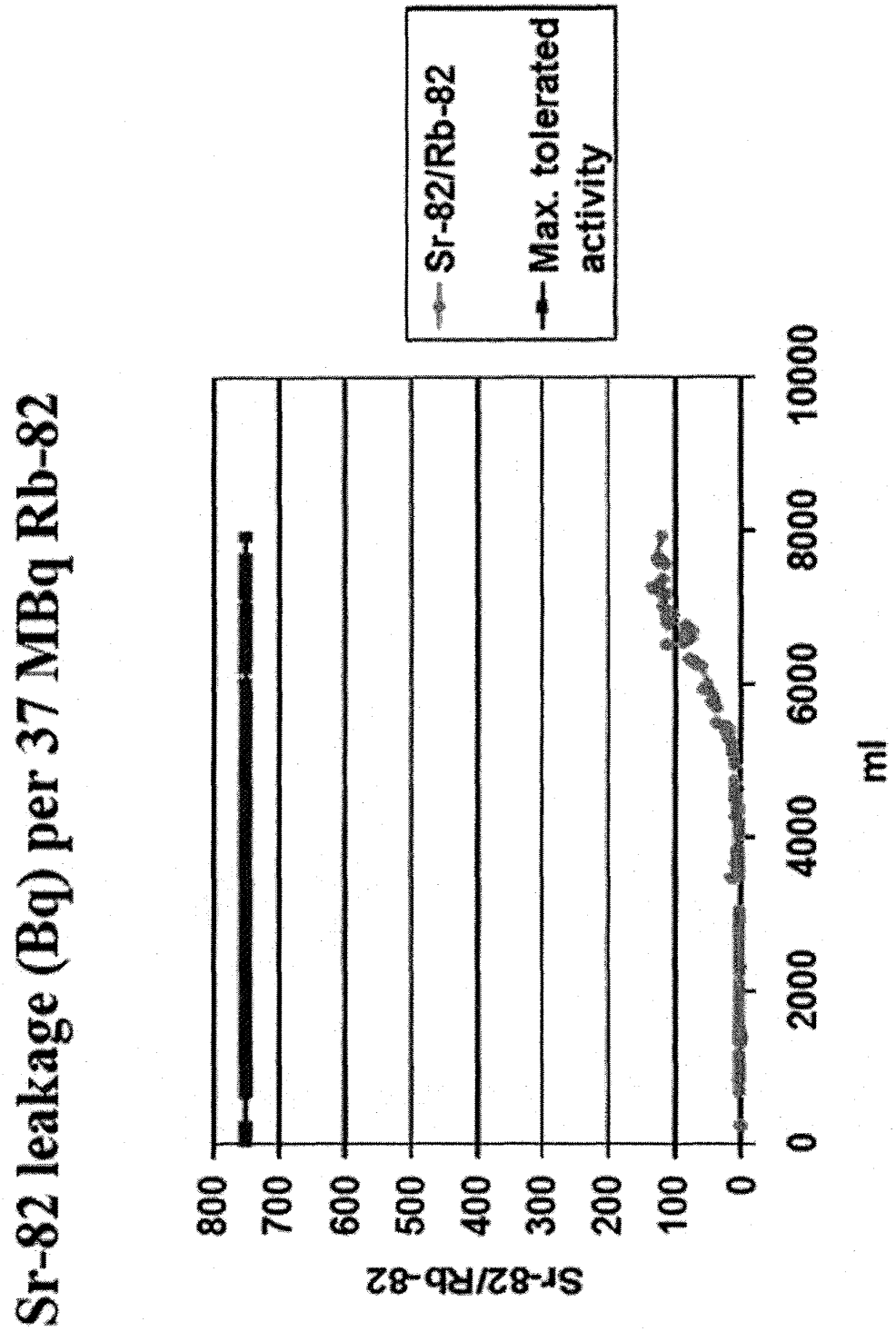
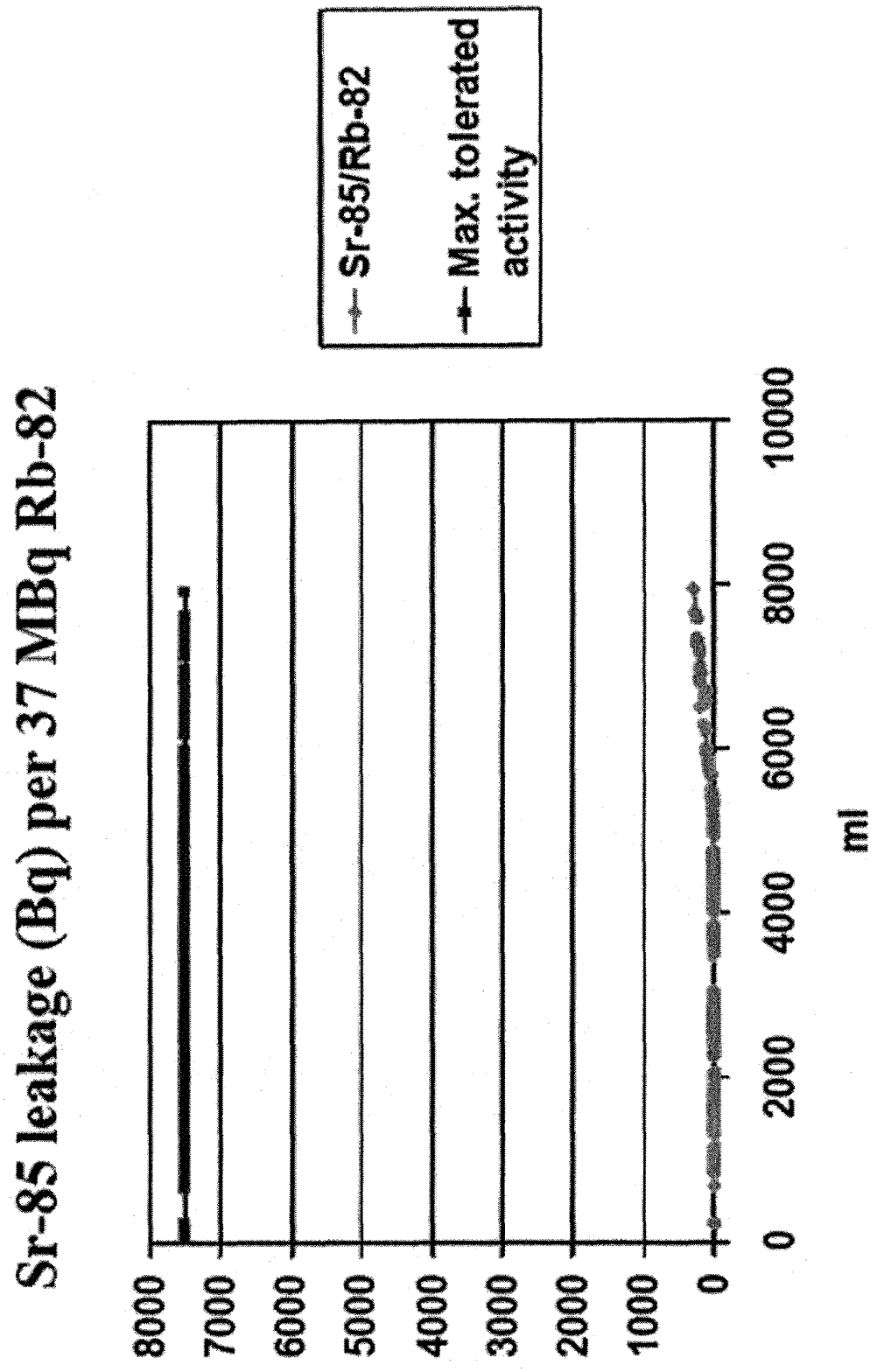

Sr-82 leakage (Bq) per 37 MBq Rb-82
Sr-82/Rb-82
Max. tolerated activity
Sr-82/Rb-82
800
700
600
500
400
300
200
100
0
0
2000
4000
6000
8000
10000
ml


Sr-85 leakage (Bq) per 37 MBq Rb-82
Sr-85/Rb-82
Max. tolerated activity
8000
7000
6000
5000
4000
3000
2000
1000
0
0
2000
4000
6000
8000
10000
ml

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060584

A. CLASSIFICATION OF SUBJECT MATTER
INV. G21G4/08

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)
G21G A61K B01D

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 2006/135374 A (LYNNTECH INC [US]; MOLLER TERESIA [US]; ADAMS TODD [US]; CISAR ALAN [U) 21 December 2006 (2006-12-21) paragraphs [0008], [0009], [0029] - [0040], [0042], [0092] - [0095]; figure 5	1-4,6, 9-14
X	WO 2004/105049 A (UNIV ALBERTA SIMON FRASER UNIV [CA]; ZYUZIN ALEXANDER [CA]) 2 December 2004 (2004-12-02) page 2, lines 1-18	1,4,9, 10,12-14
A	US 2007/140958 A1 (DEKEMP ROBERT A [CA]) 21 June 2007 (2007-06-21) paragraph [0019]	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 2009	07/12/2009

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/060584

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006135374 A	21-12-2006	NONE	
WO 2004105049 A	02-12-2004	US 2006022127 A1	02-02-2006
US 2007140958 A1	21-06-2007	AU 2006326814 A1	28-06-2007
		CA 2562340 A1	21-06-2007
		WO 2007071022 A1	28-06-2007
		EP 1973624 A1	01-10-2008
		JP 2009520953 T	28-05-2009

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

Electronic Acknowledgement Receipt

EFS ID:	8149892
Application Number:	12808467
International Application Number:	
Confirmation Number:	3733
Title of Invention:	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE
First Named Inventor/Applicant Name:	Stephen E. Hidem
Customer Number:	22859
Filer:	Elisabeth Lacy Belden
Filer Authorized By:	
Attorney Docket Number:	56782.1.7.2
Receipt Date:	04-AUG-2010
Filing Date:	
Time Stamp:	10:46:09
Application Type:	U.S. National Stage under 35 USC 371

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	Information Disclosure Statement (IDS) Filed (SB/08)	SIDS_56782-1-7-2.pdf	880837 a70888f0236cbcc6780edb5a5636859c9c270ac3	no	5

Warnings:	
Information:	

2	Foreign Reference	WO2004059661A1.pdf	1378510 90312f92d7372cc3550f43aebce82c4c3bd9cd9d	no	27
Warnings:					
Information:					
3	Foreign Reference	WO2006026603A2.pdf	2131441 5c57ca5831eba5bdeb48e1135fbd24aeca2aabe1	no	58
Warnings:					
Information:					
4	Foreign Reference	WO2006135374A2.pdf	2328171 b564acc91f94f50b33ee35c287905b5ebdeffa25	no	49
Warnings:					
Information:					
5	Foreign Reference	WO2008140351.pdf	7418231 d0ce814cc2983495bdb5706c807d21fd88031eaa	no	28
Warnings:					
Information:					
6	Foreign Reference	WO2010020596A1.pdf	855471 cce61168205cab3246c9da57caa8a9e4ef9f0749	no	22
Warnings:					
Information:					
		Total Files Size (in bytes):	14992661		

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.

PTO-1390 (Rev. 09-08)
Approved for use through 2/28/2010. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
56782.1.7.2	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US2009/047031	11 June 2009	11 June 2008

TITLE OF INVENTION
Infusion Systems Including Computer-Facilitated Maintenance and/or Operation and Methods of Use

APPLICANT(S) FOR DO/EO/US
Stephen E. HIDEM, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☑ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 35 U.S.C. 371.
3. ☑ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☑ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☐ has been communicated by the International Bureau.
   c. ☑ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☑ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☑ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☑ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☑ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☑ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☑ A preliminary amendment.
14. ☑ An Application Data Sheet under 37 CFR 1.76.
15. ☐ A substitute specification.
16. ☐ A power of attorney and/or change of address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.3 and 37 CFR 1.821- 1.825.
18. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
	PCT/US2009/047031	56782.1.7.2

20. Other items or information:

International Search Report, Written Opinion, Form PCT/IB/308

The following fees have been submitted	CALCULATIONS	PTO USE ONLY
21. ☑ Basic national fee (37 CFR 1.492(a)) **$330**	$ 330	
22. ☑ Examination fee (37 CFR 1.492(c)) If the written opinion prepared by ISA/US or the international preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** All other situations **$220**	$ 220	
23. ☑ Search fee (37 CFR 1.492(b)) If the written opinion of the ISA/US or the International preliminary examination report prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... **$0** Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority ..... **$100** International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... **$430** All other situations **$540**	$ 430	
TOTAL OF 21, 22 and 23 =	980	

☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing in compliance with 37 CFR 1.821(c) or (e) in an electronic medium or computer program listing in an electronic medium) (37 CFR 1.492(j)).
The fee is **$270** for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round **up** to a whole number)	RATE	
- 100 =	/50 =		x $**270**	$

Surcharge of **$130.00** for furnishing any of the search fee, examination fee, or the oath or declaration after the date of commencement of the national stage (37 CFR 1.492(h)).	$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	$	
Total claims	38 - 20 =	18	x $ **52**	$ 936	
Independent claims	5 - 3 =	2	x **$220**	$ 440	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$390**	$	
			TOTAL OF ABOVE CALCULATIONS =	$ 2356	
☐ Applicant claims small entity status. See 37 CFR 1.27. Fees above are reduced by ½.					
			SUBTOTAL =	$ 2356	
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(i)). +				$	
			TOTAL NATIONAL FEE =	$ 2356	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
			TOTAL FEES ENCLOSED =	$ 2356	
			Amount to be refunded:	$	
			Amount to be charged	$	

a. ☐ A check in the amount of $ _____ to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees.

c. ☑ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 061910.

d. ☑ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038. The PTO-2038 should only be mailed or faxed to the USPTO. However, when paying the basic national fee, the PTO-2038 may NOT be faxed to the USPTO.

ADVISORY: If filing by EFS-Web, do **NOT** attach the PTO-2038 form as a PDF along with your EFS-Web submission. Please be advised that this is **not** recommended and by doing so your **credit card information may be displayed via PAIR**. To protect your information, it is recommended paying fees online by using the electronic payment method.

NOTE: Where an appropriate time limit under 37 CFR 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Customer No. 022859
FREDRIKSON & BYRON, P.A.
200 South Sixth Street
Suite 4000
Minneapolis, Minnesota 55402-1425
US

/Elisabeth Lacy Belden/
SIGNATURE

Elisabeth Lacy Belden
NAME

50,751
REGISTRATION NUMBER

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/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	56782.1.7.2
	Application Number	
Title of Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE	

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.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephen	E.	Hidem	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Plymouth	State/Province	MN	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	4710 Juneau Lane North		
Address 2			
City	Plymouth	State/Province	MN
Postal Code	55446	Country i	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Aaron	M.	Fontaine	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Fridley	State/Province	MN	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	5663 West Bavarian Pass		
Address 2			
City	Fridley	State/Province	MN
Postal Code	55432	Country i	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Janet	L.	Gelbach	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	New Albany	State/Province	IN	Country of Residence i	US

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	56782.1.7.2
	Application Number	
Title of Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	4204 Shetland Court				
Address 2					
City	New Albany	**State/Province**	IN		
Postal Code	47150	**Country**i	US		

Applicant 4 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Patrick	M.	McDonald	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Omaha	**State/Province**	NE	**Country of Residence** i	US

Citizenship under 37 CFR 1.41(b) i	US
Mailing Address of Applicant:	
Address 1	15395 Nicholas Street
Address 2	

City	Omaha	**State/Province**	NE
Postal Code	68154	**Country**i	US

Applicant 5 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Kathryn	M.	Hunter	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Knoxville	**State/Province**	TN	**Country of Residence** i	US

Citizenship under 37 CFR 1.41(b) i	US
Mailing Address of Applicant:	
Address 1	1312 Judy Reagan Lane
Address 2	

City	Knoxville	**State/Province**	TN
Postal Code	37931	**Country**i	US

Applicant 6 Remove

Applicant Authority	◉ Inventor	○ Legal Representative under 35 U.S.C. 117	○ Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Rolf	E.	Swenson	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Princeton	**State/Province**	NJ	**Country of Residence** i	US

Citizenship under 37 CFR 1.41(b) i	US

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	56782.1.7.2
	Application Number	
Title of Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE	

Mailing Address of Applicant:			
Address 1	35 Fieldston Road		
Address 2			
City	Princeton	**State/Province**	NJ
Postal Code	08540	**Country**[i]	US

Remove

Applicant 7

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Julius	P.	Zodda	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Mercerville	**State/Province**	NJ	**Country of Residence** [i]	US

Citizenship under 37 CFR 1.41(b) [i] US

Mailing Address of Applicant:			
Address 1	3 Tigers Court		
Address 2			
City	Mercerville	**State/Province**	NJ
Postal Code	08619	**Country**[i]	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	22859		
Email Address	IP@fredlaw.com	Add Email	Remove Email

Application Information:

Title of the Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE		
Attorney Docket Number	56782.1.7.2	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	27	**Suggested Figure for Publication (if any)**	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	56782.1.7.2
	Application Number	
Title of Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE	

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).
Enter either 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	22859		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this 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(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	a 371 of international	PCT/US2009/047031	2009-06-11

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. 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(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			○ Yes ◉ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	56782.1.7.2
	Application Number	
Title of Invention	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION ABND METHODS OF USE	

If the Assignee is an Organization check here. ☒			
Organization Name	Bracco Diagnostics Inc.		
Mailing Address Information:			
Address 1	107 College Road East		
Address 2			
City	Princeton	**State/Province**	NJ
Country [i]	US	Postal Code	08540
Phone Number		Fax Number	
Email Address			
Additional Assignee Data may be generated within this form by selecting the **Add** button.		Add	

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.					
Signature	/Elisabeth Lacy Belden/			Date (YYYY-MM-DD)	2010-06-16
First Name	Elisabeth Lacy	Last Name	Belden	Registration Number	50751

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 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 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.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION (37 CFR 1.63)

☐ Declaration Submitted With Initial Filing OR ☐ Declaration Submitted After Initial Filing (surcharge (37 CFR 1.16(f)) required)

Attorney Docket Number	56782.1.7.1
First Named Inventor	Stephen E. Hidem
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Art Unit	
Examiner Name	

I hereby declare that: (1) Each inventor's residence, mailing address, and citizenship are as stated below next to their name; and (2) I believe the inventor(s) named below to be the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention titled:

INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION AND METHODS OF USE

(Title of the Invention)

the application of which

☐ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) June 11, 2009 as United States Application Number or PCT International Application Number PCT/US2009/047031 and was amended on (MM/DD/YYYY) _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Authorization To Permit Access To Application by Participating Offices

☒ If 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 World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the above-identified patent application is filed access to the above-identified patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the above-identified patent application is filed to have access to the above-identified patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the above-identified patent application with respect to: 1) the above-identified patent application-as-filed; 2) any foreign application to which the above-identified patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the above-identified patent application; and 3) any U.S. application-as-filed from which benefit is sought in the above-identified patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing the Authorization to Permit Access to Application by Participating Offices.

DECLARATION — Utility or Design Patent Application

Claim of Foreign Priority Benefits

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	NO
PCT/US2009/047031	WO	06/11/2009	☐	☐	☒
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application number(s) are listed on a supplemental priority data sheet PTO/SB/02B attached hereto.

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DECLARATION — Utility or Design Patent Application

Direct all correspondence to:	☒	The address associated with Customer Number:	22859	OR ☐	Correspondence address below

Name		
Address		
City	State	Zip
Country	Telephone	Email

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. Petitioner/applicant is advised that documents which form the record of a patent application (such as the PTO/SB/01) are placed into the Privacy Act system of records DEPARTMENT OF COMMERCE, COMMERCE-PAT-7, System name: *Patent Application Files*. Documents not retained in an application file (such as the PTO-2038) are placed into the Privacy Act system of COMMERCE/PAT-TM-10, System name: *Deposit Accounts and Electronic Funds Transfer Profiles*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

NAME OF SOLE OR FIRST INVENTOR:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle [if any])	Family Name or Surname
Stephen E.	Hidem
Inventor's Signature	Date
	4/28/2010

Residence: City	State	Country	Citizenship
Plymouth	Minnesota	U.S.A.	U.S.A.

Mailing Address			
4710 Juneau Lane North			
City	State	Zip	Country
Plymouth	Minnesota	55446	U.S.A.

☒ Additional inventors or a legal representative are being named on the 2 supplemental sheet(s) PTO/SB/02A or 02LR attached hereto

PTO/SB/02A (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Aaron M.	Fontaine

Inventor's Signature: Aaron Fontaine Date: 4/28/10

Residence: City	State	Country	Citizenship
Fridley	Minnesota	U.S.A.	U.S.A.

Mailing Address: 5663 West Bavarian Pass

City	State	Zip	Country
Fridley	Minnesota	55432	U.S.A.

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Janet L.	Gelbach

Inventor's Signature Date

Residence: City	State	Country	Citizenship
New Albany	Indiana	U.S.A.	U.S.A.

Mailing Address: 4204 Shetland Court

City	State	Zip	Country
New Albany	Indiana	47150	U.S.A.

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Patrick M.	McDonald

Inventor's Signature Date

Residence: City	State	Country	Citizenship
Omaha	Nebraska	U.S.A.	U.S.A.

Mailing Address: 15395 Nicholas Street

City	State	Zip	Country
Omaha	Nebraska	68154	U.S.A.

PTO/SB/02A (07-07)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Aaron M.	Fontaine		
Inventor's Signature			Date
Fridley Residence: City	Minnesota State	U.S.A. Country	U.S.A. Citizenship
5663 West Bavarian Pass Mailing Address			
Fridley City	Minnesota State	55432 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Janet L.	Gelbach		
Inventor's Signature Janet L Gelbach			Date 4-20-2010
New Albany Residence: City	Indiana State	U.S.A. Country	U.S.A. Citizenship
4204 Shetland Court Mailing Address			
New Albany City	Indiana State	47150 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor		
Given Name (first and middle (if any))	Family Name or Surname		
Patrick M.	McDonald		
Inventor's Signature			Date
Omaha Residence: City	Nebraska State	U.S.A. Country	U.S.A. Citizenship
15395 Nicholas Street Mailing Address			
Omaha City	Nebraska State	68154 Zip	U.S.A. Country

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Aaron M.	Fontaine
Inventor's Signature	Date
Fridley Residence: City	Minnesota State	U.S.A. Country	U.S.A. Citizenship
5663 West Bavarian Pass Mailing Address			
Fridley City	Minnesota State	55432 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Janet L.	Gelbach
Inventor's Signature	Date
New Albany Residence: City	Indiana State	U.S.A. Country	U.S.A. Citizenship
4204 Shetland Court Mailing Address			
New Albany City	Indiana State	47150 Zip	U.S.A. Country

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Patrick M.	McDonald
Inventor's Signature: Patrick M. McDonald	Date: 16-APR-2010
Omaha Residence: City	Nebraska State	U.S.A. Country	U.S.A. Citizenship
15395 Nicholas Street Mailing Address			
Omaha City	Nebraska State	68154 Zip	U.S.A. Country

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DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet
Page 2 of 2

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Kathryn M.	Hunter
Inventor's Signature Kathryn M Hunter	Date April 12, 2010
Knoxville (Residence: City)	Tennessee (State)	U.S.A. (Country)	U.S.A. (Citizenship)
1312 Judy Reagan Lane (Mailing Address)			
Knoxville (City)	Tennessee (State)	37931 (Zip)	U.S.A. (Country)

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Rolf E.	Swenson
Inventor's Signature	Date
Princeton (Residence: City)	New Jersey (State)	U.S.A. (Country)	U.S.A. (Citizenship)
35 Fieldston Road (Mailing Address)			
Princeton (City)	New Jersey (State)	08540 (Zip)	U.S.A. (Country)

Name of Additional Joint Inventor, if any:	☐ A petition has been filed for this unsigned inventor
Given Name (first and middle (if any))	Family Name or Surname
Julius P.	Zodda
Inventor's Signature	Date
Mercerville (Residence: City)	New Jersey (State)	U.S.A. (Country)	U.S.A. (Citizenship)
3 Tigers Court (Mailing Address)			
Mercerville (City)	New Jersey (State)	08619 (Zip)	U.S.A. (Country)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION

ADDITIONAL INVENTOR(S)
Supplemental Sheet

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Kathryn M.	Hunter

Inventor's Signature _____ Date _____

Residence: City	State	Country	Citizenship
Knoxville	Tennessee	U.S.A.	U.S.A.

1312 Judy Reagan Lane
Mailing Address

City	State	Zip	Country
Knoxville	Tennessee	37931	U.S.A.

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Rolf E.	Swenson

Inventor's Signature Rolf E Swenson Date 4/13/10

Residence: City	State	Country	Citizenship
Princeton	New Jersey	U.S.A.	U.S.A.

35 Fieldston Road
Mailing Address

City	State	Zip	Country
Princeton	New Jersey	08540	U.S.A.

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name (first and middle (if any))	Family Name or Surname
Julius P.	Zodda

Inventor's Signature Julius P. Zodda Date Apr. 13, 2010

Residence: City	State	Country	Citizenship
Mercerville	New Jersey	U.S.A.	U.S.A.

3 Tigers Court
Mailing Address

City	State	Zip	Country
Mercerville	New Jersey	08619	U.S.A.

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	
Filing Date	
First Named Inventor	Stephen E. Hidem
Art Unit	
Examiner Name	
Attorney Docket Number	56782.1.7.2

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3710118		1973-01-09	Holgate et al.	
	2	3774036		1973-11-20	Gerhart	
	3	3997784		1976-12-14	Picunko et al.	
	4	4286169		1981-08-25	Rossem	
	5	4562829		1986-01-07	Bergner	
	6	4585009		1986-04-29	Barker et al.	
	7	4585941		1986-04-29	Bergner	
	8	4625118		1986-11-25	Kriwetz et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Stephen E. Hidem
	Art Unit	
	Examiner Name	
	Attorney Docket Number	56782.1.7.2

	9	4679142		1987-07-07	Lee	
	10	4755679		1988-07-05	Wong	
	11	4853546		1989-08-01	Abe	
	12	5039863		1991-08-13	Matsuno et al.	
	13	5258906		1993-11-02	Kroll et al	
	14	5274239		1993-12-28	Lane et al	
	15	5475232		1995-12-12	Powers et al	
	16	5485831		1996-01-23	Holdsworth et al.	
	17	5590648		1997-01-07	Mitchell et al.	
	18	5739508		1998-04-14	Uber III	
	19	5840026		1998-11-24	Uber III et al	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Stephen E. Hidem
	Art Unit	
	Examiner Name	
	Attorney Docket Number	56782.1.7.2

	20	5885216		1999-03-23	Evans III et al	
	21	6157036		2000-12-05	Whiting et al	
	22	6442418		2002-08-27	Evans III et al	
	23	6626862		2003-09-30	Duchon et al	
	24	6767319		2004-07-27	Reilly et al.	
	25	6870175		2005-03-22	Dell et al.	
	26	6901283		2005-05-31	Evans III et al	
	27	7169135		2007-01-30	Duchon et al	
	28	7204797		2007-04-17	Reilly et al.	
	29	7256888		2007-08-14	Staehr et al	
	30	7413123		2008-08-19	Ortenzi	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Stephen E. Hidem
	Art Unit	
	Examiner Name	
	Attorney Docket Number	56782.1.7.2

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050278066	A1	2005-12-15	Graves et al.	
	2	20070140958	A1	2007-06-21	DeKemp	
	3	20070213848	A1	2007-09-13	DeKemp	
	4	20070282263		2007-12-06	Kalafut et al	
	5	20080071219		2008-03-20	Rhinehart et al	
	6	20080093564		2008-04-24	Tartaglia et al.	
	7	20080166292		2008-07-10	Levin et al	
	8	20080242915		2008-10-02	Jackson et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Stephen E. Hidem
	Art Unit	
	Examiner Name	
	Attorney Docket Number	56782.1.7.2

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	0310148	EP	A2	1989-04-05	Squibb & Sons		☐
	2	2006129301	WO	A2	2006-12-07	Spectrum Dynamics		☐
	3	2008028165	WO	A2	2008-03-06	Catholic Healthcare		☐
	4	9615337	WO		1996-05-23	Nilsson		☐
	5	9956117	WO		1999-11-04	General Hospital Corp		☐
	6	02096335	WO		2002-12-05	Hill ROM Services		☐
	7	20050002971	WO		2005-01-13	Iphase Technologies		☐
	8	2006007750	WO		2006-01-26	Universitat Zurich		☐
	9	2006074473	WO		2006-07-13	Atlas Systems		☐
	10	2007016170	WO		2007-02-08	Fago		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	
	Filing Date	
	First Named Inventor	Stephen E. Hidem
	Art Unit	
	Examiner Name	
	Attorney Docket Number	56782.1.7.2

	11	2007030249	WO		2007-03-15	Gibson		☐
	12	2007071022	WO		2007-06-28	DeKemp		☐
	13	2007104133	WO		2007-09-20	DeKemp		☐
	14	2007149108	WO		2007-12-27	Pollard		☐
	15	2008140351	WO		2008-11-20	Shimchuck		☐
	16	2008037939	WO		2008-04-03	Lemer Protection		☐
	17	2008082966	WO		2008-07-10	Medrad, Inc.		☐
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	Application Number	
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	First Named Inventor	Stephen E. Hidem
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	1	NEIL J. EPSTEIN, AHMED BENELFASSI, ROB S.B. BEANLANDS, ROBERT A. DEKEMP: "A Rb82 infusion system for quantitative perfusion imaging with 3D PET" APPLIED RADIATION AND ISOTOPES, vol. 60, 9 February 2004 (2004-02-09), pages 921-927, XP002557544 DOI: 10. 1016/j. apradiso.2004.02.002.	☐
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	3	BRACCO Brochure, "Rubidium 82 Infusion System, Easy to Operate…Automated…Complete", © Bracco Diagnostics, Inc., 0605-002NA, June 2001. (2 pages)	☐
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	6	International Search Report and Written Opinion, dated 02-25-2010 for PCT Application No. PCT/US2009/047027, 22 pages	☐
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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

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(54) Dosimetry system for strontium-rubidium infusion pump.

(57) The dosimetry system used with a strontium-rubidium infusion system is a very high speed circuit capable of measuring the radioactive dosage infused into a patient in real time. The dosimetry system is capable of receiving very short duration input pulses generated by a photomultiplier tube in response to the presence of radioactivity.

EP 0 310 148 A2

DOSIMETRY SYSTEM FOR STRONTIUM-RUBIDIUM INFUSION PUMP

The present invention relates to a strontium-rubidium infusion system. In particular, it relates to a strontium-rubidium infusion system which has an in-line, real time dosimetry system which can be used to infuse patients with Rubidium-82.

Current statistics show that approximately one-third of all deaths in the United States are related to coronary artery disease. See, for example, Pohost, G., McKusick, K., and Strauss, W., "Physiologic Basis and Utility of Myocardial Perfusion Imaging" Proceedings of the Second International Symposium on Radiopharmaceuticals, Society of Nuclear Medicine, New York 1979, pp. 465-473, and this fact has prompted extensive research to more efficiently diagnose and manage this disease. Recent advances in radiopharmaceutical development and instrument design have established myocardial scintigraphy as an important new approach for evaluating coronary artery disease and myocardial perfusion. See, for example, Pierson, R., Friedman, M., Tansley, W., Castellana, F., Enlander, D., and Huang, P., "Cardiovascular Nuclear Medicine: An Overview", Sem. Nucl. Med., 9, 224-240 (1979); Leppo, J., Scheuer, J., Pohost, G., Freeman, L., and Strauss, H., "The Evaluation of Ischemic Heart Disease Thallium-201 with Comments on Radionuclide Angiography": Sem. Nucl. Med., 10, 115-126 (1980); Vogel, R., "Quantitative Aspects of Myocardial Perfusion Imaging", Sem. Nucl. Med., 10, 146-156 (1980); Chervu, R., "Radiopharmaceuticals in Cardiovascular Nuclear Medicine", Sem. Nucl. Med., 9, 241-256 (1979); and Pitt, B., and Strauss, H., "Cardiovascular Nuclear Medicine", Sem. Nucl. Med., 7, 3-6 (1977).

Myocardial scintigraphy studies have been performed with several isotopes of potassium, rubidium, cesium, and thallium (T1-201), although the usefulness of all of these nuclides is limited by their non-optimal physical properties. In spite of its long half-life and low-gamma energy, T1-201 is currently the most widely used agent for myocardial imaging. See, for example, Poe, N., "Rationale and Radiopharmaceuticals for Myocardial Imaging", Sem. Nucl. Med., 7, 7-14 (1977); Strauss, H. and Pitt, B., "Thallium-201 as a Myocardial Imaging Agent", Sem. Nucl. Med., 7, 49-58 (1977); Botvinick, E., Dunn, R., Hattner, R., and Massie, B., "A Consideration of Factors Affecting the Diagnostic Accuracy of T1-201 Myocardial Perfusion Scintigraphy in Detecting Coronary Artery Disease", Sem. Nucl. Med., 10, 157-167 (1980); and Wackers, F., "Thallium-201 Myocardial Scintigraphy in Acute Myocardial Infarction and Ischemia", Sem. Nucl. Med., 10, 127-145 (1980).

In diagnostic procedures in which the heart is involved, it is desirable for a diagnostician to be able to view a patient's heart. Heretofore, various radioactive materials have been used together with radiological procedures for viewing internal organs of patients. It has been difficult, however, to view a heart because the radioactive substances which could be used for viewing the heart have had a very long half-life. Thus, using them with patients involves an element of danger and also reduces the number of times that a patient could be infused within any given time period. It would therefore be desirable to have a diagnostic apparatus and procedure which could be used with relative safety for viewing the heart.

Rubidium-82 is a potassium analog. That means it acts similar to potassium when it is infused into a patient. Thus it builds up at a very rapid rate, i.e., within seconds, in the patient's heart. Rubidium-82 also has the advantage of having a very short half-life, approximately 76 seconds. Therefore, it decays after a very short period of time following entry into the body, thereby allowing numerous procedures to be performed within a relatively short time period in a given patient. Rubidium-82 also has the advantage of being observable using a modified gamma camera such as a gamma camera of the type manufactured by Searle Radiographics, Inc., called the PHO Gamma IV. A problem with using Rubidium-82 in a patient involves keeping track of the amount of radiation infused into the patient. In view of the very short half-life of Rubidium-82, it is impractical to measure the radioactivity of a particular dose and to then infuse it into the patient using conventional means. An accurate method for measuring the amount of radiation being infused into the patient would be highly desirable for this particular application.

The availability of improved instrumentation has stimulated interest in the use of the positron emitter, Rubidium-82, for myocardial imaging. See for example, Beller G., and Smith, T., "Radionuclide Techniques in the Assessment of Myocardial Ischemia and Infarction," Circulation, 53 (3, Supp. 1) 123-125 (1976); Budinger, T., Yano, Y., Derenzo, S., et al., "Myocardial Uptake of Rubidium-82 Using Positron Emission Tomography," J., Nucl. Med. 20, 603 (1979); Budinger, T., Yano, Y., Derenzo, S., et al., "Infarction Sizing and Myocardial Perfusion Measurements Using Rb-82 and Positron Emission Tomography," Amer. J. Cardiol., 45, 399 (1980). Rubidium-82, an analog of the alkali metal potassium, is rapidly cleared from the blood and concentrated by the myocardium. The short half-life of the Rubidium-82 (76 sec) offers

the unique advantage of permitting repeat perfusion and blood flow studies in patients whose clinical status is rapidly changing.

Rubidium-82 is produced by the decay of its parent, strontium-82. E. R. Squibb and Sons, Inc. has developed a Rubidium-82 generator and infusion system which yields an isotonic saline solution of Rubidium-82 at physiological pH for rapid administration. In animal experiments, the safety and myocardial uptake of Rubidium-82 has been demonstrated. Therefore this agent has been selected as a candidate for clinical trials.

In the Drawing:

FIG. 1 is an overall schematic diagram of the strontium-rubidium infusion system used in conjunction with the present invention;

FIG. 2 is a front view of the infusion pump control used with the strontium-rubidium infusion system;

FIG. 3 is a front view of the dosimetry control used with the strontium-rubidium infusion system;

FIG. 4 is a graph of radioactivity measured (on the y-axis) by the dosimeter probe versus time (on the x-axis);

FIG. 5 is a perspective view of the dosimetry probe;

FIG. 6 is a schematic diagram of the interface between the dosimetry probe of FIG. 4 and the dosimetry control circuitry;

FIG. 7 is a schematic diagram of the circuit for the Single Channel Analyzer used to convert and

No. 156,285, entitled ^{82}RB GENERATING METHOD AND ELUENT, filed on June 4, 1980 by Rudi D. Neirinckx, et al.

Saline pumped through the strontium-rubidium generator 28 exits the generator 28 through tubing 30 containing Rubidium-82. The tubing 30 is connected to a diverter valve 32 having a first arm 34 which leads through tubing 38, an antibacterial filter 40, and ultimately to waste 42. A second arm 35 of the diverter valve 32 is connected through tubing 44, an antibacterial filter 48, additional tubing 50, and into an infusion needle 52. The infusion needle 52 is typically inserted into the arm 54 of a patient 56.

In the preferred embodiment of the invention, the check valve 16 is a dual back check valve of the type made by Beckton Dickenson Inc., and the antibacterial filters are of the type made by Schleicher & Schull as their type FP030/3.

In the operation of the device, the amount of radioactivity in the saline eluted from the strontium-rubidium generator 28 must be measured as it is introduced into the patient 56. Accordingly, a dosimetry probe 58 is placed adjacent to the tubing 30 where it measures the radioactivity of the rubidium-containing saline as it leaves the generator 28 and enters the diverter valve 32.

In order to use the infusion system, various procedures must be performed and controlled. In particular, the syringe 18 must be purged of air, and filled with saline, and the diverter valve 32 must be positioned. These operations are contingent upon a number of factors including the total volume to be infused into the patient 56, the total dosage to be infused into the patient 56, the minimum radioactivity which must be present in the tubing 30 before any eluate is infused into the patient 56, the total volume to be infused (Note: The total volume eluted may differ from the total volume infused into the patient 56 as some volume is likely to be diverted to waste.)

The foregoing parameters may be altered from the front panel of two different controllers shown in FIGS. 2 and 3. These are the infusion pump controller 60 and the dosimetry controller 62, repectively. The infusion pump controller 60 controls the mechanical movement of the syringe's plunger 66 via a stepping motor 64 which is connected to the plunger 66.

In the preferred embodiment of the invention, the syringe 18 is a sterile, disposable plastic syringe of the type made by Sherwood Medical and designated as Part. No. 881-514031. The infusion pump controller 60 limits the movement of the syringe plunger 66 based upon optical limit detectors 68, 70 which limit the fully displaced and fully extended positions of the plunger 66, respectively. The volume control function performed by the infusion pump controller 60 is accomplished by counting the number of pulses sent to the stepping motor 64.

With reference to FIG. 2, the front panel of the infusion pump controller 60 is shown. The infusion pump controller 60 includes an on/off power switch 72 which is used to turn on the power to the unit.

A set of thumbwheel switches 74 is used to select the total volume (ml) to be eluted. An LED display 76 shows the total volume (ml) which has been eluted. A momentary contact push-button switch 78 is used to start and to stop the movement of the plunger 66 in the forward (inject) direction.

A set of push-button potentiometers comprise the Flow Rate Control 80 which is used to determine the volume per unit time which is infused. The Flow Rate Control 80 sets the pulse rate into the stepping motor 64. An LED 82 lights when the end of travel of the plunger 66, as indicated by the optical limit detectors 68, 70 is reached. A pair of momentary contact push-button switches 84, 86 are used to control the purge and refill functions, respectively, of the syringe 18. Thus, if the purge

control switch 84 is pushed, and held, the plunger 66 continues to move in the forward direction until it reaches the forward limit detector 68. Similarly, while the refill control switch 84 is pressed and held, the plunger 66 continues to move toward the rear limit detector 70. The speed of movement of the plunger 66 during purge and refill operations are controlled by adjustable screw-type potentiometers 88, 90, respectively.

The infusion pump controller 60 is comprised of a Superior Electric Company STM103 Translator Module which is interfaced to provide signals representative of flow rate, volume eluted, and injection. It is also interfaced to be remotely controlled. A pulse called "INIT" indicates that the Translator Module has been powered. The "INIT" pulse is used to reset the displays on the dosimetry module. An "INJECT" signal indicates that the pump is injecting. Output pulses, corresponding to .1 ml steps of the syringe 18, are provided. An "End of Elution" signal is used to remotely disable the infusion pump controller 60.

With reference now to FIG. 3, the dosimetry controller 62, is comprised of a number of LED displays and thumbwheel switch sets. In addition, the dosimetry controller 62 includes an on/off switch 92 for providing power to the unit.

The first set of thumbwheel switches 94 is used to set the volume (ml) to be infused into the patient 56. The LED display 96, immediately above the thumbwheel switches 94, displays the volume of eluate which has been infused into the patient 56.

The thumbwheel switches 98 are used to set the total dose (mCi) which is to be infused into the patent 56 and the LED display 100 immediately above the total dose thumbwheel switches 98 displays the total dose which has been infused into the patient 56. Similarly, the thumbwheel switches 102 are used to set the dose rate (mCi sec.) which is to be used to determine when to switch the diverter valve 32 from the waste position to the patient 56 position. The actual dose rate which is present in the eluate within the tube 30 in front of the dosimetry probe 58 is displayed on the LED display 104. The description of the dose present in the eluate at any given time from the start of infusion will be provided hereafter. The dosimetry controller 62 further comprises a pair of LED's 106, 108 which indicate the position of the diverter valve 32. Only one of these two LED'S 106, 108, should be on at any given time.

While the normal position of the diverter valve 32 is toward waste, except when eluate is being infused into a patient 56, provision must be made to clear the tubing 44, 50 of any air prior to infusing a patient 56. Accordingly, the dosimetry controller 62 includes a toggle switch 110 which is used to hard wire the diverter valve 32 in the patient 56 position.

The present preferred embodiment of the invention also includes a set of thumbwheel switches 112 which are used to set the flow rate which will be used in internal calculations of dosimetry controller 62. It is presently anticipated by the inventor that a future version of the present invention will include automatic means for determining the flow rate based upon the settings used in the infusion pump controller 60.

Referring now to FIG. 4, a graph of the radioactive dosage present in the tubing 30 in front of the dosimetry probe 58, is shown. In the graph, the dosage is measured on the y-axis and time is measured on the x-axis. The time is referenced with zero being the time that the start/stop inject button 78 on the infusion controller 60 is pushed to commence infusion.

For approximately 10 seconds there will be no radioactivity present in the eluate from the strontium-rubidium generator 28. Thereafter, the dose rate rises at a rapid rate up to a maximum, after which the dose rate falls to a level value indicative of the steady state regeneration rate of the Sr-Rb generator 28. Thus, when the infusion starts, there is a delay initially as the dose rate builds up, a reduction in dosage after the generator 28 is partially eluted, and then there is a dosage representative of the steady state regeneration rate of the generator 28.

The setting of the dose rate thumbwheel switches 102 tells the dosimetry controller 62 at what point along the upward slope of the dosage curve to switch the diverter valve 32 from the waste position to the patient 56 position whereby the eluate will be infused into the patient 56. At that point the dose indicated by the LED's 100 will start accumulating from zero, where it had been until that point. Similarly, the patient 56 volume indicated by the LED's 96 will start to accumulate as of that time.

Once eluate is infused into the patient 56, it continues to be infused until one of various stop indications occurs. In particular, when the total patient 56 dose, set by the thumbwheel switches 98, is reached, the diverter valve 32 is returned to the waste position, and the stepping motor 64 stops, thereby preventing further infusion. Similarly, the diverter valve 32 is switched, and the stepping motor 64 is stopped when the patient 56 volume, preset by the thumbwheel switches 94 reaches its preset value or after the total volume to be eluted, set by the volume thumbwheel switches 74 reaches its preset value; or when the purge limit optical stop 68 of the syringe 18 is reached; or if the start stop inject button 78 is pushed. Any of the foregoing events causes the diverter valve 32 to

switch to the waste position, and causes the stepping motor 64 to stop. Note, however, that the purge and refill switches 84, 86 are disabled as of the time that the start/stop inject button 78 is pushed to commence the infusion.

Quantizing Radioactivity in a Liquid Stream

In order to measure the radioactivity in the saline solution which passes through the line 30 in front of the dosimetry probe 58, it is necessary to count the number of disintigrations which occur in front of the probe 58, while at the same time keeping track of the flow rate of the saline through the tube 30. Given that these quantities are known, it is possible to measure the total activity in milliCuries (mCi) in accordance with the following formula:

$$A = \frac{(C)(F)}{(V)(E)(CM)(Y)}$$

Where, A = total activity (mCi);
C = net counts;
F = flow rate (ml/min);
V = volume in detector view (ml);
E = net efficiency (counts per minute/disintegration per minute);
CM = disintegrations/minute to milliCurie conversion factor; and
Y = net yield of photon.

In the case of the present invention, the above formula can be simplified to:

$$A = \frac{(C)(F)}{K}$$

Where, A = total activity (in milliCuries);
C = net counts (from probe);
F = the flow rate; and
K = the calibration factor.

As noted, the calibration factor, K, takes into account the volume in the detector's view, the net efficiency of the probe, the conversion factor in terms of disintigrations pet minute to milliCuries, and the net yield of photons. These factors are substantially constant for any given probe and tubing combination for a reasonable amount of time. Accordingly, provision is made on the circuit board to adjust the calibration factor, K, when the instrument is serviced. However, the calibration factor, K, is not user adjustable in the normal course of operation.

Dosimetry Probe

Referring now to FIG. 5, the dosimetry probe 58 is comprised of a photomultiplier tube 120, such as the RCA C83009E 14 mm diameter 10-stage photomultiplier tube manufactured by the Electro Optics Division of RCA Corporation in Lancaster, Pennsylvania. The photomultiplier tube 120 has a face 122 through which input signals in the form of light are received. On the face 122, a plastic scintillator 124, such as a Nuclear Enterprises Type 102A manufactured in Edinburgh, Scotland, is mounted. In the preferred embodiment of the invention, the plastic scintillator 124 is glued or bonded to the face 122 of the photomultiplier tube 120. After the plastic scintillator 124 has been bonded to the face 122 of the photomultiplier tube 120, an aluminum foil covering (not shown) is placed over the face end of the photomultiplier tube 120, including the plastic scintillator 124. The purpose of the aluminum foil covering is to reflect back into the tube 120 any light which scintillates from the plastic scintillator 124 away from the tube 120. In addition, the aluminum foil covering prevents any stray light which might come into the area of the face 122 from getting into the tube 120. Following the application of the aluminum foil, a light tight material, such as black electrical tape is wrapped over the aluminum foil covered tube 120 in order to further prevent any light from entering into the tube 120. The tape-wrapped tube 120 is then inserted into a mu metal shield 126 which is intended to prevent any electromagnetic radiation effects from affecting the output of the dosimetry probe 58. In the preferred embodiment of the invention, the dosimetry probe 58 is plugged into a standard photomultiplier tube socket base 128 containing a standard resistive biasing network.

Dosimetry Circuitry

Referring now to FIG. 6, the photomultiplier tube socket base 128 includes a resistive network containing biasing resistors for placing appropriate bias voltages on the ten dynodes in the photomultiplier tube 120. Accordingly, the high voltage connection to the photomultiplier tube base 128 is automatically biased to provide appropriate operating voltages to the photomultiplier tube 120. The high voltage supply 130 used in the preferred embodiment of the invention is a 0-1000 volt, adjustable Bertan PMT-10A-P power supply manufac-

tured by Bertan Associates, Inc., Three Aerial Way, Syosset, New York. In the present application, the high voltage supply 130 is adjusted to provide an output voltage of 950 volts. The photomultipler tube socket base 128 is an RCA photomultipler tube socket base, part No. AJ2273.

An output signal goes from the dosimetry probe 58 on a line 132 to a coupling network comprising a pull up resistor 134, a coupling capacitor 136, and a output resistor 138. Accordingly, an AC signal having a peak to peak maximum of approximately 250 millivolts with negative going pulses, is provided on output line 140.

Single Channel Analyzer

Referring now to FIG. 7, the schematic diagram for a Single Channel Analyzer circuit is shown. The Single Channel Analyzer is used, because the pulses on output line 140 from the Dosimetry circuitry are very sharply defined pulses which may occur at very high frequencies. In view of the fact that it is important to count all the pulses, a very high speed comparator, such as an AM685 voltage comparator 142, manufactured by Advanced Micro Devices, 901 Thompson Place, Sunnyvale, California, with emitter-coupled logic (ECL) output, or other suitable very high speed comparator, must be used.

A biasing network 141 consisting of a series of resistors and capacitors is used as one input to the comparator 142. In view of the fact that the pulses which are handled by the comparator 142 are of very short duration, a one-shot circuit 144, comprised in the preferred embodiment of the invention, of a Motorola Type 1670 master-slave flip-flop integrated circuit, is used to stretch the pulse width up to a uniform pulse width of approximately 50 nanoseconds. The output signal from the one-shot 144 is fed into a programmable divide-by-N circuit 146, which in the preferred embodiment of the invention is comprised of a Motorola Type 10136 universal hexadecimal counter integrated circuit. The divide-by-N circuit 146 is programmable. Accordingly, a very high pulse repetition rate coming into the comparator with very short pulse widths is reformed by the one-shot to have wider, uniform pulses, and the input signal is further reformed by the divide-by-N circuit to bring the pulse repetition rate down into any desirable range. In particular, outputs of the divide-by-N circuit 146 are provided for N equal to 2, 4, 8, and 16.

Up through this point in the circuit, the devices have all been of ECL type in order to be able to handle the very high speed pulses which are detected by the dosimetry probe 58. In view of the fact that it is conventional to use transistor-transistor-logic (TTL) integrated circuits, a type 10125 ECL-to-TTL level converter circuit 150 is hooked to the output of the divide-by-N circuit 146. Thus, the ECL-to-TTL level converter circuit 150 transforms the ECL signal levels into TTL signal levels for further processing. The TTL outputs leave the ECL-to-TTL level converter circuit 150 on four lines 152, 154, 156, 158, which correspond to the TTL level of the counts into the Single Channel Analyzer divided by 2, 4, 8, and 16, respectively. The counts out on the lines 152-158 will be referred to hereafter as the "net counts".

Multiplier-Divider Circuit

Referring now to FIG. 8, there is a Multiplier-Divider circuit 160 which converts the net counts from the Single Channel Analyzer circuit, described above, into a meaningful quantity (milliCuries). The Multiplier-Divider circuit 160 accepts the "net counts" on an input line 162 which is connected to one of the lines 152-158 from the Single Channel Analyzer (i.e., the raw counts converted into TTL levels and then divided by 2, 4, 8, or 16) and multiplies them by the eluate Flow Rate divided by 100. The result is then divided by a constant, K, in order to carry out the formula:

$$A = \frac{(N)(F)}{K}$$

Where, A = total activity (in milliCuries);
N = net counts (from Single Channel Analyzer);
F = Flow Rate; and
K = the calibration factor.

The net counts, N, are first multiplied by a two digit number corresponding to the eluate Flow Rate (entered on the Flow Rate thumbwheel switches 112A, 112B, corresponding to the most significant digit (MSD) and the least significant digit (LSD), respectively, the thumbwheel switches 112A, 112B are on the front panel of the dosimetry controller 62, shown in FIG. 3. The multiplication is accomplished by cascading two TTL Synchronous Decade Rate Multiplier circuits (F74167), and sending their outputs through a NAND gate 168. The resulting output corresponds to F_{out}, where:

$$F_{out} = \frac{(N)(F)}{100}$$

The output pulses are of varying duration, so they are next fed through a pair of one-shots which process them to have a fixed duration. In the preferred embodiment of the invention, the first one-shot is comprised of one-half of an SN74123 integrated circuit 170. The first one-shot is negative edge triggered, and it provides a pulse output of approximately 200 nanoseconds. Its output is double buffered through buffers 172, 174 into a second one-shot which is comprised of one-half of a CD4098BE integrated circuit 176 in order to increase the width of the output pulses, so they will be acceptable to a CMOS divider integrated circuit 178. The second one-shot is configured to be leading edge triggered.

The output of the second one-shot is then divided by the calibration factor, K, which may have a range of between 3 and 9,999. A CD4059A integrated circuit 178 is used as a programmable divide-by-N counter. Programming is accomplished via a series of 16 DIP switches 180 mounted on the printed circuit card. Each set of four switches corresponds to the BCD settings for 1's, 10's, 100's and 1000's. Pull up resistors (not shown) are employed in the standard manner so that when the DIP switches are open the inputs to the divide-by-N circuit 178 are pulled high.

The output of the divider 178 has pulses of random widths, so another one-shot, made up of the second half of the CD4098BE 176 configured for leading edge triggering, is used. This one-shot provides an output pulse duration of approximately 20 microseconds. Before leaving the Multiplier-Divider circuit 160, the output is double buffered through buffers 182, 184 and the output signal on line 186 is sent to the Dose Rate circuit. There will be one dose corrected output pulse on line 186 for each 0.01 milliCurie of activity which passes by the dosimetry probe 58.

Display Controller Circuit

Referring now to FIG. 9, the schematic diagram for a Display Controller Circuit 190 is shown. There are three Display Controller Circuits within the dosimetry controller 62. Each Display Controller 190 is used both to interface a set of thumbwheel switches 192 and to display the quantity associated with the particular set of thumbwheel switches 192. Thus, there is one Display Controller of 190 for Dose Rate (which works with thumbwheel switches 102 and LEDs 104), one for Patient Volume (which works with thumbwheel switches 94 and LEDs 96), and one for Dose (which works with thumbwheel switches 98 and LEDs 100). Each Display Controller Circuit 190 drives four seven-segment displays 194, such as MAN71 displays.

The major component of the Display Controller Circuit 190 of the preferred embodiment of the invention is an Intersil ICM7217IJI integrated circuit 196, which is a device which provides a direct interface to the seven-segment displays 194. Each Display Controller Circuit 190 allows the user to set a level, by programming binary coded decimal (BCD) thumbwheel switches 192. The levels can then be detected. In this way, a preset limit for Dose, for example, will be detected and will be used to shut down the infusion pump. For Dose Rate, the preset level is used to switch the position of the diverter valve 32, through the valve driver circuit which will be explained hereinafter. The Patient Volume can also be preset, and the infusion pump can be stopped at the preset limit.

Dose Rate Circuit

The Dose Rate circuit 200, shown in FIG. 10, provides a visual display of the amount of radiation present in the eluate. The Dose Rate circuit 200 employs a Display Controller Circuit, of the type described above. The Dose Rate display is constantly updated to provide the user with Dose Rate information. The Dose Rate circuit 200, with the Display Controller, is programmed to set a trigger level for switching the eluate from waste to the patient 56.

The Dose Rate circuit 200 uses signals from the Multiplier-Divider circuit 160, described above, and from the Control Board which will be described hereinafter. The dose corrected output pulses on line 186 from the Multiplier-Divider circuit 160 described above (i.e., 1 pulse/.01 mCi) enter the Dose Rate circuit 200, and are double buffered by buffers 202, 204. The buffered pulses are then fed through one-half of a one-shot 206, comprised of a CD4098BE integrated circuit in the preferred embodiment of the invention. The output from the one-shot 206 is gated through NAND gate 207 to the Dose Rate Display 104 since there are three Display Controller Circuits 190, which are used for Dose (circuit "A"), Dose Rate (circuit "B"), and Patient Volume (circuit "C"), the designation "B10" at the output of NAND gate 207 means pin 10 on input connector 197 (see FIG. 9).

The heart of the Dose Rate circuit 200 is an Intersil ICM7207A Oscillator Controller integrated circuit 208. This unit, along with a dual one-shot comprised of a CD4098BE integrated circuit 210, in the preferred embodiment of the invention, provides all of the control necessary for gating, storing, and resetting the display.

The outputs of the Dose Rate Display Control-

ler Circuit provide an easy interface to determine when a predetermined count (corresponding to the dose rate which was set on thumbwheel switches 102) has been reached, and to generate a signal which is used for switching the diverter valve 32. The valve switching signal is also used to enable the Dose and Patient Volume Displays, 100, 96, respectively.

In the preferred embodiment of the invention, the valve switching signal is derived from one half of a dual D-type flip-flop, such as a CD4013BE integrated circuit 212. The flip-flop 212 is only enabled during an injection, i.e., when the infusion pump is being used to either infuse eluate into a patient 56 or to divert it to waste. The enabling "INJECT" signal is generated when the pump is injecting. Once an injection is started and a user pre-set Dose Rate limit set on thumbwheel switches 102 is met, the flip-flop 212 latches a positive Q output to switch the diverter valve 32 from the waste position to the patient position and to enable the Dose Display and the Patient Volume Display.

Control Circuit

Referring now to FIG. 11, the schematic diagram of the Control circuit 220 is shown. The purpose of the Control circuit 220 is to "oversee" all other operations. Specifically, the Control circuit 220 controls the Dose Display and Patient Volume Display. The Control circuit 220 also provides timing for resetting the Multiplier-Divider circuit 160, and it buffers various inputs and outputs to and from the infusion pump control module 60.

The basic function for turning the infusion pump off is the End of Elution signal. The End of Elution signal is derived from either the Dose Display 100 or the Patient Volume Display 96. These displays 100, 96 are gated to begin counting once the Dose Rate trigger level, the Q output from flip-flop 212, reaches its preset limit, as defined by the Dose Rate thumbwheel switches 102. Then, once the Dose or Patient Volume is met, as defined by the Dose thumbwheel switches 98 and by the Patient Volume thumbwheel switches 94, respectively, the Control circuit 220 signals the pump to stop.

Valve Driver Circuit

The Valve Driver circuit 230, shown schematically in FIG. 12, is used to control the switching of the diverter valve 32 which directs the eluate either to the patient 56 or to waste. The Valve Driver circuit 230 accepts its input from the Dose Rate circuit or from the Patient Line Purge Switch 110. The Patient Line Purge Switch 110 directly controls the valve 32.

The diverter valve 32 is a two position valve which includes electrical switches which close individually when the valve 32 is fully in either the patient or waste position. Movement of the valve 32 from one position to the other is controlled by an AC motor which includes two windings allowing it to be moved in either direction via an AC motor having two windings. When the first winding is energized, the motor moves in a clockwise direction. When the second winding is energized, the motor moves in a counterclockwise direction. At each limit of the valve movement, there is a microswitch 232, 234 which senses when the valve limit has been reached.

When one of the microswitches 232, 234 is open, i.e. switch 232, the input to an associated inverter 236 is essentially at ground. When the switch 232 closes, the input to the inverter 236 increases to approximately five volts. After the switch 232 again opens, it takes some time, due to the RC time constant of the associated resistors and capacitor, before the voltage at the input of the first inverter 236 returns to approximately zero. Accordingly, the combination of inverters and the RC network to which each of the switches 232, 234 are connected acts as a switch debouncer. Thus, the output of inverter 238 will be low when switch 232 is closed and high when switch 232 is opened. Similarly, the output of inverter 240 will be low when switch 234 is closed and high when switch 234 is opened.

NAND gate 242 normally has a high output voltage. Accordingly, as will be obvious to those of ordinary skill in the digital circuitry art, LED 106 will be on when switch 232 is closed. Otherwise, LED 106 will be off. Similarly, LED 108 will be on when switch 234 is closed. Note that these LEDs 106, 108 were previously described with reference to the dosimetry controller 62 (See FIG. 3).

When both switches 232, 234 are opened at the same time, there will be two high signals at the input of NAND gate 254. That will cause NAND gate 256 to trigger a monostable multivibrator comprised of one half of a CD4098BE integrated circuit 258 which provides a low going output pulse having a duration of approximately 700 milliseconds in the preferred embodiment of the invention. The particular time period during which this pulse is low must exceed the time period which it would take for the diverter valve 32 to be moved from one position to the other position. In the preferred embodiment of the invention the movement of the diverter valve 32 takes approximately 600 milliseconds. The outputs from the monostable multivibra-

tor are fed via EXCLUSIVE OR gate 260 into a D-type flip-flop 262 comprised of a CD4013BE integrated circuit. In the event that the diverter valve 32 did not move from one position to the other within the prescribed time period, it is presumed that a fault condition occurred, e.g. the diverter valve 32 jammed. Accordingly, the operator is advised of the fault condition by both LEDs 106, 108 flashing simultaneously. The flashing occurs as a result of the output of the flip-flop 262 which is connected on line 264 to NAND gate 242 being kept high, thereby causing NAND gate 242 to act as an astable multivibrator which oscillates between high and low outputs thereby causing the EXCLUSIVE OR gates 248, 250 to change states and to flash the LEDs 106, 108.

At the same time that one output of the flip-flop 262 goes high, the other output, on line 266 goes low. The signal on line 266 is normally high, as it is one input to NAND gate 268. The other input to NAND gate 268 is the "End of Elution" signal previously discussed. When both inputs to NAND gate 268 are high the output on line 270 is high. The output signal on line 270 turns off the infusion pump when it is low. This is the signal which remotely controls the infusion pump, as heretofore described. Thus, in the fault condition, when the signal on line 266 goes low the infusion pump is turned off. When there is no fault condition, the infusion pump will be enabled when the End of Elution signal is high.

The Q output from the dose rate circuit 200 enters the Valve Controller Circuit 230 on line 252. A series of inverters are used to buffer the Q output in order to obtain an output on line 254. The output on line 254 is used as the input to a pair of solid state relays (not shown) which selects between the two windings of the motor which drives the diverter valve 32. Thus, when the Q output is high the motor drives the diverter valve 32 into the Patient position, and when the Q output is low, the motor drives the diverter valve 32 into the Waste position.

Claims

1. A dosimetry system suitable for use in a strontium-rubidium infusion system comprising means for generating rubidium 82 in a solution which can be infused into a patient; means for infusing said solution into a patient; means for measuring the radioactivity present in said solution as it is infused into said patient; and means for controlling said means for infusing in response to the amount of radioactivity which has been infused into said patient; said dosimetry system comprising:

(a) a photomultiplier tube, having a face through which input signals in the form of light are received;

(b) a plastic scintillator mounted on said face;

(c) means for reflecting back into said tube any light which scintillates from the plastic scintillator;

(d) means for preventing stray light from striking said plastic scintillator; and

(e) a single channel analyzer electrically connected to said photomultiplier tube for receiveing pulses from said photomultiplier tube, said single channel analyzer comprising:

(i) a very high speed comparator which receives input pulses from said photomultiplier tube; and

(ii) means for accepting input pulses having pulse widths of significantly less than 50 microseconds.

2. The dosimetry system of Claim 1 further comprising means for reducing the pulse reptition rate of said input pulses.

3. The dosimetry system of Claim 2 wherein said means for reducing the pulse reptition rate of said input pulses comprises a programmable divide-by-N circuit capable of receiving a very high pulse repetition rate and bringing the pulse repetition rate down into any desirable range.

4. The dosimetry system of Claim 1, 2 or 3 wherein said means for accepting input pulses having pulse widths of significantly less than 50 microseconds is comprised of a one-shot circuit .

5. The dosimetry system of Claim 4 wherein said one-shot circuit is comprised of an emitter coupled logic flip-flop which can accept input pulses having pulse widths of significantly less than 50 microseconds.

8. The dosimetry system of any one of Claims 1 to 5 further comprising means for converting the output pulses into a measure of radioactivity.

7. The dosimetry system of Claim 6 wherein said means for converting the output pulses into a measure of radioactivity comprises a Multiplier-Divider circuit which accepts said output pulses and multiplies them by a number corresponding to the eluate Flow Rate divided by a constant, K, in order to carry out the formula:

$$A = \frac{(N)(F)}{K}$$

Where, A = total activity (in milliCuries);
N = net counts (from Single Channel Analyzer);

F = Flow Rate; and
K = the calibration factor.

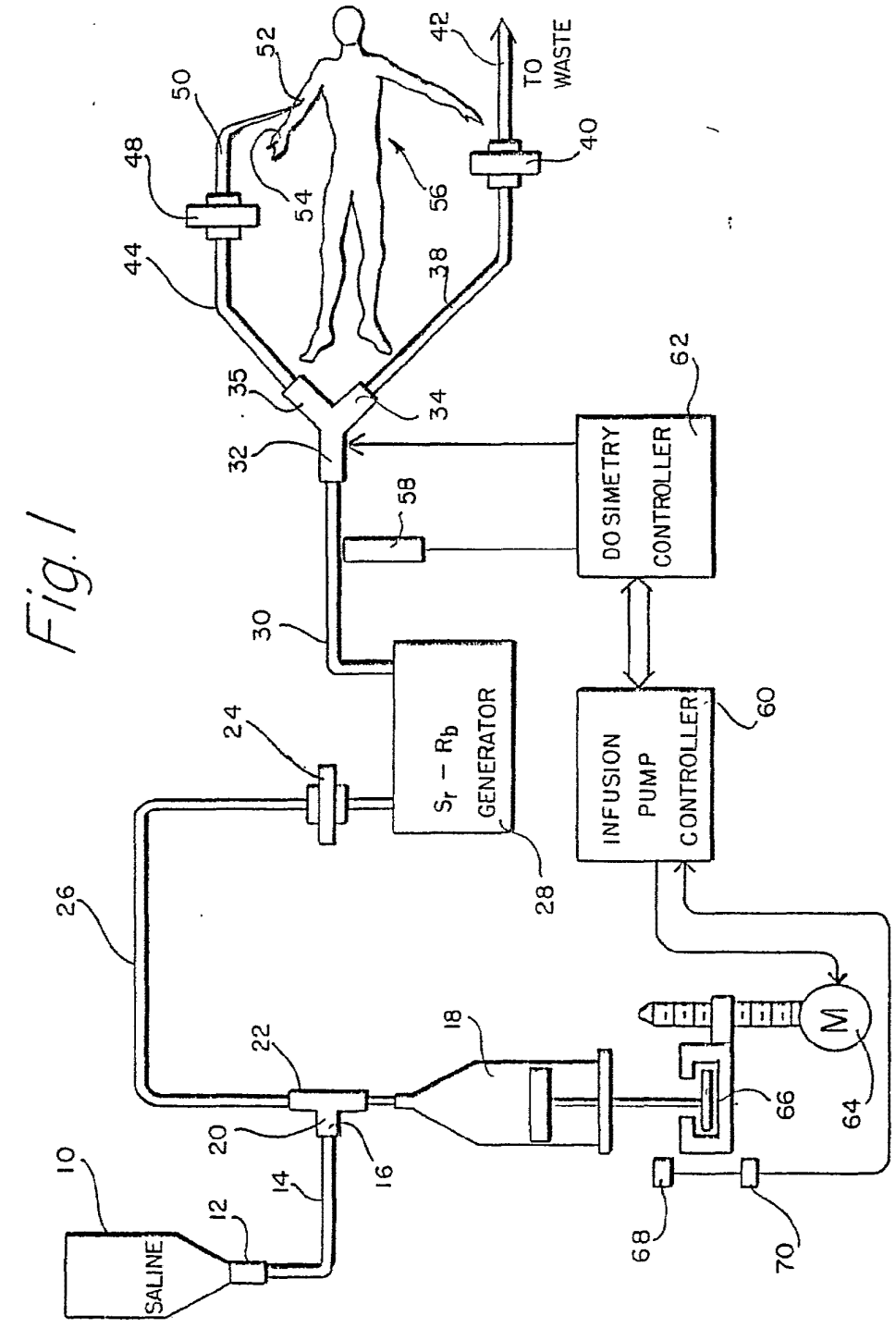
TO WASTE
42
40
52
50
48
54
56
44
38
35
34
32
62
DOSIMETRY CONTROLLER
58
30
$S_r - R_b$ GENERATOR
28
24
INFUSION PUMP CONTROLLER
60
26
M
64
66
18
22
20
16
14
10
12
SALINE
68
70

Fig. 1

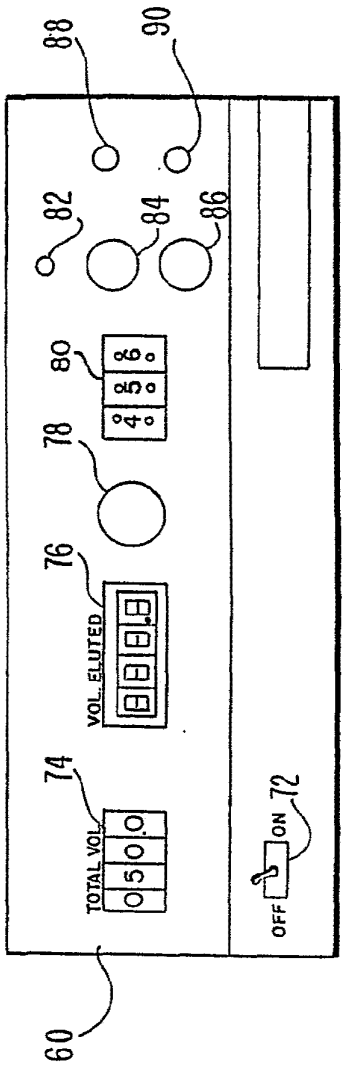
88
90
82
84
86
80
78
76
VOL. ELUTED
74
TOTAL VOL
ON
72
OFF
60

Fig. 2

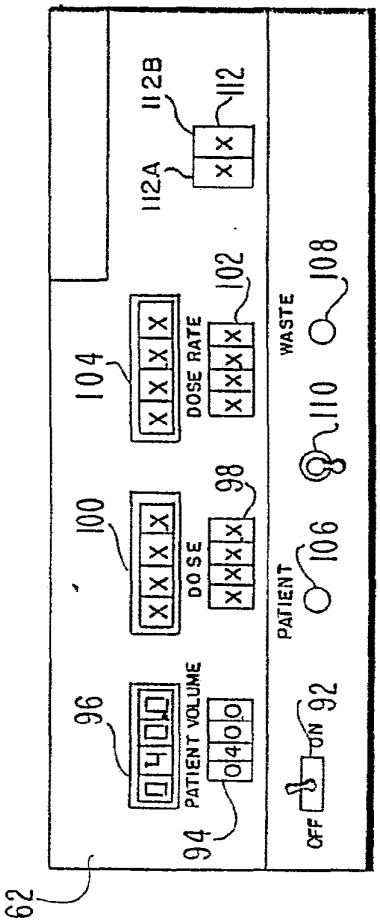
112B
112A
112
104
DOSE RATE
102
108
WASTE
110
100
DOSE
98
PATIENT
106
96
PATIENT VOLUME
94
ON
92
OFF
62

Fig. 3

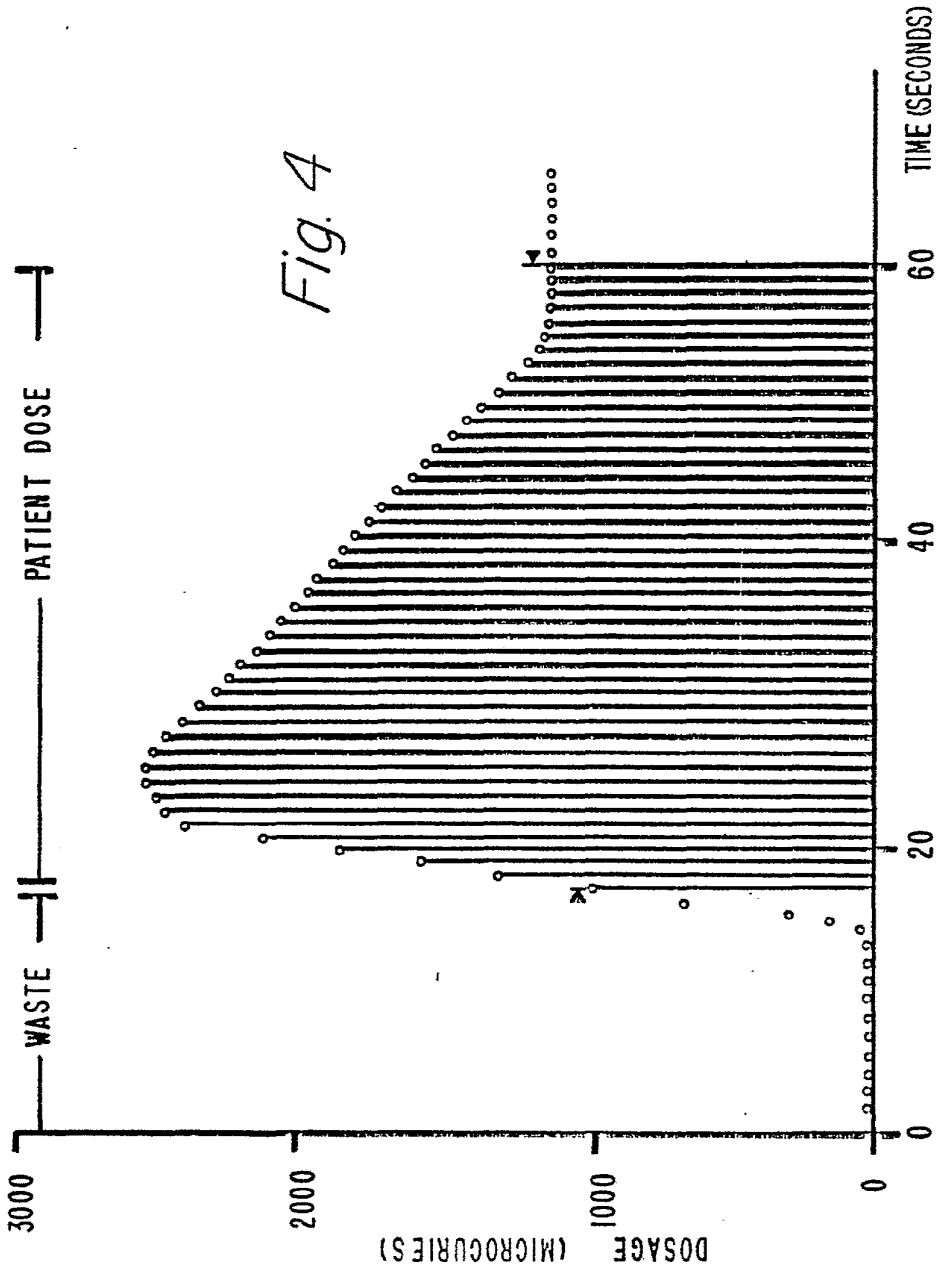
WASTE
PATIENT DOSE
3000
2000
1000
0
DOSAGE (MICROCURIES)
0
20
40
60
TIME (SECONDS)

Fig. 4

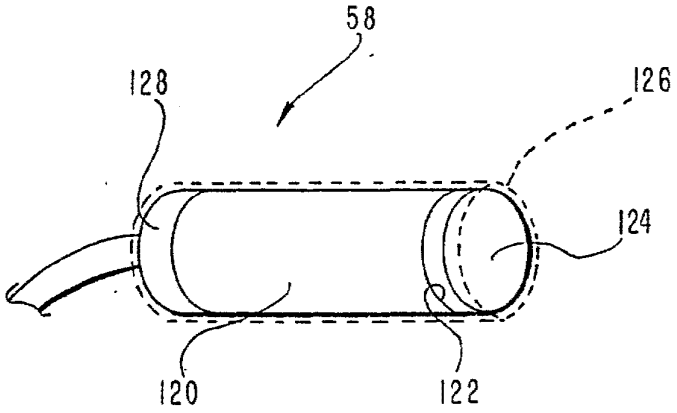
58
128
126
124
120
122

Fig. 5

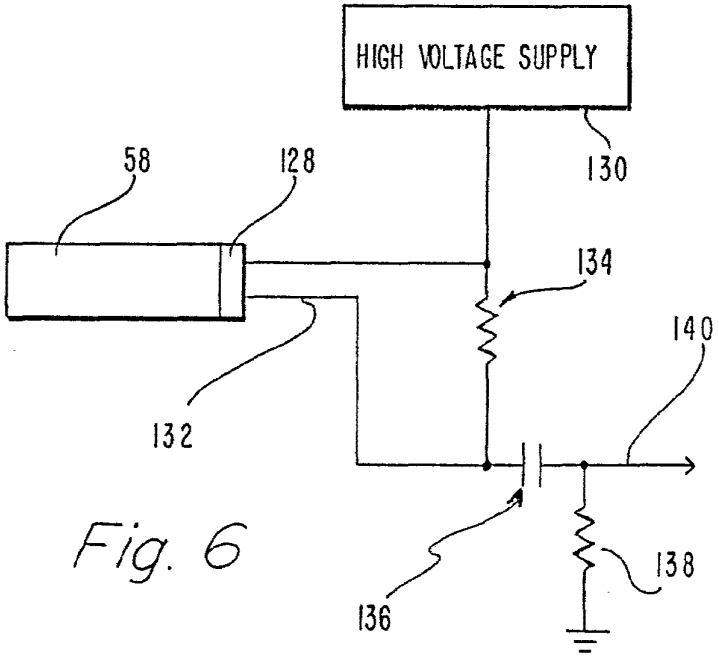
HIGH VOLTAGE SUPPLY
130
58
128
134
140
132
136
138

