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(71) Applicant: **BAYER MEDICAL CARE INC.** [US/US]; 1 Bayer Drive, Indianola, Pennsylvania 15051 (US).

(72) Inventor: **UBER, Arthur, E., III**; 7426 Ben Hur St., Pittsburgh, Pennsylvania 15208 (US).

(74) Agents: **SCHRAMM, David** et al.; Bayer Medical Care Inc., 1 Bayer Drive, Indianola, Pennsylvania 15051 (US).

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[Continued on next page]

(54) Title: COMBINED RADIOPHARMACEUTICAL IMAGING SYSTEM

(57) Abstract: An integrated radiopharmaceutical patient treatment system includes a portable radioisotope generation module configured to generate a gaseous radioisotope, a radiopharmaceutical processing module configured to dissolve the radioisotope in an injectable medical fluid, a fluid injection system in fluid communication with the radiopharmaceutical processing module and configured to inject a dose including the radioisotope and the injectable medical fluid into a patient, and at least two imaging devices configured to independently detect biological and physiological characteristics of the patient based on the dose. The radiopharmaceutical processing module may be in fluid communication with the radioisotope generation module.

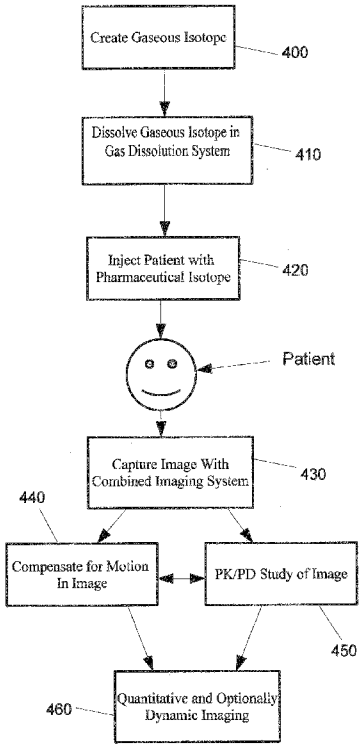


FIG. 40A

WO 2015/153946 A1

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COMBINED RADIOPHARMACEUTICAL IMAGING SYSTEM

RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Patent Application No. 61/975,336 entitled "A System and Method for Combined PET/MR Imaging" filed April 4, 2014 and, further, claims the benefit of United States Provisional Patent Application No. 62/118,517 entitled "A System and Method for Combined Gaseous/Liquid Imaging Agent Imaging", filed February 20, 2015. The disclosure of each of these documents is hereby incorporated by reference in its entirety.

BACKGROUND

Field of the Invention

[0002] The present disclosure relates to generation, preparation, and administration of pharmaceutical substances, typically intrinsically harmful or toxic pharmaceutical substances such as radioactive pharmaceutical substances, generally known as radiopharmaceuticals to human and animal subjects and, their use in imaging procedures.

Description of Related Art

[0003] Administration of radioactive pharmaceutical substances or drugs, generally termed radiopharmaceuticals, is often used in the medical field to provide information or imagery of internal body structures and/or functions including, but not limited to, bone, vasculature, organs and organ systems, and other tissue. Additionally, such radiopharmaceuticals may be used as therapeutic agents to kill or inhibit the growth of targeted cells or tissue, such as cancer cells. However, radiopharmaceutical agents used in imaging procedures and therapeutic procedures typically include highly radioactive nuclides of short half-lives and are hazardous to attending medical personnel. These agents are toxic and can have physical and/or chemical effects for attending medical personnel such as clinicians, imaging technicians, nurses, and pharmacists. Excessive radiation exposure is harmful to attending medical personnel due to their occupational repeated exposure to the radiopharmaceuticals. However, due to the short half-life of typical radiopharmaceutical agents and small applied dosages, the radiation exposure risk to benefit ratio for individual patients is acceptable. The constant and repeated exposure of medical personnel to radiopharmaceuticals over an extended period of time is a significant problem in the nuclear medicine field.

[0004] A number of techniques are used in the medical field to reduce radiation exposure to attending medical personnel associated with the creation, handling, transport, dose preparation, and administration of radiopharmaceuticals to patients. These techniques

encompass one or more of minimizing the time of exposure of medical personnel, maintaining distance between medical personnel and the source of radiation, and/or shielding medical personnel from the source of radiation. As a certain amount of close-proximity interfacing between medical personnel and radiopharmaceutical agents (including patients who have or are to receive radiopharmaceutical agents) is somewhat inevitable during the current practice of generating, preparing, and administering radiopharmaceutical agents to patients and caring for these patients, radiation shielding has considerable importance in the nuclear medicine field.

[0005] Syringes, during loading and once loaded with radiopharmaceutical agents, are commonly handled via syringe shields and shielded glove boxes or containers, but may also be transported in a suitably configured transport pig as noted previously. Syringe shields are commonly hollow cylindrical structures that accommodate the cylindrical body of the syringe and are constructed of lead or tungsten with a lead glass window that allows the handler to view the syringe plunger and liquid volume within the syringe. In radiopharmaceutical delivery applications, devices are known for remotely administering radioactive substances from syringes to minimize radiation exposures to attending medical personnel as disclosed in United States Patent No. 5,514,071 to Sielaff Jr. et al. or 3,718,138 to Alexandrov et al. An automated device for controlled administering radioactive substances is disclosed in United States Patent No. 5,472,403 to Cornacchia et al. and is incorporated herein by reference. A system approach to controlling injectors used to inject radioactive material into a patient is disclosed in published German Document No. DE 10 2005 010152.

[0006] In addition to the difficulties introduced by the hazardous nature of radiopharmaceuticals, the short half-lives of such radiopharmaceuticals further complicate the administration of a proper dosage to a patient. The radioactivity levels of the radiopharmaceutical agents used as tracers in, for instance, single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) imaging procedures are measured by medical personnel, such as radio-pharmacists or nuclear medicine technologists, to determine the radiation dose that will be administered to the individual during the course of a diagnostic procedure. The radiation dose received depends on a number of factors including the half-life of the radiopharmaceutical agent and the initial radioactivity level of the radiopharmaceutical agent at the time it is injected into the individual. One known solution is to measure or calibrate the initial radioactivity of the radiopharmaceutical and time the injection so that a dose of the desired level of radioactivity is delivered (as calculated from the half-life of the radiopharmaceutical). United States

Patent Nos. 4,562,829 and 4,585,009 to Bergner and Barker et al., respectively, and incorporated herein by reference disclose strontium-rubidium infusion systems and a dosimetry system for use therein. The infusion system includes a generator of the strontium-rubidium radiopharmaceutical in fluid connection with a syringe used to supply pressurized saline. Saline pumped through the strontium-rubidium generator exits the generator either to the patient or to waste collection. Tubing in line between the generator and the patient passes in front of a dosimetry probe to count the number of disintegrations that occur. As the geometric efficiency (or calibration) of the detector, the flow rate through the tubing, and volume of the tubing is known, it is possible to measure the total activity delivered to the patient (for example, in milliCuries). A portable fluid delivery unit is known from United States Patent No. 6,773,673 to Layfield et al., incorporated herein by reference.

[0007] As noted above, examples of the use of radiopharmaceutical agents in diagnostic imaging procedures include positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) which are noninvasive, three-dimensional imaging procedures that provide information regarding physiological and biochemical processes in patients. In effect, the radiopharmaceutical agent acts as a tracer to interact with the targeted area. An initial step in producing PET images or SPECT images of, for example, vasculature, organs and organ systems, and/or other targeted tissue is to inject the patient with a dose of the radiopharmaceutical agent. The radiopharmaceutical agent is absorbed on or by certain cells in the body structure of interest and concentrates in this area. As an example, fluorodeoxyglucose (FDG) is a slight modification to the normal molecule of glucose, the basic energy fuel of cells, which readily accepts a radionuclide as a replacement to one of the atoms of the molecule. The radiopharmaceutical "tracer" emits a positron which creates photons that can be detected as the tissue is scanned at various angles and the photons pass through a detector array. A computer is used to reconstruct a three-dimensional color tracer image of the selected tissue structure. However, during the procedure, the patient must remain immobile to reduce blurring of the image due to movement. For certain imaging processes, this may prove difficult due to involuntary movements such as respiration. This is especially true for imaging of the lung and even more so when the imaging of the lung includes gas transport and exchange phenomena.

[0008] With the foregoing background in place, exemplary current practice of generating, preparing, and administration of radiopharmaceuticals will now be described. Typical radiopharmaceutical treatment practice in the United States includes having the radiopharmaceutical agent initially generated off-site from a treatment location, typically a

hospital, by an outside nuclear medicine facility and then delivered to the treatment location for further preparation, for example, individual dosing and administration. The treatment location, for example, a hospital, orders specific radioactive substances to be ready at specific time for specific patients. These substances are prepared by the outside nuclear medicine facility and with sufficient radioactivity that they will have the desired radioactivity level at the targeted time. Further "individual" dose preparation of the radiopharmaceutical agent may occur at the treatment site. Alternatively, the outside provider may provide a "finished" radiopharmaceutical agent ready for injection to a specified patient at a specified time so that treatment site personnel are only required to confirm that the correct radioactive dosage is present in the radiopharmaceutical agent, for example, in a stand-alone radiation dosimetry device as described previously. . However with radiopharmaceuticals comprising isotopes with very short half-lives, off-site radiopharmaceutical production may not be feasible.

[0009] In Europe, radiopharmaceutical creation and dose preparation practice differs from United States practice in that these actions typically all occur within a "hot lab" in the treatment facility again, typically, a hospital. As an example, the hospital itself typically has cyclotron or isotope generators (such as technetium generators manufactured by Mallinckrodt Inc., St. Louis, MO; Amersham Healthcare, 2636 South Clearbrook Drive, Arlington Heights, Illinois 60005; or GE Healthcare Limited, Amersham Place, Little Chalfont, Buckinghamshire, United Kingdom) in a shielded location in the hot lab. Hospital personnel create or extract the radioactive isotope, perform additional chemistry steps necessary to formulate the radioactive drug (i.e., radiopharmaceutical) early in the day, and then prepare unit doses for individual patients, generally close to the time the patient is to be injected with the radiopharmaceutical.

[0010] Within the prior art, systems for delivering hazardous fluids are known as disclosed, for example, in United States Patent No. 6,767,319 to Reilly et al. and United States Patent Application Publication No. 2004/0254525 to Uber, III et al., the disclosures of which are incorporated herein by reference. Another system adapted to inject a radioactive liquid into a patient is disclosed in Japanese Publication No. JP2000-350783 (see also United States Patent Application Publication No. 2005/0085682 to Sasaki et al.), assigned to Sumitomo Heavy Industries. This published patent application discloses a system which dispenses a volume of radioactive fluid into a coiled "medicine container" situated in a radiation measuring unit. When the prescribed radiation dose is accumulated in the coiled container, another syringe pushes saline through the coiled container and into a patient. A similar device and method is disclosed in Japanese Publication No. JP2002-306609, also

assigned to Sumitomo Heavy Industries. Each of the immediately foregoing Japanese publications is incorporated herein by reference.

PCT Application Publication No. WO2004/004787, assigned to Universite Libre De Bruxelles – Hospital Erasme and incorporated herein by reference, discloses a method by which continuous measurement of radioactivity by dosimetry is eliminated. The disclosed method requires an initial calibration step but thereafter, radiation dose is calculated based on the predictable decay of radioactivity as a function of time. Japanese Publication No. JP2004-290455, assigned to Nemoto Kyorindo KK, discloses a radiation-shielded injector system which withdraws FDG from prefilled syringes and allows other fluids such as saline to be administered. European Application Publication No. EP 1616587, assigned to University of Zurich and incorporated herein by reference, discloses a radioactive fluid dispensing device that pushes FDG into tubing within a radiation dose calibrator prior to a saline injection that administers the FDG to the patient. United States Patent Application Publication Nos. 2005/0203329 and 2005/0203330 to Muto et al. disclose a robotic, automated system for extracting radioactive fluids from a vial or bulk container into a number of unit dose syringes. This system may have application in a hospital pharmacy setting. United States Patent Application Publication No. 2005/0277833, assigned to E-Z-EM, Inc. and incorporated herein by reference, discloses an injection system for handling, mixing, dispensing, and/or injecting mixtures of pharmaceutical agents. Radiation dose is monitored by discrete detectors at several locations in the apparatus.

BRIEF SUMMARY

[0011] As the foregoing demonstrates, a need exists for integrated systems and methods capable of the generation, preparation, and administration of pharmaceutical substances and, typically, harmful or toxic pharmaceutical substances such as radioactive pharmaceutical substances or drugs, to human and animal subjects and, further, to methods and systems and associated components for the generation, preparation, and administration of fluid radiopharmaceutical substances to human and animal subjects and subsequent imaging procedures.

[0012] Generally, embodiments and physical manifestations of an integrated system and method for generation, dose preparation, transportation, administration, and or imaging of radiopharmaceuticals are provided with a focus on improving safety for attending personnel, effectiveness, ease of use, and costs involved in the creation, handling, and transport of radioactive isotopes for injection into a patient. An additional benefit is improving the image

or diagnostic information acquired, which in turn can reduce the dose that is needed to give a good image or sufficient information. As an example, such measurement is accomplished by a radiation dosimeter housed within the radiation shielded enclosure, housing, or container. This dosimeter may be calibrated for the specific geometry involved and for the specific isotopes, for example, 511 keV gamma photons, thereby eliminating the need for large, bulky, expensive dosimeters.

[0013] In another aspect, the radiopharmaceutical agent may be continuously stored and or circulated within a closed system in the fluid delivery system and mixed with saline on demand, such as by actuating a handcontroller, to control the radiation dose delivered to a patient. In such an integrated fluid delivery system, methods to optimally stage, monitor, and scan patients in a clinical environment are also provided. Elements of the integrated fluid delivery system include estimating the metabolic activity of a patient upon injection of the radiopharmaceutical agent, intelligent integration of the monitoring information into a centralized server for scheduling and organizing the work queue in an analogous manner to technology currently used in cardiac telemetry units, and control of the external environment in which the patient, post injection, is staged. An integrated fluid delivery system which can continuously store and or circulate radiopharmaceutical agent to make a measured dose of radiation available "on demand" is another improvement for the nuclear medicine field. This system may optimize a radiopharmaceutical injection based on mathematical models of patient physiology, provide alternative methods of detecting radiation, and/or improved methods for isolating attending personnel from radiation emitted by a patient after injection of radiopharmaceuticals.

[0014] An exemplary application of the foregoing integrated fluid delivery system relates to the intelligent delivery and monitoring of radiopharmaceutical agents to maximize the uptake of agent into tumor sites and minimization of shunting into muscles, surrounding parenchyma, liver, and bladder. Site specific delivery (intratumoral) and monitoring using permittivity sensing is anticipated as being part of the implementation method. The explicit incorporation of physiologic levels of free glucose, metabolic analogues, renal function, tumor permeability, respiratory function, and tumor binding site dynamics into a control paradigm are desirable. The incorporation of the mentioned parameters into a predictive model, adaptive or robust controller will result in individualized injection trajectories for the fluid delivery or handling system, optionally including maintenance radiopharmaceutical dosing during the patient's stay in the staging area. Knowledge of the tumor permeability, vascularity, and other properties may be used in the estimation of a control signal for the

radiopharmaceutical. A workstation that is able to process a CE (contrast enhanced) CT (perfusion), and/or DCE (dynamic contrast enhanced) MRI stack is envisioned that the clinician or operator interacts with when performing the fluid delivery regimen. Many radiopharmaceutical procedures (both diagnostic and therapeutic) result in suboptimal outcomes such as, for example, involuntary patient movement during imaging procedures that may result in image blurring and thus reduced visualization or a reduced SUV (Standardized Uptake Value) for a lesion or tissue segment.. The concepts described herein can improve the diagnostic or therapeutic outcome, minimize the load or dose of radiopharmaceutical agent needed to perform the procedure, optimize uptake of the radiopharmaceutical agent into cancerous zones, and provide optimal timing and staging of the procedure.

[0015] Turning to specific embodiments described in detail herein, one aspect relates to an integrated radiopharmaceutical patient treatment system including a portable radioisotope generation module configured to generate a gaseous radioisotope, a radiopharmaceutical processing module configured to dissolve the gaseous radioisotope in an injectable medical fluid, a fluid injection system in fluid communication with the radiopharmaceutical processing module and configured to inject a dose including the gaseous radioisotope and the injectable medical fluid into a patient, and at least two imaging devices configured to independently detect biological and physiological characteristics of the patient based on the dose. The radiopharmaceutical processing module may be in fluid communication with the radioisotope generation module.

[0016] The injectable medical fluid may be an injectable fluid imaging agent. The injectable medical fluid may be an injectable contrast agent. The contrast agent may be selected from the group consisting of Dotarem, Gadavist, Magnevist, Omniscan, OptiMARK, and Prohance. The gaseous radioisotope may include a radioisotope selected from the group consisting of N-13, Xe-133, Kr-81m, C-11, and O-15. The radioisotope generation module may include a laser wakefield generator or other suitable small radioisotope generation module. The patient treatment system may be mobile. The at least two imaging devices may include a radioisotope imaging system such as a Positron Emission Tomography (PET) imager or a Single Photon Computed Tomography (SPECT) imager and a Magnetic Resonance (MR) imager. An integrated control system may be operatively connected to the fluid injection system and the at least two imaging devices. The integrated control system may provide automatic sequencing and timing of delivery of the dose of the gaseous radioisotope and the injectable medical fluid to the patient and the detection of the biological

and physiological characteristics of the patient performed by the at least two imaging devices. The integrated control system may also be operatively connected to the radioisotope generation module to activate the generation of the gaseous radioisotope, and the radiopharmaceutical processing module to activate the dissolution of the gaseous radioisotope in the injectable medical fluid. The integrated control system may include a graphic user interface configured to display relevant data obtained by the at least two imaging devices and to receive control data and parameters to operate the patient treatment system. The integrated control system may be in communication with a remote information system to receive at least one of the following: patient information, expected patient injection times, and patient injection volumes. A radiation protection module may be configured to contain and shield the radioisotope generation module. The fluid injection system may include a flushing liquid source configured to flush the fluid injection system after the gaseous radioisotope and injectable medical fluid have been administered to the patient. The gaseous radioisotope may be used to produce images of the respiratory system, for example as the gaseous radioisotope is removed during exhalation and diluted during inspiration by the respiratory process. In addition the volume changes of the gaseous fraction of the lung volume elements (voxels) can be analyzed. A motion compensation module may be in communication with the at least two imaging devices, for example to compensate for motion incurred during the respiratory process. The motion compensation module may be configured to compensate for blurring of an image captured by the at least one of two imaging devices or in the composite image created from the two separate imaging devices' measurements.

[0017] Another aspect relates to an integrated radiopharmaceutical patient treatment system including a gaseous radiopharmaceutical imaging agent source, a liquid imaging agent source, a gaseous radiopharmaceutical imaging agent delivery system in fluid communication with the gaseous radiopharmaceutical imaging agent source and configured to inject a dose of the gaseous radiopharmaceutical imaging agent into a patient, a liquid imaging agent delivery system in fluid communication with the liquid imaging agent source and configured to inject a dose of the liquid imaging agent into the patient, and at least two imaging devices configured to independently detect biological and physiological characteristics of the patient based on the doses injected into the patient. In certain embodiments, the gaseous radiopharmaceutical imaging agent may be dissolved in the liquid imaging agent before or during administration. In certain embodiments, the combined gaseous radiopharmaceutical imaging agent and liquid imaging agent may be pressurized to maintain dissolution of the

gaseous radiopharmaceutical imaging agent in the liquid imaging agent prior to administration into the patient.

[0018] A gaseous radiopharmaceutical imaging agent dissolution system may be configured to dissolve the gaseous radiopharmaceutical imaging agent in the liquid imaging agent. The gaseous radiopharmaceutical imaging agent dissolution system may be in fluid communication with the gaseous radiopharmaceutical imaging agent source and the liquid imaging agent delivery system. A motion compensation module may be in communication with the at least two imaging devices. The motion compensation module may be configured to compensate for blurring of an image captured by at least one of the at least two imaging devices, for example during respiration. The gaseous radiopharmaceutical imaging agent source may be a laser wakefield generator. The at least two imaging devices may include a Positron Emission Tomography (PET) imager and a Magnetic Resonance (MR) imager. An integrated control system may be operatively connected to the gaseous radiopharmaceutical imaging agent delivery system, the liquid imaging agent delivery system, and the at least two imaging devices. The integrated control system may provide automatic sequencing and timing of delivery of the doses of the gaseous radiopharmaceutical imaging agent and the liquid imaging agent to the patient and the detection of the biological and physiological characteristics of the patient performed by the at least two imaging devices. The integrated control system may also be operatively connected to the gaseous radiopharmaceutical imaging agent source to activate generation of the gaseous radiopharmaceutical imaging agent and the liquid imaging agent source to activate delivery of the liquid imaging agent.

[0019] Another aspect relates to a method of obtaining an image using a combined imaging system, including the steps of generating a gaseous radioisotope; dissolving the gaseous radioisotope in an injectable medical fluid, such as a liquid imaging agent; injecting a dose of the gaseous radioisotope and the injectable medical fluid into a patient; and capturing an image of a patient using at least two imaging devices to independently detect biological and physiological characteristics of the patient based on the dose. The method may further include the step of compensating for blurring in the image captured by the at least one of the two imaging devices or in the composite image created from the two separate imaging devices' measurements..

[0020] Further details and advantages are described herein in connection with several embodiments of methods, systems, and apparatus for the generation, preparation, transportation and administration of pharmaceutical substances, typically intrinsically harmful or toxic pharmaceutical substances such as radioactive pharmaceutical substances, to

human and animal subjects. Like parts are designated with like reference numerals throughout and, where applicable, alphabetical designations are associated with the reference numerals for clarity in describing the concepts of the inventions disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **FIG. 1** is a flowchart of an exemplary process for radiopharmaceutical generation, dose preparation, and administration to a patient.

[0022] **FIG. 2A** is a schematic representation of an integrated system for generating, dose preparation, and administration of radiopharmaceutical agents and subsequent imaging of a patient and including features for stimulating and monitoring the patient as well and integrating the various component of the system.

[0023] **FIG. 2B** is a schematic representation similar to **FIG. 2A** illustrating another embodiment of the integrated system.

[0024] **FIG. 2C** is a schematic representation of a representative physical implementation of the integrated systems of **FIGS. 2A-2B**.

[0025] **FIG. 2D** is a schematic representation of another representative physical implementation of the integrated systems of **FIGS. 2A-2B**.

[0026] **FIG. 3** is a schematic representation of a radiopharmaceutical system including features for radionuclide creation and "chemistry" processing of the radionuclide to a radiopharmaceutical and delivery of the same to a patient.

[0027] **FIG. 4A** is a schematic representation of one possible implementation of the radiopharmaceutical system **FIG. 3**.

[0028] **FIG. 4B** is a schematic representation of another possible implementation of the radiopharmaceutical system **FIG. 3**.

[0029] **FIG. 5** is a schematic representation an individual dose radiopharmaceutical device for loading radiopharmaceutical agent into a syringe or like container or transferring the radiopharmaceutical agent between syringes or like containers.

[0030] **FIG. 6** is a schematic representation of a retractable transport device that may be used to transfer containers of radiopharmaceutical agent to, for example, a dosimeter.

[0031] **FIG. 7** is a schematic representation of a multi-fluid and multidirectional fluid handling system incorporating a fluid junction in close proximity to a recipient for delivering fluids to the recipient.

[0032] **FIG. 8** is an alternative embodiment of the fluid junction shown in **FIG. 7**.

[0033] **FIG. 9** is a second alternative embodiment of the fluid junction shown in **FIG. 7**.

[0034] **FIG. 10** is a third alternative embodiment of the fluid junction shown in **FIG. 7**.

[0035] **FIG. 11** is a fourth alternative embodiment of the fluid junction shown in **FIG. 7**.

[0036] **FIG. 12** is a top view of a portion of the fluid junction shown in **FIG. 11**.

[0037] **FIG. 13** is a perspective view of an embodiment of a patient shielding system.

[0038] **FIG. 14A** is a schematic representation of a system for the generation, preparation, transportation, and administration of fluid radiopharmaceutical substances that incorporates a modular and transportable radiation-shielded transfer device for radiopharmaceutical containers.

[0039] **FIG. 14B** is a schematic representation of the radiation-shielded transfer device shown in **FIG. 14A** in transit to another location.

[0040] **FIG. 14C** is a schematic representation showing the radiation-shielded transfer device shown in **FIG. 14A** associated with a fluid delivery system or component at a receiving location.

[0041] **FIG. 15** is a schematic representation illustrating a possible implementation of the system shown in **FIGS. 14A-14C.**

[0042] **FIG. 16** is a schematic representation of another embodiment of the system for generation, preparation, transportation and administration of fluid radiopharmaceutical substances shown in **FIGS. 14A-14C**.

[0043] **FIG. 17** is a schematic representation of another embodiment of the radiation-shielded transfer device of shown in **FIGS. 14A-14C**.

[0044] **FIG. 18** is a schematic representation showing an embodiment of the radiation-shielded transfer device adapted to interface with a controlled power injector.

[0045] **FIG. 19** is a schematic representation showing another embodiment of the radiation-shielded transfer device with an associated "clip-on" dosimeter.

[0046] **FIGS. 20-21** are schematic representations showing an arrangement wherein radiopharmaceutical agent may be moved between two radiation-shielded transfer devices or two containers disposed within a single such device.

[0047] **FIGS. 22A-22B** are schematic representations of yet another embodiment of the radiation-shielded transfer device.

[0048] **FIG. 23** is a schematic representation showing the radiation-shielded transfer device of **FIG. 19** associated with a standard ionization chamber.

[0049] **FIG. 24** is a schematic representation showing a multi-dose container delivered in a transport container or pig with a specialized access port and shielded housing.

[0050] **FIG. 25** is a schematic representation of a closed loop system that continuously circulates radiopharmaceutical agent and which may be accessed on demand by a system operator.

[0051] **FIG. 26** is a schematic representation of a "slug" counting injector system for metering a calibrated fluid dose of radiopharmaceutical or another agent to a patient.

[0052] **FIG. 27** is a schematic representation of a prior art manual syringe shield.

[0053] **FIG. 28** is a schematic representation of a manual syringe shield according to one embodiment comprising a locking mechanism.

[0054] **FIG. 29** is a schematic representation of the manual syringe shield of **FIG. 28** further comprising an operable support rod.

[0055] **FIG. 30** is a schematic representation of the manual syringe shield of **FIG. 29** wherein the support rod is optionally knurled or ribbed and structure is provided to operate the support rod.

[0056] **FIGS. 31-32** are schematic representations of a syringe shield system that operates in a clamshell manner.

[0057] **FIGS. 33-34** are schematic representations of an alternative embodiment of the syringe shield system of **FIGS. 31-32**.

[0058] **FIG. 35A** is a schematic representation of a dose adjuster in accordance with other aspects of the invention set forth herein

[0059] **FIGS. 35B-35C** are schematic representative views of the dose adjuster of **FIG. 35A** according to several possible implementations.

[0060] **FIG. 36A** is a schematic representation of a fluid delivery system utilizing a power injector platform.

[0061] **FIG. 36B** is exterior or representative views of a portable implementation of the fluid delivery system of **FIG. 36A**.

[0062] **FIG. 37** is a schematic representation of a fluid delivery apparatus to which the syringe shield embodiment of **FIG. 30** may be associated or engaged with an automatic power injection apparatus or similar apparatus.

[0063] **FIG. 38** is a schematic representation of a container with several associated dosimeters spaced at locations along the length of the container.

[0064] **FIGS. 39A-39C** illustrate basic principles for calculated sensitivity for a small volume container such as in **FIG. 38** comprising three detector positions.

[0065] **FIG. 40A** is a flowchart of an alternative exemplary process for radiopharmaceutical generation, dose preparation, and administration to a patient.

[0066] **FIG. 40B** is a schematic representation of a radiopharmaceutical combined imaging system.

DESCRIPTION OF THE VARIOUS EMBODIMENTS

[0067] For purposes of the description hereinafter, spatial orientation terms, if used, shall relate to the referenced embodiment as it is oriented in the accompanying drawing figures or otherwise described in the following detailed description. However, it is to be understood that the embodiments described hereinafter may assume many alternative variations and configurations. It is also to be understood that the specific devices illustrated in the accompanying drawing figures and described herein are simply exemplary and should not be considered as limiting. In the following description, an imaging agent is a liquid, gas, or solid which interacts with the patient and affects the resulting image or data in some way. In the following description, an isotope may be defined as a variant of a particular chemical element which differs in neutron number, but has the same number of protons in each atom. A radioisotope may be defined as a radioactive isotope. A radiopharmaceutical may be defined as a pharmaceutical drug that has radioactivity and emits radioactivity particles or energy, and in the case of radiopharmaceutical used as an imaging agent, that may be detected and measured during an imaging procedure. As used generally herein, the terms "contrast" or "contrast agent" refers to an imaging agent which is a compound, drug, or substance that is injected into, breathed into, or otherwise placed in a patient which interacts with and/or measurably alters or affects an applied energy that is used by the imaging apparatus, such as electromagnetic radiation, X-rays, or ultrasound. This interaction results in a change in the system which is readable by an imaging system and subsequently converted into medical information and/or structural information, such as an image of internal features the patient or a portion of the patient.

[0068] **FIG. 1** is an exemplary flowchart showing a process for radiopharmaceutical generation, dose preparation, and administration to patient. In this disclosure, **FIG. 1** will be discussed initially in connection with two specific radiopharmaceutical agents, namely, FDG (Fluorodeoxyglucose) used for cancer imaging which uses the positron emitter 18F (fluorine with an atomic mass of 18) and Cardiolite® used in coronary imaging diagnostic procedures which uses 99mTc (a metastable isotope of technetium of atomic mass 99). Nonetheless, **FIG. 1** illustrates the overall procedure for the creation, refinement, and administration of injectable radioactive materials for diagnostic and/or treatment applications and typically those in fluid form (i.e., gas or liquid).

[0069] In **FIG. 1**, step **10** relates to creating an isotope which is the precursor material to the radiopharmaceutical agent. For example, 99mTc is created or generated in a commercially available technetium generator by natural radioactive decay of the longer-lived isotope molybdenum-99. Once created, the 99mTc is withdrawn from the generator by flushing water or saline through the generator into a container (vial, bottle, syringe, etc.). The technetium generator typically has two ports with needles or which can be accessed via needles. The first needle is used to puncture a vial of sterile saline and the second needle is associated with a vacuum source, for example, an evacuated container (vial, bottle, etc.). The vacuum source pulls saline from the saline vial through the generator into the evacuated container. This procedure is generally done manually by a radio-pharmacist. As an example, United States Patent No. 4,837,110 describes eluting with saline-copper chloride mixture, incorporated herein by reference.

[0070] In certain embodiments, the present disclosure provides a system which can utilize the benefits of combined imaging modality, for example during simultaneous PET/MR or SPECT/MR. One potential strength of the combined imaging modality is the ability to use one imaging procedure, such as MR in real time to account for or compensate for motion of the tissue that would cause significant blurring in the second or additional imaging procedure, such as PET or SPECT. This may be important for organs with involuntary movement, such as the heart, lung, and intestines and may also be important for other organs or patient body parts where motion can significantly affect attenuation correction, and thus quantification. It can also be important when the motion and the effect of the motion is one of the parameters that is being imaged, for example gas movement in, through, and out of the lungs. In certain embodiments, the system of the present disclosure may include a PET/SPECT isotope generation which can generate a radiopharmaceutical that can be injected into the patient, for example substantially concurrent with injection of a contrast agent for a secondary imaging procedure, such as an MR contrast agent, and the dual modality imaging system may be used to image the radioisotope and the contrast agent as they move through the patient's circulatory system. In specific embodiments, the radioisotope may be a gaseous radioisotope that may be dissolved in a medical fluid or patient's blood or tissue or may be dissolved in and administered with the contrast solution itself. The gaseous radioisotope and contrast agent travel through the circulatory system and to the lungs where some, most, or all of the gaseous radioisotope is ultimately exhaled during respiration, thus allowing imaging of the lung and/or lung function. Simultaneous imaging with the secondary imaging procedure, such as MR, allows for correction of potential PET image blurring and attenuation correction

errors due to chest/lung movement during respiration. The system and software therein may then track the motion of the radioisotope and contrast agent and compensate for motion of voxels of tissue as the image is acquired. Thus, for example, with one study it is possible too spatially assess or measure the perfusion of the lung tissue through the pulmonary artery, the efficiency of gas transport from the blood to the lung, and the efficiency of air or gas motion and exchange during respiration.

[0071] The dual modality imaging system and procedure described herein overcomes potential shortcomings by utilizing a radioisotope that may be incorporated into a gaseous compound, such as a compound that may be solubilized in solution, for example under increased pressure during the production and injection procedure, which then comes out of solution and is exhaled when it reaches the lungs.

[0072] In another aspect, as shown in step **400** of **FIG. 40A**, a gaseous radioactive isotope may be generated as the precursor material to the radiopharmaceutical agent. For example, N-13 gas (*i.e.*, N_2(g) in which at least one of the nitrogen atoms is ^{13}N isotopic nitrogen) may be generated as a radioisotope using a radioisotope generator, such as a laser wakefield isotope generator. In alternative aspects, other radioisotopes may be utilized with this system for combined imaging processes described herein depending on the organ or portion of the patient's body to be imaged or medical indication or condition being examined or treated. Non-limiting examples of radioisotopes useful for various aspects include C-11, O-15, F-18, Rb-82, Ga-68, Tc-99, I-123, I-131, In-111, Xe-133, Kr-81m, or other conventional medical radioisotopes which may be incorporated into gaseous molecules, saline, injectable medical fluids, conventional imaging mediums, contrast agents, agents, and compounds. For example, C-11 or O-15 may be incorporated into CO(g), CO_2(g), or O_2(g) or O-15 may be incorporated into H_2O which may be exhaled during respiration. A radioisotope generator may be a table top unit which can be used to generate the N-13 gas or other radioisotope on-site without the need for a large and expensive cyclotron. A radioisotope generator may be incorporated into a mobile cart that can be moved to different rooms on-site or interfaced with a fluid injection system as part of a cart, which can also be moved to various rooms of an imaging suite to infuse a patient. N-13 is a short lived PET radioisotope having a half-life on the order of 10 minutes. A short half-life is beneficial because it reduces the total radiation dose to which the patient is exposed. However, due to its short half-life, the radioisotope typically needs to be created near the dissolution and imaging system. Currently, this is done with relatively expensive, large, and heavy cyclotrons. Therefore, an imaging study could previously only be performed at a few imaging facilities that have a nearby cyclotron for generating the N-13

radioisotope. With the use of a radioisotope generator, such as a laser wakefield generator, which is relatively small in size and inexpensive, the N-13 radioisotope can be generated in any room of an imaging suite. Since the laser wakefield generator is easily transportable between rooms, the short half-life of the N-13 radioisotope is no longer a concern. After being generated, the N-13 radioisotope can be moved directly to a dissolution system, as will be described herein.

[0073] A laser wakefield isotope generator can be a table top unit which can be used generate the N-13 gas (i.e., N_2(g) in which at least one of the nitrogen atoms is ^{13}N) on-site without the need for a large and expensive cyclotron. Thus in the present system, a laser wakefield generator may be optionally incorporate into a cart or interfaced with a fluid injection system as part of a cart, similar to Bayer's Intego product (commercially available from Bayer Medical Care, Inc., Indianola, PA) which can be moved to various rooms of an imaging suite to infuse a patient. The cart may also incorporate the fluid mechanical system that dissolves the radioactive gas into a saline solution or other medical fluid, measures the radiation dose of the infusate prior to and/or during an injection procedure, and/or delivers it to the patient. The cart may also incorporate sufficient radiation shielding to perform these functions accurately and safely, for example to reduce radioactivity exposure levels for clinicians. Examples of suitable injection systems and protocols that may be utilized in various embodiments are described in detail in the following U.S. patents and US and international application publication nos: 6,767,319; 7,204,797; 7,713,239; 7,905,861; 8,198,599; 8,382,704; 8,454,561; 8,517,905; 8,551,074; 2008/0177126; 2011/0178359; 2011/0209764; 2013/0124103; 2013/0123567; 2013/0079581; 2013/0331635; 2013/0331634; 2013/0331691; 2013/0331801; 2014/0119621; 2014/0257015; 2014/0228617; 2014/0248159; 2014/0263319; and WO13/075127, the disclosures of which are incorporated by this reference.

[0074] The cart and fluid injection system may also have the capability to deliver additional imaging agents, other drugs or other fluids, either concurrent with the N-13/saline solution or prior to or after injection of the N-13/saline solution. The fluid injection system can provide saline or other innocuous fluid as a flushing agent to flush the various active solutions from the injection system into the patient or into a waste container, when desired. Optionally for example, in certain embodiments the fluid injection system can inject an MR contrast or other contrast agent into a patient so that the behavior of the blood can be measured by an agent which does not interact with the air in the lung and so is not affected by gas exchange but only perfusion and liquid volume. According to various embodiments,

using an MR contrast agent may also enable the visualization of all aspects of perfusion, for example the arterial blood flow to the lungs, edema, and venous outflow and more accurate morphological imaging (size and shape) of the vessels. In certain embodiments, the N-13 gas can be dissolved into the MR contrast, which optionally can be diluted with saline to improve the linearity of the imaging and/or reduce artifact creation. In alternative embodiments, other radioactive isotopes may be utilized according to the system for combined imaging processes described herein, for example depending on the organ or portion/part of the body to be imaged or medical indication or condition being examined or treated. Non-limiting examples of contrasts include Dotarem, Gadavist, Magnevist, Omniscan, OptiMARK, and Prohance. Non-limiting examples of radioisotopes useful for various embodiments include C-11, O-15, Rb-82, F-18, Ga-68, Tc-99, I-123, I-131, In-111, Xe-133, Kr--81m. or other conventional medical radioisotopes which may be incorporated into saline, medical fluids, conventional imaging mediums, contrast agents, agents, and compounds; and utilized in various embodiments of the present disclosure.

[0075] Step **20** in **FIG. 1** relates to creating, synthesizing, or placing the radioactive isotope into an injectable or deliverable form or molecule. In some instances, the radioactive isotope in its raw form is intended for injection into a patient but not typically. A more typical example is to combine the radioisotope created in step **10** with a sterile powder. For example, in the manufacture of Cardiolite®, approximately 1 to 3 mL of a solution containing the created technetium (925 to 5550 MBq, (25 to150 mCi)) is added to a sterile powder in a bulk container, typically a vial. Following the manufacturer's instructions, the vial is shaken and heated, typically in boiling water, for a predetermined period of time to promote the chemical incorporation of the technetium into the Cardiolite® molecule. After cooling, the vial (or possibly a syringe or a bottle) containing material is visually inspected for clarity and absence of particulates. The solution is now a radiopharmaceutical agent that is suitable for injection into a patient, human or animal. The Cardiolite® radiopharmaceutical agent may be stored for up to about six hours at a temperature of 15 to 25°C. The details of the chemistry and preparation of Cardiolite® are available from the manufacturer, Bristol-Meyers Squibb, 331 Treble Cove Road, N. Billerica, Massachusetts 01862. Containers (i.e., vials, bottles, syringes, etc.) of Cardiolite® are commonly stored in a shielded container to protect from radiation exposure. In another aspect, as shown in step **410** of **FIG. 40A**, the N-13 radioisotope in a gas, for example that produced by step **20** in **FIG. 1**, may be dissolved into an injectable medical fluid, such as saline, for injection into a patient (step **420** of **FIG. 40A**). Using this process, the N-13 gaseous radioisotope may be

dissolved into saline for injection into a patient. One example of such a dissolution process is disclosed in U.S. Patent No. 6,773,673 to Layfield et al., entitled "Radiation Handling System and Set", the disclosure of which is herein incorporated by reference in its entirety. For the dual modality imaging procedure, a contrast agent, such as MR contrast agent or other contrast agent, may be substantially simultaneously injected into the patient with the radioisotope/saline solution. In another aspect, the N-13 radioisotope may be dissolved into a liquid contrast agent, such as an MR contrast or other contrast agent. In either embodiment, the dual modality imaging enables the visualizations of the arterial blood flow to the lungs of the patient and more accurate morphological imaging (size and shape) of the vessels. Optionally, the dissolved N-13 radioisotope and MR contrast may be diluted with saline to improve the linearity of the imaging and/or reduce artifact creation.

[0076] Next, at step **30**, the radio-pharmacist, or any medical personnel who is charged with preparing and possibly administrating the radiopharmaceutical, manually withdraws a quantity of solution from the bulk container, often a vial, using a shielded syringe by piercing the vial septum with the syringe needle. The needle is capped and the syringe is removed from its shield and placed in a radiation dose calibrator. After the radiation dose is measured and, depending on whether there is too little or too much radiation present, the radio-pharmacist estimates the volume that needs to be added from or returned to the bulk container (i.e., vial) from the measured radioactivity and the solution volume in the syringe. This entails removing the syringe from the dose calibrator, reinserting it into a syringe shield, and piercing the septum of the bulk container to withdraw additional solution or return some solution to the bulk container or, alternatively, to a waste container. The radio-pharmacist then again repeats the dose calibration step. If the radioactivity level is correct, further radiopharmaceutical preparation may occur. However, often a third iteration of the foregoing is required and, with each iteration, the radio-pharmacist or other medical personnel is exposed to radiation emanating from the bulk container and/or the individual dosage syringe. Generally, all these manipulations are done in a shielded glove box or behind a counter top shield or L-block so that the radiation dose to the radio-pharmacist's body core is significantly less than his or her hand dose. However, a certain level of exposure to the body core is also somewhat inevitable. When the "correct" dosage is finally obtained, the radio-pharmacist records the dosage on a piece of tape that is affixed to the syringe or the syringe shield encompassing the syringe. Alternatively, a label is produced by the dose calibrator which is affixed to the syringe or the syringe shield. Often, the dosage is only within +/-10% of the correct or desired dosage for the individual patient as the success of the foregoing

procedure is tied to skill of the individual radio-pharmacist. Dose calibrators are well-known in the nuclear medicine field.

[0077] The individual patient is prepared for administration of the dose of radiopharmaceutical at step **40** by establishing access to the patient's vascular system via a needle cannula or catheter. Some radiopharmaceutical agents may be in gaseous form or are nebulized and thus are inhaled. Step **40** is shown occurring after dose preparation step **30** but it will be clear that sequential following of the flowchart of **FIG. 1** is not strictly required and, for example, patient preparation step **40** may occur in parallel with any of preceding steps **10-30**. Accordingly, a patient may be prepared in parallel with or even before step **30**, the preparation of the individual dose. Radiopharmaceuticals are alternatively delivered orally, topically, through respiration, or are injected into tissue, body cavities, or other volumes. One application of radiopharmaceutical agents is as part of a cardiac stress test wherein the patient's heart rate is increased to measure cardio-vascular performance and obtain information regarding possible vascular occlusions. Accordingly, once a conduit is established to provide the radiopharmaceutical agent to the patient, additional patient preparation may occur, such as attaching ECG electrodes to the patient and monitoring the ECG as the patient's heart rate is increased through exercise on a treadmill, stationary bicycle, or similar machine, or a pharmacological stress agent is introduced into the patient. This specific application of radiopharmaceutical agents is described in detail herein. For brevity purposes, it is sufficient to state with regard to this specific application that when the patient's heart rate is sufficiently high, the correct dose of radiopharmaceutical agent is delivered to the patient intravenously at step **50** and the dosing information is recorded in the patient's medical record. After a preset period of time elapses for dose uptake as at step **60**, the patient may be moved to an imaging unit for PET or SPECT imaging as examples. The time delay may be zero as, for example, delivery may take place while the patient is in the imaging unit and imaging may start immediately upon or even before injection of the radiopharmaceutical agent. Generally for a cardiac study, the stress is continued for one minute as the heart muscle absorbs the radiopharmaceutical. Imaging can take place some time after that event, commonly within thirty minutes.

[0078] At the imaging unit, imaging data is acquired in the present example at step **70**. It may be incumbent on the imaging unit operator to input patient-specific information about the patient into the imaging unit controller and select the proper study. As indicated, the imaging unit acquires data at step **70** with little additional operator interaction or intervention. After the data is acquired at step **70**, it can be reconstructed and analyzed at step **80** as is

known in the nuclear medicine field and, more specifically in this example, the nuclear cardiology field. At step **80**, the imaging unit controller may automatically or via operator input correct for certain variables such as attenuation by the patient, and the operator optionally reformats and adjusts the information to the preferences of the individual clinician typically a physician. Moreover, at step **80** the physician reads the case study and renders an opinion which can range from concluding that the study shows an absence of perfusion, ejection fraction, or other anomalies allowing the patient to be discharged or concluding that anomalies are present and prescribing a rest study. If a rest study is to be conducted, the patient is taken out of the imaging unit and allowed to rest further. Then, a second larger dose of Cardiolite® is typically injected. After another preset period of time, for example several minutes, imaging is conducted and this typically concludes the "stress test" procedure. In some cases the rest study is done before the stress study.

[0079] In an alternative to the foregoing example, FDG, described previously, may be administered to a patient in a somewhat similar manner to the foregoing technetium (Cardiolite®) example. However, FDG is created and prepared for dosage to the patient in a slightly different manner from Cardiolite®. In this alternative sequence, positron emitter 18F, used in making FDG, is created, (at step **10**), in a cyclotron or accelerator which is a very expensive piece of capital equipment. In the cyclotron, 18O water is bombarded with protons and some of the 18O changes into 18F. A batch of water with the 18F, generally one to two ml in volume, is sufficient to be used in several imaging procedures. The chemistry for incorporating the 18F into FDG is commonly done in a "hot" lab in close proximity to the cyclotron (at step **20**). Generally, automated chemistry units, such as the TRACERLab MX $_{FDG}$ system available from GE Medical Systems, are used to create the multiple doses of FDG in a single batch. A transportable facility for accomplishing these steps is described in United States Patent Application Publication No. 2004/0086437 to Jackson, which is incorporated herein by reference.

[0080] In the hot lab, liquid sufficient for multiple doses of FDG is placed into a shielded bulk container (vial, bottle, syringe, etc.), or it is separated into individual doses or unit doses which are placed into shielded syringes, with the radioactivity determined by the prescription and imaging time for each patient and thus rendering a prepared dose for each patient as at step **30** in **FIG. 1**. This step is usually done automatically because the radiation from 18F is much higher energy than technetium and so it is preferable to keep the radio-pharmacist distanced from the material. Comecer of Italy makes a large, multi-ton, robotic system for accomplishing this task. The FDG (bulk or individual doses) is transported to the patient

treatment site. If the cyclotron is not at the treatment site, the FDG (bulk or individual doses) is transported to the location for final dose preparation and dose delivery. If the FDG arrives in bulk form, the radio-pharmacist manually prepares individual patient doses using the manual procedures outlined previously in relation to technetium. If the FDG arrives in unit dose form, the radio-pharmacist or nuclear technologist is still required to manually confirm the dosage with a dose calibrator and make adjustments if needed.

[0081] The FDG, typically in a shielded syringe, is then transported to the injection site in, typically, a shielded transport container (i.e., a transport pig). Alternatively, some shielded containers are similar to heavy metal lunch boxes. In the injection room, a clinician, for example, a physician, nurse, or technician delivers the FDG to the patient, typically intravenously via a needle cannula or catheter inserted in the patient, as at step **40** of **FIG. 1**. For example, a saline drip bag may be connected to the patient via an IV needle. The clinician or technician then removes the shielded syringe from the transport pig and inserts the syringe needle into a port in the IV line to inject the radiopharmaceutical into the patient as at step **50** wherein dosage delivery occurs. Optionally, a flush with saline may be performed to quickly push all the FDG into the patient's body. The syringe is typically then returned to the shielded transport container (i.e., pig) and any residual dose is measured in the hot lab's dose calibrator. As an example, for normal cancer imaging rather than cardiac stress test imaging, the patient typically waits without physical activity in a darkened room for thirty to sixty minutes, as at step **60**. The patient is then transported to an imaging unit, (PET or SPECT), and imaging data is acquired to create an image as at step **70** in **FIG. 1**.

[0082] In an alternative aspect, as shown in the system of **FIG. 40B**, the gaseous radiopharmaceutical imaging agent and liquid imaging agent may be delivered separately to the patient. The gaseous radiopharmaceutical imaging agent may be generated using a gaseous radiopharmaceutical imaging agent source **500**, while the liquid imaging agent is provided separately via a liquid imaging agent source **510**. In one aspect, the gaseous radiopharmaceutical imaging agent source **500** may be a laser wakefield generator. Optionally, the gaseous radiopharmaceutical imaging agent may be dissolved in the liquid imaging agent using a gaseous radiopharmaceutical imaging agent dissolution system **520**. Alternatively, the gaseous radiopharmaceutical imaging agent may be directly delivered to the patient using a gaseous radiopharmaceutical imaging agent delivery system **530**, for example the Pulmonex II system, manufactured by Biodex of Shirley, NY. Separately, the liquid imaging agent may be delivered to the patient using a liquid imaging agent delivery system **540**. The gaseous radiopharmaceutical imaging agent may be delivered to the lungs of

the patient for direct imaging and/or subsequent absorption into the patient's blood. In an alternative aspect, the gaseous radiopharmaceutical imaging agent may be dissolved into a liquid imaging agent, such as saline, for delivery via a catheter to the patients' blood vessels, other orifice or cavity, or directly in the tissue. The gaseous radioisotope imaging agent may be administered with at least one liquid contrast agent to the patient, such as prior to, concurrent with, or after delivery of the at least one gaseous radioisotope imaging agent. The imaging system may then image the movement of these two or more imaging agents through the body and from their distribution at one or more points in time, assesses at least one physiological property of the patient. In certain embodiments, dual energy CT is one imaging modality that can differentiate different materials during a single scan and can be utilized with various embodiments described herein. In other embodiments, SPECT is a second imaging modality that may be utilized with embodiments described herein.

[0083] Referring to **FIG. 2A**, a total or integrated system **100** for generating, dose preparation, and administration of radiopharmaceutical agents is illustrated. The total or integrated system **100** includes several subsystems, modules, devices, or components which will be individually described herein. The immediately following discussion broadly describes the individual or constituent units and their physical arrangement in the total or integrated system **100** (hereinafter "integrated system **100**"). The integration of integrated system **100** is provided by one or more of: a physical arrangement or proximity of subsystems, modules, or components that facilitate an operator's execution of an imaging or therapeutic procedure by functional interoperability of system parts that enable safe, effective transfer of material, information, or control, and/or by a coordination of action desirably facilitated by an integrated system controller **110**, typically computerized or electronic, that controls, coordinates, and/or automates various subsystems, modules, devices, or components through the steps in the desired procedure.

[0084] A first subsystem is a patient support **120** which supports a patient **P** in a desired, consistent, and controllable position with respect to an imaging system or, generically, an imager **130**. In **FIG. 2A**, patient support **120** is a chair in which patient **P** is held in a semi-reclined state. In **FIG. 2B**, patient support **120a** is an examination table whereon the patient is fully reclined. Other options are possible, for example, patient **P** could be upright or erect. MRI imaging units are known that allow for imaging of upright patients as manufactured by FONAR Corp., 110 Marcus Drive, Melville, NY 11747. Another example is disclosed in United States Patent No. 5,967,983 to Ashburn, incorporated herein by reference. **FIGS. 2C-**

2D are schematic and ergonomic representations of representative physical embodiments of the integrated systems of **FIGS. 2A-2B**.

[0085] Imager **130** is used to sense energy or measure characteristics of patient **P** and create a data set, often viewed by the operator or physician as an image or set of images. Exemplary examples devices for imager **130** include nuclear medicine imagers (traditional gamma cameras, SPECT – Single Photon Emission Computed Tomography and PET – Positron Emission Tomography) in which energy is emitted from patient **P** and detected by imager **130**, CT (Computerized Tomography), wherein X-ray energy is generated by imager **130** and sensed by imager **130** after passing through patient **P**, MRI (Magnetic Resonance Imaging) which uses magnetic fields and RF energy to measure information about patient **P**, ultrasound imaging, and various light or luminescent imaging. Imager **130** and patient support **120** interact so that the operator at a console **145**, for example, associated with imager controller **140**, may select regions of patient **P** to be studied, and the study may then be conducted under the control of the imager controller **140**. Often, patient support **120** is considered a part of imager **130**. Imager controller **140** may be embedded or otherwise integrated to be part of the imager **130** to coordinate and execute the significant tasks of data acquisition, analysis, display, and control of the various parts of the imager **130**. Imager **130a** may be comprised of two or more components, as in **FIG. 2B**, for example, a SPECT camera or imager **132b** and a CT imager **132a**. Imager controller **140** may be interfaced with patient support **120** to sequentially position the region to be studied in the appropriate areas of the two imager subsystems, namely, SPECT camera **132b** and/or CT imager **132a**. Images may be taken and combined into a single image for presentation to the operator or physician for diagnosis. In embodiments, such as that depicted in **FIG. 2B**, wherein there are two or more different imaging devices combined in a single imager or are in close proximity to each other so that they can be used successively on a single patient, it is preferable that fluid handling system **150a**, described herein, include imaging contrast fluids or fluids appropriate for each of the imaging modalities. Alternatively, there are PET/CT imaging systems with both imagers contained in a single housing, and more recently PET/MR imaging systems with the capability to simultaneously acquire PET and MR information. For use with MR systems or combination systems including MR, it is important that selected components of the system, for example the delivery system be compatible with the MR system as is the Spectris Solaris available from Bayer AG of Pittsburgh, PA, or that they be kept at a safe operating distance. If some components or aspects of the system **590**, for example, isotope creation, radiopharmaceutical creation, dissolution, or dose measurement are not MR

compatible, then there can be a physical separation between selected aspects of the system. For example the dose may be prepared and places in a syringe, and the syringe may be transported and placed in shielded MR compatible injector, for example that of US 2013/0331691 A1.

[0086] Another aspect of integrated system **100** includes a subsystem or module **150** for fluid handling and delivery or administration to patient **P** in integrated system **100**. Within fluid handling system **150**, one or more fluid handling devices **152**, are provided. Such delivery devices or pumps are commonly referred to as fluid injectors and each "injector" **152** is separately identified in **FIG. 1** by a numerical identifier. One possible embodiment for fluid handling system **150** is described herein in connection with **FIGS. 3-4**. Exemplary devices for fluid injectors **152** are also described herein. However, it will be clear from **FIG. 2A** that one or more of fluid injectors **152** may be fluidly connected to patient **P** via an intravenous ("IV") fluid line **153** terminating in a needle cannula or a catheter (not shown) and appropriately inserted into patient **P** by medical personnel in advance of conducting the intended procedure. Fluid injectors **152** are desirably individually controlled by integrated system controller **110** to deliver one or more fluids, sequentially or simultaneously, at volumes and time varying flow rates in accordance entered or selected sequences or protocols of integrated system controller **110**. Accordingly, integrated system **100** provides the ability to coordinate singular or multiple fluid injectors **152** which may be useful for more sophisticated medical procedures such as target cancer treatments or physiological function studies. The number of fluid injectors **152** and, accordingly, the number of individual fluids to be delivered to patient **P** is only limited by the needs of the medical procedure. Multi-fluid fluid handling system **150** could be incorporated into integrated system **100** as the only fluid delivery component of system or could be augmented by other fluid delivery vehicles as desired. Aspects of an injection system useful to facilitate the safe dosing of multiple patients from a bulk or multi-patient container are disclosed in United States Patent Nos. 5,569,181; 5,806,519; 5,843,037; 5,739,508; and 5,840,026; and their progeny, all incorporated herein by reference. Multi-fluid fluid handling system **150** may be mounted in various ways that are commonly used in the medical field for fluid delivery units associated with imaging devices or scanners. Mounting on a wheeled pedestal or from an overhead counterpoise are exemplary options. Wall mounting is a third option. And, while multi-fluid fluid handling system **150** is illustrated separately from imager **130**, this device may be incorporated into the body of imager **130** pursuant to the disclosure of United States Provisional Patent Application No. 60/807,532, filed July 17, 2006, and entitled "Integrated Medical Imaging Systems".

[0087] Another aspect of integrated system **100** optionally includes a patient monitor or measurement subsystem **160**, module, or component which is in addition to, in combination with, or possibly substitutes for patient monitoring and measuring functions performed by imager **130**. An exemplary and non-limiting listing of such measurements include heart rate, ECG (electrocardiogram), blood pressure, EEG (electroencephalography – brain activity measurement), EMG (electromyography – measurement related to muscle activity), blood oxygenation level, blood glucose level, insulin level, etc.

[0088] In the case of cardiac stress test procedures, it may be desirable to add or integrate a patient stimulus unit or apparatus **170** into integrated system **100**. One example of patient stimulus unit or apparatus **170** is an apparatus or device on which patient **P** can physically exercise to increase the stress on the heart, such as a bicycle, treadmill, stair climber, elliptical trainer, or some other exercise machine. A bicycle-type stress patient stimulus device **172** is indicated schematically in **FIG. 2A** for exemplary purposes. Within cardiac stress test procedures, it may be desirable to regulate bicycle speed, resistance, or other operational parameter via integrated system controller **110** and display these values on integrated system controller **110**. This is a physical patient stimulus. A sensory patient stimulus could be effected via input to one or more of the senses, for example, a viewing screen **174**, audio inputs, by direct electrode stimulation of muscles, or by other physiological processes. Sensory patient stimulus could be coupled with physical patient stimulus or could entirely supplant physical patient stimulus in integrated system **100**. Moreover, pharmaceutical patient stimulus could be accomplished by injection of an appropriate drug or physiologically active fluids with the goal being to stimulate or stress the patient's body, such as the heart muscle, to record images of the response. Again, this could augment one or both of physical and sensory patient stimuli. Other patient stimuli are optional, such as through electrodes, temperature, or other phenomena. It is within the scope of this disclosure to provide a system that enables a physician or researcher to use any one of or any combination of stimuli, with physical, sensory, and drug-induced patient stimulus as examples to achieve the desired stimulating effect on patient **P** in integrated system **100**.