Fig. 6

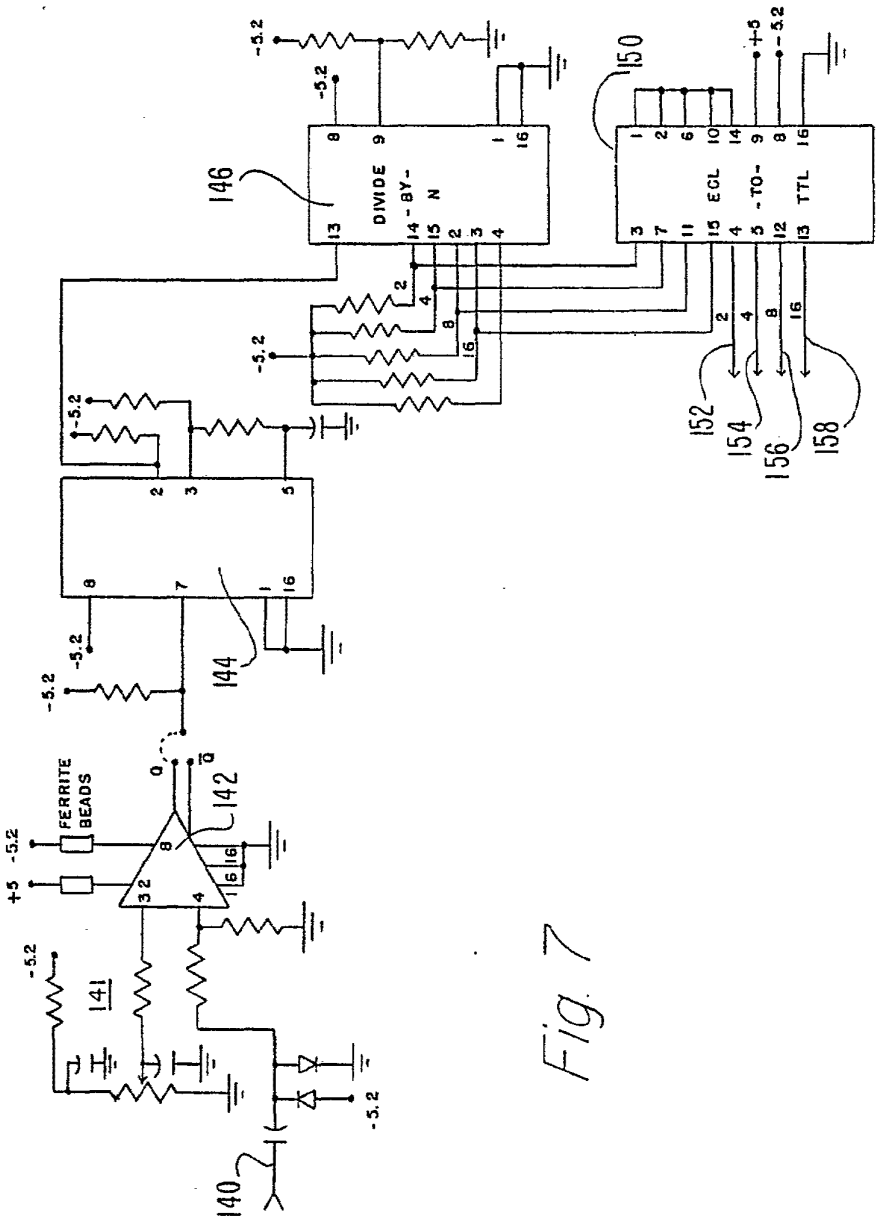
-5.2
+5
146
DIVIDE
-BY-
N
150
ECL
-TO-
TTL
152
154
156
158
144
142
FERRITE
BEADS
141
140
Q
$\overline{Q}$

Fig. 7

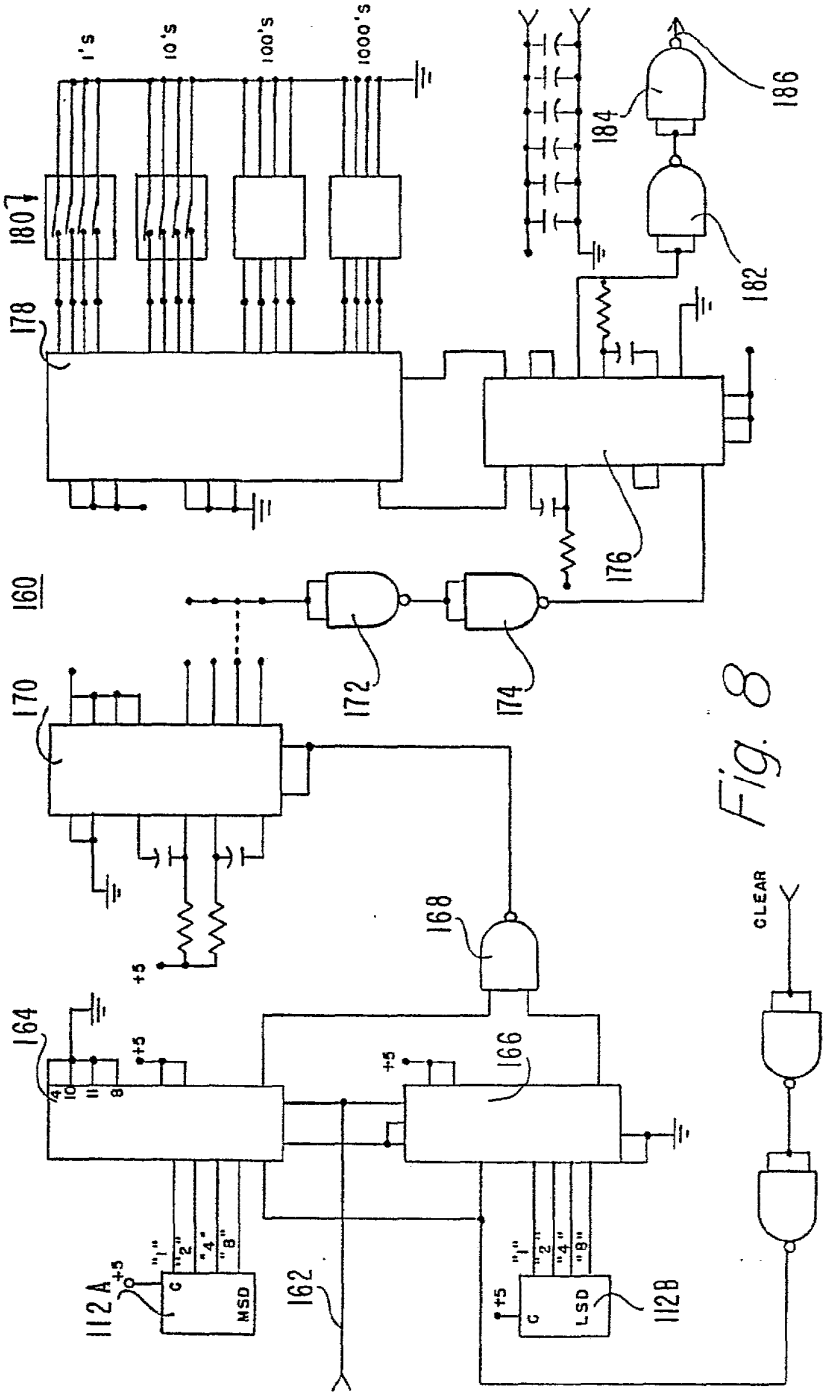
1's
10's
100's
1000's
180
178
184
186
182
176
160
172
174
170
168
164
166
CLEAR
+5
"1"
"2"
"4"
"8"
MSD
LSD
112A
112B
162

Fig. 8

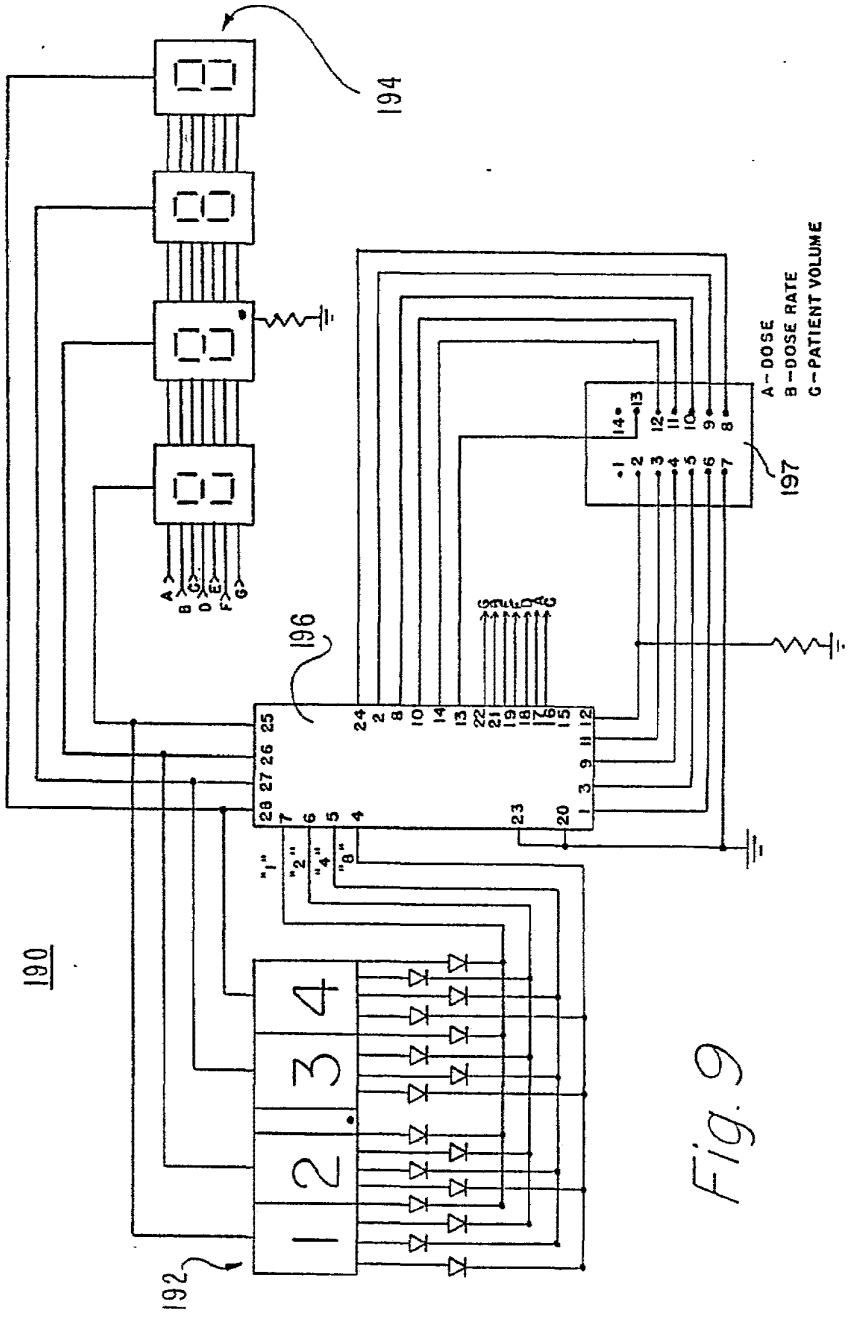

Fig. 9

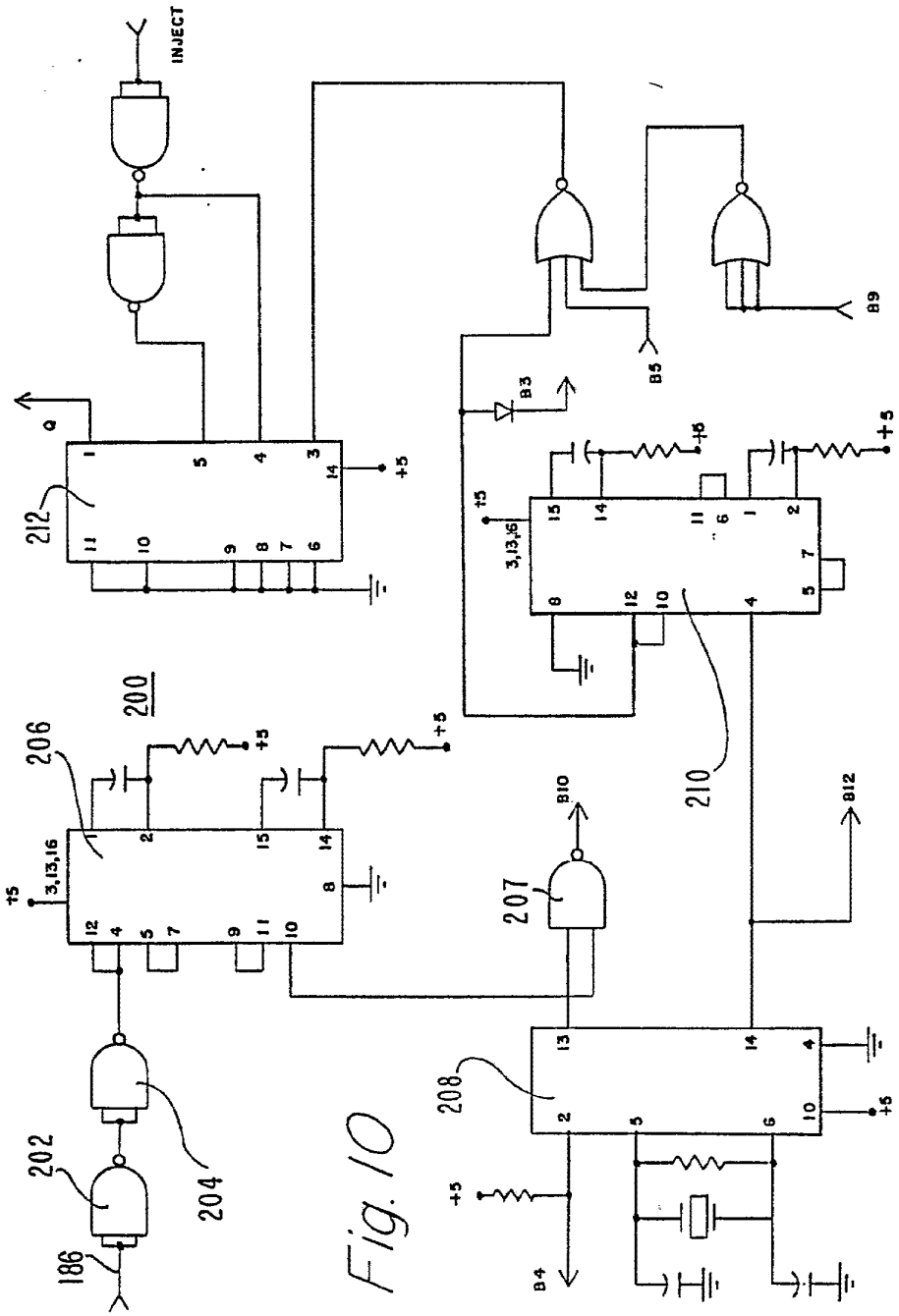
INJECT
200
206
212
210
207
208
202
204
186
B3
B5
B9
B10
B12
B4
+5
+15
3,13,16

Fig. 10

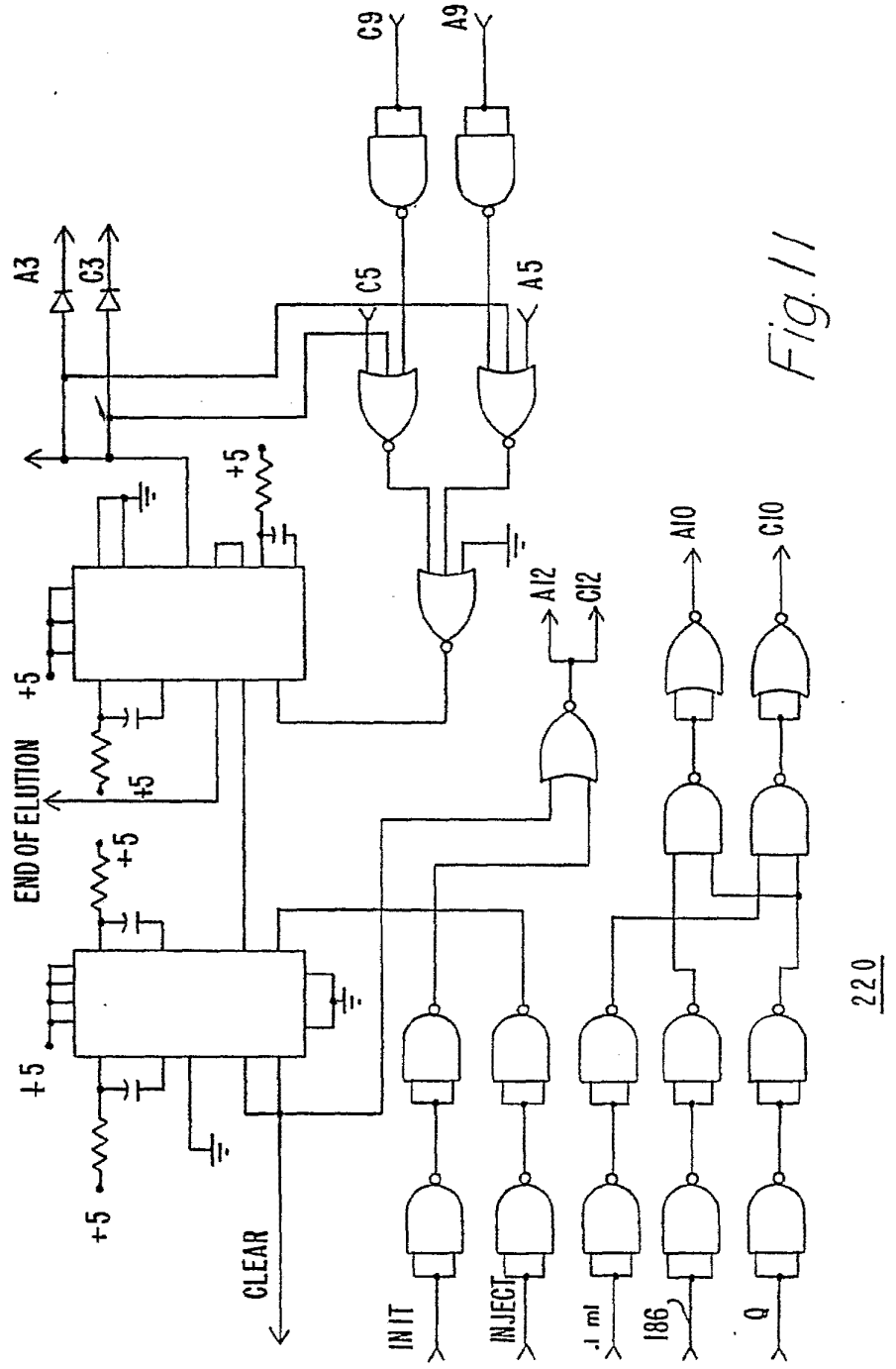
C9
A9
A3
C3
C5
A5
+5
A12
CI2
A10
C10
END OF ELUTION
CLEAR
INIT
INJECT
.1 ml
186
Q
220

Fig. 11

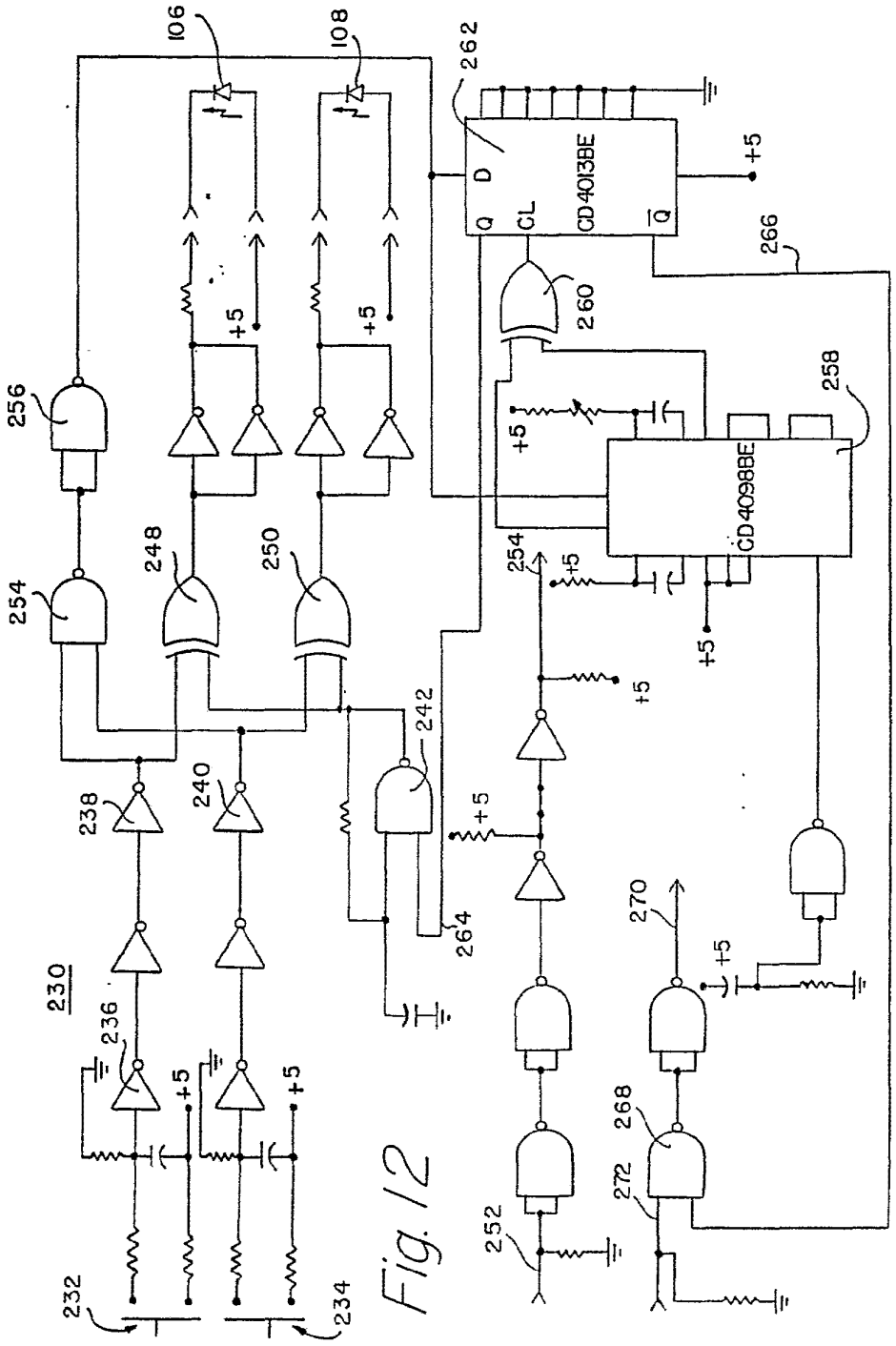
106
108
262
CD4013BE
D
Q
CL
Q
+5
266
260
256
258
CD4098BE
254
248
250
242
238
240
230
236
232
234
264
270
268
272
252

Fig. 12

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60/700,299	19 July 2005 (19.07.2005)	US
60/700,317	19 July 2005 (19.07.2005)	US
60/700,753	20 July 2005 (20.07.2005)	US
60/700,752	20 July 2005 (20.07.2005)	US
60/702,979	28 July 2005 (28.07.2005)	US
60/720,034	26 September 2005 (26.09.2005)	US
60/720,652	27 September 2005 (27.09.2005)	US
60/720,541	27 September 2005 (27.09.2005)	US
171346	10 October 2005 (10.10.2005)	IL
PCT/IL2005/001173	9 November 2005 (09.11.2005)	IL
PCT/IL2005/001215	16 November 2005 (16.11.2005)	IL
172349	27 November 2005 (27.11.2005)	IL
60/741,440	2 December 2005 (02.12.2005)	US
60/750,287	13 December 2005 (13.12.2005)	US
60/750,294	13 December 2005 (13.12.2005)	US
60/750,597	15 December 2005 (15.12.2005)	US
60/750,334	15 December 2005 (15.12.2005)	US
PCT/IL2006/000059	15 January 2006 (15.01.2006)	IL
67/763,458	31 January 2006 (31.01.2006)	US

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(54) Title: UNIFIED MANAGEMENT OF RADIOPHARMACEUTICAL DISPENSING, ADMINISTRATION, AND IMAGING

(57) Abstract: Apparatus is provided for use with at least one labeled radiopharmaceutical agent, the apparatus including a container (22) containing the at least one labeled radiopharmaceutical agent, and a portable computer-communicatable data carrier (120, 24) associated with the container (22), the data carrier (120, 24) containing imaging protocol information for use with the at least one labeled radiopharmaceutical agent. Other embodiments are also described.

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UNIFIED MANAGEMENT OF RADIOPHARMACEUTICAL DISPENSING, ADMINISTRATION, AND IMAGING

CROSS-REFERENCES TO RELATED APPLICATIONS

The present patent application is a continuation-in-part of:

(i) International Application PCT/IL2005/001215, filed November 16, 2005; and

(ii) International Application PCT/IL2005/001173, filed November 9, 2005, which:

(a) claims the benefit of the following US Provisional Patent Applications:

- 60/625,971, filed November 9, 2004;
- 60/628,105, filed November 17, 2004;
- 60/630,561, filed November 26, 2004;
- 60/632,236, filed December 2, 2004;
- 60/632,515, filed December 3, 2004;
- 60/635,630, filed December 14, 2004;
- 60/636,088, filed December 16, 2004;
- 60/640,215, filed January 3, 2005;
- 60/648,385, filed February 1, 2005;
- 60/648,690, filed February 2, 2005;
- 60/675,892, filed April 29, 2005;
- 60/691,780, filed June 20, 2005;
- 60/700,318, filed July 19, 2005;
- 60/700,299, filed July 19, 2005;
- 60/700,317, filed July 19, 2005;
- 60/700,753, filed July 20, 2005;
- 60/700,752, filed July 20, 2005;

- 60/702,979, filed July 28, 2005;
- 60/720,034, filed September 26, 2005;
- 60/720,652, filed September 27, 2005; and
- 60/720,541, filed September 27, 2005, and

(b) is a continuation-in-part of the following International Patent Applications:

- PCT/IL2005/000572, filed June 1, 2005; and
- PCT/IL2005/000575, filed June 1, 2005.

The present patent application claims the benefit of the following US Provisional Applications:

- 60/750,287, filed December 13, 2005;
- 60/750,334, filed December 15, 2005; and
- 60/750,597, filed December 15, 2005.

The present patent application is related to a US provisional patent application filed on even date herewith, entitled, "Imaging protocols."

All of the above-mentioned applications are assigned to the assignee of the present application and are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to pharmaceutical management and control, and specifically to systems and methods for radiopharmaceutical dispensing, administration, and imaging.

BACKGROUND OF THE INVENTION

US Patent Application Publication 2005/0277833 to Williams, Jr., which is incorporated herein by reference, describes techniques for handling, mixing, dispensing and/or injecting a mixture into an individual during a medical procedure. The mixture contains pharmaceutical agents and/or radiopharmaceutical agents. Also described is a mixing device capable of diluting a radiopharmaceutical agent with, for instance, a diluent, for altering a radiation dose emitted by the radiopharmaceutical agent.

US Patent Application Publication 2005/0203389 to Williams, Jr., which is incorporated herein by reference, describes techniques for an operator to control an injection device and imaging equipment from a common control console. The injection device may be used to administer a contrast medium into a patient so that imaging equipment can acquire internal images of the patient. An injection system is bundled with software and/or hardware that is used to modify an existing imaging control console so that it can be used to operate both the injection device and imaging device. In one embodiment, the common control console can access stored protocols that can contain operational parameters for the injection device, the imaging device, or both.

US Patent 4,679,142 to Lee, which is incorporated herein by reference, describes techniques for dispersing quantities of radioactive material at a user location. Billing is accomplished by monitoring the decay of material and the degree of activity following each user withdrawal.

US Patent Application Publication 2005/0261938 to Silverbrook et al., which is incorporated herein by reference, describes a method for authenticating a pharmaceutical product, the pharmaceutical product being associated with packaging having disposed thereon or therein coded data including a number of coded data portions, each coded data portion being indicative of an identity of the pharmaceutical product and at least part of a digital signature of at least part of the identity. The method includes having a computer system receive indicating data from a sensing device, the sensing device being responsive to sensing of the coded data to generate indicating data at least partially indicative of the identity of the pharmaceutical product and the signature part. The computer system determines the identity at least one determined signature part and uses these to authenticate the pharmaceutical product.

US Patent Application Publication 2005/0261936 to Silverbrook et al., which is incorporated herein by reference, describes a method for allowing a user to interact with a pharmaceutical product, the pharmaceutical product associated with packaging having disposed thereon or therein coded data, at least some of the coded data being indicative of at least an identity. The method includes having a computer system receive indicating data from a sensing device, in response to sensing of the coded data, and determine, using the indicating data, at least one action. The computer system then performs the action associated with the pharmaceutical product, the action including at least one of providing

information to a user; updating tracking information relating to the pharmaceutical product; performing a transaction relating to the pharmaceutical product; authenticating the pharmaceutical product; and receiving feedback from the user.

US Patents 5,882,338 and 6,019,745 to Gray, which are incorporated herein by reference, describe a medical syringe comprising a cylindrical barrel having therein a plunger which can be axially driven by a plunger rod. The plunger rod passes through an aperture in the center of a finger grip having two finger grip projections at opposite sides thereof. A data carrier means in the form of an electrically or magnetically operable device is mounted near the end of one of the two finger grip projections, with preferably a device mounted near the end of each finger grip projection. The device carries data relating to the medicament contained or to be contained within the syringe, and can be read by a suitably adapted syringe pump when the syringe is mounted thereon to be driven by the syringe pump.

US Patent 6,970,735 to Uber, III et al., which is incorporated herein by reference, describes a system for producing a contrast-enhanced medical image of a patient, including a source of a contrast or enhancement medium, a pressurizing unit in fluid connection with the source of contrast or enhancement medium, an energy source operable to apply energy to a region of the patient, an imaging unit providing a visual display of an internal view of the patient based upon a signal resulting from the energy applied to the region of the patient, and a control unit. In an embodiment, the signal is affected by a condition of the contrast or enhancement medium in the patient. To control an imaging procedure, the control unit adjusts the condition of the contrast or enhancement medium in the patient based upon the signal. A communication interface preferably enables information between an injector subsystem and an imaging subsystem.

US Patents 5,781,442, 6,671,563, 6,915,170, and 6,731,989 to Engleson et al., which are incorporated herein by reference, describe a care management system in which the management of the administration of care for patients is automated. Hospital information systems are monitored and the information from those systems is used in verifying the administrations of care to patients. The care management system monitors ongoing administrations for progress and automatically updates records and provides alarms when necessary. The care management system is modular in nature but is fully integrated among its modules. Particular lists of data, such as the termination times of all

ongoing infusions, provide hospital staff current information for increased accuracy and efficiency in planning. Features include the automatic provision of infusion parameters to pumps for accurate and efficient configuration of the pump, and providing an alarm when an unscheduled suspension of an infusion exceeds a predetermined length of time. A passive recognition system for identifying patients and care givers is described.

US Patent Application Publication 2003/0055685 to Cobb et al., which is incorporated herein by reference, describes techniques for monitoring administration of a medical product within a delivery device using a medicine data storage device attached to the delivery device, which includes a product identifier identifying the medical product and an intended patient identifier identifying a patient intended to receive the medical product. Before administering the medical product to an individual patient, the product identifier and the intended patient identifier are uploaded into a reader, and a patient identifier is accessed from the reader's memory or uploaded from a patient identification device associated with the individual patient into the reader. The patient identifier is compared with the intended patient identifier to determine whether the individual patient is intended to receive the medical product. Once it is confirmed that the individual patient is intended to receive the medical product, the medical product is administered to the individual patient.

US Patent Application Publication 2005/0131270 to Weil et al., which is incorporated herein by reference, describes a system including a radiation treatment agent to treat tissue in response to received X-ray radiation and an identifier associated with the radiation treatment agent. The identifier may be usable to identify a radiation treatment plan. In some embodiments, a radiation treatment plan associated with a patient is generated, the radiation treatment plan is associated with an identifier and a patient identifier identifying the patient, a radiation treatment agent is prepared for delivery to the patient according to the radiation treatment plan, and the radiation treatment agent is associated with the identifier.

US Patent 6,985,870 to Martucci et al., which is incorporated herein by reference, describes a medication delivery system comprising a medical container holding a prescribed medication to be delivered to a patient, a tag adapted to be worn by the patient, a handheld computing device, and an electronic medication delivery device. Data on the medication is contained in a first label on the medication container. The first label also

contains the instruction on how the medication is delivered to the patient, including the appropriate settings for an electronic medication delivery device for delivering the medication to the patient. Patient data is contained in a second label on the tag worn by the patient. The medication data, medication delivery instruction, and patient data are provided in machine readable formats. The handheld computing device reads the medication data and the medication delivery instruction on the medication container and the patient data on the patient tag. The handheld computing device stores the information obtained and performs a matching check to confirm that the medication data matches with the patient data. Upon a confirmed match, it transmits the medication delivery instruction to the electronic medication delivery device, which downloads the instruction, programs the delivery device, and prompts an operator to begin delivering the medication to the patient according to the downloaded instruction.

US Patent Application Publication 2005/0029277 to Tachibana, which is incorporated herein by reference, describes a drug container having an identification tag fixed or detachably provided at a predetermined position of the container, the tag having recorded thereon drug data on a kind and a concentration of a drug, and upper and/or lower limits of a flow rate for continuous infusion, or time and flow rate for one-shot administration.

US Patent Application Publication 2005/0277911 to Stewart et al., which is incorporated herein by reference, describes techniques for programming a medical therapy in a medical device. The medical device has a controller, a memory, a processor, and an input device. The memory is preloaded with at least one of a plurality of patient profiles and condition profiles. The memory is further preloaded with an associated medication therapy for a plurality of the profiles. The input device receives profile data, comprising at least one of a patient profile data and a condition profile data for a specific patient, and the processor processes the received profile data and provides as output one of the preloaded medication therapies based on the processed profile data.

US Patent 6,506,155 to Sluis, which is incorporated herein by reference, describes an ultrasound imaging system including a data entry device that reads storage media that is assigned to each patient on which the system is to be used or the operator of the system to obtain ultrasound images. The storage media, which comprises a barcode, smartcard, or personal digital assistant, contains patient identifying information. The patient or

procedure identifying information is used to access a digital requisition that is referenced by the patient identifying information. The digital requisition is stored in a disk drive included in the ultrasound imaging system or in a clinical information system accessed through a communication link included in the ultrasound imaging system. The digital requisition includes information pertaining to an ultrasound examination procedure that is to be performed on the patient, which is used to automatically set up the ultrasound imaging system. The digital requisition may also include the patient's medical history or information about the patient that can be associated with ultrasound images obtained from the patient.

US Patent Application Publication 2005/0121505 to Metz et al., which is incorporated herein by reference, describes patient-centric data acquisition protocol selection systems and methods, and identification tags therefor. A patient-centric data acquisition protocol selection system comprises a programmable identification tag capable of allowing predetermined information about a patient to be stored therein and retrieved therefrom; a medical imaging system capable of communicating with the programmable identification tag; and programming associated with the medical imaging system for selecting an optimal data acquisition protocol. The medical imaging system reads information from the programmable identification tag and then the programming selects an optimal data acquisition protocol based, at least in part, on the predetermined information about the patient that is stored in the programmable identification tag.

PCT Publication WO 04/004787 to Van Naemen et al., which is incorporated herein by reference, describes a method for dispensing individual doses of a radiopharmaceutical solution, which consists of a radioactive parent solution diluted with a diluting solution. Also described is a computer-generated dose dispenser for dispensing individual doses of a radiopharmaceutical solution at a specified speed. The method and device are described as being particularly suitable for use in the field of nuclear medicine, and more in particular for use for PET scan applications.

US Patent 6,032,155 to de la Huerga, which is incorporated herein by reference, describes techniques for administering a prescribed medication to a patient. A medication administration system and apparatus dispense the prescribed medication, verify that the medication is given to a correct patient by an authorized healthcare worker, and track and record the administration of the medication. The system utilizes a workstation connected

to a database containing prescribed medication dose information for various patients. A healthcare worker uses the workstation to manually or automatically dispenses the medication the portable container. An information device is secured to the portable container during transport and administration of the medication to the intended patient. The information device prevents access to the medication or warns the healthcare worker of a potential error if the medication is delivered to the wrong patient or administered by an unauthorized healthcare worker. The information device records actual consumption information, and delivers this information back the workstation database or to a hospital or pharmacy database.

US Patent 5,317,506 to Coutre et al., which is incorporated herein by reference, describes an infusion management and pumping system. Infusion prescriptions are generated and monitored by a pharmacy management system. Labels for each infusion to be given to a patient are generated and printed in a barcode format. Each label contains data regarding a prescribed infusion program, including the drug or drugs to be infused, the infusion regimen, the expiration date, and the patient to whom the infusion is to be administered. The management system checks for incompatibilities between drugs that are being prescribed for simultaneous infusion. Each label generated by the management system is attached to the container which holds the infusion solution. The data on the label is transferred to an infusion pumping system by a barcode reader at the infusion pumping system. The pumping system checks that all necessary data has been entered. During operation, the pumping system checks for a variety of alarm conditions and stores any alarms in a ranking according to urgency. The infusion pumping system is responsive to remote or biofeedback instructions to alter the planned infusion program. Central computer records processing receives infusion data and provides infusion, inventory, and use analysis.

US Patent 5,039,863 to Matsuno et al., which is incorporated herein by reference, describes an automatic radioisotope filling apparatus, which is equipped with a radioisotope vial containing a radioisotope solution, a saline vial containing a physiological saline solution, a dilution vial to which a predetermined amount of the radioisotope solution and a predetermined amount of the physiological saline solution are to be transferred to prepare a diluted radioisotope solution, a radiation detector for measuring the radioactive intensity of the diluted radioisotope solution prepared in the dilution vial, and a plurality of label vials containing a drug to be labeled.

US Patent Application Publication 2004/0051368 to Caputo et al., which is incorporated herein by reference, describes a system for delivering medical fluid to a patient. The system includes a medical container including a Radio Frequency Identification (RFID) tag storing data related to the medical fluid therein. A RF reader receives data signals transmitted from the RFID tag that include a desired flow rate for delivering the fluid to the intended patient. A pump coupled to the reader includes a pumping mechanism for pumping the medical fluid from the container, and a pump controller for receiving the data including the desired flow rate from the reader. The pump controller automatically controls the pumping mechanism to pump the medical fluid from the medical container at the desired flow rate based upon the data.

US Patent Application Publication 2005/0171815 to Vanderveen, which is incorporated herein by reference, describes a centralized medication management system for monitoring, managing and controlling medication delivery from a central location. A central computer displays medication orders and ongoing medication administrations for a health care facility. The central computer checks medication delivery against a database of medication administration guidelines, including guidelines for medication interactions with other medications and with patient conditions, and provides an indication of any detected incompatibilities. A clinician at the central location may adjust the medication administration parameters in response to detected incompatibilities and communicate with a caregiver at the point of care to provide decision support. In an embodiment, the central location is a pharmacy at the healthcare facility.

US Patent Application Publication 2005/0240441 to Suzuki, which is incorporated herein by reference, describes a hospital information system. The system enables an RF reader, comprising a personal digital assistant (PDA), to read tag information recorded by RF tags either attached to, or embedded in, various types of a patient wrist bands, injection medicine bottles, patient charts, and medical instrument cases. The PDA transmits a query to a server via a wireless LAN for confirmation from the server. The server collates the query with the content of a medical practice order recorded in its data base, and registers a completion of instructed operation for an instructed item in the database, and replies with a notification if the transmitted readout data from the PDA is correct. If the readout data is incorrect, the PDA is notified and instructed to perform another reading.

US Patent Application Publication 2001/0049608 to Hochman, which is incorporated herein by reference, describes an automated drug administering system such an injection device or infusion pump, which is provided with means for reading information from a container holding the drug. The information is then checked for accuracy before the administration of the drug. Optionally, an ID tag on the patient and/or the health care professional providing the drug may also be scanned and checked. The information thus gathered is sent to another station where it is logged for future use and analyzed.

US Patent 6,743,202 to Hirschman et al., which is incorporated herein by reference, describes apparatus for sharing information on syringe configuration between syringes and injector systems, comprising a storage system to store encoded information on syringe configuration. The encoded information is readable by a detection circuit in an injector. In one embodiment, the storage system is an electronic storage system in which information relevant to the syringe configuration is encoded. A method comprises the step of conveying syringe configuration information to a detector in an injector for use with the syringe.

US Patent Application Publication 2005/0148869 to Masuda, which is incorporated herein by reference, describes a liquid syringe having various kinds of data items recorded in a two-dimensional code format. A liquid injector optically reads the two-dimensional codes, decodes them, and executes a predetermined operations corresponding to the decoded results. Recording, for example, a variable pattern for the liquid of interest in the two-dimensional code format on the liquid syringe makes it possible for the liquid injector to inject the liquid in accordance with the predetermined variable pattern.

US Patent 6,346,886 de la Huerga, which is incorporated herein by reference, describes an electronic identification apparatus having data storage memory on board a removable transceiver device. The transceiver device also includes a processor and a transponder for receiving information pertaining to the object/person to which it is attached and storing the information in memory. The transceiver also transmits stored data to a control computer or the external devices. The transceiver is mounted on a base, such as a wristband, and the apparatus includes an attachment sensor indicating whether the transceiver is attached to the base. If the transceiver has been removed from the base,

the processor performs one or more lockdown operations to prevent the stored data from being used in connection with another object or person. The lockdown operations include clearing the contents of the memory, disabling access to the memory, suppressing the display of stored data and activating an alarm.

US Patent Application Publication 2004/0156081 to Bril et al., which is incorporated herein by reference, describes a color-coded signature, for securing documents or encrypting images. The encrypted image comprises an array of printed positions formed using a group of inks each of which has a predetermined spectrum. The positions are selected to form a predetermined image, either real or virtual, when the image is viewed through an optical processor. The optical processor may further use a distorted grating or a distorted lens. The correct image is the spectrum, as distorted by the optical processor. An image formed using inks having the same colors as experienced by the human eye, or even by a standard spectrometer will fail to form the correct predetermined image.

The following patents and patent application publications, all of which are incorporated herein by reference, may be of interest:

US Patent Applications 2005/0131579 and 2005/0088306, and US Patent 6,935,560, all to Andreasson

US Patent 6,851,615 to Jones

US Patent application 2005/0131397 and US Patent 6,861,954 to Levin

US Patent 6,519,569 to White et al.

US Patent 5,692,640 to Caulfield et al.

US Patents 6,475,192 and 6,733,478 to Reilly et al.

US Patent 6,958,053 to Reilly

US Patent Application Publications 2005/0261937 and 2005/0261938 to Silverbrook et al.

US Patent 6,994,249 to Peterka et al.

US Patent 6,843,357 to Bybee et al.

US Patent 6,425,174 to Reich

US Patent 6,722,499 to Reich

US Patent 5,536,945 to Reich

US Patent RE36,693 to Reich

US Patent 5,519,931 to Reich

US Patent Application Publication 2005/0198800 to Reich

US Patent 6,576,918 to Fu et al.

US Patent Application Publication 2005/0247893 to Fu et al.

US Patent 5,927,351 to Zhu et al.

US Patent 5,828,073 to Zhu et al.

US Patent 6,162,198 to Coffey et al.

US Patents 6,338,007 and 6,116,461 to Broadfield et al.

US Patent 5,944,190 to Edelen

PCT Publication WO 04/032151 to Besing et al.

US Patent Application Publication 2005/0234424 to Besing et al.

US Patent 4,296,785 to Vitello et al.

US Patent 3,446,965 to Ogier et al.

US Patent 6,355,024 to Small et al.

US Patent 6,468,261 to Small et al.

US Patent 5,580,541 to Wells et al.

US Patent 3,535,085 to Shumate

US Patent 4,853,546 to Abe et al.

US Patent 5,329,976 to Haber et al.

US Patent 5,304,165 to Haber et al.

US Patent 5,911,252 to Cassel

US Patent 5,475,232 to Powers et al.

PCT Publication WO 05/002971 to Tochon-Danguy et al.

US Patent Application Publication 2005/0278066 to Graves

US Patent 5,479,969 to Hardie et al.

US Patent 5,309,959 to Shaw et al.

US Patent 6,870,175 to Dell et al.

US Patent 6,767,319 to Reilly et al.

US Patent 6,976,349 to Baldwin et al.

US Patent 6,957,522 to Baldwin et al.

US Patent 6,915,619 to Baldwin

US Patent 6,813,868 to Baldwin et al.

US Patent 5,893,397 to Peterson et al.

US Patents 5,885,216, 5,806,519, and 6,901,283 to Evans, III et al.

US Patent Application Publication 2004/0084340 to Morelle et al.

US Patent 6,269,340 to Ford et al.

US Patent Application Publication 2004/0193453 to Butterfield et al.

US Patent 4,476,381 to Rubin

US Patent 6,643,537 to Zatezalo et al.

US Patent Application Publication 2005/0108044 to Koster

US Patent 6,851,615 to Jones

US Patent 5,840,026 to Uber, III et al.

US Patent 6,685,678 to Evans et al.

US Patent Application Publication 2003/0183226 to Brand et al.

US Patent Application Publications 2005/0107914 and 2005/0113945 to Engleson et al.

US Patent Application Publication 2002/0198738 to Osborne

US Patent Application Publication 2002/0099334 to Hanson et al.

US Patents 6,317,648 and 6,522,945 to Sleep et al.

US Patent 6,155,485 and 6,318,630 to Coughlin et al.

US Patent 6,202,923 to Boyer et al.

US Patent 6,915,823 to Osborne et al.

US Patent Application Publication 2004/0205343 to Forth et al.

US Patent 5,493,805 to Penuela et al.

US Patent 5,973,598 to Beigel

US Patent Application Publication 2005/0149350 to Kerr et al.

US Patent 5,884,457 to Ortiz et al.

The following patents and patent application publications, which describe gamma cameras and imaging processing techniques, and which are incorporated herein by reference, may be of interest:

US Patent Application Publication 2005/0205792 to Rousso et al.

PCT Publication WO 05/118659 to Dichterman et al.

PCT Publication WO 05/119025 to Nagler et al.

US Patent Application Publication 2004/0204646 to Nagler et al.

PCT Publication WO 04/042546 to Kimchy et al.

US Patent Application Publication 2004/0054248 to Kimchy et al.

US Patent Application Publication 2004/0015075 to Kimchy et al.

US Patent Application Publication 2004/0054278 to Kimchy et al.

US Patent Application Publication 2005/0266074 to Zilberstein et al.

US Patents 5,939,724, 5,587,585, and 5,365,069 to Eisen et al.

US Patent 6,943,355 to Shwartz et al.

US Patents 6,242,743 and 5,757,006 to DeVito et al.

US Patent 6,137,109 to Hayes

US Patent 6,388,258 to Berlad et al.

US Patent 6,429,431 to Wilk

US Patent 6,838,672 to Wagenaar et al.

US Patents 6,740,882, 6,545,280, 6,229,145, 5,519,221, and 5,252,830 to Weinberg

US Patent 6,713,766 to Garrard et al.

US Patent 6,765,981 to Heumann

US Patent 6,664,542 to Ye et al.

US Patent 6,080,984 to Friesenhahn

US Patent 5,818,050 to Dilmanian et al.

US Patent 6,728,583 to Hallett

US Patent 5,481,115 to Hsieh et al.

US Patent 6,723,988 to Wainer

US Patent 6,940,070 to Tumer

US Patent 6,635,879 to Jimbo et al.

US Patent 6,353,227 to Boxen

US Patent 6,184,530 to Hines et al.

US Patent Application Publication 2005/0145797 to Oaknin et al.

US Patent Application Publication 2004/0251419 to Nelson et al.

US Patent Application Publication 2003/0001098 to Stoddart et al.

PCT Publication WO 98/16852 to DeVito et al.

PCT Publication WO 05/059840 to Nielsen et al.

SUMMARY OF THE INVENTION

In some embodiments of the present invention, an end-to-end automated system for medical imaging comprises a plurality of integrated elements that are configured to electronically exchange information among one another. The elements include an automated radiopharmaceutical dispensing system, a portable information-bearing radiopharmaceutical agent container, a patient management system, a portable patient-specific data carrier, an automated administration system, and an automated

imaging system. The systems perform their respective automated functions at least in part responsively to the exchanged information. The elements typically authenticate one another via the exchanged information, in order to ensure that only authorized elements participate in the system, and that the systems perform only authorized and appropriate functions.

The exchanged information typically includes patient-specific data, radiopharmaceutical agent-specific data, and/or patient- or radiopharmaceutical agent-specific imaging protocol data. Such data enable the systems to customize their respective automated functions for specific patients, radiopharmaceutical agents, indications, and/or imaging procedures. For some applications, the exchanged information includes commercial license information relating to the use of a specific protocol with a specific radiopharmaceutical agent, and one or more of the systems are configured to verify the license information before performing their respective functions.

In some embodiments of the present invention, the information-bearing radiopharmaceutical agent container and/or the patient-specific data carrier is configured to contain protocol information for performing an imaging procedure using the labeled radiopharmaceutical agent held by the container. For some applications, the protocol information includes SPECT imaging protocol information, and the imaging system uses the protocol information to perform a SPECT imaging procedure using the labeled radiopharmaceutical agent contained in the container. For some applications, the agent container contains a single dose of the labeled radiopharmaceutical agent, which dose is appropriate for use with the imaging protocol.

In some embodiments of the present invention, the information-bearing radiopharmaceutical agent container or the patient-specific data carrier is configured to contain at least one kinetic parameter of the labeled radiopharmaceutical agent contained in the container. The imaging system uses the kinetic parameter to perform a dynamic SPECT imaging procedure.

In some embodiments of the present invention, the information-bearing radiopharmaceutical agent container contains radiopharmaceutical information regarding the labeled radiopharmaceutical agent contained in the container. The portable patient-specific data carrier is configured to contain patient information regarding the patient, and imaging protocol information for use with the labeled radiopharmaceutical

agent, such as SPECT imaging protocol information. The imaging system uses the protocol information to perform an imaging procedure, such as a dynamic SPECT imaging procedure. For some applications, the patient-specific data carrier comprises a coupling mechanism configured to be coupled to the patient. For example, the coupling mechanism may comprise a bracelet, a watch, a necklace, or another wearable article.

In some embodiments of the present invention, the information-bearing radiopharmaceutical agent container contains a first identifier value, and the patient-specific data carrier contains a second identifier value. The imaging system is configured to perform an imaging procedure responsively to a detection of a correspondence between the first and second identifier values. For some applications, the first identifier value equals the second identifier value, while for other applications the values do not equal one another, but instead correspond to one another based on information provided by an element of the end-to-end system. For some applications, the first and/or second identifier values are arbitrarily assigned, or pre-loaded into the data carrier my a manufacturer or distributor, while for other applications at least one of the identifier values comprises a patient identifier, or another meaningful value. For some applications, at least one of the information-bearing agent container and the patient-specific data carrier performs the detection of the correspondence, while for other applications the imaging system or another element of the end-to-end system performs the detection of the correspondence.

In some embodiments of the present invention, the imaging system comprises a SPECT imaging system configured to utilize the information contained in the labeled radiopharmaceutical agent container and/or the patient-specific data carrier to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

The integration of the elements of the end-to-end system, and the exchange of authenticatable information among the elements generally increase patient safety, by ensuring that each patient receives the prescribed labeled radiopharmaceutical agent and dosage, and undergoes the desired imaging protocol. For some applications, one or more

elements of the end-to-end system are configured to perform their respective function only upon being triggered by another element of the system. For example, the administration or imaging system may perform its function only upon being triggered by the information-bearing radiopharmaceutical agent container, by the patient-specific data carrier, and/or, in the case of the administration system, by the imaging system.

In some embodiments of the present invention, the automated radiopharmaceutical dispensing system comprises an information manager that is configured to receive radiopharmaceutical information regarding a labeled radiopharmaceutical agent and patient information regarding a patient. Responsively to the information, the dispensing system automatically dispenses a dose of the labeled radiopharmaceutical agent to an agent container, and stores the radiopharmaceutical information and at least a portion of the patient information in a data carrier associated with the container. For some applications, the radiopharmaceutical information is selected from the group consisting of: imaging protocol information for use with the labeled radiopharmaceutical agent, such as a SPECT imaging protocol; at least one kinetic parameter useful for performing a dynamic SPECT imaging procedure using the at least one labeled radiopharmaceutical agent; and authenticatable information regarding a commercial license for use of a SPECT imaging protocol with the at least one labeled radiopharmaceutical agent.

In some embodiments of the present invention, the dispensing system is configured to receive a mother vial containing a labeled radiopharmaceutical agent in a quantity sufficient for preparation of a plurality of doses of the labeled radiopharmaceutical agent. Associated with the mother vial is a data carrier containing information regarding the labeled radiopharmaceutical agent, such as the formulation, radioactivity information, and protocol information. The information manager of the dispensing system receives at least a portion of the labeled radiopharmaceutical agent information from the data carrier.

In some embodiments of the present invention, use of the end-to-end automated system enables customization of one or more aspects of the imaging process, from dispensing to diagnosis. Customization typically includes one or more of the following:

- The dispensing system customizes the dispensed dose for a specific patient, based on radiopharmaceutical information and patient-specific information. Typically, the dispensing system customizes the dispensed

dose (e.g., the radioactivity level thereof) based in part on the scheduled time of the scheduled time of administration of the dose, and/or the scheduled time of the imaging procedure to be performed using the dose.

- The administration system customizes the administered dose for a specific patient, based on radiopharmaceutical information and patient-specific information. For some applications in which the administration system customizes the administered dose, the radiopharmaceutical agent container contains a standard, non-customized dose.

- The imaging system customizes image acquisition, image reconstruction, image analysis, and/or diagnosis, based on radiopharmaceutical information and patient-specific information, such as patient physiology and/or known and/or suspected disease of the patient.

Such customization is typically based at least in part on information provided by the manufacturer or distributor of the radiopharmaceutical agent. Such information may be in the form of lookup tables and/or expert system rules.

As used in the present application, including in the claims, "labeled" means radiolabeled, and "unlabeled" means not radiolabeled.

There is therefore provided, in accordance with an embodiment of the present invention, apparatus for use with at least one labeled radiopharmaceutical agent, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent; and

a portable computer-communicatable data carrier associated with the container, the data carrier containing imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

For some applications, the apparatus comprises a device configured to write the imaging protocol information to the data carrier.

For some applications, the data carrier additionally contains administration protocol information useful for administering the at least one labeled radiopharmaceutical agent.

In an embodiment, the imaging protocol information comprises instructions for performing an imaging procedure using the at least one labeled radiopharmaceutical agent. Alternatively or additionally, the imaging protocol information comprises an identifier of an imaging protocol. Further alternatively or additionally, the imaging protocol information comprises a parameter of the at least one labeled radiopharmaceutical agent. Still further alternatively or additionally, the imaging protocol information comprises a parameter useful for configuring at least one aspect of an imaging procedure performed using the at least one labeled radiopharmaceutical agent.

In an embodiment, the container contains a single dose of the radiopharmaceutical agent, which dose is appropriate for use with the imaging protocol information. Alternatively, the container contains a plurality of labeled radiopharmaceutical agents mixed together. For some applications, the container is shaped so as to define a plurality of chambers, each of which contains a respective one of a plurality of labeled radiopharmaceutical agents.

In an embodiment, the data carrier comprises a first data carrier, which contains a first identifier value, the apparatus further comprises a second computer-communicatable data carrier, which contains a second identifier value, and the apparatus is configured to operate responsively to a detection of a correspondence between the first and second identifier values. For some applications, at least one of the first and second data carriers is configured to perform the detection of the correspondence. Alternatively or additionally, the apparatus comprises a correspondence-detection element configured to perform the detection of the correspondence.

In an embodiment, at least one of the first and second data carriers contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

For some applications, at least one of the first and second identifier values comprises an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

In an embodiment, exactly one of the first and second data carriers comprises a coupling mechanism configured to be coupled to a patient to whom the labeled radiopharmaceutical agent is to be administered.

In an embodiment, the apparatus comprises an imaging system comprising imaging functionality, the imaging system configured, responsively to the detection of the correspondence, to drive the imaging functionality to perform an imaging procedure using the at least one labeled radiopharmaceutical agent.

In an embodiment, the data carrier is physically coupled to the container. For some applications, the data carrier contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered, and the imaging protocol information comprises imaging protocol information selected for the patient. For some applications, the imaging protocol information comprises an identifier of an imaging protocol.

For some applications, the imaging protocol information comprises imaging protocol information customized for the patient.

In an embodiment, the imaging protocol information comprises SPECT imaging protocol information, such as dynamic SPECT imaging protocol information. For some applications, the SPECT imaging protocol information comprises at least one kinetic parameter of the at least one labeled radiopharmaceutical agent, the at least one kinetic parameter useful for performing a dynamic SPECT imaging procedure using the at least one labeled radiopharmaceutical agent.

In an embodiment, the apparatus comprises an imaging system, which comprises a communication element, configured to read the imaging protocol information from the data carrier; and a control unit, comprising imaging functionality, which is configured to perform an imaging procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

In an embodiment, the imaging system comprises a camera, wherein the imaging functionality comprises image acquisition functionality, and wherein the image acquisition functionality is configured to perform an image acquisition procedure using the camera, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element. For some applications, the image acquisition functionality configures a total acquisition time of the image acquisition procedure at least in part responsively to the imaging protocol information. Alternatively or additionally, the camera comprises a plurality of detectors, and wherein the image acquisition functionality is configured to configure, at least in part

responsively to the imaging protocol information, at least one motion of at least one of the detectors during the image acquisition procedure. For some applications, the control unit is configured to configure, at least in part responsively to the imaging protocol information, a waiting time between administration of the labeled radiopharmaceutical agent and commencement of the image acquisition procedure. For some applications, the image acquisition functionality is configured to perform a gated image acquisition procedure at least in part responsively to the imaging protocol information.

In an embodiment, the imaging functionality comprises image reconstruction functionality, and wherein the image reconstruction functionality is configured to perform an image reconstruction procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

In an embodiment, the imaging functionality comprises image analysis functionality, and wherein the image analysis functionality is configured to perform an image analysis procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

In an embodiment, the imaging functionality comprises diagnosis functionality, and wherein the diagnosis functionality is configured to perform a diagnostic procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

In an embodiment, the imaging procedure includes a three-dimensional dynamic imaging study, and wherein the imaging functionality is configured to perform the three-dimensional dynamic imaging study, and to configure the study at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

In an embodiment, the data carrier is not physically coupled to the container, and wherein the data carrier contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered. For some applications, the data carrier comprises a coupling mechanism configured to be coupled to the patient. In an embodiment, the data carrier comprises a first data carrier, and wherein the apparatus further comprises a second computer-communicatable data carrier physically coupled to

the container, the second data carrier containing radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent.

There is also provided, in accordance with an embodiment of the present invention, apparatus for use with at least one labeled radiopharmaceutical agent, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent; and

a computer-communicatable data carrier associated with the container, the data carrier containing authenticatable information regarding a commercial license for use of SPECT imaging protocol information with the at least one labeled radiopharmaceutical agent.

In an embodiment, the apparatus comprises an imaging system, which comprises:

a communication element, configured to read the authenticatable license information from the data carrier;

a control unit, comprising imaging functionality, the control unit configured to:

authenticate the authenticatable license information, and

only upon authentication, drive the imaging functionality to perform an imaging procedure using the SPECT imaging protocol information.

For some applications, the apparatus comprises a device configured to write the authenticatable license information to the data carrier.

For some applications, the data carrier is physically coupled to the container.

There is further provided, in accordance with an embodiment of the present invention, apparatus comprising a portable computer-communicatable data carrier containing authenticatable information regarding a commercial license for use of SPECT imaging protocol information.

For some applications, the data carrier additionally contains patient information regarding a patient upon whom an imaging procedure using the SPECT imaging protocol information is to be performed.

For some applications, the authenticatable license information is encrypted.

In an embodiment, the apparatus comprises an imaging system, which comprises:

a communication element, configured to read the authenticatable license

information from the data carrier;

a control unit, comprising imaging functionality, the control unit configured to:

authenticate the authenticatable license information, and

only upon authentication, drive the imaging functionality to perform an imaging procedure using the SPECT imaging protocol information.

For some applications, the apparatus comprises a device configured to write the authenticatable license information to the data carrier.

For some applications, the data carrier comprises a coupling mechanism configured to be coupled to a patient upon whom an imaging procedure using the SPECT imaging protocol information is to be performed.

There is still further provided, in accordance with an embodiment of the present invention, apparatus comprising:

a first portable computer-communicatable data carrier containing a first identifier value;

a second portable computer-communicatable data carrier containing a second identifier value; and

an imaging system comprising imaging functionality, the imaging system configured, responsively to a detection of a correspondence between the first and second identifier values, to drive the imaging functionality to perform an imaging procedure on a patient.

For some applications, at least one of the first and second data carriers is configured to perform the detection of the correspondence. Alternatively or additionally, the imaging system comprises a correspondence-detection element configured to perform the detection of the correspondence.

For some applications, at least one of the first and second data carriers contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

For some applications, at least one of the first and second identifier values comprises an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

In an embodiment, one of the first and second data carriers comprises a coupling

mechanism configured to be coupled to a patient to whom the labeled radiopharmaceutical agent is to be administered.

For some applications, the apparatus comprises a device configured to write at least one of the first and second identifier values to the respective first and second data carriers.

In an embodiment, at least one of the first and second data carriers contains radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent, the imaging system comprises a communication element, configured to read the radiopharmaceutical information from the at least one of the data carriers, and the imaging system is configured to configure the imaging procedure at least in part responsively to the read radiopharmaceutical information. For some applications, the apparatus comprises a container containing the at least one labeled radiopharmaceutical agent. For some applications, one of the first and second data carriers is physically coupled to the container.

In an embodiment, the imaging functionality comprises a nuclear camera. For some applications, the nuclear camera comprises a SPECT camera.

There is yet further provided, in accordance with an embodiment of the present invention, apparatus for use with first and second portable computer-communicatable data carriers containing first and second identifier values, respectively, the apparatus comprising an imaging system, which comprises:

imaging functionality; and

a control unit configured to drive the imaging functionality to perform an imaging procedure on a patient, responsively to a detection of a correspondence between the first and second identifier values.

For some applications, the imaging system comprises a correspondence-detection element configured to perform the detection of the correspondence.

There is additionally provided, in accordance with an embodiment of the present invention, apparatus for use with at least one labeled radiopharmaceutical agent for administration to a patient, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent;

a first computer-communicatable data carrier physically coupled to the container,

the first data carrier containing radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent; and

a second portable computer-communicatable data carrier containing patient information regarding the patient, and imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

For some applications, the imaging protocol information comprises SPECT imaging protocol information.

For some applications, the patient information comprises an identifier of the patient.

For some applications, the second data carrier comprises a coupling mechanism configured to be coupled to the patient.

For some applications, the first data carrier contains a first patient identifier, the patient information contained in the second data carrier comprises a second patient identifier, and the apparatus comprises an administration system, which comprises:

a first communication element, configured to read the first patient identifier from the first data carrier;

a second communication element, configure to read the second patient identifier from the second data carrier; and

a control unit, configured to compare the first patient identifier to the second patient identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

For some applications, the first data carrier contains a first protocol identifier, the imaging protocol information contained in the second data carrier comprises a second protocol identifier, and the apparatus comprises an administration system, which comprises:

a communication element, configured to read the first and second protocol identifiers from the first and second data carriers, respectively; and

a control unit, configured to compare the first protocol identifier to the second protocol identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

For some applications, the first data carrier contains a first protocol identifier, the imaging protocol information contained in the second data carrier comprises a second protocol identifier, and the apparatus comprises an administration system, which comprises:

a first communication element, configured to read the first protocol identifier from the first data carrier;

a second communication element, configured to read the second protocol identifier from the second data carrier; and

a control unit, configured to compare the first protocol identifier to the second protocol identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

In an embodiment, the apparatus comprises an administration system, which comprises:

a communication element; and

a control unit, configured to:

generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container, and

drive the communication element to transmit information regarding the administration to the second data carrier.

For some applications, the apparatus comprises a device configured to write the imaging protocol information to the first data carrier. Alternatively or additionally, the apparatus comprises a device configured to write the patient information to the second data carrier.

In an embodiment, the imaging protocol information comprises imaging protocol information selected for the patient. For some applications, the imaging protocol information comprises an identifier of an imaging protocol. For some applications, the imaging protocol information comprises imaging protocol information customized for the patient.

In an embodiment, the first data carrier contains a first patient identifier, the patient information contained in the second data carrier includes a second patient identifier, and the apparatus comprises an administration system, which comprises:

a communication element, configured to read the first and second patient identifiers from the first and second data carriers, respectively; and

a control unit, configured to compare the first patient identifier to the second patient identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

For some applications, the administration system comprises an automated administration device, configured to administer the at least one labeled radiopharmaceutical agent to the patient upon being triggered by the administration signal.

For some applications, the control unit is configured to generate the administration signal to trigger the administration of the at least one labeled radiopharmaceutical agent by instructing a healthcare worker to administer the at least one labeled radiopharmaceutical agent to the patient.

There is yet additionally provided, in accordance with an embodiment of the present invention, apparatus for use with at least one labeled radiopharmaceutical agent for administration to a patient, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent;

a computer-communicatable data carrier associated with the container, the data carrier containing data regarding at least one of: the labeled radiopharmaceutical agent and the patient; and

a SPECT imaging system comprising:

a communication element, configured to read the data; and

a control unit, configured to utilize the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

For some applications, the data carrier contains the data regarding the labeled radiopharmaceutical agent. Alternatively or additionally, the data carrier contains the data regarding the patient.

For some applications, the control unit is configured to utilize the read data to customize the administration of the labeled radiopharmaceutical agent. Alternatively or additionally, the control unit is configured to utilize the read data to customize the acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered. Further alternatively or additionally, control unit is configured to utilize the read data to customize the reconstruction of the SPECT image. Still further alternatively or additionally, the control unit is configured to utilize the read data to customize the analysis of the SPECT image. Alternatively or additionally, the control unit is configured to utilize the read data to customize the diagnosis of a condition of the patient based at least in part on the analysis.

For some applications, the apparatus comprises a device configured to write the data to the data carrier.

There is also provided, in accordance with an embodiment of the present invention, a SPECT imaging system for use with a container containing at least one labeled radiopharmaceutical agent for administration to a patient, and data regarding at least one of: the labeled radiopharmaceutical agent and the patient, the system comprising:

a communication element, configured to read the data; and

a control unit, configured to utilize the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

For some applications, the system comprises a device configured to write the data to the container.

There is further provided, in accordance with an embodiment of the present invention, an automated radiopharmaceutical dispensing system for use with a container and a computer-communicatable container data carrier associated with the container, the system comprising:

a robot, configured to manipulate the container;

a communication element; and

a control unit, configured to:

receive radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent, the radiopharmaceutical information selected from the group consisting of: imaging protocol information for use with the at least one labeled radiopharmaceutical agent, and authenticatable information regarding a commercial license for use of an imaging protocol with the at least one labeled radiopharmaceutical agent,

receive patient information regarding a patient,

drive the robot to automatically dispense a dose of the labeled radiopharmaceutical agent to the container, and

drive the communication element to transmit to the container data carrier at least a portion of the radiopharmaceutical information and at least a portion of the patient information.

For some applications, the control unit is configured to receive the radiopharmaceutical information regarding a plurality of labeled radiopharmaceutical agents, and drive the robot to automatically dispense respective doses of the labeled radiopharmaceutical agents to the container.

For some applications, the patient information includes an identifier of an imaging protocol assigned to the patient for performance using the dose, and wherein the control unit is configured to drive the communication element to transmit the imaging protocol identifier to the container data carrier.

For some applications, the control unit is configured to drive the communication element to transmit to the container data carrier at least one of: a time of dispensing of the labeled radiopharmaceutical agent to the container, and information regarding a radioactivity of the dose at the time of dispensing.

In an embodiment, the apparatus comprises:

a mother vial that contains the labeled radiopharmaceutical agent prior to dispensing thereof; and

a computer-communicatable mother vial data carrier associated with the mother vial, which mother vial data carrier contains the radiopharmaceutical information,

wherein the control unit is configured to receive the radiopharmaceutical

information from the mother vial data carrier.

For some applications, the radiopharmaceutical information comprises the imaging protocol information. For some applications, the imaging protocol information comprises SPECT imaging protocol information, which may comprise at least one kinetic parameter of the at least one labeled radiopharmaceutical agent.

In an embodiment, the radiopharmaceutical information comprises the authenticatable information regarding the commercial license. For some applications, the information regarding the commercial license comprises information regarding the commercial license for use of a SPECT imaging protocol with the at least one labeled radiopharmaceutical agent. For some applications, the control unit is configured to authenticate the authenticatable license information, and to drive the robot to automatically dispense the dose only upon authentication.

There is still further provided, in accordance with an embodiment of the present invention, apparatus for use with a container, the apparatus comprising:

a mother vial having a volume of at least 10 ml, which contains at least 5 ml of a non-diluted labeled radiopharmaceutical agent, and at least 5 ml of saline solution; and

an automated radiopharmaceutical dispensing system, configured to contain the mother vial, and to dispense at least one dose from the mother vial to the container.

There is additionally provided, in accordance with an embodiment of the present invention, a method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

associating a portable computer-communicatable data carrier with the container; and

writing, to the data carrier, imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

There is yet additionally provided, in accordance with an embodiment of the present invention, a method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

associating a computer-communicatable data carrier with the container; and

writing, to the data carrier, authenticatable information regarding a commercial license for use of SPECT imaging protocol information with the at least one labeled

radiopharmaceutical agent.

There is also provided, in accordance with an embodiment of the present invention, a method comprising:

providing a portable computer-communicatable data carrier; and

writing, to the data carrier, authenticatable information regarding a commercial license for use of SPECT imaging protocol information.

There is further provided, in accordance with an embodiment of the present invention, a method comprising:

writing first and second identifier values to first and second computer-communicatable data carriers, respectively;

detecting a correspondence between the first and second identifier values; and

perform an imaging procedure on a patient responsively to the detecting.

There is still further provided, in accordance with an embodiment of the present invention, a method for use with at least one labeled radiopharmaceutical agent for administration to a patient, the method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

physically coupling a first computer-communicatable data carrier to the container;

writing, to the first data carrier, radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent; and

writing, to a second portable computer-communicatable data carrier, patient information regarding the patient, and imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

There is additionally provided, in accordance with an embodiment of the present invention, a method comprising:

placing, in a container, at least one labeled radiopharmaceutical agent for administration to a patient;

associating a computer-communicatable data carrier with the container;

writing data to the data carrier regarding at least one of: the labeled radiopharmaceutical agent and the patient;

reading the data from the data carrier at a SPECT imaging system;

utilizing the read data to customize at least one function of the system selected

from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

There is yet additionally provided, in accordance with an embodiment of the present invention, a method for use with a container containing at least one labeled radiopharmaceutical agent for administration to a patient, and data regarding at least one of: the labeled radiopharmaceutical agent and the patient, the method comprising:

reading the data at a SPECT imaging system; and

utilizing the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

There is also provided, in accordance with an embodiment of the present invention, a method for use with a container and a computer-communicatable container data carrier associated with the container, the method comprising:

receiving, by an automated radiopharmaceutical dispensing system, radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent, the radiopharmaceutical information selected from the group consisting of: imaging protocol information for use with the at least one labeled radiopharmaceutical agent, and authenticatable information regarding a commercial license for use of an imaging protocol with the at least one labeled radiopharmaceutical agent;

receiving, by the dispensing system, patient information regarding a patient;

automatically robotically dispensing, by the dispensing system, a dose of the labeled radiopharmaceutical agent to the container; and

transmitting to the container data carrier, by the dispensing system, at least a portion of the radiopharmaceutical information and at least a portion of the patient information.

There is further provided, in accordance with an embodiment of the present invention, a method for automatically dispensing a labeled radiopharmaceutical agent to a

container, comprising:

providing a mother vial having a volume of at least 10 ml;

filling the mother vial with at least 5 ml of a non-diluted labeled radiopharmaceutical agent, and with at least 5 ml of saline solution;

placing the mother vial in an automated radiopharmaceutical dispensing system; and

dispensing at least one dose from the mother vial to the container.

There is also provided, in accordance with an embodiment of the present invention, a method for setting a dose of a labeled radiopharmaceutical agent for use for performing an imaging procedure on a patient for studying a physiological characteristic of the patient, the method including:

selecting the radiopharmaceutical agent;

receiving information regarding a medical parameter of the patient not directly related to the physiological characteristic of the patient; and

setting the dose at least in part responsively to the received information.

There is further provided, in accordance with an embodiment of the present invention, a substance associated with a time-dependent substance intake program generated by a computer controlled functionality employing a machine readable multi-parameter human physiological profile including at least one of a kinetic and intra-body location dependent parameter and a machine readable multi-parameter substance profile, including at least one kinetic parameter.

There is still further provided, in accordance with an embodiment of the present invention, a computer controlled functionality employing a machine readable multi-parameter human physiological profile including at least one of a kinetic and intra-body location dependent parameter and a machine readable multi-parameter substance profile, including at least one kinetic parameter, for indicating a time-dependent substance intake program.

There is yet further provided, in accordance with an embodiment of the present invention, a substance associated with a time-dependent substance intake program generated by a computer controlled functionality employing a machine readable multi-parameter human physiological profile including at least one of a kinetic and

intra-body location dependent parameter and a machine readable multi-parameter substance profile, including at least one kinetic parameter.

There is also provided, in accordance with an embodiment of the present invention, a time-dependent substance intake program generated by a computer controlled functionality employing a machine readable multi-parameter human physiological profile including at least one of a kinetic and intra-body location dependent parameter and a machine readable multi-parameter substance profile, including at least one kinetic parameter.

There is further provided, in accordance with an embodiment of the present invention, a substance formulated in accordance with a time-dependent substance intake program generated by a computer controlled functionality employing a machine readable multi-parameter human physiological profile including at least one of a kinetic and intra-body location dependent parameter and a machine readable multi-parameter substance profile, including at least one kinetic parameter.

There is still further provided, in accordance with an embodiment of the present invention, an apparatus, method, and/or functionality for generation of a machine readable multi-parameter human physiological profile including at least one of a kinetic and intra-body location dependent parameter, including providing a time-dependent substance intake program; a data acquisition system which acquires data from the patient passing through the intake program; and a computerized analysis using a machine readable multi-parameter substance profile, including at least one kinetic parameter.

There is yet further provided, in accordance with an embodiment of the present invention, an apparatus, method, and/or functionality for generation of a human physiological profile, including providing a substance intake program; a data acquisition system which acquires data from the patient passing through the intake program; and a computerized analysis using a substance profile, including at least one kinetic parameter.

There is also provided, in accordance with an embodiment of the present invention, an interactive pharmaceutical-containing, machine-readable information-bearing, customized medicine module suitable for use in computerized customized medicine, said customized medicine module including a computerized

customized medicine machine-interfaceable pharmaceutical-containing delivery module and a computerized individualized medicine machine-readable information-containing carrier containing at least data regarding said pharmaceutical which is required for use of said pharmaceutical in computerized customized medicine, said data being useful in computerized customized medicine machine actuation of said pharmaceutical-containing delivery module.

There is additionally provided, in accordance with an embodiment of the present invention, a computerized customized medicine machine including:

a computerized patient imager;

a computerized pharmaceutical deliverer employing a pharmaceutical-containing, machine-readable information-bearing, customized medicine module; and

a customized medicine protocol controller including:

an interactive patient imager interface including patient information receiving functionality and patient imaging actuation functionality; and

an interactive pharmaceutical deliverer interface including patient information receiving functionality and patient information-responsive pharmaceutical delivery actuation functionality.

There is also provided, in accordance with an embodiment of the present invention, an interactive pharmaceutical-containing, machine-readable authenticated, authenticated customized medicine module suitable for use in computerized customized medicine, said customized medicine module including a computerized customized medicine machine-interfaceable pharmaceutical-containing module and a computerized individualized medicine machine-readable authentication-containing carrier containing at least authentication data regarding said pharmaceutical which is required for use of said pharmaceutical in computerized customized medicine, said data being useful in said computerized customized medicine machine.

There is further provided, in accordance with an embodiment of the present invention, a computerized customized medicine preparation machine including:

a computerized patient information manager;

a computerized customized medicine pharmaceutical information manager;

a computerized authenticated customized medicine module authenticator; and

a computerized pharmaceutical-containing, machine-readable information-bearing, customized medicine module generator including:

a computerized generator protocol manager operative to receive patient information from said patient information manager, to receive authentication of an authenticated customized medicine module from said authenticator, to receive customized medicine pharmaceutical information relating to at least one pharmaceutical contained in said authenticated customized medicine module from said pharmaceutical information manager and to prepare customized medicine information to be included in said customized medicine module; and

a computerized pharmaceutical-containing, machine-readable information-bearing, customized medicine module preparer operative to associate said customized medicine information prepared by said protocol manager in an authenticatable machine readable form with a quantity of said pharmaceutical contained in said authenticated customized medicine module, thereby providing a pharmaceutical-containing, machine-readable information-bearing, customized medicine module.

There is still further provided, in accordance with an embodiment of the present invention, an interactive pharmaceutical-containing, machine-readable information-bearing, individualized medicine module suitable for use in computerized individualized medicine, said individualized medicine module including a computerized individualized medicine machine actuable pharmaceutical-containing delivery module and a computerized individualized medicine machine-readable information-containing carrier containing at least data regarding said pharmaceutical which is required for use of said pharmaceutical in computerized individualized medicine, said data being useful in computerized individualized medicine machine actuation of said pharmaceutical-containing delivery module.

For some applications, said data is in an encrypted format, readable by said computerized individualized medicine machine upon receipt of a predetermined authentication.

There is also provided, in accordance with an embodiment of the present invention, a computerized individualized medicine machine including:

a computerized patient imager;

a computerized pharmaceutical deliverer employing a pharmaceutical-containing, machine-readable information-bearing, individualized medicine module; and

an individualized medicine protocol controller including:

an interactive patient imager interface including patient image receiving functionality and patient imaging actuation functionality; and

an interactive pharmaceutical deliverer interface including patient image receiving functionality and patient image-responsive pharmaceutical delivery actuation functionality.

There is further provided, in accordance with an embodiment of the present invention, use of a high definition, high sensitivity camera for determination of an optimal parameter for a labeled radiopharmaceutical agent, the optimal parameter selected from the group consisting of: optimal dose, optimal mode of administration, optimal mode of acquisition of data with respect to the labeled radiopharmaceutical agent, optimal mode of data processing with respect to the labeled radiopharmaceutical agent, and optimal mode of presentation of information acquired with respect to the labeled radiopharmaceutical agent.

There is still further provided, in accordance with an embodiment of the present invention, a labeled radiopharmaceutical agent that is manufactured or designed or indicated for use with or sold with any one of the above techniques.

The present invention will be more fully understood from the following detailed description of embodiments thereof, taken together with the drawings, in which:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of an end-to-end automated system for medical imaging, in accordance with an embodiment of the present invention;

Fig. 2 is a flow chart showing an end-to-end method for medical imaging, in accordance with an embodiment of the present invention;

Fig. 3 is a schematic illustration of a patient-specific data carrier, in accordance with an embodiment of the present invention;

Fig. 4 is a schematic illustration of a patient management system, in accordance with an embodiment of the present invention;

Fig. 5 is a schematic illustration of a radiopharmaceutical dose calculation system, in accordance with an embodiment of the present invention;

Figs. 6A-E are tables showing exemplary preconfigured SPECT protocols and parameters thereof, in accordance with respective embodiments of the present invention;

Fig. 7 is a schematic illustration of a mother vial and attached data carrier, in accordance with an embodiment of the present invention;

Fig. 8 is a schematic illustration of a data carrier coupled to a radiopharmaceutical agent container, in accordance with an embodiment of the present invention;

Figs. 9A-H are schematic illustrations of respective embodiments of a radiopharmaceutical agent container and data carrier coupled thereto, in accordance with respective embodiments of the present invention;

Fig. 10 is a schematic illustration of an administration system, in accordance with an embodiment of the present invention;

Fig. 11 is a schematic illustration of an imaging system, in accordance with an embodiment of the present invention;

Fig. 12 is a schematic illustration of an automated radiopharmaceutical dispensing system, in accordance with an embodiment of the present invention;

Figs. 13A-C are schematic illustrations of a system for carrying out a data transfer process, in accordance with an embodiment of the present invention;

Fig. 14 is a schematic illustration of a radioisotope automatic elution system, in accordance with an embodiment of the present invention;

Fig. 15 is a schematic illustration of a mother vial preparation system, in accordance with an embodiment of the present invention;

Figs. 16A-B are illustrations of color spectra and a color-coded signature, respectively, in accordance with an embodiment of the present invention;

Fig. 17 is a schematic illustration of a computer-readable medium, a portion of which is shaped so as to define a physical key, in accordance with an embodiment of the present invention; and

Fig. 18 is a graph showing particle energy vs. photon count at a detector of a

camera, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF EMBODIMENTS

Fig. 1 is a schematic illustration of an end-to-end automated system 10 for medical imaging, in accordance with an embodiment of the present invention. System 10 comprises a plurality of integrated elements that are configured to electronically exchange information among one another. The elements include an automated radiopharmaceutical dispensing system 20, a portable information-bearing radiopharmaceutical agent container 22, a portable patient-specific data carrier 24, an automated administration system 26, and an automated imaging system 28. The systems perform their respective automated functions at least in part responsively to the exchanged information. The elements typically authenticate one another via the exchanged information, in order to ensure that only authorized elements participate in the system, and that only authorized and appropriate functions are performed. Each of the elements is described in detail hereinbelow.

End-to-end imaging method

Fig. 2 is a flow chart showing an end-to-end method for medical imaging, in accordance with an embodiment of the present invention. At a radiopharmaceutical provisioning step 100, a manufacturer 102 (Fig. 1) or distributor provides a mother vial 104 (Fig. 1) containing an unlabeled radiopharmaceutical agent, and information associated with the radiopharmaceutical agent. Such an unlabeled radiopharmaceutical agent typically comprises a pharmaceutical substance, for example an antibody such as Capromab Pendetide marketed by Cytogen Corp. under the name ProstaScint and used in the detection of prostate cancer metastases, or sestamibi used in cardiac perfusion studies and marketed under the name of Cardiolite by Bristol Meyers Squibb Corporation, an ion, or another biological metabolized substance, or a substance which is not metabolized but nevertheless undergoes an interaction with the body. The information is stored in a mother vial data carrier 106 associated with mother vial 104, as described hereinbelow with reference to Fig. 7. For some applications, data carrier 106 is physically coupled to mother vial 104, while for other applications the data carrier is provided as a separate element associated with the mother vial. As described hereinbelow with reference to Fig. 7, the information stored in data carrier 106 typically includes information regarding the

radiopharmaceutical agent, such as the formulation, pharmacologic kinetic parameters, radioactivity information, and/or protocol information.

At a labeling step 110, the unlabeled radiopharmaceutical agent is labeled with an appropriate radioisotope, to produce a labeled radiopharmaceutical agent. Such labeling is typically performed using conventional methods, including mixing the agent with a solution containing the radioisotope, heating the mixture, and performing quality testing on the labeled radiopharmaceutical agent. For some applications, step 110 is performed using conventional radiopharmacy labeling techniques, while for other applications system 10 comprises a mother vial preparation system 700, which automatically performs all or a portion of the labeling, as described hereinbelow with reference to Fig. 15. The radioisotopes are provided by a radioisotope supplier 111, such as a conventional radiopharmacy or an automatic elution system 600, described hereinbelow with reference to Fig. 14. Data carrier 106 is typically updated with radioactivity-related information, including the time of labeling, the radioactivity of the radioisotope at the time of labeling, and the volume of the labeled radiopharmaceutical agent, as described hereinbelow with reference to Fig. 7.

For some applications, the only active constituent of the labeled radiopharmaceutical agent is the radioisotope; in other words, the radioisotope is not bound to a biologically active substance. For example, the labeled radiopharmaceutical agent may consist essentially of thallium (as well as pH-balancing constituents, salt ions, and preservatives). As used in the present application, including in the claims, a "labeled radiopharmaceutical agent" means either: (a) an agent comprising a diagnostic radioisotope, such as thallium, or (b) an agent comprising a radioisotope bound to a biologically active substance, such as an antibody, a pharmaceutical compound, an ion, or another biological metabolized substance, or a substance which is not metabolized but nevertheless undergoes an interaction with the body.

At a patient registration and imaging protocol assignment step 112, a healthcare worker 206 uses a patient management system 160 to register a patient into system 10, and to assign appropriate administration and imaging protocols for the patient, as described in detail hereinbelow with reference to Fig. 4. At an information transfer step 114, patient management system 160 assigns a portable patient-specific data carrier 24 to the patient, and transmits information to data carrier 24, including at least a patient

identifier (typically, the patient's identification code and/or name), and the assigned administration and imaging protocols. Additional patient data parameters recorded may include physiological data such as girth, height and weight. The patient management system additionally transmits an order for one or more patient-specific doses of the appropriate labeled radiopharmaceutical agent(s) to dispensing system 20 or a conventional radiopharmacy.

At a dose dispensing step 116, dispensing system 20 dispenses the ordered customized dose of the labeled radiopharmaceutical agent from mother vial 104, as described in detail hereinbelow with reference to Fig. 12. Prior to dispensing the dose, dispensing system 20 typically authenticates the mother vial using information stored in mother vial data carrier 106. For some applications, dispensing system 20 verifies the authenticity of a commercial license contained in data carrier 106. Typically, all or a portion of the information used for such verification is encrypted, and dispensing system 20 decrypts the information during the verification procedure. Alternatively or additionally, dispensing system 20 accesses, over a network, information stored at a remote site, and utilizes the information for such verification. The dispensing system dispenses the dose based on patient-specific prescription information, radiopharmaceutical agent-related information stored in data carrier 106, and/or patient-specific information provided by an element of system 10. Such patient-specific information may include, for example, age, weight, Body Mass Index (BMI), body dimensions, metabolic rate, hemodynamic state, and/or kinetic parameters of the labeled radiopharmaceutical agent as determined during previous imaging procedures performed on the patient. For some applications, dosage information is provided directly or indirectly by patient management system 160 and/or a radiopharmaceutical dose calculation system 152, which are described hereinbelow with reference to Figs. 4 and 5, respectively.

At an information transfer step 118, dispensing system 20 transfers patient-specific information and radiopharmaceutical-related information to a data carrier 120 physically coupled to container 22, as described hereinbelow with reference to Figs. 9A-H and 10. "Physically coupled," as used in the present application, including the claims, includes both direct and indirect physical coupling. For example, data carrier 120 may be indirectly physically coupled to container 22 via shielding of container 22, or shielding of a cylinder in which container 22 is stored during transport and handling

thereof. The patient-specific information includes the patient's identification code and/or name, and the assigned administration and imaging protocols. The radiopharmaceutical-related information typically includes: (a) all or a portion of the information provided by the manufacturer in data carrier 106, such as described hereinbelow with reference to Fig. 7, e.g., intended use, formulation, pharmacologic kinetic parameters, and protocol information; (b) information regarding the radioactivity and volume of the dose; and (c) time of dispensing, as described in detail hereinbelow with reference to Fig. 8. In addition, the dispensing system typically prints and attaches a conventional information label to container 22, such as in order to comply with regulatory labeling requirements. For applications in which the labeled radiopharmaceutical agent(s) is dispensed using conventional radiopharmacy techniques, dispensing system 20, or another element of system 10, such as dose calculation system 152, typically transfers the radiopharmaceutical-related information to data carrier 120. Alternatively, all or a portion of the information is transferred directly from mother vial data carrier 106 to container data carrier 120.

At an administration step 122, administration system 26 receives radiopharmaceutical agent container 22, and administers the labeled radiopharmaceutical agent contained therein to the appropriate patient. As described hereinbelow with reference to Fig. 10, for some applications, administration system 26 comprises an automated administration device, which is configured to administer the labeled radiopharmaceutical agent, while for other applications, a healthcare worker manually administers the agent upon receiving a signal to do so from system 26. Prior to administration, system 26 authenticates container 22 and verifies the identity of the patient, using information provided by patient-specific data carrier 24 and container data carrier 120, and, optionally, another element of system 10, such as a physician station 115. Typically, all or a portion of the information used for such verification is encrypted, and administration system 26 decrypts the information during the verification procedure. Alternatively or additionally, administration system 26 accesses, over a network, information stored at a remote site, and utilizes the information for such verification. Administration system 26 verifies that the patient identification codes contained in patient-specific data carrier 24 and container data carrier 120 match one another, and, typically, verifies that the administration and/or imaging protocols contained in the data carriers match one another. Typically, at least a portion of the information stored in data

carrier 120 of container 22 is transferred to data carrier 24, either directly, via administration system 26, or via a communication element. For some applications, system 26 generates a signal for a healthcare worker confirming that a proper match has been made between agent container 22 and the patient. The system also typically verifies that the current time is the proper administration time, as per the administration protocol, and that container 22 contains the proper dose, as per the selected protocol. Optionally, system 26 is configured to administer the labeled radiopharmaceutical agent only if such matches are confirmed by the system. For some applications, administration system 26 verifies the authenticity of a commercial license contained in data carrier 120, and performs the administration only upon verification of the authenticity.

For some applications, administration system 26 customizes the administration of the labeled radiopharmaceutical agent using information provided by data carrier 24, data carrier 120, physician station 115, and/or patient management system 160. For example, system 26 may customize a time-dependent administration profile of the labeled radiopharmaceutical agent, such as a rate of administration. Alternatively or additionally, system 26 may administer less than the entire dose of the labeled radiopharmaceutical agent, e.g., based on feedback from imaging system 28 during an imaging procedure.

For some applications, such as dynamic studies, administration system 26 administers the labeled radiopharmaceutical agent during an imaging procedure performed by imaging system 28. For these applications, the administration system is in communication with the imaging system during the administration, in order to assure information regarding time-dependent administration is accurately communicated between the administration system and the imaging system. For some applications, imaging system 28 reads information from patient-specific data carrier 24, and transmits at least a portion of the information to administration system 26, thereby obviating the need for the administration system to directly read such information from the data carrier. For some applications, imaging system 28 triggers the commencement of administration. (It is to be understood that although the imaging system triggers administration of the agent, for some applications the agent is not administered until a healthcare worker provides a final authorization to do so, such as to comply with regulatory safety requirements.) For some applications, the labeled radiopharmaceutical agent(s) is administered in a closed loop with an imaging procedure performed by imaging system 28; administration system 28 modifies one or more parameters of the administration in

real time based on feedback received from imaging system 28, and/or based on real-time measurements of physiological parameters of the patient (e.g., systemic blood concentrations) during the imaging procedure. For some protocols, the administration system administers a preliminary bolus injection, and, based on feedback from imaging system 28 and/or on physiological parameters of the patient, configures one or more parameters of a subsequent administration of the same or a different labeled radiopharmaceutical agent.

At an information transfer step 123, before, during and/or after administration of the labeled radiopharmaceutical agent, system 26 electronically updates patient-specific data carrier 24 with details of the administration, such as:

- an identification code of container 22 and/or an administration device;
- an identification code of the patient to which the labeled radiopharmaceutical agent was dispensed, which should match the patient code already stored in data carrier 24;
- the administered labeled radiopharmaceutical agent;
- the volume of the labeled radiopharmaceutical agent administered;
- the time of administration;
- the time profile of administration;
- the radioactivity of the labeled radiopharmaceutical agent at the time of administration;
- the radioactivity of the labeled radiopharmaceutical agent when dispensed to container 22;
- the time of measurement of the radioactivity when dispensed to container 22; and/or
- at least a portion of the radiopharmaceutical information provided by data carrier 106 of mother vial 104.

For some applications, data carrier 120 of container 22 communicates administration information to patient-specific data carrier 24, either directly or via administration system 26. For some applications, system 26 provides similar updates to

other elements of system 10, such as patient management system 160, management control component 150, physician station 115, and/or imaging system 28. Alternatively or additionally, a healthcare worker manually updates one or more of the data carrier and/or system elements. Typically, for safety purposes, after administration system 26 has read all necessary information from data carrier 120, administration system 26 permanently disables data carrier 120 of container 22, in order to ensure that the data carrier is not accidentally reused for another patient.

Reference is still made to Fig. 2. After or during administration of the labeled radiopharmaceutical agent, imaging system 28 performs an imaging procedure on the patient, at an imaging step 124. Imaging system 28 is described hereinbelow with reference to Fig. 11. Prior to performing the imaging procedure, system 28 verifies one or more of the following:

- the identity of the patient, using information provided by patient-specific data carrier 24;
- the authenticity of patient-specific data carrier 24, typically using information provided by the data carrier itself, a coded signature 256, as described hereinbelow in the section entitled "Signature," and/or a key 852, as described hereinbelow with reference to Fig. 17;
- that patient-specific data carrier 24 has been brought within a certain distance of imaging system 28, e.g., within about 30 cm;
- the identity of the manufacturer or distributor of the radiopharmaceutical agent, using information stored in data carrier 120;
- that a selected camera of imaging system 28, imaging protocol, and patient identification code, as provided to imaging system 28 by one or more elements of system 10, match those stored in patient-specific data carrier 24;
- the authenticity of a commercial license contained in patient-specific data carrier 24. For some applications, system 28 verifies that the license has not been previously used, for example by verifying that a registration code associated with the license has not been previously received by system 28 and/or system 10; and/or

- that administration system 26 used (or is about to use, for procedures in which administration occurs during imaging) the correct container 22 and associated data carrier 120 for the prescribed imaging procedure, and administered (or is about to administer) the appropriate dose of the labeled radiopharmaceutical agent(s) at time(s) appropriate for performance of the imaging procedure.

Typically, all or a portion of the information used for such verification is encrypted, and imaging system 28 decrypts the information during the verification procedure. Alternatively or additionally, imaging system 28 accesses, over a network, information stored at a remote site, and utilizes the information for such verification.

For some applications, system 28 generates a signal for a healthcare worker confirming that a proper match has been made between the patient and one or more of the components described above. Optionally, system 28 is configured to perform the imaging procedure only if such a match is confirmed by the system.

Typically, system 28 customizes the imaging procedure using information provided by administration system 26, data carrier 24, and/or physician station 115. Such information typically includes information regarding the time of labeled radiopharmaceutical administration, the labeled radiopharmaceutical agent (e.g., radioactive strength, time of preparation, and/or kinetic parameters), patient-specific physiological information, and/or imaging protocol information. Parameters of the imaging procedure that are typically customized include, but are not limited to: total acquisition time; detector motions, such as detector angular and translational motions, detector step size (i.e., the density of the step size, typically expressed in degrees), and detector dwell time at each view; type of study, such as standard, active vision (as described in the above-mentioned International Application PCT/IL2005/001173), or gated; definition of the region of interest (ROI), for example, based on the size of the heart; and/or attenuation correction parameters, which are typically based on physiological parameters such as body mass, BMI, and girth.

At an image reconstruction step 126, imaging system 28 uses the acquired imaging data for image reconstruction. For some applications, system 28 customizes the image reconstruction procedure using information provided by administration system 26, data carrier 24, and/or physician station 115.

Imaging system 28 analyzes the reconstructed image, at an analysis step 128. For some applications, system 28 customizes the analysis procedure using information provided by administration system 26, data carrier 24, and/or physician station 115.

The imaging system, or a separate diagnostic system of system 10, assists with developing a diagnosis based on the analysis, at a diagnosis step 130. Typically, system 28 customizes the diagnostic procedure using information provided by administration system 26, data carrier 24, and/or physician station 115. For some applications, authentication is performed to verify that the imaging was performed as intended. Reconstruction and analysis are preferably based on lookup tables and expert system rules, for example, as provided by the radiopharmaceutical manufacturer, and may be patient customized, taking into account known patient physiology and/or suspected disease. Alternatively or additionally, the lookup tables and/or expert system diagnostic rules are configured to provide such customization. For some applications, customization and/or diagnostic techniques are performed that are described in the above-mentioned International Application PCT/IL2005/001173.

The diagnosis and/or the results of the imaging procedure are typically transmitted to physician station 115, for use by an attending healthcare worker 206. Alternatively or additionally, the diagnosis and/or the results of the imaging procedure are transmitted to a database 132 (Fig. 1). The accumulated results of a number of such imaging procedures for a large population are analyzed in order to develop, optimize, update, or otherwise re-evaluate imaging protocols, and update appropriate lookup tables and/or expert system rules for the use of the radiopharmaceutical agent. For example, the database may contain quantitative data regarding absolute blood flow measurements from healthy patients and patients with varying level of diseases. For some applications, such data is used to obtain disease-specific tissue signatures by performing quantitative analysis of normal and diseased tissue. Alternatively or additionally, the information in database 132 is used for: (a) comparing the results of an imaging procedure (images, and/or quantitative information and/or analyses) with historical results of the patient, in order to classify disease state and/or (b) comparing the results of an imaging procedure with similar results from a patient population, in order to classify disease state.

Typically, physician station 115 comprises one or more standard personal computers or servers with appropriate memory, communication interfaces and software

for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the physician station in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM.

During or after steps 124 through 128, imaging system 28 updates the data stored in patient-specific data carrier 24 and/or other elements of system 10, such as patient information system 160, and/or physician station 115, to reflect details of the imaging procedure performed. In addition, for some applications, imaging system 28 transfers data to the specific camera used for the procedure, such as patient details, radiopharmaceutical information, and/or administration information, which information is received from data carrier 24, or from other elements of system 10.

The patient-specific data carrier

Reference is made to Fig. 3, which is a schematic illustration of patient-specific data carrier 24, in accordance with an embodiment of the present invention. Data carrier 24 is configured to be held or worn by the patient, and, for some applications, comprises a coupling mechanism configured to be coupled to the patient, which coupling mechanism, comprises, for example, a bracelet, watch, or necklace (Fig. 3A shows the data carrier integrated into a watch or bracelet 170). Data carrier 24 is computer-communicatable, and typically comprises an RFID tag, smart card, disk-on-key (e.g., a USB key), or other electronic memory, as described below. Data carrier 24 is configured to hold information regarding the patient and a selected imaging procedure, as described immediately hereinbelow with reference to Fig. 4.

One or more communication elements 240 are provided for reading data from and transmitting data to data carrier 24 e.g., using a proprietary or standard wireless protocol, e.g., Bluetooth, WiFi, W-LAN, or IEEE 802.11. Alternatively, the communication element is brought into physical contact with data carrier 24, and reads and/or writes the information using an electrical contact, or other coupling technique, such as inductive coupling. Respective communication elements 240 are typically in data communication with patient management system 160, physician station 115, dispensing system 20, administration system 26, and/or imaging system 28. For some applications, communication elements 240 comprise one or more coils for transmitting and receiving electromagnetic radiation. Typically, the communication elements are configured to have

a short effective transmission range, e.g., no more than between about 20 and 40 cm, such as about 30 cm. Such a short range reduces the likelihood of accidental communication with a data carrier other than the intended data carrier.

For some applications, a portion of the patient information stored in the data carrier is also printed in human- and/or machine-readable form on the data carrier. For example, a name 172 and identification code 174 of the patient, and/or a barcode 176 may be printed on the data carrier.

Data carrier 24 comprises circuitry 178, which comprises memory and logic. For some applications, data carrier 24 is passive, in which case it is configured to receive energy from communication element 240. For other applications, data carrier 24 comprises a power source (not shown). For some applications in which the data carrier comprises a power source, the data carrier comprises a communication element for communicating and/or energizing another electronic apparatus. Alternatively or additionally, the data carrier comprises a communication element configured for wireless communication.

For some applications, data carrier 24 further comprises a user output 180 for outputting information to the patient or healthcare workers. For example, output 180 may comprise a display screen, light, and/or sound generator, which circuitry 178 drives to communicate information, such as when communications have been established with other elements of system 10, e.g., data carrier 120, administration system 26, imaging system 28, and/or patient management system 160. For some applications, circuitry 178 is configured to additionally function as an alarm clock; for example, the circuitry may drive display 180 to alert the patient prior to a scheduled administration or imaging procedure.

Typically, for safety purposes, upon completion of all the imaging procedures associated with a given patient-specific data carrier 24, system 10 permanently disables the data carrier, in order to ensure that the data carrier is not accidentally reused for another patient.

The patient management system

Reference is made to Fig. 4, which is a schematic illustration of patient management system 160, in accordance with an embodiment of the present invention.

Patient management system 160 manages patient-related administrative and medical information, and typically comprises at least one workstation 200 in communication with one or more servers 202. Typically, workstation 200 and servers 202 comprise standard personal computers and/or computer servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the workstation and servers in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM.

System 160 performs the following functions:

- receives and registers new patients into system 10, typically into management and control component 150 thereof;
- assigns patient identification codes;
- assigns, issues, and transfers information to patient-specific data carriers 24;
- receives and tracks patient prescriptions for radiopharmaceuticals, and communicates the prescriptions to other elements of system 10, such as dispensing system 20, administration system 26, and/or management and control component 150; and/or
- suggests and assigns imaging protocols based on the patient's imaging needs and patient-specific information.

During reception of a new patient 204, healthcare worker 206 manually enters patient information into workstation 200. Alternatively or additionally, all or a portion of the patient information is provided electronically by another healthcare system or electronic information source. System 160 typically verifies the healthcare worker's identity and access privileges by interrogating a computer-commuticatable identity tag 208 held by the worker, and/or by checking the validity of a password entered into workstation 200 by the healthcare worker.

The patient information provided to system 160 typically includes:

- the patient's general details, such as name, age, gender, address, telephone number, profession, attending and/or treating physician, health insurance plan, and next of

kin;

- the patient's medical profile, such as medical condition, medical history, family medical history, BMI, weight, allergies, sensitivity to one or more chemical compounds, metabolic rate, and other physiological conditions;
- medications prescribed to the patient;
- the patient's imaging history; and/or
- information regarding the desired imaging, including reason for imaging, type of imaging, body structure or organ to be imaged, and known or suspected pathology.

In an embodiment of the present invention, upon entry of such patient information into patient management system 160, the system automatically suggests one or more imaging protocols that may be appropriate for the patient's imaging needs and medical condition. When making such suggestion, the system takes into consideration, in addition to the information regarding the desired imaging, such factors as the patient's general details, medical profile, imaging history, and guidelines for medication interactions. The system typically selects the suggested protocol(s) from a database of preconfigured protocols, which is described hereinbelow with reference to Figs. 6A-E. Healthcare worker 206 selects one of the suggested protocols, or selects another non-suggested protocol directly from the protocol database.

For some applications, the system suggests one or more customizations of the selected protocol, as described hereinbelow with reference to Figs. 6A-E, which the healthcare worker may accept, decline, or modify, in whole or in part. These suggested customizations are typically based on (a) physiological parameters of the patient, such as age, weight, BMI, metabolic rate, and/or hemodynamic state, and/or kinetic parameters of the radiopharmaceutical agent as determined during previous imaging procedures performed on the patient, and/or (b) a medical profile group to which the patient is assigned, such as high, normal, or low BMI, or high BMI - diabetic, or high BMI - normal metabolic rate. (For some applications, such profile groups are stored in a database of management and control component 150.) Alternatively or additionally, the healthcare worker may customize the protocol manually.

Upon selection and customization of the protocol, patient management system 160 schedules, typically automatically:

- a specific imaging system 28 capable of performing the selected imaging procedure;
- a date and time for performing the imaging procedure; and
- a date(s) and time(s) for administration of labeled radiopharmaceutical agent(s).

Patient management system 160 transmits the entered and generated patient-specific information, including the selected protocol, to the patient's patient-specific data carrier 24. The transmitted patient-specific information typically includes:

- the patient's identification code and name;
- an identifier of the selected imaging protocol(s), such as a name and/or an identification code thereof, and/or additional imaging protocol information, such as described hereinbelow with reference to Figs. 6A-E;
- an identifier of the selected administration protocol(s), such as a name and/or an identification code thereof;
- the scheduled imaging system 28;
- the scheduled imaging date and time;
- the scheduled administration date(s) and time(s);
- the patient's personal details;
- the patient's medical profile; and/or
- the patient's imaging history.

The patient management system transmits an order for one or more patient-specific doses of the appropriate labeled radiopharmaceutical agent(s) to dispensing system 20, such as via management and control component 150. Typically, the patient management system additionally transmits at least a portion of the entered and generated patient-specific information to one or more of: (a) management and control component 150, (b) dose calculation system 152, (c) administration system 26, and/or (d) imaging system 28. Typically, a different subset of the information is transmitted to each of these entities.

As described hereinabove with reference to Fig. 3, for some applications, a portion of the patient information stored in data carrier 24 is also printed in human- and/or machine-readable form on the data carrier. For example, a name 172 and identification code 174 of the patient, and/or a barcode 176 may be printed on the data carrier. For such applications, system 160 comprises a printer 210, which is configured to print the information directly on data carrier 24, or to print the information on an adhesive label, which healthcare worker 206 attaches to data carrier 24. For some applications, printer 210 comprises communication element 240, and the printer is configured to both print the information on the data carrier and transmit the information to the data carrier, typically generally at the same time.

In an embodiment of the present invention, system 10 comprises at least one web server, which is configured to accept orders for an imaging procedure over an intranet or the Internet, placed by a physician or other healthcare worker. Such orders can typically be modified up until a deadline, such as midnight before the day of the scheduled imaging procedure.

The management and control component

Reference is again made to Fig. 1. In an embodiment of the present invention, system 10 comprises management and control component 150, which coordinates a portion of the interaction and communication among the elements of system 10. The remainder of the interaction and communication occurs directly between the elements of the system, and/or via other elements of the system. For some applications, component 150 issues a password and/or computer-communicatable identity tags 208 to healthcare workers 206 authorized to interact with one or more elements of system 10. For example, tag 208 may comprise an RFID tag, smart card, disk-on-key (e.g., a USB key), minidisk, or other electronic memory, or a machine-readable code, e.g., a barcode. As appropriate, healthcare workers 206 may be assigned various permission levels, such as permission to view or modify particular system and/or patient data.

Typically, management and control component 150 comprises one or more standard personal computers or servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the management and control component in electronic form over a network, for example, or it may alternatively

be supplied on tangible media, such as CD-ROM.

The dose calculation system

Reference is made to Fig. 5, which is a schematic illustration of radiopharmaceutical dose calculation system 152, in accordance with an embodiment of the present invention. The dose calculation system manages and tracks, typically automatically, radiopharmaceutical inventory, ordering, dose dispensing, and disposal. Typically, the dose calculation system comprises one or more standard personal computers or servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the dose calculation system in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM. The dose calculation system receives information from dispensing system 20 regarding doses drawn from the inventory.

Dose calculation system 152 typically comprises:

- an ordering sub-system 154, which orders radiopharmaceutical products from radiopharmaceutical manufacturers, distributors, and/or radiopharmacies, typically automatically, such as when the dose calculation system identifies that inventories of a given radiopharmaceutical are lower than needed;
- a receipt and verification sub-system 155, which manages the receipt and registration of radiopharmaceutical products. The receipt and verification sub-system checks the received products against orders placed by the ordering sub-system, and typically performs license management. When a received mother vial 104 includes a mother vial data carrier 106, the sub-system reads information contained in the data carrier to verify that the order has been accurately fulfilled, and, typically, verifies the authenticity of the mother vial;
- a dose calculation sub-system 156, which calculates customized doses of labeled radiopharmaceutical agents for patients based on patient-specific information, protocol information, and/or prescription information, and communicates the customized doses to patient management system 160

and/or dispensing system 20; and/or

- a waste-disposal sub-system 157, which tracks radioactive waste disposal by system 10, such as disposal of radioactive materials contained in waste container 512, described hereinbelow with reference to Fig. 12. For some applications, sub-system 157 additionally tracks radioactive waste disposal of materials in the clinical environment not associated with system 10.

Ordering sub-system 154 and waste-disposal sub-system 157 typically operate in accordance with per country requirements for radiopharmaceutical use. A reporting sub-system reports to relevant nuclear regulatory commissions as required, based on information obtained from the other sub-systems.

In an embodiment of the present invention, dose calculation sub-system 156 designs a cocktail of labeled radiopharmaceutical agents or a series of labeled radiopharmaceutical agents to carry out the desired imaging. When designing such a cocktail or series, the sub-system considers constraints imposed by the physical properties of the agents and by the patient history, and other requirements, such as safety and efficacy requirements. The sub-system determines an appropriate dose for the specific patient having particular physiological parameters (e.g., weight, BMI, and age), and determines the times at which multiple agents are to be administered to the patient in order to achieve optimal imaging.

For some applications, sub-system 156 determines that a plurality of labeled radiopharmaceutical agents are to be administered together and thus must be combined in a single preparation, i.e., a cocktail. For other applications, the sub-system determines that a plurality of labeled radiopharmaceutical agents are to be administered separately at different times and thus must be contained in separate containers 22. As appropriate, sub-system 156 takes into consideration differing half-lives of the plurality of labeled radiopharmaceutical agents, in conjunction with the prescribed time of the imaging procedure. For example, a simultaneous imaging protocol is provided for assessing cardiac perfusion using a cocktail comprising Tc-99m sestamibi injected at rest, and thallium-201 injected at stress, wherein the desired activities at imaging time of the Tc-99m sestamibi and the thallium are 6 mCi and 4 mCi, respectively. When calculating the necessary activity of the dispensed dose, sub-system 156 accounts for the respective half-lives of Tc-99m (6 hours) and thallium-201 (64 hours) in view of the planned time

interval between the dispensing time and administration time. For example, if dispensing is performed 24 hours before administration, sub-system 156 calculates the activities of the Tc-99m and thallium-201 at the time of dispensing to be 96 mCi and 5.5 mCi, respectively.

Protocol information

Reference is made to Figs. 6A-E, which is a table showing exemplary preconfigured SPECT protocols and parameters thereof, in accordance with respective embodiments of the present invention. These protocols are appropriate, for example, for use with the SPECT imaging methods and apparatus described hereinbelow with reference to Fig. 11, and/or in the co-assigned patent applications and/or patent application publications incorporated herein by reference hereinabove. For some applications, the techniques described herein utilize additional protocols described in above-mentioned International Application PCT/IL2005/001173, International Application PCT/IL2005/001215, filed November 16, 2005, above-mentioned US Provisional Patent Application 60/628,105, above-mentioned US Provisional Patent Application 60/675,892, or in one or more of the other co-assigned patent applications and/or patent application publications incorporated herein by reference. Alternatively or additionally, the techniques described herein utilize protocols for non-SPECT imaging modalities, such as PET or CT, or other imaging modalities known in the art. The preconfigured protocols are stored in a database, which is typically used by patient management system 160 for suggesting protocols and/or by dose calculation sub-system 156, as described hereinabove with reference to Figs. 4 and 5, respectively.

For each of the exemplary protocols shown in Fig. 6A, the table indicates general parameters for a rest phase and a stress phase of the protocol. For example, for the "single isotope / low dose / fast imaging" protocol, the table shows that the radiopharmaceutical (RP) for the rest phase of the protocol is less than 0.3 mCi of Thallium, that the waiting time after injection of the radiopharmaceutical is 2 minutes, and that the image acquisition duration is 15 minutes. Parameters for the stress phase are similarly indicated, with the addition of the type of stress (exercise, e.g., treadmill or bicycle, or pharmaceutical, e.g., adenosine). The "thallium stress perfusion" and "simultaneous dual isotope stress perfusion" protocols are optionally dynamic.

For each of the exemplary protocols shown in Figs. 6B-E, the table indicates

administration parameters, detector parameters, scanning parameters, and analysis parameters for the protocol. For example, for Protocol A of Figs. 6B-C ("Cardiac mapping"), the table indicates:

- the labeled radiopharmaceutical agent is Tc-99-sestamibi (MIBI);
- the protocol is a fast protocol, with image acquisition completed prior to substantial uptake of the agent by the liver;
- the injection is by a single bolus;
- image acquisition begins either about 2 minutes after injection, or during or immediately administration, for applications in which the administration is performed while the patient is already placed at camera 452 (Fig. 11);
- the detected photon energy is 140 KeV with an energy resolution of 15%, i.e., the total range of energy levels detected by the detectors 454 of camera 452 (Fig. 11) is set to be 15% of the emitted energy level of the labeled radiopharmaceutical agent (140 Kev). Typically, this range is not centered around the emitted energy level, but instead is shifted towards lower energy levels;
- the total scan time is 120 seconds;
- four detectors 454 of camera 452 are assigned as outer (distal) detectors, and six detectors 454 are assigned as inner (proximal) detectors, as described hereinbelow with reference to Fig. 11;
- each of the inner detectors has an angular range of between 90 and 120 degrees, and each of the outer detectors has an angular range of between 40 and 60 degrees;
- the total number of angular orientations assumed by the detectors in aggregate is 1200, i.e., 10 detectors times 120 orientations each;
- each angular step of the inner detectors is one degree, and each angular step of the outer detectors is 0.3 to 0.5 degrees (corresponding to the range of 40 to 60 degrees described above);
- the dwell time at each step is one second, for both the inner and outer detectors;

- the imaging procedure is gated using 16 to 32 frames;
- the analyses to be performed include intensity image and ejection fraction.

For some applications, the protocol information includes additional information not shown in Figs. 6B-E, such as:

- additional scanning parameters, such as whether the detectors perform multiple scans (in all the protocols shown in the table, the detectors typically perform a single scan); and
- additional analysis parameters, such as:
  - saturation handling (in the first cardiac mapping protocol shown in the table, no saturation handling is performed, while in the second cardiac mapping protocol shown in the table, the analysis is configured to dismiss saturated pixels);
  - whether the analysis handles scatter from multiple sources (in the protocols shown in the table, the analysis does not handle scatter from multiple sources);
  - reconstruction resolution (in all of the protocols shown in the table, the image reconstruction resolution is 2.5 mm in the z-direction, and 5 mm in the x- and y-directions); and
  - parameters that provide the diagnosis system (e.g., expert system) with information regarding how to interpret the results of the imaging study, such as kinetic parameters, predefined pathological values, or patient-specific physiological parameters (e.g., BMI, age, or a group to which the patient is assigned).

Reference is made to Protocol E of Figs. 6B-C. In this cardiac mapping protocol, simultaneous image acquisition is performed using, typically using full conventional doses of both thallium and MIBI-Tc. The detected photon energy of the thallium is 167 KeV, rather than the 72 KeV that is conventionally detected during nuclear imaging procedures. Unlike conventional SPECT cameras, the camera described hereinbelow with reference to Fig. 11 is sufficiently sensitive to detect a clinically-relevant count of the relatively low percentage (8%) of photons emitted at the 167 KeV energy level.

(Detection of 72 KeV energy is generally not practical when a conventional dose of MIBI-Tc is used, because the scatter from the 140 KeV energy level of MIBI-Tc masks the 72 KeV photons emitted by the thallium.)

Reference is made to Protocol I of Figs. 6D-E. In this cardiac dynamic mapping protocol, image acquisition typically begins prior to administration of the radiopharmaceutical agent, such as at one minute prior to administration, as shown in the table. This allows the imaging system to complete one full scan of the region of interest prior to administration of the radiopharmaceutical agent, in order to ensure that the imaging system is able to acquire photons of radiation beginning immediately after the radiopharmaceutical agent is administered.

Typically, a selected preconfigured protocol is customized based on physiological parameters of the specific patient, and/or a medical profile group of the patient, as described hereinabove with reference to Fig. 4. Such customization typically includes customization of the radiopharmaceutical agent, administration parameters, and/or imaging parameters.

For some applications, one or more of the following parameters of the radiopharmaceutical agent are customized:

- the dose, or for multiple radiopharmaceutical agents, the respective doses;
- the radioactivity;
- for cocktails, the ratio of the different radiopharmaceutical agents; and/or
- the volume of the dose, or for multiple radiopharmaceutical agents, the volumes of the respective doses.

For some applications, one or more of the following parameters of the administration are customized:

- the dose administered, or for multiple radiopharmaceutical agents, the respective doses per administration;
- the type of administration, e.g., a single bolus, a plurality of boluses (e.g., two boluses), pulsatile administration, or constant drip administration;
- the labeled radiopharmaceutical agent for each administration, whether a single agent or a cocktail of agents;

- the time of the administration with respect to the time of imaging;
- the timings of multiple administrations with respect to each other and with respect to other activities, such as rest or stress (physical or pharmacological);
- the administration device, e.g., a syringe, a dual-needle syringe, a pump, or an IV line; and/or
- the mode of administration, e.g., manual, automatic, or computer driven.

For some applications, one or more of the following parameters of the imaging procedure are customized. For some applications, such parameters are separately specified for individual components of camera 452 of imaging system 28, or groups of components, such as for individual detectors 454 or groups of detectors of camera 452, described hereinbelow with reference to Fig. 11.

- total acquisition time, and/or acquisition time for a plurality of phases of acquisition;
- detector scanning plan, including detector motions, such as detector angular and translational motions, detector step size (i.e., the density of the step size, typically expressed in degrees), number of detectors utilized for image acquisition, and detector dwell time at each view;
- detector sensitivity;
- detection energy resolution;
- detector calibration plan;
- definition of the region of interest (ROI);
- gating parameters;
- energy bands, i.e., a plurality of non-overlapping energy windows;
- collimator positioning, shape, structure, and orientation;
- multiple/interlaced scans;
- zooming parameters;
- uniformity/non-uniformity of scan;

- Compton scatter map calculation and correction parameters;
- optimal energy window;
- optimal energy resolution, i.e., the range of energy level windows for which detection is enabled; and/or
- adaptivity of scan pattern to acquired counts, e.g., active vision parameters (as described in the above-mentioned International Application PCT/IL2005/001173).

In an embodiment of the present invention, system 10 uses high definition protocols in conjunction with SPECT imaging techniques to enable personalized functional imaging at higher speeds and resolutions than can be achieved using conventional radiopharmaceutical protocols and imaging technology, using imaging techniques described herein and/or incorporated herein by reference. Alternatively or additionally, the system uses low dose protocols that enable personalized functional imaging at higher resolutions but with substantially lower doses than possible using conventional methods.

In an embodiment of the present invention, system 10 uses a protocol pursuant to which a patient undergoes a rest thallium (Tl-201-thallous chloride) and stress Tc-99-sestamibi (MIBI) study having a total study duration of between about 60 and about 90 minutes, and a total image acquisition duration of between about 0.5 and about 6 minutes, e.g., about four minutes. For example, pursuant to the protocol:

- about 3 mCi of thallium may be administered to the patient as a bolus IV injection,
- the patient may rest for between about 10 and about 15 minutes,
- an image acquisition having a duration of about two minutes may be performed,
- the patient may be physically stressed,
- about 20-30 mCi of Tc-99-sestamibi may be administered as a bolus IV injection, and
- a second image acquisition having a duration of about two minutes may be performed.

Such dual-isotope imaging is generally useful for assessing myocardial perfusion of patients with suspected ischemic syndromes and a variety of other conditions. Alternatively, in an embodiment, the rest phase is performed using an approximately 8 to 10 mCi dose of Tc-99-sestamibi, in which case image acquisition typically commences about 30 minutes after injection of the sestamibi. Further alternatively, in an embodiment, image acquisition for the rest phase is performed about two minutes after injection of the thallium, the stress is pharmacological (e.g., using adenosine), and image acquisition for the stress phase is performed essentially immediately after injection of the sestamibi. Still further alternatively, in an embodiment, the rest phase is performed using Tc-99-sestamibi, and image acquisition commences essentially immediately upon injection of a dose of about 8 to 10 mCi.

In accordance with respective embodiments of the present invention, dual-radiopharmaceutical protocols include the administration and simultaneous imaging of the following combinations of labeled radiopharmaceutical agents. Typically, the labeled radiopharmaceutical agents are administered as a mixture (i.e., a cocktail) before or during a simultaneous imaging procedure; alternatively, the labeled radiopharmaceutical agents are administered separately before or during a simultaneous imaging procedure.

- (a) I-123 BMIPP, a fatty acid imaging agent that has been available in Japan for many years, and is currently in Phase III clinical trials in the United States, and (b) a myocardial perfusion agent (e.g., Tc-99m sestamibi, Tc-99m tetrofosmin, or Tl-201-thallous chloride), for simultaneously studying myocardial perfusion and fatty acid metabolism;
- (a) Tl-201-thallous chloride and (b) Tc-99m pertechnetate, for differentiating an organ from its anatomical surroundings, such as differentiating parathyroid glands from the thyroid gland;
- (a) In-111 DTPA, and (b) Tc-99m-MAG3, for differentiating pathological processes in a given organ, such as performing differential diagnosis of a hypo-perfused kidney, e.g., to study true glomerular filtration rate and tubular secretion simultaneously;
- a cocktail of labeled radiopharmaceutical agents, for studying cancer, including simultaneous diagnosis, prediction of therapy response, and

monitoring of therapy, such as simultaneously identifying a tumor, and characterizing tumor perfusion and metabolic activity, e.g., in order to provide a disease signature; and

- the combinations shown in the following table.

TABLE 1

First radiopharmaceutical	First application	Second radiopharmaceutical	Second application
^{201}Tl	Myocardial perfusion	Tc-99m-teboroxime	Myocardial perfusion
		Tc-99m-sestamibi	
		Tc-99m-tetrophosmin	
^{201}Tl	Myocardial perfusion	Tc-99m-PYP	Infarct Imaging
^{201}Tl	Myocardial perfusion	Tc-99m-Annexin	Apoptosis
^{201}Tl	Myocardial perfusion	^{123}I-BMIPP	Hypoxia
Tc-99m-teboroxime	Myocardial perfusion	^{111}In-Annexin	Apoptosis
Tc-99m-teboroxime	Myocardial perfusion	^{123}I-Fatty acid	Metabolism
^{111}In-WBC	Infection	Tc-99m-SC	Bone Marrow
^{111}In-DTPA	Kidney (GFR)	Tc-99m-MAG3	Kidney (tubular secretion)
Tc-99m-RBC	Blood pool	^{111}In-Prostascint	Prostate cancer
Tc-99m-HMPAO	Cerebral blood flow	^{123}I-IBZM	Dopamine D2 receptors

In an embodiment of the present invention, system 10 uses protocols for studying the kinetics of thallium. For some applications, such protocols provide dynamic information regarding myocardial function, such as blood flow, rate of thallium uptake, thallium accumulation/redistribution, thallium metabolism, and/or thallium and/or metabolite secretion and/or wash-out (active or passive). Kinetic perfusion

radiopharmaceutical modeling provides absolute myocardial perfusion measurements, coronary flow reserve, and parametric representation of cellular function.

In accordance with respective embodiments of the present invention, thallium protocols include:

- protocols using a conventional dose of thallium, with a substantially reduced SPECT image acquisition duration, e.g., less than about 6 minutes, such as less than about 2 minutes, e.g., about 0.5 minutes. By way of comparison, conventional thallium SPECT imaging procedures generally have image acquisition durations of between about 10 and about 20 minutes. For some applications, the thallium protocol is customized for a specific patient, as described hereinabove;

- protocols using a conventional dose of thallium and a conventional image acquisition duration, with a substantially increased image resolution. For some applications, acquired photon counts are at least 5 times greater than those acquired using conventional SPECT techniques, e.g., at least 10 times greater, resulting in an image with substantially higher resolution; and

- dynamic protocols for myocardial perfusion studies that provide absolute quantitative measurements. For example, images of the heart may be reconstructed from list mode data, with a temporal resolution of 5-10 seconds. This temporal resolution is typically appropriate for the measurement of the kinetics of uptake and wash-out of thallium from the myocardium, as well as those of an input bolus as it passes through the left ventricle. Such data enables the measurement of absolute myocardial blood flow at rest and during peak stress.

In an embodiment of the present invention, system 10 uses protocols for cardiac stress testing studies, using, for example, Tc99m-sestamibi, Tc-99m tetrofosmin, or thallium. Such protocols differentiate between healthy cardiac tissue and scarred or poorly perfused cardiac tissue. Perfusion defects that appear after exercise or pharmacologic stress suggest either vascular occlusion or myocardial infarction. For some applications, such studies are performed gated to the patient's ECG, in order to study cardiac wall motion. Wall motion studies allow calculation of key cardiac function

parameters, such as ejection fraction and estimated cardiac output.

In accordance with respective embodiments of the present invention, cardiac stress testing protocols, which use, for example, Tc99m-sestamibi, Tc-99m tetrofosmin, or thallium, include:

- protocols using a conventional dose, with a substantially reduced SPECT image acquisition duration, e.g., less than about 6 minutes, such as less than about 2 minutes, e.g., about 0.5 minutes. By way of comparison, conventional cardiac stress testing SPECT imaging procedures generally have image acquisition durations of between about 10 and about 20 minutes. For some applications, the protocol is customized for a specific patient, as described hereinabove. For some applications, such as when the protocol uses Tc99m-sestamibi, image acquisition is performed immediately following administration of the labeled radiopharmaceutical agent, before the agent reaches the liver, thereby reducing interference by the liver on the resulting images.

- protocols using a dose of the labeled radiopharmaceutical agent that is substantially lower than conventional SPECT protocols using the agent. For example, the dose may be between about 50% and about 90% lower than a conventional dose, e.g., about 50% lower than a conventional dose. By using the image acquisition techniques described herein and/or incorporated herein by reference, even at such reduced doses, acquired photon counts are typically at least 5 times greater than those acquired using conventional SPECT techniques at conventional SPECT doses, e.g., at 10 times greater, and image acquisition duration is typically about 50% less than conventional durations, e.g., about 80% less (such as four minutes instead of 20 minutes). Alternatively, the dose may be reduced by about 90%, and the image acquisition duration is approximately the same as conventional image acquisition durations.

In an embodiment of the present invention, system 10 uses Tc-99m teboroxime for performing a SPECT myocardial perfusion study. This radiopharmaceutical is extracted by the myocardium in proportion to myocardial blood flow throughout the entire range of achievable flow rates. When conventional imaging techniques are used, the wash-out rate

of Tc-99m teboroxime from cardiac tissue is so rapid that there is inadequate time for imaging, because the radiopharmaceutical rapidly and avidly accumulates in the liver, which emits gamma rays that blind the imaging of the heart. By using the imaging techniques described herein and/or incorporated herein by reference, sufficient photon counts are obtained in an image acquisition period of no more than approximately two minutes, immediately following administration. The use of such a short period enables the completion of image acquisition prior to substantial uptake of the radiopharmaceutical by the liver, thereby enabling the effective clinical use of Tc-99m teboroxime for cardiac imaging.

In an embodiment of the present invention, a dynamic multiple isotope combination protocol is provided for studying different pathological processes of the same organ, such as studying acute myocardial ischemia. In accordance with this protocol, the following labeled radiopharmaceutical agents are administered as bolus IV injections:

(a) an approximately 2 mCi dose of I-123-BMIPP, followed by a wait of about 48 hours;

(b) an approximately 1 mCi dose of Tl-201-thallous chloride; and

(c) either (i) an approximately 10 mCi dose of Tc-99m-sestamibi or (ii) an approximately 10 mCi dose of Tc-99m-teboroxime.

Agents (b) and (c) are administered as a cocktail, or as separate injections at approximately the same time. Simultaneous image acquisition of all three radiopharmaceutical agents is performed during or soon after administration of agents (b) and (c), typically using an up to about 30 minute acquisition time, such as between about 5 and about 15 minutes, which is faster than that of standard imaging protocols. Typically, camera 452 of imaging system 28, described hereinbelow with reference to Fig. 11, performs image acquisition using an energy window of between about 2% and about 10% of the emitted energy levels of the radiopharmaceutical agents. Typically, detectors 454 of camera 452 sweep the region of interest once every approximately 10 to approximately 15 seconds. The I-123-BMIPP identifies the ischemic/infarcted area of the myocardium, while the other radiopharmaceutical agents identify the perfused area of the myocardium. Simultaneous imaging provides more accurate identification of myocardial perfusion pathologies than is generally possible using conventional imaging techniques

and protocols.

In an embodiment of the present invention, system 10 uses one or more of the protocols described in the above-mentioned US provisional application filed on even date herewith, entitled, "Imaging protocols."

In some embodiments of the present invention, the protocols described herein (including those shown in Figs. 6A-E), and in the co-assigned patent applications incorporated herein by reference, are performed using values that vary from those provided in the protocols by +/- 20%, e.g., +/- 5%, +/- 10%, or +/- 15%. Furthermore, in some embodiments, the protocols are performed with a range of doses from 50%, 75%, 90%, or 100% of the dosage value given for the respective protocol, up to 10 times the dosage value given for the respective protocol (such as up to 2, 4, 6, or 8 times the given dosage value). For example, a dose shown as 3 mCi for a given protocol may, in some embodiments, have a range of 1.5 mCi to 30 mCi, or from 2.7 mCi to 6 mCi. Similarly, in some embodiments, the protocols are performed with a range of acquisition durations (total scan times) from 50%, 75%, 90%, or 100% of the duration value given for the respective protocol, up to 5 times the duration value given for the respective protocol, such as up to 1.5, 2, 3, or 4 times the given duration value. Other protocol values, such as waiting times, energy windows/resolution, angular range, angular step, and dwell time, may also have a range from 50%, 75%, 90%, or 100% of the value given for the respective protocol, up to 5 times the value given for the respective protocol, such up to 1.5, 2, 3, or 4 times the given value.

In respective embodiments of the present invention, all of the protocols described herein and/or in the co-assigned patent applications incorporated herein by reference are enabled to generate clinically-valuable images. A "clinically-valuable image" is an image of an intra-body region of interest (ROI) containing the labeled radiopharmaceutical agent(s), which image fulfills one or more of the following criteria:

- the image is generated according to a protocol, including at the radiopharmaceutical dose specified by the protocol, using a high-definition SPECT camera, for example, camera 452 of imaging system 28, described hereinbelow with reference to Fig. 11, which camera, during the imaging of the ROI, is capable of acquiring at least one of 5000 photons emitted from the ROI during the image acquisition procedure, such as at least one

of 4000, 3000, 2500, 2000, 1500, 1200, 1000, 800, 600, 400, 200, 100, or 50 photons emitted from the ROI. In one particular embodiment, the camera is capable of acquiring at least one of 2000 photons emitted from the ROI during the image acquisition procedure;

- the image is generated according to a protocol, including at the radiopharmaceutical dose and image acquisition duration specified by the protocol, using a high-definition SPECT camera, for example, camera 452, which, during the imaging of the ROI, is capable of acquiring at least 200,000 photons, such as at least 500,000, 1,000,000, 2,000,000, 3,000,000, 4,000,000, 5,000,000, 8,000,000, or 10,000,000 photons, emitted from a portion of the ROI having a volume of no more than 500 cc, such as a volume of no more than 500 cc, 400 cc, 300 cc, 200 cc, 150 cc, 100cc, or 50 cc. In one particular embodiment, the camera is capable of acquiring at least 1,000,000 photons emitted from a volume of the ROI having a volume of no more than 200 cc;

- the image has a resolution of at least 7x7x7 mm, such as at least 6x6x6 mm, 5x5x5 mm, 4x4x4 mm, 4x3x3 mm, or 3x3x3 mm, in at least 50% of the reconstructed volume, wherein the labeled radiopharmaceutical agent as distributed within the ROI has a range of emission-intensities R (which is measured as emitted photons / unit time / volume), and wherein at least 50% of the voxels of the reconstructed three-dimensional emission-intensity image of the ROI have inaccuracies of less than 30% of range R, such as less than 25%, 20%, 15%, 10%, 5%, 2%, 1%, or 0.5% of range R. For example, the agent may emit over a range from 0 photons/second/cc to 10^5 photons/second/cc, such that the range R is 10^5 photons/second/cc, and at least 50% of the voxels of the reconstructed three-dimensional intensity image of the ROI have inaccuracies of less than 15% of range R, i.e., less than 1.5 x 10^4 photons/second/cc. For some applications, the study produce a parametric image related to a physiological process occurring in each voxel. In one particular embodiment, the image has a resolution of at least 5x5x5 mm, and at least 50% of the voxel have inaccuracies of less than 15% of range R;

- the image is generated according to a protocol, including at the radiopharmaceutical dose and image acquisition duration specified by the protocol, the image has a resolution of at least 7x7x7 mm, such as at least 6x6x6 mm, 5x5x5 mm, 4x4x4 mm, 4x3x3 mm, or 3x3x3 mm, wherein the labeled radiopharmaceutical agent has a range of intensities R (photons / unit time / volume), and wherein at least 50% of the voxels of the reconstructed three-dimensional intensity image of the ROI have inaccuracies of less than 30% of range R, such as less than 25%, 20%, 15%, 10%, 5%, 2%, 1%, or 0.5% of range R. For some applications, the study produce a parametric image related to a physiological process occurring in each voxel; and/or

- the image has a resolution of at least 20x20x20 mm, such as at least 15x15x15 mm, 10x10x10 mm, 7x7x7 mm, 5x5x5 mm, 4x4x4 mm, 4x3x3 mm, or 3x3x3 mm, wherein values of parameters of a physiological process modeled by a parametric representation have a range of physiological parameter values R, and wherein at least 50% of the voxels of the reconstructed parametric three-dimensional image have inaccuracies less than 100% of range R, such as less than 70%, 50%, 40%, 30%, 25%, 20%, 15%, 10%, 5%, 2%, 1%, or 0.5% of range R. For example, the physiological process may include blood flow, the values of the parameters of the physiological process may have a range from 0 to 100 cc / minute, such that the range R is 100 cc / minute, and at least 50% of the voxels of the reconstructed parametric three-dimensional image have inaccuracies less than 25% of range R, i.e., less than 25 cc / minute. In one particular embodiment, the image has a resolution of at least 5x5x5 mm, and at least 50% of the voxels have inaccuracies of less than 25% of range R.

The mother vial

Reference is made to Fig. 7, which is a schematic illustration of mother vial 104 and attached data carrier 106, in accordance with an embodiment of the present invention. Data carrier 106 is computer-communicatable, and typically comprises an RFID tag, smart card, disk-on-key (e.g., a USB key), compact disc, minidisk, disposable

computer-readable medium, or other electronic memory, or a machine-readable code, e.g., a barcode. Mother vial 104 is shown contained within shielding 272, to which data carrier 106 is attached. Alternatively, the data carrier is attached directly to the mother vial, or otherwise associated with the mother vial, such as by being stored in proximity to the mother vial, e.g., in a tray that also contains the mother vial.

Data carrier 106 typically contains at least some of the following information:

- a coded signature 256, for authenticating mother vial 104;
- radiopharmaceutical information, a portion of which is typically supplied by the manufacturer, and a portion of which is typically generated by dispensing system 20 in conjunction with dispensing the radiopharmaceutical agent(s). For some applications, a portion of the information is generated by mother vial preparation system 700, described hereinbelow with reference to Fig. 15, in conjunction with preparing the radiopharmaceutical. The information includes, for example:
  - the name of and/or information regarding the manufacturer;
  - the indicated use(s) (e.g., "Formulation for Cardiac Dynamic Studies");
  - the pre-labeled composition;
  - the time of preparation of the labeled radiopharmaceutical agent(s);
  - the radioactivity at the time of preparation;
  - the total solution volume;
  - the pre-labeled-composition expiration date;
  - the appropriate labeling isotope(s);
  - the decay scheme(s) of the appropriate labeling isotope(s);
  - the radiopharmaceutical biodistribution as a function of time;
  - the radiopharmaceutical clearance rate;
  - the percent clearance by the liver;
  - the percent clearance by the kidneys;
  - the breakdown rate;

- the liver uptake as a function of time; and/or
- radiopharmaceutical kinetic parameters, such as described hereinbelow, which parameters may be stored in one or more lookup tables;

- administration protocol information, such as described hereinbelow;
- image acquisition protocol information, such as described hereinbelow;
- image reconstruction protocol information, such as described hereinbelow;
- image analysis protocol information, such as described hereinbelow;
- expert system protocol information, such as described hereinbelow;
- radiolabeling information, which, for some applications, is generated by mother vial preparation system 700, described hereinbelow with reference to Fig. 15. Such information includes, for example:
  - the labeling radioisotope(s), e.g., Tc-99m;
  - time of labeling;
  - activity of the radioisotope(s) per volume at the time of labeling;
  - total solution volume in the mother vial; and/or
  - ratio of radioisotopes (e.g., Tc-99m to Tc-99) at the time of labeling.

If the labeled radiopharmaceutical agent stored in the mother vial is radiolabeled by mother vial preparation system 700, as described hereinbelow with reference to Fig. 15, the labeling information is provided by the mother vial preparation system. Otherwise, the labeling information is provided by the pharmacist and/or conventional labeling system that radiolabels the unlabeled radiopharmaceutical agent.

The radiopharmaceutical kinetic parameters are used by imaging system 28 for performing dynamic imaging studies, for example as described in the above-mentioned International Patent Application PCT/IL2005/001173, and/or in the above-mentioned US provisional application filed on even date herewith, entitled, "Imaging protocols". For some applications, respective sets of these parameters are provided for:

- different patient populations, such as a healthy population and populations which suffer from various pathologies;

- different organs and/or tissue types, for example, brain tissue, cardiac tissue, liver tissue, and tumor tissue;
- different pathologies;
- different patient physiologies;
- different organs, according to the physiology of the specific patient;
- different patient groups, as expected according to the physiology of the specific patient;
- different pathologies, as expected according to the physiology of the specific patient;
- different organs, as measured for the specific patient;
- different patient groups, as measured for the specific patient; and/or
- different pathologies, as measured for the specific patient.

Such kinetic parameters may include, for example:

- volume of blood in a voxel;
- density of blood in a tissue within a voxel;
- labeled radiopharmaceutical agent concentration in the blood within a voxel;
- labeled radiopharmaceutical agent concentration in a tissue within a voxel;
- total labeled radiopharmaceutical agent concentration in a voxel;
- labeled radiopharmaceutical agent concentration in the systemic blood circulation;
- linearity with blood flow;
- receptor binding for molecular radiotracers;
- labeled radiopharmaceutical accumulation/redistribution in tissue;
- labeled radiopharmaceutical metabolic rate;
- diffusion coefficient from the blood to the tissue (i.e., rate of wash-out,

passive or active);

- diffusion coefficient from the tissue to the blood (i.e., rate of uptake, passive or active); and/or
- accumulation rate in a tissue within a voxel.

The administration protocol information is used by administration system 26 to set parameters of administration of the labeled radiopharmaceutical agent(s) contained in container 22. This protocol information may include, for example:

- the dose administered, or for multiple radiopharmaceutical agents, the respective doses per administration;
- the type of administration, e.g., a single bolus, a plurality of boluses (e.g., two boluses), pulsatile administration, or constant drip administration;
- the labeled radiopharmaceutical agent for each administration, whether a single agent or a cocktail of agents;
- the time of the administration with respect to the time of imaging;
- the timings of multiple administrations with respect to each other and with respect to other activities, such as rest or stress (physical or pharmacological);
- the administration device, e.g., a syringe, a dual-needle syringe, a pump, or an IV line;
- the mode of administration, e.g., manual, automatic, or computer driven; and/or
- an algorithm for customizing the administration based on physiological parameters of the specific patient.

The image acquisition protocol information is used by imaging system 28 to set parameters of the image acquisition process. For some applications, such parameters are separately specified for individual components of camera 452 of imaging system 28, or groups of components, such as for individual detectors 454 or groups of detectors. Such acquisition protocol information may include, for example:

- the name(s) and/or identification code(s) of one or more protocols for

which the radiopharmaceutical agent contained in mother vial 104 is suitable;

- total acquisition time, and/or acquisition time for a plurality of phases of acquisition;
- detector scanning plan, including detector motions, such as detector angular and translational motions, detector step size (typically expressed in degrees), and detector dwell time at each view;
- detector sensitivity;
- detector energy resolution;
- detector calibration plan;
- definition of the region of interest (ROI);
- gating parameters;
- energy bands, i.e., a plurality of non-overlapping energy windows;
- collimator positioning, shape, structure, and orientation;
- multiple/interlaced scans;
- zooming parameters;
- uniformity/non-uniformity of scan;
- Compton scatter map calculation and correction parameters;
- optimal energy window;
- optimal energy resolution, i.e., the range of energy window levels detected; and/or
- adaptivity of scan pattern to acquired counts, e.g., active vision parameters (as described in the above-mentioned International Application PCT/IL2005/001173).

For some applications, the optimal energy window is set at least in part responsively to the BMI of the patient. For example, the width of the energy window (i.e., the energy resolution) may be inversely related to the BMI, because the tissue of patients with higher BMIs tends to create more scatter. To compensate for narrower

energy windows, a longer acquisition time and/or a higher dose of radiopharmaceutical agent is typically used. For some applications, the protocol information includes a look-up table of BMIs and associated energy windows. For some applications, the energy window is non-symmetrical around a peak of the energy curve.

The image reconstruction protocol information is used by imaging system 28 to set parameters of the image reconstruction process. Such parameters may include, for example:

- calibration parameters;
- timing of acquisition;
- reconstruction parameters and algorithms;
- priors, i.e., mathematical constants signifying pre-imaging phase knowledge about system behavior;
- multi-resolution reconstruction parameters;
- non-uniform reconstruction grid;
- filters;
- noise modeling and handling;
- mode selection;
- information derived during image acquisition and/or gating;
- protocols for handling interfering organs;
- protocols describing the precise procedure to be followed in radiopharmaceutical administration, time management, patient activity status, imaging process, and other parameters that can affect imaging results;
- optimization parameters per dose and/or cocktail of doses; and/or
- attenuation correction parameters, which are typically based on physiological parameters such as body mass, BMI, and girth.

For some applications, imaging system 28 uses one or more of these parameters to perform the image reconstruction process using techniques described in one or more of

the co-assigned patent applications incorporated herein by reference.

The image analysis protocol information includes analysis algorithms and/or parameters of the image analysis process, which are used by imaging system 28 for performing diagnostic analysis of the reconstructed image. For some applications, such analysis includes tracer kinetics analysis. Such parameters may include, for example:

- information for selection of a model of tracer kinetics;
- information for selection of one or more time scales for tracer kinetics;
- tracer parameters;
- information for analysis of multiple time points;
- information for analysis regarding the clinical meaning of radiation distribution within the patient's body for the purpose of making a clinical diagnosis regarding the patient's health state;
- information for identifying the signatures of multiple labeled radiopharmaceutical agents; and/or
- optimization parameters per dose and/or cocktail of doses.

The expert system protocol information, such as expert system rules, is used by imaging system 28 to set parameters of the expert system used for assisting with diagnosis. For some applications, the expert system is implemented using techniques described in the above-mentioned International Application PCT/IL2005/001173, or in one or more of the other co-assigned patent applications incorporated by reference. Such parameters may include, for example:

- classification of the patient into a patient population;
- multi-parameter vectors of radiopharmaceutical kinetic parameters for different patient populations, such as a healthy population and populations which suffer from various pathologies, and for different tissue types, for example, brain tissue, cardiac tissue, liver tissue, or tumor tissue;
- patient history;
- multi-dimensional thresholds for defining healthy-disease state;
- disease signature classifications per pathology and/or organ (typically per

patient population); and/or

- optimization parameters per dose and/or cocktail of doses.

The portable information-bearing radiopharmaceutical agent container

Fig. 8 is a schematic illustration of data carrier 120, in accordance with an embodiment of the present invention. As mentioned above, data carrier 120 is physically coupled to radiopharmaceutical agent container 22. Data carrier 120 is computer-communicatable, and typically comprises an RFID tag, smart card, disk-on-key (e.g., a USB key), compact disc, minidisk, disposable computer-readable medium, or other electronic memory, or a machine-readable code, e.g., a barcode. One or more communication elements 240 are provided for reading data from and transmitting data to data carrier 24. Respective communication elements 240 are typically in data communication with dispensing system 20 and administration system 26. For some applications, communication elements 240 comprise one or more coils for transmitting and receiving electromagnetic radiation. Typically, the communication elements are configured to have a short effective transmission range, e.g., no more than between about 20 and 40 cm, such as about 30 cm. Such a short range reduces the likelihood of accidental communication with a data carrier other than the intended data carrier.

Data carrier 120 comprises circuitry 250, which comprises memory and logic. For some applications, data carrier 120 is passive, in which case it is configured to receive energy from communication element 240. For other applications, data carrier 120 comprises a power source (not shown). For some applications in which the data carrier comprises a power source, the data carrier comprises a communication element for communicating and/or energizing another electronic apparatus. Alternatively or additionally, the data carrier comprises a communication element 252 configured for wireless communication. For some applications, data carrier 24 further comprises a user output 254 for outputting information to the patient or healthcare workers. For example, output 254 may comprise a display screen, light, and/or sound generator, which the circuitry drives to communicate information, such as when communications have been established with other elements of system 10, e.g., data carrier 120, administration system 26, or imaging system 28. For some applications, data carrier 120 further comprises coded signature 256, which is typically encrypted, color-coded, or both encrypted and color-coded, as described hereinbelow in the section entitled "Signature."

The information contained in data carrier 120 typically includes some or all of the following:

- an administration-device identification code;
- an identifier, such as an identification code and/or name, of the patient for which the specific attached radiopharmaceutical agent container 22 is intended;
- the formulation of the labeled radiopharmaceutical agent(s) contained in attached container 22;
- the time of dispensing of the labeled radiopharmaceutical agent(s) to container 22;
- activity of the labeled radiopharmaceutical agent(s), at the time of dispensing of the labeled radiopharmaceutical agent(s) to container 22;
- the assigned protocol(s) for use with the labeled radiopharmaceutical agent(s) contained in attached container 22;
- the intended time(s) and date(s) of administration of the labeled radiopharmaceutical agent(s) contained in container 22;
- the intended activity(ies) of the labeled radiopharmaceutical agent(s) at the time of administration thereof;
- the intended time profile of administration (single bolus, slow-drip administration, or any other form of administration);
- the identification code of mother vial 104 from which the labeled radiopharmaceutical agent(s) contained in container 22 were dispensed; and/or
- at least a portion of the radiopharmaceutical information stored in data carrier 106 of mother vial 104, as described hereinabove with reference to Fig. 7. This information is typically electronically transferred from data carrier 106 during dispensing of the labeled radiopharmaceutical agent(s) to container 22, as described hereinabove with reference to step 118 of Fig. 2 and hereinbelow with reference to Fig. 12.

As mentioned above, for some applications, all or a portion of the information contained in patient-specific data carrier 24 is alternatively or additionally stored in data carrier 120. Such information is described hereinabove with reference to Fig. 7. For some applications, a portion of the information stored in the data carrier is also printed in human- and/or machine-readable form on the data carrier and/or on the container, for example as a barcode 260, as shown below in Figs. 9A-H.

In an embodiment of the present invention, radiopharmaceutical agent container 22 comprises all or a portion of a drug administration device, such as a syringe or an inhalation device, packaging for an oral dosage form, or radiopharmaceutical packaging.

Reference is made to Figs. 9A-H, which are schematic illustrations of respective embodiments of radiopharmaceutical agent container 22 and data carrier 120, in accordance with respective embodiments of the present invention. In all of these embodiments, data carrier 120 is physically coupled to agent container 22.

Fig. 9A is a schematic illustration of radiopharmaceutical agent container 22 comprising a manual syringe 270, in accordance with an embodiment of the present invention. Syringe 270 is protected by shielding 272, to which data carrier 120 is coupled. Alternatively, the data carrier is coupled directly to an exposed portion of the syringe, such as the end of the plunger of the syringe, as shown in the figure.

Fig. 9B is a schematic illustration of radiopharmaceutical agent container 22 comprising an automatic administration device 280, in accordance with an embodiment of the present invention. Device 280 comprises a chamber 282 for containing the labeled radiopharmaceutical agent(s), a needle 283, a controller 284, a drive 286, and a power source 288. For some applications, controller 284 is preprogrammed with administration instructions, while for other applications, the controller is coupled to administration system 26 and receives an administration signal therefrom prior to administration, or in real time during administration. Administration device 280 typically includes an interlock 290 to prevent administration without verification, for example, of the patient's identity. For some applications, device 180 comprises a flow meter 292, which measures the volume of labeled radiopharmaceutical agent administered. Controller 284 uses this flow information for regulating parameters of the administration, such as rate of administration and total amount of agent administered. Shielding 272 protects medical personnel from the radioactivity of the labeled radiopharmaceutical agent.

Fig. 9C is a schematic illustration of a multi-chamber embodiment of radiopharmaceutical agent container 22, in accordance with an embodiment of the present invention. In this embodiment, container 22 comprises a plurality of chambers in fluid isolation from one another, each of which chambers contains a labeled radiopharmaceutical agent. In the embodiment shown in Fig. 9C, the container comprises two such chambers, a first chamber 282A and a second chamber 282B. Alternatively, the container comprises more than two chambers (configuration not shown). For some multi-chamber applications, container 22 comprises automatic administration device 280, as shown in Fig. 9C, while for other multi-chamber applications, container 22 comprises a plurality of manual syringes 270, as described hereinabove with reference to Fig. 9A (multi-chamber configuration not shown). For some applications, a separate needle 283 is provided for each injection, while for other applications, container 22 is configured to utilize a single needle 283 for the plurality of injections. For example, needle 283 may be configured to slide along a needle mount 294, so as to service the plurality of chambers.

Fig. 9D is a schematic illustration of another configuration of radiopharmaceutical agent container 22, in accordance with an embodiment of the present invention. In this embodiment, container 22 comprises automatic administration device 280, as described hereinabove with reference to Fig. 9B, and controller 284 is configured to perform all or a portion of the functions of data carrier 120. For some applications, one or more of the elements of data carrier 120 are provided separately from the controller. For example, communication element 252 or user output 254 may be provided separately from the controller.

Figs. 9E-G are schematic illustrations of another configuration of radiopharmaceutical agent container 22 comprising manual syringe 270, in accordance with an embodiment of the present invention. In this embodiment, syringe 270 comprises a transmitter 296 fixed with respect to a plunger 298 of the syringe, and shielding 272 is configured so as to modulate effective transmission by transmitter 296. For example, shielding 272 may be shaped so as to define a longitudinal slot 300 along a portion of the shielding. This modulation serves to send, from syringe 270 to administration system 26 and/or imaging system 28, a signal indicative of a time of administration of the labeled radiopharmaceutical agent(s) contained in container 22. The techniques of this embodiment are typically useful when registration of the time of administration with imaging system 28 is important, such as for dynamic studies.

Figs. 9E-G respectively illustrate three steps for administration using these techniques. Fig. 9E shows a first step, during which transmitter 296 is exposed, and therefore effectively transmits a signal. Fig. 9F shows a second step, during which transmitter 296 is shielded by shield 272. Fig. 9G shows a third step, in which transmitter 296 is again exposed. This sequence of exposing, shielding, and again exposing the transmitter serves to signal that administration has occurred. The receiver of the signal (administration system 26 and/or imaging system 28) records the time that this signal is detected. For some applications, other techniques are used to automatically transmit an indication of when the labeled radiopharmaceutical agent(s) are administered. For example, a transmitter may be mounted on shield 272, and may send a signal when electrical contact is established between electrodes (not shown) on plunger 298 and shield 272 at the end of complete motion of the plunger into syringe 270.

Fig. 9H is a schematic illustration of a syringe adaptor 320, in accordance with an embodiment of the present invention. Adaptor 320 comprises shielding 272 and data carrier 120 coupled thereto. The adaptor is configured to placed on a standard administration device, such as a standard syringe. In an embodiment of the present invention, an adaptor similar to adaptor 320 is provided for use with other components of an end-to-end imaging system, such as Tc-99m vials, mother vials, dispensing tools, and dilution containers. Alternatively or additionally, data carrier 120 is configured to be couplable to such other components.

In an embodiment of the present invention, data carrier 120 is configured to be couplable to a standard administration device, such as a syringe. For example, the data carrier may be couplable to the barrel, plunger, or conventional shielding of a conventional syringe, or another syringe known in the art.

The administration system

Reference is made to Fig. 10, which is a schematic illustration of administration system 26, in accordance with an embodiment of the present invention. Administration system 26 comprises a control unit 350, at least one communication element 240, and, for some applications, an automated administration device 352. Typically, control unit 350 comprises a standard personal computer or server with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the

control unit in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM. For some applications, administration system 26 comprises a single communication element 240 that communicates with both patient-specific data carrier 24 and data carrier 120 of container 22, while for other applications the administration system comprises separate communication elements 240 for communicating with data carriers 120 and 24 respectively. For example, a communication element for communicating with data carrier 120 may be integrated into or coupled to automated administration device 352.

Upon authenticating container 22, verifying the identity of the patient, and performing additional verifications, as described hereinabove with reference to step 122 of Fig. 2, control unit 350 generates an administration signal that triggers administration to the patient of the labeled radiopharmaceutical agent(s) stored in container 22. For applications in which administration system 26 comprises automated administration device 352, container 22 is operatively coupled to device 352, and the signal drives administration device 352 to administer the labeled radiopharmaceutical agent(s) stored therein to the patient. Automated administration device 352 is configured to perform intravenous (IV) injection, intramuscular (IM) injection, subcutaneous injection, transdermal application, oral administration, nasal administration, inhalation, transcervical application, transrectal administration, or another type of administration known in the art. (It is to be understood that although the administration signal triggers administration of the agent, for some applications automated administration device 352 does not administer the agent until a healthcare worker provides a final authorization to do so, such as to comply with regulatory safety requirements.) For applications in which administration system 26 does not comprise automated administration device 352, the administration signal triggers administration of the agent by instructing a healthcare worker to manually administer the agent to the patient.

For some applications, based on administration protocol information received from data carrier 120 of radiopharmaceutical agent container 22 and/or patient-specific data carrier 24, control unit 350 customizes the administration of the labeled radiopharmaceutical agent(s) contained in agent container 22. Such administration protocol information typically includes all or a portion of the administration protocol information described hereinabove with reference to Fig. 7. For some applications, administration system 26 administers a plurality of labeled radiopharmaceutical agents,

either sequentially or premixed together within a single agent container 22 (i.e., as a cocktail).

For some applications, administration system 26 administers the labeled radiopharmaceutical agent(s) responsively at least in part to acquisition of a signal associated with the agent(s). For example, acquisition of the signal may comprise detection of photons emitted from the agent(s), in order to determine a radioactivity level.

For some applications, administration system 26 monitors uptake and/or clearance of the labeled radiopharmaceutical agent(s) by (a) measuring physiological parameters, e.g., from samples of blood, saliva, or secretions, e.g., urine, breath, feces, or sweat, or (b) by performing an imaging procedure using imaging system 28. For some applications, these measurements are used to estimate pharmacokinetics of the radiopharmaceutical agent(s) in organs, and/or to predict optimal imaging timing (the optimal time to perform the imaging, and/or the optimal timing parameters of the imaging procedure). For some applications, based on these estimates, an expected level of uptake of the radiopharmaceuticals in a target organ is determined, enabling diagnosis of pathologies based on absolute uptake levels in the target organ.

The imaging system

Reference is made to Fig. 11, which is a schematic illustration of imaging system 28, in accordance with an embodiment of the present invention. Imaging system 28 comprises a control unit 450, a communication element 240, a camera 452, and an imaging workstation 453. Typically, control unit 450 and imaging workstation 453 comprise one or more standard personal computers or servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the control unit and imaging workstation in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM.

Control unit 450 typically comprises: (a) image acquisition functionality, which is configured to drive camera 452 to perform image acquisition of the patient; (b) image reconstruction functionality, which is configured to perform an image reconstruction procedure on the acquired image; (c) image analysis functionality, which is configured to perform an image analysis procedure on the reconstructed image; and (d) diagnosis

functionality, which is configured to perform a diagnostic procedure using the results of the image analysis procedure. It will be appreciated that control unit 450 may comprise a plurality of personal computers or servers, each of which performs one or more of these procedures, and that one or more of these computers or servers may be located remotely from camera 452. Imaging workstation 453 displays the reconstructed images and allows the attending healthcare worker to view and manipulate the images.