[0089] Given the state of the art with respect to electronics, computers, software, and control systems, integrated system controller **110** may be embodied in a single physical unit as shown in **FIG. 2A** or dispersed, possibly preferably, in two or more separate computers or sub-control units (not shown but readily within the skill of one skilled in the art) and which are operationally coordinated in a manner sufficient to achieve the same operational control afforded by integrated system controller **110**. Integrated control of integrated system **100**

allows the goals of the procedure to be accomplished with minimized operator input which reduces the possibility of operator over-tasking and, thus, reduces the chances for human error. Integrated control also enables automatic sequencing, timing, and coordination of diverse aspects such as patient positioning, stimulus, fluid delivery, and image acquisition that are beyond the ability of a human to coordinate alone. An additional aspect that tends to promote the segmentation or distribution of integrated system controller **110** is that different subsystems, components, or devices may be manufactured by different manufacturers and may optionally be able to operate without incorporation or integration into this total system. Thus, they will need to have sufficient control, communications, and user interface capability to operate on their own. By use of communications protocols, for example, those disclosed for communications between an injector and imager in United States Patent No. 6,970,735 to Uber, III et al. and incorporated herein by reference, imager and injector subsystems with fully independent operation can be made to act as a single unit from the operator's point of view. Further communication protocols may also be used for communications between an injector, an imager, and external communication sources as disclosed in U.S. Patent Nos. 7,457,804, 7,996,381, and 8,521,716, incorporated by reference in their entirety herein. The systems and methods shown in **FIG. 40B** may also include an integrated control/coordination/analysis system **590**, which performs the same functions as the integrated system controller **110**. The integrated control/coordination/analysis system **590** may be provided with a user interface **600** to permit a clinician or another operator to use the integrated control/coordination/analysis system **590**. By using one or more computers or similar computing devices having a non-transitory computer-readable storage medium capable of storing computer readable programming code or instruction and one or more processing units to execute, configure, analyze, or otherwise implement the methods, processes, and transformational data manipulations necessary to carry out the methods described herein, the user may interact with the integrated control/coordination/analysis system **590** via the user interface **600** to capture patient images. The coordination can include data transmission, optionally through hard copy such as text or bar code printing and reading, to full integration and control of higher level or even detailed functions of the subsystem. For example, the control/coordination/analysis system **590** shown in **FIG. 40B** may be in communication with the gaseous radiopharmaceutical imaging agent source **500** and the liquid imaging agent source **510** to generate and deliver the gaseous imaging agent and the liquid imaging agent. Further, the control/coordination/analysis system **590** may be in communication with the gaseous radiopharmaceutical imaging agent delivery system **530** and

the liquid imaging agent delivery system **540** to coordinate and activate the delivery of the gaseous radiopharmaceutical imaging agent and the liquid imaging agent to the patient. Any of the many published communications standards such as Ethernet or CAN may be used as well. Integrated system controller **110** includes one or more user interfaces **115** through which the operator can set up or program the operation of integrated system **100**, enter patient information, and monitor the operation of integrated system **100**. Part of the benefit of integration is that the operator need only enter a piece of information once and it is available throughout the system. As with integrated system controller **110**, one user interface **115** may serve to control the whole integrated system **100**, several subsystems, or a single subsystem. Alternatively, there can be several interfaces that provide similar or redundant control functions located in different places, for example, at the patient's side, at imager **130**, at a remote data access and analysis location **180** such as a radiology reading room or in a shielded control room to enable the operator to control or monitor integrated system **100** from the most convenient location.

[0090] One embodiment of a process for use of embodiments of the dual modality system may be as follows. The desired isotope, for example, N-13 gas, is generated in the generator. The dissolution or other chemistry is performed in the cart. The dose is measured, either before or preferably after the dissolution or chemistry, for example, by one or more sensors incorporated into the system. The dose is delivered directly to the patient or transported in a container and injected by a physically separate injection system, for example using one of the embodiments described here, optionally along with other imageable contrast fluids, such as MR contrast or other contrast agents. The data to create images is acquired over time by the imager. Appropriate data analyses are conducted by the one or more processors of the system and the clinician preferred data representations are provided to the clinician for diagnosis and treatment of the patient. The system is controlled and/or monitored by a technician or operator, utilizing wired or wireless (for example Wi-Fi) hardware and software, such as a CPU, GUI, tablet, hand-held computer or other processor or computational device.

[0091] Furthermore, integrated system controller **110** may also communicate information to and from other external information sources or networks via communications connection or interface **190**. One example is the ability to send data or images to a PACS (Picture Archiving and Storage) system for subsequent access, "reading", and diagnosis by a doctor. Retrieving data or images from a PACS system for comparison with the current study is also advantageous. A second communications connection of significant benefit is to a Hospital Information System (HIS). This communications connection or interface **190** allows data

about scheduling and patient **P** to be brought into the integrated system controller **110** to inform the operator of the procedure and patient conditions. This communications connection or interface **190** enables procedure results and notes to subsequently be communicated to physicians, patient records, and other appropriate systems. Examples indicating the benefits of communications between injectors and imagers are disclosed in United States Patent Nos. 5,840,026 and 6,970,735, incorporated herein by reference previously.

[0092] An exemplary use of integrated system **100**, as noted previously, is in performing cardiac stress tests. This test is typically prescribed when it is suspected that a patient **P** has a serious heart problem, specifically reduced perfusion or blood flow to a region of the heart when under stress. A technetium stress test is often prescribed by a cardiologist to confirm or eliminate the diagnosis. To conduct this test, patient **P** arrives at an imaging center and the necessary paperwork is completed. The procedure is explained to patient **P** and informed consent is received. An intravenous line is placed in the patient's arm and ECG electrodes are attached to his or her limbs and/or his or her chest and/or back. This can be done either before or after patient **P** is placed on patient support **120**. Information or data about patient **P** is entered into integrated system controller **110** either by the operator and/or through communications connection or interface **190**. A recommendation on patient dosing can be derived from data such as the study to be conducted, the patient's weight and build (BMI – body mass index), and mass of heart, if known. If this is a repeat study for this patient **P**, information about previous dosing may be accessed, and the current dosing is optionally made to be consistent with the previous study for quantitative comparison and trend analysis. After operator confirmation, an imaging agent, for example, a dose of Cardiolite® or Myoview® is prepared by fluid handling (i.e., injector) subsystem **150**.

[0093] With patient **P** on patient support **120**, a blood pressure monitor is attached, usually to the arm opposite the intravenous line. Fluid handling system **150** is interfaced to the patient's IV fluid line **153**. Optionally at this time, imager **130** is positioned appropriately relative to patient **P**. Patient **P** is then stimulated to increase his or her heart rate. For example, physical stimulation may be initiated by patient **P** pedaling bicycle-type patient stimulus device **172**. Heart rate is monitored and, when patient **P** reaches the target heart rate, for example, 80% of their age-adjusted maximum heart rate, integrated system controller **110** recognizes this condition and automatically, or upon confirmation by the operator, injects patient **P** with radiopharmaceutical agent. Patient **P** continues pedaling for approximately one minute. During that minute the radiopharmaceutical agent is taken up into the heart

muscle in proportion to perfusion or circulation that the muscle receives. After that minute, patient **P** is told to stop pedaling and rest. When the patient's heart rate returns to near normal, or at least to a slow enough rate, imager **130** is started. Images are acquired in synchrony with the ECG so that images may be retrospectively reconstructed to show the shape of the heart and its perfusion at different phases of the heartbeat. Perfusion defects may be seen on the images and optionally measured quantitatively. The consistency and accuracy in dosing, timing, and imaging provided by the concepts of this disclosure will increase the usefulness of quantitative assessments which is rarely done in current practice in the nuclear medical field. Wall motion and ejection fraction are commonly also assessed.

[0094] If patient **P** is unable to operate a bicycle-type or another physical exertion patient stimulus device **172**, for example, because of joint problems or age, pharmacological stressors may be used, such as dobutamine. In this case, fluid injector **152(2)**, as an example, in fluid handling system **150** is used to deliver dobutamine in gradually increasing quantities until a target heart rate is achieved. One important consideration is to arrange tubing connections to fluid injector **152(2)** so that a large dose of dobutamine is not injected into patient **P** when fluid injector **152(1)**, for example, delivers the imaging radiopharmaceutical agent. A simple way to accomplish this result is to have separate, small diameter tubes or multiple lumens in a single tube from the dobutamine injector **152(2)** and the radiopharmaceutical agent injector **152(1)** connected very near the location where the IV fluid line **153** enters into the patient's arm.

[0095] If the stress test is normal, that is, if the heart muscle seems to be well-perfused, then there is no need for a subsequent resting test. If a part of the heart muscle is abnormal, that is under-perfused, and then a resting test is typically conducted. A significantly higher dose of the same imaging radiopharmaceutical agent is prescribed, computed, and injected but without any exercise or stressor drug to increase heart rate. After about a minute, another image may be acquired. As a general assessment, areas that are normally perfused on both images are considered healthy. Areas that are under-perfused in the stress test but normal on the rest test are at risk for a heart attack. Areas that are under-perfused on both images represent tissue damaged by a previous heart attack.

[0096] In the foregoing technetium stress test example, imager **130** is commonly not able to take an image during the time that patient **P** is being positioned and during the exercise interval used to increase heart rate. Also, it is normal practice to not observe the technetium in the patient's heart until several minutes after injection, commonly 15-30 minutes. An alternative arrangement in this integrated system **100** in to place an imager head or detector in

association with imager **130** on a mechanical support, track, arm, or even a motorized positioning system or robotic arm to enable a single imager **130** to be shared with two patient support and stimulus apparatus **120**, **170** "stations". Thus, imager **130**, which may be the most expensive component of integrated system **100**, may be more efficiently utilized in integrated system **100**. Thus, integrated system **100** is not limited to just one of each of the subsystems, devices, or components discussed hereinabove. Exemplary benefits of the integrated system **100** illustrated in this example include the ability to automatically acquire information about patient **P** and the study, determine the dose to be provided based upon patient and study parameters, ensure accuracy and consistency of dose better than can be done manually, and automatically inject the dose when the heart rate or other patient parameters are appropriate.

[0097] A second exemplary use of integrated system **100a** (**FIG. 2B**) in a clinical procedure that would benefit from the "integrated" aspects of integrated system **100a** is a dynamic PET or PET/CT scan. Dynamic studies involve observing or measuring the different uptake, pharmaco-dynamics and pharmacokinetics, of an imaging radiopharmaceutical agent into different tissues. The concentration/time curves may be used to differentiate tissue and disease that cannot be sufficiently differentiated using a static image at a single specific point in time. Specific examples are provided hereinafter. A PET/CT scanner is closer to that of **FIG. 2B** where a patient lies on a horizontal patient support **120a** that moves them between a PET and a CT section of imager **130a**.

[0098] To conduct a dynamic PET/CT scan using integrated system **100a** as illustrated in **FIG. 2B**, patient **P** arrives at the imaging center and the necessary paperwork is completed. The procedure is explained and informed consent is received. Intravenous fluid line **153** is associated with the patient's arm. There is generally no need to monitor the patient's ECG, although, if the region of interest includes the heart, this can be done to enable retrospective gating for image reconstruction. Information or data about patient **P** is entered into integrated system controller **110a**, either by the operator and/or through communications connection or interface **190a**. From data such as the study to be done, the patient's weight, build (BMI – body mass index), and/or lean body mass, a recommendation on dosage to be given may be derived. If this is a repeat study for this patient **P**, information about previous doses may be accessed and the current dose is optionally made to be consistent with the previous study for quantitative comparison unless overridden by the attending operator or physician. After operator confirmation of the quantity recommended by the system, the imaging radiopharmaceutical agent, a dose of PET agent, typically FDG is optionally prepared and

delivered by fluid handling system **150a**. Once patient **P** is properly positioned on patient support **120a**, fluid injector **152a(1)**, as an example, is connected to IV fluid line **153**, the FDG is prepared, imager **130a** started, and the FDG is injected. For a typical dynamic study, the whole dose of a few milliliters is injected as quickly as possible, for example, in one or two seconds, and followed with a saline flush to ensure complete delivery to the patient. Imager **130a** then acquires images of the initial uptake. A common protocol involves images of one minute length for the first five minutes, then two minute lengths for the next ten minutes, and then five minute lengths for the next forty-five minutes.

[0099] A research group from Heidelberg (Strauss et al., "Shortened PET Data Acquisition Protocol for the Quantification of F18-FDG Kinetics", J Nuc Med (2003) 44:12, 1933-1939, incorporated herein by reference) has found that acquiring images during the first ten minutes and then acquiring an image from fifty-five to sixty minutes after injection provides information that is sufficient for a dynamic scan. If this Heidelberg protocol is followed, the PET imager can be much more efficiently used, with four patients being scanned in the hour that one could be done previously. A factor in enabling this Heidelberg protocol is having integrated system **100a** accurately inject a customized dose of imaging radiopharmaceutical agent, right at imager **130a** for the dynamic study. A second factor in enabling the Heidelberg protocol is registration of the final image with the initial set of images. This is preferably done using a PET/CT imager and using bony landmarks for the image registration. In further detail, a low resolution CT image is done for landmark identification and attenuation correction. The imaging radiopharmaceutical agent is injected and the initial dynamic series of PET images is acquired. Patient **P** is removed from patient support **120a** and goes into a quiet room to wait. At a point optionally about forty-five minutes after the injection, integrated system controller **110a** alerts the operator that the patient needs to be brought back in ten minutes. This can be done many ways, including through a pager or cell phone. Thereby, approximately fifty-five minutes after injection, patient **P** is brought back to patient support **120a** and positioned in approximately the same position. A low resolution CT is performed to select the PET imaging area and correct for attenuation. Then, the five minute PET image is acquired. The operator selects the region or regions of interest for which the dynamics are to be computed. The low resolution CT images from the two imaging sessions are used to synchronize or align in all three dimensions the regions of interest between the two sessions. Algorithms in integrated system controller **110a** fit curves to the pixel or voxel information and extract the uptake constants, as described in the above-referenced Heidelberg protocol and paper. It is also preferred that integrated system

controller **110a** alert the operator if there will be a conflict for imager resources, for example, if the operator is setting up to scan one patient, and that patient's scan overlaps with the time slot needed to complete the 55-60 minute final scan of a previous patient. Similarly, with integrated system controller **110a** having information about the patients to be scanned for the day, it can recommend sequencing of dynamic and non-dynamic scans to maximize the utilization of imager **130a**.

[00100] As described in the foregoing, current practice in nuclear medicine typically consists of static images taken well after a radiopharmaceutical tracer has circulated through the patient's blood and has been taken up by targeted tissue. PET images with FDG are normally taken at least an hour after injection. SPECT images of cardiac perfusion with technetium-99m sestamibi, or thallium-201, for example, are acquired over a 20-30 minute period after the patient has exercised or has received an infusion of cardiac stress drugs such as adenosine or dobutamine. One reason often cited for relying upon equilibrium images in nuclear medicine is the need to integrate the relatively low number of disintegration events over time in order to improve the signal to noise statistics.

[00101] Other imaging modalities such as CT and MR are making use of the information in images sampled more frequently in time. This "dynamic imaging" approach, described previously in connection with **FIG. 2B**, yields additional physiological information such as quantitative perfusion and blood flow, utilization of metabolites in tissue, and tumor vascularization. With the CT and MRI modalities, images with good statistics may be acquired quickly from large ensembles of molecules. However, as the sensitivity of detectors for nuclear medicine improves, it will be possible to extract more signal and, thus, create less noisy quantitative information from multiple, time-sampled PET and SPECT images. A few representative applications are described hereinafter. The process shown in **FIG. 40A** utilizes a combined imaging system at step **430** to capture an image of the patient. In one aspect, the combined imaging system may include a combined PET/MR imaging system. As shown in step **430** of **FIG. 40A**, as either part of the combined PET/MR system or in a separate work station, one or more computer programs may implement one or more algorithms that create images of the PET radiopharmaceutical spatial distribution, preferably compensating for motion of the patient (step **440** of **FIG. 40A**), as a videographical image so that the clinician can visually assess the lung function. As shown in the system of **FIG. 40B**, the motion may be compensated in the images using a motion compensation module **560**, which may be operatively connected to the control/coordination/analysis system **590**. A module **560** or system of this type is described in an article by Christian Würslin et al in the Journal of

Nuclear Medicine - J Nucl Med 2013; 54:464–471 DOI: 10.2967 /jnumed.112.105296, incorporated herein by reference. Motion compensation module **560** may operate by using one imaging modality, for example CT or MR, with high temporal and spatial resolution to acquire a series of images over the same time a second imaging modality, for example PET or SPECT acquires a series of images or time based data set. It then determined voxels, (volume elements) in one image of one of the image sequences and subsequently maps the movement and size change of these voxels over time on the series of images. This movement creates a map of points in 4D (3D + time) space that correspond to each voxel. The data from the second image sequence is mapped from the 4D space in which it was acquired into voxel space using the map measured above, which reduces or eliminates the blurring and signal amplitude reduction that motion could have otherwise caused. Alternatively, using one of the many 3D visualization techniques and pharmacokinetic (PK) and/or pharmacodynamics (PD) analysis or techniques system **570** (step **450** of **FIG. 40A**), quantitative and optionally dynamic imaging may be produced with the combined PET/MR system (step **460** of **FIG. 40A**) via a quantitative and optionally dynamic imaging system **580**. It is preferable that the data use for this analysis be motion corrected. The motion compensation module **560** may be in communication with the PK/PD analysis system **570** to coordinate the correction of the captures images. In a further aspect, the computer software can model the dynamic processes, preferably accounting for one or more of perfusion, tissue absorption and diffusion, membrane transportation, airway geometry, and gas transport within the airways. In this aspect, the communication of information to the clinician can include image data or numerical data for regional or overall lung function.

[00102] In dynamic imaging, PET images of FDG are used to distinguish inflammation from malignant processes in tissue. (Zhuang, et al., "Dual Time Point F18-FDG PET Imaging for Differentiating Malignant from Inflammatory Processes", J Nuc Med (2001) 42:9, 1412-1417, incorporated herein by reference). In general, dynamic images with radioisotopes may be combined with dynamic (kinetic) compartmental models to estimate underlying physiological parameters that differentiate between clinical states. (Coxson, et al., "Consequences of Using a Simplified Kinetic Model for Dynamic Pet Data", J Nuc Med (1997) 30:4, 660-667; and Sugawara, et al., "Germ Cell Tumor: Differentiation of Viable Tumor, Mature Teratoma, and Necrotic Tissue with FDG PET and Kinetic Modeling", Radiology, April 1999, 249-256, both incorporated herein by reference). Tumor metabolism may also be characterized from PET FDG images, and blood flow may be mapped with O-15 water images taken several minutes apart. (Zasadny, et al., "FDG Metabolism and Uptake

Versus Blood Flow in Women with Untreated Primary Breast Cancers", Eur J Nuc Med (2003) 30:2, 274-280, incorporated herein by reference). Recent developments in dynamic SPECT ("d-SPECT") using Teboroxime Tc-99m have shown value in identifying and quantifying cardiac flow defects while eliminating the problem of overlapping liver and heart distributions due to differences in uptake rates for those tissues. (Celler, et al., "Investigation of the Dynamic SPECT (dSPECT) Method for Teboroxime Using a 4-D Kinetic Thorax Model dMCAT", Sixth International Meeting on Fully Three-Dimensional Image Reconstruction in Radiology and Nuclear Medicine, 2001, incorporated herein by reference).

[00103] There is also a class of tracer studies that will benefit from dynamic imaging. These are "receptor blocking studies". In these studies, several fluids are injected into a patient's vasculature, typically a radioactive and non-radioactive version of the same chemical agent. These agents compete for specific receptor targets in tissue or on the surfaces of cells, thereby affecting the uptake of the radioactive components that can be imaged by SPECT or PET. The integrated system **100**, **100a** described in this disclosure will allow for time-sequenced administration of radioactive and non-radioactive agents in order to saturate the receptors without exceeding radiation dose limits or mass limits prescribed for an individual patient. In general, this dynamic administration of drugs or agents will require an additional fluid (such as normal saline) to flush the infusion lines of any residual materials. In other instances, it will be necessary to use an additional fluid to dilute the active drugs or agents to be isotonic with respect to blood, plasma, or extra-cellular fluid. A specific example of such dynamic receptor studies is described by Morris, et al. ("Comparison of Two Compartmental Models for Describing Receptor Ligand Kinetics and Receptor Availability in Multiple Injection PET Studies", Journal of Cerebral Blood Flow and Metabolism, (1996) 16:5, 841-853, incorporated herein by reference). A radio-tracer with high specific activity ("hot") is injected over thirty minutes, for example by fluid injector **152(1)** in integrates system **100** followed by an infusion of the non-radioactive ("cold") version of the tracer, for example, by fluid injector **152(2)**. A third fluid injector **152(3)** could deliver saline to quickly flush each dose into the patient and also slowly administer saline to prevent the venous catheter from clotting or occluding. The radioactive molecule is displaced from receptor sites by the non-radioactive molecule. This process is repeated and imaged over a period of two to three hours with different concentrations of the hot and cold agents. The images allow rate parameters to be calculated and utilized in a compartmental model to quantify the health of target tissue. Because dynamic nuclear imaging is critically dependent on knowledge of time, there is a need for an individual patient "timer" to alert an operator or a computer

system to perform certain actions or to collect data. The timer can range in sophistication from a simple clock, which is started when the patient is injected with one of several medical fluids, and which is set to trigger an alarm or an action automatically or manually at a specified time. A more sophisticated timing device could store information such as: time of injection, radiation level at time of injection, calculated current radiation, patient name, reason for the scan, etc. The timing device could have a communication channel with an injector, physiological monitor, imaging system, or external information management system, either directly to said device or to integrated system controller **110** and thence to the other devices. In addition, the timer device could also be used to store patient-specific physiological information about metabolism and other functions to more accurately determine the optimal injection of drugs, sampling of blood, or triggering of imaging systems. The timer device may be associated with the patient, even to the point of being carried by the patient, clipped to clothing, or strapped to their body. Alternatively, the timer device may exist as an integrated function in integrated system controller **110** or one of the subsystems or devices, for example, imager **130**, and the patient can be distinguished by a hospital wrist bracelet with text, bar, RF encoding, or a similar device.

[00104] Current practice uses alternate doses of hot (radioactive) and cold (non-radioactive or already decayed) agents or pharmaceuticals separated in time to observe the "competition" for receptor sites as mentioned above. However, because of the limitations of the chemical process and the radioactive decay, there is always some cold receptor material in the hot dose, and the ratio of hot to cold receptor material is changing over time. To provide more consistent input functions and thus enable better assessment of the patient's physiological response and condition, it is desirable to inject consistent doses or ratios of both hot and cold agents. This titration can be accomplished by systems and devices of this invention wherein the hot agent is delivered through a first fluid injector or pump **152(1)** and a cold agent is delivered through a second fluid injector or pump **152(2)**. It is anticipated that a third fluid injector or pump **152(3)** be filled with saline to quickly flush fluids from the IV fluid line **153** connected to patient **P** and for a slow infusion to keep the vascular access open during the procedure. To accomplish this, it is necessary to first measure or know (based upon the properties and reproducibility of the chemical synthesis performed) the starting ratio of hot to cold agent and the activity of the hot agent in the "hot" fluid injector or dose pump **152(1)**. Subsequently, by knowing the half-life of the isotope being used, the ratio of hot to cold agent can be calculated at the time of any injection. This ratio is used to then calculate the amount of cold agent that should be injected with the hot agent to maintain a constant ratio of

hot to cold agent in the dose. Injecting the hot agent "with" the cold agent can be accomplished in many ways, for example, simultaneously injecting the two agents for the same duration, injecting one right after the other at a constant flow rate, alternating partial injections of one and then the other, or any of an almost infinite number of injection protocols that achieves, in a physiologically appropriate timeframe, the condition of presenting the desired concentration of hot agent to the recipient with the desired ratio of hot to cold agent over time of the study.

[00105] An example is illustrated via Table 1 (below), using a hot agent with an arbitrary half-life of 40 minutes, an initial starting concentration of 90% hot agent, and a hot agent

	Time		Hot Agent		Cold Agent	Hot Agent Volume	Cold Agent in Hot Volume	Cold Agent Volume	Total volume
	minutes		mCi/ml	"mCi/ml"	"mCi/ml"	ml	mCi	ml	ml
1	0		9.000	1.000	10				
2	20	hot	6.364	3.636	10	0.157	0.571	0.843	1.000
3	40	cold	4.500	5.500	10			1.000	1.000
4	60	hot	3.182	6.818	10	0.314	2.143	0.686	1.000
5	80	cold	2.250	7.750	10			1.000	1.000
6	100		1.591	8.409	10	0.629	5.285	0.371	1.000
7	120		1.125	8.875	10	0.889	7.889	0.111	1.000
8	140		0.795	9.205	11	1.257	11.571	-0.234	1.023
	A		B	C	D	E	F	G	H

activity of 9mCi/ml. For example, this hot agent is to be delivered by a first fluid injector or pump **152(1)**. A second fluid injector or pump **152(2)** contains only cold agent at the same total molecular concentration, for example, 10mCi/ml. Although the second agent is not hot and thus has no radioactive decay, as is known to those in the health physics field, 1 Curie is $3.7x10^{10}$ disintegrations per second and given the half-life, the concentration is thereby specified and can be calculated. To simplify this example, all concentrations in the Table 1 are expressed in mCi/ml as if all those molecules were hot.

[00106] At time 0 (column A, row 1 of Table 1), the drug is prepared with a hot activity of 9mCi/ml (column B) and a concentration of the hot agent at 90%. Thus, the "hot" agent fluid injector or pump **152(1)** contains 1mCi/ml of cold agent at time 0 (column C). The second fluid injector or pump **152(2)** contains cold agent at a concentration of 10mCi/ml (column D). This concentration does not change.

[00107] In this example, by the time the recipient (patient **P**) is prepared, 20 minute has elapsed (row 2). By this time, the concentration of the hot agent in fluid injector or pump **152(1)** is 6.364mCi/ml (column B). The physician or researcher will set the system to deliver their desired dose of hot agent and the desired ratio of hot to cold agent to the recipient, for

this example 1mCi at a constant hot to cold ratio of 1:9, or what is the equivalent, at a total (hot + cold) of 10mCi. After entering this information into the system, the system continually or periodically computes the volume from the "hot" agent fluid injector or pump **152(1)** and the "cold" agent fluid injector or pump **152(2)** to be delivered to the recipient. In this example, at the 20 minute point, 0.157ml (column E) is delivered from the "hot" agent fluid injector or pump **152(1)** and 0.843ml (column G) is delivered from the "cold" agent fluid injector or pump **152(2)**. In the "hot" agent fluid injector or pump **152(1)** is 0.571mCi of cold agent (column F).

[00108] In this example, the recipient is then imaged for approximately 20 minutes to allow sufficient time for the kinetics of the physiology to be determined. At 40 minutes (row 3), a dose of all cold agent is delivered. The operator has selected the same total dose of 10mCi for this injection, so 1ml of fluid is delivered from the "cold" agent fluid injector or pump **152(2)** and nothing is delivered from the "hot" agent fluid injector pump **152(1)**. Again, the recipient is imaged for 20 minutes to collect the data on the dynamics of the physiological displacement of the hot agent by the cold agent. After that time, now at 60 minutes from the creation of the compound, a hot dose is to be administered. While the physician, technician, researcher or other user may select any of the physically achievable desired doses of hot agent and ratio of hot to cold agent, this example assumes that the same dose of 1mCi hot agent and 1:9 ratio will be used. This can be used, for example, when some outside stimulus is stimulating the recipient. This stimulus can be anything but may be, for example, another molecule, agent, or drug that also competed with the hot and cold agent, or which selectively binds with or incapacitates the hot or cold agent. In this example, at time 60 minutes (row 4) the hot agent concentration has been reduced to 3.182mCi/ml (column B). To achieve the user's programmed dosing, the system injects 0.314ml (column E) from the "hot" agent fluid injector or pump **152(1)** and 0.686ml (column G) from the "cold" agent fluid injector or pump **152(2)**. The dose from the "hot" agent fluid injector or pump **152(1)** contains 2.142mCi of cold agent (column F). At 80 seconds, a cold dose of 1ml is injected.

[00109] At 100 minutes and even at 120 minutes, it is possible to achieve an injection of 1mCi of hot agent and 9mCi of cold agent. The system can compute an injection that achieves the operator's desires. However, by 140 minutes (row 8), it is not possible to inject 1mCi of hot agent with a 1:9 hot to cold ratio. The rote computation shows a negative number –0.234ml of cold agent to be injected. Of course this is physically impossible, pulling a volume out of the recipient (i.e., patient **P**) is not desirable and will not remove only cold agent, so the system needs to take or recommend alternative actions. One alternative is

to inform the operator while the initial setup is being made of the time when it will no longer be possible to meet their goals of hot and cold agent doses. Then, the operator may take appropriate actions, for example, changing (i.e., shorten) the test protocol segments so that the desired ratio can be achieved over the time of the test. A second alternative is to request that the operator select a different ratio, and optionally to suggest such a ratio. A third option, depending upon the specific molecules being used as the hot and cold agents, is to use a fourth fluid injector or pump **152(4)** with a pharmaceutical which selectively binds to the cold agent and eliminates it from interacting in the physiological process under study. If the hot and cold agents are molecularly identical, as can occur with 99mTc studies, this will be impossible to achieve. However, in the case of many other isotopes, such as positron emitters, for example, FDG, the hot agent FDG is chemically slightly different than glucose to which it returns. Thus, it is possible to select and inject an entity that binds with the glucose and not with the FDG. This property is part of the reason FDG is so useful in medical imaging. FDG is taken into the cells in a manner similar to glucose for metabolism but, as it goes through the enzymatic pathway, it cannot be metabolized by one of the cells' enzymes. A molecule with properties similar to this enzyme could be used to selectively bind to glucose and not to the FDG.

[00110] In this example, because the hot and cold agents have the same starting total concentrations, the total volume is identical for all injections. This is not a limitation of the system but has been chosen only for simplicity of this example. If the total concentrations were different, the total volume delivered would change as well.

[00111] The foregoing integrated systems **100**, **100a** may be adapted for patient-based dose planning for diagnosis and therapy. Diagnostic imaging with radiopharmaceuticals is currently performed by intravenous administration of a single bolus of drug with a hand syringe. Therapeutic radiopharmaceuticals, such as Bexxar® or Zevalin®, are typically infused at a relatively slow and constant rate over a few minutes. The prescribed radiation dose usually accounts for patient weight but little consideration is typically given to the characteristics of tissue to be imaged or treated. The disclosed integrated systems **100**, **100a** provide for optimization of radio-isotope injection for diagnostic and therapeutic purposes, customized for individual patients. This disclosure has previously described computer software that implements a kinetic compartmental model. Rate constants and transfer coefficients between compartments are derived from images and physiological measurements. A key to the success of such dynamic models is accurate knowledge of the concentration of radioactivity in tissue and in the blood. This knowledge is even more

important for radioisotopes with short half-lives, such as Cu-64, Tc-94, C-11, and Rubidium-82, because they decay on a time scale comparable to physiological processes. For rapidly decaying isotopes, a kinetic model can be obtained by monitoring three parameters: (1) total dose of radiation injected; (2) instantaneous radiation dose rate; and (3) relative proportion of "hot" and "cold" reagent, often used in receptor blocking studies. The integrated systems **100**, **100a** described previously are capable of measuring and controlling all of these parameters. These parameters are analogous to parameters of importance in CT or MR contrast enhanced imaging with injected X-Ray contrast agents, namely, total volume injected, flow rate, and contrast dilution. The disclosed integrated systems **100**, **100a** measure radioactive dose in the blood by automatically or manually withdrawing samples of blood at specific time intervals, as described hereinafter. In addition, it is necessary to know the dose "input function", which is the instantaneous radioactivity rate of the injected radioisotope. Instantaneous radioactive decay rate may be determined most accurately at the patient injection site. A dosimeter or radiation detector located as close as possible to the injection site provides the necessary data, as further described herein. Additionally, such a radiation detector in close proximity to the injection sit could monitor for extravasations or infiltrations, where the injected radiopharmaceutical leaks out of the vein and pools or collects in nearby tissue.