As mentioned above with reference to steps 124 through 130 of Fig. 2, imaging system 28 typically customizes one or more of these procedures at least in part responsively to imaging protocol information and/or patient-specific information read by communication element 240 from patient-specific data carrier 24.

For some applications, camera 452 comprises a commercially available diagnostic structural or functional camera, such as a SPECT or PET camera, and/or utilizes imaging techniques described in one or more of the patents and patent applications described hereinabove in the section entitled "Background of the Invention." Alternatively, camera 452 utilizes techniques described in the above-mentioned International Application PCT/IL2005/001173, in above-mentioned PCT Publication WO 05/119025, and/or in the other above-mentioned co-assigned patent applications and/or patent application publications.

In an embodiment of the present invention, camera 452 comprises a plurality of detectors 454, each of which is coupled to a respective angular orientator 456. Each of the detectors comprises a plurality of gamma ray sensors, such as a pixelated CZT array, and a collimator. For example, the array may include 16x64 pixels. Control unit 450 drives, typically separately, each of the orientators to orient its respective detector in a plurality of orientations with respect to a region of interest (ROI). Control unit 450 produces a SPECT image from a plurality of radiation acquisitions acquired with the detectors in different relative orientations.

In an embodiment of the present invention, camera 452 is configured to begin an image acquisition procedure by performing a relatively brief, preliminary scan, and, based on the results of this preliminary scan, to determine one or more parameters of the full image acquisition procedure, such as dwell time per orientation of each detector 454. Typically, this determination further takes into account imaging protocol and/or patient-specific information received by imaging system 28 from patient-specific data

carrier 24, such as the activity of the labeled radiopharmaceutical agent at the time of administration, the time of administration, the patient's BMI (which may be used to estimate a perfusion percentage), and the pharmacokinetics of the labeled radiopharmaceutical agent.

In an embodiment of the present invention, camera 452 is configured to individually set a total angular range of each of detectors 454 responsively to the detector's orientation with respect to the ROI. For example, at least one detector closer to the ROI (a "proximal detector" or an "inner detector") may have a greater total angular range than at least one detector further from the ROI (a "distal detector" or an "outer detector"). The distal detectors are typically located nearer to the ends of a frame holding the detectors, while the proximal detectors are typically located nearer to center of the frame. The use of narrower angular ranges for some of the detectors generally reduces the photon acquisition time spent by these detectors in orientations aimed outside of the ROI. Alternatively, at least one distal detector has a greater total angular range than at least one proximal detector. In order to reduce the total angular range for a given detector, camera 452 typically drives the associated angular orientator 456 to: (a) increase the dwell time of the detector in at least a portion of its orientations, and/or (b) reduce the angle by which the detector is moved during each orienting of the detector. For some applications, camera 452 sets the angular range of the detectors based on protocol information received by imaging system 28 from patient-specific data carrier 24. For example, the number of distal and proximal detectors, and their respective angular ranges, may be specified by the protocol information, as described hereinabove with reference to Figs. 6B-E.

In an embodiment of the present invention, camera 452 comprises a plurality of detectors 454, each of which is coupled to a respective angular orientator 456. Each of the detectors comprises a plurality of gamma ray sensors, such as a pixelated CZT array, and a collimator. Control unit 450 drives, typically separately, each of the orientators to orient its respective detector in a plurality of orientations with respect to a region of interest (ROI). Control unit 450 produces a SPECT image from a plurality of radiation acquisitions acquired with the detectors in different relative orientations.

In an embodiment, camera 452 is configured to drive one of orientators 456 to move its respective detector 454 through a plurality of sequential angular positions, e.g., positions 1, 2, 3, ..., 18, 19, and 20. Typically, a linear relationship relates the sequential

positions, such that, for example, positions 1, 2, 3, ..., 20 represent 1°, 2°, 3°, ..., 20°, or, 2°, 4°, 6°, ..., 40°. Alternatively, a non-linear relationship relates the sequential positions. Higher or lower angular resolutions are typically obtainable, as well.

For some applications, camera 452 steps the orientator in a first pass through a subset of the positions spanning most of the range of positions, and in a second pass the camera steps the orientator through a different subset of the positions. At each position, data are acquired by the detector. For example, during the first pass, the camera may drive the orientator to step through positions 1, 5, 9, 13, and 17, and the detector acquires data at each of these positions. During the second pass, the orientator steps through positions 2, 6, 10, 14, and 18. During two subsequent passes, data are acquired at the remainder of the positions. In this manner, a single-direction interlaced scan of the data is acquired by camera 452.

In an embodiment, a back-and-forth interlaced scan is acquired in which data are sampled when the orientator is moving in both directions. For example, during the first pass, the camera may drive the orientator to step through positions 1, 5, 9, 13, and 17. During the second pass, the orientator steps through positions 18, 14, 10, 6, and 2. During the third pass, the orientator steps through positions 3, 7, 11, 15, and 19, while during the fourth pass, the orientator steps through positions 20, 16, 12, 8, and 4. Fifth and higher passes, if desired, typically repeat the motions used in the earlier passes.

For some applications, the positions in a pass are not ordered from lowest-to-highest or highest-to-lowest. For example the positions of a pass may be 1, 15, 11, 19, and 17. Typically, the positions are, however, distributed generally evenly throughout the range of positions, in order to acquire photon counts representative of the entire region of interest.

As appropriate for a given scanning protocol using interlaced scanning, one or more, or even all of orientators 456 are driven to step through their respective positions in an interlaced fashion.

Typically, execution of an interlaced scan as provided by these embodiments of the present invention allows an operator of camera 452, such as an imaging technician or other healthcare worker, to acquire a high-resolution image of the ROI in about 105% to 115% of the amount of time as would be used if orientator 456 were stepped through the positions sequentially. (Typically, each orientation takes between about 50 and about 200

msec, depending upon the angle of the step.) The high-resolution image is completely acquired after the orientator has stepped through each of its positions. In some cases, additional value is attained by interlacing the scanning, however, as this allows the performance of dynamic studies, in which a plurality of images are acquired during a respective plurality of the time periods, i.e., during each complete pass of the orientator. Although each these images is typically of lower resolution than the high-resolution image acquired using photon counts acquired during all of the passes, the images nevertheless have sufficient resolution to produce clinically-meaningful data for each time period of a dynamic study.

For some applications, interlacing the scanning allows an operator to see an initial, lower-resolution scan of the ROI. If, for example, an adjustment of any form is desired, this can often be seen within the first few seconds of a scan. The present scan is terminated, the adjustment made, and a second scan initiated. In the absence of interlacing, it is typically necessary to wait until a scan has completed until an assessment of the scan's results can be made.

For some applications, it is desirable to know whether the patient has moved during a scan. Patient movement is one reason for lower quality images, and when identified it can typically be corrected by suitable instruction and then a second scanning procedure initiated. Interlaced scanning, as provided by these embodiments of the present invention, allows the operator to immediately assess whether there has been patient movement between one pass and a subsequent pass. In an embodiment, the imaging system displays to an operator the scans obtained from the various passes in rapid succession at the same location on a monitor. As appropriate, the imaging system cycles quickly through the scans repeatedly (e.g., pass 1, pass 2, pass 3, pass 4, pass 1, pass 2, pass 3, pass 4...), e.g., displaying each scan for between about 0.2 and about 2 seconds, allowing an operator to see whether there is jitter between successive scans. If so, patient movement is typically the cause and image acquisition is repeated. For some applications, the scan is acquired in exactly two passes, e.g., the orientator steps through positions 1, 3, 5, ..., 19 during a first pass, and through positions 2, 4, 6, ..., 20 during a second pass, or through positions 20, 18, 16, ..., 2 during the second pass.

Images acquired using these techniques, or other non-interlacing techniques described herein, are generally used to perform one or more of the following image

reconstructions: (a) reconstruction of intensity image, (b) reconstruction of intensity over time, followed by fitting a model of the kinetics (which describe for each voxel a parameter set describing its time curve), and followed by presenting a three-dimensional map of the parameters, and/or (c) direct reconstruction of a three-dimensional parametric representation, without performing a reconstruction of an intensity map, typically by plugging an equation of a kinetic model into a reconstruction algorithm, and generating a result directly in terms of the value of the parameters per voxel (the parameters may include, for example, flow, diffusion coefficients, metabolism rate, or bio-clearance rate).

The radiopharmaceutical dispensing system

Reference is made to Fig. 12, which is a schematic illustration of automated radiopharmaceutical dispensing system 20, in accordance with an embodiment of the present invention. System 20 comprises a control unit 500, at least one robot 502, and at least one communication element 504, which, for some applications, is coupled to robot 502. Control unit 500 typically comprises a conventional personal computer running a conventional operating system, such as Windows XP, with appropriate memory, communication interfaces and software for carrying out the functions described herein. This software may be downloaded to the control unit in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM. Control unit 500 is in communication with other elements of system 10, for example via management and control component 150. The control unit notifies appropriate elements of the system upon successful completion of dispensing of a dose.

At least one radiolabeled mother vial 104 is placed in a shielded vials complex 505 of dispensing system 20. Control unit 500 authenticates the mother vial, by actuating communication element 504 to read authentication information stored in data carrier 106, and/or by verifying a coded signature 256 coupled to the mother vial, as described hereinbelow in the section entitled "Signature." Upon successful authentication, control unit 500 actuates communication element 504 to read radiopharmaceutical-related information from data carrier 106 of the mother vial, including the radiopharmaceutical agent type, isotope type, batch, lot, radiochemical purity (RCP), preparation time, and half-life information. Dispensing system 20 assays the radioactivity per unit volume of the labeled radiopharmaceutical agent contained in the mother vial. Robot 502 picks up an empty syringe 506 from a syringe tray 508, draws a predetermined amount of solution

from mother vial 104, and brings the syringe to a dose calibrator 510. The syringe used for the assaying is typically discarded into a waste container 512. Typically, robot 502 brings the mother vial to a weighing station 507 for verification that the vial contains the indicated solution volume.

Dispensing system 20 receives a patient-specific dose request for at least one specific labeled radiopharmaceutical agent, having a specific dose, radioactivity, and solution volume. Such a dose is typically calculated by dose calculation sub-system 156 of dose calculation system 152, as described hereinabove with reference to Fig. 5, and/or by patient management system 160, described hereinabove with reference to Fig. 4. Alternatively or additionally, dispensing system 20 is configured to customize, modify, or verify the dose. Further alternatively, dispensing system 20 receives the order from another hospital or radiopharmacy information system, or the order is manually inputted into system 20.

To fill the request, control unit 500 calculates a required volume of the labeled radiopharmaceutical agent and a required volume of saline solution for dilution, if any. To perform this calculation, control unit 500 uses (a) information read from data carrier 106 (such as the half-life of the labeling isotope of the labeled radiopharmaceutical agent), and (b) the assayed radioactivity of the labeled radiopharmaceutical agent. Alternatively, dose calculation sub-system 156 performs all or a portion of this calculation.

For some applications, control unit 500 authenticates mother vial license information read from data carrier 106, in order to verify that a license is available for dispensing the requested dose. Dispensing proceeds only if a license is available and authenticated. The use of such a license generally provides increased quality control of the imaging process, by verifying that only approved manufacturers (or distributors) are able to provide radiopharmaceutical agents for use with system 10. A lack of precision in any aspect of an imaging procedure, which may result from the use of an agent that has not been tested and approved for use with system 10, often causes a deterioration of the resultant image quality and/or ability to make accurate and/or quantitative diagnoses.

Control unit 500 actuates robot 502 to pick up an empty radiopharmaceutical agent container 22 from tray 508. Typically, but not necessarily, container 22 comprises a syringe, such as described hereinabove with reference to Figs. 9A-H. Container 22 has coupled thereto a data carrier 120. For some applications, syringes 506 and containers 22

are stored in a single tray, as shown in Fig. 12, while for other applications, they are stored in separate trays. Robot 502 typically authenticates container 22, by actuating communication element 504 to read authentication information stored in data carrier 120 and/or verifying coded signature 245 coupled to the container, as described hereinbelow in the section entitled "Signature."

Robot 502 removes the needle cap from container 22, turns the container over, and brings container 22 to the appropriate mother vial 104. The robot actuates the container to draw the calculated volume of labeled radiopharmaceutical agent from the mother vial, typically by inserting the needle of container 22 through a membrane of mother vial 104, and withdrawing a plunger of container 22 until the desired volume of agent has been drawn from the mother vial. The robot typically brings the syringe to dose calibrator 510 for quality control assaying of radioactivity. If necessary, robot 502 brings container 22 to a saline vial 514, and actuates the container to draw the required volume of saline solution into the container. Robot 502 replaces the needle cap on the container, and turns the container over. Alternatively, saline solution is drawn prior to drawing the labeled radiopharmaceutical agent from mother vial 104. For some applications, a needle of the container 22 is changed between drawings.

For dispensing a cocktail of labeled radiopharmaceutical agents, each having a respective dose, robot 502 repeats these steps for a plurality of mother vials 104, typically changing the needle of container 22 between drawings. During dispensing of such a cocktail, robot 502 typically draws first from the mother vial containing the lower or lowest radiation labeled radiopharmaceutical agent, such as to reduce any effect the assaying of the first agent may have on the assaying of the subsequent agent(s).

System 20 typically performs a quality control check on the dispensed radiopharmaceutical solution to confirm that the solution contains the desired dose(s) of the radiopharmaceutical agent(s) and radioactivity level.

Control unit 500 activates communication element 504 to write radiopharmaceutical information to data carrier 120 of container 22, as described hereinabove with reference to Fig. 8 and step 118 of Fig. 2. For some applications, the data carrier is coupled to the container prior to placement of the container in dispensing system 20, while for other applications, robot 502 couples a data carrier to each container during or after the dispensing process. Similarly, for some applications in which coded

signature 256 is provided, the coded signature is attached to container 22 prior to placement of the container in dispensing system 20, while for other applications, robot 502 couples a coded signature to each container during or after the dispensing process.

Robot 502 brings the filled container to a shield body tray 530, and inserts the container into a container shield 532. The robot picks up a shield cap 534 from a shield cap tray 536, and secures it to container shield 532. For some applications, data carrier 120 is coupled to shield 532 or cap 534, rather than directly to container 22. Alternatively, separate data carriers 120 are coupled to the container and the shield or cap.

In an embodiment of the present invention, dispensing system 20 comprises a print area 540, at which dispensing system 20 prints and attaches at least one conventional label to container 22, shield 532, and/or cap 534, in order to comply with regulatory labeling requirements. The dispensing system typically prints yet another conventional label for placement on a basket that holds a plurality of containers 22 for transport within or between healthcare facilities.

After the dispensing of container 22 has been completed, robot 502 brings the container to a completed container tray (tray not shown in the figure).

In an embodiment of the present invention, dispensing system 20 comprises at least one diluted mother vial which has a greater volume than a conventional mother vial. For example, the diluted mother vial may have a volume of at least about 10 ml, e.g., at least about 20 ml, such as 21 ml, while a conventional mother vial may have a volume of less than 10 ml, e.g., less than 7 ml, such as 5.8 ml. The labeled radiopharmaceutical agent solution from a conventionally-sized mother vial 104 is transferred to the diluted mother vial, and the balance of the additional volume of the diluted mother vial is filled with saline solution. The resulting diluted solution is used by dispensing system 20 to fill containers 22 with low-dose labeled radiopharmaceutical agents useful for performing low-dose imaging procedures, such as those described in the above-mentioned International Application IL/2005/001173, in above-mentioned PCT Publication WO 05/119025, or in one or more of the other co-assigned patent applications incorporated herein by reference. Alternatively, the resulting lower-dose solution is used for time-dependent administration protocols, pursuant to which a desired total dose is divided into several sub-doses for sequential administration over time. For mechanical handling and administration reasons, each sub-dose must have a minimum volume, e.g., at least 1

ml.

The information contained in data carrier 106 of conventionally-sized mother vial 104 is transferred to a data carrier 106 of the dilution mother vial, with appropriate adjustments to reflect the diluted dose of the labeled radiopharmaceutical agent.

In an embodiment of the present invention, a method for automatically dispensing a labeled radiopharmaceutical agent comprises providing a mother vial having a volume of at least 10 ml, e.g., at least 20 ml; filling the mother vial with at least 5 ml of a non-diluted labeled radiopharmaceutical agent, and with at least 5 ml of saline solution; placing the mother vial in automated radiopharmaceutical dispensing system 20; and dispensing at least one dose from the mother vial to a container. For some applications, dispensing system 20 further dilutes the dose by dispensing saline solution to the container from a saline solution container.

It is noted that dispensing system 20 is theoretically able to dispense similar low doses to containers 22 by drawing a small volume of labeled radiopharmaceutical agent from a conventionally-sized mother vial, and diluting the agent with saline solution drawn from saline vial 512, as described above. However, the drawing of such a small volume may present mechanical challenges for achieving precise volumes within acceptable variations.

Reference is made to Figs. 13A-C, which are schematic illustrations of a system for carrying out a data transfer process, in accordance with an embodiment of the present invention. In this embodiment, information is transferred directly from data carrier 106 of mother vial 104 to data carrier 120 of container 22 while container 22 draws the labeled radiopharmaceutical agent from mother vial 104. As shown in Fig. 13A, container 22 is lowered to mother vial 104 (which is contained within shielding 520 of vials complex 505), as indicated by an arrow 522. As shown in Fig. 13B, as container 22 draws labeled radiopharmaceutical solution from mother vial 104, data carrier 120 of the container is positioned in a vicinity of data carrier 106 of the mother vial. Container 22 is raised from mother vial 104, as indicated by an arrow 524 in Fig. 13C. Information transfer takes place during one or more of the steps illustrated in Figs. 13A-C.

For some applications, information is transferred to data carrier 120 of container 22 during assaying of the contents of the container at dose calibrator 510.

In an embodiment of the present invention, dispensing system 20 is configured to dispense to a plurality of containers 22 for a single patient, or to a plurality of independent chambers within a single container 22 (such as first and second chambers 282A and 282B, described hereinabove with reference to Fig. 9C). For some applications, the plurality of containers are permanently coupled to one another, while for other applications the plurality of containers are removably coupled to one another. Alternatively, the plurality of containers are not coupled to one another, in which case they may be stored in association with one another, e.g., in a single tray.

For some applications, dispensing system 20 utilizes one or more of the dispensing techniques described in the references mentioned hereinabove in the Background of the Invention section, *mutatis mutandis*.

In an embodiment of the present invention, system 10 does not comprise dispensing system 20. System 10 is instead electronically or manually interfaced with a conventional radiopharmacy. Patient management system 160 places orders with the radiopharmacy for a particular dose of a labeled radiopharmaceutical agent for a particular patient. Upon dispensing of the dose into a conventional container, such as a syringe, data carrier 120 is physically coupled to the container, and information is written to the data carrier, such as the identity of the labeled radiopharmaceutical agent, the time of dispensing, the measured radioactivity level, and/or other information described herein as being contained in the data carrier, such as with reference to Fig. 8. For some applications, system 10 comprises a module for automatically measuring the radioactivity level and recording the information in the data carrier. Optionally, the module is in communication with system 10, such as via management control component 150, and receives additional patient-specific or protocol-related information from system 10, and records the information in data carrier 120. For some applications, the radiopharmacy dispenses the labeled radiopharmaceutical agent to one of the novel radiopharmaceutical agent containers 22 described herein.

The radioisotope elution system

Reference is made to Fig. 14, which is a schematic illustration of a radioisotope automatic elution system 600, in accordance with an embodiment of the present invention. System 600 automatically elutes a radioisotope, such as technetium Tc-99m, into radioisotope vials 610. The radioisotope is used for radiolabeling the unlabeled

radiopharmaceutical agent, as described hereinabove with reference to step 110 of Fig. 2. Vials 610 are coupled to radioisotope data carriers 612 containing information about the radioisotope, such as a vial code, the time of preparation, the activity at the time of preparation, and total solution volume. Labels 612 are computer-communicatable, and typically comprise an RFID tag, smart card, disk-on-key (e.g., a USB key), compact disc, minidisk, disposable computer-readable medium, or other electronic memory, or a machine-readable code, e.g., a barcode. For some applications, information contained in data carrier 612 is encrypted for enabling authentication. Alternatively or additionally, data carrier 612 and/or vial 610 comprise coded signature 256, as described hereinabove. The coded signature typically comprises an encrypted signature and/or a color-coded signature, as described hereinbelow in the section entitled "Signature."

The automatic elution process typically begins with a determination by dose calculation system 152 (Fig. 5) of an optimal elution frequency, for example:

- 18 hours, 6 hours, 18 hours, 6 hours, ... ,;
- 23 hours, 1 hour, 23 hours, 1 hour, ... ,;
- 18 hours, 1 hour, 5 hours, 18 hours, 1 hour, 5 hours, ... ,; or
- 18 hours, 6 hours, 23 hours, 1 hour, 18 hours, 6 hours, 23 hours, 1 hour, ... ,.

Dose calculation system 152 electronically notifies a control system 616 of elution system 600 of the desired elution frequency. For applications in which the radioisotope comprises Tc-99m, it will be appreciated that the ratio of Tc-99 to Tc-99m, which is determined by the elution frequency, is important for molecular imaging by an antibody, and there is generally an optimal range of the ratio of Tc-99 to Tc-99m, which should be taken into consideration when preparing Tc-99m with an antibody. Typically, control system 616 comprises one or more standard personal computers or servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the control system in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM.

Sterile, empty vials 610 of predetermined volumes (e.g., 10 ml or 20 ml), and typically comprising caps 618, are placed on a conveyor belt 620. A first robot 622 places

a shield 624 on each vial 610. Alternatively, the vials 610 are manually shielded. Conveyor belt 620 moves shielded vial 610 into position under a radioisotope generator 626, such as a TC-99m generator. At a required elution time, a second robot 628 lifts the shielded empty vial 610, and, under sterile conditions, removes cap 618 and engages the shielded empty vial 610 with generator 626.

Upon engagement of vial 610 with generator 626, both a first electronic valve 630 of a saline tank 632 and a second electronic valve 634 of generator 626 open, and vial 610 is filled, while a flow meter 636 monitors the amount of saline flow. After flow of a predetermined volume, control system 616 automatically shuts first electronic valve 630 of saline tank 632 and second electronic valve 634 of generator 626.

Filled, shielded vial 610 is automatically disengaged from generator 626, and is automatically sealed under sterile conditions with a shielded seal 638. Filled, shielded vial 610 is lowered back to conveyor belt 620. The conveyor belt moves filled, shielded vial 610 past an assaying and labeling station 640, which assays and labels the vial with data carrier 612, a barcode 642, and/or coded signature 256. For some applications, coded signature 256 is placed on data carrier 612, while for other applications it is placed on vial 610. For still other applications, separate coded signatures 256 are placed on both vial 610 and data carrier 612, and are used to match the vial with the data carrier. For example, a color-coded signature may be printed on vial 610, either prior to the elution or together with the application of data carrier 612, and an encrypted signature may be stored in the data carrier 612. Alternatively, the encrypted signature may be printed.

It will be appreciated that the elution process is subject to modifications and alterations based on communication and information that is received from system 10. For example, a log book of elution system 600 may specify a Tc-99m vial of 1000 mCi, yet a communication request from dose calculation system 152 may modify the order to be a Tc-99m vial of 200 mCi, based on new requirements, e.g., low-dose administration.

The mother vial preparation system

Reference is made to Fig. 15, which is a schematic illustration of a mother vial preparation system 700, in accordance with an embodiment of the present invention. System 700 automatically labels mother vials 104, containing unlabeled radiopharmaceutical agents, with appropriate radioisotopes. System 700 attaches a data

carrier 106 to each mother vial 104, and writes the information to the data carrier that is described hereinabove with reference to Fig. 7. Alternatively, the manufacturer or distributor attaches data carrier 106 to mother vial 104, and writes at least a portion of the information to the carrier.

Prior to beginning the radiolabeling process, a control unit 702 of system 700 authenticates radioisotope vial 610 and mother vial 104, and verifies that radioisotope vial 610 contains the correct radioisotope at the correct radioactivity, and that mother vial 104 contains the correct unlabeled radiopharmaceutical agent. For some applications, such authentication and/or verification is performed by authenticating coded signature 256 of data carrier 612 of radioisotope vial 610. For some applications, such authentication includes authentication of a commercial license associated with the use of mother vial 104. Typically, control unit 702 comprises one or more standard personal computers or servers with appropriate memory, communication interfaces and software for carrying out the functions prescribed by relevant embodiments of the present invention. This software may be downloaded to the control unit in electronic form over a network, for example, or it may alternatively be supplied on tangible media, such as CD-ROM.

Conveyor belt 620 carries shielded radioisotope vial 610 from radioisotope automatic elution system 600 to mother vial preparation system 700. Alternatively, for embodiments in which elution system 600 is not provided, the radioisotope vial is manually placed on conveyor belt 620. The conveyor belt brings vial 610 to a radioisotope filling point 710.

System 700 typically comprises a plurality of dose preparation platforms 712, each of which contains premixed mother vials 104 containing unlabeled radiopharmaceutical agents that require radiolabeling with the radioisotope contained in radioisotope vial 610, e.g., Tc-99m. In the example shown in Fig. 15, preparation platforms 712 comprise a Tc-99m-teboroxime dose preparation platform, a Tc-99m-pertechnetate dose preparation platform, a Tc-99m-sestamibi dose preparation platform, and a Tc-99m-MDP dose preparation platform.

A robot 720 picks up a syringe 722 from a first syringe platform 724, or a micro-syringe 726 from a second syringe platform 728, and travels along a second conveyer belt 730 to filling point 710. It will be appreciated that other types syringes and/or other dispensing tools may also be used. Upon reaching filling point 710, syringe

722 or 726 draws a predetermined amount of radioisotope solution from radioisotope vial 610. The robot typically travels to an assay station 732, which assays the radioisotope solution. Syringe 722 or 726 is then discarded at a discard station 734.

Robot 720 picks up another syringe 722 or 726 from the platform 724 or 728, fills the syringe with a predetermined amount of the radioisotope from vial 610, and travels along second conveyor belt 730 to one of dose preparation platforms 712. At the dose preparation platform, the syringe injects a predetermined amount of radioisotope into mother vial 104 of the dose preparation platform, thereby labeling the unlabeled radiopharmaceutical agent contained in the mother vial.

Robot 720 discards the syringe at discard station 734, picks up a new syringe, draws a predetermined amount of solution from labeled mother vial 104, and assays the solution at assay station 732, in order to determine the radioactivity of the labeled radiopharmaceutical agent contained in mother vial 104. Following the assaying, robot 720 discards the syringe at discard station 734. Typically, system 700 performs one or more quality control procedures on the labeled radiopharmaceutical agent.

System 700 updates data carrier 106 of mother vial 104 with radiolabeling information, such as the time of labeling, and the activity of the radioisotope at the time of labeling, the total solution volume in the mother vial, and the ratio of radioisotopes (e.g., Tc-99m to Tc-99) at the time of labeling, for applications in which the unlabeled radiopharmaceutical agent is labeled with more than one radioisotope.

It is noted that system 700 is configurable to vary a radioactivity of the radioisotope used to label a given radiopharmaceutical agent in order to produce labeled radiopharmaceutical agents of various levels of radioactivity (for example, Tc-99m-teboroxime of 500 mCi and Tc-99m-teboroxime of 50 mCi). For some applications, system 700 comprises at least one cocktail dose preparation platform 736, for labeling a cocktail of radiopharmaceutical agents (for example, Tl-201-thallous chloride, Tc-99m-sestamibi, and I-123-BMIPP).

It will be appreciated that the mother vial preparation process is subject to modifications and alterations based on communication and information that is received from system 10. For example, a log book of system 700 may specify a mother vial of 500 mCi, yet a communication request from dose calculation system 152 may modify the order to be a mother vial of 200 mCi, based on new requirements, e.g., low-dose

administration.

The exercise room

In an embodiment of the present invention, system 10 comprises at least one exercise room, which comprises one or more pieces of exercise equipment, typically including at least one treadmill. The exercise room, and the equipment therein, is typically in communication with one or more elements of system 10, such as patient-specific data carrier 24, management and control component 150, administration system 26, data carrier 120 of radiopharmaceutical agent container 22, and/or imaging system 28. For example, the exercise room may report the duration, time, and type of exercise to imaging system 28, administration system 26, and/or management control component 150, for synchronizing the exercise with administration and imaging. For some applications, the exercise room receives instructions regarding the duration, time, and/or type of exercise to be performed for a given patient, and schedules an appropriate exercise session in a log book. For some applications, the exercise room sends the patient an SMS-like message notifying the patient of the scheduled session, and/or reminding the patient about a scheduled session. For some applications in which data carrier 24 is integrated into watch or bracelet 170, as described hereinabove with reference to Fig. 3, watch or bracelet 170 is configured to receive and display the SMS-like message to the patient.

Signature

In accordance with an embodiment of the present invention, coded signature 256 comprises a signature encrypted using an encryption algorithm, which is either proprietary or known in the art, e.g., Advanced Encryption Standard (AES), Data Encryption Standard (DES), or Triple DES (3DES). Typically, the encryption algorithm utilizes a symmetric key cipher, as is known in the art.

For some applications, coded signature 256 is stored in one of the data carriers described herein. Alternatively or additionally, the coded signature is printed on the apparatus, e.g., as a barcode.

For some applications, coded signature 256 comprises a color-coded signature, which is implemented using techniques described in the above-mentioned US Patent Application Publication 2004/0156081 to Bril et al. Techniques described in the '081

publication include the use of an encrypted image comprising an array of printed positions formed using a group of inks each of which has a predetermined spectrum. The positions are selected to form a predetermined image, either real or virtual, when the image is viewed through an optical processor. The optical processor may further use a distortion, such as a distorted grating or a distorted lens. The correct image is the spectrum, as distorted by the optical processor. An image formed using inks having the same colors as experienced by the human eye, or even by a standard spectrometer, will fail to form the correct predetermined image. Alternatively or additionally, special inks may be used, so that no two ink combinations are exactly alike, and only registered ink combinations provide the correct spectrum. Furthermore, the special inks may be mixtures of 5 or more colors.

Fig. 16A illustrates color spectra 800 of several dyes, for example dyes B, D1, G, D2, and R, each having a well-defined spectral peak, as described in the '081 publication. When dye B and dye G are mixed, the human eye may see a color substantially the same as the color of dye D1. When dye D1 and dye D2 are mixed, the human eye may see a color substantially the same as the color of dye G.

Fig. 16B illustrates a color-coded signature 802, as described in the '081 publication. A color patch 804, which to the human eye may seem a plain orange, for example, may have a first portion 806A, consisting of dye B and dye G, combined to form a hue which is substantially the same as that of dye D1, and a second portion 806B, consisting of dye D1. To the human eye, the color-coded signature 802 appears as a homogeneous patch.

An optical processor 820 comprises an imaging spectrograph, which comprises a grating 822 and, typically, a lens 824. In the example shown in Fig. 16B, the spectrograph produces three structures: a structure 821 formed by diffraction of dye D1 through the grating, a structure 823 formed by diffraction of dye G, and a structure 825 formed by diffraction of dye B. Optical processor 220 thus reveals the authentic spectra of the color-coded signature 802.

For some applications, optical processor 820 comprises two lenses 824 of substantially equal power, one to create a parallel beam at the input to the grating, just before the grating, and one to create an image at the focal point after the grating. Alternatively, a single lens 824, having twice the power of the two lenses, may be placed

just before or just after the grating.

For some applications, a more complex color coding is achieved by using a distorted lens or a distorted grating, such that spectral structure 821, 823, and 825 may be reproduced only when an optical processor having the exact distortion is used. It will be appreciated that a single hue may be produced by mixing several dyes, for example, 3, 5, or 10. It will be appreciated that each printing house may be allocated only a specific mix of dyes, so that no two printing houses may have identical dye combinations, and no two printing houses may reproduce the same color-coded signatures 802.

For some applications, color-coded signature 802 is printed directly on an element of system 10, for example, on radiopharmaceutical agent container 22 (Fig. 1), or on radioisotope vial 610 (Fig. 14). Alternatively or additionally, a label, for example, mother vial data carrier 106 or data carrier 120 (Fig. 1) is color-coded, or includes a color-coded patch or pattern, operative as color-coded signature 802.

For some applications, an encrypted signature 256 and a color-coded signature 802 are combined. The resulting color-coded machine-readable signature 256 is authenticated by optical processor 820. For example, an encrypted signature may be provided on a label colored with a coded color. Alternatively or additionally, encrypted signature 256 is printed on a color-coded background, or with color-coded dyes. Alternatively or additionally, coded signature 256 comprises a color-coded barcode. For some applications, the color-coded barcode may appear black or another color to the eye, but reveal a unique spectrum to optical processor 820. For some applications, the color-coded machine-readable signature further comprises a date, to prevent the recycling or re-use of signatures.

Physical key

Reference is made to Fig. 17, which is a schematic illustration of a computer-readable medium 850, a portion of which is shaped so as to define a physical key 852, in accordance with an embodiment of the present invention. A communication element 854 is shaped so as to define a dedicated slot 856 having a geometry matching that of key 852. Only keys having the particular geometry of slot 856 can be inserted into the slot. Key 852 thus enables authentication of computer-readable medium 850. Computer-readable medium 850 may comprise, for example, a disk-on-key apparatus or a

chip, having, for example, a USB-type connector.

For some applications, patient-specific data carrier 24 comprises computer-readable medium 850, and a communication element of imaging system 28 and/or administration system 26 is shaped so as to define slot 856. Alternatively or additionally, healthcare worker identity tag 208 comprises computer-readable medium 850, and workstation 200, elution system 600, dispensing system 20, administration system 26, and/or imaging system 28 is shaped so as to define slot 856. For some applications, computer-readable medium 850 further comprises coded signature 256, as described hereinabove, while for other applications, key 852 is relied upon in lieu of coded signature 256.

For some applications, authentication, as described herein, is alternatively or additionally based on additional parameters, such as a manufacturer's attribute.

In an embodiment of the present invention, information is transferred from one element of system 10 to another element thereof by physically transferring an electronic information-carrying chip from one element to the other. For example, upon administration of the labeled radiopharmaceutical agent contained in container 22, information may be transferred from data carrier 120 to patient-specific data carrier 24 by physically transferring a memory chip of data carrier 120 to data carrier 24.

Managing Compton residuals

Reference is made to Fig. 18, which is a graph showing particle energy vs. photon count at a detector 454 of camera 452 of imaging system 28 (Fig. 11), in accordance with an embodiment of the present invention. In this embodiment, dose calculation sub-system 156 of radiopharmaceutical dose calculation system 152, described hereinabove with reference to Fig. 5, takes Compton residuals into consideration when calculating doses of a first and a second labeled radiopharmaceutical agent to be mixed together in a cocktail, or to be separately administered for the same image acquisition procedure. If the first agent were to be provided at a relatively high dose and the second agent were to be provided at a lower dose, the first agent would produce a first peak 900A around a first energy level E^1, and the second agent would produce a second peak 902 around a second energy level E^2. A Compton residual 904A produced by the first agent at least partially masks second peak 902. For some applications, in order to prevent such masking, dose

calculation sub-system 156 reduces the dose of the first agent, thereby producing a first peak 900B and a corresponding Compton residual 904B having lower counts than initial first peak 900A and Compton residual 904A, respectively. Compton residual 904B is sufficiently low so as not to mask second peak 902. By using techniques described hereinabove and/or incorporated herein by reference, camera 452 is sufficiently sensitive to acquire sufficient counts emitted from the lower dose of the second agent. For example, the first and second agents may comprise MIBI-Tc and thallium, respectively, which emit energy at 140 KeV and 72 KeV, respectively.

Alternatively, calculation sub-system 156 determines that the dose of the first labeled radiopharmaceutical agent cannot be reduced sufficiently to prevent such Compton masking. To make such a determination, the sub-system typically takes into consideration constraints applied by the physical properties of the first agent, patient-specific information, and/or camera 452. The sub-system may thus determine that the two agents must be prepared as separate doses for non-simultaneous administration. Alternatively, the sub-system determines that the dose of the second agent is to be increased, so as to prevent the masking. To make such a determination, the sub-system typically takes into consideration constraints applied by the physical properties of the first agent, patient-specific information, camera 452, and/or safety and/or regulatory requirements.

Information-bearing radiopharmaceuticals

In an embodiment of the present invention, a portion of the patient, radiopharmaceutical, and/or protocol information described herein is chemically stored together with a labeled radiopharmaceutical agent in a container, such as radiopharmaceutical agent container 22 or mother vial 104. For some applications, such information is chemically stored by providing a chemical indicative of and/or encoding the information, and mixing the chemical with the radiopharmaceutical agent. Alternatively, such information is chemically stored by attaching a chemical marker indicative of the information to the radiopharmaceutical agent, or otherwise chemically modifying the radiopharmaceutical agent to store the information. The information-indicative chemical indicator (i.e., chemical or chemical marker) has properties which are machine-readable, for example, using optical, spectral, fluorescence, or isotope emission techniques.

For some applications, the information is stored by setting a level of a parameter of the chemical indicator, such as concentration or radioactivity, which level is indicative of the information. For example, a plurality of concentrations 0, A_1, A_2, A_3, ..., A_{max} may be defined, each of which represents a respective value. At all of the defined concentrations, the chemical indicator is biologically inert and/or safe in the body, and does not affect the sterility and/or properties of the radiopharmaceutical agent. The plurality of concentrations are sufficiently different from one another so as to be independently measurable and identifiable, such as by measuring a spectral signature of the chemical indicator. For some applications, a plurality of different chemical indicators are used, each of which has defined levels of a parameter representing respective values. The values represented by the plurality of chemical indicators together represent the information.

For some applications, the level of the parameter of the chemical indicator changes over time, e.g., the radioactivity of the chemical indicator declines because of radioactive decay, thereby providing an indication of elapsed time. Such elapsed time may be used, for example, to determine the timing of preparation of the radiopharmaceutical agent and/or subsequent processes, as well as validating whether such timing is within an allowed time window.

For some applications, dispensing system 20 applies the code to the labeled radiopharmaceutical agent and/or container 22 during the dispensing process, and administration system 26 and/or imaging system 28 reads and verifies the stored information. A dedicated reader may be provided for such reading, or a camera of imaging system 28 may be configured to perform such reading.

The scope of the present invention includes embodiments described in the following applications, which are assigned to the assignee of the present application and are incorporated herein by reference. In an embodiment, techniques and apparatus described in one or more of the following applications are combined with techniques and apparatus described herein:

- International Application PCT/IL2005/001173, filed November 9, 2005;
- International Application PCT/IL2005/000572, filed June 1, 2005;
- International Application PCT/IL2005/000575, filed June 1, 2005;

- International Application PCT/IL2005/001215, filed November 16, 2005;
- US Provisional Application 60/625,971, filed November 9, 2004;
- US Provisional Application 60/628,105, filed November 17, 2004;
- US Provisional Application 60/630,561, filed November 26, 2004;
- US Provisional Application 60/632,236, filed December 2, 2004;
- US Provisional Application 60/632,515, filed December 3, 2004;
- US Provisional Application 60/635,630, filed December 14, 2004;
- US Provisional Application 60/636,088, filed December 16, 2004;
- US Provisional Application 60/640,215, filed January 3, 2005;
- US Provisional Application 60/648,385, filed February 1, 2005;
- US Provisional Application 60/648,690, filed February 2, 2005;
- US Provisional Application 60/675,892, filed April 29, 2005;
- US Provisional Application 60/691,780, filed June 20, 2005;
- US Provisional Application 60/700,318, filed July 19, 2005;
- US Provisional Application 60/700,299, filed July 19, 2005;
- US Provisional Application 60/700,317, filed July 19, 2005;
- US Provisional Application 60/700,753, filed July 20, 2005;
- US Provisional Application 60/700,752, filed July 20, 2005;
- US Provisional Application 60/702,979, filed July 28, 2005;
- US Provisional Application 60/720,034, filed September 26, 2005;
- US Provisional Application 60/720,652, filed September 27, 2005;
- US Provisional Application 60/720,541, filed September 27, 2005;
- US Provisional Application 60/750,287, filed December 13, 2005;
- US Provisional Application 60/750,334, filed December 15, 2005; and/or
- US Provisional Application 60/750,597, filed December 15, 2005.

As used in the present application, including in the claims, a "clinical

environment" means any facility or institution in which at least one of radiopharmaceutical preparation, dispensing, and administration occur, including, for example, a radiopharmaceutical manufacturing facility, a pharmacy, a hospital, a doctor's clinic, a day clinic, an out-patient clinic, a laboratory, and a geriatric center.

It will be appreciated by persons skilled in the art that the present invention is not limited to what has been particularly shown and described hereinabove. Rather, the scope of the present invention includes both combinations and subcombinations of the various features described hereinabove, as well as variations and modifications thereof that are not in the prior art, which would occur to persons skilled in the art upon reading the foregoing description.

CLAIMS

1. Apparatus for use with at least one labeled radiopharmaceutical agent, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent; and

a portable computer-communicatable data carrier associated with the container, the data carrier containing imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

2. The apparatus according to claim 1, wherein the apparatus comprises a device configured to write the imaging protocol information to the data carrier.

3. The apparatus according to claim 1, wherein the data carrier additionally contains administration protocol information useful for administering the at least one labeled radiopharmaceutical agent.

4. The apparatus according to claim 1, wherein the imaging protocol information comprises instructions for performing an imaging procedure using the at least one labeled radiopharmaceutical agent.

5. The apparatus according to claim 1, wherein the imaging protocol information comprises an identifier of an imaging protocol.

6. The apparatus according to claim 1, wherein the imaging protocol information comprises a parameter of the at least one labeled radiopharmaceutical agent.

7. The apparatus according to claim 1, wherein the imaging protocol information comprises a parameter useful for configuring at least one aspect of an imaging procedure performed using the at least one labeled radiopharmaceutical agent.

8. The apparatus according to claim 1, wherein the container contains a single dose of the radiopharmaceutical agent, which dose is appropriate for use with the imaging protocol information.

9. The apparatus according to claim 1, wherein the container contains a plurality of labeled radiopharmaceutical agents mixed together.

10. The apparatus according to claim 1, wherein the container is shaped so as to define a plurality of chambers, each of which contains a respective one of a plurality of labeled radiopharmaceutical agents.

11. The apparatus according to any one of claims 1-10,

wherein the data carrier comprises a first data carrier, which contains a first identifier value,

wherein the apparatus further comprises a second computer-communicatable data carrier, which contains a second identifier value, and

wherein the apparatus is configured to operate responsively to a detection of a correspondence between the first and second identifier values.

12. The apparatus according to claim 11, wherein at least one of the first and second data carriers is configured to perform the detection of the correspondence.

13. The apparatus according to claim 11, wherein the apparatus comprises a correspondence-detection element configured to perform the detection of the correspondence.

14. The apparatus according to claim 11, wherein at least one of the first and second data carriers contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

15. The apparatus according to claim 11, wherein at least one of the first and second identifier values comprises an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

16. The apparatus according to claim 11, wherein exactly one of the first and second data carriers comprises a coupling mechanism configured to be coupled to a patient to whom the labeled radiopharmaceutical agent is to be administered.

17. The apparatus according to claim 11, wherein the apparatus comprises an imaging system comprising imaging functionality, the imaging system configured, responsively to the detection of the correspondence, to drive the imaging functionality to perform an imaging procedure using the at least one labeled radiopharmaceutical agent.

18. The apparatus according to any one of claims 1-10, wherein the data carrier is physically coupled to the container.

19. The apparatus according to claim 18, wherein the data carrier contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered, and wherein the imaging protocol information comprises imaging protocol information selected for the patient.

20. The apparatus according to claim 19, wherein the imaging protocol information comprises an identifier of an imaging protocol.

21. The apparatus according to claim 19, wherein the imaging protocol information comprises imaging protocol information customized for the patient.

22. The apparatus according to any one of claims 1-10, wherein the imaging protocol information comprises SPECT imaging protocol information.

23. The apparatus according to claim 22, wherein the SPECT imaging protocol information comprises dynamic SPECT imaging protocol information.

24. The apparatus according to claim 23, wherein the SPECT imaging protocol information comprises at least one kinetic parameter of the at least one labeled radiopharmaceutical agent, the at least one kinetic parameter useful for performing a dynamic SPECT imaging procedure using the at least one labeled radiopharmaceutical agent.

25. The apparatus according to any one of claims 1-10, comprising an imaging system, which comprises:

a communication element, configured to read the imaging protocol information from the data carrier; and

a control unit, comprising imaging functionality, which is configured to perform an imaging procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

26. The apparatus according to claim 25, wherein the imaging system comprises a camera, wherein the imaging functionality comprises image acquisition functionality, and wherein the image acquisition functionality is configured to perform an image acquisition procedure using the camera, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

27. The apparatus according to claim 26, wherein the image acquisition functionality configures a total acquisition time of the image acquisition procedure at least in part responsively to the imaging protocol information.

28. The apparatus according to claim 26, wherein the camera comprises a plurality of detectors, and wherein the image acquisition functionality is configured to configure, at

least in part responsively to the imaging protocol information, at least one motion of at least one of the detectors during the image acquisition procedure.

29. The apparatus according to claim 26, wherein the control unit is configured to configure, at least in part responsively to the imaging protocol information, a waiting time between administration of the labeled radiopharmaceutical agent and commencement of the image acquisition procedure.

30. The apparatus according to claim 26, wherein the image acquisition functionality is configured to perform a gated image acquisition procedure at least in part responsively to the imaging protocol information.

31. The apparatus according to claim 25, wherein the imaging functionality comprises image reconstruction functionality, and wherein the image reconstruction functionality is configured to perform an image reconstruction procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

32. The apparatus according to claim 25, wherein the imaging functionality comprises image analysis functionality, and wherein the image analysis functionality is configured to perform an image analysis procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

33. The apparatus according to claim 25, wherein the imaging functionality comprises diagnosis functionality, and wherein the diagnosis functionality is configured to perform a diagnostic procedure, and to configure the procedure at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

34. The apparatus according to claim 25, wherein the imaging procedure includes a three-dimensional dynamic imaging study, and wherein the imaging functionality is configured to perform the three-dimensional dynamic imaging study, and to configure the study at least in part responsively to the imaging protocol information read from the data carrier by the communication element.

35. The apparatus according to any one of claims 1-10, wherein the data carrier is not physically coupled to the container, and wherein the data carrier contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

36. The apparatus according to claim 35, wherein the data carrier comprises a coupling mechanism configured to be coupled to the patient.

37. The apparatus according to claim 35, wherein the data carrier comprises a first data carrier, and wherein the apparatus further comprises a second computer-communicatable data carrier physically coupled to the container, the second data carrier containing radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent.

38. Apparatus for use with at least one labeled radiopharmaceutical agent, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent; and

a computer-communicatable data carrier associated with the container, the data carrier containing authenticatable information regarding a commercial license for use of SPECT imaging protocol information with the at least one labeled radiopharmaceutical agent.

39. The apparatus according to claim 38, comprising an imaging system, which comprises:

a communication element, configured to read the authenticatable license information from the data carrier;

a control unit, comprising imaging functionality, the control unit configured to:

authenticate the authenticatable license information, and

only upon authentication, drive the imaging functionality to perform an imaging procedure using the SPECT imaging protocol information.

40. The apparatus according to claim 38, wherein the apparatus comprises a device configured to write the authenticatable license information to the data carrier.

41. The apparatus according to any one of claims 38-40, wherein the data carrier is physically coupled to the container.

42. Apparatus comprising a portable computer-communicatable data carrier containing authenticatable information regarding a commercial license for use of SPECT imaging protocol information.

43. The apparatus according to claim 42, wherein the data carrier additionally contains patient information regarding a patient upon whom an imaging procedure using the

SPECT imaging protocol information is to be performed.

44. The apparatus according to claim 42, wherein the authenticatable license information is encrypted.

45. The apparatus according to claim 42, wherein the apparatus comprises a device configured to write the authenticatable license information to the data carrier.

46. The apparatus according to claim 42, wherein the data carrier comprises a coupling mechanism configured to be coupled to a patient upon whom an imaging procedure using the SPECT imaging protocol information is to be performed.

47. The apparatus according to any one of claims 42-46, comprising an imaging system, which comprises:

a communication element, configured to read the authenticatable license information from the data carrier;

a control unit, comprising imaging functionality, the control unit configured to:

authenticate the authenticatable license information, and

only upon authentication, drive the imaging functionality to perform an imaging procedure using the SPECT imaging protocol information.

48. Apparatus comprising:

a first portable computer-communicatable data carrier containing a first identifier value;

a second portable computer-communicatable data carrier containing a second identifier value; and

an imaging system comprising imaging functionality, the imaging system configured, responsively to a detection of a correspondence between the first and second identifier values, to drive the imaging functionality to perform an imaging procedure on a patient.

49. The apparatus according to claim 48, wherein at least one of the first and second data carriers is configured to perform the detection of the correspondence.

50. The apparatus according to claim 48, wherein the imaging system comprises a correspondence-detection element configured to perform the detection of the correspondence.

51. The apparatus according to claim 48, wherein at least one of the first and second

data carriers contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

52. The apparatus according to claim 48, wherein at least one of the first and second identifier values comprises an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

53. The apparatus according to claim 48, wherein one of the first and second data carriers comprises a coupling mechanism configured to be coupled to a patient to whom the labeled radiopharmaceutical agent is to be administered.

54. The apparatus according to claim 48, wherein the apparatus comprises a device configured to write at least one of the first and second identifier values to the respective first and second data carriers.

55. The apparatus according to any one of claims 48-54,

wherein at least one of the first and second data carriers contains radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent,

wherein the imaging system comprises a communication element, configured to read the radiopharmaceutical information from the at least one of the data carriers, and

wherein the imaging system is configured to configure the imaging procedure at least in part responsively to the read radiopharmaceutical information.

56. The apparatus according to claim 55, wherein the apparatus comprises a container containing the at least one labeled radiopharmaceutical agent.

57. The apparatus according to claim 56, wherein one of the first and second data carriers is physically coupled to the container.

58. The apparatus according to any one of claims 48-54, wherein the imaging functionality comprises a nuclear camera.

59. The apparatus according to claim 58, wherein the nuclear camera comprises a SPECT camera.

60. Apparatus for use with first and second portable computer-communicatable data carriers containing first and second identifier values, respectively, the apparatus comprising an imaging system, which comprises:

imaging functionality; and

a control unit configured to drive the imaging functionality to perform an imaging procedure on a patient, responsively to a detection of a correspondence between the first and second identifier values.

61. The apparatus according to claim 60, wherein the imaging system comprises a correspondence-detection element configured to perform the detection of the correspondence.

62. Apparatus for use with at least one labeled radiopharmaceutical agent for administration to a patient, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent;

a first computer-communicatable data carrier physically coupled to the container, the first data carrier containing radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent; and

a second portable computer-communicatable data carrier containing patient information regarding the patient, and imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

63. The apparatus according to claim 62, wherein the imaging protocol information comprises SPECT imaging protocol information.

64. The apparatus according to claim 62, wherein the patient information comprises an identifier of the patient.

65. The apparatus according to claim 62, wherein the second data carrier comprises a coupling mechanism configured to be coupled to the patient.

66. The apparatus according to claim 62, wherein the first data carrier contains a first patient identifier, wherein the patient information contained in the second data carrier comprises a second patient identifier, and comprising an administration system, which comprises:

a first communication element, configured to read the first patient identifier from the first data carrier;

a second communication element, configure to read the second patient identifier from the second data carrier; and

a control unit, configured to compare the first patient identifier to the second patient identifier, and, upon detecting a match, generate an administration signal that

triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

67. The apparatus according to claim 62, wherein the first data carrier contains a first protocol identifier, wherein the imaging protocol information contained in the second data carrier comprises a second protocol identifier, and comprising an administration system, which comprises:

a communication element, configured to read the first and second protocol identifiers from the first and second data carriers, respectively; and

a control unit, configured to compare the first protocol identifier to the second protocol identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

68. The apparatus according to claim 62, wherein the first data carrier contains a first protocol identifier, wherein the imaging protocol information contained in the second data carrier comprises a second protocol identifier, and comprising an administration system, which comprises:

a first communication element, configured to read the first protocol identifier from the first data carrier;

a second communication element, configured to read the second protocol identifier from the second data carrier; and

a control unit, configured to compare the first protocol identifier to the second protocol identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

69. The apparatus according to claim 62, comprising an administration system, which comprises:

a communication element; and

a control unit, configured to:

generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container, and

drive the communication element to transmit information regarding the administration to the second data carrier.

70. The apparatus according to claim 62, wherein the apparatus comprises a device configured to write the imaging protocol information to the first data carrier.

71. The apparatus according to claim 62, wherein the apparatus comprises a device configured to write the patient information to the second data carrier.

72. The apparatus according to any one of claims 62-71, wherein the imaging protocol information comprises imaging protocol information selected for the patient.

73. The apparatus according to claim 72, wherein the imaging protocol information comprises an identifier of an imaging protocol.

74. The apparatus according to claim 72, wherein the imaging protocol information comprises imaging protocol information customized for the patient.

75. The apparatus according to any one of claims 62-71, wherein the first data carrier contains a first patient identifier, wherein the patient information contained in the second data carrier includes a second patient identifier, and comprising an administration system, which comprises:

a communication element, configured to read the first and second patient identifiers from the first and second data carriers, respectively; and

a control unit, configured to compare the first patient identifier to the second patient identifier, and, upon detecting a match, generate an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

76. The apparatus according to claim 75, wherein the administration system comprises an automated administration device, configured to administer the at least one labeled radiopharmaceutical agent to the patient upon being triggered by the administration signal.

77. The apparatus according to claim 75, wherein the control unit is configured to generate the administration signal to trigger the administration of the at least one labeled radiopharmaceutical agent by instructing a healthcare worker to administer the at least one labeled radiopharmaceutical agent to the patient.

78. Apparatus for use with at least one labeled radiopharmaceutical agent for administration to a patient, the apparatus comprising:

a container containing the at least one labeled radiopharmaceutical agent;

a computer-communicatable data carrier associated with the container, the data carrier containing data regarding at least one of: the labeled radiopharmaceutical agent and the patient; and

a SPECT imaging system comprising:

a communication element, configured to read the data; and

a control unit, configured to utilize the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

79. The apparatus according to claim 78, wherein the data carrier contains the data regarding the labeled radiopharmaceutical agent.

80. The apparatus according to claim 78, wherein the data carrier contains the data regarding the patient.

81. The apparatus according to claim 78, wherein the control unit is configured to utilize the read data to customize the administration of the labeled radiopharmaceutical agent.

82. The apparatus according to claim 78, wherein the control unit is configured to utilize the read data to customize the acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered.

83. The apparatus according to claim 78, wherein the control unit is configured to utilize the read data to customize the reconstruction of the SPECT image.

84. The apparatus according to claim 78, wherein the control unit is configured to utilize the read data to customize the analysis of the SPECT image.

85. The apparatus according to claim 78, wherein the control unit is configured to utilize the read data to customize the diagnosis of a condition of the patient based at least in part on the analysis.

86. The apparatus according to any one of claims 78-85, wherein the apparatus comprises a device configured to write the data to the data carrier.

87. A SPECT imaging system for use with a container containing at least one labeled radiopharmaceutical agent for administration to a patient, and data regarding at least one of: the labeled radiopharmaceutical agent and the patient, the system comprising:

a communication element, configured to read the data; and

a control unit, configured to utilize the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

88. The system according to claim 87, wherein the system comprises a device configured to write the data to the container.

89. An automated radiopharmaceutical dispensing system for use with a container and a computer-communicatable container data carrier associated with the container, the system comprising:

a robot, configured to manipulate the container;

a communication element; and

a control unit, configured to:

receive radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent, the radiopharmaceutical information selected from the group consisting of: imaging protocol information for use with the at least one labeled radiopharmaceutical agent, and authenticatable information regarding a commercial license for use of an imaging protocol with the at least one labeled radiopharmaceutical agent,

receive patient information regarding a patient,

drive the robot to automatically dispense a dose of the labeled radiopharmaceutical agent to the container, and

drive the communication element to transmit to the container data carrier at least a portion of the radiopharmaceutical information and at least a portion of the patient information.

90. The system according to claim 89, wherein the control unit is configured to receive the radiopharmaceutical information regarding a plurality of labeled

radiopharmaceutical agents, and drive the robot to automatically dispense respective doses of the labeled radiopharmaceutical agents to the container.

91. The system according to claim 89, wherein the patient information includes an identifier of an imaging protocol assigned to the patient for performance using the dose, and wherein the control unit is configured to drive the communication element to transmit the imaging protocol identifier to the container data carrier.

92. The system according to claim 89, wherein the control unit is configured to drive the communication element to transmit to the container data carrier at least one of: a time of dispensing of the labeled radiopharmaceutical agent to the container, and information regarding a radioactivity of the dose at the time of dispensing.

93. The system according to claim 89, comprising:

a mother vial that contains the labeled radiopharmaceutical agent prior to dispensing thereof; and

a computer-communicatable mother vial data carrier associated with the mother vial, which mother vial data carrier contains the radiopharmaceutical information,

wherein the control unit is configured to receive the radiopharmaceutical information from the mother vial data carrier.

94. The system according to any one of claims 89-93, wherein the radiopharmaceutical information comprises the imaging protocol information.

95. The system according to claim 94, wherein the imaging protocol information comprises SPECT imaging protocol information.

96. The system according to claim 95, wherein the imaging protocol information comprises at least one kinetic parameter of the at least one labeled radiopharmaceutical agent.

97. The system according to any one of claims 89-93, wherein the radiopharmaceutical information comprises the authenticatable information regarding the commercial license.

98. The system according to claim 97, wherein the information regarding the commercial license comprises information regarding the commercial license for use of a SPECT imaging protocol with the at least one labeled radiopharmaceutical agent.

99. The system according to claim 97, wherein the control unit is configured to

authenticate the authenticatable license information, and to drive the robot to automatically dispense the dose only upon authentication.

100. Apparatus for use with a container, the apparatus comprising:

a mother vial having a volume of at least 10 ml, which contains at least 5 ml of a non-diluted labeled radiopharmaceutical agent, and at least 5 ml of saline solution; and

an automated radiopharmaceutical dispensing system, configured to contain the mother vial, and to dispense at least one dose from the mother vial to the container.

101. A method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

associating a portable computer-communicatable data carrier with the container; and

writing, to the data carrier, imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

102. The method according to claim 101, comprising writing, to the data carrier, administration protocol information useful for administering the at least one labeled radiopharmaceutical agent.

103. The method according to claim 101, wherein writing the imaging protocol information comprises writing instructions for performing an imaging procedure using the at least one labeled radiopharmaceutical agent.

104. The method according to claim 101, wherein writing the imaging protocol information comprises writing an identifier of an imaging protocol.

105. The method according to claim 101, wherein writing the imaging protocol information comprises writing a parameter of the at least one labeled radiopharmaceutical agent.

106. The method according to claim 101, wherein writing the imaging protocol information comprises writing a parameter useful for configuring at least one aspect of an imaging procedure performed using the at least one labeled radiopharmaceutical agent.

107. The method according to claim 101, wherein placing comprises placing a single dose of the radiopharmaceutical agent in the container, which dose is appropriate for use with the imaging protocol information.

108. The method according to claim 101, wherein placing comprises placing, in the container, a plurality of labeled radiopharmaceutical agents mixed together.

109. The method according to claim 101, wherein the container is shaped so as to define a plurality of chambers, and wherein placing the at least one labeled radiopharmaceutical agent in the container comprises placing a plurality of labeled radiopharmaceutical agents in respective chambers.

110. The method according to any one of claims 101-109, wherein associating the data carrier comprises associating a first data carrier with the container, and wherein the method comprises:

writing a first identifier value to the first data carrier;

writing a second identifier to a second computer-communicatable data carrier;

detecting a correspondence between the first and second identifier values; and

performing an operation responsively to the detecting.

111. The method according to claim 110, wherein detecting comprises detecting the correspondence by at least one of the first and second data carriers.

112. The method according to claim 110, wherein detecting comprises detecting by a correspondence-detection element separate from the first and second data carriers.

113. The method according to claim 110, comprising writing, to at least one of the first and second data carriers, an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

114. The method according to claim 110, wherein writing at least one of the first and second identifier values comprises writing an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

115. The method according to claim 110, comprising coupling exactly one of the first and second data carriers to a patient to whom the labeled radiopharmaceutical agent is to be administered.

116. The method according to claim 110, wherein performing the operation comprises, responsively to the detecting of the correspondence, performing an imaging procedure using the at least one labeled radiopharmaceutical agent.

117. The method according to any one of claims 101-109, wherein associating the data carrier with the container comprises physically coupling the data carrier to the container.

118. The method according to claim 117, wherein the data carrier contains an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered, and wherein writing the imaging protocol information comprises writing imaging protocol information selected for the patient.

119. The method according to claim 118, wherein writing the imaging protocol information comprises writing an identifier of an imaging protocol.

120. The method according to claim 118, wherein writing the imaging protocol information comprises writing imaging protocol information customized for the patient.

121. The method according to any one of claims 101-109, wherein writing the imaging protocol information comprises writing SPECT imaging protocol information.

122. The method according to claim 121, wherein writing the SPECT imaging protocol information comprises writing dynamic SPECT imaging protocol information.

123. The method according to claim 122, wherein writing the SPECT imaging protocol information comprises writing at least one kinetic parameter of the at least one labeled radiopharmaceutical agent, the at least one kinetic parameter useful for performing a dynamic SPECT imaging procedure using the at least one labeled radiopharmaceutical agent.

124. The method according to any one of claims 101-109, comprising:

reading the imaging protocol information from the data carrier; and

performing an imaging procedure, and configuring the procedure at least in part responsively to the imaging protocol information read from the data carrier.

125. The method according to claim 124, wherein performing the imaging procedure comprises performing an image acquisition procedure, and configuring the procedure at least in part responsively to the imaging protocol information read from the data carrier.

126. The method according to claim 125, wherein performing the image acquisition procedure comprises configuring a total acquisition time of the image acquisition procedure at least in part responsively to the imaging protocol information.

127. The method according to claim 125, wherein performing the image acquisition procedure comprises performing the image acquisition procedure using a camera having a plurality of detectors, and configuring, at least in part responsively to the imaging protocol information, at least one motion of at least one of the detectors during the image

acquisition procedure.

128. The method according to claim 125, wherein performing the image acquisition procedure comprises configuring, at least in part responsively to the imaging protocol information, a waiting time between administration of the labeled radiopharmaceutical agent and commencement of the image acquisition procedure.

129. The method according to claim 125, wherein performing the image acquisition procedure comprises performing a gated image acquisition procedure at least in part responsively to the imaging protocol information.

130. The method according to claim 124, wherein performing the imaging procedure comprises performing an image reconstruction procedure, and configuring the procedure at least in part responsively to the imaging protocol information read from the data carrier.

131. The method according to claim 124, wherein performing the imaging procedure comprises performing an image analysis procedure, and configuring the procedure at least in part responsively to the imaging protocol information read from the data carrier.

132. The method according to claim 124, wherein performing the imaging procedure comprises performing a diagnostic procedure, and configuring the procedure at least in part responsively to the imaging protocol information read from the data carrier.

133. The method according to claim 124, wherein performing the imaging procedure comprises performing a three-dimensional dynamic imaging study, and configuring the study at least in part responsively to the imaging protocol information read from the data carrier.

134. The method according to any one of claims 101-109, wherein associating the data carrier with the container does not comprise physically coupling the data carrier to the container, and comprising writing, to the data carrier, an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

135. The method according to claim 134, comprising coupling the data carrier to the patient.

136. The method according to claim 134, wherein associating the data carrier comprises associating a first data carrier with the container, and comprising writing, to a second computer-communicatable data carrier, radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent, and physically coupling the second data

carrier to the container.

137. A method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

associating a computer-communicatable data carrier with the container; and

writing, to the data carrier, authenticatable information regarding a commercial license for use of SPECT imaging protocol information with the at least one labeled radiopharmaceutical agent.

138. The method according to claim 137, comprising:

reading the authenticatable license information from the data carrier;

authenticating the authenticatable license information; and

only upon authentication, performing an imaging procedure using the SPECT imaging protocol information.

139. The method according to any one of claims 137-138, wherein associating comprises physically coupling the data carrier to the container.

140. A method comprising:

providing a portable computer-communicatable data carrier; and

writing, to the data carrier, authenticatable information regarding a commercial license for use of SPECT imaging protocol information.

141. The method according to claim 140, comprising writing, to the data carrier, patient information regarding a patient upon whom an imaging procedure using the SPECT imaging protocol information is to be performed.

142. The method according to claim 140, wherein writing the authenticatable license information comprises encrypting the authenticatable license information.

143. The method according to claim 140, comprising:

reading the authenticatable license information from the data carrier;

authenticating the authenticatable license information; and

only upon authentication, performing an imaging procedure using the SPECT imaging protocol information.

144. The method according to any one of claims 140-143, comprising coupling the data carrier to a patient upon whom an imaging procedure using the SPECT imaging protocol

information is to be performed.

145. A method comprising:

writing first and second identifier values to first and second computer-communicatable data carriers, respectively;

detecting a correspondence between the first and second identifier values; and

perform an imaging procedure on a patient responsively to the detecting.

146. The method according to claim 145, wherein detecting comprises detecting the correspondence by at least one of the first and second data carriers.

147. The method according to claim 145, wherein detecting comprises detecting by a correspondence-detection element separate from the first and second data carriers.

148. The method according to claim 145, comprising writing, to at least one of the first and second data carriers, an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

149. The method according to claim 145, wherein writing at least one of the first and second identifier values comprises writing an identifier of a patient to whom the labeled radiopharmaceutical agent is to be administered.

150. The method according to claim 145, comprising coupling one of the first and second data carriers to a patient to whom the labeled radiopharmaceutical agent is to be administered.

151. The method according to any one of claims 145-150, comprising:

writing, to at least one of the first and second data carriers, radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent;

reading the radiopharmaceutical information from the at least one of the data carriers; and

configuring the imaging procedure at least in part responsively to the read radiopharmaceutical information.

152. The method according to claim 151, comprising placing the at least one labeled radiopharmaceutical agent in a container.

153. The method according to claim 152, comprising physically coupling one of the first and second data carriers to the container.

154. The method according to any one of claims 145-150, wherein performing the imaging procedure comprises performing a nuclear imaging procedure.

155. The method according to claim 154, wherein performing the nuclear imaging procedure comprises performing a SPECT imaging procedure.

156. A method for use with at least one labeled radiopharmaceutical agent for administration to a patient, the method comprising:

placing at least one labeled radiopharmaceutical agent in a container;

physically coupling a first computer-communicatable data carrier to the container;

writing, to the first data carrier, radiopharmaceutical information regarding the at least one labeled radiopharmaceutical agent; and

writing, to a second portable computer-communicatable data carrier, patient information regarding the patient, and imaging protocol information for use with the at least one labeled radiopharmaceutical agent.

157. The method according to claim 156, wherein writing the imaging protocol information comprises writing SPECT imaging protocol information.

158. The method according to claim 156, wherein writing the patient information comprises writing an identifier of the patient.

159. The method according to claim 156, comprising coupling the second data carrier to the patient.

160. The method according to claim 156, wherein writing the patient information to the second data carrier comprises writing a second patient identifier to the second data carrier, and comprising:

writing a first patient identifier to the first data carrier;

reading the first and second patient identifiers from the first and second data carriers, respectively; and

comparing the first patient identifier to the second patient identifier, and, upon detecting a match, generating an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

161. The method according to claim 156, wherein writing the imaging protocol information to the second data carrier comprises writing a second protocol identifier to the second data carrier, and comprising:

writing a first protocol identifier to the first data carrier;

reading the first and second protocol identifiers from the first and second data carriers, respectively; and

comparing the first protocol identifier to the second protocol identifier, and, upon detecting a match, generating an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

162. The method according to claim 156, comprising:

generating an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container; and

transmitting information regarding the administration to the second data carrier.

163. The method according to any one of claims 156-162, wherein writing the imaging protocol information to the second data carrier comprises writing imaging protocol information selected for the patient.

164. The method according to claim 163, wherein writing the imaging protocol information comprises writing an identifier of an imaging protocol.

165. The method according to claim 163, wherein writing the imaging protocol information comprises writing imaging protocol information customized for the patient.

166. The method according to any one of claims 156-162, wherein writing the patient information to the second data carrier comprises writing a second patient identifier to the second data carrier, and comprising:

writing a first patient identifier to the first data carrier;

reading the first and second patient identifiers from the first and second data carriers, respectively; and

comparing the first patient identifier to the second patient identifier, and, upon detecting a match, generating an administration signal that triggers administration to the patient of the at least one labeled radiopharmaceutical agent contained in the container.

167. The method according to claim 166, comprising automatically administering the at least one labeled radiopharmaceutical agent to the patient upon triggering by the administration signal.

168. The method according to claim 166, wherein generating the administration signal comprises instructing a healthcare worker to administer the at least one labeled

radiopharmaceutical agent to the patient.

169. A method comprising:

placing, in a container, at least one labeled radiopharmaceutical agent for administration to a patient;

associating a computer-communicatable data carrier with the container;

writing data to the data carrier regarding at least one of: the labeled radiopharmaceutical agent and the patient;

reading the data from the data carrier at a SPECT imaging system;

utilizing the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

170. The method according to claim 169, wherein writing the data comprises writing the data regarding the labeled radiopharmaceutical agent.

171. The method according to claim 169, wherein writing the data comprises writing the data regarding the patient.

172. The method according to claim 169, wherein utilizing the read data comprises utilizing the read data to customize the administration of the labeled radiopharmaceutical agent.

173. The method according to claim 169, wherein utilizing the read data comprises utilizing the read data to customize the acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered.

174. The method according to claim 169, wherein utilizing the read data comprises utilizing the read data to customize the reconstruction of the SPECT image.

175. The method according to claim 169, wherein utilizing the read data comprises utilizing the read data to customize the analysis of the SPECT image.

176. The method according to any one of claims 169-175, wherein utilizing the read data comprises utilizing the read data to customize the diagnosis of a condition of the patient based at least in part on the analysis.

177. A method for use with a container containing at least one labeled radiopharmaceutical agent for administration to a patient, and data regarding at least one of: the labeled radiopharmaceutical agent and the patient, the method comprising:

reading the data at a SPECT imaging system; and

utilizing the read data to customize at least one function of the system selected from the group consisting of: administration of the labeled radiopharmaceutical agent, acquisition of a SPECT image of the patient to whom the labeled radiopharmaceutical agent is administered, reconstruction of the SPECT image, analysis of the SPECT image, and diagnosis of a condition of the patient based at least in part on the analysis.

178. The method according to claim 177, comprising writing the data to the container.

179. A method for use with a container and a computer-communicatable container data carrier associated with the container, the method comprising:

receiving, by an automated radiopharmaceutical dispensing system, radiopharmaceutical information regarding at least one labeled radiopharmaceutical agent, the radiopharmaceutical information selected from the group consisting of: imaging protocol information for use with the at least one labeled radiopharmaceutical agent, and authenticatable information regarding a commercial license for use of an imaging protocol with the at least one labeled radiopharmaceutical agent;

receiving, by the dispensing system, patient information regarding a patient;

automatically robotically dispensing, by the dispensing system, a dose of the labeled radiopharmaceutical agent to the container; and

transmitting to the container data carrier, by the dispensing system, at least a portion of the radiopharmaceutical information and at least a portion of the patient information.

180. The method according to claim 179, wherein receiving the radiopharmaceutical information comprises receiving the radiopharmaceutical information regarding a plurality of labeled radiopharmaceutical agents, and wherein dispensing comprises dispensing respective doses of the labeled radiopharmaceutical agents to the container.

181. The method according to claim 179, wherein the patient information includes an identifier of an imaging protocol assigned to the patient for performance using the dose, and wherein transmitting comprises transmitting the imaging protocol identifier to the container data carrier.

182. The method according to claim 179, wherein transmitting comprises transmitting to the container data carrier at least one of: a time of dispensing of the labeled radiopharmaceutical agent to the container, and information regarding a radioactivity of the dose at the time of dispensing.

183. The method according to claim 179, wherein receiving the radiopharmaceutical information comprises:

providing, to the dispensing system, a mother vial that contains the labeled radiopharmaceutical agent prior to dispensing thereof, and a computer-communicatable mother vial data carrier associated with the mother vial, which mother vial data carrier contains the radiopharmaceutical information; and

receiving the radiopharmaceutical information from the mother vial data carrier.

184. The method according to any one of claims 179-183, wherein receiving the radiopharmaceutical information comprises receiving the imaging protocol information.

185. The method according to claim 184, wherein receiving the imaging protocol information comprises receiving SPECT imaging protocol information.

186. The method according to claim 185, wherein receiving the imaging protocol information comprises receiving at least one kinetic parameter of the at least one labeled radiopharmaceutical agent.

187. The method according to any one of claims 179-183, wherein receiving the radiopharmaceutical information comprises receiving the authenticatable information regarding the commercial license.

188. The method according to claim 187, wherein receiving the information regarding the commercial license comprises receiving information regarding the commercial license for use of a SPECT imaging protocol with the at least one labeled radiopharmaceutical agent.

189. The method according to claim 187, wherein dispensing comprises authenticating the authenticatable license information, and dispensing the dose only upon authentication.

190. A method for automatically dispensing a labeled radiopharmaceutical agent to a container, comprising:

providing a mother vial having a volume of at least 10 ml;

filling the mother vial with at least 5 ml of a non-diluted labeled

radiopharmaceutical agent, and with at least 5 ml of saline solution;

placing the mother vial in an automated radiopharmaceutical dispensing system; and

dispensing at least one dose from the mother vial to the container.