[00112] Sequential images (PET or SPECT) provide additional data to estimate the clearance of radioactive drugs from blood and tissue by the kidneys and liver. Images can be used to calculate the rate of uptake and clearance of radioactive drug from chemical receptors in target tissue such as a tumor. Software also accounts for the rate of radioactive decay. Knowledge of the dose input function, blood radioactivity, and other parameters extracted from images and physiological sensors allow a computer system, for example, integrated system controllers **110**, **110a**, to calculate a customized, optimum injection profile for each patient. This profile may differ significantly from the simple bolus or constant infusion of radioisotopes currently in practice and for simplicity of understanding in the example above. Additional information about blood flow and perfusion of diseased tissue, obtained from CT or MR images can also improve the performance of the computer model. Ultimately, the systems and methods described herein can be applied to the optimization of both diagnostic nuclear imaging and therapeutic drug delivery to targeted tissue.

[00113] As described previously in connection with **FIG. 1**, preparing a radiopharmaceutical agent for administration to a patient involves several steps including creating or obtaining a radionuclide, processing the radionuclide to create an injectable

radiopharmaceutical, and packaging a dose, or multiple doses, for later administration to the patient. In the current process for preparing a radiopharmaceutical agent for patient administration, during and between the foregoing steps there is frequent transportation of materials and supplies due to several factors such as immobile equipment, hazardous chemicals and/or processes, economies of scale which make it advantageous to conduct a given process in a certain location, or other constraints on the processes such as short half-lives of certain radionuclides. Moreover, during the conventional process for preparing a radiopharmaceutical agent for patient administration, quality-control tests must be performed at certain instances to ensure the radiopharmaceutical agent is appropriate to be administered to a patient. Among these tests are visual inspections, chromatography, and radioactivity measurements.

[00114] After the radiopharmaceutical agent (hereinafter "radiopharmaceutical") has been created, it may be used directly or stored for eventual administration to the patient. Fluid radiopharmaceuticals may be stored in individual-dose syringes, individual-dose vials, or multi-dose vials as noted previously. One challenge to creating such individual dose packages is that the radioactive decay inherent to these radiopharmaceuticals will cause a given volume of radiopharmaceutical product to reduce in activity over time. For those radiopharmaceuticals with a short half-life, the change in activity over a few hours can mean the difference between having an imaging procedure with good or poor diagnostic quality. The same half-life sensitivity can be true for multi-dose vials of radiopharmaceutical unless either the administration times and doses are known in advance, or else enough radiopharmaceutical is added to the vial to ensure a minimum activity level for the variety of possible patient radiopharmaceutical administration times from that vial.

[00115] In the situation in which the radiopharmaceutical is prepared in a multi-dose format, the multi-dose volume of radiopharmaceutical must be divided into single doses which get administered to individual patients. This dividing of doses may occur at the point of administration if an administration device is able to control the amount of activity administered to the patient. More typically, however, the contents of the multi-dose vials are divided into single doses by a nuclear medicine pharmacist or technologist in a hot lab, as noted previously. The individual radiopharmaceutical dose is then transported to the patient location at which time the entire contents of the single-dose container are administered to the patient.

[00116] In view of the foregoing, it would be advantageous to perform one of more of the steps of **FIG. 1**, such as creating an isotope (step **10**), creating and injectable drug (step **20**),

and dose preparation (step **30**) in a single system. Such a radionuclide creation and "chemistry" processing system **200** is shown in **FIGS. 3-4**, described hereinafter. Such a creation and processing system **200** is generally adapted to perform the functions of one or both of obtaining or creating a radionuclide and chemical processing thereof to achieve individual radiopharmaceutical doses or multi-doses. Radioactivity monitoring and quality control functions may also be embedded in the integrated creation and processing system **200**, for example, in a dosing unit or component thereof. Waste disposal, radiation protection, and patient administration/injection functions are also desirably performed by the "integrated" or universal system **200**. **FIGS. 4A-4B** show views of possible implementations of a stand alone (i.e., non-mobile) or a mobile or portable system **200**, respectively, in accordance with the concepts described herein. The following discussion relates to a mobile embodiment of system **200** which, if desired, may be used as part of integrated systems **100**, **100a** described previously or simply as a creation and processing system **200** to create a radionuclide and process the same into a form suitable for injection into a patient(s). Accordingly, system **200** described herein may be used simply to fill individual containers (i.e., vials, bottles, syringes, etc.) with radiopharmaceutical doses which may be used for individual patients and may comprise, if desired, the capability to deliver such doses to patients. Accordingly, system **200** is not intended to be limited to use in integrated systems **100**, **100a** described hereinabove but has wider applications to the nuclear medicine field generally.

[00117] A desirable embodiment of a portable or mobile system **200**, as shown in **FIG. 3**, is as a portable or mobile system comprised of several subsystems, modules, or components that are selectable to provide a variety of configurations and designs to meet the requirements of a patient treatment facility. For example, an imaging suite in a hospital that receives individual doses of radiopharmaceuticals from a radiopharmacy may choose to integrate only HIS integration, patient administration, waste disposal, and radiation protection modules, whereas an imaging suite which produces its own radionuclides may choose to integrate all the modules into their system. It is recognized that each subsystem to be discussed hereinafter may contain its own embedded sensors, controllers, communication subsystem, and power generation/storage devices. It is well known in the medical field to move functionality among shared resources, such as a system-wide power subsystem, or to leave that functionality as embedded within the subsystem, such as batteries for mobile subsystems. The ability to either embed or to move to a shared platform applies to microprocessor-based

functionality, graphic user interfaces (GUI's), communications, power, and thermal management such as fans.

[00118] In the depicted embodiment, a plurality of subsystems or modules are provided in system **200** and include by way of non-limiting example: a control computer **210**; a radionuclide generation module **220**; a radiopharmaceutical "chemistry unit" or processing module **230**; a quality control module **240**; dose extraction module **250**; a patient administration/injection module or delivery area **260**; a waste disposal module **270**; and radiation protection and support component or module **280**. Each of the foregoing subsystems, modules, or components will now be described. By way of general reference, the abbreviations used in **FIG. 3** are as follows: **SW** – Shielded Window; **SF** – sterile filter; **DD** – Drip Diaper; **QC** – quality control; **TG** - Technetium Generator; and **P** – represented Patient.

[00119] Control computer **210** is shown in this depicted embodiment as a single computer, although alternative embodiments could use control computer **210** to coordinate among various embedded controllers for each controlled module as will be appreciated by those skilled in the computer field. Control computer **210** optionally includes a GUI **212** (**FIGS. 4A-4B**) for displaying relevant data and entering relevant control data and parameters into control computer **210**. As one example, the GUI **212** includes a patient organizer that displays, for example, a list of upcoming injections displayed in chronological order. This GUI **212** optionally includes a softkey labeled with "prepare this dose" next to each patient's procedure information. For example, in a cardiac stress test situation, the GUI **212** would list two procedures for each patient, the stress procedure and the rest procedure, and "prepare this dose" would be selectable for each individual procedure. When the user selects "prepare this dose" for a given procedure, control computer **210** coordinates the actions of the other subsystems or modules to create, for example, an individually labeled syringe or other container with the required dose for that procedure. The GUI **212** also optionally displays a graphic schedule of all active patients in the imaging suite. This facilitates the suite's workflow by displaying, in one place, the procedural steps which are active, their expected duration, and the current status of each patient. An optional attachment is for a wireless handheld device, such as a personal data assistant ("PDA"), to be integrated with control computer **210** to display similar GUI information while at the same time allowing the attending operator the freedom to view that information throughout the imaging suite, rather than just at the GUI **212** of control computer **210**.

[00120] Control computer **210** is also optionally configurable to communicate with an imaging suite's information system, for example, an HIS system. Using this capability enables automatic population of patient information, expected patient injection times, and radiopharmaceutical production schedules for the suite into, for example, the GUI **212**. This communication is also able to be used to update the information in the HIS system with actual injection times, volumes, and activity levels, along with any observations during the procedure. The benefit of using this feature is that the attending technologist does not have to switch between the GUI **212** associated with control computer **210** and the HIS system GUI, but rather can populate the HIS system while still at the patient side immediately upon injection. This creates workflow efficiencies as well as eliminates steps which could otherwise lead to data entry errors.

[00121] Radionuclide generation module **220**, in this embodiment, is identified as a technetium generator (TG) such as a Mallinckrodt Ultra-TechneKow® DTE Technetium Tc99m Generator. Radionuclide generation module **220** may be selected to meet the intended needs of those employing system **200**. Radionuclide generation module **220** produces a sterile, non-pyrogenic isotonic solution of a suitable radioisotope, in the present example Sodium Pertechnetate Tc99m, by periodically drawing saline through a lead shielded column containing molybdenum Mo99. Radionuclide generation module **220** is desirably contained within a shielded compartment of radiation protection module **280** (described herein) in order to prevent excess radiation from leaving system **200**. It will be appreciated that other methods are available to produce radioisotopes including nuclear fission (reactor breeding), neutron activation processes, charged particle induced reactions (accelerators/cyclotrons), as well as the foregoing example of a radionuclide generator. In one aspect, the radionuclide generation module **220** may be a laser wakefield generator such as a portable laser wakefield generator. Radionuclide generation module **220** may also be provided within an individualized shielded compartment provide as part of radiation protection and support component or module **280**.

[00122] In one embodiment, radionuclide generation module **220** may produce bulk doses of a radionuclide suitable for the creation of multiple individual doses of radiopharmaceuticals. In another embodiment, the radionuclide generator is "milked on demand," producing only the amount of radionuclide needed for a single dose of a radiopharmaceutical. System **200** is configurable to either type of operation via control computer **210**. In either case, a "self-flush" mode may be incorporated that could be triggered by control computer **210** during extended periods of non-use, such as at night. This

self-flush clears excess inactive radionuclide material that has converted to the radionuclide of interest, for example, technetium, but has already decayed to its non-radioactive and non-usable state. When self-flush is used, the radionuclide generation module **220** is milked to extract the radionuclide during the period of non-use at a time sufficiently before normal operation, for example, six hours before preparation of the first dose and the fluid containing the radionuclide material is diverted directly to a waste container **272** of waste disposal module **270**. Another alternative example includes two (or more) different radionuclide generation modules **220** in the same system **200**. This allows system **200** to be used to create different radiopharmaceuticals for different imaging procedures, as well as to mix different radionuclides which are incorporated in different or identical pharmaceuticals into a compound radiopharmaceutical to support dynamic imaging studies.

[00123] For radionuclides which cannot be produced on a system, such as cyclotron-produced radionuclides, radionuclide generation module **220** is designed to be replaced with a container, such a vial, bottle, or syringe, containing the radionuclide produced at an outside facility. This radionuclide container may be for a single dose of radionuclide or for a bulk dose suitable for multiple patient injections. Optionally, the container holding the bulk quantity is tipped at an angle so that the tip of a needle, for example, (through which individual doses are extracted) reaches the lowest point in the container to ensure all fluid is available to be delivered into individual doses. Moreover, multiple containers of radionuclides (beyond a singular container) may also be utilized in place of radionuclide generation module **220**. This modular design enables system **200** to be used for a variety of molecular imaging suites and procedures rather than a single site and a single imaging procedure. System **200** is designed for both fluid and data exchanges between radionuclide generation module **220** and radiopharmaceutical "chemistry unit" or module **230**. Control computer **210**, or individual embedded computers as described previously, is used for coordinating both the data and fluid flows.

[00124] Radiopharmaceutical processing "chemistry" module **230** receives radionuclide(s) and creates radiopharmaceuticals through a variety of standard radio-pharmacy procedures. The radiopharmaceutical processing module **230** is contained within radiation protection module **280** (described herein), for example, within an individualized compartment within module **280** to prevent excessive radiation from leaving system **200**. Radiopharmaceutical processing module **230** includes, for example, an agitation subsystem, multiple fluid delivery or handling subsystems to move reagents into an output container (i.e., vial, bottle, or syringe), a heating subsystem, and a control subsystem to coordinate a variety of pumps,

valves, agitation devices, and heating units. In one embodiment, quality control system/module **240** (described herein) is integrated as a component of radiopharmaceutical processing system or module **230**. In another embodiment, the control subsystem of radiopharmaceutical processing module **230** includes software on control computer **210** rather than on a separate embedded controller of this module. In another embodiment, radiopharmaceutical processing module **230** includes a spectrometer to compare the spectrum of the produced radionuclide in module **220** against known spectra of radionuclides and ensure the fluid is the correct radionuclide before creating the radiopharmaceutical.

[00125] Radiopharmaceutical processing module **230** is in fluid communication with radionuclide generation module **220** or the containers of radionuclides in the case in which the radionuclide generation module **220** is replaced with delivered container(s) of radionuclide(s), patient administration module **260**, and waste disposal module **270**. An optional embodiment includes one or more in-line dosimeter or radiation detectors **232a** and an optical clarity detector **232b** in the fluid output path of the radiopharmaceutical processing module **230** for radioactivity level quality control. Optionally, radiation monitors may be associated with syringes (not shown in **FIGS. 3-4**) used in radiopharmaceutical processing module **230**. In-line dosimeters and radiation monitors may be used throughout system **200** to measure dosages in syringes and like fluid carrying and/or containing components to measure radiation levels throughout system **200** and this information may be communicated to control computer **210** and used as a basis to control operation of the various subsystems or modules. Another variation is to deliver radiopharmaceutical fluid through a solid-state dosimetry subsystem into individual-dose syringes or transport pigs which may be labeled for the individual patient and procedure as is described elsewhere hereinabove. These individual dose syringes (or like containers such as vials or bottles) could be mounted in patient administration module **260** to be filled with radiopharmaceutical and then transported for use in another area using a suitable radiation-shielded transport device or system, examples of which are provided herein in connection with **FIGS. 14-20**. Optionally, the fluid output from radiopharmaceutical processing module **230** is delivered, in real time, to patient administration/injection subsystem or module **260** (described herein) for direct fluid injection into patient **P**.

[00126] In one embodiment, radiopharmaceutical processing module **230** is coordinated via control computer **210** wherein the attending operator chooses to prepare an individual dose. Control computer **210** then coordinates the activities of radiopharmaceutical processing module **230**, including such steps as verifying the extracted radionuclide material from

radionuclide generation module **220**, extracting a specific volume of radionuclide fluid, extracting a specific amount of one or more reagents, heating and/or agitating a container at various points throughout the procedure, and delivering a completed radiopharmaceutical fluid into a container for eventual patient injection. Another option is to use the GUI **212** associated with control computer **210** to facilitate the production of radiopharmaceutical agents by displaying text or graphics indicative of a molecular imaging procedure, for example, cardiac rest procedure, brain perfusion procedure, PET/MR procedure, SPECT/MR procedure, or FDG PET procedure. The user may then select the upcoming procedure rather than the individual radiopharmaceutical to be used. The radiopharmaceutical that is produced upon selection of an upcoming procedure is a configurable feature of system **200**.

[00127] The radiopharmaceutical processing module **230** may be contained within a compartment or structure of shielded radiation protection module **280** which could include an airflow management system. This may have two aspects or functions. The first filters the incoming air through a HEPA filter to effectively create a clean hood environment so that it can operate in compliance with the United States Pharmacopiea Chapter 797 requirements for compounding sterile pharmaceuticals. The second aspect ensures that effluent air is filtered via a HEPA filter, ULPA filter, and/or charcoal filters, or similar filtering apparatus before it leaves the compartment to reduce the chance for an aerosol to be released into the room. This filter could contain a built-in dosimeter which sends a signal to control computer **210** which alerts the operator if there is an unexpected release to the air, or to change the filter when the activity level is above a settable threshold value. In another variation for limited volumes, all effluent air is directed to an expandable fluid container, such as an expandable bag, which can be easily removed and disposed of once the radioactivity inside the bag decays to an acceptable level. In another variation, radiopharmaceutical processing module **230** is connected to a facility venting system for venting to the outside.

[00128] An agitation subsystem of radiopharmaceutical processing module **230** could be a vibration table or, in another embodiment, fluid agitation may be accomplished via ultrasonic means. Another example of fluid agitation that may be used in radiopharmaceutical processing module **230** is piezoelectric actuators. Another possible agitation inducing apparatus for the agitation subsystem or module includes a single-axis mechanism, such as a motor, gear motor, or four-bar mechanism, to automatically shake the fluid container in a back and forth relatively circular motion. Another embodiment uses a single-axis mechanism, such as a linear slide, ball screw, or four-bar mechanism, to shake the fluid container in an up and down relatively linear motion.

[00129] As noted in the foregoing, radiopharmaceutical processing module **230** optionally includes a built-in dosimetry subsystem. This dosimeter is optionally used to measure the radioactivity level of the radionuclides produced by radionuclide generation module **220** and is also optionally used to measure the radioactivity level of the delivered radiopharmaceuticals. Another feature of radiopharmaceutical processing module **230** enables the user to add fluids, such as patient red blood cells, into the radiopharmaceutical process. An exemplary device for this purpose is to integrate the use of features similar to those available on the Mallinckrodt UltraTag® RBC in radiopharmaceutical processing module **230**. An optional embodiment radiopharmaceutical processing module **230** includes directing the radiopharmaceutical output of the radiopharmaceutical processing module **230** directly into transport pigs or into modular shipping containers which mechanically interface with system **200**, for example, by clipping into a receptacle in the shielded radiation protection module **280** or, alternatively, placing the transport pigs or modular shipping containers in place of patient injection module **260**.

[00130] Quality control subsystem or module **240** is used to ensure the correct radiopharmaceutical fluid is delivered in the correct quantity (fluid volume and radioactivity level) to the correct patient. One check performed by this subsystem is an optical clarity check which ensures that undesired particulates are not mixed within the fluid. One possible embodiment uses a computer-controlled vision system **242** to accomplish this optical clarity check. This vision system may include a camera, light, and computer software to inspect the fluid for particulates. Complete vision subsystems to accomplish this functionality are available on the market, for example, from Cognex, Inc. Another embodiment includes a camera and light but instead of automatically assessing the clarity via software, images from the camera are displayed on a GUI (the control computer GUI **212** or a separate display), with a button for the operator to push to accept the fluid and a separate button to push to reject the fluid for lack of clarity. Another embodiment replaces the optical clarity check with a light scattering check or a spectroscopic clarity check using a sensor **232b**. Another embodiment is for the radiopharmaceutical fluid to be viewable through a leaded glass, shielded window **SW** with appropriate lighting so the operator can choose to accept or reject the fluid after viewing the fluid through the leaded glass window. Optionally, the leaded glass window can include a magnification lens to facilitate viewing of the fluid. In another embodiment, the radiopharmaceutical processing module **230** places the radiopharmaceutical into a leaded glass vial associated with the quality control module **240**, which the operator

views for clarity. A still further embodiment includes a magnifying lens built into the leaded glass vial to facilitate the manual optical clarity check.

[00131] A further aspect of quality control module **240** includes an optional particulate filter in the fluid path between radiopharmaceutical processing module **230** and an output fluid container, such as sterile filter **SF**. This particulate filter prevents any particulates that may have been generated during the radionuclide generation process or during the radiopharmaceutical chemistry process from entering the vial or syringe or other container from which the fluid will be injected into a patient. A further aspect of the quality control system or module **240** is to prevent bacterial contamination of any part of the system that is in physical contact with fluid that will enter a patient. There are places and times where connections must be made in system **200** and it is desirable that sterility be preserved at these locations. For example, the technetium generator **220** can be used for many days, but the fluid path elements will probably be exchanged every 24 hours. In this case, it is desirable to sterilize the connection to technetium generator **220** before making a connection thereto. This is commonly done by manually swabbing a rubber septum with alcohol before piercing it with a sterile needle. One embodiment of preventing this contamination is to optionally include an ultraviolet light sterilization subsystem to sterilize connections or optionally selected aspects of system **200**. This subsystem flashes UV light for a sufficient time to ensure sterility, for example, ten seconds, before the radiopharmaceutical fluid container is used to inject fluid into the patient. A different embodiment accomplishes the same sterilization using an ozone-generation subsystem. A further aspect of quality control module **240** includes application of antimicrobial surface treatments into the design of the various compartments and surfaces of the system. A further aspect of quality control module **240** includes the optional integration of an alcohol swab into a vial cap, or syringe plunger if syringes are used, at the time the radiopharmaceutical processing module **230** creates the dose. The operator then has easy access to a swab to be used immediately before connecting the vial or syringe with patient administration or injection module **260**. Another subsystem of quality control module **240** is to optionally include a crystal photomultiplier, gas chromatography, or other subsystem to determine the specific radionuclide(s) in system **200**. The energy spectrum of the fluid in system **200** is then compared with known spectra of a variety of radionuclides to ensure the correct isotope(s) is in system **200**. Quality control module **240** communicates its status and any alarms to the operator preferably through control computer **210**.

[00132] In some situations, only a single dose of a radiopharmaceutical will be needed in a whole day's worth of procedures. In other cases, one more dose may be needed for an unanticipated study. In this case, it would be desirable if the pharmaceutical to be combined with the radioisotope came sealed in a pre-prepared syringe **262**, such as may be present in patient administration module **260** as described herein. The pre-prepared syringe **262** could be placed into a syringe pump **264** in the patient administration module **260.** The radioisotope could be delivered unmodified to the syringe **262** from technetium generator **220**. The activity or dose could be measured using in-line dosimeters **232a**, **232b**. Since only a single dose is being prepared for a single patient relatively soon before use, it does not have to take place in the desirably more heavily shielded and sterility optimized components comprising the radiopharmaceutical processing module **230**, unless a specific capability is needed which can only be accomplished in this module **230**, or the patient administration module **260** is occupied for one patient and the radiopharmaceutical to be produced with the single dose syringe or vial is for a subsequent patient.

[00133] The radiopharmaceutical which is produced in radiopharmaceutical processing module **230** and verified as acceptable in quality control module **240** may be contained in a vial or syringe, possibly contained within a transport pig, as an individual dose for an individual patient or as a bulk quantity of a radiopharmaceutical which can be used for multiple patients or procedures. As noted previously, system **200** may be adapted to deliver an individual dose to patient **P** by producing the dose and then filling it into syringe **262** mounted to an actuating syringe pump **264**, as shown in **FIG. 3**, or other container in patient administration module **260**. Syringe pump **264** may be actuated under the command of control computer **210** to deliver the dose to patient **P**. Thus, syringe **262** and syringe pump **264** may form the patient administration module **260** in the embodiment of system **200** as shown in **FIG. 3**. In another variation, syringe **262** receives a bulk quantity of radiopharmaceutical fluid from radiopharmaceutical processing module **230**.

[00134] Moreover, in a further variation showing the flexibility of system **200**, radiopharmaceutical processing module **230** may assay the radioactivity level of the dose and optionally print a label for the dose container (a shielded syringe **262**) which includes information such as radiopharmaceutical type, fluid volume, radioactivity level, procedure type, and patient information. The label may be in human-readable text, symbology, or a combination of both. A further option is to place the labels in a slide-in, slide-out receptacle on top of a vial as the dose container or on the top of a plunger of a syringe as the dose container instead of on the sides of these containers to make it easier to read the printed

labels. Another variation includes the option of writing label information into an RFID device that is included on the dose container. In one embodiment, the RFID tag is located on the syringe so that it is transported with the dose to syringe **262** in patient administration module **260** where it is read by a component in module **260** for further quality control. This syringe **262** can then be placed in a shield and transported and utilized in a remote delivery device as discussed elsewhere herein. Thus, patient administration module **260** according to this variation of system **200** forms a "fill station" for filling appropriate containers with radiopharmaceutical. Accordingly, it should be clear from the foregoing that system **200** is able to perform any desired combination of producing, refining, quality-checking, and delivering radiopharmaceutical fluid to a patient. A final step may be simply to load the radiopharmaceutical into a shielded syringe **262**, as an example, and transport the same to remote location where its contents are injected into a patient.

[00135] An optional component of patient administration module **260** comprises the use of a biologically inert fluid, such as a saline solution in container **266**, in coordination with a fluid path **268** leading to patient **P**. A control valve **269** may be associated with syringe **262** and saline source **266** to alternately place these fluid delivery elements into fluid communication with patient fluid path **268**. Accordingly, saline from saline source **266** may be used to flush fluid path **268** of radioactive fluid. If desired, control valve **269** may be configured so that saline from saline source **266** may be drawn into syringe **262** and syringe pump **264** may then be used to direct a bolus of saline into fluid path **268** (upon proper activation of control valve **269**) so that syringe **262** may also be flushed of residual radioactive fluid in addition to the components of fluid path **268** (tubes, hoses, etc.) between syringe **262** and patient **P**. A suitable arrangement for flushing fluid path **268** of residual hazardous fluid may be found in United States Patent No. 6,767,319 to Reilly et al. previously incorporated by reference.

[00136] Another feature of individual dose production capability, wherein patient administration module **260** may be operable as a container "fill station" allows a user or operator to "dial-in", or alternatively to select via GUI **212**, a dose quantity (radioactivity level) and press a single "fill" button. After the fill button is pressed, system **200** extracts the selected amount of radiopharmaceutical fluid into an individual dose container (such as syringe **262**), optionally prints a label for this container, optionally automatically applies the label to the container, and optionally writes relevant information to an RFID tag on the individual dose container. An optional feature is to write the relevant label and/or RFID information onto a "memory stick," such as a USB memory drive now commonly used with

personal computers and associated with the dose container. The individual dose memory stick is transported with the individual dose container and is used subsequently to ensure the correct dose is used for the correct procedure for the correct patient. At each step following the creation of the data on an individual memory stick, later or "downstream" devices are able to update information on the memory stick with relevant information, for example, the time at which the dose was injected into the patient. Optionally, an easy-to-use means is provided to ensure the correct memory stick remains with the correct dose. Examples are receptacles in a syringe shield into which the memory stick easily snaps, a keychain-type device that mates a memory stick to a dose container, and the like. A further option is to label the memory sticks and individual dose containers with symbols, such as numbers, that are readily viewable by the operator to ensure the same symbol is on the memory stick as is on the container. Optionally these symbols are produced by the labeling subsystem of control computer **210**. A memory stick may be recycled through a process in which the memory stick is inserted into a USB port of control computer **210** and the like, and a program is selected to erase information off of the memory stick. It is preferred that this program first communicates with an HIS system to upload relevant patient information before erasing the contents of the memory stick.

[00137] It should be clear from this disclosure that a variety of dosimetry arrangements may be used to ensure the correct amount of radioactivity level is extracted for each individual dose. For example, a bulk fluid container, for example, in place of technetium generator **220** can be wholly inserted into a dosimeter, such as a commercially available Capintec, Inc. assaying system, and the amount that the radioactivity of the bulk fluid decreases is representative of the amount of radioactivity which was extracted for the individual dose. A different embodiment is to place the individual dose container, for example, a filled syringe **262**, inside a dosimeter and measure the amount of radioactivity of the fluid delivered to the individual dose container directly. A non-radioactive fluid is typically used to flush all of the extracted radioactive fluid into the individual dose container before measuring the dose level. An optional embodiment of this feature is to use solid state dosimeters which are incorporated into a syringe or vial shield. Using this embodiment, the shield which contains the solid state dosimeter(s) is connected to a controller which includes a display screen. The display shows the amount of radioactivity measured by the dosimeter(s). This display may also contain a user-selectable list of radionuclides which is used by the dosimeter controller to calculate the radioactivity level based on calibration constants derived for each radionuclide. Multiple dosimeters may be used to provide

redundancy and confirmation of leak free fluid transportation. When the correct dose is in a syringe, for example, the syringe shield is disconnected from the controller and transports with the syringe to, for example, a remote fluid injector. Optionally, such patient injection module **260** operates at the patient administering device and can include a similar dosimeter controller and display that the operator can use to verify the activity level of the radiopharmaceutical just prior to injecting the radiopharmaceutical into the patient. An enhancement of the foregoing is to incorporate a writable RFID tag along with the dosimeters, into the container shield. The dosimeter controller is enabled to write the dose information (activity level, radionuclide, time of day) into the RFID tag. This information is optionally used by patient administration module **260** to ensure accurate delivery of the correct amount of the correct radiopharmaceutical.

[00138] A further dosimeter embodiment is to place the dosimeter (for example, dosimeter **232a**) in-line with a fluid delivery line, and control the amount of fluid extracted in real time based on dosimetry measurements of the fluid passing through the in-line dosimeter(s). A preferable embodiment of this implementation is to use solid state dosimeters as the in-line devices. A still further embodiment is to extract a small, known amount, for example less than one milliliter, of the bulk fluid into a container in a dosimeter at the time the bulk fluid is placed in the individual dose production module. The dosimeter measures the activity level of a fluid which has the same radioactive decay rate and initial radioactivity density. Therefore a calculation is made for all individual doses produced from this one bulk amount of radiopharmaceutical. This calculation determines the volume of fluid to extract from the bulk dose based on the radioactivity level of the known volume of sampled fluid and the desired radioactivity amount for the individual dose. The individual dose is then extracted by a fluid delivery means which delivers an accurate volume of fluid into the individual dose container without the need for in-line dosimetry, or for dosimetry of the final individual dose.

[00139] Another variation of individual dose production processing uses dose information which is received from the hospital information system (HIS) and automatically produces each individual dose of radiopharmaceutical at the time scheduled for delivery to the patient, for example, using system **200** of **FIG. 3**. This embodiment includes the option for an operator to select "create this dose now" rather than waiting for the scheduled time. A further feature is to reschedule individual doses via operator interactions. These rescheduling features facilitate changes to patient workflow for those occasions when patients arrive at the imaging suite either early or late, or for when patient workflow and imaging equipment availability support the opportunity to reschedule the injection of radiopharmaceutical into

the patient. A still further enhancement includes extracting individual doses into syringes (such as syringe **262**) which have distinguishing characteristics, such as different sizes or colors. These distinguishing characteristics help the operator to easily identify the type of procedure this dose is to be used for. For example, the dose may be placed into a red-tinted syringe for the stress portion of a cardiac stress test and the rest dose placed into a blue-tinted syringe. A desirable embodiment of the individual dose production module incorporates dripless syringes which further incorporate reflux valves (i.e., Halkey-Roberts valves) to enable dripless connections to needles or tubing as these syringes are being filled and when they are used for patient injection.

[00140] In yet another variation, the individual dose production capability includes the ability to create an individual dose syringe using a pre-filled bulk or individual dose of radiopharmaceutical contained in a different syringe **262(2)**, as shown in **FIG. 5**. This embodiment includes the process of attaching the pre-filled bulk dose of radiopharmaceutical to a dosimeter **300** in which an individual dose syringe **262(1)** is located. Inside the dosimeter **300** is a linear drive mechanism **302** which pulls back on syringe plunger **304** in the direction of arrow **A** causing the radiopharmaceutical fluid to be drawn into the individual dose syringe **262(1)**. An option of this embodiment is the ability to control the amount of activity to be drawn into the individual dose syringe **262(1)** using a wired or wireless handheld remote operator interface **306**.

[00141] Another embodiment suitable for use in individual radiopharmaceutical dose production and handling situations includes the ability to extract the individual dose into an interim, expandable, storage container such as a bag. This bag is then labeled including, optionally, writing information into an RFID tag attached to the bag. At the time of patient injection, the entire extractable contents of this dose are delivered to the patient in a single bolus by squeezing the expandable bag container. In another embodiment also suitable for use in individual radiopharmaceutical dose production and handling situations, an individual dose syringe **262** is extracted into a retractable pig **310** as shown in **FIG. 6**. This retractable pig **310** is designed to mate with the top of a typical dosimeter **312**. When not mated with the dosimeter **312**, the fluid-containing part of the pig **310** can be retracted inside of a telescoping shielded area or portion **314** and a cap **316** placed over the opening to prevent the pig **310** from being extended out of the shielded area **314**. When the operator needs to assay the amount of radioactivity in the pig **310**, the operator removes the cap **316**, mates the pig **310** with the dosimeter **312**, and pushes down on the top of the pig **310** to extend the fluid-containing portion into the active area of the dosimeter **312**. A suitable telescoping

arrangement for use between shielded area **314** and the main body of pig **310** may be adopted from United States Patent No. 4,092,546 to Larrabee, incorporated herein by reference.

[00142] As described hereinabove, patient injection module **260** is that part of system **200** which may be used to deliver the radiopharmaceutical directly into patient **P**. As further noted previously, this module may be an integrated part of system **200** of **FIG. 3**, in which case system **200** also retains a fluid injection capability and, if made in portable form, may be "rolled" to close proximity to patient **P** before the patient **P** is connected to module **260** via patient fluid path **268**, typically terminating in a needle cannula or catheter. An alternative configuration, also described previously, comprises patient injection module **260** as "fill station". In this configuration, individual dose syringe **262** is filled in "fill station" module **260** of system **200**. Once filled with radiopharmaceutical, individual dose syringe **262** may be removed from system **200** and inserted into a separate patient injection system (such as fluid injection system **700** discussed herein in connection with **FIG. 36A**). A desirably feature of such a remote patient injection system is for a bulk supply of radiopharmaceutical to be extracted, processed, and loaded into individual dose syringes **262** or like containers in system **200** which, once loaded into a fluid injection system enables delivery of a known, measured subset of the bulk fluid quantity into one or more patients. Whether patient administration module **260** is integrated into a system **200**, is used as a "fill station" or potentially operates as a separate, stand alone platform used to inject a radiopharmaceutical into a patient, a desirable feature of the patient injection module **260** is its own modular design. Such modularity includes the ability to include a number of fluid injection devices (such as multiple syringe pumps **264**), which enables the injection of 1, 2, 3, or n ($n > 3$) fluids into a patient. For example, system **200** can be used to inject a single radiopharmaceutical such as Cardiolite® into a patient via a single syringe pump **264** or multiple syringe pumps **264** may be provided for multiple fluids. In the embodiment illustrated in **FIG. 3** (i.e., a single depicted syringe pump **264**), as described previously, patient injection module **260** may include a separate saline delivery fluid path associated with saline source **266** which is used to ensure the total dose of radiopharmaceutical is administered to patient **P** by pushing saline into patient **P** after administration of the radiopharmaceutical.

[00143] Another feature of the patient administration module **260** includes injection of adenosine, or another cardiac stimulation fluid, into patient **P** before the radiopharmaceutical is delivered, for example, with the use of a second syringe pump or like device as part of patient administration module **260**. When the patient attains a desired heart rate and

maintains that heart rate for a sufficient time as determined by the protocol of the procedure, the patient administration module **260** is used to inject the radiopharmaceutical into the patient. This radiopharmaceutical administration may include an automatic flush of patient fluid path **268** with saline to ensure the entire dose is administered to patient **P**. A further feature includes adding fluid delivery paths in a modular fashion to inject multiple fluids including, for example, stress agents, two or more different radiopharmaceuticals, saline, and additional pharmaceutical fluids. The use of multiple fluid deliver devices or platforms facilitates the workflow of dynamic molecular imaging studies for those studies in which multiple radiopharmaceuticals, and potentially a variety of other medicaments are given to the patient intravenously.

[00144] Whether patient administration module **260** is embodied as part of a system **200** or is a distinct or stand-alone platform (akin to fluid injection system **700** discussed in detail herein), it is desired that the actual injection procedure be as simple as possible for the technologist (or other clinical staff member) because this allows that person to focus on the patient and other aspects of the procedure instead of devoting a significant amount of attention to the injection device or platform itself. Therefore, it is preferred that patient administration module **260** (or fluid injection system **700**) include a setup procedure which includes obtaining a correct radiopharmaceutical dose and other fluids, priming all tubing to ensure excessive air is not injected, connecting to a patient fluid path **268**, and otherwise preparing system **200** for fluid injection. After the setup is completed, it is preferred that patient administration module **260** (or fluid injection system **700**) deliver the correct fluids to patient **P** with a simple, one-button triggering of the injection.

[00145] Patient administration module **260** may be controlled to deliver fluid in a variety of ways. For example, the radiopharmaceutical dose can be injected slowly into a continuous saline stream from saline source **266** which is already being injected or infused into a patient. Additionally, the radioactivity at the patient injection site may be measured to confirm that the radiopharmaceutical is entering patient **P** and is not subject to an extravasation at the injection site. Moreover, the amount of radiopharmaceutical to inject may be determined at injection time as a function of various patient parameters, for example, weight.

[00146] Other variations of patient administration module **260** may include arranging shielding which shields the clinical staff from excess radiation exposure from the radiopharmaceutical as well as from patient **P** after the radiopharmaceutical is injected into the patient **P**. For example, the components of radiation protection module **280** may be heavily shielded to protect the operator from the radionuclide generation,

radiopharmaceutical preparation, and patient administration areas and also from patient **P**. Radiation protection module **280** may be embodied as a mobile work station (as in **FIG. 4B**) that includes drawers **211** and possibly internal shelving to hold medical disposables, medical tubing, tape, battery chargers, and the like. **FIG 4B** is revealing in another manner as this figure demonstrates that is it is desirable to keep patient fluid path **268** as short as reasonably possible to reduce radiation exposure to people in the area while the radiopharmaceutical is being administered. This can be very important when a dose is being given as a slow infusion or when the radiation dose is high, as in radiotherapy situations. One way to accomplish this result and still provide the flexibility desired is to have any extra tubing contained in a shielded space or compartment in radiation protection module **280**.

[00147] For those embodiments discussed in the foregoing wherein information is written as a bar code, stored on an RFID tag, written to a USB memory stick, or otherwise encoded and associated with a radiopharmaceutical container, patient injection module **260** (and desirably fluid injection system **700**) is designed to read the encoded information. This encoded information retrieval is done for quality control, for example, to write the patient's identification and dose information to GUI **212** and have the attending operator verify that the correct dose is present. This information retrieval is also done to facilitate workflow. For example, the amount of dose to inject into a patient can be a writable parameter and patient injection module **260** (and desirably fluid injection system **700**) upon reading that information, can adjust its fluid delivery via computer control to inject the correct amount, or dose, of the radiopharmaceutical and other fluids to patient **P**. It is preferred that patient injection module **260** (and desirably fluid injection system **700**) also includes the ability to write additional information into the encoded information so that the actual injection time and dose information is recorded for future recall and uploading to an HIS system, as an example. In one exemplary embodiment patient administration module **260** is an extension of a commercially available power injector, for example, the MEDRAD, Inc. Pulsar Injector. This commercially available injector is extended by using new syringe embodiments which can cooperate with a syringe shield, such as a lead, lead loaded acrylic, or tungsten compound, around the syringe body. The shield protects from excessive radiation exposure while, at the same time, does not affect the ability of the power injector to deliver fluid at its designed volumes and flow rates.

[00148] In the embodiment of patient injection module **260** that is incorporated into the design of portable system **200**, radionuclide generation and radiopharmaceutical production including all quality control steps are controlled to produce a single dose of a

radiopharmaceutical at the time it is needed for patient injection. Patient injection module **260** therefore injects the entire amount of the single dose, with optional other fluids as well, without the need for an additional syringe or vial to contain the radiopharmaceutical fluid between the time it is produced and the time it is delivered. Optionally, radiopharmaceutical production is controlled to produce a bulk quantity of the radiopharmaceutical, and the patient injection module **260** draws the correct amount of fluid (alternatively repeatedly draws fluid until it records that the correct amount of radioactivity has been drawn) and injects the radiopharmaceutical directly into the patient **P**.

[00149] System **200** includes a waste disposal module **270** as noted previously. Waste module **270** includes a waste container **272** into which excess waste fluids are placed so they can be held until the radioactive decay renders them radioactively harmless. Typically, these fluids are held in a secure location in a facility's hot lab and disposed of as bio-waste after sufficient radioactive decay. It is contemplated that different embodiments may support different clinical workflows. For example, a single container may be used for both waste fluids and waste materials (tubing, tape, swabs, and the like). Alternately, two or more waste containers **272** may be used to keep the waste fluids separate from other waste materials. In one alternative, waste disposal module **270** includes a single waste container **272**, such as a bag or plastic container, which is housed inside a shielded compartment. At scheduled intervals, or when the fluid level is high, this bag or plastic container can be removed from system **200** to be stored in a safe location to allow time for the radioactive decay to occur. A separate bag or plastic container is then placed into system **200** to collect upcoming fluid waste. Another alternative or variation is to reduce the size of waste container **272** and its associated shielding by using an individual, smaller, waste container **272** that is sized to support the waste anticipated for a single patient procedure. This waste container **272** is then replaced at the same time as disposable patient tubing is replaced for the next procedure. Additionally, this disclosure contemplates the use of a cloth, similar to a disposable diaper that is placed underneath all fluid connection points. This cloth is used to catch any drips that may occur and can be disposed of in waste container **272** that holds waste material. Alternatively or in addition, hand held shielded wipes with disposable absorbent cloths and plastic backing can be made available as part of system **200**. Such shielded wipes could also be a holder for the disposable diaper, and can optionally be removed, held by the operator, and used to wipe up drips elsewhere if they occur. Preferably, the absorbent in the shielded wipes contains a colored agent such that the color changes when it absorbs any liquid.

[00150] It is preferable that internal fluid path **290** in system **200** be provided in modular or kit form so that set-up is as economical and non-labor intensive as possible. It is also apparent that various adaptations to internal fluid path **290** can be designed to accomplish the functions described herein. For example, internal fluid path **290** typically comprises a plurality of individual fluid lines **292** for conducting fluids between the various subsystems and modules forming system **200**. Control of fluid flows within internal fluid path **290** is desirably provided by a plurality of individual control valves **294** which may be individually controlled by control computer **210** and which are further desirably electro-mechanical devices. A suitable control valve embodiment for the various control valves **294** in internal fluid path **290** are automated stopcock valves. Within internal path **290**, there is also provided a main waste conduit **296** leading to waste container **272** and a saline supply conduit **298** connecting a second source of saline **299** to technetium generator forming radionuclide generation module **220** in the embodiment illustrated in **FIG. 3**. A syringe **252** and associated syringe pump **254** may be provided as part of internal fluid path **290** to form a dose extraction module **250** of system **200**. Dose extraction module **250** is used to pull a dose or doses of fluid from technetium generator or bulk vial comprising radionuclide generation module **220** and delivers this fluid via internal fluid path **290** to one or more of the chemistry/processing units forming radiopharmaceutical processing module **230**. Additionally, a series of fluid pumps including a first pump **256**, such as a peristaltic pump, may form part of dose extraction module and be in fluid communication with internal fluid path **290** to pull saline from second saline source or container **299** and delivers saline to one or more one or more of the chemistry/processing units of radiopharmaceutical processing module **230** and, if desired, syringe **262** in patient administration module **260**. A second fluid pump **258** may also be provided in fluid communication with internal fluid path **290** and may be used to flush waste fluids to waste container **272** of waste module **270**. Second pump **258** may be used to pull fluid from any of the modules and components of system **200** and deposit waste fluids into waste container **272**.

[00151] Within internal fluid path **290**, a multi-patient fluid path **290(MP)** may be provided and comprised by the fluid path elements of internal fluid path **290** located "below" patient administration module or area **260**. The fluid conducting elements of multi-patient or multi-use fluid path **290(MP)** may be installed, for example, once in the morning and used or "reused" all day. A single patient or single-use fluid path **290(SP)** is generally comprised by the fluid path elements of internal fluid path **290** located in and "above" patient administration module **260**. These components are changed for each patient **P**, thereby

forming a disposable, single use fluid path. It will be appreciated that single patient or single-use fluid path **290(SP)** may be connected by control valve **269** to patient fluid path **268** discussed previously. A suitable "breakpoint" between single patient or single-use fluid path **290(SP)** and multi-patient or multi-use fluid path **290(MP)** is sterile filter **SF**. Sterile filter **SF** may optionally be part of single-use fluid path **290(SP)** or multi-patient or multi-use fluid path **290(MP)** as desired. Optionally, sterile filter **SF** may consist of two sterile filters, one of which stays with multi-patient or multi-use fluid path **290(MP)** and the second of which is disposed of after each use and forms part of single patient or single-use fluid path **290(SP)**. Optionally, fluid paths for different radiopharmaceuticals (or other fluids) may each run through a separate line to a separate sterile filter (not shown) in patient administration area or module **260**. This variation has the advantage of more assuredly preventing any cross contamination of one fluid into another, but has the difficulty of additional fluid path elements to manage. At the end of the day, as an example, all radioactive liquids are preferably flushed into shielded waste container **272** using second fluid pump **258** so that internal fluid path **290** has little or no radioactivity remaining when removed the next morning. It is desirable to include a radiation monitor, detector, or dosimeter in proximity to waste container **272**, optionally inside the shielding of waste container **272** so that the radiation level may be monitored to inform the operator that it is safe to open the waste container **272** and dispose of the waste therein as non-radioactive trash. For FDG, this can generally be after an overnight decay. For technetium and other longer-lived isotopes, it is desirable that shielded waste container **272** be removed from system **200**, exchanged for an empty shielded waste container **272**, and separately stored for a sufficient time that the waste can be disposed of as non-radioactive waste.

[00152] The final module of system **200** is the previously-mentioned radiation protection and support component or module **280**. It is obvious that this module includes shielding appropriate for the entire spectrum of radionuclides expected to be used in system **200** and provides the physical support and transport structure (for example, wheeled) for the other modules discussed previously. Generally, this module comprises an upright radiation shield component or divider **281** that divides system **200** into a radioactive pharmaceutical and patient side **282** and an operator side **283**. Shield component **281** forms a main support column of module **280**. Each "side" of shield component **281** may include additional radiation protection sufficient for the quantity of radioactivity to be contained. The operator will work on the operator side **283** as needed to connect parts of the system **200**. During preparation and administration of a dose to patient **P**, the operator will also generally be on

the operator side **283** formed by radiation shield **281** so that the operator is as protected as much as possible, including from radiation emanating from the patient. Doors (not shown) close and shield the patient side **282** of system **200** and can also contain aerosols and direct clean air as described herein. Accordingly, patient side **282** may be compartmentalized (such as formed as a cabinet) for the various radioactive fluid handling components provided on the patient side **282** and which may be individually radiation shielded for components such as technetium generator **220** and waste container **272** as described previously.

[00153] One feature of radiation protection module **280** is the use of shielding glass window **284** (**SW**) and appropriate lighting to enable the operator to view activities and fluid levels in patient administration module **260** and desirably anywhere inside system **200**. Alternatively, shielding glass window **284** is replaced with a video camera (with appropriate lighting) on the radioactive or patient side **282** of the shielding glass window **284** with a display monitor on the "outside" radiation protected or operator's side **283** of system **200**. Desirably, the camera's pointing direction is designed to be controlled by a simple electromechanical means, such as is popular on commercially-available webcams, which is accessible on system **200** such as proximate to GUI **212**. The vertical support aspects of radiation shield **281** are shielded to protect the operator from radiation emanating from patient **P** and from the radiochemistry aspects of system **200**. It is expected that the technetium generator and/or bulk containers comprising radionuclide generation module **220** will remain shielded to provide additional shielding. Bulk containers may remain in transport pigs with only the tops of the pigs being removed for fluid access. If such bulk containers arrive in "smart pigs" as disclosed herein, fluid access is gained without opening the smart transport pig at all. It is further anticipated that the chemistry/processing units forming radiopharmaceutical processing module **230** will also have sufficient shielding around and between them that radiation from one unit will not affect the dosimetry of another unit. This shielding further protects the system operator as well. Another feature of radiation protection module **280** includes the ability to remove part of the system's shielding along with the dose to be injected. This shielding may be in the form of a portable container or, preferably, as a larger portable shield section which protects the system operator from exposure to the fluid contents and also protects the system operator from exposure to radiation after the radiopharmaceutical has been injected into patient **P**. A further enhancement is that the portable shield is designed to surround the patient's arm in addition to enclosing the radiopharmaceutical dose when the radiopharmaceutical is brought to the patient administration module **260**. This sleeve-like shield may remain on the patient's arm during a

cardiac stress test procedure and continue to shield the radioactivity even though patient **P** moves while exercising. **FIGS. 4A-4B** show exemplary variations of the radiation protection and support component or module **280**, particularly alternative constructions of shielding window **284**. It should also be noted that there are cases where a radiopharmaceutical is used very infrequently. In this case, the patient treatment facility may purchase a single patient dose, and deliver this dose using the per-patient injection capability of patient administration module **260**.

[00154] As described previously, integrated systems **100**, **100a** are capable of delivering one or more fluids, typically liquids that contain drugs such as radiopharmaceuticals, to patient **P**. In most fluid delivery systems known in the medical field, all the fluids that leave a delivery device, typically a pump, travel down a delivery tube and into the patient. Often, some of the fluid is disposed of or diverted to a waste container. Some known fluid delivery systems, such as that illustrated in United States Patent No. 5,806,519 to Evans, III et al. have the ability to draw back a small volume of fluid so that blood can be pulled into a fluid path element to confirm that a vascular access device is in the target vessel and is not clogged. This fluid is subsequently injected into the patient or discarded. Fluid path elements from a fluid delivery system to the patient can contain several milliliters (ml) of fluid. For example, a low pressure connector tube manufactured by MEDRAD, Inc. of Pittsburgh, PA is sixty inches in length and has a nominal inner diameter (ID) of 0.060 inches. Thus, the volume in the tube is about three ml.

[00155] Thus, a multi-fluid and multidirectional fluid handling system **990** is now disclosed and shown in **FIG. 7** which may be utilized as part of or as the whole fluid handling system **150**, **150a** in integrated systems **100**, **100a** discussed previously in connection with **FIGS. 2A-2B**. As shown in **FIG. 7**, fluid handling system **990** provides systems and methods and supporting components and devices that enable a preferred, safe, relatively inexpensive priming fluid, such as saline, to be used to prime or fill a fluid delivery path and the fluid delivery lines, typically tubing, forming the same to enable injection of a drug, such as a radiopharmaceutical, with little or no delivery of the priming fluid to a recipient **R** (human, animal, cell, or a container). Optionally, after the drug is injected, fluid handling system **990** is configured to replace the drug in the delivery lines with the preferred, safe priming fluid to be ready for the next drug injection. This result is achieved by having, for example, two separate fluid paths to a point close to the delivery point, the recipient **R**, with one fluid path connected to a delivery side, portion, or subsystem of fluid handling

system **990** and the other connected to a withdrawal side, portion, or subsystem of fluid handling system **990**.

[00156] Referring now in detail to **FIGS. 7-12**, a delivery side or subsystem "**D**" of fluid handling system **990** has, for example, a saline flush pump **920** optionally connected to an associated fluid reservoir so that it can be refilled, a drug pump **930** optionally connected to an associated fluid reservoir and optionally appropriately shielded for containing radioactive, chemotherapy, or other hazardous substances. A third pumping unit **940** with an associated optional fluid reservoir for refilling is also shown. Additional pumping units can be optionally be added as desired. The series of pumps **920**, **930**, **940** could be, for example, CavroXLP6000 pumps made by Tecan of San Jose, CA. The pumps **920**, **930**, **940** are controlled by microprocessors or computers that are part of pumps **920**, **930**, **940** and an operator interacts with fluid handling system **990** through an interface, for example, on a computer **991** which communicates with and commands and coordinates the individual fluid pumps **920**, **930**, **940**, other actuatable components or elements, and receives sensor or input measurements, such as heart rate or respiration. Connections between the various system components or elements are shown as lines **915**, **916**, **917**, **918**, **919** for illustration and may be any suitable connections known in the computer communications field, such as hard wired point-to-point communications or various networking arrangements, wireless communications, or the transfer of data via a card or some other physical object. Valving to allow controlled fluid delivery and refilling may be done in any number of equivalent ways, for example, automatically via dual one-way check valves, by an electromechanical control effected by control computer **991**, for example, pinch valves or rotation of stopcocks, or by manual operation. Electromechanical control is particularly desirable.

[00157] Optionally, a dosimeter **980** is provided in fluid handling system **990** at an appropriate location to measure radioactive or chemical dose or concentration of drugs flowing through the fluid path of fluid handling system **990**. Alternative sensing methods known to those skilled in the medical fluid delivery art may be used. Fluid from delivery side, subsystem, or module **D** is conducted to recipient **R** via a fluid junction **900** connected to first fluid path **901**. In a region near recipient **R**, there is fluid communication between fluid junction **900** and a second fluid path **902**. Suitable and exemplary fluid connections comprising fluid junction **900** between first fluid path **901** and second fluid path **902** are illustrated in **FIGS. 8-12**. Equivalent fluid connections may be developed by those skilled in the medical fluid delivery art.

[00158] Second fluid path **902** communicates with a second fluid handling system, generally used as a withdrawal subsystem or module and forming the "withdrawal" side "**W**" of fluid handling system **990**. In this example, withdrawal side, subsystem, or module has two fluid pumps, a first pump **950** that can remove and discard "waste" and a second pump **960** that can also remove a fluid, for example, blood and conduct it into an associated reservoir such as a sample container. Alternatively, second pump **960** can be used to deliver an additional fluid. This is especially useful if the fluid is not compatible in some way or property with that being delivered via delivery or first side or subsystem **D**.

[00159] With the basic components of fluid handling system **990** set forth, operation and associated benefits of fluid handling system **990** will now be described. The following operational steps are merely exemplary in explaining the operation of fluid handling system **990** and should not be considered as limiting. In a first step of this example, saline flush pump **920**, for example, a syringe pump, is filled with saline from a reservoir. Likewise, drug pump **930**, another syringe pump, is filled with a drug, such as a radioactive version of a drug that bonds with a neurotransmitter receptor, and third pump **940**, a third syringe pump, is filled with a non-radioactive version of the same drug. Before connecting fluid paths **901** and **902** to recipient **R**, a manifold **910** or similar device is filled with saline, and delivery fluid path **901** of fluid path **901** through dosimeter **980** is likewise filled with saline all the way through to a recipient delivery point or element **900p** of fluid junction **900** by pumping saline from or via saline flush pump **920**. Air in the line is expelled out though this process all the way to delivery point or element **900p**. Delivery point or element **900p** is typically a small gauge needle cannula. The volume to fill delivery fluid path **901** is either known based upon the specific elements used in fluid path **901** and programmed into control computer **991** or control computer **991** "learns" the fill volume by proceeding slowly or manually under operator observation, and the operator indicates when the air has been fully purged and delivery fluid path **901** is full of liquid. Withdrawal side or subsystem **W** and fluid path **902** associated therewith is primed or purged of air when waste pump **950** is activated to pull fluid toward this pump, typically at the same flow rate and at the same time as saline flush pump **920**. Accordingly, fluid flows down delivery fluid path **901** and up withdrawal fluid path **902** without significant fluid exiting delivery point or element **900p**. This synchronous operation is continued until fluid paths **901**, **902** are purged of air and full of saline.

[00160] With fluid paths **901**, **902** purged of air and full of saline, the operator can insert delivery point or element **900p**, a needle cannula in most cases, into a vein, other vessel, tissue, or other target in recipient **R**. Fluid handling system **990** is now ready to deliver drug

via drug pump **930**. However, delivery fluid path **901** is now full of saline. To avoid delivering all the saline to recipient **R**, waste pump **950** operates at approximately the same flow rate and at the same time as drug pump **930** so that, as drug flows into delivery fluid path **901**, saline flows out or through withdrawal fluid path **902** and no saline is delivered to recipient **R**. When it is determined, for example, via a sensor, time, or desirably volume calculation that drug has reached fluid junction **900** connecting fluid paths **901**, **902**, waste pump **950** is stopped while drug pump **930** continues and the intended drug is delivered to recipient **R**. When the intended volume of drug to be delivered by drug pump **930** has been reached, drug pump **930** is stopped and saline flush pump **920** is activated and pushes just enough saline into delivery fluid path **901**, including manifold **910**, and delivery point or element **900p**, so that all the drug is delivered to recipient **R** and fluid path **901** is now refilled with saline and an injection cycle is considered complete.

[00161] Alternatively in the foregoing, drug pump **930** can continue pumping drug until control computer **991** determines that a desired dose has been delivered from delivery fluid path **901** and into recipient **R**. At this point, drug pump **930** is stopped. This determination is especially useful if the determination of sufficiency of dose is based upon some sensor or other measurement, possibly in real time, and not just after a predetermined volume has been delivered or predetermined amount of time has elapsed. In this situation, it cannot be known ahead of time when to stop the drug flow and start the saline flush. Delivery fluid path **901** is now full of drug and, if this is a radioactive drug, it represents an exposure hazard for the operator. To eliminate this hazard, drug pump **930** is reversed to return the drug in delivery fluid path **901** to drug pump **930** (if a syringe pump) or the drug reservoir, for example, when drug pump **930** is a peristaltic pump. To avoid pulling blood or other material from recipient **R**, waste pump **950** pumps fluid out at the same flow rate and during the same time that drug pump **930** pulls fluid in. These two pumps stop when control computer **991** determines that all drug has be returned to drug pump **930** or the associated upstream reservoir. Drug pump **930** then stops, and waste pump **950** can optionally continue for a small volume to flush the drug out of fluid delivery point or element **900p** and into recipient **R**. When delivery point or element **900p** is purged of drug, waste pump **950** ceases operation. This last event generally completes an injection cycle according to this alternative mode or operation and the line has again been flushed of the hazardous radiopharmaceutical or drug. Alternatively, once drug pump **930** is stopped and delivery fluid path **901** is now full of drug, the drug in fluid path **901** can be sent to the waste pump **950** by pumping fluid out of saline pump **920** and into

waste pump **950** until fluid path **901** is cleared of drug. This reduces the radioactivity in fluid path **901**.

[00162] It is important that the delivery rates and withdrawal rates be slow enough that cavitation does not occur. Cavitation occurs if inlet pressure to waste pump **950** falls below the vapor pressure of any gas in the saline or of water itself. If this happens, a bubble can temporarily form and some liquid will be delivered into recipient **R**. Then, when the flow rate decreases, some blood will be withdrawn from recipient **R** as the bubble collapses. The pressure drops in the fluid path elements of fluid paths **901**, **902** can be calculated to a reasonable approximation and then confirmed through experimental measurement to allow designers to select fluid path elements and flow rates sufficiently low to avoid this problem and yet high enough to provide the needed injections.

[00163] After imaging recipient **R**, if desired, "cold' or non-radioactive drug is delivered from pump **940**, for example, in the receptor studies described previously. To avoid dumping saline into recipient **R**, waste pump **950** is again activated at the same flow rate to remove the saline. After the proper volume has been delivered, waste pump **950** is stopped and the non-radioactive drug is delivered to recipient **R**. Any of the finishing procedures discussed previously may be used to ensure that delivery fluid path **901** is purged of drug and full of saline. After imaging recipient **R**, if desired, another dose of "hot" or radioactive drug is given at a similar or different dose using the protocol described previously to deliver only the desired fluid to recipient **R**. Additional doses of "cold" or "hot" drug may be given to complete the study of receptor kinetics. Only the volumes of the "hot" or "cold" drug are delivered to recipient **R**.