FIG. 1

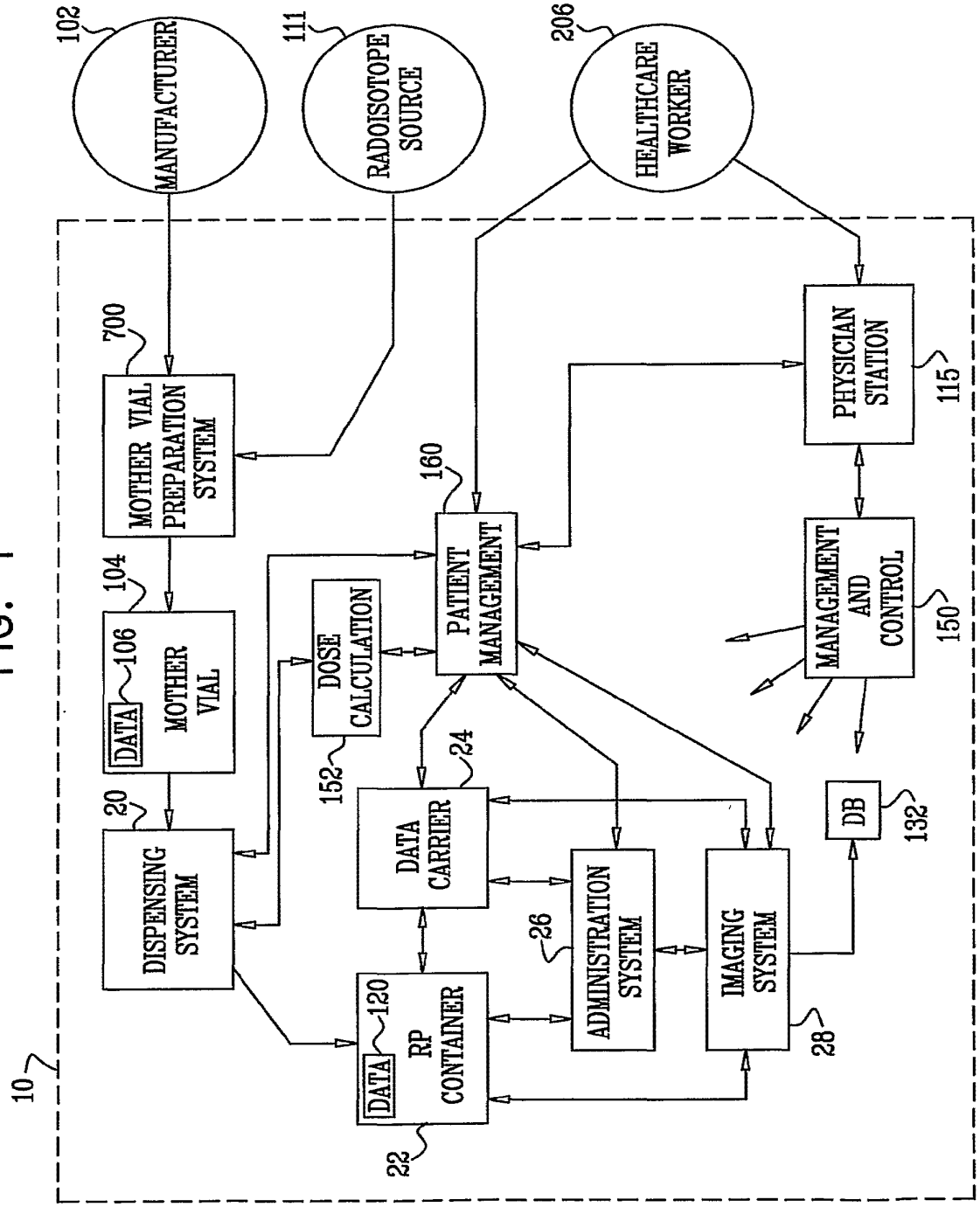

102
MANUFACTURER
111
RADOISOTOPE SOURCE
206
HEALTHCARE WORKER
700
MOTHER VIAL PREPARATION SYSTEM
104
DATA
106
MOTHER VIAL
20
DISPENSING SYSTEM
160
PATIENT MANAGEMENT
DOSE CALCULATION
152
24
DATA CARRIER
120
DATA
RP CONTAINER
22
26
ADMINISTRATION SYSTEM
IMAGING SYSTEM
28
PHYSICIAN STATION
115
MANAGEMENT AND CONTROL
150
DB
132
10

FIG. 2

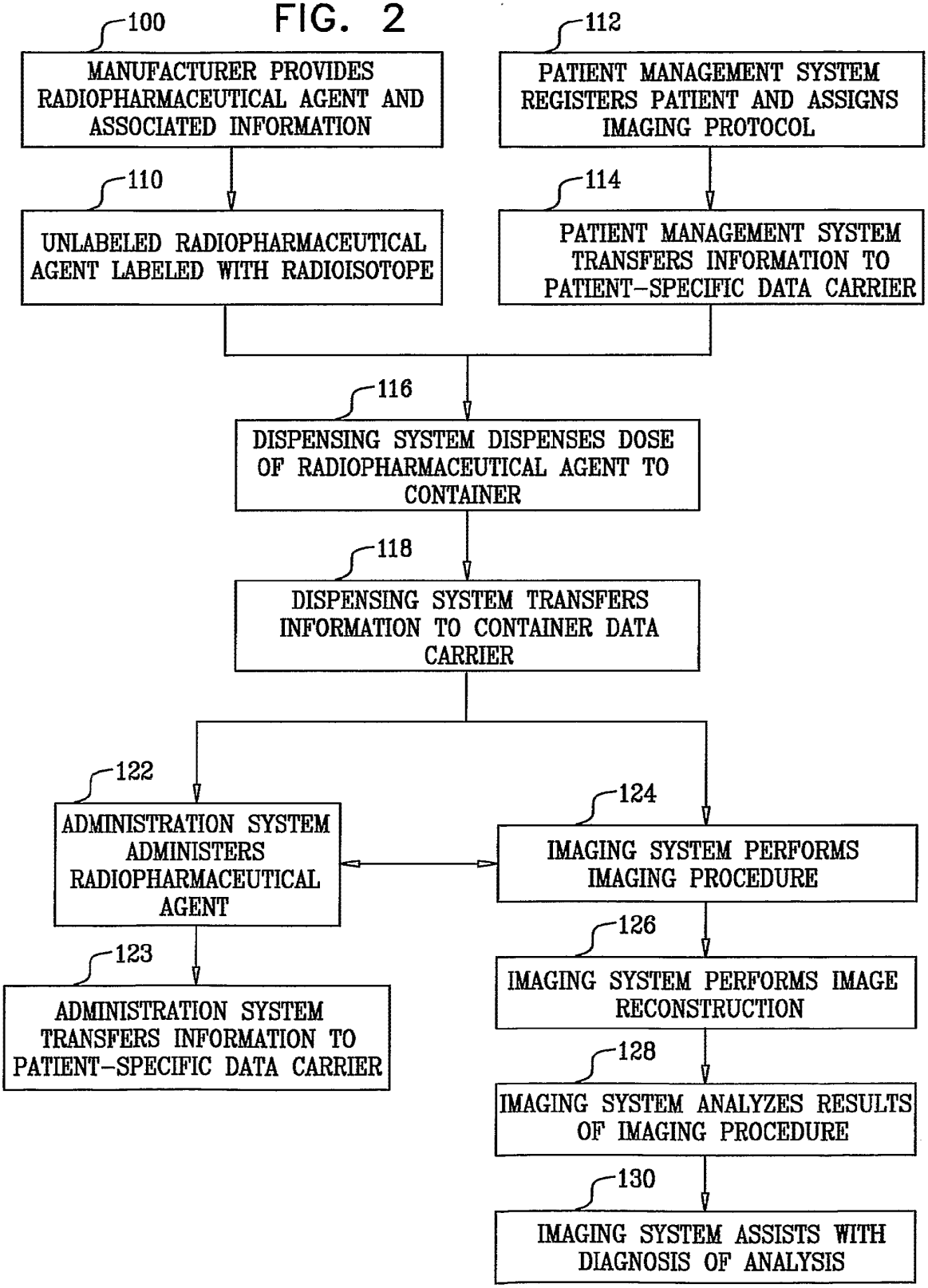

100
MANUFACTURER PROVIDES RADIOPHARMACEUTICAL AGENT AND ASSOCIATED INFORMATION
110
UNLABELED RADIOPHARMACEUTICAL AGENT LABELED WITH RADIOISOTOPE
112
PATIENT MANAGEMENT SYSTEM REGISTERS PATIENT AND ASSIGNS IMAGING PROTOCOL
114
PATIENT MANAGEMENT SYSTEM TRANSFERS INFORMATION TO PATIENT-SPECIFIC DATA CARRIER
116
DISPENSING SYSTEM DISPENSES DOSE OF RADIOPHARMACEUTICAL AGENT TO CONTAINER
118
DISPENSING SYSTEM TRANSFERS INFORMATION TO CONTAINER DATA CARRIER
122
ADMINISTRATION SYSTEM ADMINISTERS RADIOPHARMACEUTICAL AGENT
123
ADMINISTRATION SYSTEM TRANSFERS INFORMATION TO PATIENT-SPECIFIC DATA CARRIER
124
IMAGING SYSTEM PERFORMS IMAGING PROCEDURE
126
IMAGING SYSTEM PERFORMS IMAGE RECONSTRUCTION
128
IMAGING SYSTEM ANALYZES RESULTS OF IMAGING PROCEDURE
130
IMAGING SYSTEM ASSISTS WITH DIAGNOSIS OF ANALYSIS

FIG. 3

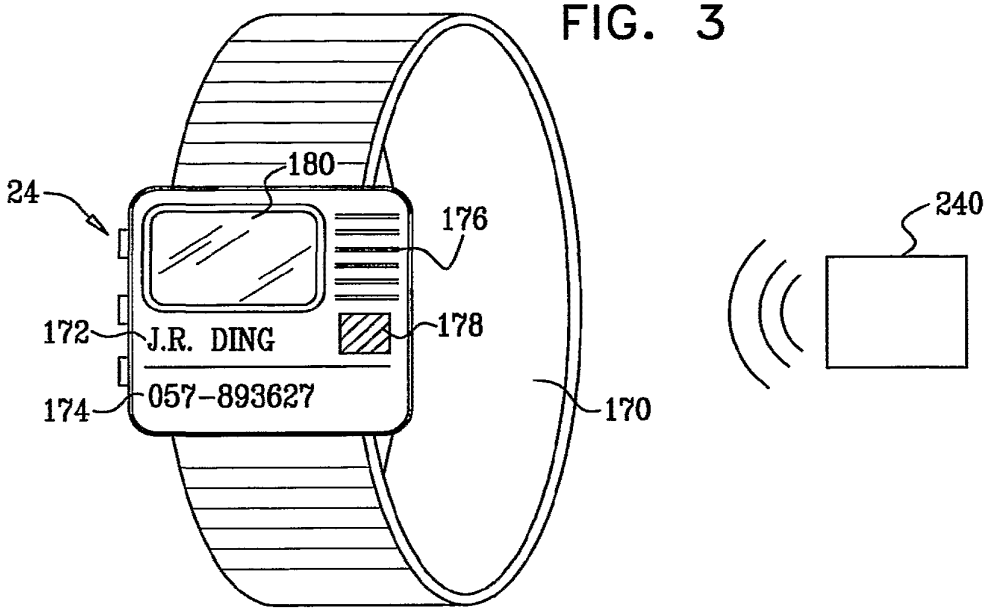

24
180
176
172
J.R. DING
178
174
057-893627
170
240

FIG. 4

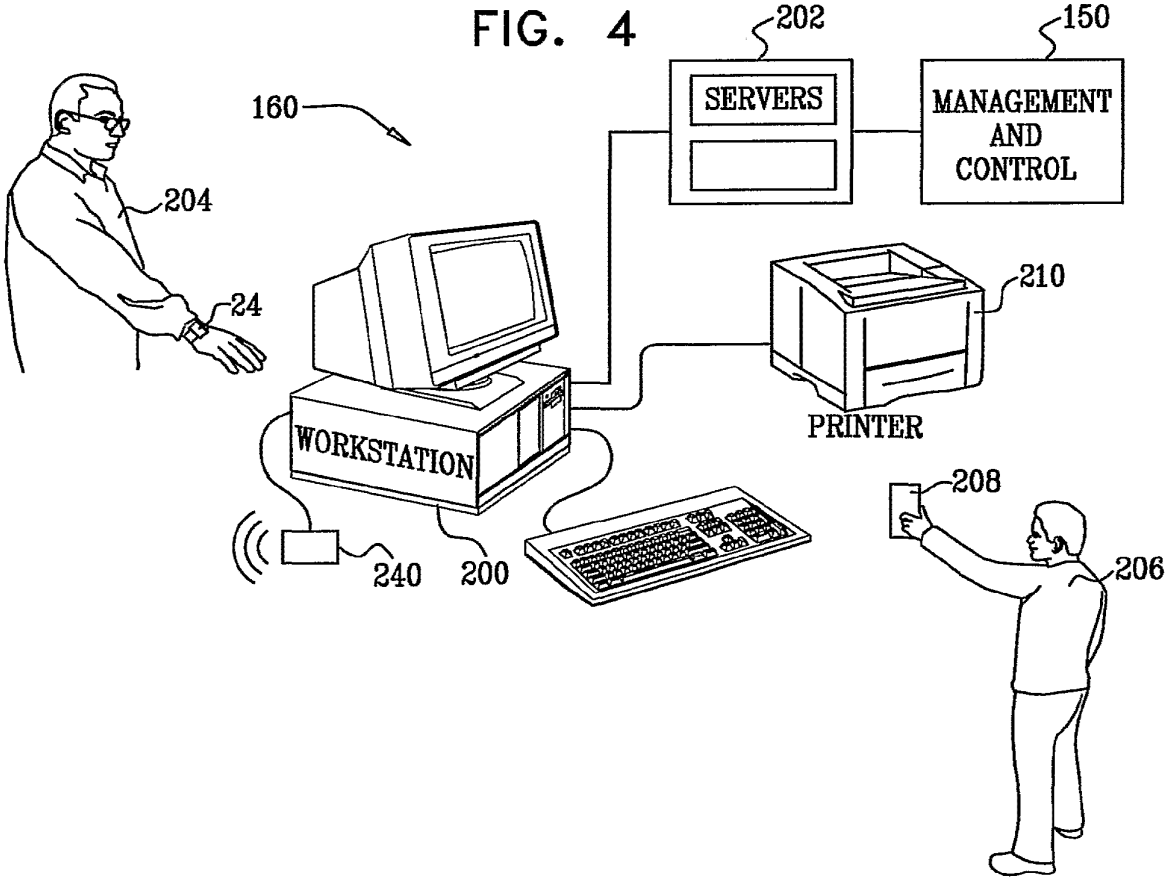

202
150
SERVERS
MANAGEMENT AND CONTROL
160
204
24
210
PRINTER
WORKSTATION
208
240
200
206

FIG. 5

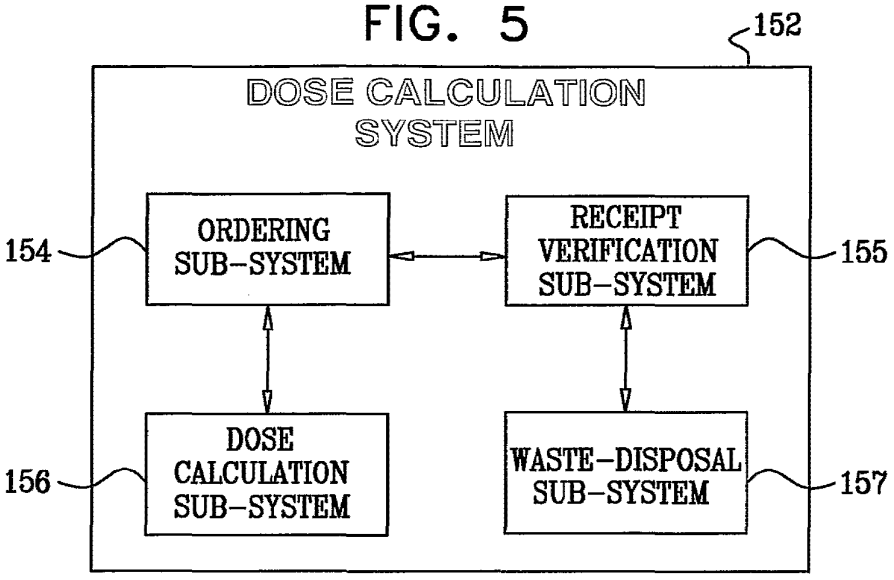

152
DOSE CALCULATION SYSTEM
154
ORDERING SUB-SYSTEM
RECEIPT VERIFICATION SUB-SYSTEM
155
156
DOSE CALCULATION SUB-SYSTEM
WASTE-DISPOSAL SUB-SYSTEM
157

FIG. 6A

	REST PHASE				STRESS PHASE				
	INJECTION		WAITING TIME [MIN]	ACQUISITION DURATION [MIN]	STRESS	INJECTION		WAITING TIME [MIN]	GATED ACQUISITION DURATION [MIN]
	RP	DOSE [mCi]				RP	DOSE [mCi]		
SINGLE ISOTOPE/ LOW DOSE/FAST IMAGING	TL	<0.3	2	15	EXERCISE	TL	<3	10-15	1.5
DUAL ISOTOPE/ LOW DOSE/FAST IMAGING	TL	<0.3	2	15	EXERCISE	Tc-MIBI	30	30-60	1.5
GATED REST THALLIUM (STUNNING)	TL	1.5	2	5 (GATED)	EXERCISE	Tc-MIBI	30	30-60	1.5
THALLIUM STRESS PERFUSION	Tc-MIBI	3	30	1.5	PHARMA	TL	3	0	10 (DYNAMIC)
SIMULTANEOUS DUAL ISOTOPE STRESS PERFUSION	Tc-MIBI	3	20		EXERCISE/PHARMA	TL	3		10 (DYNAMIC)
DYNAMIC IMAGING	TL	0.3			PHARMA (ADENOSINE)	TL	3		10 (DYNAMIC)

FIG. 6B

NO.	PROTOCOL NAME	KEY FEATURES AND PROPERTIES	ADMINISTRATION PARAMETERS			DETECTOR PARAMETERS
			DOSE (mCi)	INJECTION PROFILE	INJECT TO ACQUISITION TIME	DETECTED PHOTON ENERGY / RESOLUTION
A	CARDIAC MAPPING	MIBI-TC, FAST, BEFORE LIVER UPTAKE	20-40	BOLUS	2 MIN, OR ADMIN UNDER THE CAMERA	140 KeV / 15%
B	CARDIAC MAPPING	MIBI-TC AFTER LIVER UPTAKE	20-40	BOLUS	30+ MIN	140 KeV / 15%
C	CARDIAC MAPPING	SIMULTANEOUS FAST DUAL-ISOTOPE TL-201+ LOW DOSE MIBI-TC	TL-201: 3.5-5; MIBI-Tc-99m: 4-8	2 BOLUS (BEFORE AND AT PEAK STRESS)	TL INJECTED PREVIOUSLY AT REST, TC UNDER CAMERA OR 2 MIN	Tc-140 KeV, Tl-72 KeV / 15%
D	CARDIAC MAPPING	SIMULTANEOUS DUAL-ISOTOPE TL-201+ LOW DOSE MIBI-TC	TL-201: 3.5-5; MIBI-Tc-99m: 4-8	2 BOLUS (BEFORE AND AT PEAK STRESS)	SAME AS ONE OF FIRST 2 CARDIAC MAPPING PROTOCOLS	Tc-140 KeV, Tl-72 KeV / 15%
E	CARDIAC MAPPING	SIMULTANEOUS DUAL-ISOTOPE FULL TL-201+ FULL DOSE MIBI-TC	TL-201: 3.5-5; MIBI-Tc-99m: 20-40	2 BOLUS (BEFORE AND AT PEAK STRESS)	SAME AS ONE OF PROTOCOLS A OR B	Tc-140 KeV, Tl-167 KeV / 10%
F	CARDIAC MAPPING - UNDERWEIGHT (**BMI<18.5**)	MIBI-TC-99M AFTER LIVER UPTAKE	15-20	BOLUS	30+ MIN	140 KeV / 15%
G1	CARDIAC MAPPING - NORMAL (**18.6<BMI<24.9**)	MIBI-TC-99M AFTER LIVER UPTAKE	20-30	BOLUS	30+ MIN	140 KeV / 10%
G2	CARDIAC MAPPING - OVERWEIGHT (**25<BMI<29.9**)	MIBI-TC-99M AFTER LIVER UPTAKE	30-35	BOLUS	30+ MIN	140 KeV / 10%

FIG. 6C

NO.	SCANNING PARAMETERS						ANALYSIS PARAMETERS	
	TOTAL SCAN TIME	COLUMNS DIFFERENCES / UNIFORM SCAN	ANGULAR RANGE	TOTAL # ANGULAR ORIENT-TATIONS	ANGULAR STEP / INTERLACE	DWELL TIME	GATED ANALYSIS OF VOLUMES	ANALYSIS ALGORITHM / PARAMETERS
A	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	120X10	a) 0.3-0.5 DEG b) 0.75-1 DEG	1 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
B	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	120X10	a) 0.3-0.5 DEG b) 0.75-1 DEG	1 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
C	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	120X10	a) 0.3-0.5 DEG b) 0.75-1 DEG	1 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
D	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	120X10	a) 0.3-0.5 DEG b) 0.75-1 DEG	1 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
E	UP TO 1200 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	240X10	a) 0.15-0.25 DEG b) 0.375-0.5 DEG	5 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
F	90 SEC	a) 4 X OUTER b) 6 X INNER	a) 20-35 DEG b) 45-60 DEG	60X10	a) .3-.75 DEG b) 0.75-1DEG	1 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
G1	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 30-45 DEG b) 75-90 DEG	120X10	a) 0.5-0.75 DEG b) 0.625-1 DEG	1.5 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
G2	120 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	120X10	a) 0.3-0.5 DEG b) 0.75-1 DEG	2 SEC	YES, 16-32 FRAMES	INTENSITY IMAGE, EJECTION FRACTION

FIG. 6D

NO.	PROTOCOL NAME	KEY FEATURES AND PROPERTIES	ADMINISTRATION PARAMETERS			DETECTOR PARAMETERS
			DOSE (mCi)	INJECTION PROFILE	INJECT TO ACQUISITION TIME	DETECTED PHOTON ENERGY / RESOLUTION
H	CARDIAC MAPPING - OBESE (BMI>30)	MIBI-TC AFTER LIVER UPTAKE	35-40	BOLUS	30+ MIN	140 KeV / 6%
I	CARDIAC DYNAMIC MAPPING	TEBOROXIME-TC	20-40	BOLUS	-1 MIN (IMAGE BEFORE INJECT), OR SIMULTANEOUSLY WITH INJECT	140 KeV / 15%
J	CARDIAC DYNAMIC MAPPING (2-STEP)	TEBOROXIME-TC	20-40	(i) INITIAL SMALL BOLUS FOR IDENTIFYING ROI, (ii) FULL BOLUS FOR DYNAMIC STUDY	(i) 5+ MIN (ii) -1 MIN (IMAGE BEFORE INJECT)	140 KeV / 15%
K	TUMOR SCAN (MULTIPLE BODY SEGMENTS - HEAD TO LEGS)	MDP-TC-99M AFTER LIVER UPTAKE	20-40	BOLUS	30+ MIN	140 KeV / 15%
L	TUMOR SCAN (MULTIPLE BODY SEGMENTS - HEAD TO LEGS), FOCUSED SCAN	MDP-TC-99M AFTER LIVER UPTAKE	20-40	BOLUS	30+ MIN	140 KeV / 15%
M	TUMOR SCAN WITH COCKTAIL (MULTIPLE BODY SEGMENTS - HEAD TO LEGS), FOCUSED SCAN	FDG (METABOLISM), MIBI-TC-99M AND TL (PERFUSION)	TL-201: 3.5-5; MIBI-TC-99M: 20-40; 18-F FDG 10-30	BOLUS	30+ MIN	Tc-140 KeV, Tl-72 KeV, FDG 511 KeV / 10%

FIG. 6E

NO.	SCANNING PARAMETERS						ANALYSIS PARAMETERS	
	TOTAL SCAN TIME	COLUMNS DIFFERENCES / UNIFORM SCAN	ANGULAR RANGE	TOTAL # ANGULAR ORIENT-TATIONS	ANGULAR STEP / INTERLACE	DWELL TIME	GATED ANALYSIS OF VOLUMES	ANALYSIS ALGORITHM / PARAMETERS
H	180 SEC	a) 4 X OUTER b) 6 X INNER	a) 40-60 DEG b) 90-120 DEG	160X10	a) 0.25-0.375 DEG b) 0.6-0.75 DEG	1.2 SEC	YES, 8-16 FRAMES	INTENSITY IMAGE, EJECTION FRACTION
I	<= 600 SEC	a) 2 X OUTER b) 8 X INNER	a) 40-60 DEG b) 90-120 DEG	600X10	a) continuous b) continuous INTERLACED SCAN	1 SEC	YES, 8 FRAMES	KINETIC PARAMETES, PREDEFINED PATHOLOGICAL VALUES
J	(i) 60 SEC FOR IDENTIFYING ROI (ii) 600 SEC DYNAMIC STUDY	a) 2 X OUTER b) 8 X INNER	a) 40-60 DEG b) 90-120 DEG	(i) 60X10 (ii) 600X10	(i) a) 0.75-1 DEG b) 0.75-0.75-1 DEG (ii) a) continuous b) continuous INTERLACED SCAN	1 SEC	YES, 8 FRAMES	KINETIC PARAMETES, PREDEFINED PATHOLOGICAL VALUES
K	240 SEC PER BODY SEGMENT	16	40-60 DEG	120X16	0.3-0.5 DEG	2 SEC	NO	INTENSITY IMAGE, PREDEFINED PATHOLOGICAL VALUES
L	(i) 120 SEC PER BODY SEGMENT (ii) 60 SEC PER ROI	16	(i) 45-60 DEG (ii) 15-20 DEG	(i) 120X16 (ii) 60x16	(i) 0.375-0.5 DEG (ii) 0.25-0.3	1 SEC	NO	INTENSITY IMAGE, PREDEFINED PATHOLOGICAL VALUES
M	(i) 120 SEC PER BODY SEGMENT (ii) 60 SEC PER ROI	16	(i) 45-60 DEG (ii) 15-20 DEG	(i) 120X16 (ii) 60x16	(i) 0.375-0.5 DEG (ii) 0.25-0.4	1 SEC	NO	INTENSITY IMAGE, PREDEFINED PATHOLOGICAL VALUES

FIG. 7

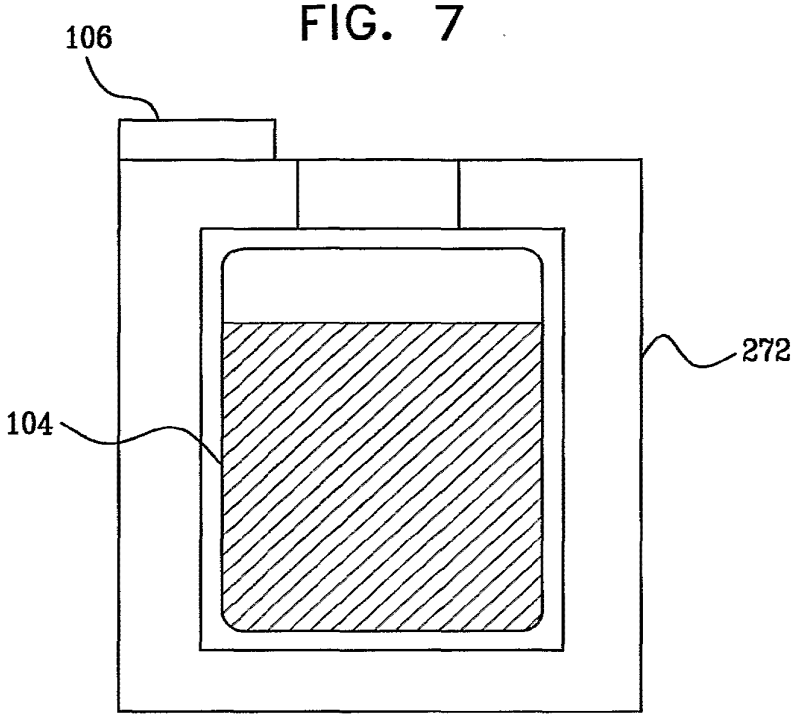


FIG. 8

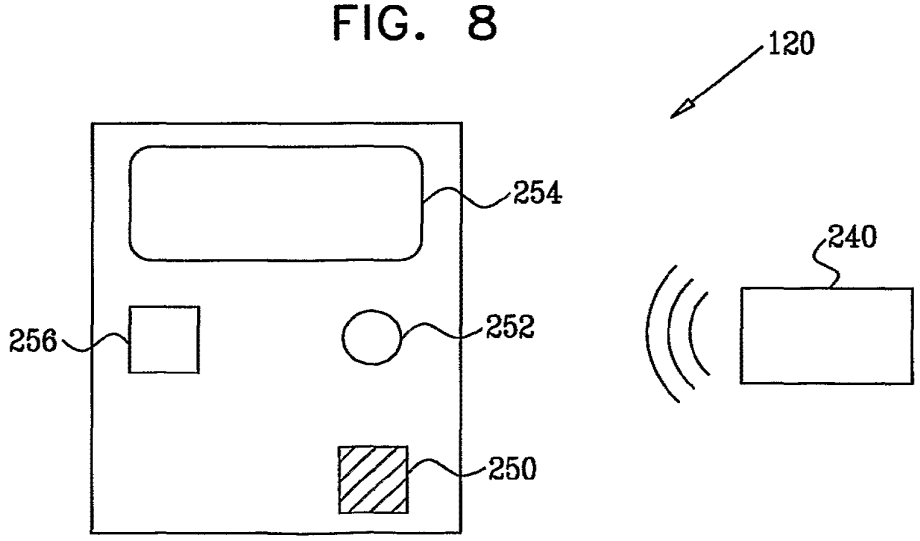


FIG. 9A

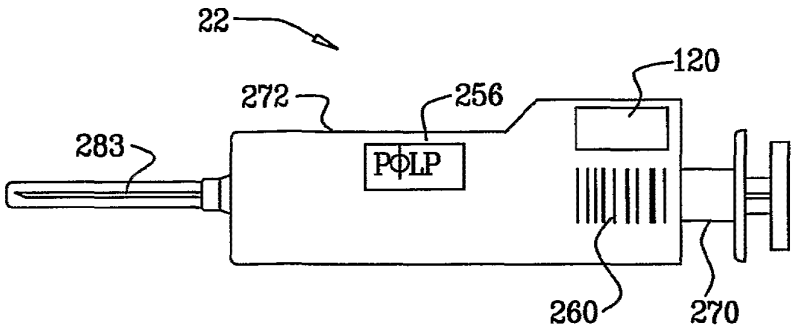


FIG. 9B

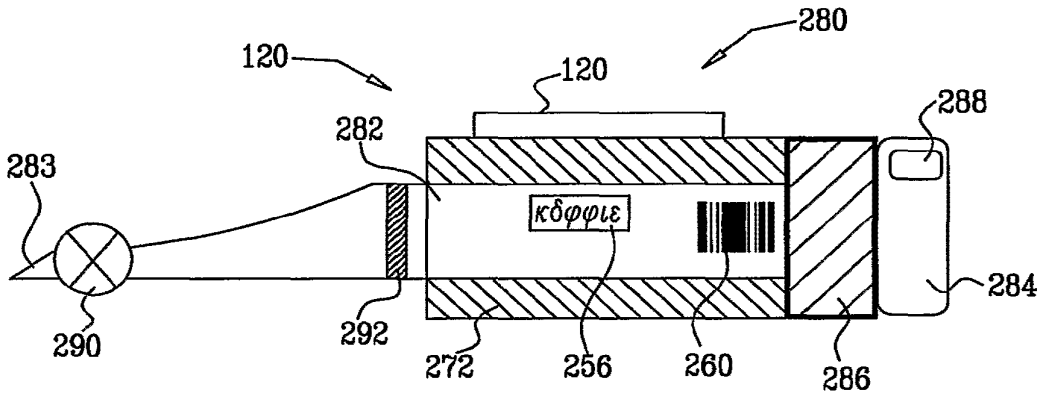


FIG. 9C

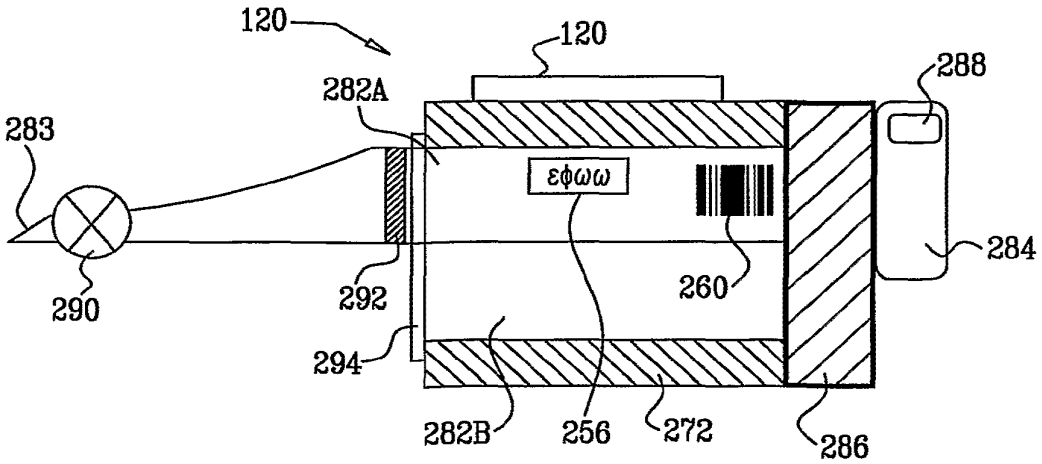


FIG. 9D

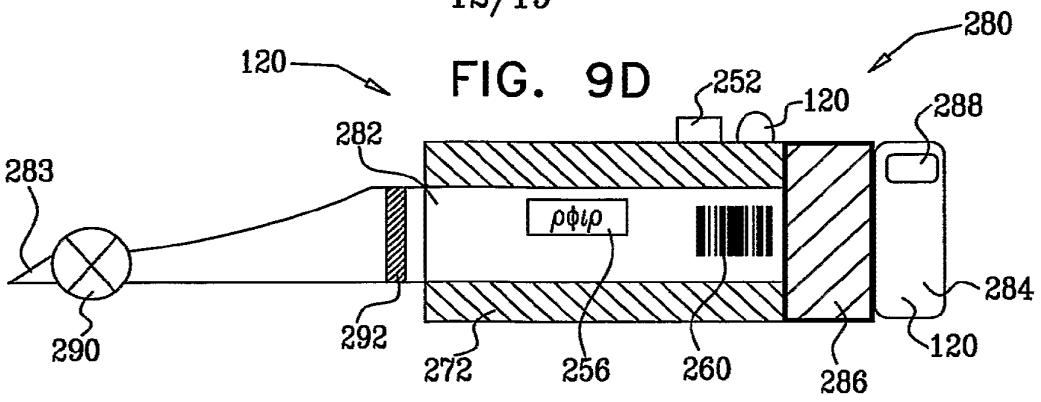


FIG. 9E

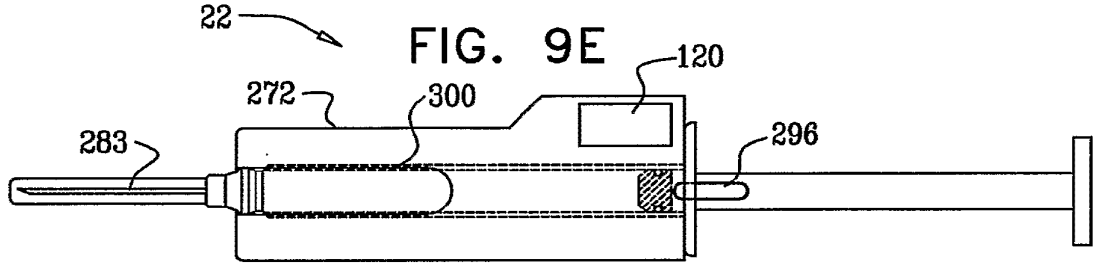


FIG. 9F

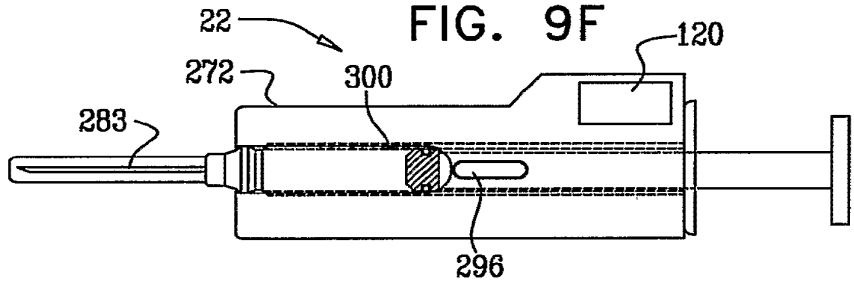


FIG. 9G

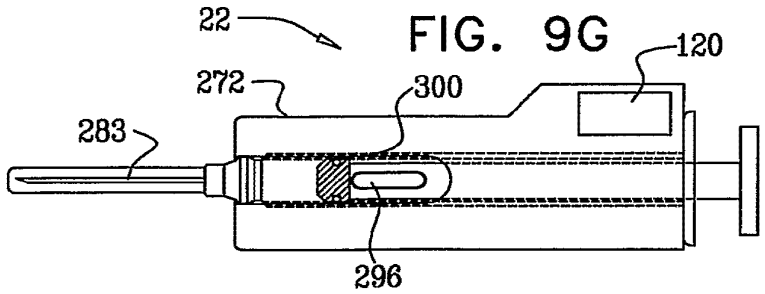


FIG. 9H

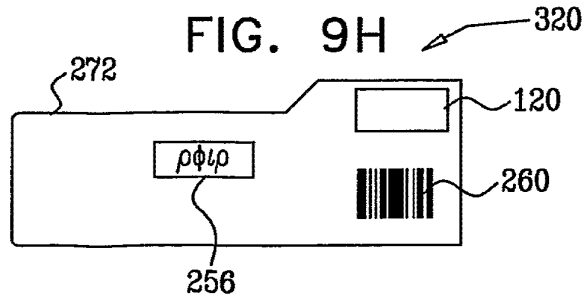


FIG. 10

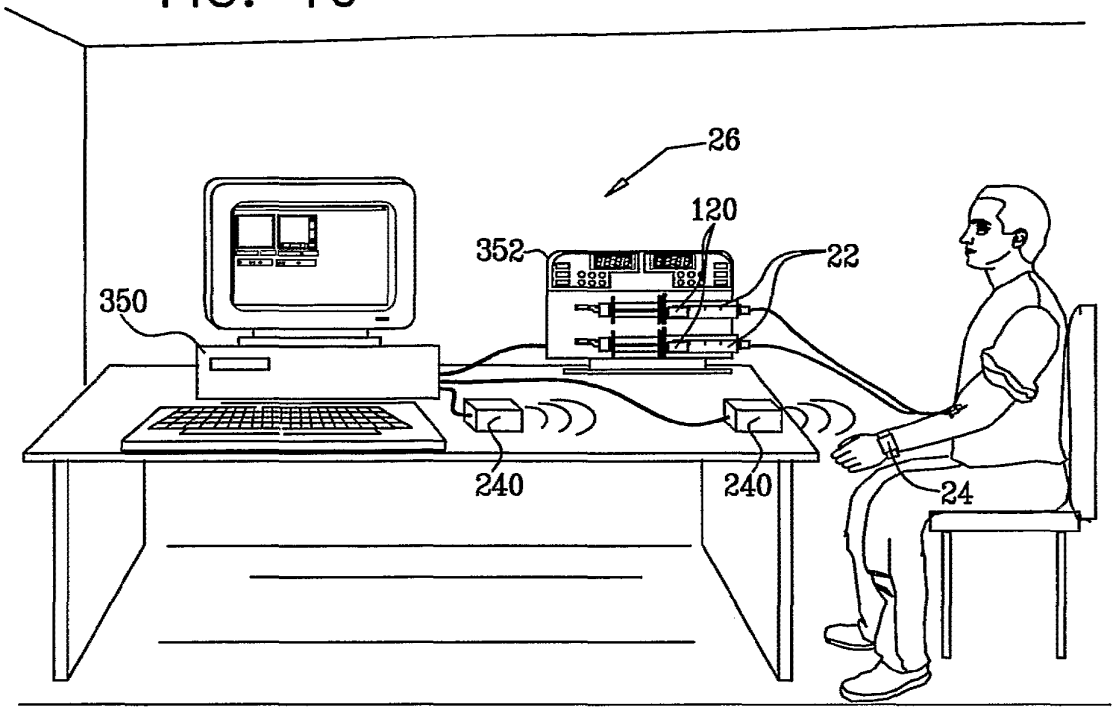
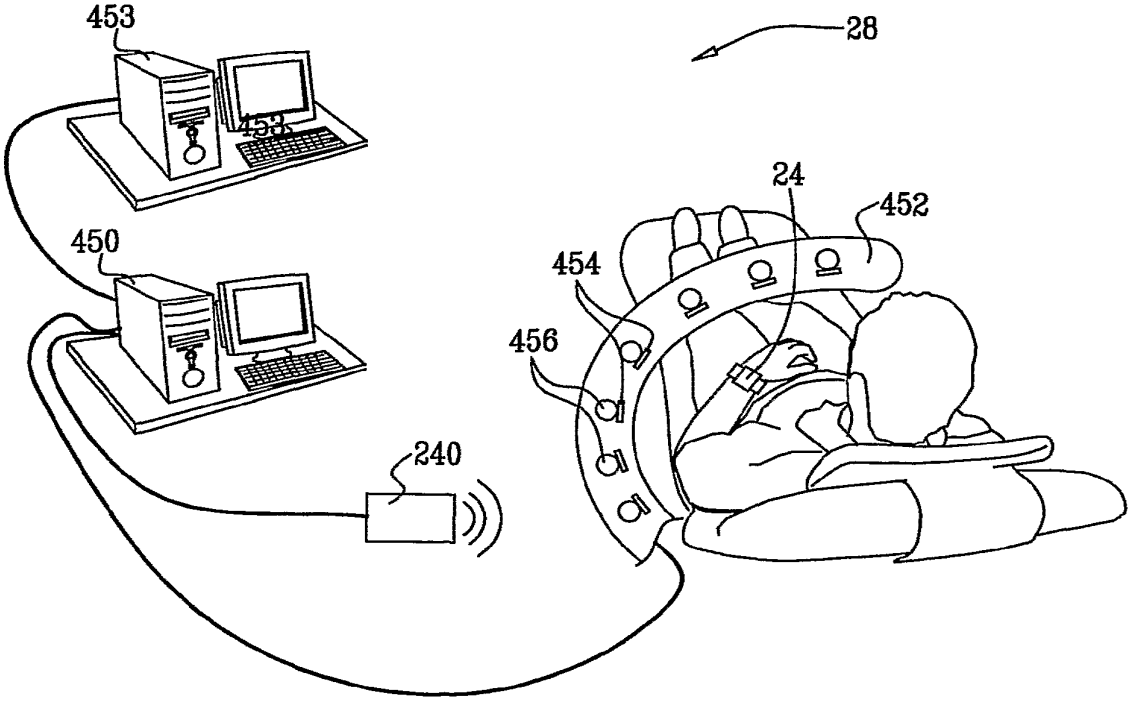


FIG. 11



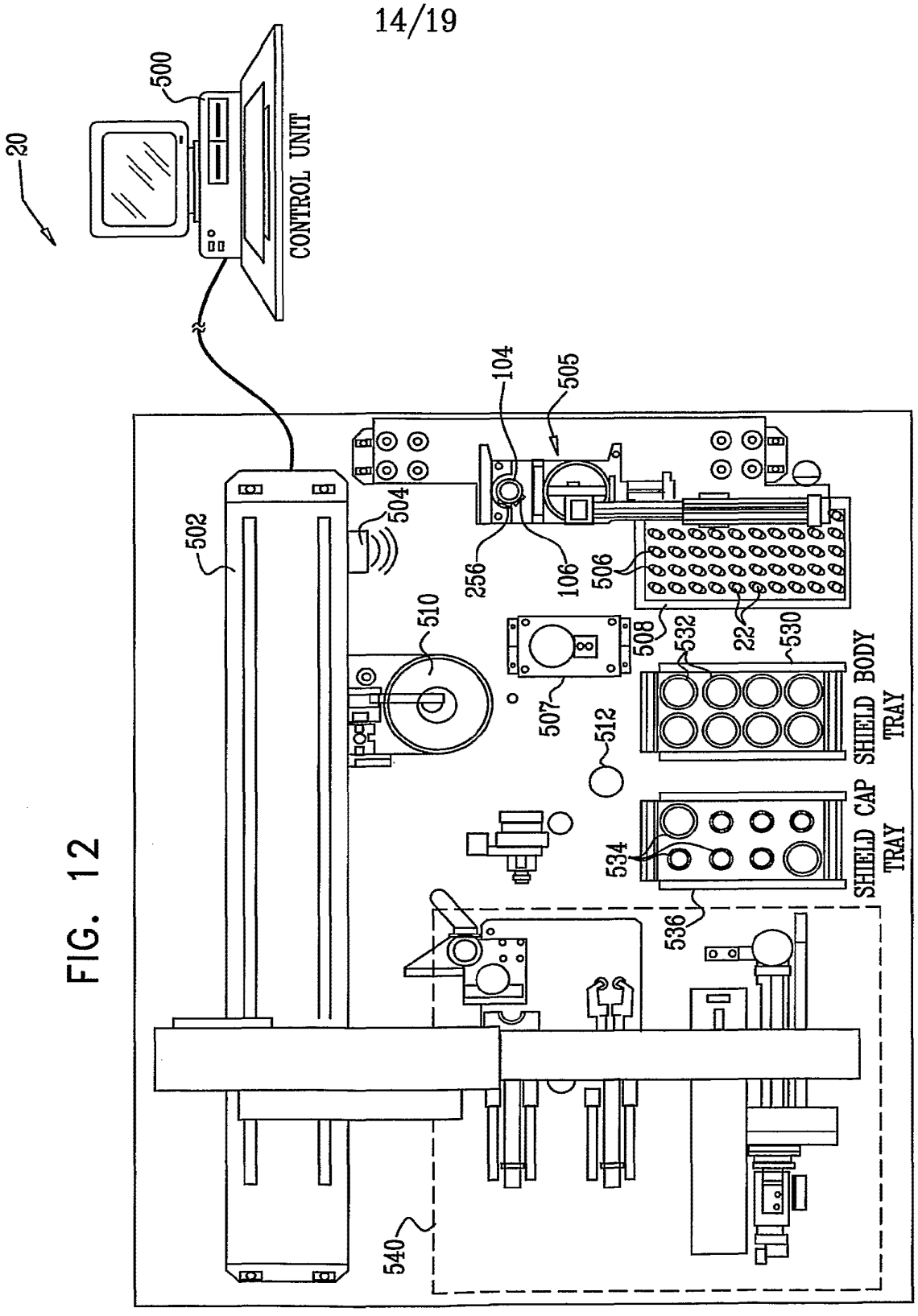

20
500
CONTROL UNIT
104
505
502
504
256
106
506
510
508
532
22
530
507
512
SHIELD BODY TRAY
534
SHIELD CAP TRAY
536
540

FIG. 12

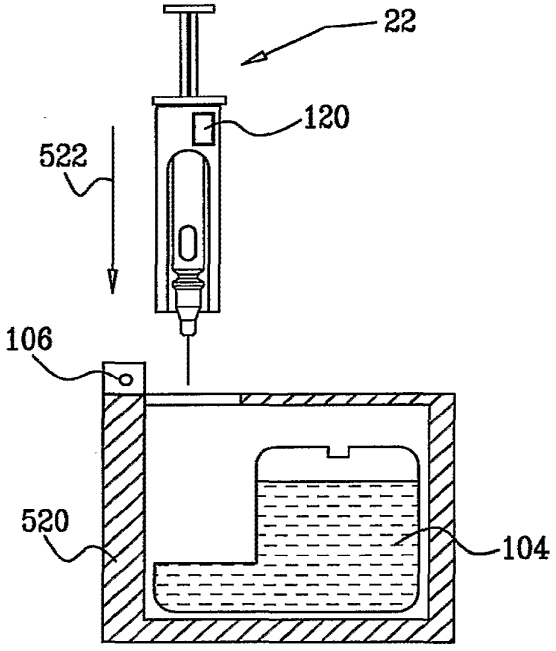


FIG. 13A

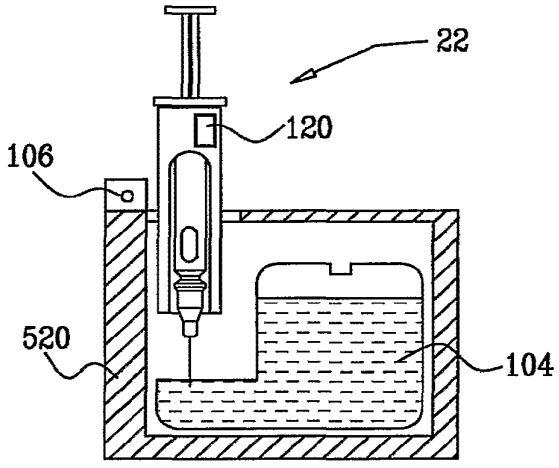


FIG. 13B

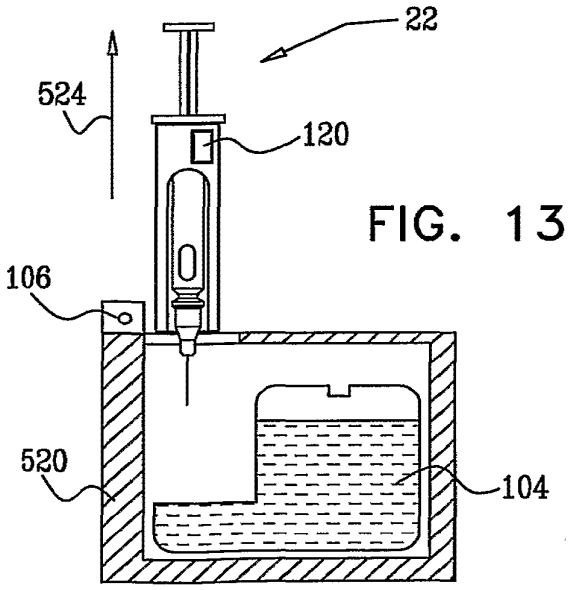


FIG. 13C

FIG. 14

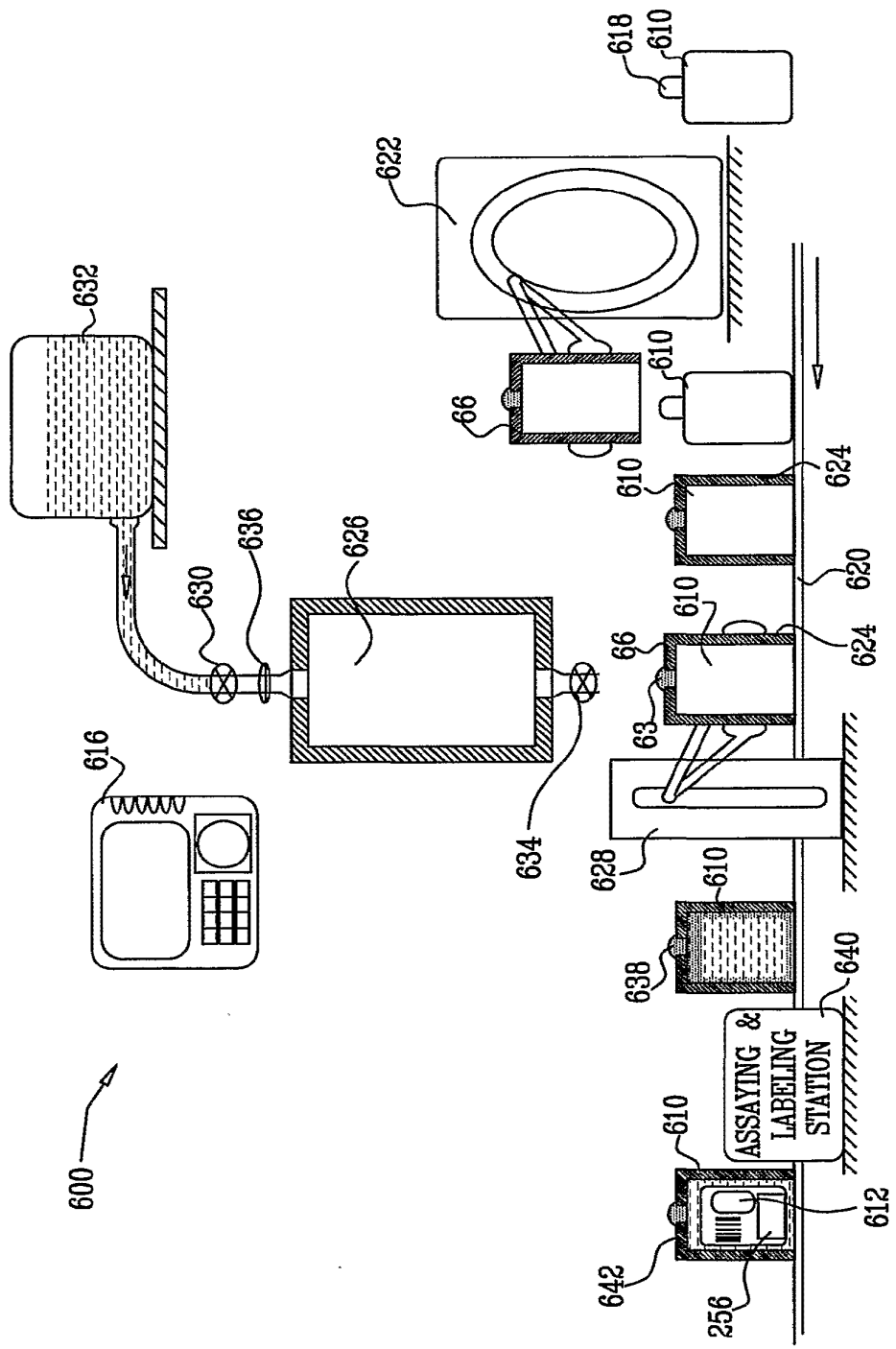

600
616
632
630
636
626
634
622
618
610
66
624
620
63
628
638
640
ASSAYING & LABELING STATION
612
642
256

FIG. 15

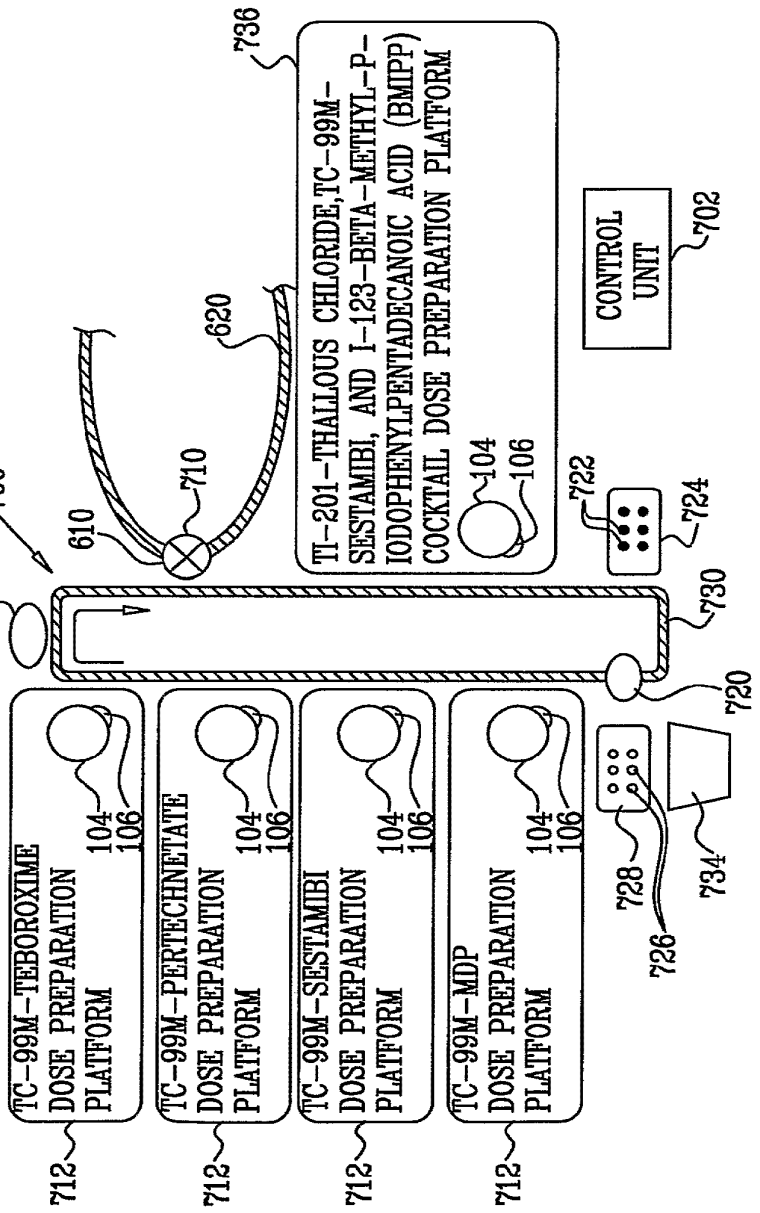

700
732
610
710
620
736
TI-201-THALLOUS CHLORIDE,TC-99M-SESTAMIBI, AND I-123-BETA-METHYL-P-IODOPHENYLPENTADECANOIC ACID (BMIPP) COCKTAIL DOSE PREPARATION PLATFORM
104
106
722
724
730
720
CONTROL UNIT
702
TC-99M-TEBOROXIME DOSE PREPARATION PLATFORM
TC-99M-PERTECHNETATE DOSE PREPARATION PLATFORM
TC-99M-SESTAMIBI DOSE PREPARATION PLATFORM
TC-99M-MDP DOSE PREPARATION PLATFORM
712
728
726
734

FIG. 16A

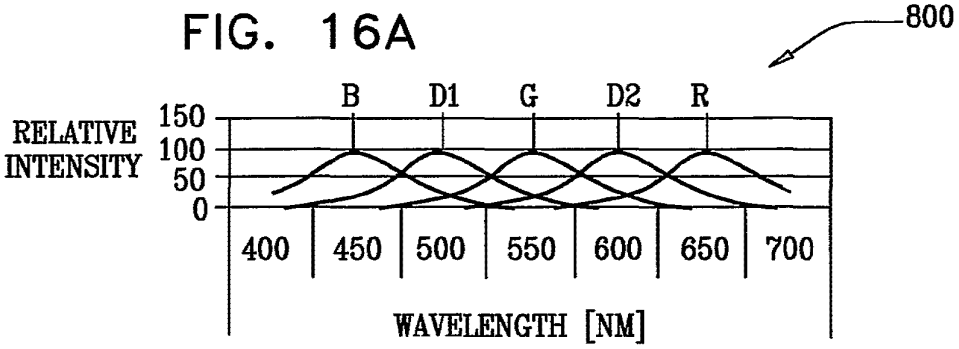


FIG. 16B

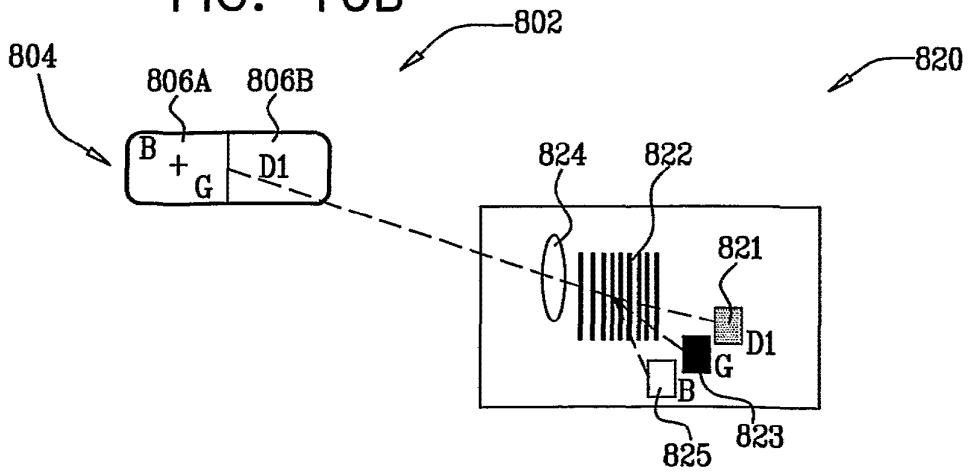


FIG. 17

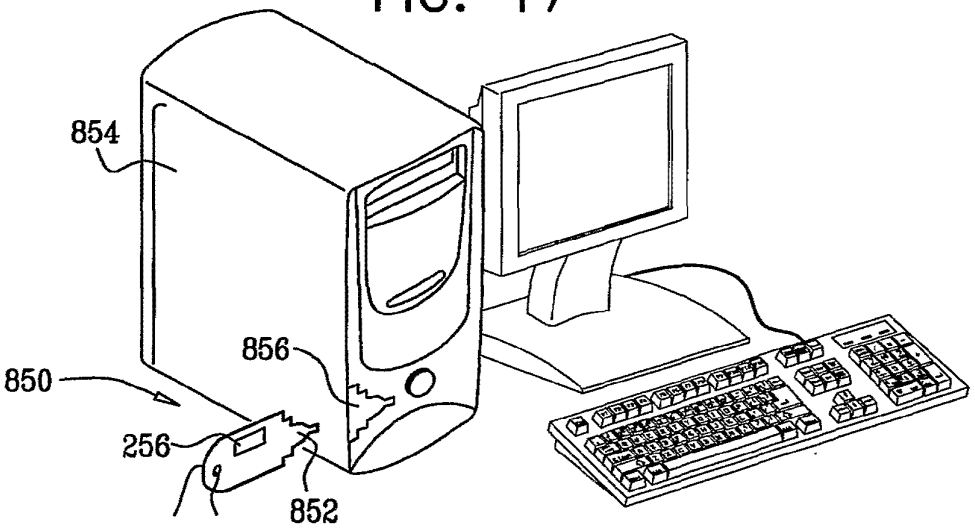
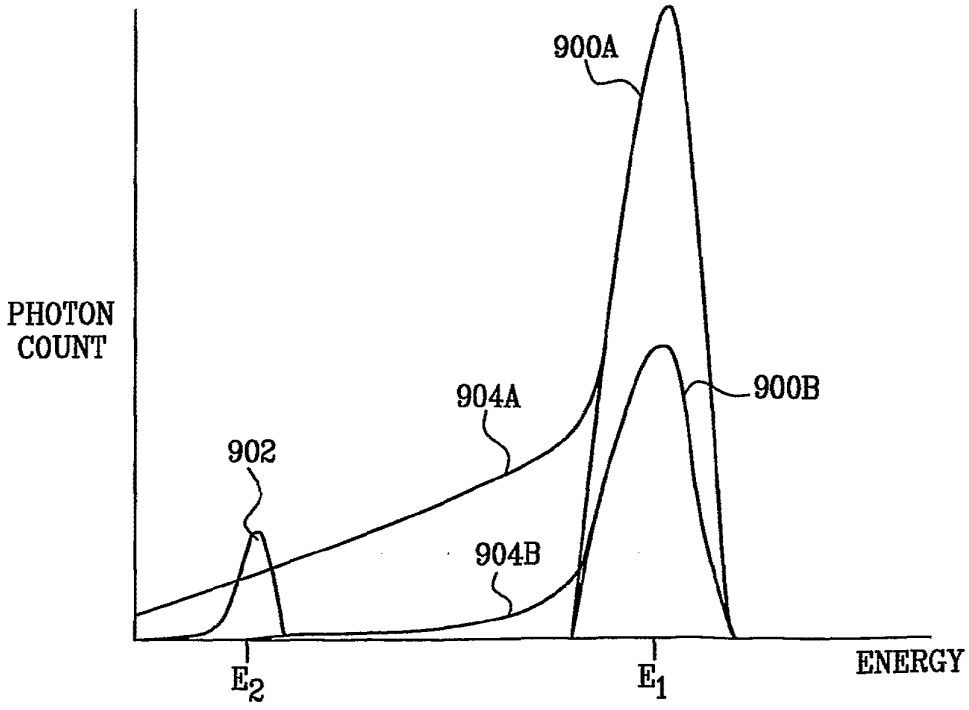

854
856
850
256
852

FIG. 18


900A
PHOTON COUNT
904A
900B
902
904B
E2
E1
ENERGY

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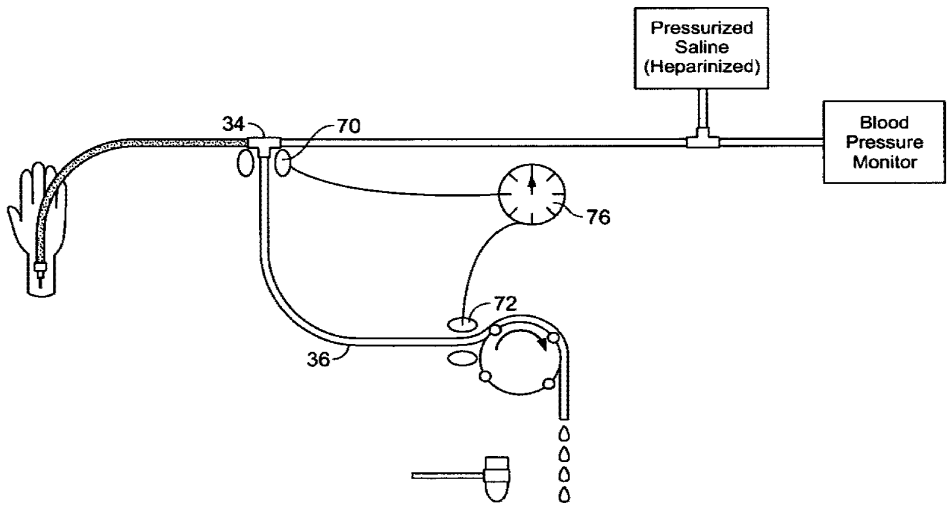
(54) Title: AUTOMATED BLOOD DRAW SYSTEM



(57) Abstract: An automated blood draw system operates in conjunction with an arterial or venous line. The aspiration mechanism allows the rate of aspiration, volume of aspirate, and the time interval of aspiration to be predetermined. Blood can be collected in sequential collection vials for subsequent analysis of a given laboratory parameter, or delivered directly to integrated analysis devices. While a predetermined volume of aspirate can be wasted, excessive aspiration is prevented by monitoring waste obtained in a collection receptacle. A flush system maintains the patency of the line without contamination of the specimen.

WO 2008/028165 A2

TITLE OF THE INVENTION

AUTOMATED BLOOD DRAW SYSTEM

FIELD OF THE INVENTION

(0001) The invention relates to devices used to secure blood samples from humans and animals for purposes of medical studies and patient care. More specifically the invention relates to automated blood drawing devices.

BACKGROUND OF THE INVENTION

(0002) Periodic sampling of blood is important in a number of applications including applications related to medical studies and in monitoring patient progress and/ or overall health. For example, it is often desirable to determine blood glucose levels over time after a meal in order to determine the efficacy of the body in metabolizing glucose, especially as it relates to diabetic care. Traditionally, blood drawn for the purposes of monitoring blood parameters has been done manually. In a hospital or other research or medical environment, a phlebotomist will manually draw blood by accessing a port on an existing venous or arterial line by inserting a needle in a shunt and drawing blood out using a syringe. In order to best assess the patient's health and/or to make the best study of blood and the body systems being analyzed, blood is often drawn at particular intervals known as time-points. When the blood sampling time-points are spread out, it is possible to manually draw blood,

with a needle and syringe, without the need to pre-establish a blood line with an access port.

(0003) In many applications, the time-points needed for periodic blood sampling is large and blood is sampled frequently. In these cases, manual sampling of blood has numerous disadvantages. Often, manual sampling relies on a healthcare professional that has additional responsibilities besides sampling blood from the patient. In these cases the risk that a time-point sampling could be delayed or missed entirely is high. However, to avoid missing a time-point sample one or more full time attendants are required. This is an expensive and labor intensive requirement.

(0004) Even where the blood drawing technician timely arrives to sample blood, the temporal resolution of the time-point sampling is low. It is difficult for the technician to accurately determine the exact time that the blood was drawn, and in some cases the difference between the actual time-point sampling versus the desired time-point sampling may vary, for example, by tens of seconds to several minutes. With frequent sampling, such variance is counterproductive to the tests being performed.

(0005) It is therefore an object of the present invention to provide an improved system for obtaining periodic time-point sampling of blood so as to, for example, ease the labor requirements of time-point blood sampling and to significantly reduce or eliminate inherent error in manual blood sampling performed according to the current methodology.

SUMMARY OF THE INVENTION

(0006) It is an object of the present invention to provide for an improved automated blood drawing apparatus. The improved automated blood drawing system allows for accurate and efficient sequential sampling of blood with reduced risk of contamination and ease of use.

(0007) For the purposes of obtaining periodic blood sampling from a patient or research participant, in a first embodiment of the device of the present invention, a 3-way valve assembly is incorporated into a venous or arterial line in close proximity to a patient. The valve assembly is comprised of a first, second and third port. The venous or arterial line is connected to a first port of the valve assembly and an isotonic saline source is connected via a fluid line to the second port of the valve assembly. The first and second ports are thereby configured as fluid entry points into the valve assembly. The third port is attached to aspiration tubing for the purpose of draining the valve assembly into, either a sample collecting receptacle or into a waste receptacle, as will be described below. Arterial or venous blood or saline solution may pass through the valve assembly and enter a fluid line connected to the third port of the valve assembly. The valve assembly is configured to alternatively inhibit the flow of blood or the saline solution depending on the valve assembly setting.

(0008) In one embodiment of the invention, the valve assembly is a commercially available 3-way stopcock assembly. The 3-way stopcock assembly may be

manually controlled; however, automated control is preferred and provided for in embodiments of the present invention. Automated control may be accomplished, in one embodiment, by a rotary servo motor clamped to a stopcock assembly comprised of the 3-way stopcock and a durable holding device or base. The 3-way stopcock is used to control the flow of fluids from a set of tubes attached, respectively, to the source of blood and to a source of flushing solution.

(0009) As will be understood by those having ordinary skill in the art, the automated or manual control of the valve assembly as configured in one embodiment will allow for the valve be used to open and/or close, alternatively, two separate positions (blood and flushing solution) in the system. Therefore, when the valve assembly is connected to tubing as described above and the stopcock is turned to a first position, either manually or through automation, saline solution will be drawn from its source, through the stopcock from the fluid line attached at the second port and into aspiration tubing attached at the third port of the valve assembly. Alternatively, when the stopcock is in a second position, saline solution is prohibited from flowing through the valve body and into the aspiration tubing. Instead, blood will flow from the arterial or venous line, though the valve body and into the aspiration tubing. It will be understood by persons having ordinary skill in the art that a stop position can be included in the valve assembly or that a separate valve can be installed

upstream of the main valve assembly in the saline solution line such that the flow of fluid can be stopped completely as needed.

(00010) Fluid flow through the plurality of fluid lines is controlled by an infusion pump. Activation of the infusion pump results in fluid flow from the venous or arterial line or from the saline source depending on the setting of the valve assembly. In a preferred embodiment of the invention, the infusion pump is pre-programmed for a specific fluid flow rate, to allow for a specific volume of fluid and/or to operate for a specific period of time. In this way, the healthcare professional can predetermine the volume of blood to be drawn from a patient at a specific blood sampling time-point.

(00011) The infusion pump used in such embodiments acts in coordination with an automated control system for the valve assembly. Coordination of the infusion pump and automated valve assembly may be accomplished via serial port programming of the infusion pump and valve assembly control. For example, PC based systems used to control anesthetic drug infusions have been adapted for use with a variety of commercially available medical infusion pumps. Alternatively, the infusion pump may be independently operated by a relay switch controlling power to the infusion pump while the valve assembly is manually or independently automatically operated.

(00012) For example, when a sampling of blood is desired, the valve assembly is automatically set to allow blood from the venous or arterial line to flow through the valve assembly and into the aspiration tubing. When the desired

amount of blood has been obtained, the valve assembly may be automatically programmed to inhibit flow from the arterial or venous line and to allow fluid flow from the saline source into the aspiration tubing. Flushing of the aspiration tubing following blood sampling is desired. Once flushing of the aspiration tubing has been obtained, the infusion pump is programmed to shut off until the next scheduled blood sampling time-point.

(00013) Blood flowing into the aspiration tubing is collected for simultaneous or subsequent analysis of a given blood parameter or for blood drug concentration. Blood may be collected upon exit from the aspiration tubing in a blood collecting vial. Placement of the blood vial in the stream of the blood exiting the aspiration tubing is accomplished automatically via a commercially available fraction collector suitable for the purpose. Alternatively, blood may be collected in a bolus in heat sealable tubing. Date and time stamping of the bolus identifies the samples for subsequent analysis.

(00014) Appropriate safety features are preferably incorporated into the blood drawing apparatus. In those applications where blood exiting the aspiration tubing flows into an open vial, introduction of air into the arterial or venous line is of particular concern. To avoid the unwanted introduction of air, prior flushing of the aspiration tubing prior to a given sampling may be accomplished. Alternatively, an infusion pump may be incorporated with an internal sensor able to detect air entering the fluid lines. Other safety features, such as

pressurized expulsion of blood from the aspiration tubing may be used independently or in coordination with other safety features of the system.

(00015) Malfunction and erroneous programming of the automated blood drawing apparatus is of particular concern as it may result in excessive pumping of venous or arterial blood from the a patient, or infusion of excessive saline into the venous or arterial line attached to the patient. A float sensor may be incorporated into an overflow tank so as to monitor excessive wasting of blood or saline flowing from the aspiration tubing. An alarm may be activated when the waste tank contents reach a predetermined level and power from the infusion pump may be automatically cut. Alternatively, an optical sensor may be incorporated at a desired location in at least one of the plurality of fluid lines so as to detect and calculate the volume of blood flowing through the tubing at a given sampling time. Once the volume exceeds a predetermined limit the user is notified or the system may be programmed to automatically shut off. Other sensing devices may be used independently or in addition to the safety features already described, such as mechanical, ultrasonic, or other acceptable flow sensing technologies.

(00016) An automated blood drawing apparatus consistent with the present invention may be adapted for use in systems currently established for manual blood drawing and monitoring. For example, manual systems have been developed for simultaneous monitoring of blood pressure in between blood sampling.

These systems may be successfully adapted utilizing the automated features described herein.

(00017) Other modifications and improvements of currently available and described devices will become apparent to those skilled in the art from the detailed description of the invention below. The current invention is not limited by the specific and preferred embodiments described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

(00018) Further objects of the invention, together with additional features contributing thereto and advantages occurring therefrom, will be apparent from the following description of the invention when read in conjunction with the accompanying drawings; wherein:

(00019) FIG. **1** depicts a schematic representation of a single time-point sampling of blood by an automated blood drawing apparatus according to a specific embodiment of the present invention;

(00020) FIG. **2** depicts a schematic representation of the blood collection vials on a carousel-type device and a waste collector all used in association with a specific embodiment of the present invention;

(00021) FIG. **3** depicts a specific embodiment of the automated blood draw device incorporated into an arterial line pre-established to monitor blood pressure;

(00022) FIG. **4** depicts a specific embodiment of the automated blood draw device utilizing optical sensors and a timing element to improve efficiency of the device;

(00023) FIG. **5** depicts a specific embodiment of the automated blood draw device wherein coordination of apparatus components is accomplished via a single computer;

(00024) FIG. **6** depicts a specific embodiment of the automated blood draw device wherein sampled blood is collected in a bolus of pliable material;

(00025) FIG. **7** depicts another specific embodiment of the automated blood draw device wherein sampled blood is collected in a bolus of pliable material.

DETAILED DESCRIPTION OF THE INVENTION

(00026) While the present invention is susceptible of embodiment in various forms, there is shown in the drawings and will hereinafter be described a presently preferred embodiment with the understanding that the present disclosure is to be considered an exemplification of the invention and is not intended to limit the invention to the specific embodiments illustrated. It should be further understood that the title of this section of the specification, namely "Detailed Description of the Invention", relates to a requirement of the United States Patent Office, and does not imply, nor should be inferred to limit the subject matter disclosed herein.

(00027) Referring to **FIG. 1**, In a particular embodiment of the present invention a valve assembly is comprised of a 3-way stopcock **8**, a solid base and a rotary servo motor, all of which are known to persons having ordinary skill in the art. Disposable 3-way stopcocks appropriate for the patient environment are commercially available and preferred for their ease of use. The 3-way

stopcock is provided with means for selectively determining the position of an internal valve within the stopcock body to allow fluid flow through the stopcock body from one of two input ports and out of a third port.

(00028) A solid base, such as of metal or hard plastic, is provided to receive and securely clamp the stopcock body. Ideally, placement of the stopcock valve assembly at the base is accomplished without tools. For example, the stopcock assembly may be placed by press fitting the assembly to the base. The solid base may also be associated with means providing easy access by a health care professional to the 3-way stopcock. Additionally, a rotary servo motor may be clamped to the stopcock body and base to allow automated operation of the internal valve so as to determine at least two positions of the valve. The rotary servo motor in conjunction with the 3-way stopcock and solid base comprises the valve assembly.

(00029) It will be apparent to one skilled in the art that the invention is not limited to the specific valve assembly described. For example, the 3-way stopcock may be replaced in appropriate applications with a 1-way or 4-way stopcock incorporated into the previously described valve assembly. Alternatively, T-branches as commonly known in the art may be used to interconnect tubing. A T-branch is comprised of a first, second and third port that can accept the blood line **2**, flushing line **4** and aspiration line **6** of **FIG. 1** respectively. In lieu of the valve apparatus of the stopcock, multiple blunt pinchers may be used to facilitate or inhibit fluid flow in the plurality of fluid lines. Before

use, the interconnected tubing would be pressed into the jaws of the pinchers. In one embodiment of the invention, servo motors may be used to control the pinchers, enabling one or more sections of tubing to be pinched closed while simultaneously releasing one or more sections of tubing, thereby facilitating fluid flow. Other modifications of the valve assembly consistent with the spirit and scope of the present invention will be obvious to those skilled in the art. The preceding is included for completeness of the description and while numerous elements described are not shown in the illustration, persons having ordinary skill in the art will understand the use and placement of such elements.

(00030) Referring now to **FIG. 1**, in one particular embodiment of the invention utilizing a valve assembly with a 3-way stopcock, the 3-way stopcock **8** valve assembly is associated with a patient blood line **2**. The blood line **2** is connected at an origin position to a patient, in a manner well known to medical and research professionals, and at a terminal position to a first port **10** of the 3-way stopcock **8**. Preferably, the length of the blood line **2** is kept small so the total volume of blood required to fill the blood line is minimized and excessive blood waste from the patient is avoided. In an alternative embodiment of the invention, the blood line is a previously established venous or arterial line wherein the valve assembly is incorporated into the venous or arterial line at a position in close proximity to the patient.

(00031) A fluid line **4** is connected at an origin position to a flushing solution source **16** and at a terminal position to a second port **12** of the 3-way stopcock **8** valve assembly. It will be understood by persons having ordinary skill in the art that the flushing solution will be utilized to cleanse the valve and aspiration tubing preceding each blood sampling as will be described in detail below. In a specific embodiment of the invention, the flushing solution source **16** attached to the origin of the fluid line **4** is comprised of an isotonic saline solution. In some applications it may be desirable to utilize an isotonic flushing solution with additives, such as heparin, to better effectuate clearing of the automated blood apparatus of blood in between sampling. The flushing solution is utilized in applications according to the invention so as to flush the stopcock valve and the aspiration tubing after a given sampling of blood and to further ensure fluid flow through the stopcock valve and the plurality of fluid lines does not become obstructed.

(00032) Finally, aspiration tubing **6** is connected at an origin position to a third and final port **14** of the 3-way stopcock **8** valve assembly. The terminus of the aspiration tubing allows for elimination of fluid originating from either the blood line **2** or the fluid line **4** into appropriate collecting means or into a waste collection tub **26** (see **FIG. 2**). Where it is desired to incorporate the valve assembly into a pre-existing venous or arterial line, the pre-existing line is cut and the cut termini of the venous or arterial line are attached at the first and third ports of a 3-way stopcock as previously described, forming the

blood line and the aspiration tubing respectively. The flushing line **4** is then established as previously described.

(00033) Referring now to **FIG. 1A**, when the 3-way stopcock is manually or automatically set to a first position the flushing solution **16** is drawn into the flushing line **4**, through the stopcock **8** and into the aspiration tubing **6** attached at the third port of the stopcock. Flushing solution is prohibited from entering the blood line **2** attached to the first port of the stopcock. Alternatively, as shown in **FIG. 1B**, when the 3-way stopcock is set to a second position blood is drawn into the blood line **2**, through the stopcock **8** and into the aspiration tubing **6**. Blood is prohibited from flowing into the fluid line **4** attached to the second port of the stopcock when the stopcock is in either the first or second position. Flushing solution and blood passing through the stopcock body and into the aspiration tubing is collected, wasted and/or analyzed as described in detail herein.

(00034) Referring generally to **FIG. 1**, fluid flow from the flushing solution source **16** or from the blood line **2** is controlled by an infusion pump **18**. When the infusion pump is inactive, fluid flow through the stopcock body **8** is inhibited. Upon activation of the infusion pump, fluid flows through the stopcock body **8** and into the aspiration tubing **6**. Activation of the infusion pump may be manually effectuated. Alternatively, in a preferred embodiment of the invention, activation of the infusion pump **18**, the rate of fluid flow into the aspiration tubing **6**, the volume of aspirate, and/or the time interval of

aspiration are pre-programmed and automated. In one embodiment of the invention, an analog infusion pump operable by a relay switch controls power to the infusion pump. Alternatively, serial port programming of the infusion pump **18** can be used to control fluid flow through the stopcock body **8** and into the aspiration tubing **6**. For example, PC based systems used to control anesthetic drug infusions have been adapted for use with a variety of commercially available medical infusion pumps and may be successfully adapted for use with the present invention.

(00035) According to one embodiment of the invention, blood is collected upon exit from the aspiration tubing **6** in a vial **20** of an appropriate size for the application. Preferably, vial placement in the blood stream is accomplished automatically. For example, **FIG. 1** depicts a linear actuator **28** that may be used to place a vial **20** in one of two positions. A first position, shown in **FIG. 1A**, places the vial **20** out of the stream of fluid flowing from the aspiration tubing **6**. When the linear actuator **28** is in this position, fluid flowing from the aspiration tubing **6** is collected in a waste receptacle. A second position of the linear actuator **28**, shown for example in **FIG. 1D**, places a collection vial **20** in the path of blood flow and allows for the collection of blood exiting from the aspiration tubing **6**.

(00036) Alternatively, it may be desirable to sequentially obtain blood from the aspiration tubing **6** in multiple collection vials. An apparatus, such as a fraction collector able to hold multiple vials and sequentially place them in a

stream of blood flowing from the aspiration tubing may be used. In one embodiment of the invention demonstrated at **FIG. 2**, a rotating tray **22** capable of holding a plurality of vials **24** is used for the purposes of obtaining sequential blood samples automatically and without manual intervention. Flushing solution and stagnant blood exiting the aspiration tubing **6** is collected in a waste tub **26** located beneath the rotating tray **22**. When the waste fluid has been fully cleared from the aspiration line **6**, the rotating tray automatically places the next available collection vial **24** into the blood stream thereby collecting the desired time-point blood sample. In one specific embodiment of the invention, the rotating tray may be coupled with a point-of-care analyzer such as an ACT monitor to analyze blood parameters in the collected sample. While the sample is being analyzed, the adjacent vial is positioned to gather the next sample. This system allows for automation of several samples sequentially. The ACT analysis cartridge may be changed by the health care provider at change of shift or at set intervals.

(00037) Referring again to **FIG. 1**, a time-point sampling of blood from a patient according to one embodiment of the invention is shown. The 3-way stopcock **8** valve is manually or automatically set to a first position to allow flushing solution **16** to flow into the aspiration tubing **6**. The infusion pump **18** is activated manually or automatically to completely flush the stopcock body **8** and the aspiration line **6**, as shown at **FIG. 1A**. Flushing solution exits from the aspiration tubing **6** into a waste receptacle. Adequate flushing of the

aspiration tubing allows for accurate blood sampling and prevents contamination of the aspiration line.

(00038) Referring now to **FIG. 1B** and **1C**, once the aspiration line **6** has been adequately flushed, the stopcock valve is manually or automatically set to a second position, thereby allowing blood to flow through the stopcock body **8** and into the aspiration tubing **6**. The infusion pump **18** is activated manually or automatically to allow blood from the blood line **2** to enter the aspiration tubing **6**. The blood line **2** will be filled with stagnant blood left over from the previous time-point blood sampling and must be eliminated from the system before the time-point blood sample is collected, as shown in **FIG. 1C**. Likewise, flushing solution filling the stopcock body and the aspiration tubing must be eliminated from the system, as shown in **FIG. 1B**. Stagnant blood and flushing solution are eliminated from the system and collected in a waste container. The linear actuator **28** may be manually operated or automated in conjunction with the infusion pump **18** to ensure the vial **20** remains in a first position out of the stream of fluid exiting the aspiration tubing **6** until such time that the flushing solution and stagnant blood have cleared the system.

(00039) In one embodiment of the invention, a second infusion pump may be placed along the blood line **2** between the stopcock **8** and the patient to allow for flushing of the blood line **2** in between blood sampling. The infusion pump is activated at the end of a time-point blood sampling either before or after the aspiration tubing **6** has been flushed. Appropriate flushing solution **16** flows

through the valve body and into the blood line **2**, and toward the patient. The infusion pump may be manually or automatically operated to ensure excessive flushing solution does not enter the blood line **2** and thereby the patient. An appropriate valve assembly is selected in systems calling for flushing of the blood line between time-point blood sampling and other modifications apparent to one skilled in the art are within the scope of the invention.

(00040) Referring now to **FIG. 1D**, the linear actuator **28** is manually or automatically activated to move the collection vial **20** into the stream of blood exiting the aspiration tubing **6**. A time-point sampling of blood is collected manually or automatically. In a preferred embodiment of the invention, the blood sample is collected automatically. The system is pre-programmed to calculate the amount of blood flowing into the aspiration tubing from the patient. System dependent parameters that may be entered by a technician include the length of the blood line **2**, the length of the aspiration tubing **6**, the infusion pump **18** speed or the volume rate of fluid flowing through the aspiration tubing **6** and/ or the volume of blood to be sampled at each time-point. In certain applications, it may be desirable to deliver a quantity of flushing solution to the collection vial, for example, to deliver an additive such as heparin present in the flushing solution. In this manner, vials pre-packaged containing heparin or any other desired additive may be obviated.

(00041) Once the desired volume of blood for a time-point sample has entered the aspiration tubing **6**, the stopcock **8** valve is set to a first position to allow

flushing solution **16** to enter the stopcock body and flow into the aspiration tubing **6**. In this manner, the total volume of blood drawn from the patient at each time-point sampling is carefully calculated and the system may be programmed to minimize wasting. Minimization of wasting is particularly important where a number of time-point blood samples are required over a relatively short period of time.

(00042) After the desired volume of blood has been collected in the collection vial **20**, the linear actuator **28** moves the collection vial out of the stream of blood exiting the aspiration tubing **6**, as shown in **FIG. 1E** and **1F**. To provide for accurate blood sampling and to prevent contamination the aspiration tubing must be flushed between sequential blood draws. The stopcock **8** and aspiration tubing **6** are completely flushed with flushing solution **16**. In one embodiment of the invention, the automated blood draw system is programmed to allow the residual blood and a predetermined amount of flushing solution to pass through the aspiration tubing **6** and into the waste collection container. Flushing is coordinated to avoid collection of flushing solution in the blood collection vials and to minimize blood waste.

(00043) Once the aspiration tubing **6** has been completely flushed, the infusion pump **18** is manually or automatically shut off to inhibit the flow of fluid through the system. The automated blood draw system is inactive until the next scheduled time-point blood sampling is desired. Blood collected in the collection vial **20**

is manually or automatically stored or processed and a new collection vial prepared for the next sampling.

(00044) A specific embodiment of the invention has been described whereby time-point blood samples are collected in collection vials **20**. Alternatively, a time-point blood sample may be collected as a bolus within a heat-sealable sheath of pliable tubing as shown in **FIGS. 6** and **7**. Referring to **FIG. 7**, blood exiting the aspiration tubing is introduced into the pliable collection tubing material **164**. Once the desired volume of blood has entered the collection tubing, heating and pressure means, for example heated wires and pressure rollers, are provided for heat-sealing at a first **182** and second **184** position along the tubing length, thereby creating a bolus **176** of blood of the desired volume. A time-point sample identifying stamp may be pressed into a crimped portion **178** of the pliable material. Air may be evacuated from the bolus prior to heat sealing to ensure the integrity of the sample prior to processing. The heat sealed bolus is then cut from the remaining tubing utilizing, for example, a plurality of cutting elements **170** and **172** adjacent the heating elements **160**, **162**. Flushing of the aspiration tubing may then proceed as previously described and the tubing material advanced for a subsequent sampling.

(00045) In one embodiment of the invention, referring to **FIG. 6**, an automated device for pinching, cutting, and advancement of the pliable collection tubing containing a bolus of blood may utilize first **202** and second **200** rolling

elements positioned adjacent heated wires **204**, **206**. The heated wires may be pre-spaced to an appropriate separation to achieve the desired bolus volume. The heated wires **204**, **206** are capable of pressing in on the pliable tubing **212** while heating the material so as to seal the tubing material upon cooling. A guillotine **208** for cutting the heat sealed bolus is provided adjacent the second roller means. Preferably, when the collected bolus has been sealed from the unused collection tubing, means are provided **210** for time marking either directly to the tubing or to a label attached to the tubing the time at which the blood sample was sealed and any other identifying information that may be helpful when later handling the bolus. Collection tubing used in accordance with the invention should be supplied with sufficient excess material to allow for collection of the desired number of blood samples without the risk of running out of the pliable collection tubing.

(00046) In some applications, it may be desirable to further automate the device to allow for immediate analysis of one or more blood parameters. For example, it is often necessary to perform real-time evaluation of the Activated Clotting Time (ACT) of a given blood sample. In current practice, a health care provider is often required to manually recover a collected sample of blood so as to perform real-time ACT analysis. The present invention may be successfully practiced to automate the ACT analysis so as to provide faster and more efficient blood parameter readings.

(00047) An automated blood sampling device according to a specific embodiment of the present invention may be pre-programmed to periodically determine the Activated Clotting Time of an aspirated volume of blood. Automated means known in the art are adapted to perform ACT analysis of a blood volume collected in a collection vial as previously described and to provide real-time display of ACT. Alternatively, blood may be delivered automatically to a testing apparatus that is moved into the stream of blood exiting the aspiration tubing after a blood sample has been obtained in a collection vial. The testing apparatus is adapted to perform ACT analysis on the sample in the usual way. It will be obvious to one skilled in the art that further automation of the invention to allow for blood parameter analysis is not limited to the specific embodiments described.

(00048) The invention may also be successfully adapted for practice with an arterial line that has been established to monitor blood pressure and to allow the delivery of pressurized saline. In these applications it is possible to allow for the periodic sampling of blood while maintaining the functionality of the blood pressure monitoring system.

(00049) Referring to **FIG. 3**, a normal arterial line **30** is provided with access means in the form of a port **32** adjacent the insertion of the arterial line **30** into a patient. The port **32** provides access to the patient's bloodstream for delivery of medication. Upstream of the port **32**, a 3-way stopcock **34** is inserted by cutting the pre-existing arterial line and attaching the cut termini to a first **50**

and third **52** port of the stopcock body. Aspiration tubing **36** is attached to a second **54** port of the stopcock body. The stopcock **34** is inserted such that the pressurized saline source **38** and blood pressure monitoring means **40** are located upstream.

(00050) Fluid lines incorporating the pressurized saline source **38** and blood pressure monitoring means **40** into the automated blood drawing device are set up in the usual manner. For example, a second 3-way stopcock **46** receives fluid lines from the saline source **38** and blood pressure monitoring means **40** at a second **56** and third **58** port of the stopcock **46** body respectively. The transmission line **60** is attached at an origin to the third port **52** of the stopcock **34** and at a terminus to the third port **62** of the stopcock **46** receiving fluid lines from the saline source **38** and blood pressure monitoring device **40**. The first **34** and second **46** stopcocks may be manually or automatically controlled, for example, utilizing rotary servo motors.

(00051) The saline source **38** connected via the upstream stopcock **46** may be used to flush the aspiration tubing **36** and optionally the arterial line **30** in between time-point blood sampling. The stopcock valves, infusion pump, and linear actuator **44** used to collect sample blood may be manually or automatically controlled. System flushing, blood collection, and wasting of flushing fluid and stagnant blood is accomplished in the manner previously described. The pressurized saline source **38** acts similarly to the flushing solution **16** of **FIG.**

1 when the stopcock **46** valve is set in a first position allowing pressurized saline to flow through the stopcock body and into the transmission line **60**.

(00052) It will be readily apparent to one skilled in the art that pre-programming of the automated blood draw system is preferred. In one embodiment of the invention, multiple programming interfaces may be used to independently control an infusion pump, a stopcock valve assembly comprised of a servo motor and a blood fraction collecting device. User interfaces are commonly associated with commercially available servo motors, infusion pumps and fraction collectors.

(00053) Alternatively, referring to **FIG. 5**, in a preferred embodiment of the invention, a single user interface **104** is provided for programming a computer **106**. For example, a single computer interface **104** may be used to accept programming input to control a servo motor **100**, an infusion pump **18** and vial carousel **102** according to the present invention. Appropriate system parameters are entered into the computer and a microprocessor coordinates the operation of the component parts to achieve the desired result by generating output signals **108**, **110**, **112**. While systems with a single user interface are preferred, the present invention is not limited to single user interface systems or to systems designed for automated operation.

(00054) The computer **106** may also be adapted to receive output signals **114**, **116**, **118** generated by monitoring devices. Monitoring devices may include, for example, a fluid waste container **120** or fluid sensors **122**, **124**. The present

invention is not limited to the specific monitoring devices described herein, and one skilled in the art will recognize obvious modifications that are within the scope of the present invention.

(00055) The automated blood drawing system according to the present invention may be further automated to provide for more precise measuring of blood flow through the stopcock body and into the aspiration tubing. In one embodiment of the present inventions, referring to **FIG. 4**, optical sensor switches are provided in cooperation with timing means and together are adapted to measure the quantity of blood passing through the aspiration tubing at a given sampling. A first optical sensor **70** is placed along the aspiration tubing **36** adjacent the valve body **34**. A second optical sensor **72** is placed along the aspiration tubing **36** at a position downstream of the valve body **34** and before the open end of the aspiration tubing **36**. The optical sensors are able to detect whether blood or flushing solution is flowing through the aspiration tubing **36** adjacent the respective sensor based on the absorption properties of the liquid.

(00056) The first **70** and second **72** optical sensors are provided with means for communicating with a timer **76**. The timer **76** may be, for example, a mechanical timer, a digital recorder, or a computer. In a preferred embodiment of the invention, when blood enters the aspiration tubing **36** from the valve body **34** the first optical sensor **70** sends a signal to a timing computer **76**, resulting in the initiation of the timing clock. When the blood reaches the second sensor **72**, a signal is sent to the timing computer **76**. The

computer then calculates the rate of blood flow through the aspiration tubing **36** based on pre-programmed system parameters and the timing between activation of the first and second optical sensors. This information may be used by the computer to coordinate other system components resulting in efficient blood sampling. Likewise, the optical sensors are able to calculate the rate of flushing solution passing through the aspiration tubing so as to ensure adequate flushing of the line.

(00057) The information obtained from the optical sensors and delivered to the computer may also be used to generate a time stamp for a given time-point blood sampling. The exact timing of the blood draw, the volume of blood obtained, and other pertinent system parameters may be recorded to a database for future reference. Other modifications of the system utilizing optical sensors to coordinate functionality of various components within the scope of the present invention will be apparent to those skilled in the art.

(00058) Consistent with the scope of the invention, appropriate safety features may be incorporated into particular embodiments of the invention. For example, in those applications where collection blood is delivered directly into an open vial, accidental introduction of air into the arterial or venous line is a particular safety concern. Referring to **FIG. 1A**, to prevent unwanted introduction of air into the plurality of fluid lines, isotonic saline solution may be run through the aspiration tubing **6** before the stopcock **8** valve is set to a second position, thereby allowing blood to enter the aspiration tubing **6**. In

addition, the infusion pump **18** may be adapted with an internal alarm programmed to sound when air enters the aspiration tubing **6**.

(00059) In another embodiment of the invention adapted to prevent air from entering the system, blood and saline may be pressure forced through the stopcock body and aspiration tubing rather than allowing sample or waste fluid to drip freely from the terminus of the aspiration tubing and into the desired collection receptacle or waste collector. A valve that opens only after exceeding a minimum pressure may be used since the infusion pump creates pressure downstream of the valve.

(00060) An additional safety consideration is a potential malfunction or erroneous programming of the automated blood draw system that may result in excessive pumping of arterial or venous blood through the aspiration tubing and into the collection container. A fluid float, such as those commonly used to indicate gas level in a closed tank may be used to monitor the level of waste collected in a waste container. An alarm may be programmed to activate when excessive fluid is collected. In an alternative embodiment of the invention, power to the infusion pumps may be cut when the fluid level in the waste container has passed a pre-determined level indicating excessive fluid waste by the system.

(00061) In another embodiment of the invention, an optical system sensitive to the difference in light absorption between clear flushing solution and opaque blood may be used to monitor when blood is being aspirated. Such a device

may be placed at a point along the aspiration tubing before or after the infusion pump. The volume of aspirated blood may be calculated, based for example on the length of time the infusion pump has been operational, volume of through-flow per second for the tubing and infusion pump used, and/or on whether blood or saline was being pumped through the system during the infusion pumps operation. If this blood volume exceeds a pre-set limit of aspiration, the user would be notified and/or power to the infusion pump would be cut.

(00062) In yet another embodiment of the invention, a flow sensor may be placed around or in series with the section of tubing coming from the patient's blood line, before the intersection of the blood line with the saline line, to monitor the amount of blood flowing out of the patient. This flow sensor could be mechanical (e.g., paddle wheel), ultrasonic (e.g., Doppler), or be comprised of other accepted flow sensing technology. When total volume of blood outflow exceeds a pre-set limit of aspiration, the user would be notified and/or power to the infusion pump would be cut. Additional safety features within the scope of the present invention will be apparent to one skilled in the art.

(00063) A specific embodiment of an automated blood drawing apparatus according to the present invention has been described for the purpose of illustrating the manner in which the invention is made and used. It should be understood that the implementation of other variations and modifications of the invention and its various aspects will be apparent to one skilled in the art, and that the

invention is not limited by the specific embodiments described. Therefore, it is contemplated to cover the present invention and any and all modifications, variations, or equivalents that fall within the true spirit and scope of the basic underlying principles disclosed and claimed herein.

CLAIMS

1. An automated blood drawing apparatus for drawing blood samples at scheduled time intervals from a human or animal, comprising:

a branching element capable of transmitting fluid and engaging at least three fluid lines;

the first fluid line being capable of transmitting blood from a human or animal to the branching element;

the second fluid line being capable of delivering a flushing solution from a flushing solution source to the branching element;

the third fluid line being capable of transmitting fluid arriving at the branching element from either the first or second fluid line to collection means located at the terminus of the third fluid line;

the collection means comprising at least one collection receptacle and a waste container;

the collection means being capable of moving the collection receptacle to a first position to allow fluid exiting the third fluid line to empty into the collection receptacle or to a second position to allow the fluid exiting the third fluid line to empty into the waste container, wherein the collection receptacle is moved to a first or second position in response to an input signal;

at least one pumping means capable of initiating fluid flow through the branching element and the plurality of fluid lines upon activation, the pumping means being selectively activated or deactivated in response to an input signal;

at least one selection means for selectively inhibiting fluid flow in at least one of the fluid lines while the pumping means is activated, the selection means being capable of selective activation in response to an input signal;

wherein activation of one or more selection means allows blood to flow from the first fluid line through the branching element and into the third fluid line or allows flushing solution to flow from the second fluid line through the branching element and into either the first or third fluid line;

computer means capable of providing an input signal to the pumping means, the selection means, and the collecting means in response to system generated information;

the system generated information being produced by the computer means in response to programming information entering the computer means from at least one user interface and from at least one monitoring device;

the system generated information resulting in output signals allowing for coordination of the pumping means, selection means, and the collecting means such that efficient blood sampling occurs at scheduled time intervals without excessive blood waste.

2. An automated blood drawing apparatus according to claim **1**, wherein the collection means is comprised of a fraction collector and a waste receptacle;

the fraction collector being comprised of a carousel tray and a plurality of collection receptacles;

wherein in response to an input signal, the carousel tray is moved to a first position whereby one of a plurality of collection receptacles is placed into a stream of fluid exiting the third fluid line;

wherein in response to a second input signal, the carousel tray is moved to a second position whereby the first collection receptacle is moved out of the stream of fluid exiting the third fluid line, fluid exiting the fluid line thereby being collected in a waste container located beneath the carousel tray;

wherein subsequent input signals result in the carousel tray being moved so as to place additional collection vials sequentially in and out of the stream of fluid exiting the third fluid line.

3. An automated blood drawing apparatus according to claim **1**, wherein a monitoring device determines the volume of fluid in the waste receptacle;

said monitoring device being capable of generating an output signal to the computer means when the fluid level in the waste container exceeds a pre-determined level;

said output signal resulting in sounding of an alarm and deactivation of the pumping means, thereby preventing excessive blood or flushing solution aspiration.

4. An automated blood drawing apparatus according to claim **1**, wherein the blood is captured in a bolus of pliable tubing.

5. An automated blood drawing apparatus according to claim **4**, wherein the pliable tubing is sealed at one end and the collection means is further comprised of sealing means, cutting means and advancement means;

the pliable tubing material being capable of softening in response to an application of a specific temperature stimulus, whereby removal of the temperature stimulus results in the pliable material hardening relative to its softened state;

the sealing means being comprised of at least two heating elements, each capable of applying heat or pressure at two positions tangent to the pliable tubing, said tangents being parallel one to the other;

the advancement means being capable of advancing a section of pliable tubing into a position relative to the sealing means such that the first heating element is located at a position adjacent a cut end of the pliable tubing and the second heating element is located at position below the first heating element;

the second heating element is capable of applying heat and pressure to the pliable tubing in response to an input signal, whereby application of heat and pressure to the pliable tubing results in melting of the pliable tubing and a sealing of the tubing upon cooling;

the collection receptacle formed by sealing at the second heating element is capable of accepting fluid from the open end of the third fluid line when placed in the stream of fluid;

the first heating element is capable of applying heat and pressure to the pliable tubing of the collection receptacle in response to an input signal generated once fluid has been introduced into the receptacle, whereby application of heat and pressure to the open end of the collection receptacle results in melting of the pliable tubing and sealing of the collection receptacle, thereby creating a bolus of fluid;

the cutting means is capable of cutting the sealed bolus from the remainder of the pliable tubing;

after cutting, the advancement means is capable moving the bolus out of proximity of the sealing means and advancing additional pliable tubing into a position relative to the sealing means.

6. An automated blood drawing apparatus according to claim **4**, wherein fluid exiting the third fluid tube enters a length of pliable tubing and exits into a waste receptacle;

the pliable tubing being positioned along a surface;

first and second heat sealing elements are positioned along a length of pliable tubing,

the heat sealing elements being capable of pressing the pliable tubing down on the flat surface, thereby heating the pliable material and adhering it to itself upon cooling;

the pliable tubing is sealed so as to obtain a bolus of blood in the tubing between the first and second sealed portion;

cutting means cutting the pliable tubing adjacent the sealed portion so as to free the bolus of blood from the remaining tubing material;

a cutting means further cutting the pliable tubing so as to allow fluid to flow through the remaining pliable tubing and into a waste container.

7. An automated blood drawing apparatus according to either of claims **5** and **6**, wherein system generated information is affixed or stamped to the bolus.

8. An automated blood drawing apparatus according to claim **1**, wherein a monitoring device is comprised of at least two optical sensors in communication with a timing means;

the first optical sensor being located at a position along the third fluid line and adjacent the branching means;

the second optical sensor being located at a position along the third fluid line downstream of the first optical sensor;

the timing means being capable of monitoring time;

the first and second optical sensors being capable of generating an output signal to the timing means in response to changes in the opacity of fluid flowing through the third fluid line;

the first output signal being generated when a change in opacity indicates either blood or flushing solution has entered the third fluid line, said output signal resulting in the timing means polling time;

the second output signal being generated when a change in opacity indicates either blood or flushing solution has reached a position along the third fluid line corresponding to the location of the second optical sensor, said output signal resulting in the cessation of time polling by the timing means, whereby the polled time may be used by the computer to generate system generated information.

9. An automated blood drawing apparatus for drawing blood samples at scheduled time intervals from a human or animal, comprising:

at least two branching elements each capable of transmitting fluid and engaging at least three fluid lines;

the first fluid line of the first branching element is comprised of a blood line being capable of transmitting blood from a human or animal to the first branching element;

the second fluid line of the first branching element being capable of delivering a flushing solution from a flushing solution source to the first branching element;

the third fluid line of the first branching element being comprised of an aspiration line being capable of transmitting fluid arriving at the first branching element from either the blood or second fluid line to collection means located at the terminus of the aspiration line;

the second branching element being incorporated upstream of the second fluid line, such that the second branching element also engages the second fluid line;

the first fluid line of the second branching element is comprised of a flushing line capable of delivering a flushing solution from a flushing solution source through the second branching element to the second fluid line;

the third fluid line of the second branching element is comprised of a monitoring line attached to a blood pressure monitoring device capable of monitoring the blood pressure of a human or animal;

the collection means comprising at least one collection receptacle and a waste container;

the collection means being capable of moving the collection receptacle to a first position to allow fluid exiting the third fluid line to empty into the collection receptacle or to a second position to allow the fluid exiting the third fluid line to empty into the waste container, wherein the collection receptacle is moved to a first or second position in response to an input signal;

at least one pumping means capable of initiating fluid flow through the branching elements and the plurality of fluid lines upon activation, the pumping means being selectively activated or deactivated in response to an input signal;

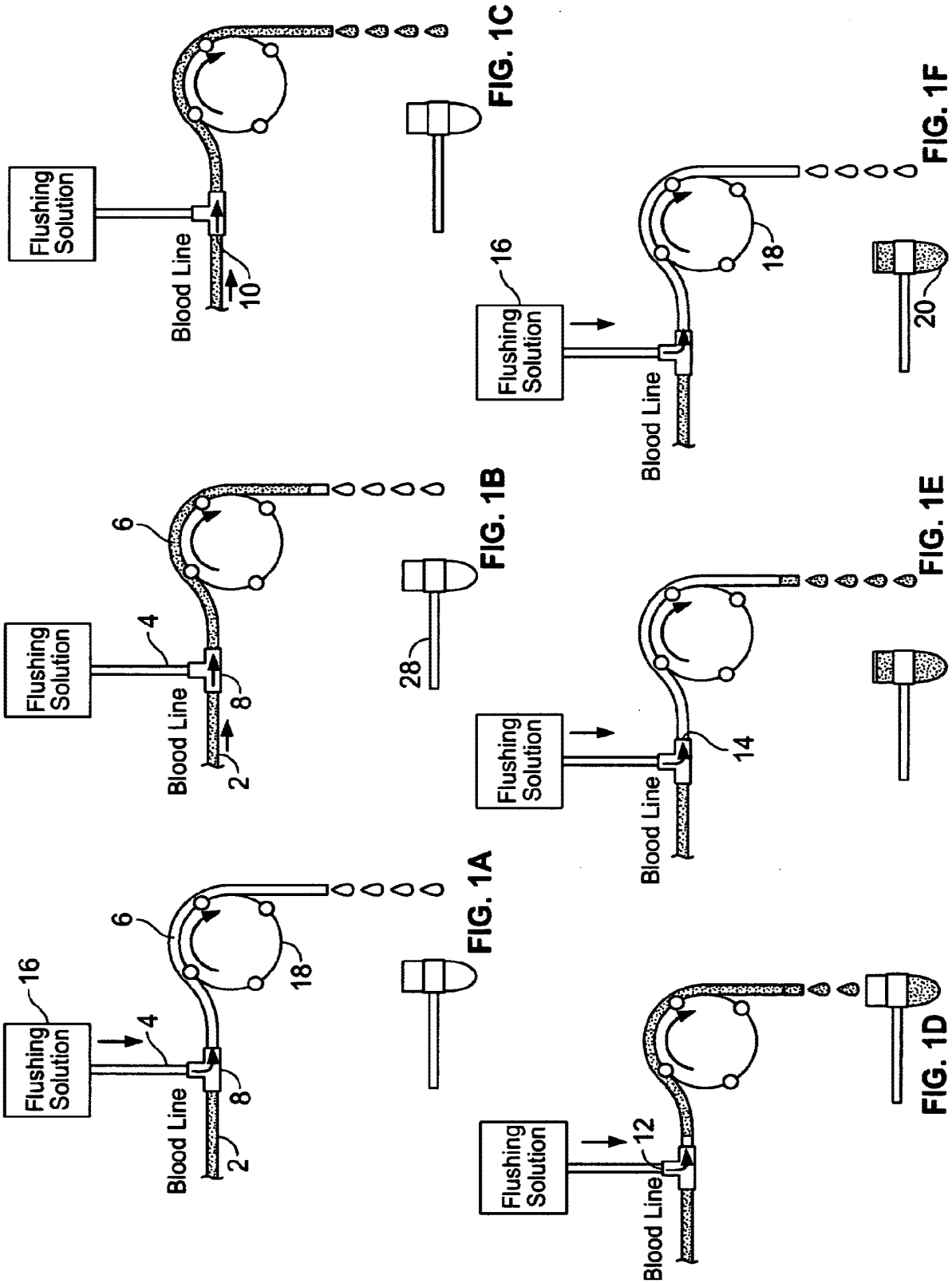
at least two selection means for selectively inhibiting fluid flow in at least two of the fluid lines while the pumping means is activated, the selection means being capable of selective activation in response to an input signal;

wherein activation of one or more selection means allows blood to flow from the blood fluid line through the first branching element and into the aspiration line or allows flushing solution to flow from the flushing line, through the second branching element, into the second fluid line, through the first branching element and into either the blood or third aspiration line, or allows the blood pressure monitoring device to monitor the blood pressure of a human or animal, the blood line, second fluid line, and monitor line forming a continuous fluid line when the blood pressure monitoring device is active;

computer means capable of providing an input signal to the pumping means, the selection means, and the collecting means in response to system generated information;

the system generated information being produced by the computer means in response to programming information entering the computer means from at least one user interface and from at least one monitoring device;

the system generated information resulting in output signals allowing for coordination of the pumping means, selection means, and the collecting means such that efficient blood sampling occurs at scheduled time intervals without excessive blood waste.


Flushing Solution
Blood Line
10
FIG. 1C
Flushing Solution
16
18
20
Blood Line
FIG. 1F
Flushing Solution
4
6
8
2
Blood Line
28
FIG. 1B
Flushing Solution
14
Blood Line
FIG. 1E
Flushing Solution
16
4
6
18
8
2
Blood Line
FIG. 1A
Flushing Solution
12
Blood Line
FIG. 1D

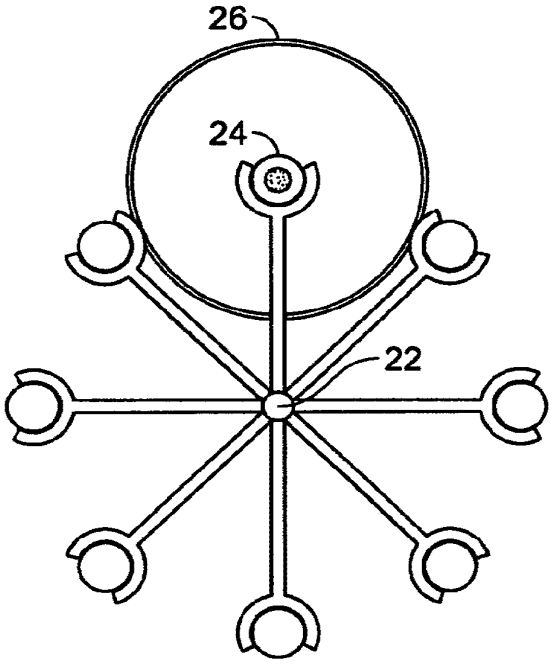


FIG. 2A

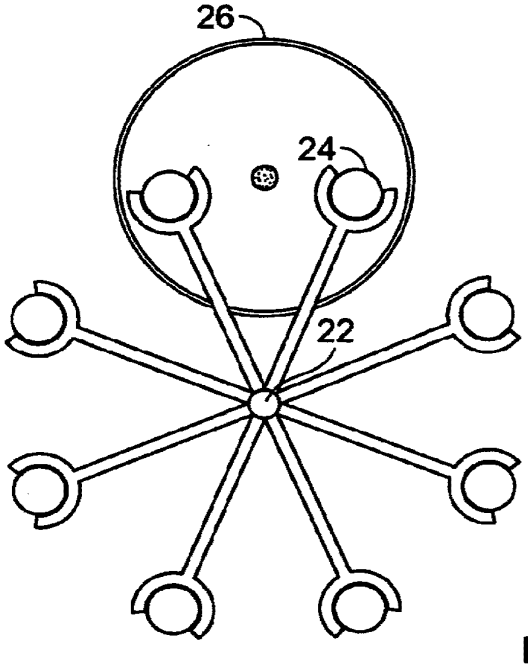


FIG. 2B

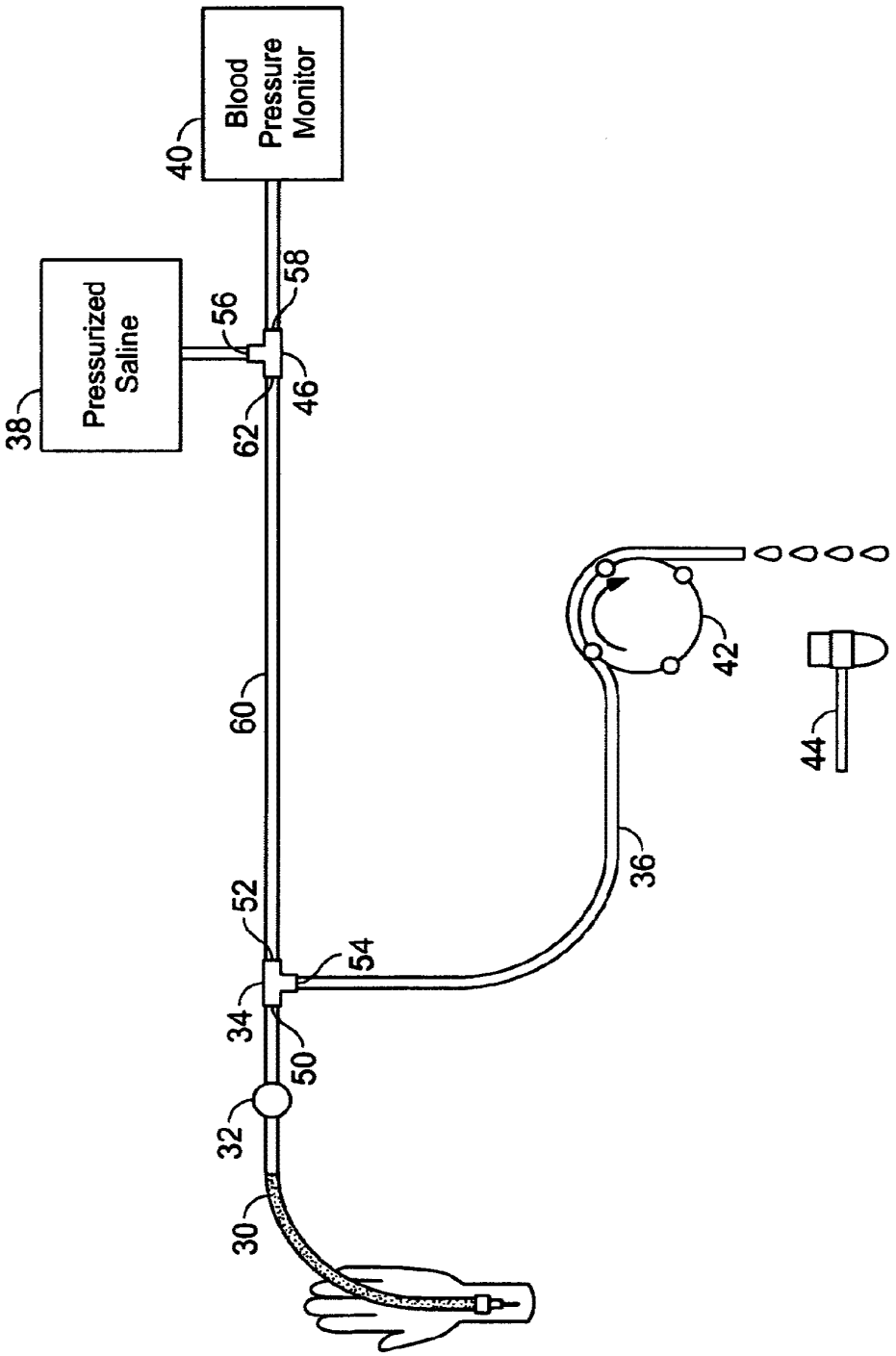

Blood Pressure Monitor
40
Pressurized Saline
38
56
58
46
62
60
52
54
34
50
32
30
36
42
44

FIG. 3

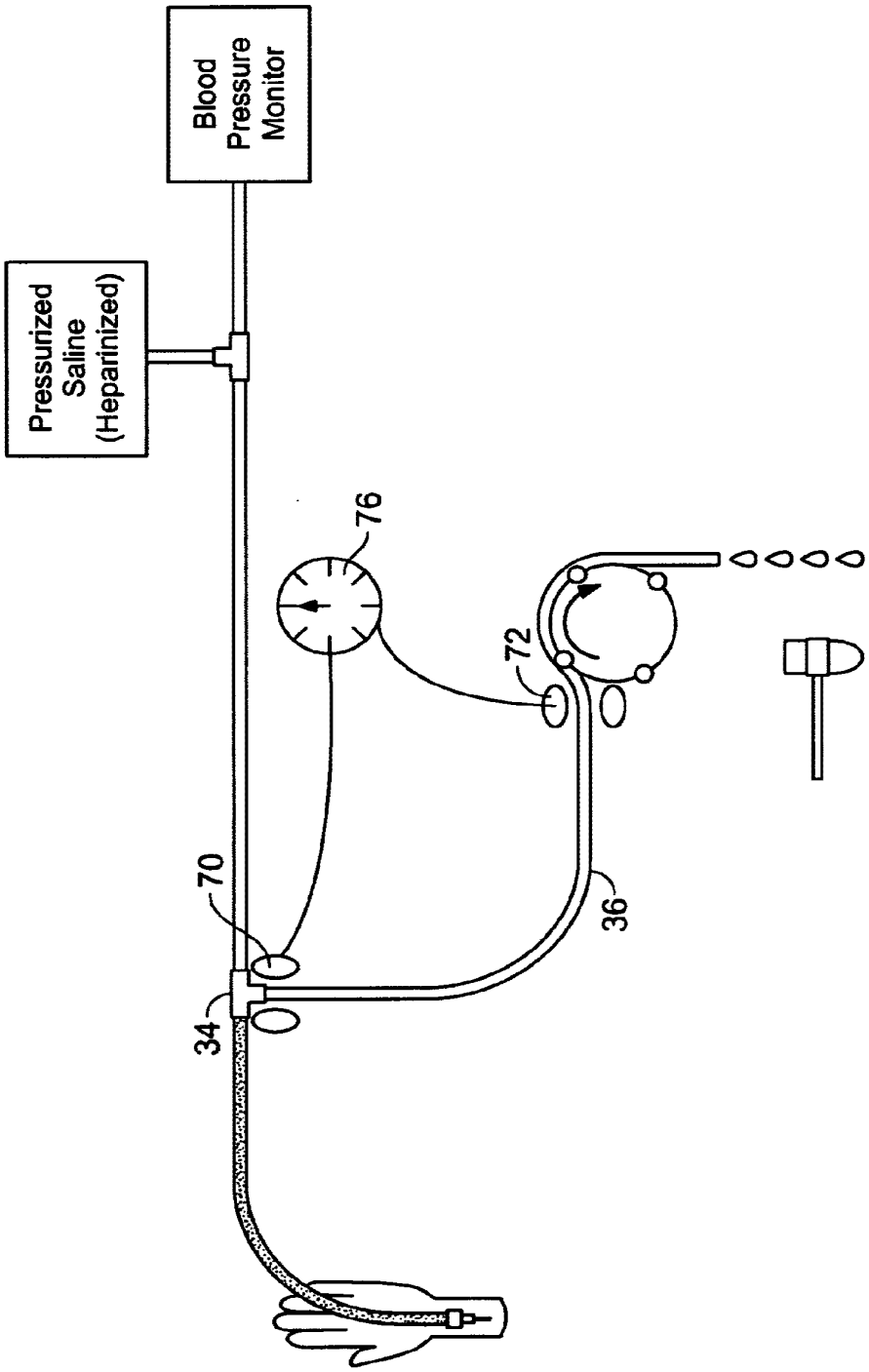

Blood Pressure Monitor
Pressurized Saline (Heparinized)
76
72
70
36
34

FIG. 4

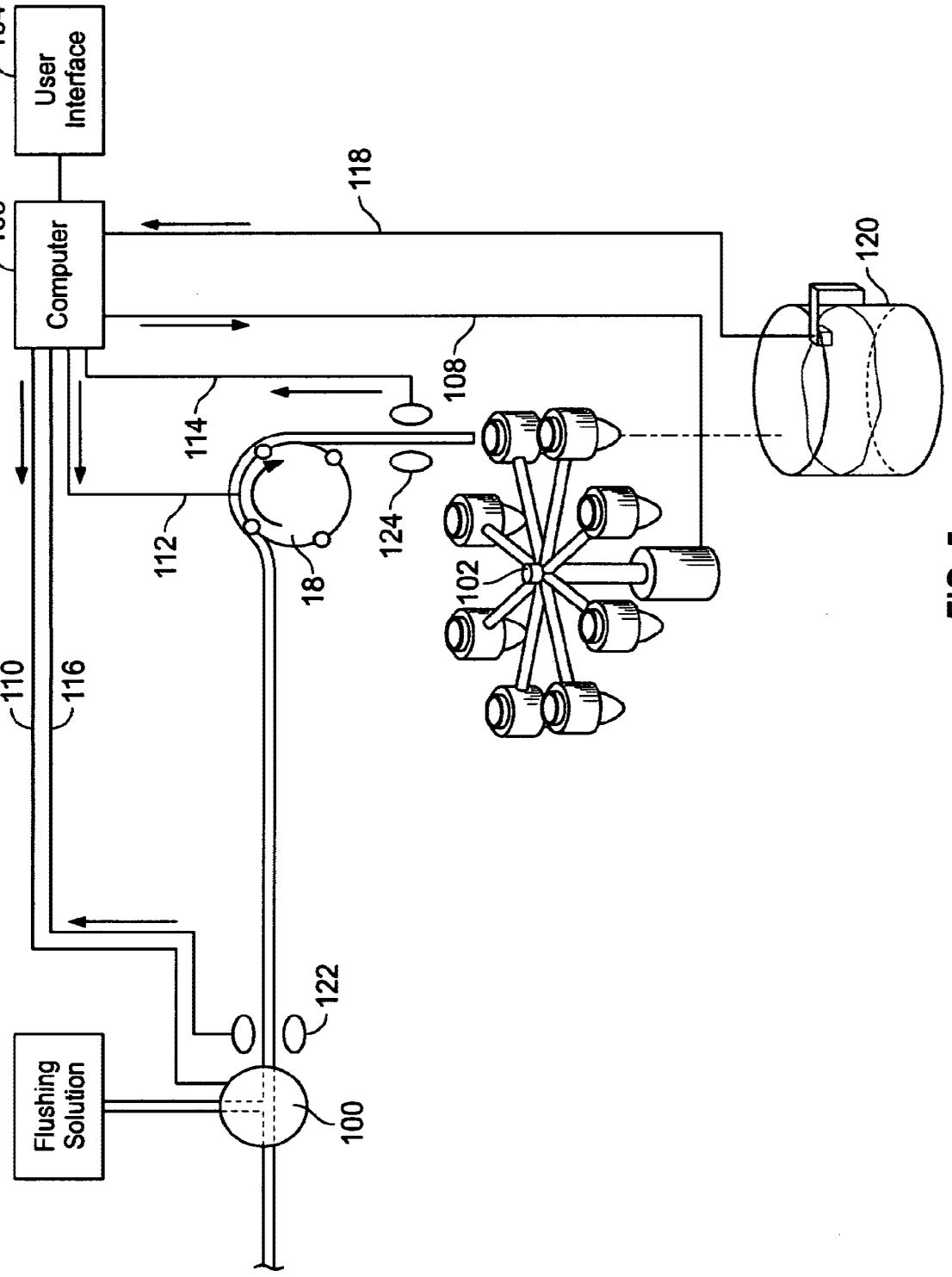

104
User Interface
106
Computer
118
120
108
114
112
124
18
102
110
116
122
Flushing Solution
100

FIG. 5

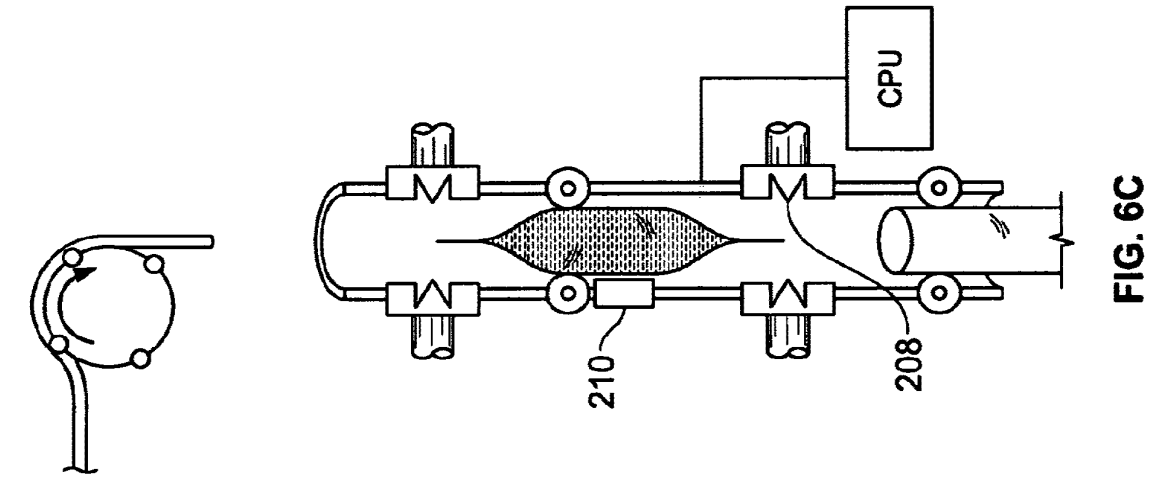


FIG. 6C

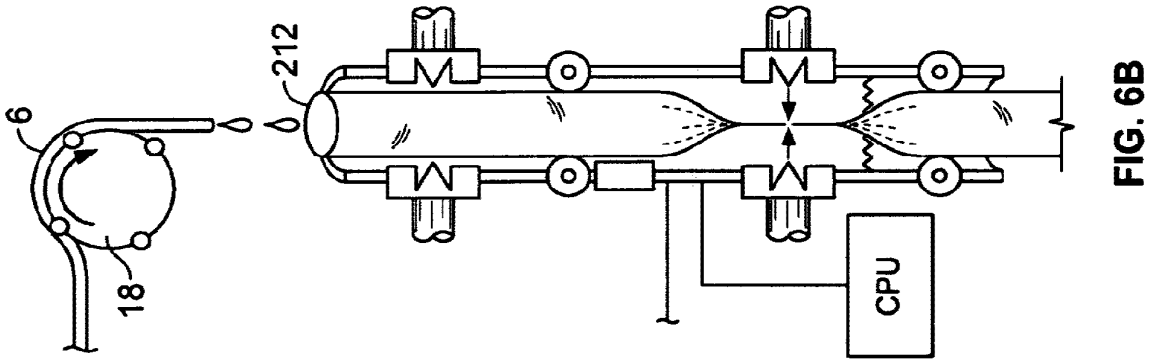


FIG. 6B

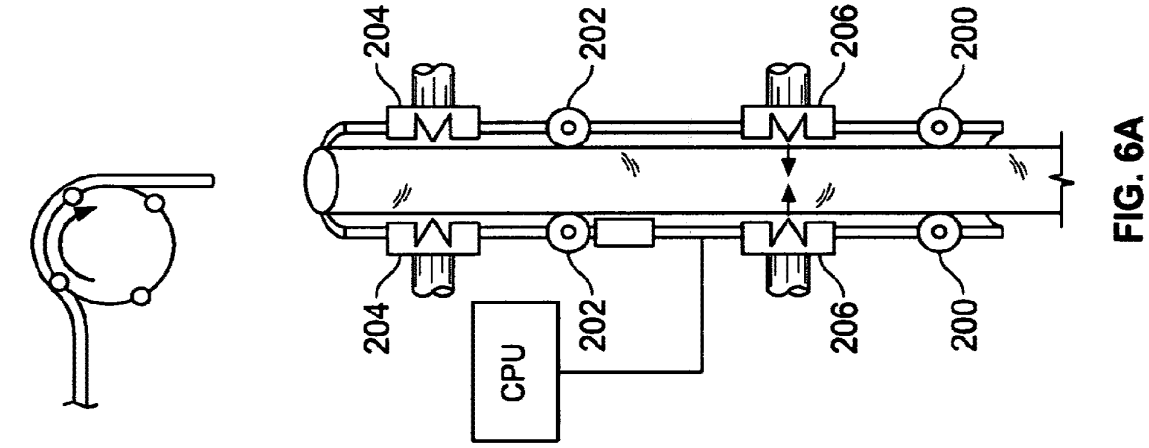


FIG. 6A

FIG 7A

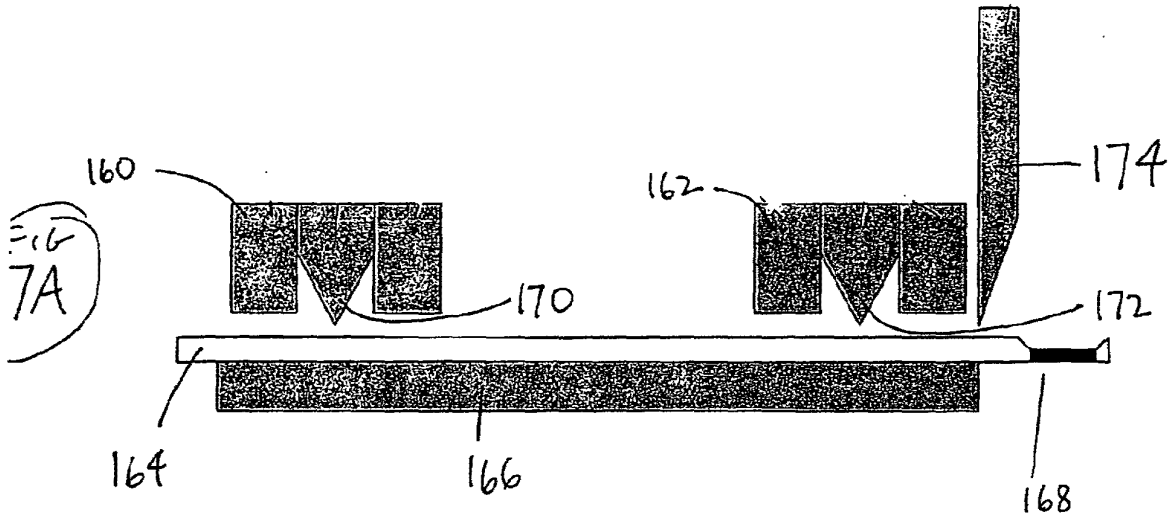


FIG 7C

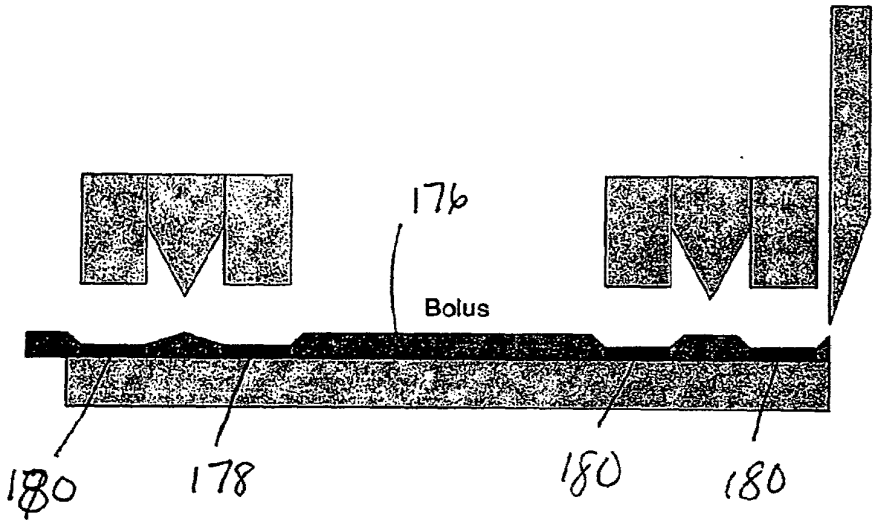
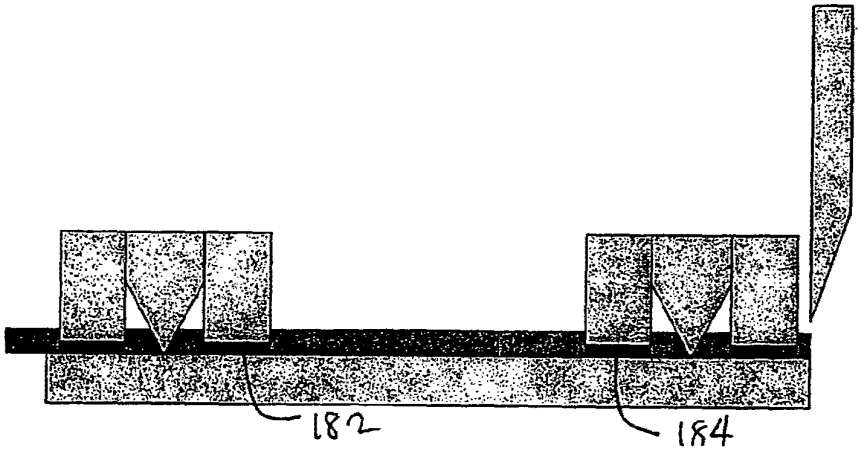


FIG 7B



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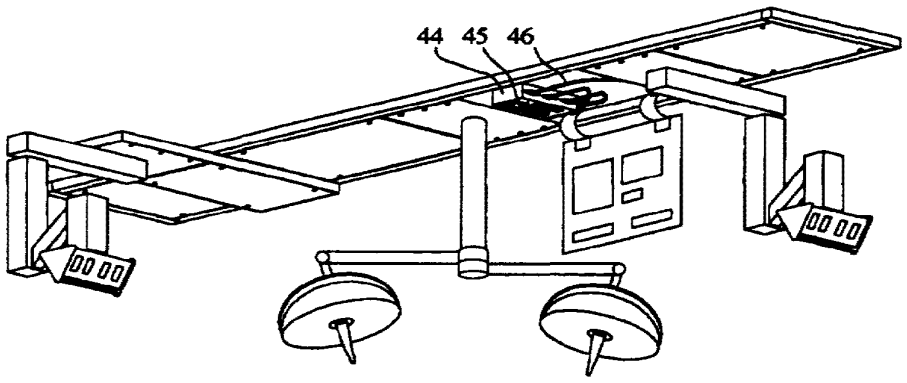
(54) Title: MOUNTING DEVICE FOR HOSPITAL EQUIPMENT, MEDICAL SUPPORT SERVICE UNIT THEREFOR AND SERVICE MOBIL



(57) Abstract

Supportive structure to be attached to a ceiling of a hospital room for supporting hospital equipment. The supporting structure comprises beams attached to the ceiling and forming a rectangular space. Inside the space, there are non-interchangeable gas connectors attached to a gas supply of the hospital and a gas-tight electric box comprising terminals connected to the electric supply of the hospital. The equipment is mounted on support plates, which in turn are supported by support profiles attached to beams. The equipment is connected to the non-interchangeable gas connectors inside the space. Gas-tight hoses are provided between the electric box and the equipment for enclosing the electric wires between the terminals of the electric box and the equipment. In this way separate gas-tight passages are provided for the electric wires, avoiding hazard risks. The support plates support medical support service units for intensive care rooms forming a support structure for equipment necessary close to the bed in an intensive care room, such as a monitor (90), suction units (97), blood pressure monitors. The service unit is a rectangular frame (85, 86, 87, 88) supported by a pivotable arm (82, 83, 80) and a bearing (84), in order to extend essentially vertically from the arm and downwards to adjacent the floor. The rectangular space is sufficiently open for allowing sight through the frame for supervision of the patient. The space outside the vertical beams is free for service staff to work. The service unit can also be supported by a stand including wheels.

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TITLE: Mounting device for hospital equipment, medical support service unit therefor and service mobil

AREA OF INVENTION

The present invention relates to a mounting device for mounting hospital equipment in the ceiling of a operation room and medical support service unit mounted in said mounting device as well as a service mobil to be used in hospital rooms.

PRIOR ART

A mounting device for mounting equipment in the ceiling of a hospital room is previously known from e.g. EP-A2-0 215 212. Said mounting device comprises electric wires and/or fluid ducts. Moreover, it includes a support device for medical equipment.

EP-A2-0 257 299 discloses a support arm suspended in the ceiling and for supporting equipment close to a bed at a hospital.

Another support arm system and mounting equipment for a hospital is disclosed in CH-A5-568 459 (correspondig to US -A-3,931,452).

US-A-5,108,064 discloses a applicance support for use in particular in intensive care stations and comprising a support arm for receiving support members for the appliances and supply connections for operating the same.

EP-A1-0 219 274 discloses a support frame for medical appartuses to be used close to the bed at a hospital and supported by wheels.

An intravenous infusion device mobile is disclosed in EP-B1-477 551. The mobile carries a number of infusion devices necessary for the patient. DE-C1-41 04 814 discloses an intravenous infusion device in more details.

The mounting devices for support close to the ceiling of a hospital room and as disclosed in the prior art have the drawbacks that they do not solve the problem of separating the supply means for gas and electricity, which results in a potential risk.

Moreover, in a hospital room, the equipment to be used at the bed side need to be supported in a convenient and practical way. The prior art support devices have drawbacks as to the practicallity and availability of the electric connectors as well as gas connectors.

Within intensive care there is required many service functions such as: several types of drip and infusion systems for nutrition, liquid balance and drug supply; monitoring systems for various vital systems; respiratory support systems and also complete take-over of respiration.

All the above service must be present since the actual need cannot be pre-planned. It is also required that the personnel can conveniently reach the patient for exchanging drip cannulas, making free the respiratory tracts and even be able to do heart massage.

The necessary equipment has to be supported, either by a ceiling attached support

system or by a mobile provided with wheels.

DISCLOSURE OF THE INVENTION

According to the present invention, there is provided a supportive structure intended to be attached to the ceiling of the hospital room for supporting hospital equipment and comprising support beams and profiles enclosing internal gas connections and electric connections. The connections for electricity are separated in a gas tight enclosure preventing any contact with gases, which may leak from the gas supplies. Thus, a completely safe installation is obtained.

According to the present invention, there is also provided a new medical support service unit for intensive care which is more convenient and less cumbersome than previous systems, and is moveable in relation to the bed and still is sufficiently rigid to support also heavy equipment. Thus, there is provided a medical support service unit for intensive care rooms comprising connectors for gas supply and suction, electric power supply and other electric connectors as required and forming a support structure for equipment necessary close to the bed in an intensive care room, such as a monitor, suction units, gas supply units, blood pressure monitors. According to the invention, the unit comprises a rectangular frame of beams, encircling a rectangular space, said frame being supported by a pivotable arm and a bearing mounted in the ceiling of the room, in order to extend essentially vertical from the arm and downwards to adjacent the floor of said room. The rectangular space encloses equipment which are well protected inside the frame, and said rectangular space is sufficiently open for allowing sight through the frame for supervision of the patient and contact with other staff and the area around the vertical beams being free for service. The vertical beams comprises electric connections and outlets mounted in or at the vertical beams. A gas panel is mounted across the vertical beams.

A further object of the present invention is to provide a mobile where all equipment needed for the intravenous supply services can be included, such as intravenous pumps of the peristaltic or syringe type, nipples, catheters, needles, valves and other small parts, monitors which analyses and monitors the operation of the equipment and the vital functions of the patient. In this way all equipment required for this function can be gathered to one unit. A complete medical support system is obtained for intensive or critical care, which means that the nurses and doctors are given ample place to do their contributions to the care of the patient. The ergonomic and working environmental situation is enhanced, which means that the staff feel more safe and will not be stressed.

Further details appear from the attached patent claims.

SHORT DESCRIPTION OF THE DRAWINGS

Further objects, features and advantages of the present invention will appear from the following detailed description of preferred embodiments shown on the attached drawings.

Fig. 1 is a perspective view of a supportive structure according to the invention.

Fig. 2 is an enlarged cross-sectional view of a part of the supportive structure

according to the invention.

Fig. 3 is an enlarged cross-sectional view of another part of the supportive structure according to the invention.

Fig. 4 is a perspective view similar to Fig. 1 and shows the gas conduits.

Fig. 5 is a perspective view of the lower side of the supportive structure and shows the electric box.

Fig. 6 is a perspective view in an enlarged scale of the electric box according to the invention.

Fig. 7 is a perspective view of an equipment mounted beside the supportive structure in a side bracket.

Fig. 8 is an exploded view of the side bracket mounting according to Fig. 7.

Fig. 9 is a perspective view of a service unit according to prior art.

Fig. 10 is a perspective view similar to Fig. 1 of a preferred embodiment of a service unit according to the invention.

Fig. 11 is a perspective view of the service unit according to Fig. 10 from the other side.

Fig. 12 is a side view of the unit seen from the bedside without any equipment.

Fig. 13 is an end view of the unit according to Fig. 12.

Fig. 14 is a side view of the unit according to Fig. 12 seen from the nurse side.

Figs. 15 and 16 are elevation views of the side of the vertical beams.

Fig. 17 is a cross-sectional view of a vertical beam with a bracket mounted thereon.

Fig. 18 is a perspective view of a ventilation mobile, seen from the nurse side.

Fig. 19 is a perspective view of the ventilation mobile according to Fig. 18, seen from the patient side.

Fig. 20 is a perspective view of a critical care mobile according to the invention, seen from the patient side.

Fig. 21 is a perspective view of the critical care mobile according to Fig. 20, seen from the opposite side compared to Fig. 3.

Fig. 22 is a perspective view of a pump module intended to be attached to the mobile according to Figs. 20 and 21.

Fig. 23 is a perspective view of a standard mobile according to the invention, seen from the nurse side.

Fig. 24 is a perspective view of the standard mobile according to Fig. 23, seen from the opposite side compared to Fig. 23.

Fig. 25 is a perspective view of the standard mobile according to Figs. 23 and 24, seen from the patient side and used for another purpose.

Fig. 26 is a perspective view of the standard mobile according to Fig. 25, seen from the opposite side compared to Fig. 25.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 is a perspective veiw of the supportive structure comprising steel girders making up the installation.

The supportive structure comprises a rectangular framework of rigid square steel girders. In the drawings there are shown two longitudinal girders 1, 2, each for example 3600 mm long, interconnected by two transversal girders 3, 4, each for example 600 mm long. Several vertical L-beams 5 - 12 are welded to the square girders at suitable locations as shown on the drawings. Further horizontal L-beams 13 - 17 interconnect the vertical L-beams to form a supportive structure as shown on the drawing.

Each vertical L-beam is intended to be connected to mounting members 18, one of which is shown on the drawing above L-beam 6. It is to be understood that such mounting members are positioned above each of the vertical L-beams.

The mounting member comprises a vertical, hollow, square beam 19 attached to a support plate 20. The support plate 20 is attached to the ceiling of the operating room by several screws 21, schematically shown on the drawing.

The square beem 19 of the mounting member 18 has an inner dimension suitable for entering the vertical L-beam inside it. As an example, the square beem can have an external size of 50 x 50 mm, and a wall thickness of about 2 mm, and thus the inside dimension is about 46 x 46 mm. The L-beam can have a corresponding dimension so that it fits inside the square beam, such as a width of 45 mm.

When mounting the supporting structure in an operating room, the mounting members are attached to the ceiling in appropriate locations. The vertical L-beams 5 - 12 are introduced into the square beams until the supportive structure is horizontal, and then the L-beams 5 - 12 are welded to the square beams. In this way it is possible to obtain a horizontal supportive structure also when the ceiling is not completely horizontal or is uneven.

As mentioned above, the supportive structure comprises four girders, such as square girders of steel and having a dimension of 50 x 50 mm. The girders have to be strong enough for supporting heavy equipment and can be made with a wall thickness of 2,4 mm.

In order to adapt this supportive structure to support different operating equipment, such as operation lamps, connector centrals for gas supply and electric supplies etc., there is provided according to the invention a support profile made from extruded aluminum having a shape shown in Fig. 2 to the left, and being generally L-shaped. The support profile is intended to be placed along the longitudinal girders. If the support profile is as long as the girder, such as 3600 mm, then the support profile has recesses for passing the vertical L-beams 5 - 12.

The support profile 22 is shown in more details in Fig. 2 and comprises a first horizontal leg 23 intended to be placed on the horizontal upper surface 24 of the girder, and a vertical leg 25 intended to the placed along the vertical side surface 26 of the girder facing the inside of the rectangular space formed by the supportive structure. The horisontal leg 23 has a hook flange 27 passing a short distance along the opposite vertical side surface of the girder

facing outwards. Thus, the support profile is hanged upon the girder by placing the hook flange 27 over the girder and the profile will hang as shown in Fig. 2. The support profile has several other flanges, the operation of which will be described below.

Somewhere along the upper horizontal surface of the support profile, there is a flange 28 inclined about 45° upwards as shown to the left in Fig. 2. This flange is for supporting a ceiling or lid plate 39 extending from one girder to the other and covering the whole supporting structure at the top. Preferably, the ceiling plate 39 is extending inclined upwards about 50 mm and then extends in a horizontal direction. The ceiling plate 39 is attached to the flange 28 by rivets or screws.

The support profile is further provided with a depending flange 29 close to the intersection between the horizontal and vertical legs 23, 25 forming a pocket 30 facing downwards and extending along the entire length of the support profile. Furthermore, the vertical leg 25, at the bottom is provided with a horizontal flange or support surface 31 extending inside the rectangular area of the supportive structure. The object of the pocket 30 and the surface or flange 31 is to support an L-beam, as shown in broken lines in Fig. 2. The pocket 30 is provided with an enlargement 32 enabling the introduction of a L-beam 33 as shown in Fig. 2 by broken lines.

As shown at the right side of Fig. 3, each girder is provided with a cover profile 34 extending along the entire length of the girder. The cover profile is locked in place by a lock profile 35, which can be placed on intermediate positions or can be a longitudinal profile. The lock profile 35 is screwed to the hook flange 27 of the support profile 22, thus completing the grip around the girder. In this way, a very reliable support profile construction is attached to the girders.

As shown to the left in Fig. 2, a longitudinal L-beam 33 can be inserted with its vertical leg into said pocket 30 and resting upon the support surface 31. The L-beam 33 has three holes along its horizontal leg, into which holes are inserted screws for supporting any equipment to be attached to the supportive structure. Such equipment is mounted on a strong support plate 36 having a standardized size, such as 600 x 300 mm. The girders are mounted so that the distance between a depending inverted T-flange 37 of one girder to the corresponding T-flange 37' of the other girder is 600 mm. The above-mentioned L-beam 33 has a length of 300 mm. Thus, the support plate 36 for the equipment can be inserted between the T-flanges and attached to the L-beams arranged as described above. By drawing the screws, the L-beam 33 and the support plate 36 will squeeze the support surface 31 therebetween forming a tight attachment between the support plate 36, the L-beam 33 and the support profile 22. Preferably, the L-beam has a cushion 38 outside the holes as shown in Fig. 2, to the right.

By loosening the screws, the support plate will be moveable along the length of the support profiles and thus along the girders, in order to place the equipment where needed. When the right position has been obtained, the screws are tightened. The equipment can be

remounted by loosening the screws and removing them completely, whereupon the support plate is free from the L-beams. Mounting and dismounting of the equipment can take place without making or leaving screw holes in the supportive structure.

When the equipment has been mounted as mentioned above, the spaces between the support plates of respective equipment is downwardly covered by lid plates 40, which preferably are of standard size, or can be cut to the desired size. It is preferred to use a modular size, so that the support plates are placed within modules of a width of 300 mm.

The lid plates 40 are shown in more details in Fig. 3 and are provided with hooks 41, hooking around one of the edges of the inverted T-flange 37. The other side interact with the corresponding edge by a locking arrangement such as an excentric lock (not shown). When the lock is disengaged, the lid plate 40 can be swung down hanging in the hooks 41 when access to the interior of the supportive structure is required a shown in broken lines in Fig. 3.

As shown in Fig. 4, gas conduits 42 are entering the supportive structure from above. Such gas conduits come from the hospital central supply of gas into each room at convenient locations and are connected to non-interchangeable connectors inside the supportive structure. From such connectors, the gas is further supplied to the equipment needing gas supply.

Moreover, electric wires 43 enter the supportive structure from above, as also shown in Fig. 4. These wires enter an electric box 44 (see Fig. 5), provided with suitable terminals. The box is completely gas tight and the holes, through which the wires enter the box are sealed. Thus, there is provided separate and sealed compartments for the electric supply as is required for avoiding risks in connection with gases, such as oxygen gas.

The electric box has a removeable and sealed cover, which is removed in Fig. 5 exposing the terminals 45 inside the box 44. The electric box is also provided with further holes, which originally are sealed or unbroken. When an equipment needs electric supply, a hose 46 is provided from the electric box to the equipment as shown more clearly in Fig. 6. The hose 46 is gas tightly attached to the electric box by a coupling 47 connected to the box 44 with screws and having a sealing thereto. The other end of the hose is connected to the equipment in a similar way. The electric wires are placed inside said hose and connected to the terminals 45 in the electric box and to the contactors (not shown) of the equipment. Thus, the electric wires are places inside said hose and are sealed from any space that might include gas. Thus, there is obtained a completely safe mounting of electric wires in combination with gas conduits.

As further shown in Figs. 5 and 6, the lid plate 40 is shown swung down and hanging in the hooks 41. The inside surface of said lid plate 40 can be provided with circuit diagrams and instruction notes 48 as shown. Morover, the lid plate is provided with several holes 49. These holes operate as vent holes for venting any gas leaking from the gas non-interchangable couplings to the surroundings. Further such holes 49 are provided in the bottom closures of the supportive structure where necessary.

As shown in Fig. 3, the cover profile 34 is provided with a horizontal flange 47

extending outwards from the space occupied by the supportive structure. This flange 47 is intended to support an extra ceiling 48 of the room, such as a slab, which is often used for obtaining a more clean ceiling surface in the operation room.

It is obvious that the lock profile 35 can be constructed as an integral portion of the cover profile 34 if this is more convenient.

Sometimes it is desired to place the equipment displaced in the side direction in relation to the supportive structure. Such a bracket mounting is shown in more details in Figs. 7 and 8. The side bracket is made up of four U-beams forming a rectangular frame 50. The frame is provided with a transversal beam 51. Said beam 51 and one transversal side 52 of said frame are connected to the L-beams 33 as shown in Fig. 2 so that the entire frame 50 is moveable along the supportive structure shown at 53. The frame 50 is locked in position by several screws 54 engaging said L-beams 33 as described above. The frame 50 is provided with screw bolts 55 adapted for engagement with a support plate 56 of the equipment as shown in Fig. 16. The final mounting is shown in Fig. 7.

Fig. 9 is a perspective view of a service unit according to the prior art, the POWER COLUMN from Hill-Rom. It comprises a rectangular column 61 extending from the ceiling 62 to the floor 63 and fixed thereto. The column is about 2400 mm x 600 mm x 200 mm. The column is mounted about 45° in relation to the adjacent wall. A bed is placed so that the head portion thereof is close to the column. Usually, the bed extends perpendicular to the wall.

The column is provided with several electric outlets 64 and connectors along the vertical short sides 65. Along the long side 66 facing the bed, there is mounted equipment of different types, such as suction devices 69, gas outlets 68. Moreover, a monitor 70 is mounted at a support 71. On the backside there is mounted a shelf 72, where the nurse can write on the patient card, and several boxes 73 for different purposes such as including small details used at the place and a waste basket.

There are several drawbacks with such a service column. It is fixed at the floor which makes it necessary to move the bed, if access to the bed should be required from all four sides in an emergency situation. It happens sometimes that the weight of the patient is monitored by weighting units between the bed and the floor, and a movement of the bed disturbs such a set-up and requires re-calibration of the weighting units.

Since the column is fixed to the floor, it is difficult to clean around the column.

The equipment, and specifically the monitor extends rather long out from the column, which takes up a lot of place. When the nurse makes her patient records, she is positioned behind the column and cannot see the patient, if an emergency situation should arise.

If new equipment is to be mounted, such as a further suction outlet, it is necessary to make new holes in the column construction which is difficult and disturbs other intensive care patients and functions.

A service unit for an intensive care room obviating all the above-mentioned drawbacks with the fixedly mounted column, is shown in Figs. 10 and 11.

The service unit according to the invention hangs in a support arm supported from the ceiling of the room. Such support arms are frequently used in hospitals, especially in operating rooms.

A support plate 80 is attached to the ceiling fixture by several bolts 81. To the support plate 80 is attached a support arm 82 extending horizontally below the ceiling and being pivotable by bearings 83. At the end of the arm, there are further bearings 84 attached to the middle of a horizontally extending beam 85. At the end of beam 85, two vertical beams 86, 87 are attached interconnected at the lower end by a bottom beam 88. Thus, beams 85, 86, 87 and 88 form a rectangular frame as shown in Figs. 10 and 11. The rectangular frame is supported at its vertical symmetry axis by said bearing 84. The bottom beam 88 is placed a short distance above the floor, such as 30 cm above the floor for the necessary convenient cleaning of the floor.

The support plate is attached in the room so, that the rectangular frame can be positioned close to the wall in a first position when not used and swung out close to the head end of an adjacent bed when used. The rectangular frame is pivotable around its vertical symmetry axis as shown by arrow 89.

The equipment which must be present close to the bed, is mounted in the free space between the vertical beams 86 and 87, as shown by monitor 90 mounted on a shelf 91. The equipment is inserted between the vertical beams and facing the bed side.

On the backside shown in Fig. 10, there is inserted between the vertical beams other types of equipment necessary for the nurse, such as a writing table 92 or commode for the nurse where she can have the patient record and further things for writing purposes. The commode may comprise small boxes containing needles, connector and other accessories for drip, drainage etc.

Alternatively, the commode can be replaced by a PC-station connected to a centralised patient monitoring and recording system, including a video display and keyboard.

At the bottom there is a file box 93. Above the table 92 there is a further shelf 94 for placing stationery, scalpels and other small things handy when arranging for drips etc. A lamp 95 provides a good working light.

It is clear from Figs. 10 and 11 that a nurse doing her patient records can still observe the patient, through the free space in the interior of the rectangular frame. Only the vertical beams occlude the sight.

At the side usually facing the bed and shown in Fig. 11 there is provided all equipment needed for the patient, such as the monitor 90 mentioned above, a gas panel 96 having gas inlets and a connector for suction connected to a suction collector bottle 97. Several horizontal support rails 98 extend between the vertical beams for supporting further equipment, such as an oxygen therapy unit, timers in case of heart arrest, etc. A lamp 99 provides convenient lighting to the support service system equipment arranged on the unit. The lamp has an oval light up area only to light up the equipment.

A support stand 100 for infusion bags can be attached to the vertical beams as explained in more details below.

The service unit according to Figs. 10 and 11 is shown without equipment and in side and end views in Figs. 12, 13 and 14. The same details as in Figs. 10 and 11 have the same reference numerals.

In Fig. 13 there is shown a different type of lamp 101 included below the shelf 94.

As appears clearly from Fig. 12, the gas panel 96 is provided with several modules 102, 103, 104, 105 and 106. Modules 103 and 105 are blank modules without anything mounted. Module 104 comprises three medical gas pressure indicators showing bright red warning colour when pressure is too low from the central supply, such as oxygen, nitrous oxide and compressed air. To the left, 102 and to the right 106 are two modules having suction units. Other modules can be mounted at positions 103 and 105 without any mechanical work.

The gas panel is connected to the hospital's central gas supply via flexible hoses inside beam 86, beam 85, through bearing 84, arm 82, bearing 83 and support plate 80.

At the sides of the vertical beams 86 and 87 there are several connectors for electric power supply and for signal lines. Thus, the left beam 86, seen according to Fig. 12 is provided with the connectors shown in Fig. 15. Such connectors are power supply outlet 107 and small signal connector 108 intended for the monitor 90. Thus, the wires to the monitor are short. At the bottom there are shown five outlets 109 for power supply (220 V). In between there are two blank modules 110, 111, but these modules can be provided with electric outlets and connectors if required. Other module configurations can easily be arranged.

The corresponding right beam 87 is provided with other connectors as required and shown in Fig. 16. The electric power supply wires and signal wires are enclosed inside the vertical beams 86 and 87 and pass to the hospital's central supply and network the same way as the gas lines.

Thus, it is clear that the rectangular frame can include all functions and equipment necessary for the service function intended. It is easy to adapt the rectangular frame to whatever need should there be.

Since the interior of the rectangular frame is available, compared to the column shown in Fig. 9, the large equipment such as the monitor etc. can be housed between the vertical beams 86, 87 so that they do not occupy large area and do not extend far away from the frame. Such equipment will be positioned below the support bearing 84, and thus, the rectangular frame will be steadily supported by the bearing 84. The equipment will not tend to twist the frame. Thus, a stable service unit is obtained in spite of the fact that it is moveable, which makes it easy to clean the floor. Such equipment is inserted inside the space limited by the vertical beams interleaved from one side or the other. The area outside the vertical beams is free for the support service and comprises the outlets necessary for the service, such as gas outlets and electric outlets.

It is noted that the bearings 83, 84 are of a type allowing very limited movement but

rotation around the vertical axis of the bearing. Thus, the rectangular frame is rather rigid and do not move easily, unless movement is wanted. Since all equipment is rather central in the frame, it will be still further stable.

The stability can be further improved by adding a lock in the bearing so that they are locked in position as soon as the frame has been moved into place. Such lock can be a friction clutch or key locking. The lock can be operated by hand, via a wire that can be pulled by hand, or be electrically and/or magnetically operated. Such lock can be included in one or both of the bearings 83, 84.