[00164] Fluid pumps **920**, **930**, **940**, **950**, **960**, and **970** can be any generally positive displacement pump or other pump with a sufficiently accurate flow or volume meter so that the fluid flows can be matched as described above. Syringe pumps are schematically shown for exemplary purposes and have the benefit of potentially incorporating the total needed reservoir volume for delivery to recipient **R**. Peristaltic pumps, as noted previously, are suitable alternatives and have the advantage of being relatively easy to prime. A disposable gear pump, as discussed in United States Patent Application No. 11/403,119, filed April 12, 2006, and entitled "Fluid Delivery System with Pump Cassette" is another possible pump device for fluid pumps **920**, **930**, **940**, **950**, **960**, and **970**.

[00165] Similarly, fluid junction **900** may have many embodiments as illustrated in **FIGS. 7-12**, with various features that meet the general needs. **FIG. 8** shows a fluid junction **900** achieved by having fluid junction **900** end in a needle cannula forming delivery point or

element **900p** of smaller outside diameter (OD) than the ID of delivery fluid path **901**. Delivery point or element **900p** is simply inserted into the flexible tube forming delivery fluid path **901**. This arrangement works especially well if the tubing forming delivery fluid path **901** is soft tubing such as silicone tubing. The junction formed by insertion of a needle cannula in the tubing of delivery fluid path **901** can be held in place with a dab of medical grade adhesive or even "super glue" for animal use. **FIG. 9** shows a similar process used for the addition of a third line **903** which can be used for sampling blood or fluids or delivering additional fluids. **FIG. 10** shows a separate T-piece connector **905** into which are press-fit tubing elements forming delivery fluid path **901**, withdrawal fluid path **902**, and delivery point or element **900p** (needle cannula). The tubing components may be solvent bonded into the T-piece connector **905**, or a medical grade adhesive can alternatively be used. **FIG. 11** illustrates an alternative connector **905'** which holds three fluid conduits (**901**, **902**, **903**) in side-by-side, generally parallel relationship. This arrangement has the benefit of providing a handle structure for manipulating delivery point or element (needle cannula) **900p** for insertion into recipient **R**. Again, solvent bonding and medical grade adhesive are two exemplary methods of securing the arrangement of **FIG. 11**.

[00166] It is also possible for fluid junction **900** to be a stopcock that can be rotated remotely, for example, by an electromagnetic stepper or a hydraulic actuator as illustrated in **FIG. 7**. A hydraulic actuator has the benefit of being able to operate in close proximity to an MRI system. The hydraulic actuator is operated by a hydraulic pump **970** connected via a hydraulic fluid line **904** to fluid junction **900**. Hydraulic pump **970** is controlled by the control computer **991**. Pinch valves, either hydraulic or electromagnetically actuated, may also be used.

[00167] As noted in the foregoing, fluid handling system **990** may be used to collect a blood sample. A method of obtaining a blood sample is to connect a conventional blood sampling system to fluid conduit **903** (**FIG. 9**) and coordinate its operation with that of system **990**. Another sampling arrangement, involves two additional syringe pumps and a tubing set with sufficient volume to contain all the blood samples for one recipient **R**. A sample of blood is drawn into a sample holding tubing set or line by activating a first pump (not shown) to withdraw blood from the recipient **R**. When a sample of sufficient volume is withdrawn, a second pump (not shown) is activated to inject a viscous fluid into the sample holding tubing line and is injected at the same rate that first pump is withdrawing fluid (i.e., blood). Thus, the sampling of blood is stopped and a "slug" or segment of viscous fluid is used to separate successive blood samples. One viscous fluid that can be used is X-ray

contrast, for example, iso-osmolar contrast such as Visipaque® manufactured by Electric Healthcare (Amersham, Inc.). When it is time for another blood sample, the process is repeated. After all the blood samples are taken, the sample tube line is removed and the separate blood samples are dispensed into appropriate containers, such as blood collection tubes, for analysis. An alternative to a viscous liquid is air, carbon dioxide, or another gas. The bubbles effectively separate the different blood samples. This arrangement allows samples of a few microliters to be drawn. If desired, after a sample is drawn, an equal volume of saline can be administered to the animal to make up for the volume withdrawn.

[00168] As noted in the foregoing, fluid handling system **990** may be used to collect a blood sample. A method of obtaining a blood sample is to connect a conventional blood sampling system to fluid conduit **903** (**FIG. 9**) and coordinate its operation with that of system **990**. Another sampling arrangement, involves two additional syringe pumps and a tubing set with sufficient volume to contain all the blood samples for one recipient **R**. A sample of blood is drawn into a sample holding tubing set or line by activating a first pump (not shown) to withdraw blood from the recipient **R**. When a sample of sufficient volume is withdrawn, a second pump (not shown) is activated to inject a viscous fluid into the sample holding tubing line and is injected at the same rate that first pump is withdrawing fluid (i.e., blood). Thus, the sampling of blood is stopped and a "slug" or segment of viscous fluid is used to separate successive blood samples. One viscous fluid that can be used is X-ray contrast, for example iso-osmolar contrast such as Visipaque® manufactured by Electric Healthcare (Amersham, Inc.). When it is time for another blood sample, the process is repeated. After all the blood samples are taken, the sample tube line is removed and the separate blood samples are dispensed into appropriate containers, such as blood collection tubes, for analysis. An alternative to a viscous liquid is air, carbon dioxide, or another gas. The bubbles effectively separate the different blood samples. This arrangement allows samples of a few microliters to be drawn. If desired, after a sample is drawn, an equal volume of saline can be administered to the animal to make up for the volume withdrawn.

[00169] As described in the foregoing, fluid handling system **990** is associated with one animal recipient **R** for the duration of a sophisticated study. Alternatively, a slightly simplified version of system **990** can be used to provide doses to successive animals with only the need to change some of the elements of fluid paths **901**, **902** as desired based upon the sterility needed. It may be sufficient in most cases that only the needle **901p** needs to be changed. The isolation of the reusable portion from the per-recipient portion can be improved by including a slit silicone rubber disk **906**, **906'** similar to those used at the end of

central venous catheters and upside down dispensing bottles. Using the split silicone septum also provides the benefit that there is no fluid flow to or from the patient until the pressure differential is sufficiently high to open the septum. It may be desirable that detailed operation of fluid handling system **990** as to the details of significantly reducing or eliminating the delivery of priming fluid to the recipient **R** is generally transparent to or hidden from the attending operator, although this may be under operator control or influence as necessary, for example, during the initial setup of system **990**. The operator only needs to specify the volume or activity of the fluid to be delivered to the recipient, the coordinated operations of the waste and other pumps are not selected or affected by the operator's choices.

[00170] After injection with a radiopharmaceutical agent, a patient or recipient is a potential source of radiation harmful to attending personnel. In normal practice, as mentioned previously, after injection with a radiopharmaceutical agent, a patient is usually kept in a shielded room isolated from other patients and attending personnel for about an hour until the radiotracer has distributed sufficiently for imaging. A possible alternative to current practice is to provide a patient enclosure system **980** that is shaped and configured to enclose the patient's body or major portions thereof. The patient enclosure may be portable and would eliminate the need for a separate shielded room. Patient enclosure system **980** is envisioned as a shielded chamber that keeps the patient relatively immobile and free of visual or auditory stimuli. Additionally, monitoring devices may be built into the enclosure to monitor patient vital signs such as heart rate, temperature, respiration, and metabolic rate (by monitoring respiratory gases). An example of a patient enclosure system **980** according to the foregoing concept is shown in **FIG. 13**, wherein monitoring devices **982** or openings for permitting patient (vital sign) leads to be passed to the exterior of the patient enclosure system **980** are provided on the body the patient enclosure system **980**. As shown, it is envisioned that a ventilation device **984**, for example, exhausted directly to outside air, may be provided for the comfort of the patient. Patient enclosure system **980** may resemble in size and appearance a conventional tanning booth.

[00171] In a typical prior art radiopharmaceutical delivery situation, medical and/or transport personnel are required to handle a drug container at several steps along the delivery of a radiopharmaceutical agent to a patient which increases radiation exposure risk to these personnel. The information about the drug in a shielded container is generally conveyed on a paper label, bar code, or optionally in a magnetic or electronic medium. The information is manually entered or transferred into a laboratory information system. The dose is manually confirmed before injection. Separate pumps, if used at all, are manually programmed based

upon the prescription for the patient or protocol for the research to deliver the drug. In **FIGS. 14-16**, an embodiment of a system **1000** for the generation, preparation, and administration of fluid radiopharmaceutical substances to human and animal subjects is schematically illustrated employing an RS device **1002** according to one embodiment. System **1000** provides a distinct improvement over the prior art radiopharmaceutical delivery situation just described by drastically decreasing the exposure time of medical and other personnel to radiopharmaceutical agents. Within system **1000**, RS device **1002** encloses and houses an RP container **1004** for transport and other purposes pursuant to aspects of the invention contemplated by this disclosure. As shown, RS device **1002** is generally a shielded container or housing that encloses and houses RP container **1004** for transport as well as having the ability to obtain dosimetry data and record data associated with the drug (radiopharmaceutical) contained in RP container **1004** and, further, data associated with RS device **1002** generally. The modularity of RS device **1002** greatly minimizes or even eliminates radiation exposure risk to attending personnel which may include radio-pharmacists, transport personnel, clinicians, etc. Specific details of RS device **1002** are provided hereinafter. **FIG. 15** illustrates a possible exemplary configuration of RS device **1002** for use in radiopharmaceutical system **1000**.

[00172] As revealed by **FIGS. 14A-14C**, RS device **1002** according to this embodiment is initially associated with components capable of generating a suitable radioisotope, such as an isotope generator **1006**, and a chemistry unit **1008** capable of reducing or transforming the generated radioactive substance into an injectable form. Such components as isotope generator **1006** and chemistry unit **1008** are discussed in detail earlier in this disclosure. As further revealed by **FIGS. 14A-14C**, RS device **1002** is disposed in or associated with a fill system or module **1010** wherein RP container **1004** is loaded with radiopharmaceutical. Desirably, RS device **1002** engages or interfaces with fill system or module **1010** via mechanical interconnection. As will be appreciated from the foregoing, RS device **1002**, as a modular component, is intended to detachably mate with fill system **1010** which itself is likewise a modular component. Fill system **1010** includes components which permit the direct transfer of "injectable" radiopharmaceutical agent from chemistry unit **1008** to RP container **1004**, namely, a pump device **1012**. Pump device **1012** is controlled by a pump control **1014** which is interfaced with a fill system control **1016**. Fill system control **1016** generally operates as a master control for subservient pump control **1014** and a fill system user interface **1018** is used to program and input data to fill system control **1016** for operation of pump device **1012** as well as for other components of RS device **1002** as described herein.

As further shown in **FIG. 14A**, both isotope generator **1006** and chemistry unit **1008** may be interfaced with fill system control **1016** via a communications interface **1020** and, therefore, operation of these two units may be effected by fill system control **1016** via communications interface **1020**.

[00173] Generally, RP container **1004** is a syringe used to hold FDG as an example but may also be a vial, bottle, or similar container. In the form illustrated in **FIGS. 14-16**, a single RP container **1004** is contained within RS device **1002** but this is merely exemplary for explaining aspects of the invention and RS device **1002** may be configured to contain multiple RP containers **1004**. RS device **1002** includes an outer housing **1022** and an internal shielded container or housing **1023** wherein RP container **1004** is physically contained. A dosimeter **1024** is further positioned within internal shielded housing **1023** in operational proximity to RP container **1004** and desirably provides continuous, periodic, or as requested real-time measurement of a radiation dose from RP container **1004**. It is contemplated that dosimeter **1024** may be a disposable, single use, or few use item, for example, an inexpensive solid state device made of semi-conducting materials (i.e., silicon, germanium) capable of converting gamma photons emitted by radioactive substances into a real-time electrical current in a very predictable manner. Alternatively, dosimeter **1024** may be reusable and be protected from contamination by a disposable member, sleeve, or shield. Dosimeter **1024** is connected to a dosimeter control **1026** which again is interfaced for control purposes with fill system control **1016**. A further aspect of RS device **1002** is a device and drug data recording device **1028** which permits the recording of pertinent data concerning the radiopharmaceutical in RP container **1004**, such as the date and time of manufacture and initial radioactivity level, dosimeter calibration curve, container volume, type of fluid, etc. This component may also include identifying indicia (serial number) or other data in electronic or physical form regarding RS device **1002**. Moreover, this component interfaces directly with dosimeter control **1026** so that continuous dosimeter readings are recorded and which may be displayed, for example, on fill system user interface **1018** for inspection by attending personnel such as the radio-pharmacist charged with filling RP container **1004** with a desired radiopharmaceutical agent. A monitor which can alert or alarm may be associated with or part of dosimeter control **1026** to alert the operator if there is any change from the steady half-life decay that could indicate a leakage of liquid or a failure of some other system component.

[00174] As **FIG. 14A** demonstrates, generation, dosage preparation, and transfer of injectable radiopharmaceutical agent to RS device **1002** may be accomplished with minimal

(or no) physical contact between a radioactive fluid and production personnel, typically a radio-pharmacist. The radiopharmaceutical is delivered straight from production to its container already pre-loaded into a transport device, namely RS device **1002,** without physical contact occurring between a human being and the radiopharmaceutical. The provision of pump device **1012** in fill system **1010** and the ability to control this pump device **1012** via suitable electronics allows a correct dosage to be loaded into RP container **1004** and this dosage may be recorded in device and drug data recording device **1028**. Dosimetry data is also continuously available at the fill system user interface **1018** on demand. Essentially, it is conceivable according to the foregoing disclosure that a dose of radiopharmaceutical is retained within RS device **1002** until it is injected into a patient.

[00175] As **FIG. 14B** illustrates, when a correct dosage of radiopharmaceutical is dispensed or loaded into RP container **1004** and dosimetry confirmed, RS device **1002** may be "unplugged" in total from fill system **1010**. As noted previously, additional data regarding the radiopharmaceutical may be recorded on device and drug data recording device **1028**, such as date and time of manufacture, initial radioactivity level, expiration time, manufacturer, etc. This component may also include identifying data concerning RS device **1002** itself. **FIG. 14B** shows with an arrow **A**, RS device **1002** in transport to a patient treatment facility. At the patient treatment facility, for example, a hospital, RS device **1002** is desirably docked with a fluid delivery system or installation **1030**, as shown in **FIG. 14C**. Fluid delivery system **1030** includes a primary fluid delivery device in the form of a pump device **1032** adapted to be placed in fluid communication with RP container **1004** when RS device **1002** is docked physically with fluid delivery system **1030**. As with fill system **1010**, pump device **1032** may be controlled by a pump control **1034**. Pump control **1034** is interfaced for control purposes with a fluid delivery system control **1036** in a similar manner to the way pump control **1014** is interfaced with fill system control **1016** discussed previously. Fluid delivery system control **1036** generally operates as a master control for pump control **1034** and a fluid delivery system user interface **1038** is used to program and input data to fluid delivery system control **1036** for operation of pump device **1032**.

[00176] As further shown in **FIG. 14C**, other components may be interfaced with fluid delivery system control **1036** including a communications interface **1040** whereby, for example, communications connection may be made to an HIS (Hospital Information System). This allows data about scheduling and the patient to be injected with radiopharmaceutical agent to be brought into the integrated fluid delivery system control **1036** to inform the operator of the procedure and patient conditions or data. The communications connection or

interface **1040** further enables the procedure results and notes to be subsequently communicated to physicians, patient records, and other appropriate systems. As shown separately in **FIG. 14C**, specific data or control inputs may be provided concerning the patient to be injected, including patient data **1042** and the prescribed dosage or patient prescription **1044**, which is provided to fluid delivery system user interface **1038** or, potentially, fluid delivery system control **1036**. Alternatively, patient specific data and prescribed dosage data may be provided via an HIS connection provided by communications interface **1040**. In any of the foregoing alternatives, the fluid delivery system operator has access to patient data and prescribed dosage via fluid delivery system control **1036** and fluid delivery system user interface **1038**.

[00177] **FIG. 14C** further shows that, with RS device **1002** docked with fluid delivery system **1030**, fluid delivery system control **1036** is operatively associated with device and drug data recorder **1028** and dosimeter control **1026** and may interrogate these components for any of the data items identified previously but, at this stage, dosimetry information regarding the radiopharmaceutical within RP container **1004** is likely very important. This designated importance is because the fluid delivery system operator will likely be concerned with confirming the dosimetry of the radiopharmaceutical so that this data may be compared to that inputted from patient data input **1042**, patient prescription input **1044**, or both. Other data may also be of value such as the date and time the RP container **1004** was filled with radiopharmaceutical, its initial radioactivity, initial volume, etc. if, for example, a specific ratioed hot/cold mix was to be injected. Fluid delivery system **1030** furthermore desirably at least includes a secondary fluid delivery system **1046** typically for the delivery of saline following or preceding the injection of radiopharmaceutical to patient **P**. As saline delivery is well-known in the medical field, it is sufficient to note for this disclosure that saline delivery may be automated or controlled via fluid delivery system control **1036**. Additional fluids, pumps, and pump controls may be employed as well to deliver additional fluids that are needed for the various procedures for which the device will be used. **FIG. 15** is a schematic representation of RS device **1002** pursuant to the foregoing and showing how RS device **1002** may dock with fluid delivery system **1030** which includes a schematic representation of a patient fluid path **1047** leading to a patient. It will be apparent that RS device **1002** may also be "filled" using the features of system **200** described previously, wherein RS device **1002** may be filled with a desired radiopharmaceutical dose while "docked" physically in the patient administration module **260** (which may also operate as a

"fill station") of system **200** as described previously. Optionally, an RS device **1002** may be mated with the patient injection module **260** of system **200**.

[00178] **FIG. 16** shows another embodiment of system **1000'** which is similar to that shown in **FIGS. 14A-14C** but with several modifications. In system **1000'**, isotope generator **1006'** and chemistry unit **1008'** are similar in configuration to that described previously. In system **1000'**, however, fill system **1010'** comprises a separate pump device **1012'** that is controlled by pump control **1014'** and is used to directly fill RP container **1004'**. RP container **1004'** is then inserted into separate, stand-alone dosimeter **1024'** which has an associated dosimeter control **1026'**. In system **1000'**, fill station control **1016'** is eliminated or segmented from that disclosed hereinabove in that pump control **1014'** and dosimeter control **1026'** are distinct or separate control devices that respectively operate pump device **1012'** and dosimeter **1026'**. Moreover, fill system user interface **1018** described previously is also eliminated or segmented in favor a two distinct user separate user interfaces **1018a'**, **1018b'** respectively associated with pump control **1014'** and dosimeter control **1026'** for entering data for operation of these devices. Once a dosage reading is taken with dosimeter **1026'**, RP container **1004'** is inserted into shielded housing **1023'** of RS device **1002'** and dosimetry information is communicated to drug data recording device **1028'**. RS device **1002'** may then be transported to fluid delivery system **1030'** as represented by arrow **A'** in **FIG. 16**.

[00179] At fluid delivery system **1030'**, RP container **1004'** is removed from shielded housing **1023'** of RS device **1002'** and inserted into a dosimeter **1024'** similar to that present in fill station **1010'** and now forming part of fluid delivery system **1030'**. A dosimetry reading is taken and this may be compared to the readings stored on drug data recording device **1028'** of RS device **1002'** which is interfaced with dosimeter control **1026'** via dosimeter user interface **1018b'** at fluid delivery system **1030'**. Dosimeter control **1026'** may conduct a dosimetry comparison to ensure that the delivery radiopharmaceutical agent is of proper strength and has the expected radioactive decay level for the time elapsed since RP container **1004'** at fill station **1010'**. Patient data input **1042'** and desirably patient prescription input may also be linked or provided as an input to dosimeter user interface **1018b'** in the manner described previously in connection with system **1000** (i.e., from a hospital information system and the like). RP container **1004'** may then be associated with delivery pump device **1032'** of fluid delivery system **1030'**. In a similar manner to fill station **1010'**, dosimeter **1024'** comprises an associated dosimeter control **1026'** and dedicated user interface **1018b'** and pump device **1032'** comprises an associated pump control **1032'** and

dedicated user interface **1018a'** so that dosimeter **1026'** and pump device **1032'** may be separately controlled in fluid delivery system **1030'**. A secondary fluid delivery system **1046'** may also form part of fluid delivery system **1030'** in the manner described previously, with pump device **1032'** and secondary fluid delivery system **1046'** providing radiopharmaceutical agent and another fluid, typically saline, to patient fluid path **1047'** either sequentially or simultaneously. It will be apparent with respect to both systems **1000**, **1000'** that the disclosed control devices and user interface devices may be provided in close proximity to the device which is operated by the control device and associated user interface or such control devices and associated user interfaces may be remote from the operated devices and linked by wires or wirelessly to the operated devices. Hand-held control devices with associated user interface elements are also within the scope of this disclosure.

[00180] Another embodiment of RS device **1002a** shown schematically associated with a chemistry unit **1008a** and isotope generator **1006a** described herein above is shown in **FIG. 17**. In this embodiment, RP container **1004a** is shown disposed within RS device **1002a** and shielded by shielded container or housing **1023a** in a similar manner to the foregoing. Dosimeter **1024a** is further disposed within in shielded container **1023a**, which forms the shielding transport structure of RS device **1002a** in this embodiment. Dosimeter **1024a** is located in suitable proximity to the body of RP container **1004a**, in this case a syringe **1048** comprising a movable plunger **1050** and disposed in an internal chamber or cavity defined within RS device **1002a**. Syringe **1048** may be filled within RS device **1002a** in the manner described previously, for example, via a pump device associated with chemistry unit **1008** or disposed between chemistry unit **1008** and RS device **1002a** or by movement of plunger **1050** as described herein. As in the foregoing embodiments, it is desirable that dosimeter **1024a** housed in shielded housing **1023a** performs real-time measurement of radiation dose from the syringe **1048** with data displayed, for example, on a user interface associated with the exterior of shielded housing **1023a**, as depicted generally in **FIG. 15** discussed previously. It is possible to use an inexpensive dosimeter, perhaps even a disposable dosimeter, because the energy of gamma rays from a positron-emitting material, such as FDG, is always 511 KeV and inexpensive solid state devices for this purpose may be used for any of the dosimeter devices identified in this disclosure if desired.

[00181] As further shown in **FIG. 17**, RS device **1002a** is configured so that it can optionally mate with a reusable drive mechanism **1052**. Drive mechanism **1052** is generally adapted to engage or interface with syringe plunger **1050** via a piston actuator **1054** to effect movement of syringe plunger **1050** in syringe **1048**, for example, to fill and dispense fluid

into/from syringe **1048**. Syringe plunger **1050** may comprise a rear disc seal **1055** with may be radiation shielded to prevent a rear "shine' of radioactivity from escaping RS device **1002a** and shielded housing **1023a** in particular. For example, the inlet to syringe **1048** may be connected to the output of chemistry unit **1008a** via a control valve **1056**. As described previously, chemistry unit **1008a** is typically provided as part of radiopharmaceutical system **1000**. Control valve **1052**, which may be a remotely controlled valve, may be used to respectively open or close either or both of an inlet port **1058** and an outlet port **1060** in the body of RS device **1002a** to place syringe **1048** in fluid communication with chemistry unit **1008** and, for example, a waste dump **W**. Drive mechanism **1052** is adapted to engage or cooperate with the body of RS device **1002a** and shielded housing **1023a** thereof so that piston actuator **1054** engages or interfaces with syringe plunger **1050** to operate and effect movement of the same. However, as shown, drive mechanism **1052** may generally be considered to be part of RS device **1002** and just a separable component therefrom. Accordingly, drive mechanism **1052** may readily separate from the body of RS device **1002a** so that it may be used on multiple different RS devices **1002a**.

[00182] In operation, when it is desired to fill syringe **1048** with radiopharmaceutical agent, a motor coupled or linked to piston actuator **1054** may be operated to withdraw syringe plunger **1050** in syringe **1048** thereby drawing in fluid through inlet port **1058** leading to control valve **1056**, desirably remotely operated to an open position. When syringe **1048** is filled with a selected dose of agent, control valve **1056** is operated to close the fluid connection with chemistry unit **1008a**. If an incorrect amount of fluid is contained within syringe **1048**, control valve **1056** may be operated so that the inlet to syringe **1048** is in fluid communication with waste dump **W**, typically a shielded waster container well-known in nuclear medicine field, to allow excess radiopharmaceutical agent to be dispensed from syringe **1048** via forward actuation of piston actuator **1054** to eject a selected amount of excess radiopharmaceutical agent into waste dump **W**. Optionally, several RS devices **1002a** may be connected in series so that they can be individually filled with individual doses from the chemistry unit. They can optionally be provided as a preconnected set of sterile units, similar to that of United States Patent No. 5,569,181, incorporated herein by reference, to improve the sterility of the filling. After filling, the units are separated and capped. Once a correct amount of radiopharmaceutical agent is present in syringe **1048**, RS device **1002a** may be transported in total to a patient treatment site. At the patient treatment site, when it is desired to deliver the dose of radiopharmaceutical agent to a patient, outlet port **1060** is intravenously connected with the patient via a suitable sterile path. At this point, drive

mechanism **1052** may be actuated in a controlled manner to cause syringe plunger **1050** to move distally or forward in syringe **1048** and inject the radiopharmaceutical agent into the patient. This is accomplished generally in the manner described previously, wherein the motor driving piston actuator **1054** moves the piston actuator **1054** forward to engage syringe plunger **1050** and move the syringe plunger **1050** distally or forward within syringe **1050**. The interface between piston actuator **1054** may be any convenient interface whereby the piston actuator **1054** engages syringe plunger **1050** to effect movement thereof. An opening **1061** is provided in shielded container **1023a** of RS device **1002a** to allow piston actuator **1054** to physically interface with syringe plunger **1050**. As will be apparent, a sterile path is desirably provided between outlet port **1060** and any external connection with the outside environment (i.e., waste dump **W** or patient). In another variation, it is possible for dosimeter **1024a** to be a part of reusable drive mechanism **1052**. Depending upon the cost of the dosimeter, this may be preferable in some situations.

[00183] More typically, however, RS device **1002a** may be adapted to engage a controlled power injector **1062**, such as the MEDRAD, Inc. Stellant DX Injector, or the injector disclosed in United States Patent Application Publication No. 2004/0254533 (Serial No. 10/326,582), incorporated herein by reference. In this configuration, shown in **FIG. 18**, drive mechanism **1052** is removed from the body of RS device **1002a** and the RS device **1002a** directly associated with, for example mechanically engaged with, power injector **1062**. Power injector **1062** includes a piston actuator **1064** which desirable interfaces with syringe plunger **1050** in a similar to piston actuator **1054** discussed previously. Power injector **1062** desirably includes a cradle structure or support **1066** for supporting RS device **1002a** to the power injector **1062** and, further, may serve as a locking structure for physically locking or docking RS device **1002a** to injector **1062**. A handle or other similar carrying apparatus **1068** may be provided for manipulating and transporting RS device **1002a**. Handle or carrying apparatus **1068** is typically integral with shielded container **1023a** of RS device **1002a** and may be used as part of the structure used to mount and optionally lock RS device **1002a** to power injector **1062**. The use of a controlled power injector may be preferred for the fluid dispensing procedure discussed in connection with **FIG. 17** due to the ability to precisely control the fluid delivery from syringe **1048** as is known to those versed in the use of controlled power injectors for fluid delivery procedures. Once the radiopharmaceutical dose is delivered to patient **P** via actuation of syringe plunger **1050** within syringe **1048** by power injector **1062** or, alternatively by actuation of syringe plunger **1050** by drive mechanism **1052**, the entire RS device **1002a** is desirably returned to a radiopharmacy for processing. As

described herein, prior to returning the used or spent RS device **1002a** to a radiopharmacy, the internal components of RS device **1002a** may be flushed with saline to ensure substantially complete injection of radiopharmaceutical agent into the patient and, further, to ensure maximum removal of radiopharmaceutical agent. Typically, the returned RS device **1002, 1002a** is "shelved" for a calculated period of time to allow any residual or retained radioactive material to decay to a safe level. Disposable components in RS device **1002**, **1002a**, such as RP container **1004** and dosimeter **1024** in RS device **1002** and syringe **1048** in RS device **1002a**, as examples, are removed and disposed of according to regulatory standards. Replacement "disposables" may be loaded into RS devices **1000**, **1002a** making this device suitable for subsequent refilling and reuse. In this way, there is almost no radiation dose exposure to end-use processing personnel.

[00184] Another embodiment of a self-contained RS device **1002b**, which eliminates the need for an internal dose calibrator in shielded container **1023b**, is shown in **FIG. 19**. This embodiment of RS device **1002b** is adapted for association with power injector **1062** discussed previously. A removable, shielded end cap **1070** is provided in place of drive mechanism **1052** discussed previously which is removed to allow piston actuator **1064** associated with injector **1062** to engage syringe plunger **1050b** of syringe **1048b** in the manner described previously. A concentric hole or opening **1061b** in the body of RS device **1002b** and, more particularly, in shielded housing **1023b**, coaxial with syringe plunger **1050b** allows engagement of piston actuator **1064** with syringe plunger **1050b**. The motorized drive mechanism **1052** discussed previously or even a manually-driven piston to push syringe plunger **1050b** may also be utilized if desired. The embodiment of RS device **1002b** shown in **FIG. 19** also eliminates the need for an internal dosimeter as in RS devices **1002**, **1002a** discussed previously. In this embodiment, an in-line, "clip on" dosimeter **1024b** is used to calibrate radiation dose and is coupled directly to a patient tube **1072** leading to a patient **P**. Dosimeter **1024b** desirably provides radiation dose in real time as fluid flows to patient **P**. In accordance with the embodiment of **FIG. 19**, an instantaneous radiation dose to the patient **P** can preferably be measured and integrated over the duration of an injection, which continues until the prescribed radiation dose has been delivered to the patient **P**. The clip-on dosimeter **1024b** is typically in continuous communication with the control system of injector **1062** or to another control computer. As further shown in **FIG. 19**, saline **1074** may be associated with patient tube **1072** via a delivery pump **1076**, such as a peristaltic pump or syringe pump, and a control valve **1078** to permit flushing of patient tube **1072** once the radiation dose is injected into patient **P**. If the dosimeter **1024b** is in the position shown in **FIG. 19**, it sees

alternatively radioactive drug and saline. Alternatively, the dosimeter **1024b** may be positioned between the RS device **1002b** and control valve **1078**. In this case, it only sees the radioactive drug unless the pump is reversed at some point a saline is pulled into syringe **1048**.