Moreover, the space between the vertical beams is free so that the patient can be observed even if the personnel is behind the service unit.

In Fig. 17 there is shown a cross-section through a corner of the vertical beams 86, 87. The beam is provided with vertical grooves 115, 116 in which a bracket 112 can engage. To the bracket 112 can be attached further equipment such as a holder 100 for infusion bags etc. The bracket 112 is locked to the beam by a latch 118 and a screw connection 117 as shown. Other types of equipment can also be attached in this manner.

In Fig. 11 there is shown a treatment lamp 113 attached to the end of the pivotable arm 82. This lamp will be relatively fixed even when the rectangular frame is pivoted around the axis of bearing 84. Thus, said lamp 113 can conveniently be used for illuminating the patient being treated with a constant light. moreover, in Fig. 10 there is shown a telephone 114 in a convenient place. It is easy to install telephone lines in the rectangular frame or the beams.

Critical care of today manage to handle more and more severely ill patients, due to the high capacity of the technique of today in combination with specially educated doctors and nurses. However, this make it necessary to use a great number of different equipment around the patient. In addition to equipment analysing and monitoring the patient, he also requires supply of a lot of nutrients, blood plasma, different anaesthesia etc. Such supply must be controlled which means that old-fashion drop controlled infusion cannot be used any longer and are replaced with electronically controlled infusion pumps and syringes. Up to sixteen such pumps can be used at the same time for a single patient. One common way of using such automatic pumps today is to attach such a pump to the infusion stand with a coupling. The pump is provided with electric power via a wire and is connected to supervisory equipment via a signal cable. It is realised that such a system will be a mess of wires and hoses if used for sixteen pumps. The environment in such critical care rooms can be stressing for the nurses leading to errors and mistakes. It is necessary to further structure and integrate the different functions at such a critical care room.

Fig. 17 shows a ventilation mobile including equipment necessary for respiratory support and for keeping the respiratory ways free, such as oxygen supply units and suction units, as well as further equipment necessary for the critical care, such as supplies for anaesthesia gases. The ventilation mobile is supported by several swivel wheels.

The ventilation mobile 121 comprises a bottom frame 122 supported by several wheels

123 to form a transportable unit. Two vertical pillars 124, 125 extend from the bottom frame to define a vertical rectangular space. Each vertical pillar comprises several outlets for electric power supply 127 and medical gas outlets 126. All power outlets are supplied with 220 V mains power by a power wire 128 connected to a power outlet 129 at the wall of the room and the signal outlets are connected to a corresponding wall mounted signal connector 130, if used (no wire shown in Fig. 17). Moreover, the mobile is provided with a suction unit panel 131 connected to the hospital's central supply of gas via lines or hoses 132, 133, 134. As shown, power wire 128 and hoses 132, 133, 134 are supported by a pivotable arm 135 having hooks 136 supporting said wire and hoses. In this way the pivotable arm 135 can be made smaller and cheaper, compared to if the arm should enclose the hoses.

The vertical pillars 124, 125 and the bottom frame 122 form a vertical rectangular space inside which equipment can be mounted without extending into the space needed for the treatment of the patient. Thus, a large monitor is shown at the top on a shelf, which can be inclined. Moreover, the pillars encloses a writing table facing away from the bed, where the nurse can make the necessary recording and still observe the patient through the open space between the pillars.

As shown in broken lines in Fig. 19, the mobile can be provided with the equipment desired for a specific patient, such as a ventilator supported by said mobile bottom frame 122.

As further shown in Figs. 20 and 21, the same mobile can instead be constructed as an intravenous mobile or critical care mobile 140. In this case it is not necessary to have gas supplies from the hospital's central supply, but the mobile is only connected to 220 V by a power wire (not shown). The mobile can also be connected to the hospital's central computer system, in order to take advantage of the computerised patient recording system used at many hospitals today. Such wires are connected to wall mounted outlet sockets.

As appears from Figs. 20 and 21, the critical car mobile has the same bottom frame 122, wheels 123 and vertical pillars 124, 125. The side of the mobile facing the bed is provided with several mounting rails, for example four rails 141 as shown in Fig. 21. On said rails 141 are mounted several infusion pumps represented by rectangular boxes 142 if Fig. 20. Said infusion pumps can be of the peristaltic type providing infusion solutions from infusion bags hanging on hooks 143 of a stand 144. There are two such stands 144, one at each pillar, each stand being provided with five hooks. The infusion pumps can also be of the syringe type providing a beneficial agent to the patient, such as antibiotics, insulin etc.

The CC (critical care) mobile 140 is furthermore provided with a shelf 145 bridging the two pillars 124, 125 at the upper end thereof. The shelf 145 can support a monitor (not shown) or whatever is needed in the specific circumstance, such as fluid balance monitors and other analysis and monitoring equipment. Two of the rails support infusion pumps 142. The two bottom rails 141 support one shelf 146, which can be used for syringe pumps and a second shelf 147 which can be used for accessories, such as needles, catheters, etc. If more infusion or syringe pumps are needed, such pumps can replace on or both of said shelves 146,

147.

At the side opposite the patient, the CC mobile 140 is provided with a writing table 148 and a few drawers 149 for enclosing accessories at a convenient position for the nurse.

The pillars 124, 125 of the CC mobile 140 are provided with outlet sockets for providing electric power and signal wires to the pumps etc. of the mobile.

Fig. 22 shows the infusion pump sets in more details regarding the attachment to the rails 141. The infusion pumps are mounted in modules, for example a module 150 of two infusion pumps or a module 151 of three infusion pumps as shown in Fig. 22. Each module 150, 151 is interconnected so that only one power wire and one signal wire are needed for each module. The module comprises a holder 152, which in principle is a spring loaded hook, grasping around the support rail 141 when brought into engagement therewith.

Each module is provided with handles 153 for easy mounting and dismounting. The modules are stored in the hospital equipment store and when needed taken out and hooked on the support rail. As many pumps as required are mounted and used. By such a module system, it is possible to adapt each mobile to the requirements of each patient. Each module is provided with some co-operating means for engagement with the respective infusion pump. In this way, pumps of different manufacturers can be mounted together if that is desired.

Figs. 23 and 24 shows a standard mobile according to the invention. The standard mobile 160 is provided with a bottom frame 162 of a more simple structure having four wheels 163 and a single vertical pillar 164. The single pillar is provided with four support rails 161, two infusion bag stands 165, a couple of shelves 166, 167, 168, and a writing table 169. Moreover, an electric panel 170 is provided instead of providing the pillar with electric outlets. This standard mobile 160 can in principle have the same equipment as the CC module 140 described above, but it is smaller and designed for more normal IC cases.

As shown in Figs. 25 and 26, the standard mobile 160 can alternatively be provided as a surgical mobile having one or two individual operation suction units 171, 171' connected to a gas panel 172. Moreover, there is provided a top shelf 173 for any equipment, such as a monitor or a fiber optical light source etc., and a table 174 with a drawer for other equipment, e.g. electrosurgical units. As shown in Fig. 26, there is provided an electric panel 175 with automatic circuit breakers. The gas panel 172 and electric panel 175 are connected to the hospital's central supply via flexible cables 176 and hoses 177 supported by a stand 178 as shown in Fig. 26. The pillar 179 is provided with compressed air outlets 180 for connection to any surgical tools. The upper shelf 173 is pivotable for convenient access from all sides.

Such a standard mobile can be used for many purposes within a hospital.

Although several embodiments have been described above with reference to the appended drawings, it is obvious to a skilled person that different modifications can be made to the embodiments shown on the drawings and different combinations can be made without departing from the inventive idea of the invention. Such modifications obvious to a skilled person reading this specification is intended to be within the scope of the invention.

PATENT CLAIMS

1. Supportive structure intended to be attached at a ceiling of a hospital room for supporting hospital equipment, comprising supporting beams (1, 2, 3, 4) and suppport profiles (22) for supporting the equipment and for forming a space enclosing gas connections and electric connections for said equipment, c h a r a c t e r i z e d in that gas ducts (42) are adapted to enter said space and connected to outlets for connection to said equipment, and that electrical wires (43) are adapted to enter inside an electric box (44), comprising contacts (45) and being gas tight, and in that hoses (46) are adapted between said equipment and said electric box and including gastight connections (47) for comprising said electrical wires (43) between the contacts in said electric box and said equipment.

2. Structure according to claim 1, c h a r a c t e r i z e d by a framework of beams (1, 2, 3, 4), being attached, by several vertical beams (5 - 12), to mounting members (18) attached to the ceiling, so that said framework is adapted essentially horizontally close to the ceiling, whereby said support profiles (22) each comprises a horisontal leg (23) intended to cooperate with an upper surface of the corresponding beam and a vertical leg (25) intended to cooperate with the inner surface of the corresponding beam; and in that said support profile (22) each comprises a connection means (33, 30, 31) for connection to said equipment and for supporting it.

3. Structure according to claim 2, c h a r a c t e r i z e d in that said connection means comprises a longitudinal L-beam (33), the vertical leg of which being adapted to be inserted in a pocket (30) adapted in the support profile (22) and the horizontal leg of which being adapted to cooperate with a flange surface (31) so that said L-beam is supported by said support profile (22) and in that said L-beam is provided with a connection means for connection to said equipment.

4. Structure according to claim 3, c h a r a c t e r i z e d in that said equipment is mounted at a support plate (36) extending over said rectangular framwork and in that the support plate is provided with several holes corresponding to holes in said L-beam so that said support plate can be attached to said L-beam and at the tightening of the screws, jamming said flange surface between said support plate and said L-beam.

5. Structure according to claim 2, 3 or 4, c h a r a c t e r i z e d in that said support profile (22) further comprises a hook flange (27) adapted to hook around said beam at the opposite side of said vertical leg.

6. Structure according to claim 5, c h a r a c t e r i z e d in that said support profile (22) comprises a lock profile (35) adapted to be attached to said hook flange (27) and a cover profile (34) adapted below said beam so that said beam is completely surrounded by said support profile, at least along a portion of the length thereof.

7. Structure according any one of the previous claims, c h a r a c t e r i z e d in that said space is covered by plates (36, 40) at least one of which being provided with ventilation holes (49).

8. Structure according any one of the previous claims, c h a r a c t e r i z e d in that said gas connections are non-interchangeable gas connections.

9. Medical support service unit for intensive care rooms comprising connectors, such as for gas supply and suction, electric power supply and other electric connectors as required and forming a support structure for equipment necessary close to the bed in an intensive care room, such as a monitor (90), suction units (97), blood pressure monitors, c h a r a c t e r i z e d by

a rectangular frame, preferably of four beams (85, 86, 87, 88), encircling an essentially rectangular space, said frame being supported by a pivotable arm (82, 83, 80) and a bearing (84), in order to extend essentially vertical from the arm and downwards to adjacent the floor of said room;

said rectangular space enclosing equipment (90, 92) interleaved from one side or the other which are well protected by the frame, and said rectangular space being sufficiently open for allowing sight through the frame for supervision of the patient and the area around the vertical beams being free for service.

10. Service unit according to claim 9, c h a r a c t e r i z e d in that said rectangular frame comprises two vertical beams (86, 87) interconnected at the top and bottom by horizontal beams (85, 88), the upper horizontal beam being connected to said bearing (84) at the pivotable arm (82, 83) at or adjacent the middle of the horizontal beam (85).

11. Service unit according to claim 9 or 10, c h a r a c t e r i z e d in that said rectangular frame comprises electric connections (108) and outlets (107, 109) mounted in or at the vertical beams (86, 87).

12. Service unit according to claim 9, 10 or 11, c h a r a c t e r i z e d in that a gas panel (96) is mounted across the vertical beams.

13. Service unit according to anyone of claims 9 - 12, c h a r a c t e r i z e d in that said vertical beams (86, 87) comprises grooves extending along the beams for attachment of brackets (112) for supporting holders (100) or other equipment.

14. Service unit according to anyone of claims 9 - 13, c h a r a c t e r i z e d by a locking device in one or both of the bearings (83, 84) for further improving the stability of the rectangular frame.

15. Service mobile for carrying medical equipment, comprising a bottom frame (122) supported by wheels (123), **characterised** by at least one vertical pillar (124, 125) including electric outlets of power type and signal type, said pillar supporting equipment required for monitoring vital functions and for the medical service, such as infusion pumps of the peristaltic or syringe type, oxygen therapy units, surgical suction units, gas supplies etc.

1 / 16

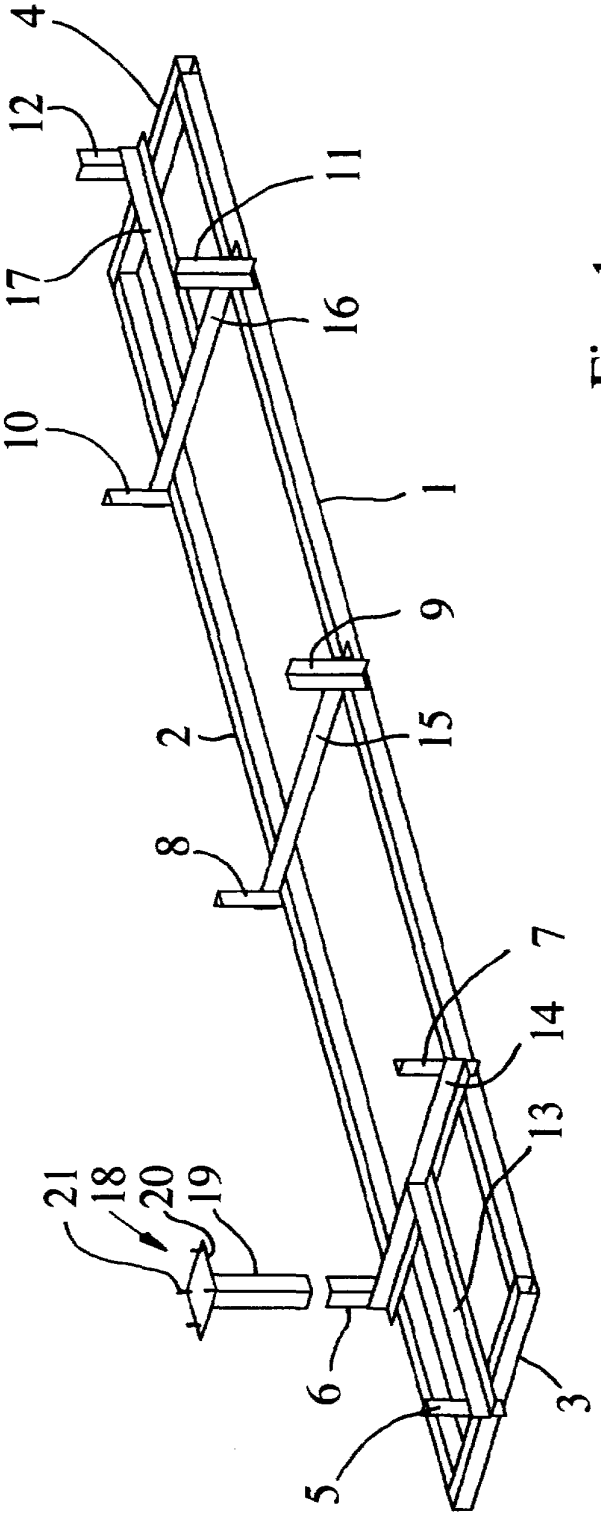


Fig. 1

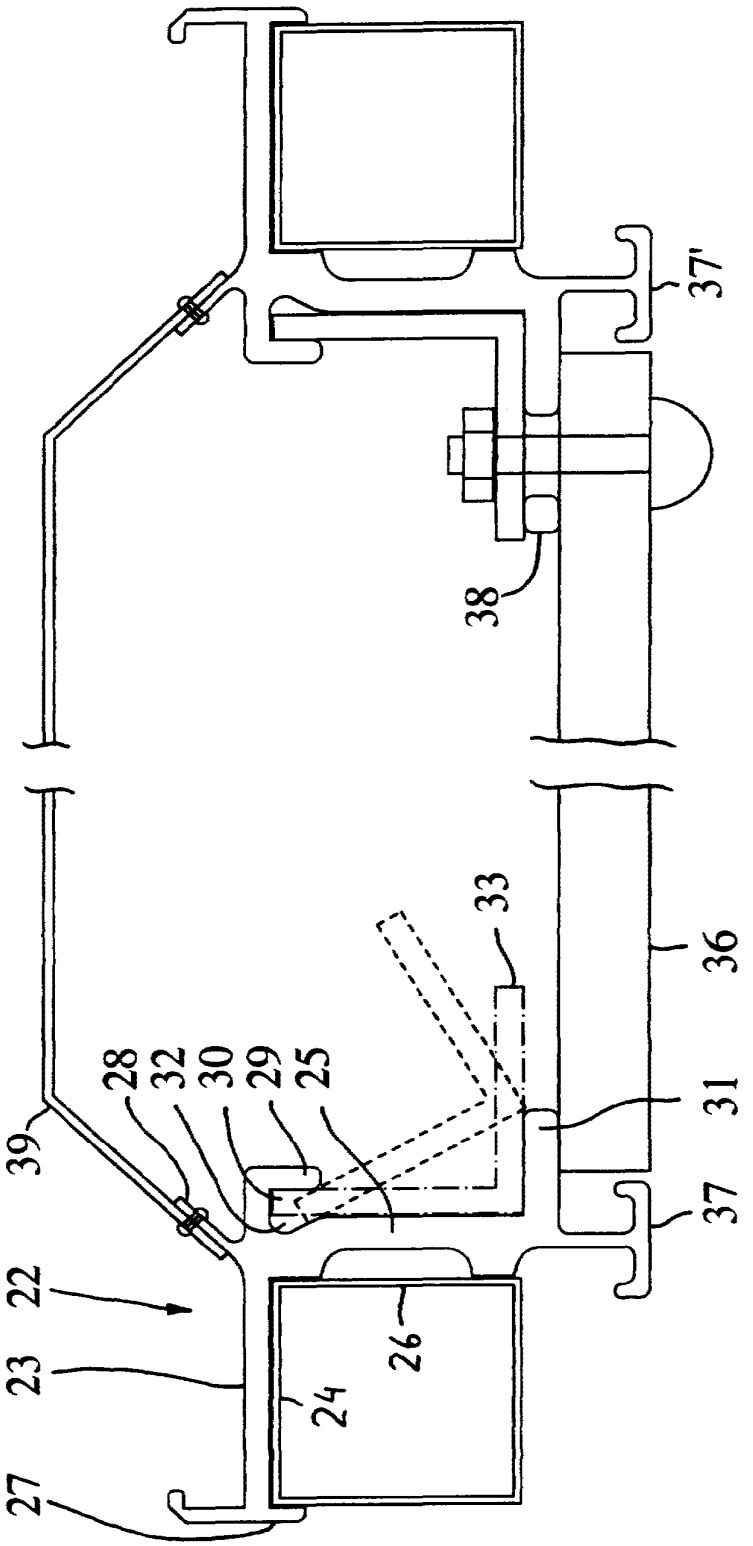


Fig. 2

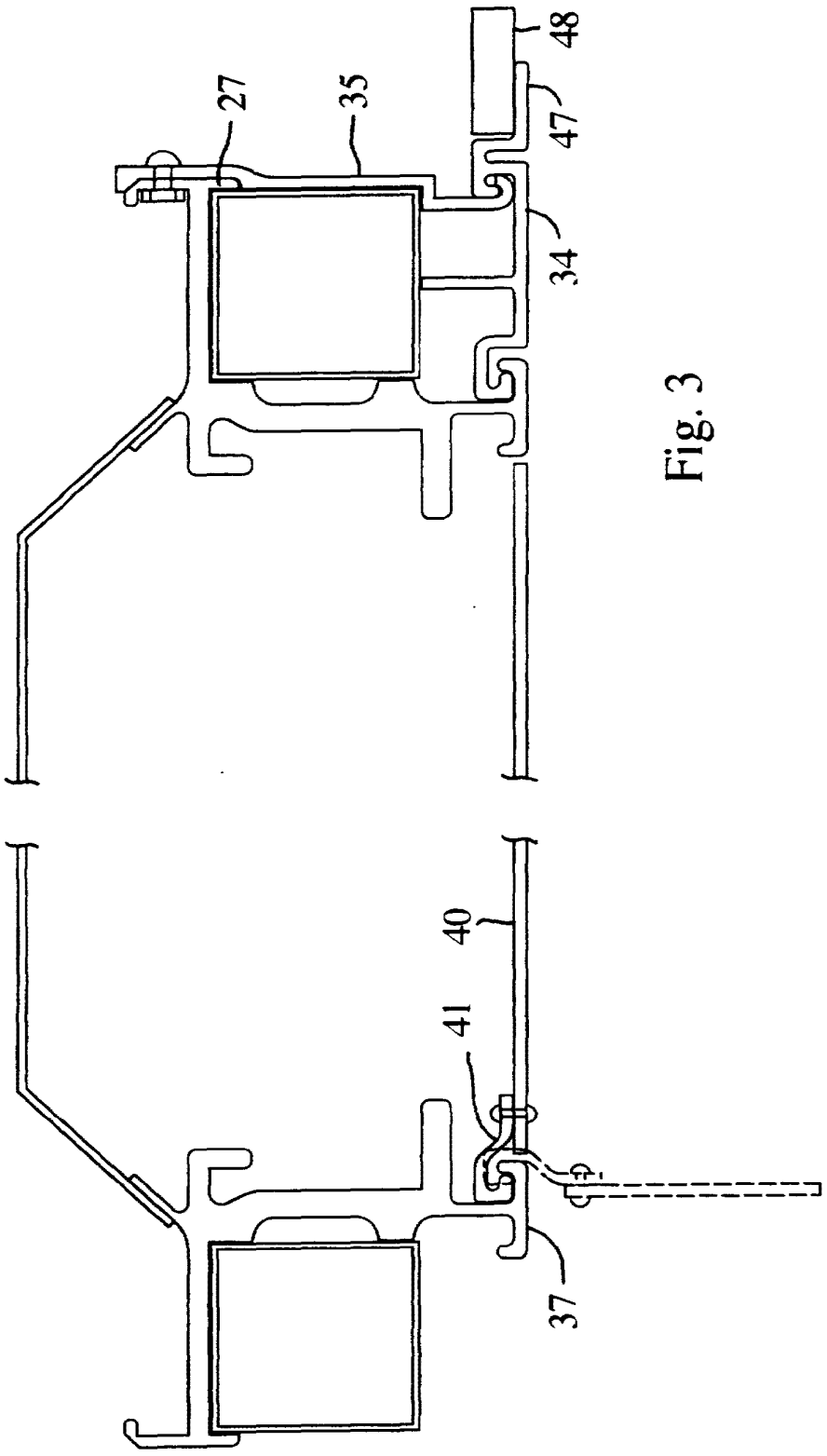


Fig. 3

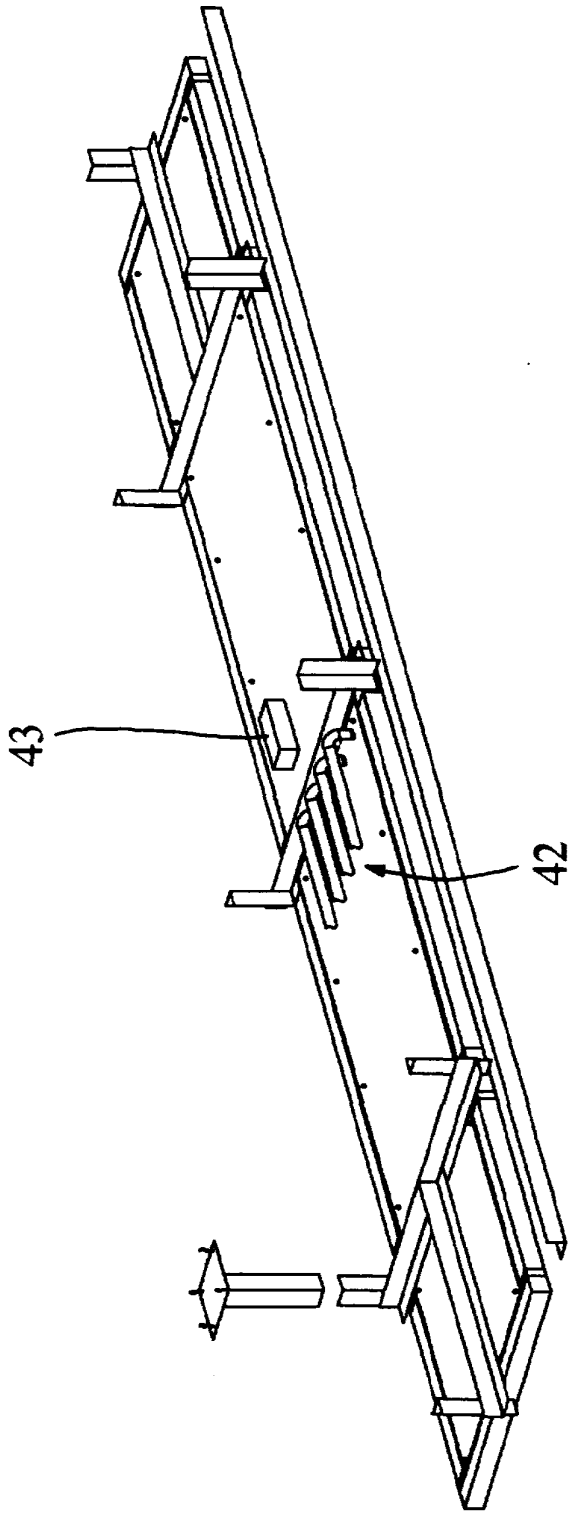
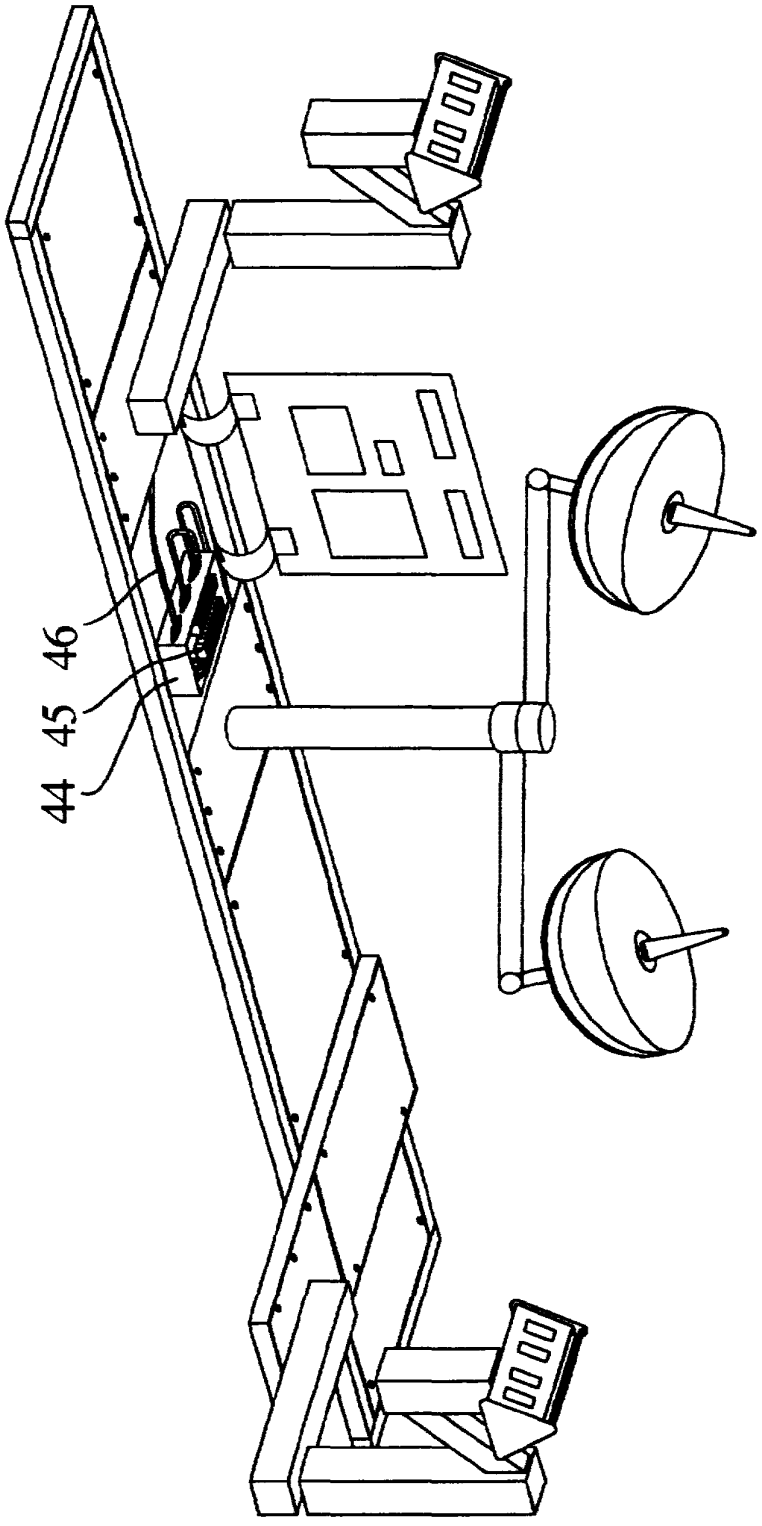


Fig. 4

Fig. 5



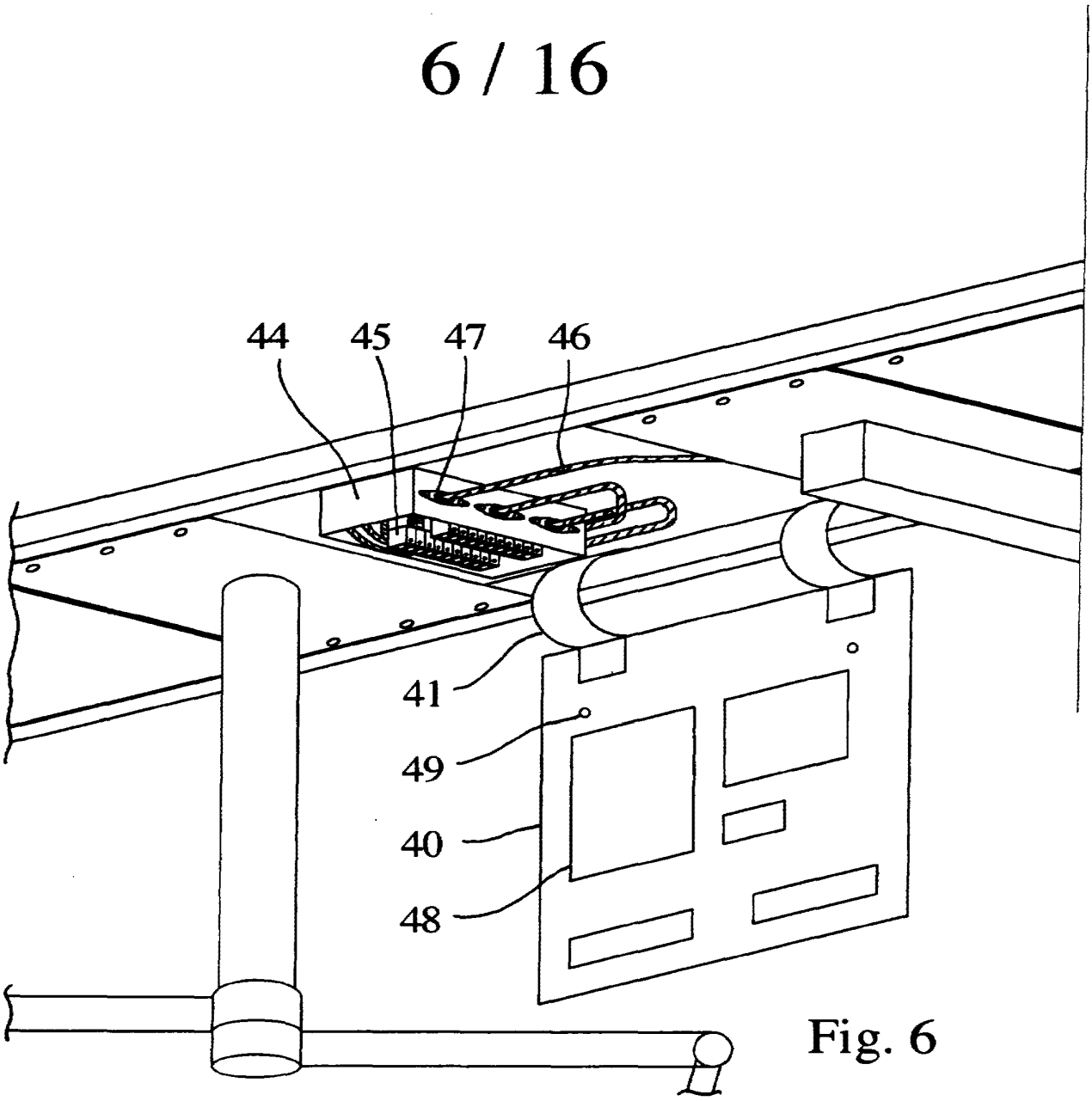


Fig. 6

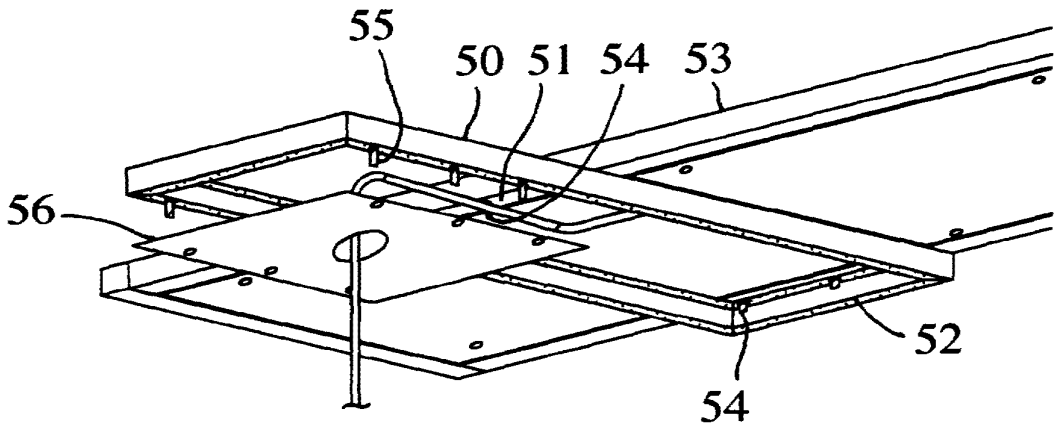


Fig. 8

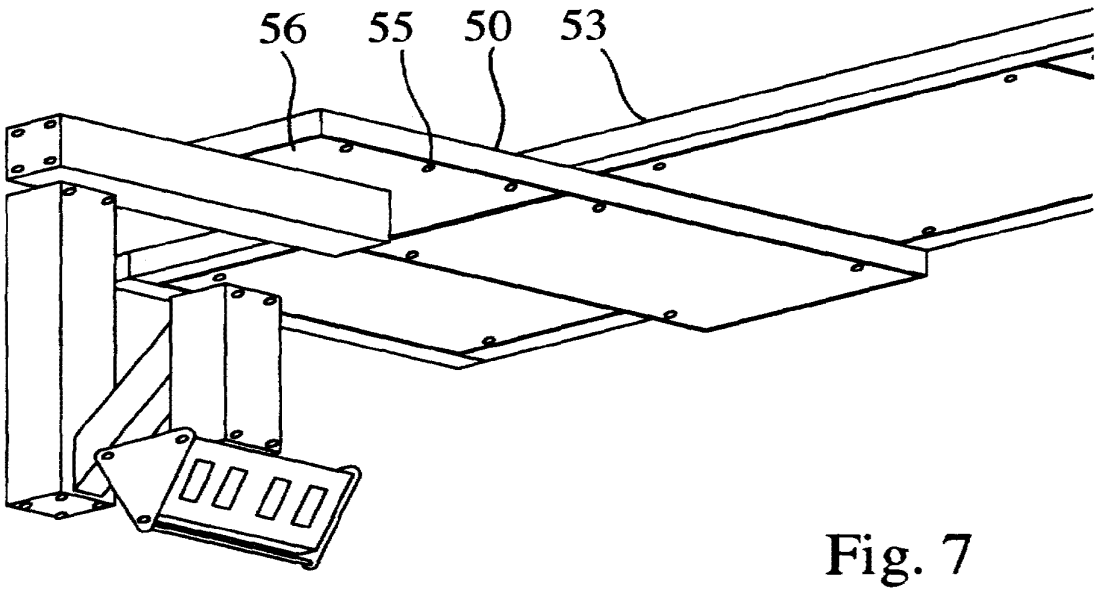


Fig. 7

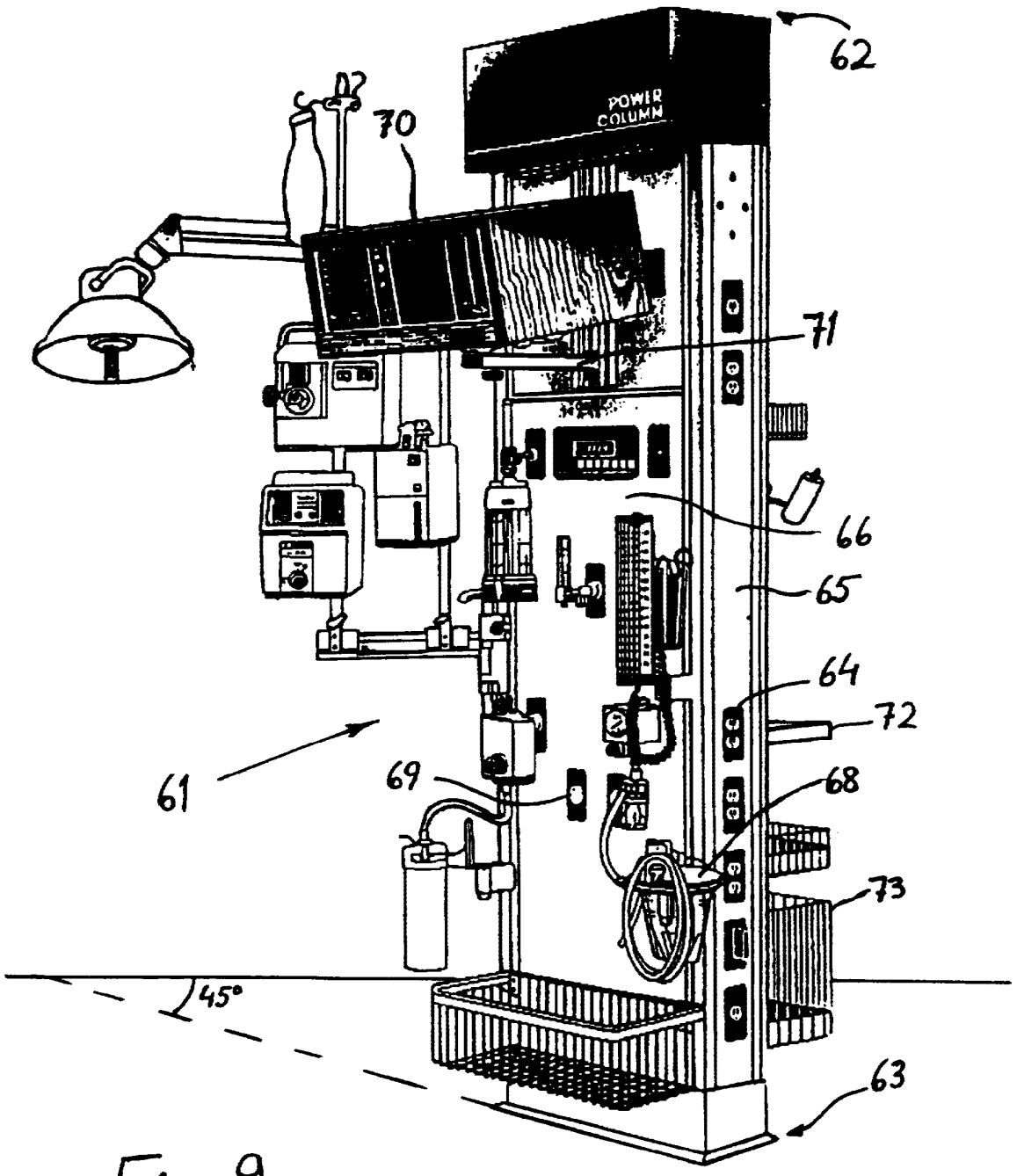


Fig. 9

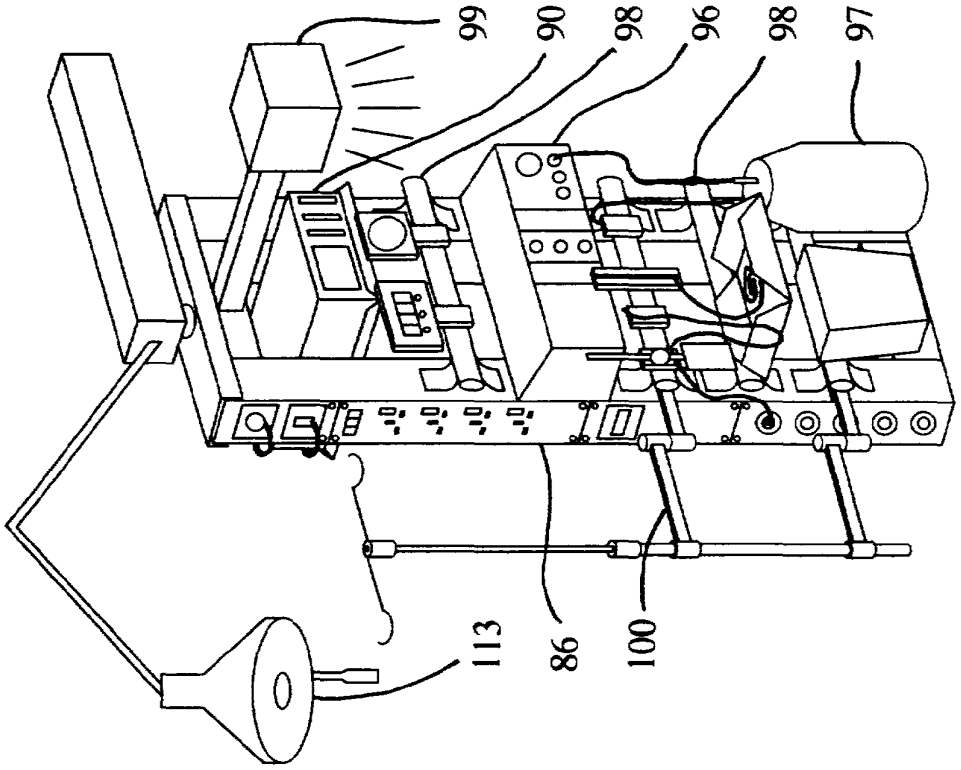

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Fig. 11

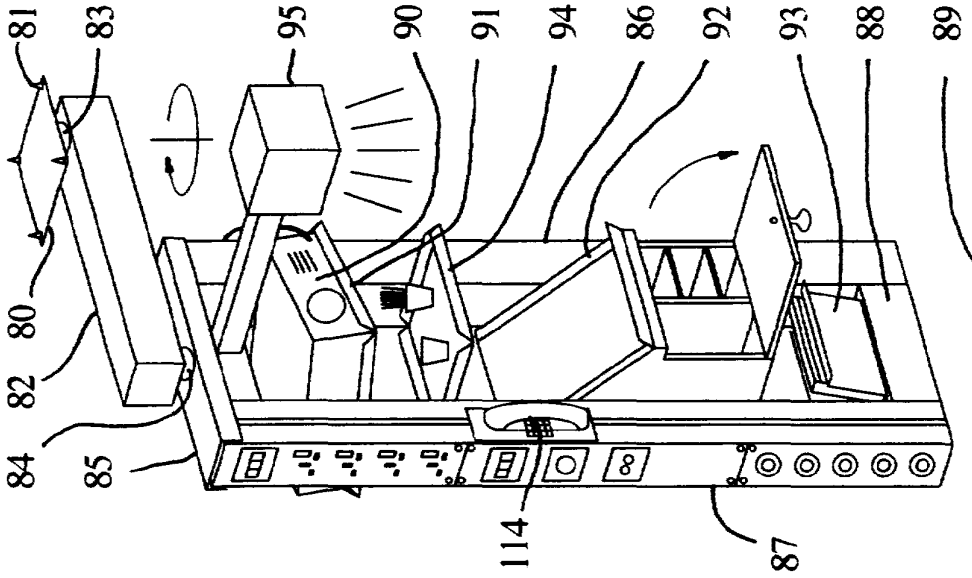
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Fig. 10

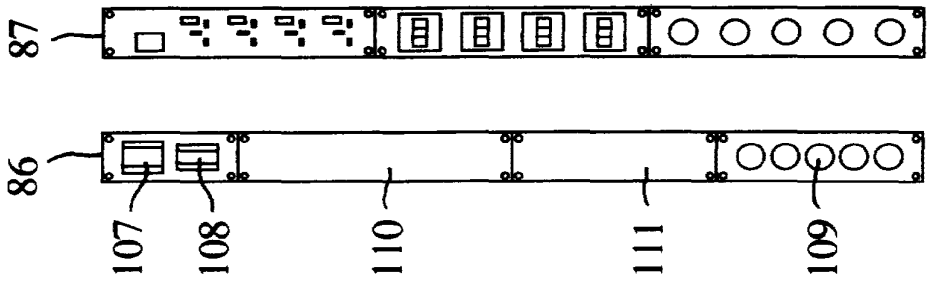

Fig. 15 Fig. 16

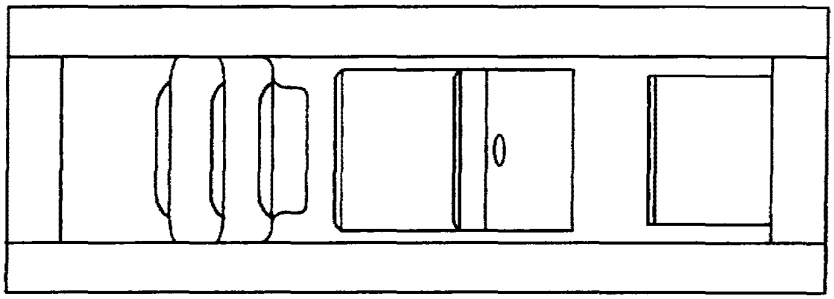

Fig. 14

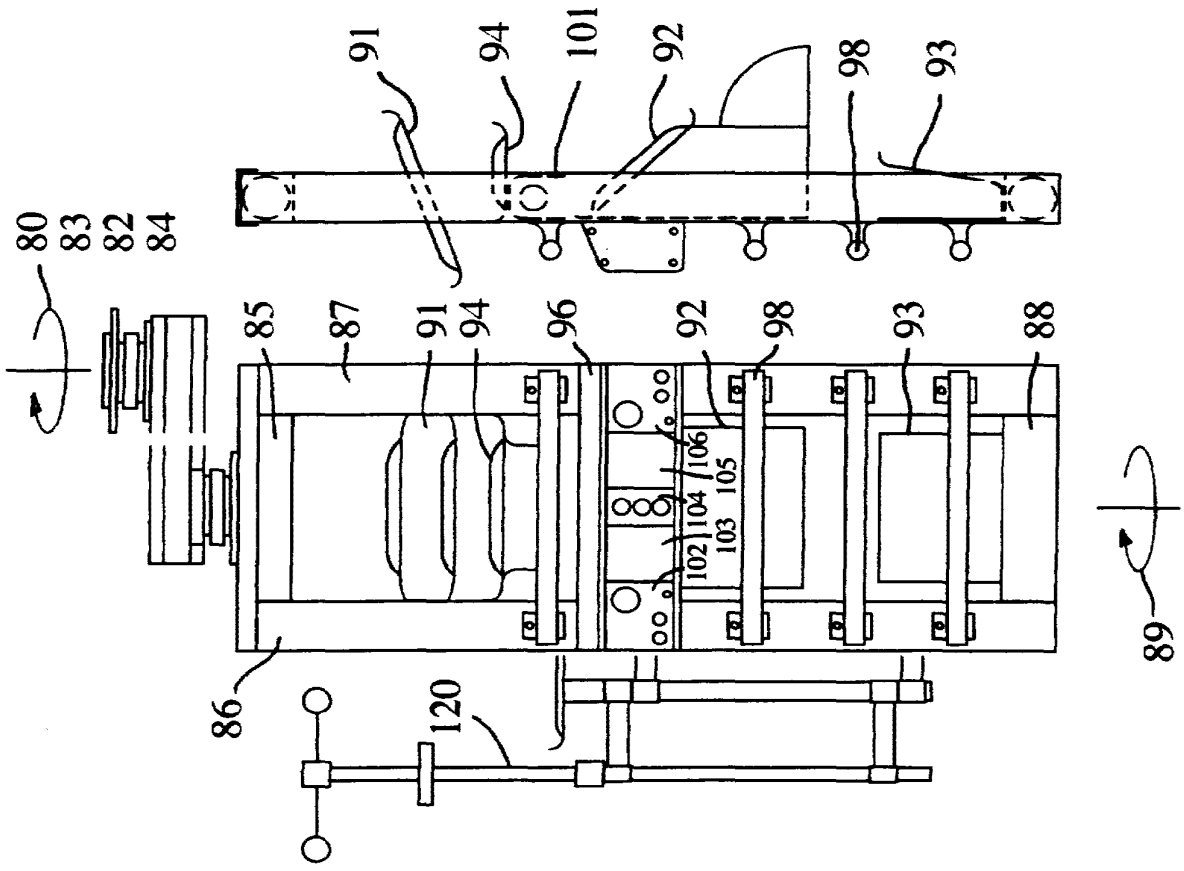

Fig. 13

Fig. 12

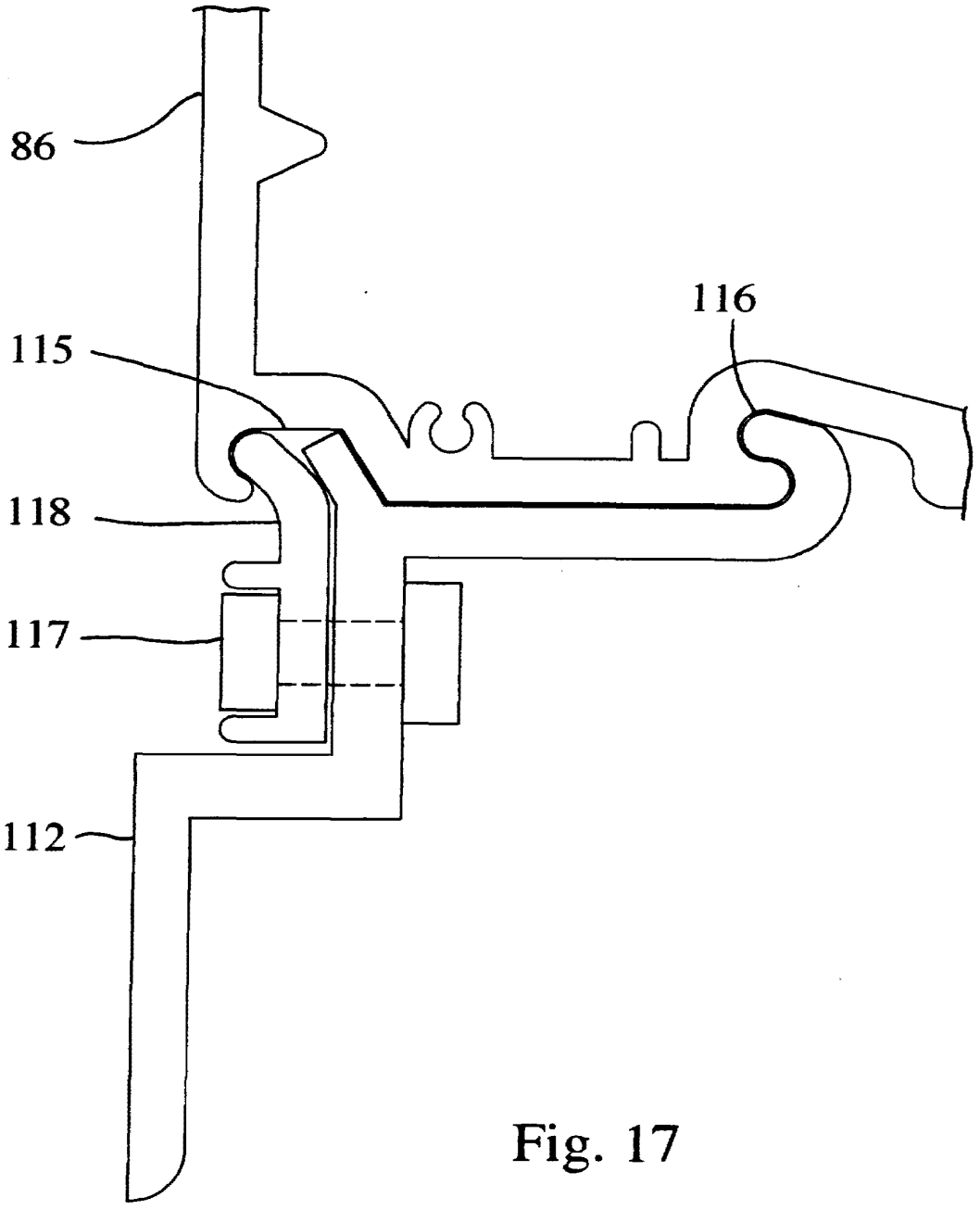

Fig. 17

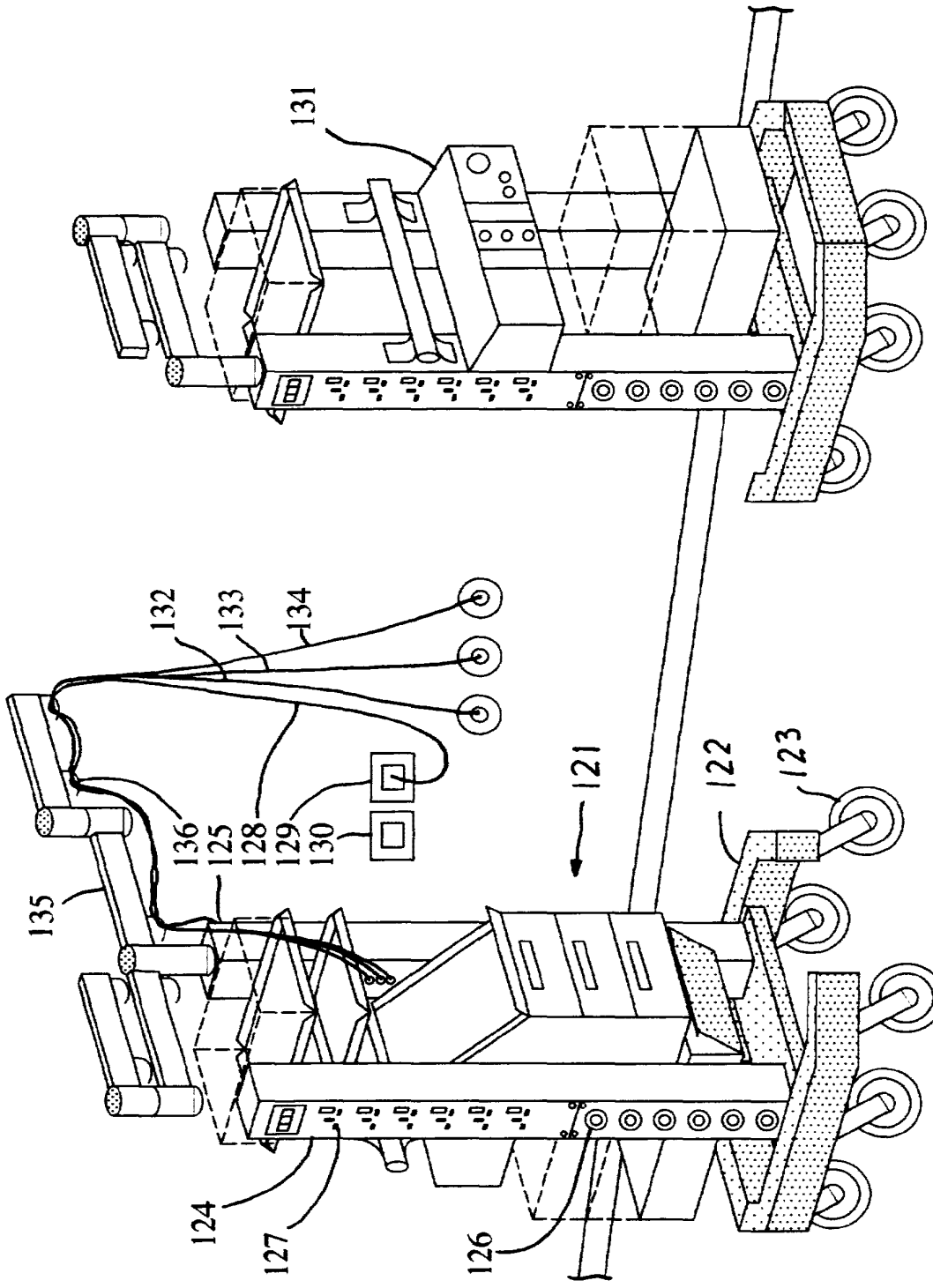

Fig. 19

Fig. 18

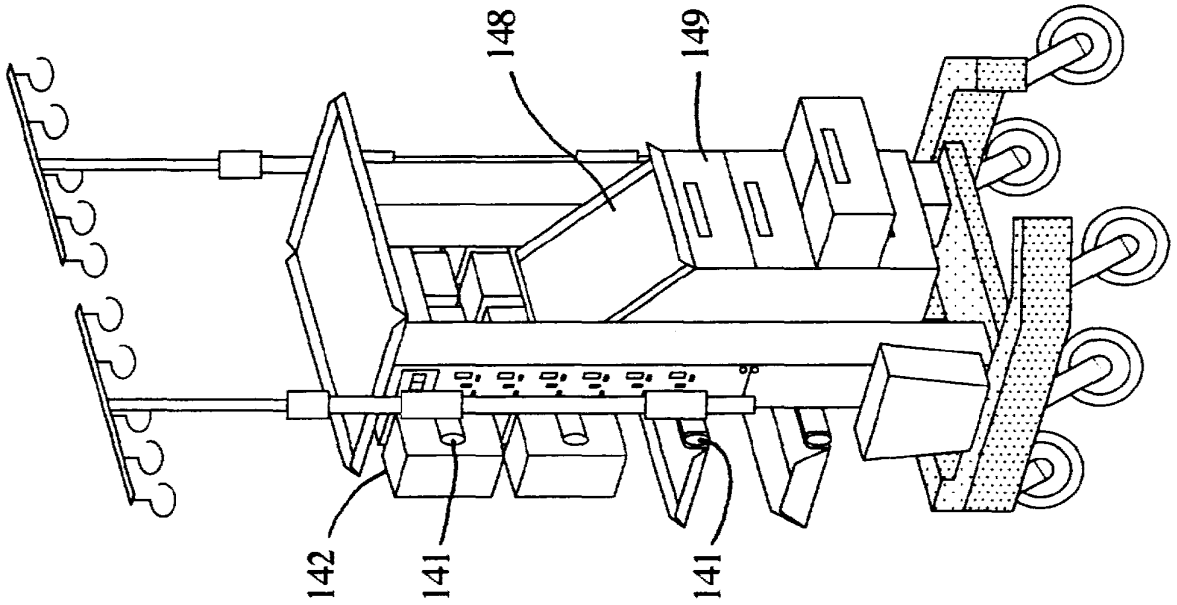
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Fig. 21

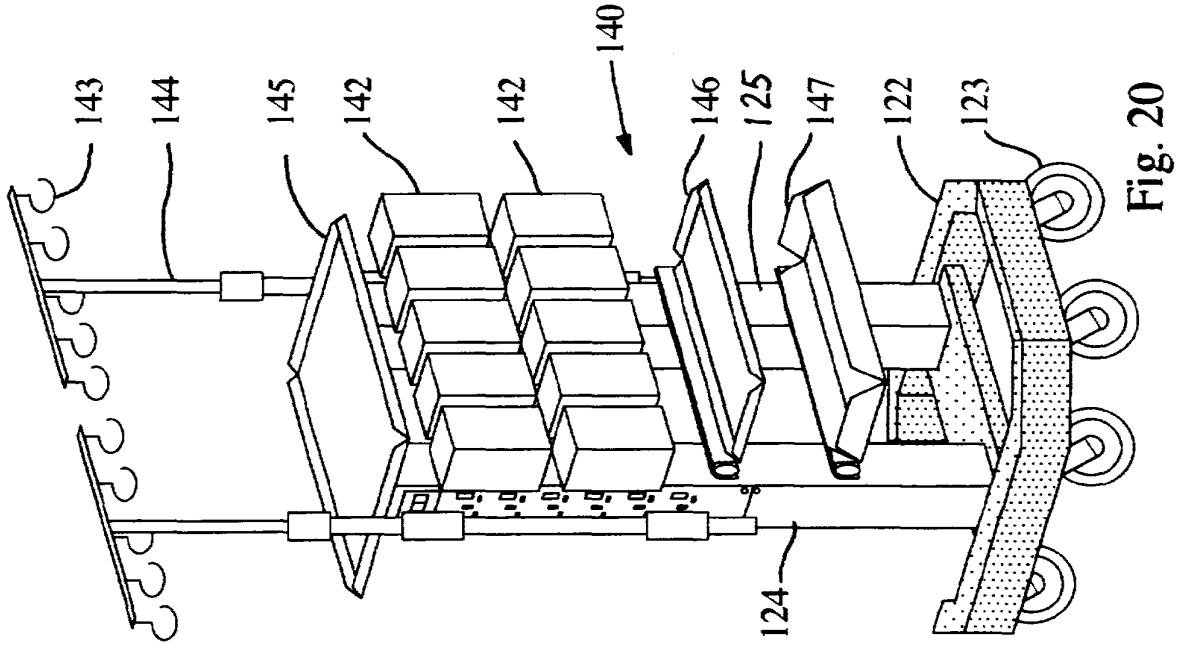
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Fig. 20

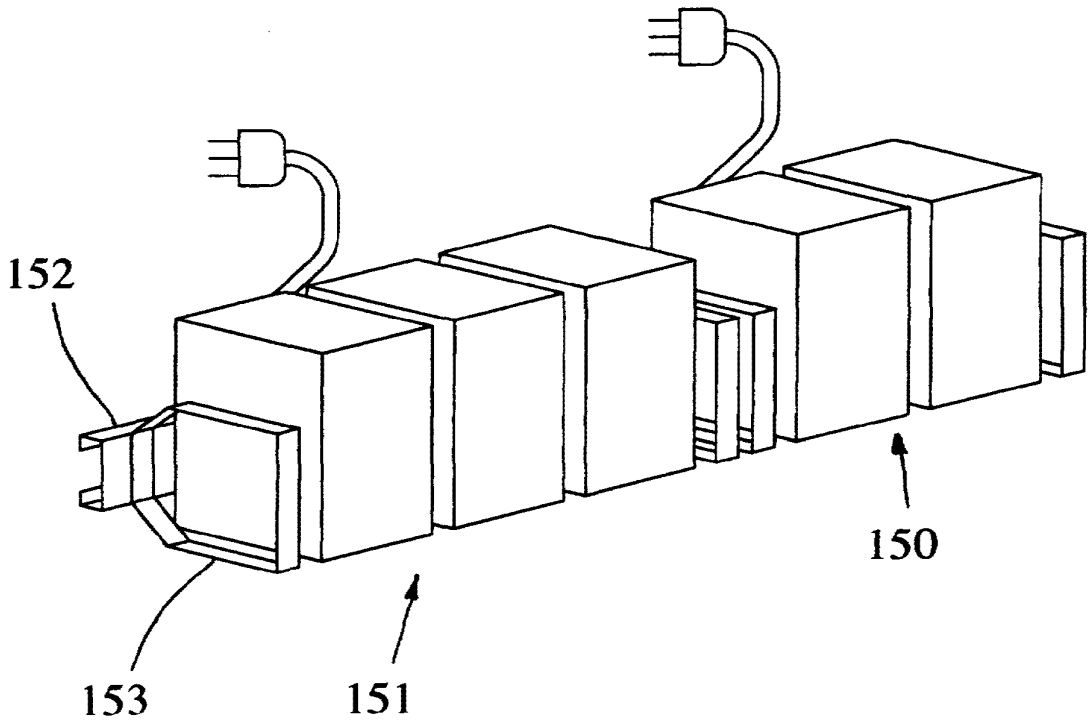

Fig. 22

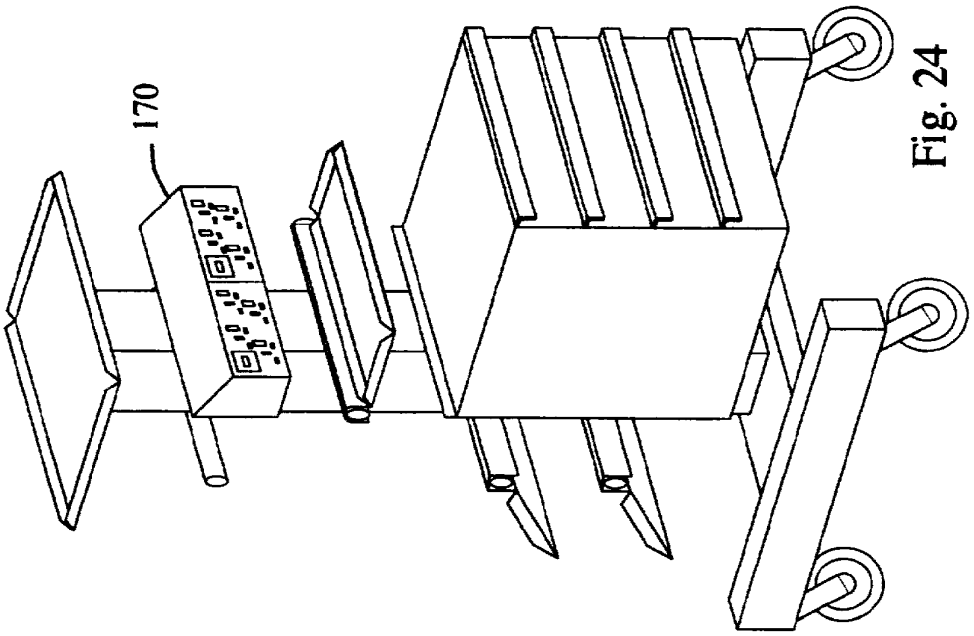

Fig. 24

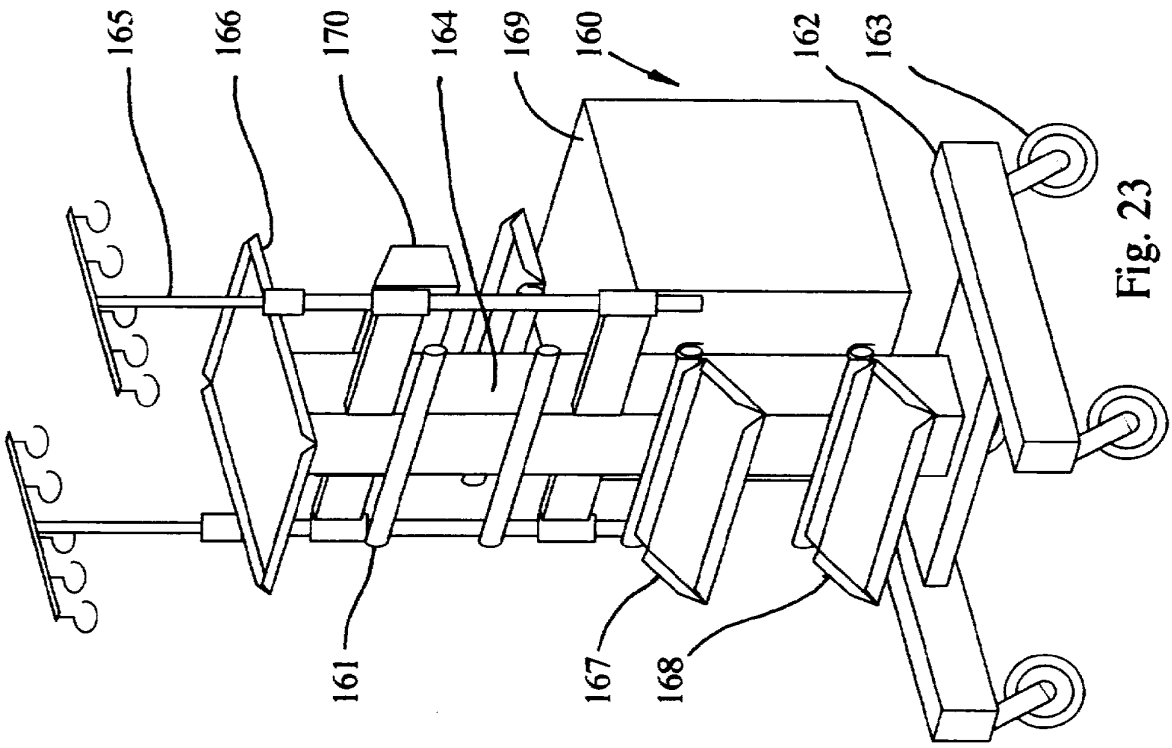

Fig. 23

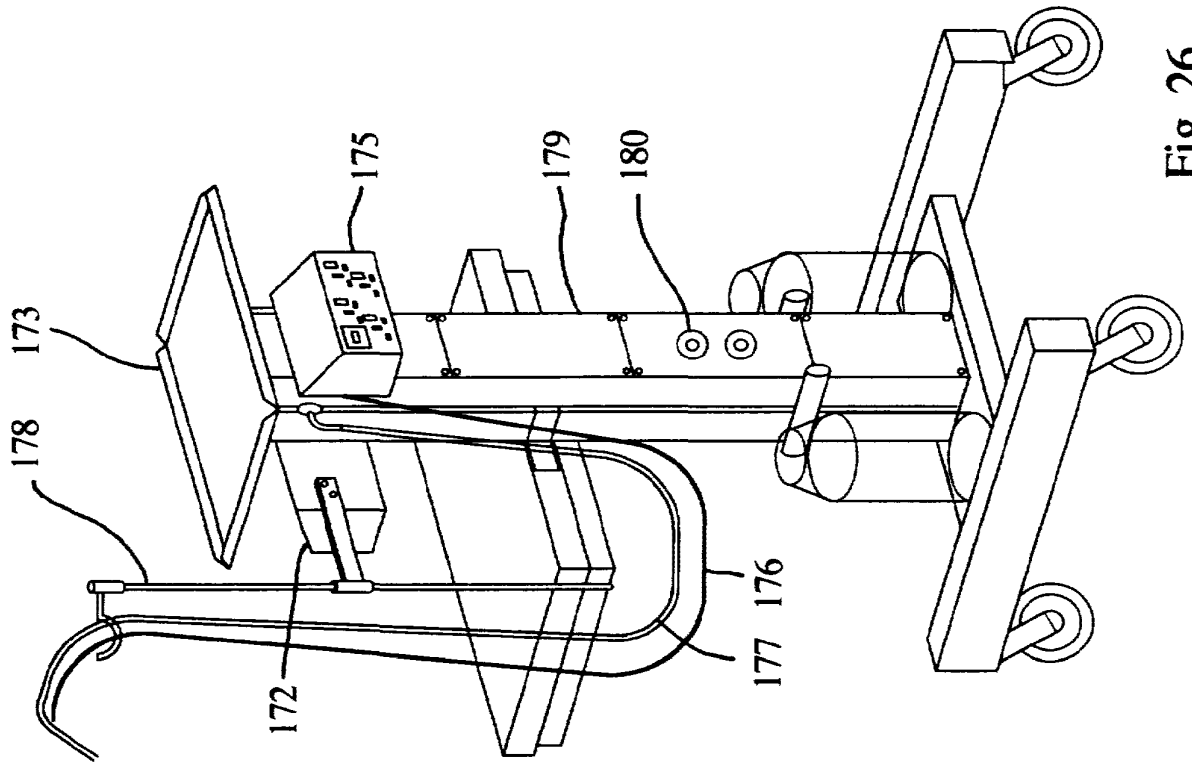

Fig. 26

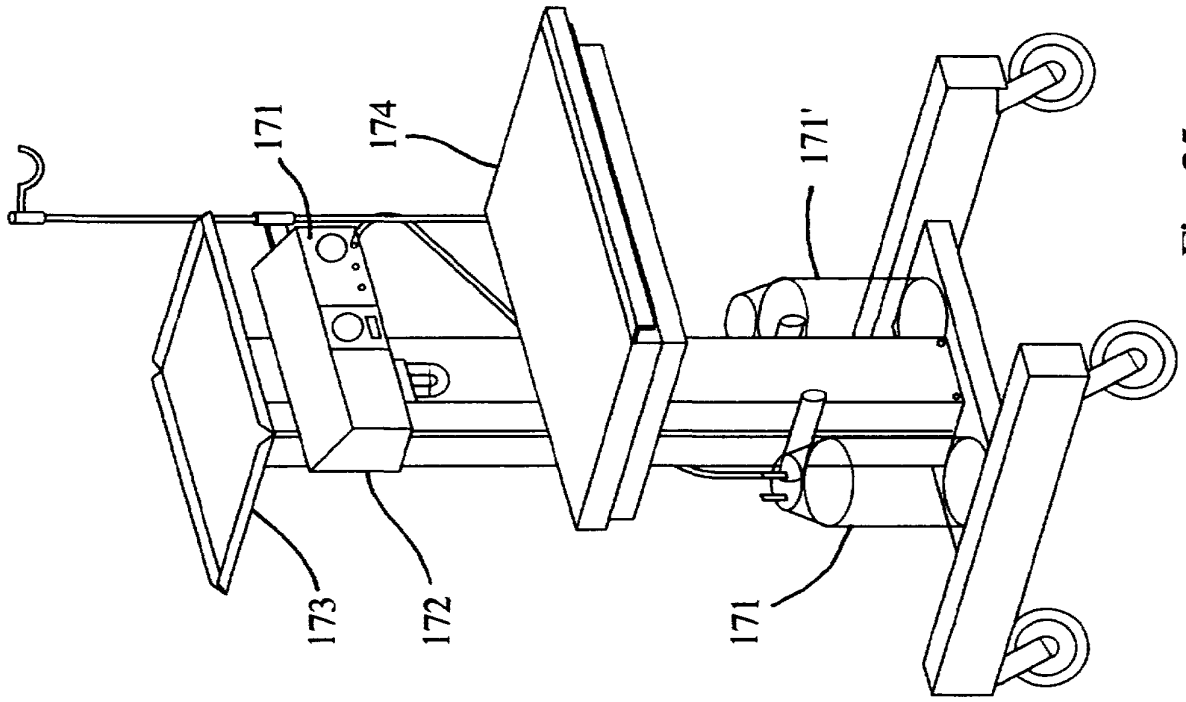

Fig. 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01346

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: E04B 9/06, A61G 12/00, A61B 19/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61B, A61G, E04B, E04F, E04H

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, 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	EP 0215212 A2 (TRILUX-LENZE GMBH & CO. KG), 25 March 1987 (25.03.87), column 4, line 37 - column 6, line 8, figures 1-4	1,2,7,8
X	CH 568459 A5 (A.L.H., NILSSON), 31 October 1975 (31.10.75), column 3, line 42 - column 4, line 45, figures 1-5	1,7,8
A		15
A	EP 0257299 A2 (KREUZER, F.), 2 March 1988 (02.03.88), column 2, line 13 - line 43, figures 1, 2	1,7,8

[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" erlier 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
12 February 1996	15 -02- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Ingemar Hedlund Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01346

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 4993683 A (F. KREUZER), 19 February 1991 (19.02.91), column 2, line 21 - line 58, figures 1-3	9
A		15
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 95/01346

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

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

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

Supportive structure intended to be attached at a ceiling of a hospital room according to claims 1-8.

Medical support service unit for intensive care rooms according to claims 9-14.

Service mobile for carrying medical equipment according to claim 15.

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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT
Information on patent family members

05/01/96

International application No.
PCT/SE 95/01346

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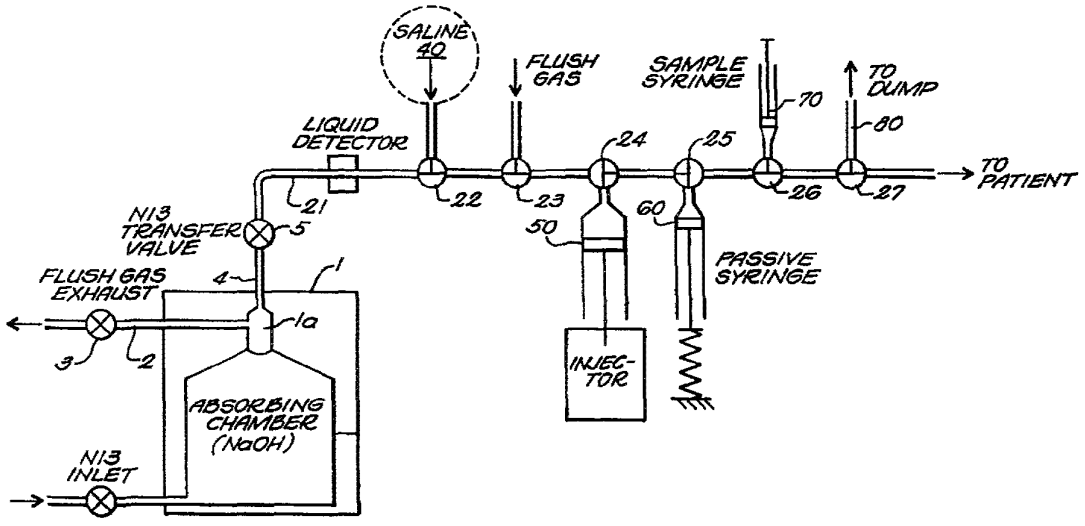

(57) Abstract

A radioactive material such as an unstable isotopic gas is provided to a receiving chamber (1) directly from a source to form a purified or enriched bubble. The bubble is passed to a fluid handling set for preparation of the reagent or other delivery system. In an exemplary embodiment trace amounts of nitrogen–13 are concentrated in a receiving chamber and passed into a small bubble of carrier gas. The carrier gas is then delivered into a fluid handling set. The fluid handling set connects to a pressure syringe (50) and a passive syringe (60), and further includes a plurality of flushable valves (22–27) interconnected as a closed unit by tubing (21) to form a switchable or finite state flow network in which the pressure syringe may back flush the tubing, mix the isotope in a delivery liquid, and transfer the mixed liquid to an output for diagnostic imaging or other use.

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RADIATION HANDLING SYSTEM AND SET

CROSS-REFERENCE TO RELATED APPLICATIONS

Not Applicable.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

Not Applicable.

BACKGROUND OF THE INVENTION

The present invention relates to the preparation and use of radioactive isotopes for biological purposes such as labeling, marking, imaging and diagnostics. Such applications generally utilize a single element containing minor amounts of an unstable isotope, which must be generally formed into a simple compound that is incorporated into a solution or reagent which undergoes a known or predictable interaction with the biological system being studied. Thus, for example, radionuclides are often added as labels to a substance that binds to a nucleic acid to indicate the presence of a particular substrate, termination or functional group. Similarly, materials which are taken up by particular biological systems may be labeled for treatment or imaging purposes. Aerosols or radio-labeled fluids may also be used for blood flow or lung function diagnostic imaging studies.

In general, it is necessary that radioactive materials be handled in such a way as to not expose the operator to radiation. Thus they are preferably handled under robotic control or automated conditions. It is desirable that the radioisotopes involved have a short half life, so as to automatically limit the exposure of the subject to radiation, and to facilitate proper disposal. However, materials with a short half life cannot be compounded in advance or stored for lengthy times. Such radionuclides must therefore be manufactured at or near to the site of intended use. In these cases the purification and preparation of the radionuclide in a suitable delivery system must also be accomplished locally. The brevity of the nuclide half life may further complicate its handling and processing. These factors have sometimes prevented the acceptance or use of otherwise worthwhile radionuclide-based procedures.

It would therefore be desirable to provide a convenient system for preparing radionuclides for biological use.

It would also be desirable to provide such a system for handling a radionuclide in an automated fashion without exposing the operator to radiation.

It would further be desirable to provide such a system useful for short-lived materials or small batches to enable the routine use of such materials in individual procedures.

SUMMARY OF THE INVENTION

These and other desirable features are achieved in a system in accordance with the present invention by providing a radioactive marker material such as an unstable isotopic gas to a receiving chamber directly from a source to undergo initial cleansing or concentration, and passing the material into a fluid handling set for automated preparation of the reagent or actual delivery system. In an exemplary embodiment, trace amounts of ^{13}N, created by proton bombardment of a target at a cyclotron, pass to a receiving chamber, are cleansed and pass into a small bubble of carrier gas. The carrier gas is then delivered into a fluid handling set. The fluid handling set includes or connects to a pressure syringe and a passive syringe, and further includes a plurality of flushable valves interconnected by tubing in a closed unit to form a flow network in which the pressure syringe may back-flush the tubing, mix the isotope in a delivery liquid, and transfer the mixed liquid to an output for diagnostic imaging or other use. The fluid handling set, which is a closed and preferably sterile unit, may include the receiving chamber 1, and it mounts in a fixed console of operating motors and condition sensors to control the various steps of fluid handling and delivery, and to effect safety functions which enable the system to connect directly to a catheter or to a vascular injection system for use on human beings.

In a preferred embodiment, the receiving chamber 1 is substantially rigid, but has a region of limited or unidirectional compliance. The chamber receives a flow of trace

isotope in a bulk gas, operating to remove the bulk gas while the radionuclide accumulates in a bubble at the outlet port of the chamber. Compliance of the receiving chamber may be effected by means of an elastic wall tensioned against a rigid support such that the wall flexes outwardly under pressure to accommodate the inflow of carrier gas but may not bow inwardly. This maintains the chamber volume above a fixed minimum, and prevents liquid from leaving the chamber when suction is applied at the top. In an illustrative system, nitrogen-13 is generated by cyclotron bombardment of a target with accelerated particles, and when the target has attained a sufficient level of radioactivity, the sample is passed to the receiving chamber and the CO_2 with trace ^{13}NN is bubbled into a sodium hydroxide solution. The one-way compliant wall allows a large flow to be received and maintained under pressure to accommodate the different rates of carrier delivery and carrier removal effected at this stage. The CO_2 reacts with and is effectively taken up by the sodium hydroxide solution, while the desired nuclide concentrates at a gas-filled plenum at the top of the receiving chamber, where it is accessed at the outlet port using a closed sterile set to effect transfer, mixing and delivery in a form useful for medical imaging. The fluid handling set includes a plurality of three way valves or medical infusion stopcocks that are preconnected together via small bore tubing to form a flow path. Two of the stopcocks each have a third port, which are attached to syringe bodies. One operates as an active bidirectional pump, while various motors and sensors in the console operate and control the position of the stopcock handles to achieve transfer, mixing and delivery of the radionuclide.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be more fully understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Figure 1 is a flow chart illustrating major steps of the preparation process of the present system:

Figure 1A illustrates the system showing representative components in use for positron emission tomography;

Figure 2 illustrates system architecture as applied to a nitrogen 13 radionuclide;

Figure 3 illustrates a preferred construction of a receiving chamber for the system of Figure 2;

Figures 4A through 4D illustrate details of valve operation and flow for transfer of the radionuclide into a fluid handling set of the present invention;

Figure 5 illustrates an operating console for the set of the invention;

Figures 5A-5C illustrate stopcock mounting and control blocks of the console for use with a closed sterile set; and

Figure 6 illustrates another embodiment of the system and set.

DETAILED DESCRIPTION OF THE DRAWINGS

In accordance with a principal aspect of the present invention, there is provided a system for automated and isolated handling of a hazardous material, such as a radionuclide, for biological or medical use. The system includes a sterile set defining the path of the nuclide from a source or process chamber to its end use which, in the illustrated embodiment, involves injection into a patient. Other potential end uses may include specialized labeling, microanalytic or synthesis applications. As shown in Figure 1 for a representative system, the radionuclide, which in this case is nitrogen-13, passes from a source to a conditioning or purification chamber 1 which produces a small mass or bubble of the concentrated radionuclide for delivery to the preparation portion 10 of the system. The preparation portion 10 dissolves the nuclide in

a saline solution for injection in a patient, and may directly inject the prepared solution into the patient.

By way of technical background for this embodiment, the use of nitrogen-13 in gaseous form for medical imaging procedures was pioneered at the Hammersmith Hospital, in London, several decades ago. The radionuclide is produced by bombardment in a cyclotron using a number of possible target systems and sweep gases. Further details may be found in the text Short-lived Radioactive Gases for Clinical Use of J. C. Clark and P. D. Buckingham (Butterworth, London and Boston) pp 190-200. That text is hereby incorporated herein by reference. Nitrogen-13 is only very slightly soluble in blood, and when injected in solution in the blood stream, quickly leaves the blood and accumulates at the blood-air exchange interface in the lung. Its decay creates positrons which may provide excellent three dimensional PET images of the lung, for evaluation of both perfusion and ventilation. However, the difficulties of using this radionuclide have effectively prevented its adoption in hospital settings. Much of the discussion below is applicable to other gaseous radionuclides such as oxygen-15, or radionuclides incorporated in a gaseous medium, or in a liquid with appropriate modifications. However, the preparation and use of nitrogen-13 presents a number of technical difficulties and will therefore be discussed more fully to illustrate aspects of a system and components of the present invention.

In accordance with a principal aspect of the present invention the source radionuclide is provided in a relatively crude or bulk form, for example in a sweep gas or target fluid from a cyclotron, or in other primitive or intermediate form, and flows through the system to directly enter the patient or be applied to some other sterile or purified application such as marking, analysis or synthesis of a pure product. As shown in Figure 1A it is generally contemplated that the system 20 will be a small cabinet, desktop or other stand-alone unit containing the sub-assemblies 1, 10 (Figure 1), and which attaches to the source and to the patient either directly or via a small intermediate assembly. For example, the unit 20 may connect to the source through a filtration unit or the like, and to the patient via an infusion line, port or pressurized timed injector or the

like. However, most preferably the connection to the source and to the patient are as direct as possible so that little dead space, wasted volume, delay time or regions of radiation exposure are interposed between the source and the patient.

As further shown in Figure 1A, the invention generally contemplates that the unit 20 will be controlled as to several parameters discussed below by a connection to a keyboard/processor assembly 21. Also the specific nitrogen-13 embodiment is used in conjunction with an imaging or detection assembly 25. The assembly 25 of Figure 1A is a detector array which encircles the patient and is configured for positron emission tomography, to simultaneously detect the pair of annihilation photons emitted in opposite directions by positron-electron annihilations as the radionuclide decays. The detector 25 provides its detection signals to a processor for construction of a three dimensional image of the distribution of the positron-emitting radionuclide. Other suitable detectors include single-sided detector arrays, or even photographic plate cameras which register and record the received annihilation photons on a plate of film. However, a positron emission tomography (PET) instrument is the preferred detection instrument for the illustrated process.

Figure 2 illustrates functional component of the units 1, 10 of Figure 1. As shown, the unit 1 for carrying out preliminary cleansing or refinement of the radionuclide in this case includes an absorbing chamber through which the nitrogen-13 bubbles to remove the CO_2 sweep or residual target gas as the material arrives from the cyclotron source. The absorbing chamber 1 is filled with sodium hydroxide solution and is shaped with an inverted funnel cap that channels unabsorbed gas upward to a plenum 1a at the top of the chamber. Plenum 1a connects on the one hand to an exhaust port 2 controlled by an exhaust valve 3 and, on the other hand, to an outlet port 4 controlled by transfer valve 5. The outlet port connects to the main process line 21 of the sub-assembly 10, which as noted above resides within the preparation console 20 (Figure 1A) forming an inlet thereof and extending therethrough to the patient or end use. As described further below, chamber 1 may also be located within the console 20.

As further shown in Figure 2, the functional flow control and handling units appearing in the preparation console 20 include in addition to the flow line 21 a plurality of sterile three-way valves or stopcocks 22,... 27 each of which has two of its three ports connected to the line 21, and its third port connected to an inlet, outlet or syringe. The distal end of line 21 forms the output path from console 20. Each of the stopcocks 22-27 may be identical, and advantageously the stopcocks together with tube 21 are connected together and initially provided as a closed and sterile unit packaged in a manner similar, for example, to a medical infusion set. Each stopcock thus has one "free" port which is connected to allow material to enter, leave, or be moved along line 21. These third ports are attached to a source of sterile saline fluid 40, an active injector syringe 50, a source of flush fluid, and a passive holding syringe 60. In addition, a sample syringe 70 connects at stopcock 26, and an outlet line 80 to a dump, or waste vessel, extends from stopcock 27. These elements may also be connected as part of the set, although, as will be understood from the discussion below, variations are possible. The function of the sample syringe may be implemented instead by providing a small plenum with a pierceable septum connected to the third port of stopcock 26, and the line 80 may simply terminate with a spike port for attaching to a suitable collection vessel or transfer mechanism.

As further illustrated in Figure 2, the passive syringe is spring loaded so that it is normally biased to a non-extended, closed or minimal volume configuration. Thus, when a pressurized flow appears along line 21 and is directed into the syringe 60 by stopcock 25, its piston moves outwardly to form an adaptive chamber that changes volume under pressure for receiving the fluid in the line 21.

In accordance with a principal aspect of the present invention, the sterile set 21 includes a set of connected stopcocks and a syringe 50 all configured to fit within the control console (described further below) and to be manipulated by servomotor elements therein to carry out the radionuclide preparation and delivery to the patient. In a representative preparation and delivery protocol, the stopcocks are set to positions such that one or more stopcocks block the inlet, outlet or intermediate portion of the set, while

one or more stopcocks are open to interconnect various portions of the path for receiving, preparing or delivering the radionuclide. In particular, the set 21 defines a finite state flow path formed of sterile single use disposable elements that fit within a console adapted to secure and control both sets of elements. Advantageously, the console 20 may be configured as a cabinet having separate compartments and which may, for example, be hinged to open for inserting and changing the set. In the prototype, the receiving chamber 1 is housed in the back half with its outlet line 4 (Figure 1A) connecting through the middle wall of the cabinet so that the fluid line 21 (Figure 2), runs through an array of stopcock or syringe receiving recesses and control elements laid out along a path in the front half of the cabinet.

In this embodiment, the apparatus is conveniently divided into those parts that do not contact the sterile solution, and those parts which do. The parts which contact the saline directly are sterile, and are assembled from disposable medical components. These include all of the tubing downstream of the liquid detector, the stopcocks, and the three syringes 50, 60, 70 which are disposable, and are to be replaced for each patient. These components are mounted on the front panel of the main unit, so that they can be changed quickly. The remaining parts of the system do not contact the saline, and may advantageously be made of reusable components. Thus the absorbing chamber 1, and the various solenoid valves and tubing that connect to it may be permanently installed. Preferably, the system is enclosed in a cabinet which is connected to a high flow-rate vacuum to maintain a steady flow into the cabinet through its small openings, so that any leaks of radioactivity within the system are contained and the radioactive material is removed.

The cabinet is divided into three compartments. The rear compartment, accessible via a rear door, contains the absorbing chamber and a dump tank. This compartment is watertight so that a catastrophic failure of the absorbing chamber will not result in escape of sodium hydroxide. A central compartment houses all of the electronics of the apparatus, and is protected from contact with any liquid that may leak from a failing component or connection. The front of the cabinet forms a door which

encloses the front panel, allowing easy access to components of the system that need to be changed frequently. Preferably the syringes mount on this panel.

Figure 3 shows a preferred construction for the receiving chamber 1, which may be formed of a strong medical grade polymer. As shown, the receiving vessel 1 is configured with a rigid housing 101 which may for example be formed of a hard plastic and having an interior with a major lower portion configured with a sloped roof leading to a chimney-like upper portion or outlet plenum 109 of defined volume. The vessel 101 is configured to fit on a magnetic base such as a stand having an internally mounted rotating permanent magnet driver mechanism positioned below the chamber support surface, and a magnetic stirring rod 107 is positioned in the bottom of the vessel 1. The main chamber communicates through a passage 102 to a secondary chamber 101a bounded by a flexible elastic membrane or wall 104 positioned over the passage 102. This serves as a compliant chamber; the membrane 104 bends outwardly as pressure increases in the chamber 1 and fluid flows through the passage into the secondary chamber. However, housing 101 is rigid and the passage 102 is relatively small, or else may consist of a number of small passages such that the wall below the flexible sheet 104 forms a perforated plate that supports the sheet and effectively prevents the sheet 104 from moving inwardly in response to negative pressure. This arrangement provides a stable volume within chamber 1, and accommodates a large influx of fluid so that when radioactive material from the cyclotron enters the inlet, a large bolus of material may be received, increasing the pressure and allowing the material to more effectively react in the absorbing chamber at the slower process rate of absorption therein. As discussed briefly above for the illustrated CO_2/nitrogen-13 material, chamber 1 is filled with a sodium hydroxide solution and is gently stirred by a magnetic stirring rod, so the solution quickly reacts with and effectively removes all the CO_2 while the unreactive nitrogen tracer rises into the outlet plenum 109 at the top of the chamber.

Preferably, for this process, the plenum 109 is initially loaded with a small volume, e.g. a few cubic centimeters, of a carrier gas in which the nitrogen-13 is soluble. This carrier may, for example, be nitrous oxide or other suitable biocompatible

gas. It is also advantageous that the carrier be highly soluble in blood or aqueous solutions, so that as discussed further below, problems of bubble formation or potential danger of bends are avoided. Thus, operation of the receiving chamber 1 is such that the sweep gas or target predecessor material from the source is removed, and the cleansed or concentrated radionuclide resides in the plenum 109 with a carrier gas for transfer through the transfer valve to the flow path 21. The architecture of vessel 1 therefore retains the pocket of gas at the top of the chamber intact. In this way, no liquid infiltrates the tubing leading to the rest of the apparatus, where small droplets of liquid might cause false triggering of the liquid detector or blocking of the hydrophobic filter.

An important aspect of the design of the compliant compartment is that it is only compliant to positive volumes. That is, volume can be added to the chamber, but not withdrawn. Once the carbon dioxide is absorbed, and the bubble of nitrogen withdrawn, the membrane wall lies flat against the side wall of the chamber, and the chamber becomes rigid. Thus it is impossible to suck significant volumes of sodium hydroxide out of the absorbing chamber and into the rest of the system.

Skipping ahead to Figure 5, there is shown a representative front panel of the console assembly 20 with the radionuclide entry port and elements of the flow path 21 laid out thereon. As shown, the flow line 21 first passes through a liquid detector which detects the arrival of liquid in the flow line from the chamber 1 and provides a control signal used, as described further below, for switching the states of the various stopcocks and transporting the bubble of radionuclide through the processing stages of the preparation assembly 10.

As further shown in Figure 5 a hydrophobic filter 29b is placed in the flow line 21 as a barrier to entry of liquid from chamber 1 into the system 10. As shown, the fluid preparation line 21 or set, is positioned in the console 20 such that each of the stopcocks 22-27 fits within a corresponding receiving block 22a through 27a, and the injection syringe 50 and passive syringe 60 fit within a driver mounting 50a and a syringe support 60a, respectively. By way of example, the driver assembly for the injector syringe may be that of, or similar to, a manual or programmed contrast agent injector system capable

of operation to drive a standard disposable syringe at high pressures through one or more precisely timed and controlled displacements to inject preset doses or volumes into the vascular system of a patient. The mounting 60a for the passive syringe may include a spring-loaded or counter-weighted platform or pushing member against which the distal end of the plunger of the injection syringe rides, so that the biased member returns the piston to its upper position (as shown) when the state of the stopcocks allows flow and the pressure in line 21 drops below the spring bias threshold.

In the prototype embodiment, the injector drive consisted of a MedRad radiographic contrast injection instrument, and the remainder of the cabinet and control mechanism of unit 20 was built atop the injector mount so that the active syringe was conveniently located in immediate proximity to the other elements shown in Figure 2. The stopcock mounting assemblies were prepared as shown in Figures 5A through 5C, by constructing shaped plastic receiving blocks having recesses each shaped to accept a standard disposable stopcock assembly therein and to mount on a plate so that each stopcock engages a position reporting actuator mechanism, which turns the handle of the stopcock. The stopcock was placed into the housing with the handle facing forward and the housing was designed to grip the three fluid connecting stubs of the stopcock, thus securely holding the stopcock body in a fixed position that allowed stopcock position to be controlled to within about one degree. A molded coupling was used to connect the stopcock handle to a standard servomotor, which in turn was controlled by a microcontroller board connected via a serial line to a computer used to control the apparatus. The computer was programmed to control operation of the stopcocks to define different segments for receiving, transferring, mixing and delivering the material. It was also programmed to control the injection regimen of the syringe for delivery of prepared doses to the patient.

In the prototype embodiment, the servomotor assemblies were modified so that the output of an internal potentiometer was passed to an A/D converter on the microcontroller board, and this output was used to calibrate the stopcock positions and then continuously monitor the position of each stopcock. Control software in the

microprocessor with a graphical user interface allowed the user to set the position of the stopcock and displayed the position on the screen, signaling an alarm if a motor fails to drive a stopcock element to the programmed position. For preparing the nitrogen-13 tracer, the program was written to effect a sequence of control steps as described below, and delivery steps were controlled by using the injector both to control the preparation of the solution and the injection into the patient.

Figure 4 illustrates a particular sequence for transfer of the tracer bubble from the absorbing chamber 1 into the mixing syringe, which is performed by encapsulating the tracer bubble with a saline solution. In broad terms, the operating sequence proceeded as follows. Before gas is received from the cyclotron the system is readied for production. The tubing from the absorbing chamber is flushed with a gas and the remainder of the apparatus is flushed and filled with de-gassed saline solution. One suitable flush gas is nitrous oxide but many other gases may be used. The chief requirements are that the gas be biologically safe, soluble in water and be non-reactive with the reagents used (sodium hydroxide, in this case). The radioactive gas is then admitted to the absorbing chamber and is stirred with a magnetic stirrer until all carbon dioxide is absorbed. Stirring is performed gently to avoid generation of droplets which might clog the hydrophobic filter 29b (Figure 5). The bubble of remaining gas at the top of the absorbing chamber is then transferred to the injector syringe which is otherwise filled with an appropriate amount of de-gassed saline for the contemplated infusion regiment or for the amount or available radionuclide. The mixture in the injector is next dissolved by repeatedly ejecting it into the passive syringe allowing its return and again ejecting it, so that by the vigorous flow and atomizing action of ejection the tracer is quickly dissolved in the saline solution. This process of vigorous atomization mixing by repeated passage through a flow segment between syringes in a closed set thus effectively addresses the difficult problem of preparing the radionuclide solution in a manner that is both safe and quick.

Next, with the stopcocks reset to define a different flow segment, a sample of the injectate so prepared is expelled from the syringe into the sampling syringe 80. Preferably a pH sensor is also present in the apparatus downstream of the injector

syringe to detect any sodium hydroxide contamination which may have occurred, and to actuate a shutdown in that event. The strength of the prepared solution is determined and this data is entered in suitable program for the injection control or image processing. The stopcock configurations are again changed, and the injector then gives a rapid bolus of tracer solution along its output line into the patient.

Returning now to Figure 4, there is shown a representative sequence of states of the finite state flow segment operating sequence of the device, illustrating in this case the initial radionuclide transfer from the receiving chamber 1 into the preparation set 10. After the initial system preparation and cleansing in chamber 1 are completed, the state of the apparatus is as depicted in Figure 4A. The upstream tubing (on the left) of stopcock 22 is filled with flush gas and the downstream tubing (to the right) is filled with degassed saline. The syringe 50 is then operated to draw along line 21 so that, as shown in Figure 4B the bubble of radioactive gas is drawn out of the pocket 109 (Figure 3), and toward the injector syringe 50. Sodium hydroxide solution is also drawn out of the absorbing chamber 1 at the trailing edge of the bubble of carrier/tracer gas. A liquid detector 29a is installed in the assembly 10 about the line 21 just upstream of the first stopcock 22 to provide a signal when the sodium hydroxide reaches this point. The transfer valve (Figure 3) is then closed, and the controller moves the first stopcock (Figure 4C) to connect the saline reservoir and fill in behind the bubble with saline solution from the reservoir. The bubble of tracer is thus "encapsulated" by saline solution as shown in Figure 4D. This allows controlled transfer through the apparatus by operation of the injector syringe. A slight amount of tracer gas still residing in the first stopcock and liquid detector is wasted. However, it will be understood that all tubing interconnecting the various components in the processing section 10 is of small size (under one millimeter), of the type customarily used for transfer of small volumes of fluid, and thus the wasted tracer represents a very small proportion of the carrier/tracer bubble being processed.

After the bubble of gas is completely drawn into the injector syringe, the stopcocks are moved to define a new flow/transfer segment such that the injector outlet

communicates only with the adjacent passive syringe. The mixture is then vigorously expelled into the passive syringe, then again drawn back into the active syringe and re-expelled. This process of repeated ejection promotes dissolution of the gas in several ways. Firstly, the surface area of the interface is increased exponentially by atomizing the fluid and in subsequent ejections breaking bubbles of gas into many smaller bubbles. Secondly, the ejection occurs at elevated pressure, thus enhancing the mechanisms of diffusion. Finally, the strong current and highly turbulent flow during ejection mixes the liquid very well, reducing any concentration gradients that might otherwise limit the process.

After the mixing process is complete, the stopcocks are again repositioned and the syringe 50 is operated to expel to the dump a volume equal to the volume of gas originally drawn into the syringe. This assures that any undissolved gas is ejected from the system. The lines to the patient are then flushed with the prepared tracer solution, and a small (1 ml) sample is taken. For the illustrated system, the sample is used primarily to assess the activity of the solution, but it could be additionally analyzed to check the composition of the injectate, or when applied to other radionuclide systems could determine other relevant conditions or parameters.

The pH of the solution is preferably measured by a sensor installed on the line to the dump tank. Any sodium hydroxide contamination is detected at this point, before injection to a patient.

In the foregoing system, it is important that the solution injected into the patient not be super-saturated and not contain any gas bubbles. If the solution were super-saturated, there would be a risk that bubbles could spontaneously appear in the solution before infusion or that microbubbles of nitrogen would form in the bloodstream causing an artificially-induced form of decompression sickness ('the bends'). To assure that supersaturation does not occur, the volume of nitrogen withdrawn from the absorbing chamber is limited to that volume which is known to dissolve in the volume of saline being prepared, and following dissolution, the mixture is allowed to equilibrate at atmospheric pressure. Thus, even if the solution is super-saturated, excess gas will

diffuse out of the solution. Further, when, following the mixing described above, the volume at least as great as the volume of gas originally drawn in from the absorbing chamber is ejected from the top of the injector syringe to dump, both the excess undissolved gas and the gas that has come out of solution are expelled.

Preferably, an ultrasonic bubble detector is also installed on the line to the patient, as well as a bubble-trap filter. Prior to injection, the lines are flushed, and a final, visual check for microbubbles is performed.

Figure 6 illustrates another embodiment of the system and set of the present invention. In this embodiment, the compliance chamber or flexible-walled side chamber may be actively pressed. This may be done to assure complete return of the flexible wall, and thus further guard against expulsion of the sodium hydroxide solution. Furthermore, the stopcocks are located somewhat differently to provide a short direct infusion path to the patient, and to separate or shift other paths or path segments. As in the first embodiment, the pressure syringe is centrally located, and serves as a hub for drawing, expelling or moving fluid along the various segment defined by the states of the stopcock valves. Advantageously, the pressure syringe mounts vertically, so that it initially receives and segregates the gas, and subsequently expels residual bubbles to the dump.

For operation of the system, the saline may be drawn from a USP-standard infusion bag, and all parts of the apparatus that contact the solution are assembled using aseptic technique from sterile, disposable medical components. Microporous filters are installed on the line entering the system from the saline bag, and on the line out of the system to the patient. Preferably a batch of tracer solution is prepared before the batch intended for infusion, and a sample is assayed.

Preferably, the bolus infusion of tracer is given by the injector under computer control, with the computer programmed to accurately control the infusate volume and rate, to effectively synchronize with a PET camera, and to automatically adjust dosage as the tracer decays. However, preferably the hardware is designed so that if necessary, the injector can be disconnected and operated manually. In the prototype embodiment using

an existing, manually-operated contrast media injector, the addition of a microprocessor-based controller and other modifications made to the injector were such that all of its safety-features function normally, and when manually-operated, the injector was fundamentally the same device as an unmodified, FDA-approved original. The series architecture of the treatment vessel and mixing assembly, together with the unique bubble transfer mechanism and multiple redundant stops and operation safety checks thus forms a system that is safely interposed between a cyclotron target and the patient's vasculature. Repetitive ejection between syringes produces a highly effective mixing/solution mechanism using fungible disposables. Moreover, the provision of a closed, disposable set for handling and compounding the radionuclide in an automated negative pressure safety cabinet allows the operator to maintain a safe distance from radiation, and provides a convenient system for the remote handling and preparation of diverse medicines, reagents and tracer materials.

The invention has been described above in a particular application for receiving, preparing and injecting a gaseous radionuclide for pulmonary PET imaging. However, the unique remote handling, sterile mixing, and volumetric control achieved by the set and the operating console are applicable with slight changes to compounding and delivering medications, marking and synthesizing materials and other radiation-handling tasks. Thus, it should be understood that the invention is not to be limited by the particular embodiments shown and discussed above, but may take other forms and be embodied in diverse systems for preparing, reacting, formulating or delivering radionuclides or biologically active materials. The invention and its principals of operation being thus disclosed, one skilled in the art will appreciate further features and advantages of the invention, and will be lead to further variations and modifications of the invention. Accordingly, all such variations and modifications are considered to be within the spirit and scope of applicant's invention as defined by claims appended hereto and equivalents thereof. All publications and references cited herein are expressly incorporated herein by reference in their entirety.

Claims

1. A system for preparation and delivery of a biologically active, hazardous or radioactive fluid, the system comprising

a receiving system having a first port for receiving said fluid and a second port positioned for delivering said fluid

a fluid handling set including a syringe and a plurality of flushable valves interconnected as a closed unit by tubing extending to an outlet

the syringe connecting via said fluid handling set to said second port and to said outlet for drawing the fluid into the tubing and transferring said fluid to the outlet as a prepared liquid

and the fluid handling set being configured for operation of said valves to define a finite set of flow segments at different times in said set such that the syringe flushes, fills, prepares and delivers the prepared fluid without exposing the operator to radiation.

2. A system for preparation and delivery of a biologically active, hazardous or radioactive material such as a gas, the system comprising

a receiving chamber having a first port for receiving said fluid and a second port positioned for accessing an active gas present in said material

an operating assembly for mounting a fluid handling set including a pressure syringe, a passive syringe and a plurality of flushable valves interconnected as a closed unit by tubing such that the tubing connects to said second port, and the operating assembly being configured to secure and operate the pressure syringe and the plurality of valves in sequence such that the pressure syringe draws the material into the pressure syringe and transfers the material with liquid to said passive syringe so as to form a prepared liquid, and furtheroperating said valves to define a finite set of flow segments at different times in said set for flushing, filling, preparing and delivering the prepared liquid, to receive the material from a source and provide the prepared liquid to a patient.

3. A system for preparation and delivery of a biologically active, hazardous or radioactive material, the system comprising

a receiving chamber having a first port for receiving said material and a second port positioned for accumulating a desired portion of the material

a fluid handling set including a plurality of flushable valves interconnected as a closed unit by tubing and configured for automated remote operation of said valves to form a finite state flow path effective to receive and encapsulate said desired portion as a bubble, prepare said portion in a delivery liquid and transfer the delivery liquid to an output.

4. The system of claim 3, wherein said valves define flow segments at different times in said set for flushing, filling, preparing and delivering the material such that the set receives the material as a gas from a source and safely delivers the delivery liquid to the bloodstream of a patient.

5. The system of claim 4, wherein the fluid handling set includes a pressure syringe operable for drawing the material into the set, mixing the delivery liquid, and delivering the delivery liquid into the bloodstream of a patient.

6. The system of claim 3 or 4, wherein the system prepares a gaseous radionuclide for injection to perform positron emission tomographic images of the patient.

7. The system of claim 3, wherein the fluid handling set is sterile assembly and further comprises and active syringe connected to one of said valves, and a passive syringe connected to another of said valves for receiving liquid such that the set is operable to prepare said portion in said delivery liquid by ejecting said portion and delivery liquid from the active syringe into the passive syringe.

8. A system for sterile preparation of a fluid radionuclide for use, such system comprising a sterile flow set including an inlet, an outlet, a plurality of stopcocks arranged in a sequence along a flow line to define a plurality of fluid transport segments, and first

and second syringes connected to the flow line being operable to form a sterile liquid solution of said radionuclide while it remains in the flow set by repeated ejection from said first syringe to said second syringe and return to said first syringe.

9. A system according to claim 8, wherein the sterile flow set includes at least five stopcocks.

10. A system according to claim 8, wherein at least one of said syringes attaches directly to a port of one of the stopcocks.

11. A fluid handling set for use in receiving a hazardous fluid material and forming a delivery liquid, such set comprising a plurality of at least five stopcocks and tubing interconnecting said plurality of stopcocks to form a closed transport path for handling the hazardous fluid material, each stopcock further having a port for admitting material to or expelling material from said closed transport path.

12. A device for receiving a hazardous fluid material and forming a delivery liquid such as a reagent, medicine or imaging agent containing said fluid material, such device comprising

a plurality of stopcock receptacles arranged along a path,

a corresponding plurality of servomotors positioned and configured for individually controlling a stopcock each being positioned in one of the receptacles,

a syringe driver, and

a controller operative to control said servomotors to form a set of flow segments along a closed transport path for handling the hazardous fluid material, and to control said syringe driver to drive a syringe so that the syringe draws said fluid material into the transport path and moves the fluid material along ones of said flow segments so as to prepare and deliver the delivery fluid.

13. The device of claim 12, further comprising a flow set including a plurality of stopcocks interconnected by tubing to form a sterile flow path, an active syringe connected to said flow path, and a passive syringe connected to said flow path.

14. The device of claim 13, wherein the controller is operative to control said servomotors to define a path between the active syringe and the passive syringe, and to prepare the fluid material by repeated ejection of the material from the active syringe to the passive syringe.

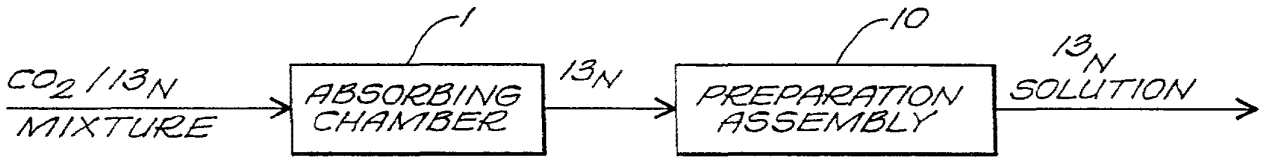
CO_2 / ^{13}N
MIXTURE
1
ABSORBING CHAMBER
^{13}N
10
PREPARATION ASSEMBLY
^{13}N
SOLUTION

FIG. 1

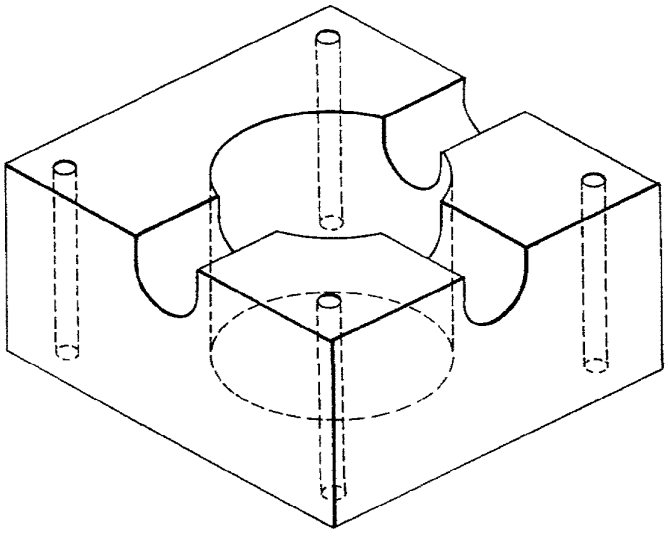

FIG. 5A

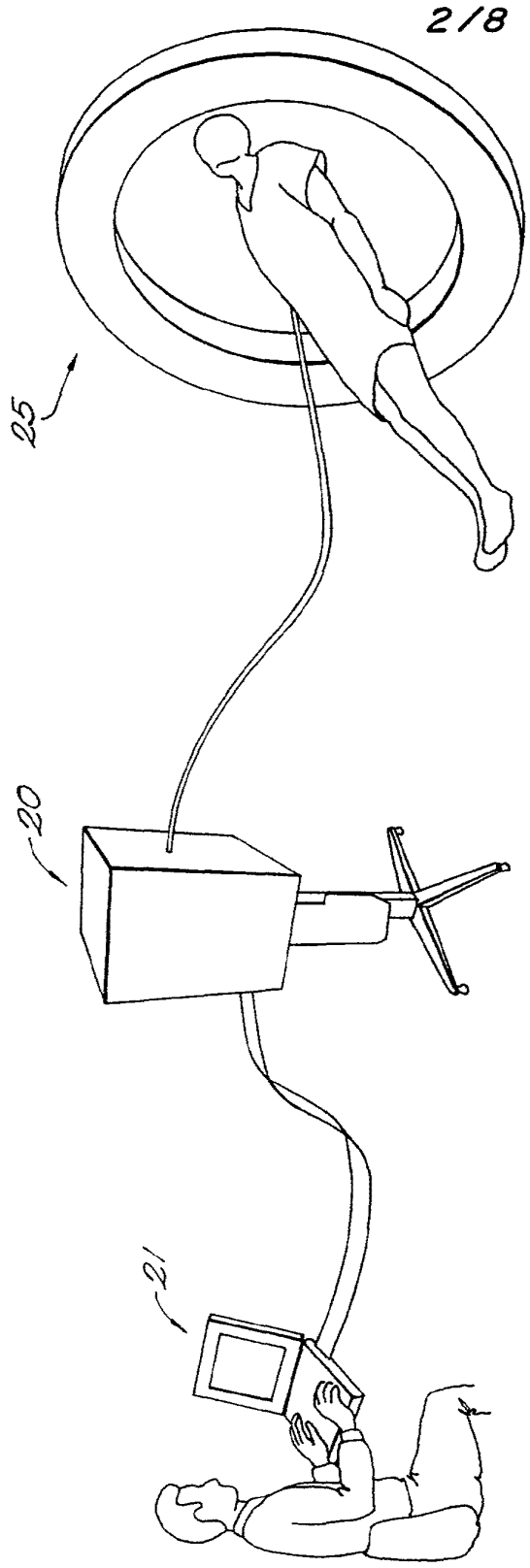

FIG. 1A

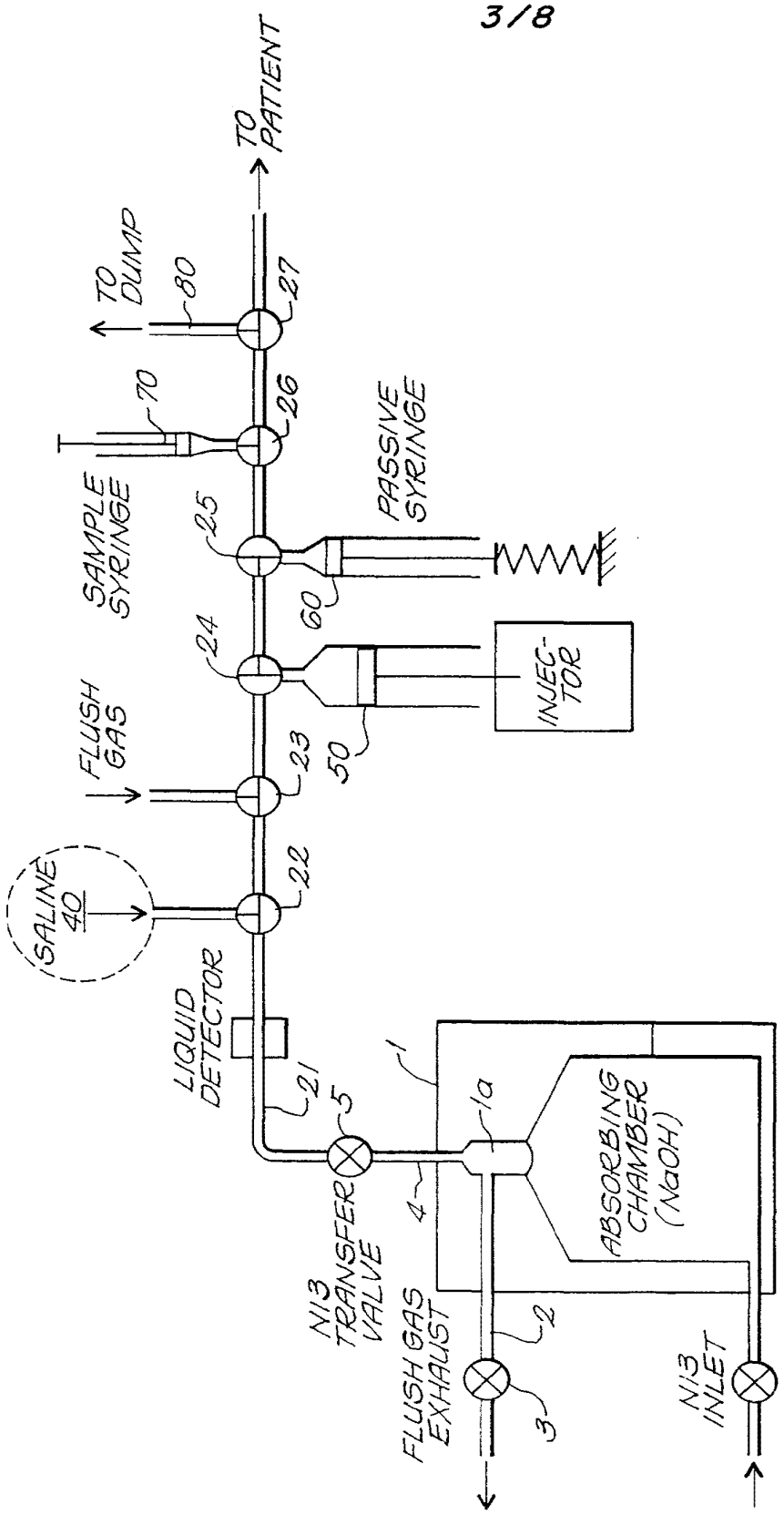
TO PATIENT
TO DUMP
80
27
70
26
SAMPLE SYRINGE
PASSIVE SYRINGE
25
60
24
INJEC-TOR
FLUSH GAS
23
50
SALINE 40
22
LIQUID DETECTOR
21
5
1
1a
ABSORBING CHAMBER (NaOH)
4
N13 TRANSFER VALVE
2
FLUSH GAS EXHAUST
3
N13 INLET

FIG. 2

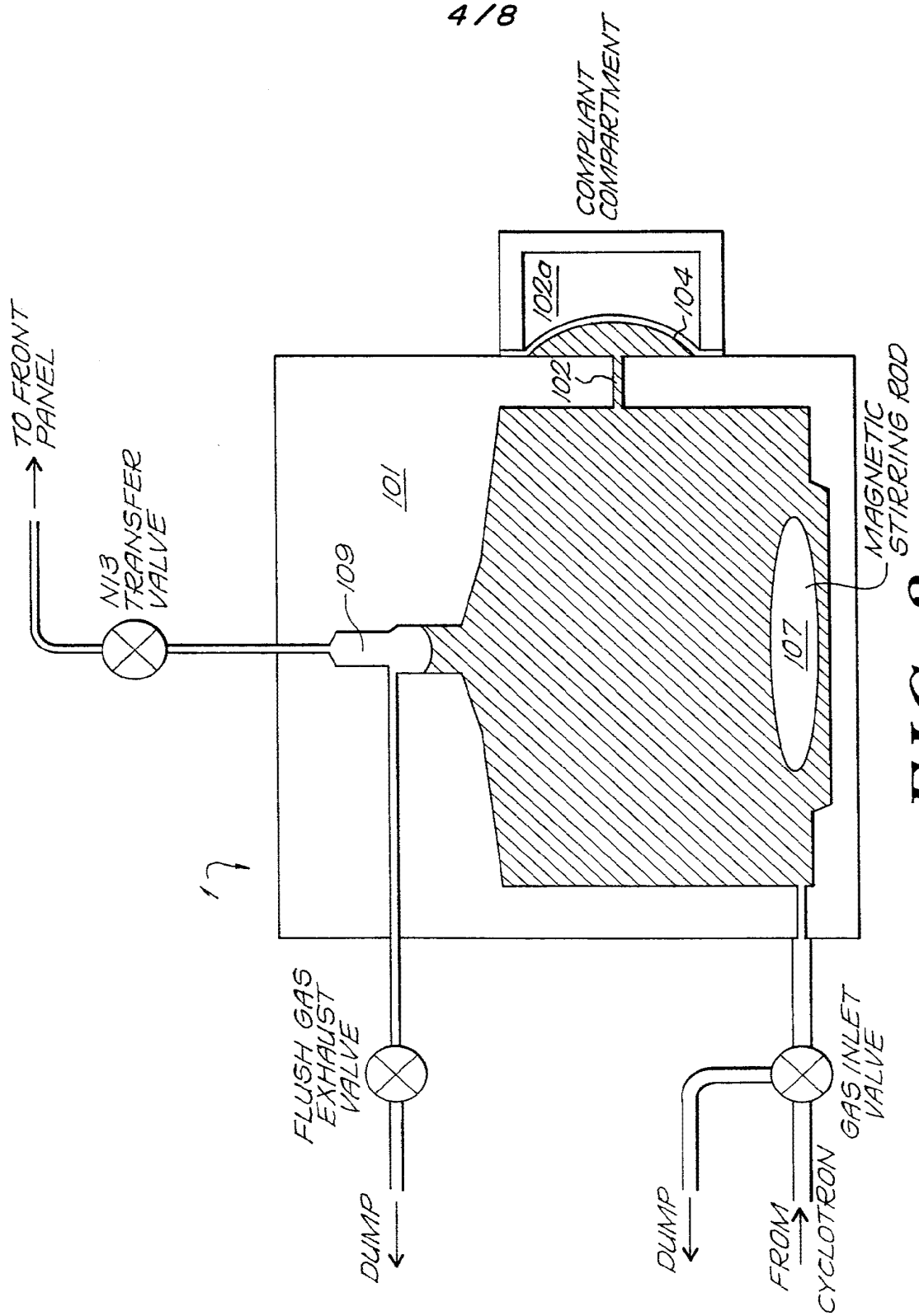
COMPLIANT COMPARTMENT
102a
104
102
TO FRONT PANEL
N13 TRANSFER VALVE
101
109
MAGNETIC STIRRING ROD
107
17
FLUSH GAS EXHAUST VALVE
DUMP
DUMP
GAS INLET VALVE
FROM CYCLOTRON

FIG. 3

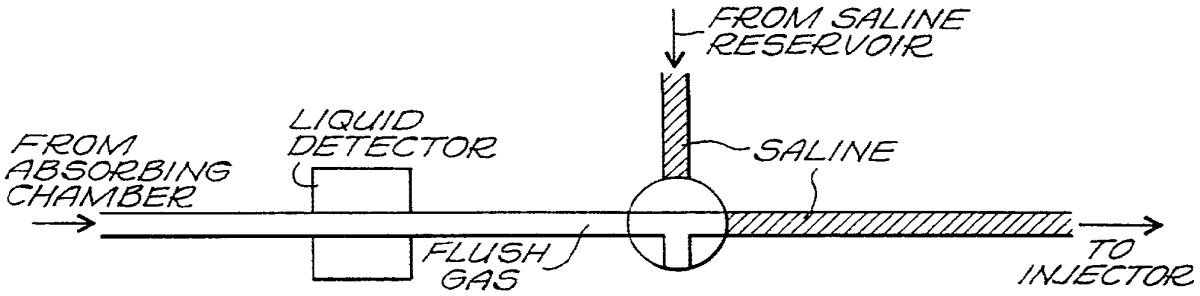

FIG. 4A

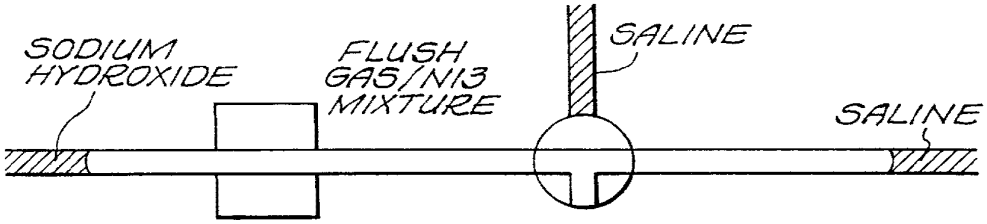

FIG. 4B

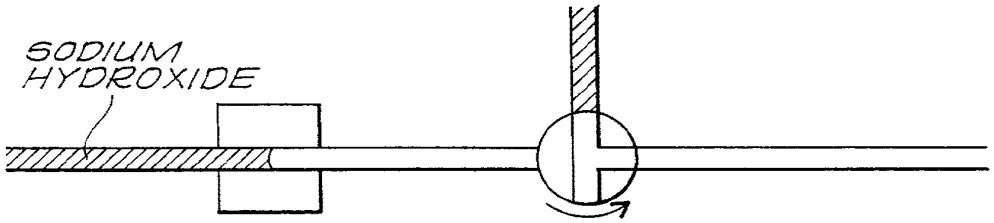

FIG. 4C

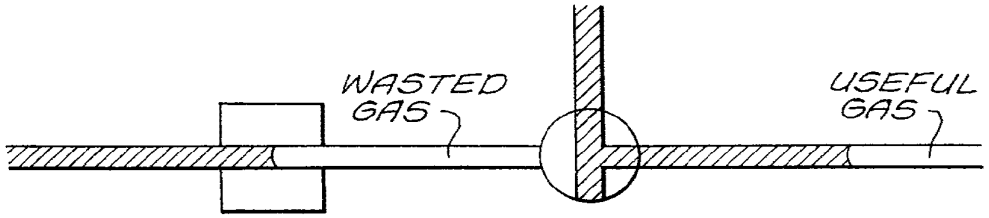

FIG. 4D

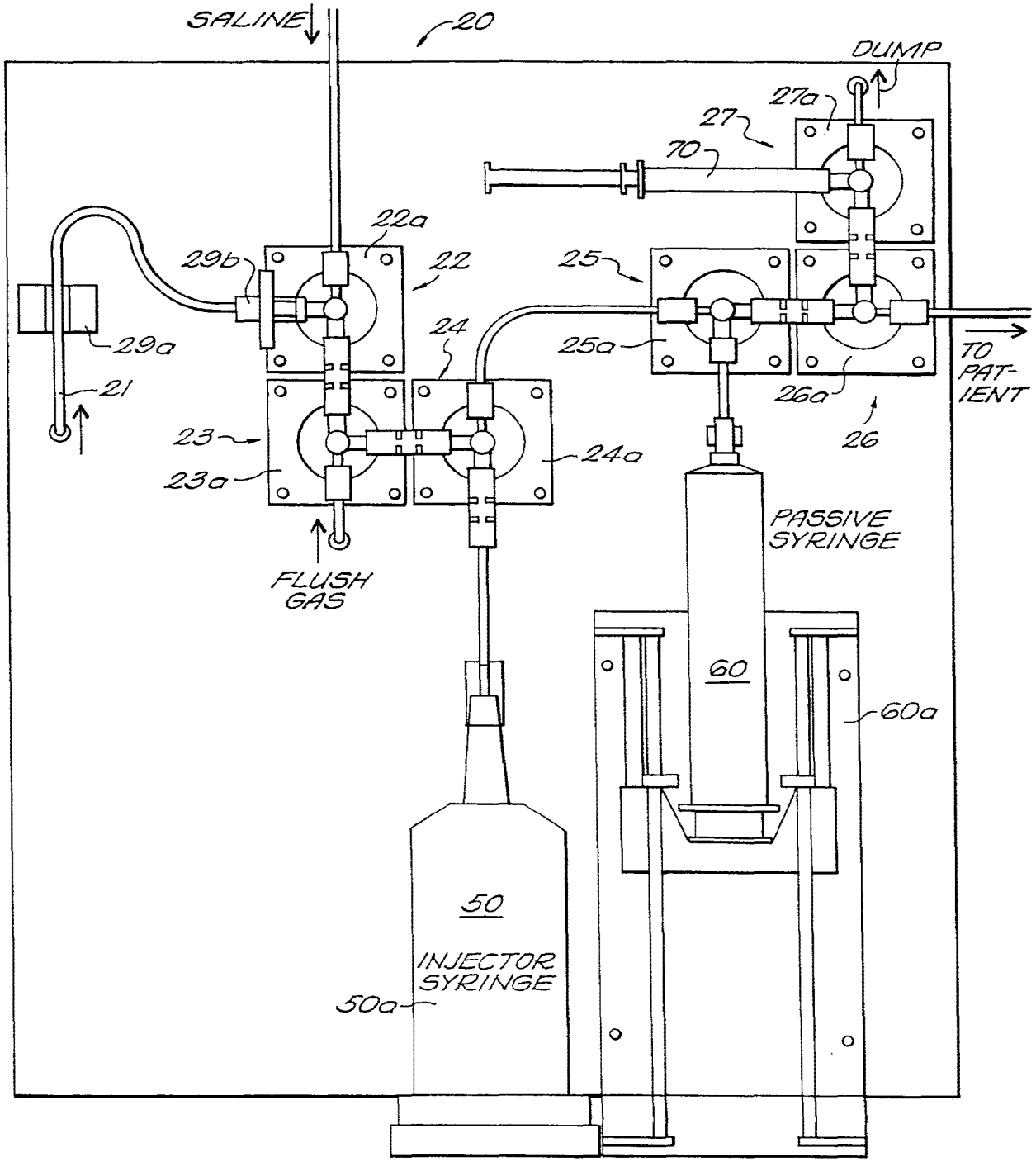
SALINE
20
DUMP
27a
27
70
22a
29b
22
25
29a
24
25a
TO PAT-IENT
21
26a
26
23
24a
23a
PASSIVE SYRINGE
FLUSH GAS
60
60a
50
INJECTOR SYRINGE
50a

FIG. 5

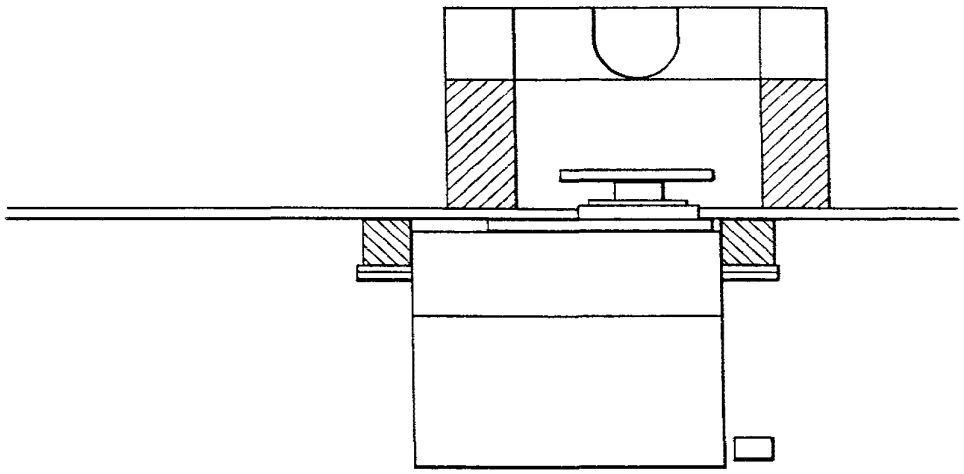

FIG. 5B

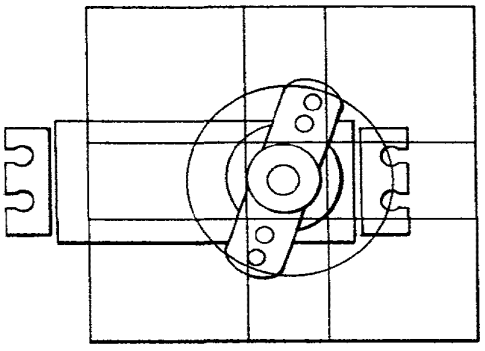

FIG. 5C

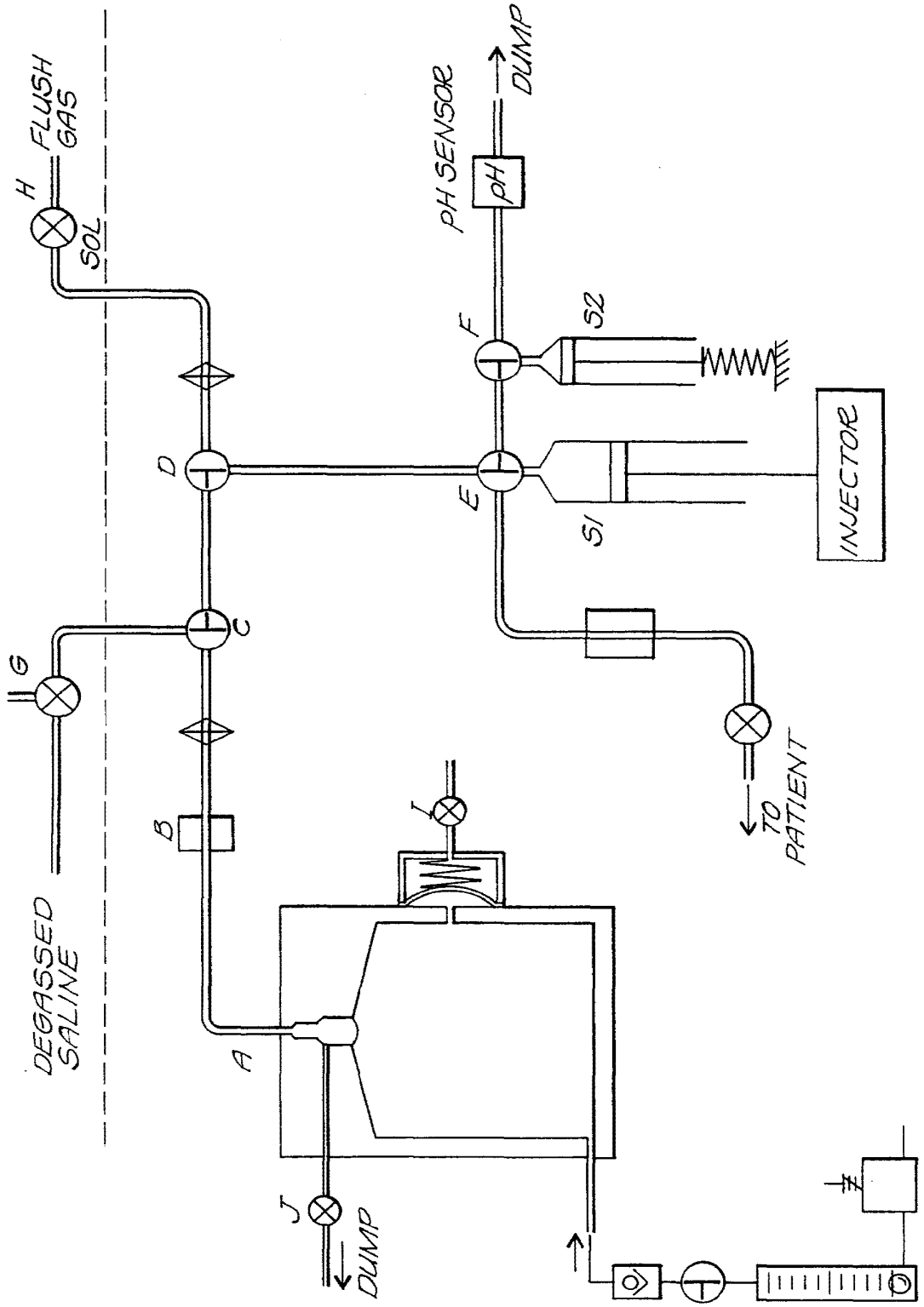
H
FLUSH GAS
SOL
PH SENSOR
pH
DUMP
F
S2
D
E
S1
INJECTOR
C
G
B
I
TO PATIENT
DEGASSED SALINE
A
J
DUMP

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/08981

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :G01N 24/00, 37/00
US CL :436/57, 174, 180; 422/81, 100, 903

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. : 436/57, 174, 180; 422/81, 100, 903

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,482,865 A (FERRIERI et al) 09 January 1996, entire document.	1-14
A	US 5,514,071 A (SIELAFF, JR. et al) 07 May 1996, entire document.	1-14
A	US 5,468,355 A (SHEFER et al) 21 November 1995, entire document.	1-14
A	US 5,223,434 A (KANNO et al) 29 June 1993, entire document.	1-14

☐ 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
19 JULY 1999

Date of mailing of the international search report
19 AUG 1999

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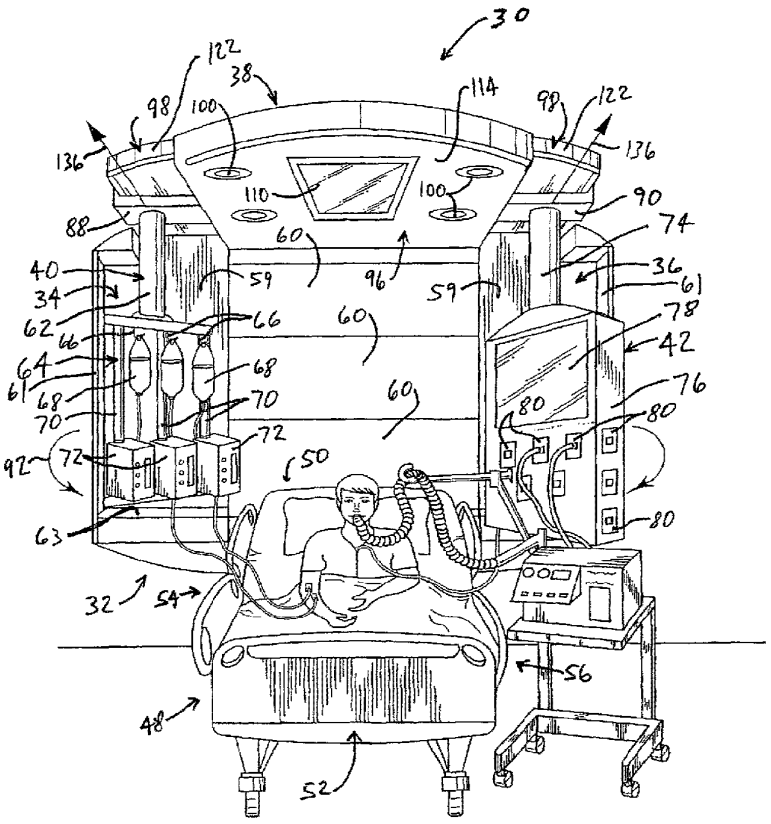
[Continued on next page]

(54) Title: ARCHITECTURAL SYSTEM ADAPTABLE TO PATIENT ACUITY LEVEL



(57) Abstract: An architectural system (30, 230, 330) adaptable to patient acuity level has headwall unit (32, 232) with a cavity (34, 36, 234, 236), a ceiling unit (38, 238, 338), and a column (40,42) coupled to the ceiling unit (38, 238, 338). The column (40, 42) is movable between a first position in which at least a majority of the column (40, 42) is situated in the cavity (34, 36, 234, 236) and a second position in which the column (40, 42) is situated outside the cavity (34, 36, 234, 236). Various types of patient-care equipment are also disclosed. The patient-care equipment is included in, or is coupleable to, one or more of the ceiling unit (38, 238, 338), the headwall unit (32, 232), or the column (40, 42).

WO 02/096335 A2

(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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.

ARCHITECTURAL SYSTEM ADAPTABLE TO PATIENT ACUITY LEVEL

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial No. 60/293,949, filed on May 25, 2001, the disclosure of which is hereby incorporated by reference herein.

BACKGROUND AND SUMMARY

The present disclosure relates to architectural systems, such as headwalls, columns, and ceiling-suspended arm assemblies used in hospitals, and particularly to an architectural system adaptable to patient acuity level. More particularly, the present disclosure relates to an architectural system that is configured to deliver services, such as medical gases, to a patient and/or that is configured to support patient-care devices for delivering intensive care services to a patient.

Architectural systems, such as headwalls, columns, and ceiling-suspended arm assemblies, through which medical gases are accessible via medical service outlets are known. Headwalls, columns, and arm assemblies having rails, tracks, or brackets for attachment of patient-care devices and having electrical outlets for delivering power to the patient-care devices are also known. Patients in critical condition are oftentimes located in an intensive care unit of a hospital, whereas patients in stable condition are oftentimes located in a standard patient room. Architectural systems in intensive care units are generally configured to hold more patient-care devices and provide more types of medical services than architectural systems found in a standard patient room.

The numbers of patients in critical condition and the numbers of patients in stable condition fluctuate in a hospital over time. Thus, at any given time there may be either a shortage or excess of spaces for patients in an intensive care unit. In addition, at any given time there may be either a shortage or surplus of standard hospital rooms. Thus, there is a need for an architectural system that is adaptable to patients having high, medium, and low acuity levels so that hospitals have the flexibility to meet the needs of the patient population at any give time.

According to this disclosure, an architectural system adaptable to an acuity level of a patient supported by a hospital bed in a patient room having a wall

and a ceiling is provided. The architectural system comprises a wall unit coupled to the wall and having a cavity, a ceiling unit coupled to the ceiling, and a column coupled to the ceiling unit for movement between a first position in which at least a majority of the column is situated in the cavity and a second position in which the column is situated outside the cavity.

Various patient-care devices and equipment are attachable to the column. Such patient care devices include, for example, IV racks, infusion pumps, ventilation equipment, heart rate monitoring equipment, and patient data acquisition equipment. In an illustrative embodiment, a number of medical service outlets, such as gas outlets and electrical outlets, are coupled to the column. Also in the illustrative embodiment, a number of doors are coupled to the wall unit for opening and closing the cavity. Thus, when the column is in the cavity, the doors may be moved to closed positions shielding the column and the equipment carried by the column from view and blocking access to the medical service outlets on the column. Opening the doors, but leaving the column in the cavity of the headwall unit, permits access to some of the medical service outlets and to some portions of the equipment carried by the column. When the column is moved out of the cavity, all of the medical service outlets and all pertinent portions of the equipment carried by the column are accessible.

Also according to this disclosure, a ceiling unit having one or more pieces of equipment coupled thereto is provided. Such equipment includes, for example, a reading light, an examination light, a display screen, air curtain generation equipment, a privacy curtain, a temperature sensor, an air quality sensor, an air purifier, aroma therapy equipment, a motion sensor, and a proximity sensor. In one illustrative embodiment, an arm assembly is coupled to the ceiling unit and supports an overbed table. The arm assembly permits the overbed table to be moved from one side of a hospital bed to an opposite side of the hospital bed.

A mobile cart is also disclosed herein. In an illustrative embodiment, the mobile cart comprises an upstanding pedestal, a plurality of legs coupled to a bottom of the upstanding pedestal, and a plurality of wheels. Each wheel is coupled to a respective leg of the plurality of legs. The legs, along with the wheels coupled thereto, are each movable between a first position extending outwardly from beneath the upstanding pedestal and a second position tucked beneath the upstanding pedestal.

The mobile cart is attachable to a ceiling-mounted column or an arm assembly. The mobile cart is also attachable to a hospital bed to be transported with the bed. When the mobile cart is attached to either the column, the arm assembly, or the bed, the wheels of the mobile cart are spaced apart for the floor. A headwall unit having a cavity configured to receive the mobile cart is also disclosed. The mobile cart carries one or more pieces of patient-care equipment such as, for example, an IV pole, an infusion pump, a ventilator control unit, a gas tank, a gas control unit, a vital signs monitor, an on-board computer, a receiver, a transmitter, and a battery.

Further according to this disclosure, a set of hospital equipment comprises a headwall, a blanket, a unit housed in the headwall, and a hose coupled to the blanket and coupled to the unit, a thermoregulation medium being moved between the blanket and the unit through the hose. The thermoregulation medium includes, for example, heated air, cooled air, a heated liquid, or a cooled liquid. In some embodiments, in which the thermoregulation medium is heated or cooled air, the blanket has a plurality of perforations through which the heated or cooled air is expelled.

Additional features will become apparent to those skilled in the art upon consideration of the following detailed description of illustrative embodiments exemplifying the best mode of carrying out the various inventions disclosed herein as presently perceived.

BRIEF DESCRIPTION OF THE DRAWINGS

The detailed description particularly refers to the accompanying figures, in which:

Fig. 1 is a perspective view of an architectural system adaptable to patient acuity level according to this disclosure showing a headwall unit behind a hospital bed on which a patient is resting, a ceiling unit extending from the headwall unit, the ceiling unit overlying the hospital bed, an IV rack situated in a first cavity of the headwall unit, and a housing having a display screen and a number of medical service outlets situated in a second cavity of the headwall unit;

Fig. 2 is a perspective view, similar to Fig. 1, showing a first column moved out of first cavity so that the IV rack carried by the first column is situated alongside a first side of the hospital bed and a second column moved out of the

second cavity so that the housing included as part of the second column is situated alongside a second side of the hospital bed;

Fig. 3 is a top plan view of a portion of the architectural system of Fig. 1 showing the first and second columns received in the first and second cavities, respectively, of the headwall unit and showing a head end of the hospital bed situated in close proximity to the headwall unit;

Fig. 4 is a top view, similar to Fig. 3, showing the first and second columns moved out of the first and second cavities, respectively, of the headwall unit and showing the hospital bed moved away from the headwall unit by a sufficient amount to permit a caregiver to stand between the head end of the hospital bed and the headwall unit;

Fig. 5 is a transverse sectional view of a portion of the architectural system of Fig. 1 showing rollers of the second column engaging a track of the ceiling unit and showing medical service lines (in phantom) extending from each of the medical service outlets, through the second column, and through the ceiling unit;

Fig. 6 is a longitudinal sectional view of a portion of the architectural system of Fig. 1 showing the second column being movable between a first position (in solid) in close proximity to the headwall unit and a second position (in phantom) spaced from the headwall unit and showing the medical lines being routed into a central region of the ceiling unit to accommodate the movement of the second column between the first and second positions;

Fig. 7 is a top plan view of a portion of the architectural system of Fig. 1 showing the first and second columns in a number of positions and showing the routing of the medical lines from the central region of the ceiling unit to the first and second columns;

Fig. 8 is a perspective view of the architectural system of Fig. 1 showing the first column carrying an IV rack having a bottom plate arranged for coupling to a pair of upright posts that are mounted to a distal end of a support arm extending from a bed frame of the hospital bed;

Fig. 9 is a side elevation view of the architectural system of Fig. 8 showing the first column (in solid) supporting the IV rack above the upright posts and showing the first column (in phantom) supporting the IV rack in the first cavity of the headwall unit;

Fig. 10 is a side elevation view, similar to Fig. 9, showing the IV rack decoupled from the first column and coupled to the hospital bed to be transported with the hospital bed;

Fig. 11 is a perspective view of a first alternative embodiment of an architectural system according to this disclosure showing the ceiling unit having lateral extensions for supporting auxiliary equipment laterally outward of the first and second columns, a first set of door panels covering the first column, and a second set of door panels being opened by varying amounts to partially uncover various portions of the second column;

Fig. 12 is a perspective view of a portion of the architectural system of Fig. 11 showing a privacy curtain moved out of an auxiliary cavity of the headwall unit and hanging from one of the lateral extensions of the ceiling unit;

Fig. 13 is a perspective view, similar to Fig. 12, showing an alternative embodiment of a privacy curtain extending downwardly from one of the lateral extensions of the ceiling unit;

Fig. 14 is a perspective view, similar to Figs. 12 and 13, but of another portion of the architectural system of Fig. 11 showing an auxiliary IV pole moved out of an auxiliary compartment of the headwall unit and hanging from one of the lateral extensions of the ceiling unit;

Fig. 15 is a perspective view of a second alternative embodiment of an architectural system according to this disclosure showing a plurality of openings formed in a perimetral region of the ceiling unit and showing air curtain generation equipment (in phantom) operating to move air out of the plurality of openings to form vertical air curtains along the foot end and opposite sides of the hospital bed;

Fig. 16 is a bottom plan view of the ceiling unit of Fig. 15 showing, in phantom, a fan and a set of channels through which air moves to reach the plurality of openings;

Fig. 17 is a perspective view of an environmentally-controlled hospital room showing a patient supported by a hospital bed in the room, a disposable thermoregulation blanket covering a portion of the patient, the disposable thermoregulation blanket being coupled via a hose to a thermoregulation unit housed in a headwall of the hospital room, and an environmental control canopy coupled to a ceiling of the hospital room above the hospital bed;

Fig. 18 is a perspective view of a mobile cart according to this disclosure showing the mobile cart having a somewhat rectangular upstanding pedestal, the pedestal having a fairly small depth dimension between a front face and a rear face of the pedestal, the mobile cart having four horizontally extending support legs coupled to the bottom of the pedestal, a set of casters coupled to distal ends of the support legs, and each support leg being pivotable relative to the pedestal about a respective vertical axis between a first position (in solid) extending outwardly from beneath the pedestal and a second position (in phantom) tucked beneath the pedestal;

Fig. 19 is a side plan view of a first hospital room showing the mobile cart of Fig. 18 being mounted to a head end of a hospital bed, a second mobile cart, like the mobile cart of Fig. 18, being suspended from a ceiling of the room by an arm assembly, the support legs of the two mobile carts all being in their respective second positions, and the casters of the two mobile carts all being spaced apart from a floor of the room;

Fig. 20 is side plan view of a second hospital room showing the mobile cart (in phantom) being situated in a cavity (in phantom) formed in a headwall of the hospital room;

Fig. 21 is a perspective view of a hospital bed supported on a floor of a hospital room and an overbed table assembly that is suspended from a ceiling of a hospital room showing the overbed table assembly including a hub unit coupled to the ceiling above the hospital bed, an arm assembly coupled to the hub unit and extending downwardly therefrom, an entertainment-and-control panel coupled to a vertical arm of the arm assembly, an overbed table coupled to the vertical arm beneath the entertainment-and-control panel, and a telephone coupled to the overbed table;

Fig. 22 is a perspective view of a portion of the overbed table assembly of Fig. 40 showing the overbed table assembly including a service-delivery housing coupled to an underside of the overbed table and a plurality of medical service outlets on an end face of the service-delivery housing; and

Fig. 23 is a top plan view of the hospital bed and the overbed table assembly of Fig. 22 showing the arm assembly moving between a first position (in solid) having the overbed table extending over a lap of the patient from a first side of the hospital bed and a second position (in phantom) having the overbed table extending over the lap of the patient from a second side of the bed and showing that

the service-delivery housing moves around a foot end of the bed as the arm assembly moves between the first and second positions.

DETAILED DESCRIPTION OF THE DRAWINGS

An first embodiment of an architectural system 30 according to this disclosure comprises a headwall unit 32 having a first cavity 34 and a second cavity 36, a ceiling unit 38, a first column 40, and a second column 42 as shown in Figs. 1 and 2. Columns 40, 42 hang downwardly from ceiling unit 36 and are each independently movable between respective storage positions situated within a respective cavity 34, 36 and a plurality of use positions situated outside of cavities 34, 36. Headwall unit 32 is configured for attachment to a wall 44 of a hospital room and ceiling unit 38 is configured for attachment to a ceiling 46 of the hospital room.

A hospital bed 48 is situated in the hospital room such that a head end 50 of the bed 48 is near headwall unit 32 and a foot end of the bed is spaced from head wall unit 32 as shown in Figs. 1-4. Columns 40, 42 are spaced apart by a sufficient distance to permit hospital bed 48 to occupy the space defined between columns 40, 42 when columns 40, 42 are situated outside of cavities 34, 36 as shown, for example, in Figs. 2 and 4. Thus, column 40 is positioned alongside a first side 54 of hospital bed 48 when outside of cavity 34 and column 42 is positioned alongside a second side 56 of hospital bed 48 when outside of cavity 36.

Columns 40, 42 each carry patient-care equipment, some of which is configured to provide medical services to high acuity patients, such as critical patients requiring intensive care. Patient-care equipment needed for medium acuity patients, such as patients requiring medical gas to aid respiration and intravenous (IV) fluids are also carried on one or both of columns 40, 42. For medium acuity patients, columns 40, 42 are usually placed in cavities 34, 36 in the respective storage positions and the needed medical services are provided to the patient from columns 40, 42 as shown in Figs. 1 and 3. Optionally, columns 40, 42 may be moved out of cavities 34, 36 for medium acuity patients. For high acuity patients, columns 40, 42 are usually moved out of cavities 34, 36 to positions alongside bed 48 so that multiple medical services are accessible to the patient and to other pieces of medical equipment as shown, for example, in Figs. 2 and 4. For low acuity patients that do not require

medical services from columns 40, 42, columns 40, 42 are usually placed in the storage positions so as to be out of the way.

Headwall unit 32 has a plurality of doors 58 that are movable between closed positions covering associated portions of columns 40, 42 and opened positions allowing access to the associated portions of columns 40, 42. For low acuity patients, doors 58 are typically closed to conceal columns 40, 42 from view. In the illustrative embodiment, each of doors 58 slides horizontally behind an associated central panel 60 of headwall unit 32. In some alternative embodiments, doors 58 slide horizontally in front of the associated central panels 60. In other alternative embodiments, doors 58 either raise or lower or pivot when moving between opened and closed positions. In the illustrative embodiment in which doors 58 slide horizontally behind panels 60, each of panels 60 is large enough to accommodate both of the associated doors 58 therebehind. It is within the scope of this disclosure for headwall unit 32 to have tracks or other surfaces (not shown) on which doors 58 slide. It is also within the scope of this disclosure for rollers (not shown) to be coupled to doors 58 and for the rollers to roll on tracks or surfaces as doors 58 move between the opened and closed positions.

In the illustrative embodiment, three doors 58 are associated with cavity 34 to cover top, middle, and lower portions of cavity 34 and three doors 58 are associated with cavity 36 to cover top, middle, and lower portions of cavity 36. In alternative embodiments, more or less than three doors are provided for covering respective cavities 34, 36. Optionally, locking mechanisms (not shown) are mounted to each door 58 for locking the respective door in the closed position to prevent a patient or any other unauthorized person from opening doors 58 to gain access to the equipment mounted on columns 40, 42.

Headwall unit 32 has a frame (not shown) to which central panels 60 couple. Headwall unit 32 has other panels or walls, such as a vertical back wall 59 and a pair of outer side walls 61 that extend from back wall in perpendicular relation therewith. In addition, headwall unit 32 has horizontal walls 63 that underlie cavities 34, 36 and inner side walls 65 that are spaced from, but parallel with, walls 61 as shown in Fig. 8. Cavities 34, 36 are defined, in part, by walls 59, 61, 63, 65. One or more of walls 59, 61, 63, 65 are coupled to the frame of headwall unit 32. In the illustrative embodiment, headwall unit 32 includes a lower portion 67 that is situated