[00185] **FIGS. 20-21** disclose an arrangement wherein radioactive pharmaceutical agent may be moved between two syringes **1048c(L)** and **1048c(R)** within, for example, a single RS device **1002c** or between two RS devices **1002c** in appropriate fluid communication as illustrated. For example, radiopharmaceutical agent may be transferred from a first, transport syringe **1048c(L)** within first RS device **1002c(L)** into a separate, single dose RP syringe **1048c(R)** located in second RS device **1002c(R)**. Syringes **1048c(L)** is desirably larger than syringe **1048c(R)** to accommodate multiple doses of radiopharmaceutical while syringe **1048c(R)** may be single dose syringe as indicated. Syringes **1048c(L)**, **1048c(R)** are shown of similar size in **FIG. 20** only for expedience in explaining features of the invention. The dose increase in one syringe **1048c(R)** and the concomitant decrease in the other syringe **1048c(L)** can both be measured via on-board dosimeters **1024c(R)**, **1024c(L)** to confirm that the system is leak free and fully functional and that the material is what was expected. Respective drive mechanisms **1052c** associated each RS device **1002c**, or a power injector as in **FIG. 18**, may be used to provide the motive forces needed to transfer fluid. Once filled with a single dose of radiopharmaceutical agent, the single dose syringe **1048c(R)** may be placed in connection with patient **P** and actuated to inject the radiopharmaceutical agent in the manner described previously and this is desirably followed by a saline flush.

[00186] Radioactive fluid is moved as described in the foregoing from a "larger" syringe **1048c(L)**, as an example, to a single dose measurement container, syringe **1048c(R)**, generally for safety purposes. For example, a volume expected to be half of a desired dose of radiopharmaceutical agent is moved from "left" syringe **1048c(L)** to "right" syringe **1048c(R)**. This dose increase on the right and decrease on the left is measured, as indicated previously, to confirm that the system is leak free and fully functional and that the radioactive material concentration is what is expected. Then the remainder of the dose is delivered from the left to the right syringes **1048c(L)**, **1048c(R)** and a second dosimetry measurement is confirmed. Finally, left syringe **1048c(L)** is isolated and disconnected from the fluid path. The radiopharmaceutical agent is then delivered from right syringe **1048c(R)** followed by a saline flush via saline source **1074c** and delivery pump **1076c**, again such as a peristaltic pump or syringe pump. Alternatively, the saline flush can be pulled directly into syringe **1048c(R)** and then delivered therefrom. This procedure provides multiple checks on the

radiation dose measurement and ensures that the whole volume in a multi-patient system can never be delivered to patient **P** by a single failure. In this embodiment, it is important to account for the radioactive fluid in the volume of the tubing forming inlet and outlet lines or ports **1058c**, **1060c** and control valves **1056c** between the two syringes **1048c(L)**, **1048c(R)**. This volume is desirably minimized. Ideally, the control valves **1056c** could be made in one plastic piece with almost no volume, utilizes pinch valves, or could be merged into one four input control valve since there is no need to directly connect left syringe **1048c(L)** to the line leading to patient **P**. The valving shown in **FIG. 21** is shown with the connection between the left and the right syringes **1048c(L)**, **1048c(R)** for dose extraction and confirmation. Rotating the inner member 90° counterclockwise connects right syringe **1048c(R)** to patient **P** for delivery. Rotating the inner member an additional 90° counterclockwise connects saline flush **1074c**, **1076c** to patient **P** for flushing of the fluid path to patient **P** including the valving and internal ports associated with the RS devices **1002c**.

[00187] **FIG. 22A** shows a no dead space valve arrangement **1080** associated with RS device **1002d** according to another embodiment. It is generally preferable that valves be operated automatically in relation to fluid delivery systems as discussed in United States Patent No. 5,840,026 to Uber, III. et al., the disclosure of which was incorporated herein by reference previously. In **FIG. 22A**, valve arrangement **1080** is shown in a position to fill or dispense syringe **1048d** from port **A**. In the case of fluid delivery, when the delivery is completed, valve arrangement **1080** is rotated approximately 120° so that the fluid path now connects port **B** to port **A**. Saline is pumped in port **B** to drive radioactive fluid from port **A** and into patient **P**. The fluid paths from ports **A** and **B** are designed so that they are tortuous, with at least no direct line of site from the outlet to the volumes where radioactive fluid is stored. Alternatively, at least two and preferably three normally closed pinch valves could replace the valve arrangement **1080** shown in **FIG. 22A**. The pinch valves could be spring biased into the off direction and could be activated via electromechanical devices or by mechanical, hydraulic, compressed air, or other forces from outside the shielding housing **1023d**. Shield housing **1023d** may be designed to open in a clam-shell mode so that tubing can be replaced after use and either flushing or a wait of sufficient time to make it safe for an operator to make such a replacement.

[00188] **FIG. 22B** shows a functionally similar arrangement as in **FIG. 22A**, with actuated syringe **1048d** being replaced by a passive syringe **1048d'** (one in which the plunger moves because of pressure changes inside the syringe barrel or body) and two peristaltic pumps $P_{A'}$ and $P_{B'}$ replacing the specific valve arrangement **1080d** and actuating mechanism for syringe

1050d described hereinabove in connection with **FIG. 22A**. A benefit of this alternative arrangement is the elimination of the need for a sliding shielding element (**1055d**) to shield radiation that would otherwise come out through opening **1061d** through which syringe plunger **1050d** may be engaged as shown in **FIG. 22A**. Also, peristaltic pumps are simpler in some aspects than syringe pumps. Connection to a source of motive power can be simply by means of a splined shaft. This is simpler than normal syringe attachment strategies. However peristaltic pumps are generally less accurate in an absolute sense than syringe pumps because their flow is a function of the internal diameter of extruded tubing, which is generally not that tightly controllable. However, in this situation, because the activity is being measured before or during delivery, delivery accuracy is generally in terms of activity and not volume. Another advantage of the embodiment of **FIG. 22B** is that the "bottom" half of claim-shell shielding housing **1023d**, **1023d'** can serve as a tray, so that if there is any liquid spilled it will be contained and not leak out. The foregoing disclosure and illustration of peristaltic pumps in **FIG. 22B** is not intended to exclude other suitable types of pumps for the intended application.

[00189] As mentioned elsewhere herein with respect to prior art methods of dose calibration, to measure the dose of a radiopharmaceutical with a normal dose calibrator, such as the CRC-15R sold by Capintec, Inc of Ramsey, NJ, the dose of radiopharmaceutical fluid in a container is removed from shielding and lowered into the center of a hollow, generally cylindrically shaped ion chamber. This geometry is used because its sensitivity or calibration is relatively insensitive to the shape and exact positioning of the radiopharmaceutical container. In a number of embodiments described in this disclosure, a dosimeter or radiation detector is explicitly included behind shielding, for example, in **FIG. 3**, or inside a shielding pig for a radiopharmaceutical, for example in **FIGS. 14A-14C** and **FIGS. 17-18** and **19-22,** so that the operator is not required to remove the radiopharmaceutical from shielding and thus be exposed to radiation. This can optionally be incorporated into various other embodiments of this invention as well. If the radiation detector is a hollow, generally cylindrical ion chamber, for example, device **1024d** in **FIGS. 22A-22B**, that surrounds a syringe, vial, or other container, then the radiation measurement will be relatively independent of the position of the radiopharmaceutical fluid in the container. Such an ion chamber may be conventional in the nuclear art as from United States Patent No. 4,804,847 incorporated herein by reference.

[00190] In general, a simplified radiation detector, for example, a tubular ion chamber or a linear solid state detector, lying along one side of a fluid volume, the current measured

increases supralinearly compared to the fluid volume in the container for a constant radiation dose density (Ci/ml). This result is because at higher volumes more liquid is near more of the ion chamber. In the example embodiments of this disclosure, because internal geometry is known and controlled it is possible to correct for this deviation through calculation and or measurements. This considerably simplifies and reduces dosimetry costs and helps make it feasible to have a dosimeter that is transported with a transport "pig" device such as RS device **1002**.

[00191] If the radiation detector is a single small area/volume detector, then its response is highly geometry dependent, and the calibration or conversion factor (mCi per current or voltage) is only applicable for that specific geometry. Referring briefly to **FIGS. 38** and **39A-39C**, these figures show application of basic principles for calculated sensitivity for a small volume dosimeter comprising three detector positions **D1**, **D2**, **D3**, all shown in **FIG. 38**. In this exemplary embodiment, all three detectors **D1**, **D2**, **D3** are 8mm radially from a center axis **L** of container **C** which has a length of 30mm. The first detector **D1** is 3mm down from a top end of container **C**. The second detector **D2** is in the middle, 15mm from the top end, and the third detector **D3** is 3mm up from the bottom end of container **C**. **FIG. 39A** shows the relative detector response (y-axis) for a 1mm thick volume of radiopharmaceutical at various positions (x-axis) from the top end of container **C**. The geometric variance of the sensitivity is apparent. In the situation where container **C** is a syringe, with a luer tip connector at the top end, "position 0" in this example, **FIG. 39B** shows the detector response as the syringe is filled with increasing volumes of a radiopharmaceutical of constant activity density (mCi/ml). The x-axis in **FIG. 39B** represents the cumulative fill in milliliters. For clarity of explanation, the effect of the luer connector, neck, and any plunger shape are excluded, and the detectors and syringe diameter are chosen to be small, for example a 0.5ml or a 1ml standard syringe. It can be seen that the response of the first detector **D1** tends to saturate and become very non-linear. The behavior of the other two detectors **D2**, **D3** is also shown. Thus, if only a single detector was used, in addition to the dosimeter measurement, information about the volume and position of fluid in container **C** needs to be known and factored into the calculation to determine the total radiation dosage because of the geometric sensitivity of the detector varies so significantly with fill volume. If the responses of detectors **D1**, **D2**, **D3** are simply added, they effectively become a single long detector and a relatively linear total response is achieved as shown in **FIG. 39C**. However, just adding the responses wastes some information that could be used to ensure safe operation.

[00192] In an optional embodiment wherein dosimeters **D1**, **D2**, **D3** are present in RS device **1002** of **FIGS. 14A-14C** and comprise dosimeter **1024**, the outputs of two or more dosimeters **D1**, **D2**, **D3** are individually measured and communicated to the dosimeter control unit **1026** using the features of RS Device **1002** of **FIGS. 14A-14C**. The dosimeter control unit **1026** can take the two or more dosimeter readings, compare them in some manner, for example, by computing the ratios of each pair of dosimeter readings, and optionally compare the ratios with the measurement of the fill volume available from pump controls **1014**, **1034** (or from power injector **1062** in the alternative embodiment of RS device **1002a** in **FIG. 18**) to ensure that there are no anomalies, errors, or problems. Two detectors and syringe piston position data provide enough information to determine if there is any error or bubbles present of nonradioactive or radioactive gas coming out of solution or such. Three detectors and syringe piston position data provide enough information to detect any error or bubbles and estimate the source of the discrepancy. The foregoing application may also be extended to integrated systems **100**, **100b** described in connection with **FIGS. 2A-2B**. Problems that can be detected in this way are bubbles in the radiopharmaceutical fluid, spills, or leaks outside the radiopharmaceutical container **1004**, or an error in any of the dosimeters **D1**, **D2**, **D3** or the fill volume measurement. If three or more dosimeters **D1**, **D2**, **D3** are present, this can be done without fill volume information, or a check of the fill volume information can be performed as well. This ability to confirm the lack of these and other problems through the use of a multiplicity of independent dosimeter measurements, optionally in cooperation with fill volume information, is important because typical radiation shielding is generally opaque, thick, and heavy, and direct observation of a radiopharmaceutical container exposes the operator to radiation. Thus, the foregoing problems, particularly small fluid leaks or air bubbles, cannot be easily known from operator observation since human senses do no respond to low doses of ionizing radiation.

[00193] In another embodiment utilizing RS device **1002e** shown in **FIG. 23**, a standard ionization chamber **1081** (dose calibrator) holds coiled tubing **1082** which may contain a measured volume of radioactive fluid delivered from unit dose syringe **1048e**. Syringe **1048d** containing, for example, FDG is held in RS device **1002e** and this radioactive fluid is pushed from syringe **1048e** via, for example, manual means or controlled power injector **1062** described previously. Saline may be pulled from a bulk container **1084** into a saline syringe **1086** and then injected into coiled tubing **1082** to flush fluid path of any residual radioactive fluid. The tubing forming the fluid path to patient **P** may be shielded **S** to reduce radiation

exposure to attending personnel. Two control valves **1087a**, **1087b**, desirably automated valves, may be used to control fluid flow in the fluid path **F** connecting to patient **P**.

[00194] In another alternative arrangement shown in **FIG. 24**, multi-dose containers **1088**, vials, for example, may be delivered in a shielded transport container or pig **1090** with a specialized access port **1092** at its top end **1094**. Access port **1092** allows an elongated needle or pipette **1096** to be guided and inserted down into a rubber septum **1098** sealing radiopharmaceutical container **1088** which reduces radiation exposure to the operator. Radiopharmaceutical agent may be withdrawn into a small syringe **1100** through, for example, a check valve **1102**. Syringe **1100** may be contained in a shielded housing **1104** as illustrated. When the syringe plunger of syringe **1100** is depressed, mechanical check valve **1102** directs flow of radiopharmaceutical agent into patient **P** through fluid path F_f which may be shielded in whole or in part along its length. A clip-on dosimeter **1106a** may be associated with fluid path F_f as described previously in this disclosure, or any of the other dosimeter arrangements described previously may be utilized. As further shown in **FIG. 24**, a second dosimeter **1106b** may be disposed within transport pig **1090**. Saline flushing may be accomplished using bulk saline container **1084f** saline syringe **1086f** in the manner described previously in connection with **FIG. 23**, for example, via a control valve **1087f**. Another embodiment has a dosimeter in operable association with vial container **1088**, and it is the dose that is removed from this vial container **1088** that is sensed to measure the dose that will be delivered to patient **P**. This system has also has the benefit that the full dose in the vial container **1088** can never be delivered to a patient **P**.

[00195] Another system for delivery a radiopharmaceutical agent to a patient **P** is shown in **FIG. 25**. This system is a closed loop system **1110** that continuously circulates radiopharmaceutical agent via a fluid pumping system or device so that agent may be delivered on demand at a desired volume. An analogous water piping arrangement to closed loop system **1110** is found in a hotel or other large facility hot water system. In these applications, a user will turn on the hot water tap and find hot water immediately instead of having to wait until the water warms the pipes. This saves time and minimizes waste. This type of closed loop pumping system can be adapted for use in delivering critical radiopharmaceuticals that require constant monitoring for strength or radiation activity or solutions that require constant movement to ensure proper mixing. This is especially true for radiopharmaceuticals that have a constantly changing radiation activity level and a short half-life, such as FDG.

[00196] Within closed loop system **1110**, a pump **1112** continuously circulates the pharmaceutical, such as radiopharmaceutical agent in the form of FDG fluid, through a dose calibrator **1114**. A fluid path **1116** connects pump **1112**, dose calibrator **1114** and, further, a transport "pig" container **1118** wherein a vial container and the like containing the source of radiopharmaceutical agent is located. In the case of FDG, as an example, this radiopharmaceutical has a short half-life of 110 minutes. Thus, it is valuable to know the radiation activity level of this agent prior to delivery, such that patients receive a proper strength for a useful diagnosis. By constantly circulating this agent through dose calibrator **1114** or other radiation detector, radiation level is continuously monitored and available which provides a known value to a system controller (not shown). This is accomplished because the volume of fluid in operable association with the dose calibrator **1114** is known and, therefore, the total radiation activity may be determined at any time. This "real time" information is the basis for delivering a correct dose to patient **P**. It is also beneficial because it does not require a secondary testing operation, which wastes time, increase procedure costs, and potentially exposes the operator to unnecessary radiation. Furthermore, patient **P** may have follow-up procedures which require the exact radiation activity level as previous procedures to ensure radiopharmaceutical uptake is the same and provide a relative disease state over time.

[00197] Closed loop system **1110** may be used to supply injection fluid to a controlled power syringe injector **I**, such as a MEDRAD, Inc. Stellant DX Injector, or the injector disclosed in United States Patent Application Publication No. 2004/0254533 previously incorporated by reference. Prior to initiating an injection the injector operator will program the injector **I**. One of the input parameters may be the radiation activity level provided by dose calibrator **1114** and, since the injector "knows" the radiation activity level, it can determine the proper injection parameters by using an internally installed algorithm or the operator can program the injection parameters by completing the calculations manually. When the operator initiates an injection, a control valve **V** diverts the fluid to patient **P** instead of the continuous circulation loop. Bulk saline **1120** may also be provided as shown to initiate flushing of control valve **V** and the portion of fluid path **1116** extending to patient **P** from control valve **V**.

[00198] Several advantages are provided by the foregoing closed loop system **1110**. For example, by providing an atmospheric vent and filter (not shown) at the point where transport pig **1118** attaches to the fluid path **1116**, it will vent any capture air in the continuous circulation loop. This venting would be accomplished automatically as fluid travels through

the fluid path **1116**. This is an inexpensive, convenient, and easy method to prevent vascular air injection to patient **P**. Additionally, connectors at transport pig **1118** provide a convenient method for changing the container housed in transport pig **1118** thereby replenishing the injection volume without having to remove other system components and reinstalling new ones. This is an advantage when the number of scheduled patients exceeds the volume of the container(s) in transport pig **1118**. Generally, multiple patients would not be exposed to cross contamination because prevention devices at the patient interface with fluid path **1116**, such as check valves and swabable valve connectors, are used. There is yet another advantage of closed loop system **1110** when using multiple transport pig containers **1118** in system **1110**. When a transport pig **1118** is changed, the remaining fluid in system **1110** does not need to be evacuated because it will soon reach equilibrium both in radiation activity and temperature as it circulates. The pump **1112** is simply stopped, transport pig **1118** is exchanged, and pump **1112** is restarted to mix the fluid. Minimizing the capacity of system **1110** through small diameter tubing in fluid path **1116** and a small chamber pump for pump **1112** can further enhance this benefit.

[00199] **FIG. 26** shows a system **1200** for metering a calibrated fluid dose of FDG **1202**, as an example (or other substance), to a patient **P**, hereinafter termed an FDG "slug" counting injector system **1200**. Injector system **1200** is useful in that it overcomes well-known inaccuracies in conventional syringes due primarily to manufacturing variations in internal diameter and to "dead space" within the syringe. The disclosed arrangement provides a means to accurately control the amount of fluid and, therefore, the radiation dose by dividing the fluid into small, discrete "slugs" **1204** of FDG of precisely uniform volume which can be collected and recombined into a total dose for injection into a patient.

[00200] In injector system **1200**, a micro-dosing syringe or multiple such syringes **1206** withdraws an FDG fluid volume less than one ml from a large container, such a large diameter syringe **1208**, and then delivers it into a length of intermediate tubing **1210**. After the fixed amount of FDG slug **1204** is injected into tubing **1210**, a slug **1212** of intermediate air or another gas or potentially a viscous liquid is injected into tubing **1210**, followed by another fixed amount of FDG slug **1204**. Air slugs **1212** could also be replaced by a physical or mechanical spacing element, such as a plastic bead or rod, which prevents successive FDG slugs **1204** from mixing. As the alternating FDG slugs **1204** and air slugs **1212** (or equivalent spacing or separator elements) are introduced into tubing **1210**, they are counted by an optical slug counter **1214**. Alternating FDG slugs **1204** could be placed in a dose calibrator or an inexpensive dosimeter which could give a reading of radioactivity level per

fixed FDG slug **1204**. Optical slug counter **1214** would then count the number of fixed FDG slugs **1204** that pass by until reaching the desired total radioactive dose. A clip-on, in-line dosimeter such as dosimeter **1106a** discussed previously in connection with **FIG. 24** could be used as the dose calibrator in this embodiment.

[00201] Once the FDG slugs **1204** and air slugs **1212** (or equivalent separator elements) drop into a vertically-positioned syringe **1206**, they would tend to naturally separate therein, for example, with air rising to the top and liquid FDG **1202** located below. This air would be expelled out of syringes **1206** either manually or through an air separator, such as a membrane filter from Celegard®, LLC., a division of Polypore®. Physical or mechanical separator elements would either float above the liquid FDG **1202** or sink below the liquid FDG **1202** depending on their relative density. Physical or mechanical separator elements would then be extracted mechanically. The fixed dose in the dose calibrator would decay naturally over time, and the activity level per fixed FDG slug **1204** would decrease accordingly. This would require more fixed FDG slugs **1204** to be delivered at the end of the day for a desired activity level, (for example, 15 fixed FDG slugs = 15 milliCuries at 9:00 am and 30 fixed FDG slugs = 15 milliCuries at 11:00 am). Alternatively, one fixed slug could be directed into the dose calibrator or directed past a dosimeter followed by a longer air column to obtain an initial radiation dose reading. Then the alternating FDG slugs **1204** and air slugs **1212** (or equivalent separator elements) could be sent down tubing **1210** and counted by optical slug counter **1214**.

[00202] As described elsewhere herein, system **200** of **FIGS. 3-4** generates, prepares, and delivers radiopharmaceuticals to a patient for an imaging study or therapeutic treatment. In the total or integrated systems **100**, **100a** of **FIGS. 2A-2B**, it is preferable that the radiopharmaceuticals be brought near the patient for the delivery such as through the use of a "mobile" system **200**. However, there are some instances where it is too difficult to take portable or mobile system **200** to the patient or bring the patient to system **200**. One example of such a situation is an in-patient PET or nuclear medicine study where it is advantageous to give the patient an FDG injection in their hospital room so that the patient can continue to be monitored and treated by using normal ward equipment and nursing staff rather than wait in a waiting area or on their bed in the hall near the imaging area where providing appropriate care is more difficult. The patient is only brought from his or her room to the imager after the appropriate time for dose uptake (step **60** described previously) is imaged relatively quickly after arrival, and is expeditiously returned to his or her room for continued care and treatment.

[00203] A second situation is for use with a portable gamma camera. While the modular and transportable nature of system **200**, typically supported on wheels for portability, assists in its transport this structure may not be easy to move due to the weight of shielding needed to appropriately protect attending medical personnel and the operator. In some situations, it may be more convenient and more efficient to keep this unit in operation in association with its normal imager or integrated system **100** and just take the individual dose to a patient, for example, with a portable gamma camera. One example of a small, portable, hand held gamma camera is the eZ-Scope manufactured by eV Products of Saxonburg, PA.

[00204] A third situation benefiting from the separate creation and delivery of individual doses of radiopharmaceutical agent is during a transition period where the hospital or health care facility may have one or more components of the total or integrated systems of **FIGS. 2A-2B**, one or more components in system **200** of **FIGS. 3-4**, or one or more of the multi-fluid and multidirectional systems of **FIG. 7**, and have some non-integrated, often preexisting, equipment as well. Some embodiments are flexible enough to produce radiopharmaceuticals to be used and delivered remotely as well as to a patient in close proximity to other embodiments described in the foregoing. For use in these situations, this disclosure further includes physically separate embodiments of systems, devices, and methods to facilitate accurate and safe delivery of the radiopharmaceuticals to the patient.

[00205] Embodiments to facilitate remote delivery of a dose of radiopharmaceutical agent to a patient or multiple doses to multiple patients were described previously in connection with **FIGS. 14-25**. The foregoing discussion relating to **FIGS. 14-16** in particular enables transfer of information as well as the radiopharmaceutical into a fluid delivery system with minimal handling of a radiopharmaceutical by the operator and thus minimal radiation dose to the operator. The remote delivery can still have significant aspects of integration, although it does not need to include physical proximity aspects. For example, the smart transport device or RS device **1002** described previously can, preferably wirelessly in real time (or through a wired communications port) or when docked with a fluid delivery system **1030** or even mobile system **200**, communicate information about the patient, dose, and time at which the dose is administered to a central controller such as the integrated system controller **110** in total or integrated system **100** described previously, optionally via a hospital information system (HIS) or other network.

[00206] If a treatment facility such as a hospital prefers a less sophisticated solution, system **200** shown in **FIGS. 3-4** can deliver a dose to a normal vial or syringe in a typical shielding configuration, for example, a cylindrical syringe shield with a lead glass window.

This shielded syringe can then be put into a lead lined syringe carrier, such as available from Pinestar Technology Inc., Greenville PA (Model 001-182). A similar shielded syringe carrier is available from Lemer Pax of Carquefou - Nantes in France (Model Ref. SC3).

[00207] With the foregoing in mind, this disclosure turns to improvements to radiation shields which may be used in to shield an operator of a syringe when the syringe is used for the simplest delivery known in the nuclear medicine field, namely, a hand-held manual delivery. A typical syringe shield **810** is shown schematically shown in **FIG. 27**. As an example, syringe shield **810** may be constructed of 0.06 inch (1.5 mm) thick tungsten that will reduce radiation exposure from Tc-99m by 94%. Alternatively, syringe shield **810** may be made of 6mm thick tungsten for use in PET emitters. Syringe shield **810** is intended to hold a sterile plastic disposable syringe **800**. Syringe **800** has a plastic body or barrel **801** with a syringe plunger **802** disposed inside syringe barrel **801** and movable within syringe barrel **801** to pressurize a fluid in the syringe barrel **801** for filling or delivery. Syringe plunger **802** is moved via a piston or piston rod **803** which commonly has a syringe piston button **804** for finger or thumb actuation, or hand applied force. A penetrating needle **805** is provided at a distal end of syringe barrel **801**. Syringe shield **810** comprises a cylinder body **811** which may be made of lead or tungsten with a lead glass window **812** for viewing the position of syringe plunger **802** in syringe barrel **801** and volume markings on the side of syringe barrel **801** so that the operator can manually control and confirm the injection of the proper amount of radiopharmaceutical. The window **812** is commonly used when manually filling the syringe **800**.

[00208] **FIG. 28** shows an improved syringe shield **810a** with a combination of different features. For example, a cuff or front shield **813** is available on syringe shields from Pinestar and may be incorporated into syringe shield **810a**. Syringe shield **810a** may also include a locking mechanisms **814** which can be a thumb screw, a spring loaded lever, or other mechanisms that can hold syringe body or barrel **801** (shown in **FIG. 27**) in shield cylinder body **811**. The benefit of locking syringe **800** into syringe shield **810a** is that the syringe shield **810a** can then be use to turn the syringe barrel **801** to make a connection to a luer fitting as an alternative to a needle for fluid delivery purposes. By grasping syringe shield **810a**, the operator receives less radiation dose than if they had to hold an unshielded syringe **800**. A shielded button or disk **815** may be placed on syringe piston button **804**. Such buttons are available, for example, from Lemer Pax.

[00209] In a modification of the foregoing syringe shields **810**, **810a**, as illustrated in **FIG. 29**, these syringe shields **810**, **810a** are combined with a support rod **816** so that shield button

or disk **815b** may be associated with shield cylinder body **811**. Support rod **816** moves in a grove or through a sliding bearing **818**. It is preferable that there be sufficient friction to help hold support rod **816** in place, as can be created with a rubber pad or spring. A locking mechanism (not shown) could be added in association with the support rod **816** so that once the syringe piston rod **803** is positioned, it cannot be moved either intentionally or inadvertently until the lock is released. By using support rod **816,** the various parts of the syringe shield **810b** are kept together and the lock or friction mechanism makes it less likely that there will be accidental movement of syringe piston rod **803**. There can be one or more flat edges on cuff or front shield **813** to reduce the chance that the syringe in the holder will roll off a flat surface. A single flat edge **820** is shown as an example.

[00210] A further embodiment of syringe shield **810c** is shown in **FIG. 30**, wherein support rod **816c** is knurled or ribbed, and a thumb wheel **822** is provided so that the operator can move the shield button or disk **815c** in or out by rotating the thumb wheel **822**. This configuration enables one handed operation to fill or deliver from syringe **800**. Thumb wheel rack and pinion arrangements can be found on plastic pipetting devices, such as the Glasfirn Safety Pi-Pump 2500, made by Glasfirn of 35396 Giessen-Wieseck, Germany.

[00211] Another embodiment of a syringe shield system **850** is shown schematically in **FIGS. 31-32**. This syringe shield system **850**, in operation, opens like a clamshell to allow a syringe **800** (shown in **FIG. 27**) to be put placed therein. This opening arrangement can be of tremendous benefit when placing syringes into or removing them from dose calibrators, as the syringe shield itself can act as a pair of shielded tongs to enable the operator to deposit and pick up a syringe from the carrier that is usually used to lower the syringe into the dose calibrator thereby providing significant shielding for their hands.

[00212] The components and operation of syringe shield system **850** will now be explained. There are four primary parts to syringe shield system **850**. Barrel shield portion **851, 852** shield the barrel **801** of syringe **800** (shown in **FIG. 27**). There are wings or handles **851h**, **852h** that are rigidly associated with barrel shield portions **851**, **852**. These wings or handles **851h**, **852h** can be the same material, for example, lead, tungsten, or lead loaded acrylic, as barrel shield portions **851**, **852** or can be a different material and be bonded or otherwise rigidly associated with the barrel shield portions **851**, **852**. Lead loaded acrylic has the benefit of the operator being able to see through this material as it is positioned to draw a dose or be placed in the dose calibrator syringe holder. The bottom cuff is also made in two cuff parts **853**, **854**. Cuff **853** is positionally associated with barrel shield portion **851** and cuff **854** is positionally associated with barrel shield portion **852**. A pin **855** serves as a

hinge pin to enable barrel shields **851**, **852** to separate when the user squeezes on wings or handles **851h**, **852h**. There is also an optional spring **856** that provides a force to close the barrel shield portions **851**, **852** when the operator releases wings or handles **851h**, **852h**. A central opening **859** is defined between barrel shield portions **851**, **852** which accommodates syringe **800**.

[00213] A modification to the clamshell syringe shield system **850a** described above is shown in **FIGS. 33-34**. By making syringe shield system **850a** from with two asymmetrical pieces **851a**, **852a**, it is possible for this device to hold and shield a variety of syringe diameters. These two asymmetrical pieces **851a**, **852a** are biased in a normally closed mode by a wire spring arrangement **860** similar to that of a wooden clothes pin operating around a central cylindrical member **862**. Central cylindrical member **862** provides additional shielding for the radiation path between the two mating ends of asymmetrical pieces **851a**, **852a**. Bottom cuffs (**853, 854**), similar to those of the previous embodiment, can be included but are not shown in this embodiment. In typical syringe barrels such as syringes barrels **801** shown in **FIG. 27**, between one and ten milliliters are commonly used and, if they are of approximately the same length, the diameter ratio that needs to be accommodated is approximately 3.1 to 1. However, if as is discussed elsewhere in this disclosure, the shielded syringe is placed in an electronic servo-controlled feedback injector or pump, small volumes can be accurately delivered from a large diameter syringe; volumes on the order of 1% or better are achievable. In this case, one size syringe **800** (as shown in **FIG. 27**), for example, 10ml can be used for all fluid deliveries, therefore, the range of syringe sizes can be greatly reduced. The manually operated syringe shield system embodiments just described can be incorporated into all the embodiments of this disclosure and can optionally incorporate additional features as well. Among the possible additional features are those related to RS device **1002**, for example, electronic dosimetry, wireless communications, and data identification devices such as a bar code or label and electronically readable storage devices such as RFID. In addition, with a rack and pinion drive or other drive mechanism, they can be matted with a motorized drive system as shown, for example, in **FIG. 37** discussed herein.

[00214] For the situations described in this disclosure wherein an injection dose is delivered to a patient at a site remote from its preparation, it may be necessary to overfill the syringe because the delay between filling and delivery may not be accurately known or controllable. In this case, it is useful to have a system that can adjust the dose in a syringe and like container without the need for a hot lab. If there is a dosimeter associated with the syringe shield, then all that is needed is a shielded waste container and the extra dose can be

put into it. If there is not a dosimeter associated with the syringe shield, then a dose adjust device or system may be used. **FIGS. 35-37** show several embodiments of such a device. **FIG. 35A** is a schematic representation of a dose adjuster **750**, while **FIGS. 35B-35C** show exterior views of an exemplary implementation of dose adjuster **750** which may be utilized in practice. The components of dose adjuster **750** are a dosimeter including radiation sensor **751**, control electronics **760**, a user interface **761**, shielding **752**, a removable shielded waste container **754** which is separable and exchangeable at interface **753** and, optionally, a motor (not shown) to move the syringe piston rod **803** in radiopharmaceutical syringe **800**. Because the dose adjuster **750** only needs to accommodate syringes up to a modest size, for example, 10ml it need not be as big as normal laboratory dose calibrators. This means that for a given thickness of shielding, the weight is reduced in proportion to the square of the diameter reduction. In addition, an array of silicon diode dosimeters (as described previously) could be used as radiation sensor **751** and the dose calibrator can be made even smaller. In use, syringe **800** is inserted into the dose adjuster **750**, either by manually removing it from its shield, or by having a telescoping shield as illustrated in **FIG. 36C**. The liquid is expelled a little bit at a time through opening **755** into waste container **754**. To prevent spills there can be a rubber septum that is pierced by the syringe needle (not shown) or, preferably, there is an absorbent material in waste container **754** that traps the small amounts of liquid that will be injected. Because shielding is not absolute or 100%, radiation from the waste will be sensed to a modest degree by radiation sensor **751**. This occurs continually, so before putting syringe **800** into the dose adjuster **750**, control electronics **760** takes a measurement that represents only the dose from the nearby waste. This measurement is subtracted or tarred from the measurement of the dose in the syringe **800**. The control electronics **760** may communicate the new adjusted dose to any of the many places mentioned elsewhere in this disclosure, for example, to an RFID or other device associated with syringe **800** or its syringe shield (not shown), to a hospital information system (HIS), to total or integrated systems **100**, **100a** described previously, etc. This communication may be done wirelessly or with wires, in real time or at some appropriate time. Labels can optionally be printed for various uses.

[00215] **FIG. 35B** shows waste container **754** being able to be removed from the front of dose adjuster **750**. The syringe piston rod **803** of syringe **800** is not accessible by hand so this embodiment utilizes a motor to grip and drive the syringe piston rod **803**. **FIG. 35C** uses a telescoping syringe shield **712**. This enables syringe **800** to be installed on dose adjuster **750** with syringe piston rod **803** extended so that the operator can express small volumes into the waste container **754** until the desired dose remains in syringe **800**. Dose adjuster **750** may be

operated as a standalone device for use in the current practice of nuclear medicine or it may be integrated into any of the various systems described herein. Once the syringe dose is adjusted to the right amount, it is ready for injection into a patient. The syringe **800** in a syringe shield **810** may be inserted directly into a fluid delivery system **700** comprising a syringe pump or, desirably, a power injector **710** as shown in **FIG. 36A**. In addition to radiopharmaceutical syringe **800**, power injector **710** has a saline syringe **712** to flush the radiopharmaceutical from patient fluid line **713**. Power injector **710** can control flow rate, volume, and pressure over time to deliver the optimum dose to the patient depending upon the study being performed. Various exemplary studies are discussed elsewhere in this disclosure and will not be repeated here. **FIG. 36B** shows a portable version of power injector **710** more akin to a syringe pump. All components associated with portable syringe pump **710** are similar to those shown in **FIG. 36A**. While syringe shield **810** is typically sufficient to shield the operator of fluid delivery system **700** from the radiopharmaceutical in syringe **800**, fluid delivery in fluid delivery system **700** is generally very quick enough that the radiation dose from the radiopharmaceutical, while it is in the tubing comprising patient fluid **713**, is relatively modest. Once the radiopharmaceutical is injected into the patient, the patient now becomes a significant source of radiation for the healthcare workers around him or her. For this reason, vertical shields on wheels are sometimes employed so that the health care worker can be near the patient but be protected from radiation emanating from the patient.

[00216] In **FIG. 36A**, power injector **710** is mounted onto a wheeled shield stand **701** that incorporates a lead glass viewing port or window **702**. Motors and control electronics are optionally contained in the body of power injector **710** which is supported on a mount **703** on the patient side of wheeled shield stand **701**. Batteries can also be contained in the body of power injector **710** if desired. Syringe **800** is contained in syringe shield **810** and this assembled unit mounted to power injector **710** while a second syringe **712** forms a source of flush saline as indicated previously. Outputs from radiopharmaceutical syringe **800** and saline syringe **712** are desirably connected together and for association or fluid connection with patient fluid path **713**. An operator user interface panel **715** is desirably provided on the operator side of wheeled shield stand **701** held by bracket **704** and connected to control electronics of power injector **710** via communications channel **714** or, optionally, via wireless communications. This arrangement along with an accompanying patient shield (not shown) is particularly advantageous when the fluid is being delivered over a length of time and the operator needs to stay near the patient or check on them at regular intervals. An operator can

walk up to the operator's side of wheeled shield stand **701**, check the injection status, and talk with the patient with a significantly reduced radiation dose to the operator. It is preferable that the fluid delivery system **700** , and optionally all the various fluid manipulating devices and systems within this disclosure, also contain battery power for the fluid moving components and associated electronics so that fluid delivery system **700** can operate without an external power source.

[00217] As shown in **FIG. 37**, another benefit of, particularly, syringe shield **810c**, discussed previously that incorporates a connection to syringe piston button **804** via shield button or disk **815c**, is that this syringe shield **810c** can easily mate with and be operated by a manual or an automatic injector or pump **870** with minimal radiation dose to the operator. A simple such embodiment is achieved by placing syringe **800** held in syringe shield **810c**, for example, onto a motorized injector **870** by means of a mount **871** which is part of housing **879**. Automatic injector or pump **870** has a drive mechanism **873**, for example, a motor with gear reduction and a gear output that mates to thumb wheel **822** and a position sensor **872** that interacts with connecting rod **816c** to sense the position of syringe piston rod **803**. Drive mechanism **873** is controlled by an electronic control circuit or computer **878** that uses feedback from position sensor **872** and inputs **877** from a user interface or other system components to move the syringe piston rod **803** at the desired flow rate for the desired time. There can be a number of automatic pumps **870** that are at different places in the handling sequence of the radiopharmaceutical. The automatic pumps **870** can be battery-powered and small enough to be carried and held by hand, and can be used to replace manual filling, dose adjustment, and fluid delivery. As mentioned elsewhere, if computer-controlled electromechanical servo-pumps are used to deliver the radiopharmaceutical or radiopharmaceuticals because of their accuracy and control of motion, it is possible for almost all procedures on human patients to be accommodated by a 10ml syringe. This standardization can lead to standardization among other equipment such as dose calibrators, syringe shields, syringe pumps, and much of the other equipment used in cardiac stress test procedures and similar nuclear-related procedures. This version of syringe shield **810c** and a suitable mating injector apparatus **870** as shown in **FIG. 37** are also applicable for use as patient administration module **160** of **FIGS. 3-4**.

[00218] Because transmission of radioactivity through shielding is an exponential function of the thickness of the shielding, the thickness of any shielding in any particular design is a function of the time the operator or others will spend in proximity to the device, the strength of the source, the type and energy of the radiation, and the effect of the weight of the

shielding. The making of these tradeoffs is well-known to those skilled in the health physics and nuclear medicine fields. Thus, the shielding thicknesses of these embodiments are either not specifically constrained, or if they are given, can be appropriately adjusted for the specific needs of the application and are discussed for example only.

[00219] The term "pump" as used in the disclosure is intended to include all means of causing a controlled fluid flow, including controlled pumps or pressure sources and regulators, for example, peristaltic pumps, gear pumps, syringe pumps, electrokinetic pumps, gravity, compressed gas, controlled gas evolving devices, spring pumps, centripetal pumps or any system which does not require continuing human exertion of motive force when the fluid is flowing, although hand activated pumps are equally suitable in many of the foregoing embodiments.

[00220] The specific radiopharmaceuticals or drugs mentioned in this disclosure or other pharmaceuticals as desired can be included in or associated with ultrasound bubbles. The systems described in the foregoing are available to deliver such bubbles to the region of interest and then ultrasound energy can be used to destroy the bubbles and promote the delivery of the associated radiopharmaceutical, drug, or other pharmaceutical to the intended tissue. The uses of ultrasound bubbles to deliver and release a drug or pharmaceutical to a region of interest is disclosed in United States Patent No. 6,397,098, assigned to the assignee of this disclosure, the disclosure of which is incorporated herein by reference.

[00221] Another aspect described hereinafter relates to systems and methods and associated components or devices for more accurately determining a radiopharmaceutical dose administered to a patient by relying on a time factor. Broadly contemplated herein is the administration of a dose on the basis of an elapsed time from when a dose was last accurately measured, for example, at the time of filling into a container to when it is injected into a patient. The foregoing concept is discussed in connection with RS device **1002** discussed previously in connection with system **1000**. In system **1000**, RS device **1002** is initially associated with fill station **1010** as a bulk radiopharmaceutical filing station and configured to hold RP container **1004** to be filled from chemistry unit **1008**. RP container **1004** is pre-located in RS device as described previously. As noted previously, device and drug data recorder **1028** has an identification arrangement ("ID") for uniquely identifying RS device **1002** and the contents of RP container **1004** and, desirably, RP container **1004** itself. Device and drug data recorder **1028** further records radiation dose information via dosimeter **1024** and dosimeter control **1026** so that this information is available to fill system control **1016** and displayable on fill system user interface **1018**. Accordingly, RS device **1002** has the

ability to read, ascertain, or measure the radiation dose (radioactivity level) present in RP container **1004**. Furthermore, device and drug data recorder **1028** desirably includes a clock ("clock 1") which establishes a time-point at which the RP container **1004** is filled with radiopharmaceutical. Accordingly, when RP container **1004** is filled at fill system **1010**, a radiation dose is recorded along with the time-point of filling. This information is then available when the RS device **1002** is transported to fluid delivery system **1030**. This version of radiopharmaceutical system **1000** and RS device **1002** therein are also applicable for use as or in patient administration module **160** of **FIGS. 3-4**.

[00222] Once transported to the fluid delivery system **1030**, the dose in the RP container **1004** may be calculated based on the time-point of filing associated with RP container **1004** and the known half-life of its contents. This calculation may be done by fluid delivery system control **1036** and may take into account the time at which the contents of RP container **1004** are to be administered to a patient. Thus, a calculation is made which takes into account two distinct time-points, the time of filling and the time at which it is desired to ascertain the radiation dose again, such as when it is to be administered to a patient and the known half-life of the radiopharmaceutical, so as to clearly establish the degree to which the radiopharmaceutical may have decayed and thus lost potency.

[00223] In another embodiment, the radiopharmaceutical dose is measured at a time of filling one or more "dose" containers, similar to RP container **1004** discussed previously. At such a time, both the time-point and radiation dose are recorded and associated with ID information on the dose container. An associated transport device or station, for example, a cart or transport container (i.e., pig), has a clock that is synchronized with a clock associated with the filling station clock so it will present a similar time base as the filling station. More particularly, the radiopharmaceutical dose is preferably measured at a single time of filling one or more dose containers. At such a time, both the time-point and radiation dose are recorded and associated with ID information on a dose container. The transport container, cart, or other transport conveyance has a clock which is synchronized with a clock associated with the filling station clock so it will present a similar time base as the filling station.

[00224] As per convention, a bulk radiopharmaceutical filing station is configured to hold a single or multiple dose containers to be filled from a bulk supply. The dose container is then placed in a shielded transport container (i.e., pig), cart, or other conveyance for transport to a patient dose administration system. Desirably, the dose container has an ID arrangement, such as a barcode or RFID, that can easily be read by suitable apparatus such as a reader **r1** at the filling station, and the filling station has another data collection arrangement **r2** for

reading, ascertaining, or measuring the radiation dose (radioactivity level) present in the dose container. Furthermore, the filling station also preferably includes a clock ("clock 1") which establishes a time-point at which the dose container is filled with radiopharmaceutical.

[00225] When the dose container is filled at the filling station, the radiation dose is recorded along with the time-point of filling. The transport container will include a clock ("clock 2") which is synchronized with clock 1. Upon being loaded into the transport container, another reader (**r3**) may read the ID information of the transport container or this may be read by a reader present at a patient dose administration system. The ID information is also preferably read immediately before radiopharmaceutical is administered to a patient.

[00226] A suitable communication link is provided between the filling station and transport container, for instance, via wireless communication between antennae at the filling station and transport container ("ant. 1" and "ant. 2", respectively). This communication link permits data to be exchanged in a manner to readily ascertain the radiation dose administered to a patient. As such, this embodiment serves to obviate the need to directly measure a dose of radiopharmaceutical administered to a patient when it is being administered to the patient. Once at a patient dose administration system, the dose in the dose container is automatically and reliably calculated without human intervention and thus possibly without error based on the time associated with the dose container and the known half-life of its contents. Thus, a calculation is made which takes into account two distinct time-points, the time of filling and the time at which it is desired to ascertain the radiation dose again, such as when it is to be administered to a patient, and the known half-life of the radiopharmaceutical so as to clearly establish the degree to which the radiopharmaceutical may have decayed and thus lost potency. The filling station and transport container clocks, clocks 1 and 2, can reference a wireless time standard such as those based at the United States Time Service of the United States Naval Observatory or the National Institute of Science and Technology (NIST). If the system is to be employed outside of the United States, similar time standards (such as governmental time standards) in other countries can also be employed. Or, a single clock, for example, a digital quartz watch, may be associated with and transported with RP container **1004** to obviate the need for synchronization of multiple clocks.

[00227] At times, it may be desirable to add a non-radioactive diluent to the dose container such that the total volume in the dose container comprises the volume of the radiopharmaceutical plus that of the added diluent. If this is the case, the radioactivity of the contents of the dose container can be measured after it has been diluted. The ID information on the dose container further provides information on the type of radionuclide that comprises

the radiopharmaceutical. Ultimately, the half-life of the radiopharmaceutical can be obtained by a look-up table in order to help calculate the radioactive decay between the two time-points mentioned previously. Alternatively, such information on the radiopharmaceutical can be entered by an operator at any suitable time.

[00228] A data repository may also be provided for recording all pertinent data. The repository could be an additional component remote from the filling station or transport container, or could be integral to the filling station or transport container. Again, the recorded information can include the time the dose container is filled, the level of radioactivity contained in the dose container immediately after the dose container is filled, the name of the radionuclide of the radiopharmaceutical or its decay half-life, and the identification information of that portable dose container recorded from the ID arrangement of the dose container. To the extent that a data repository is remote with respect to either the filling station or transport container or both, a suitable communication link (such as the wireless radio frequency link discussed hereinabove or an alternative arrangement such as an optical/infrared or wired communications link) could be employed to exchange data with the data repository. All such data exchanged can be encrypted to secure the data against unauthorized reading, and the repository itself can be secured against deliberate or unintended alteration.

[00229] The data repository can optionally be expanded is scope through various data communications devices and systems to include all data related to or generated from the medical procedures assisted by the devices and systems or using the methods of this disclosure. This can include retrieving, utilizing and storing information about, for example, the patient, patient scheduling, dosing, timing, and results of the study. It can optionally involve successively larger scopes of communication, including that among many centers for benchmarking or procedure improvement, as disclosed United States Patent Application Publication No. 2003/0212707 entitled "System and Method for Automated Benchmarking for the Recognition of Best Medical Practices and Products and for Establishing Standards for Medical Procedures", incorporated herein by reference.

[00230] GPS (Global Positioning System) receivers and transponders (either cell phone, satellite, or other means) can be incorporated in various components of this disclosure. For example, incorporating them into RS device **1002** described previously could allow tracking of the doses and possible rerouting while in transit. It could also better enable JIT (Just in Time) inventory management practices. Even within a patient treatment facility, knowing where a dose is and when it will arrive can improve patient throughput and equipment

utilization. Providing a GPS device to a patient could allow the hospital to track the patient, and if it is a cell phone with limited capability, to even call the patient and tell them that they need to report for their procedure. Alternatively, a device similar to the RF paging systems, an example of which is described in United States Patent No. 6,542,751 incorporated herein by reference, is used in busy restaurants and can be further provided with GPS systems to track the patients and then issue an "alarm" to indicate when the patient should return to the desk for further instructions.

[00231] The sophistication, integration, and flexibility of the devices, systems, and methods of this disclosure enable a flexibility and sophistication of procedures that is impossible or very difficult without the use of the various embodiments described hereinabove. An exemplary improvement mentioned in this disclosure includes the controlled dosing with "hot" and "cold" pharmaceuticals.

[00232] If a specific time course of radiopharmaceutical concentration in the blood or in a tissue is desired, and initial flow profile can be determined using the models of H. Schwilden disclosed in "A General Method for calculating the Dosage Scheme in Linear Pharmacokinetics" published in the European Journal of Clinical Pharmacology, (1981) 20:379-386, and incorporated herein by reference. With the fluid handling system **150** integrated with the imager **130**, data concerning uptake in an area of measurement or an area of interest can be used to adjust or optimize the injection during the injection, if the injection duration is long enough for this to be effective. Details of this process are discussed in United States Patent No. 5,840,026, incorporated herein by reference. It is also possible, as discussed in United States Patent No. 5,840,026 to use an appropriate detector (radiation detector in this case) on some other part of the body, such as an ear lobe or a finger to sense the approximate arrival time and level over time of the radiopharmaceutical. Time course measurements of concentration in a tissue can be used, for example, for functional imaging or for physiological monitoring of a specific region of interest. The level at one area or region of the patient can be used to trigger the beginning of the scanning of the region of interest. Or, alternatively, the scanning can be triggered or synchronized to another measurement of the patient monitor, for example, ECG, respiration, EEG, or a sensation being perceived by the patient. Additionally, fluid handling system **150** may contain a pharmaceutical and its antagonist drug so that if, because of the physiological delays, too much of the first drug is injected, patient monitor **160** can detect the overreaction and inject some of the antagonist to cancel some of the effect.

[00233] Because of the increased use of nuclear medicine, it is optionally preferable that integrated system **100** measure the radioactivity of the patient before the injection, to make sure that there is no effect from a previous study that might confound the current measurements. This could be done with the imager **130** or with a separate hand held radiation detector. For short lived isotopes, this is not a problem. This strategy could also be employed, preferably using a hand-held radiation detector or camera to assess concentration of the isotope in the liver and the bladder and thus readiness for scanning with main imager **130**.

[00234] While numerous embodiments have been disclosed with certain features, this is primarily for clarity of explanation and understanding of these features and the example synergy and benefits achieved by the specific integrations discussed. It will be recognized by those skilled in the art that other combinations or integrations are possible, and even desirable, but cannot all be described herein. For example, blood sampling discussed in relation to the concepts of **FIG. 7** can be included in the total or integrated system of **FIG. 2A**. The disclosed in-line dosimeters or other activity measurement devices may be used to assess the activity in such a sample. Likewise, a system can be envisioned that does not require every feature for it to be useful for specific applications. For example, the integrated system of **FIG. 2A** would be very useful for many medical procedures without a way to provide a stimulus to the patient. While the devices, systems, and methods of this disclosure have been described in relation to medical procedures on humans and on animals, they can be used on all biological systems. Accordingly, the foregoing description is intended to be illustrative rather than restrictive. The inventions described hereinabove are defined by the appended claims and all changes to the invention that fall within the meaning and the range of equivalency of the claims are to be embraced within their scope.

THE INVENTION CLAIMED IS:

1. An integrated radiopharmaceutical patient treatment system, comprising:

a portable radioisotope generation module configured to generate a gaseous radioisotope;

a radiopharmaceutical processing module configured to dissolve the gaseous radioisotope in an injectable medical fluid, wherein the radiopharmaceutical processing module is in fluid communication with the radioisotope generation module;

a fluid injection system in fluid communication with the radiopharmaceutical processing module and configured to inject a dose comprising the gaseous radioisotope and the injectable medical fluid into a patient; and

at least two imaging devices configured to independently detect biological and physiological characteristics of the patient based on the dose.

2. The system as claimed in claim 1, wherein the injectable medical fluid is an injectable fluid imaging agent.

3. The system as claimed in claim 2, wherein the injectable medical fluid is an injectable contrast agent.

4. The system as claimed in claim 3, wherein the contrast agent is selected from the group consisting of Dotarem, Gadavist, Magnevist, Omniscan, OptiMARK, and Prohance.

5, The system as claimed in claim 1, wherein the gaseous radioisotope includes a radioisotope selected from the group consisting of N-13, Xe-133, Kr-81m, C-11, and O-15.

6. The system as claimed in claim 1, wherein the radioisotope generation module comprises a laser wakefield generator.

7. The system as claimed in claim 1, wherein the patient treatment system is mobile.

8. The system as claimed in claim 1, wherein the at least two imaging devices comprise a Positron Emission Tomography (PET) imager and a Magnetic Resonance (MR) imager.

9. The system as claimed in claim 1, further comprising an integrated control system operatively connected to the fluid injection system and the at least two imaging devices,

wherein the integrated control system provides automatic sequencing and timing of delivery of the dose of the gaseous radioisotope and the injectable medical fluid to the patient and the detection of the biological and physiological characteristics of the patient performed by the at least two imaging devices.

10. The system as claimed in claim 9, wherein the integrated control system is also operatively connected to the radioisotope generation module to activate the generation of the gaseous radioisotope, and the radiopharmaceutical processing module to activate the dissolution of the gaseous radioisotope in the injectable medical fluid.

11. The system as claimed in claim 9, wherein the integrated control system comprises a graphic user interface configured to display relevant data obtained by the at least two imaging devices and to receive control data and parameters to operate the patient treatment system.

12. The system as claimed in claim 9, wherein the integrated control system is in communication with a remote information system to receive at least one of the following: patient information, expected patient injection times, and patient injection volumes.

13. The system as claimed in claim 1, further comprising a radiation protection module configured to contain and shield the radioisotope generation module.

14. The system as claimed in claim 1, wherein the fluid injection system further comprises a flushing liquid source configured to flush the fluid injection system after the gaseous radioisotope and injectable medical fluid have been administered to the patient.

15. The system as claimed in claim 1, further comprising a motion compensation module in communication with the at least two imaging devices, wherein the motion compensation module is configured to compensate for blurring of an image captured by the at least two imaging devices.

16. An integrated radiopharmaceutical patient treatment system, comprising:

a gaseous radiopharmaceutical imaging agent source;

a liquid imaging agent source;

a gaseous radiopharmaceutical imaging agent delivery system in fluid communication with the gaseous radiopharmaceutical imaging agent source and configured to inject a dose of the gaseous radiopharmaceutical imaging agent into a patient;

a liquid imaging agent delivery system in fluid communication with the liquid imaging agent source and configured to inject a dose of the liquid imaging agent into the patient; and

at least two imaging devices configured to independently detect biological and physiological characteristics of the patient based on the doses injected into the patient.

17. The system as claimed in claim 16, further comprising a gaseous radiopharmaceutical imaging agent dissolution system configured to dissolve the gaseous radiopharmaceutical imaging agent in the liquid imaging agent, wherein the gaseous radiopharmaceutical imaging agent dissolution system is in fluid communication with the gaseous radiopharmaceutical imaging agent source and the liquid imaging agent delivery system.

18. The system as claimed in claim 16, further comprising a motion compensation module in communication with the at least two imaging devices, wherein the motion compensation module is configured to compensate for blurring of an image captured by the at least two imaging devices.

19. The system as claimed in claim 16, wherein the gaseous radiopharmaceutical imaging agent source comprises a laser wakefield generator.

20. The system as claimed in claim 16, wherein the at least two imaging devices comprise a Positron Emission Tomography (PET) imager and a Magnetic Resonance (MR) imager.

21. The system as claimed in claim 16, further comprising an integrated control system operatively connected to the gaseous radiopharmaceutical imaging agent delivery system, the liquid imaging agent delivery system, and the at least two imaging devices,

wherein the integrated control system provides automatic sequencing and timing of delivery of the doses of the gaseous radiopharmaceutical imaging agent and the liquid imaging agent to the patient and the detection of the biological and physiological characteristics of the patient performed by the at least two imaging devices.

22. The system as claimed in claim 21, wherein the integrated control system is also operatively connected to the gaseous radiopharmaceutical imaging agent source to activate generation of the gaseous radiopharmaceutical imaging agent and the liquid imaging agent source to activate delivery of the liquid imaging agent.

23. A method of obtaining an image using a combined imaging system, comprising the steps of:

a) generating a gaseous radioisotope;

b) dissolving the gaseous radioisotope in an injectable medical fluid;

c) injecting a dose of the gaseous radioisotope and the injectable medical fluid into a patient; and

d) capturing an image of a patient using at least two imaging devices to independently detect biological and physiological characteristics of the patient based on the dose.

24. The method of obtaining an image using a combined imaging system as claimed in claim 23, further comprising compensating for blurring in the image captured by the at least two imaging devices.

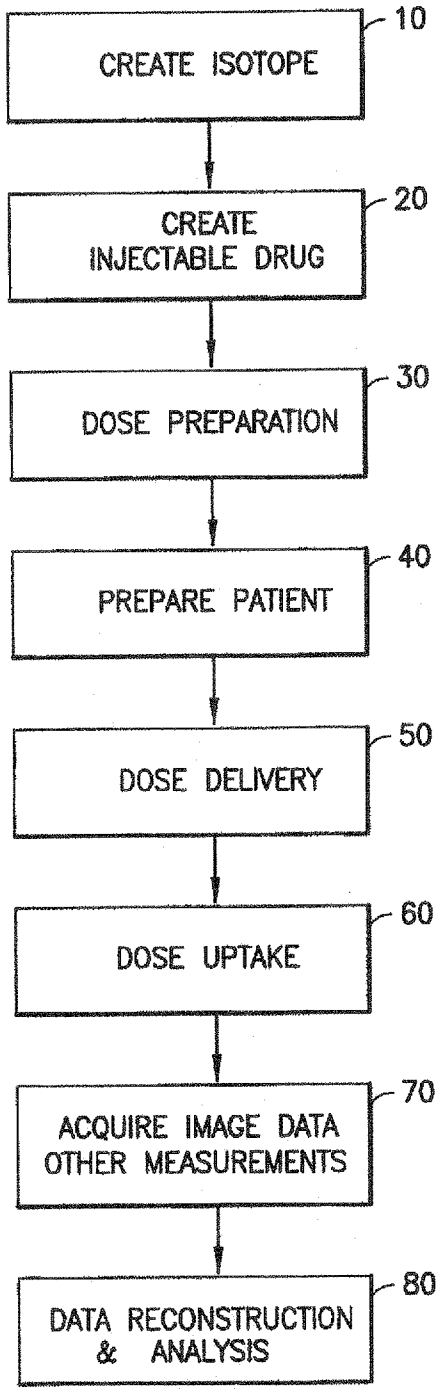

CREATE ISOTOPE
10
CREATE INJECTABLE DRUG
20
DOSE PREPARATION
30
PREPARE PATIENT
40
DOSE DELIVERY
50
DOSE UPTAKE
60
ACQUIRE IMAGE DATA OTHER MEASUREMENTS
70
DATA RECONSTRUCTION & ANALYSIS
80

FIG.1

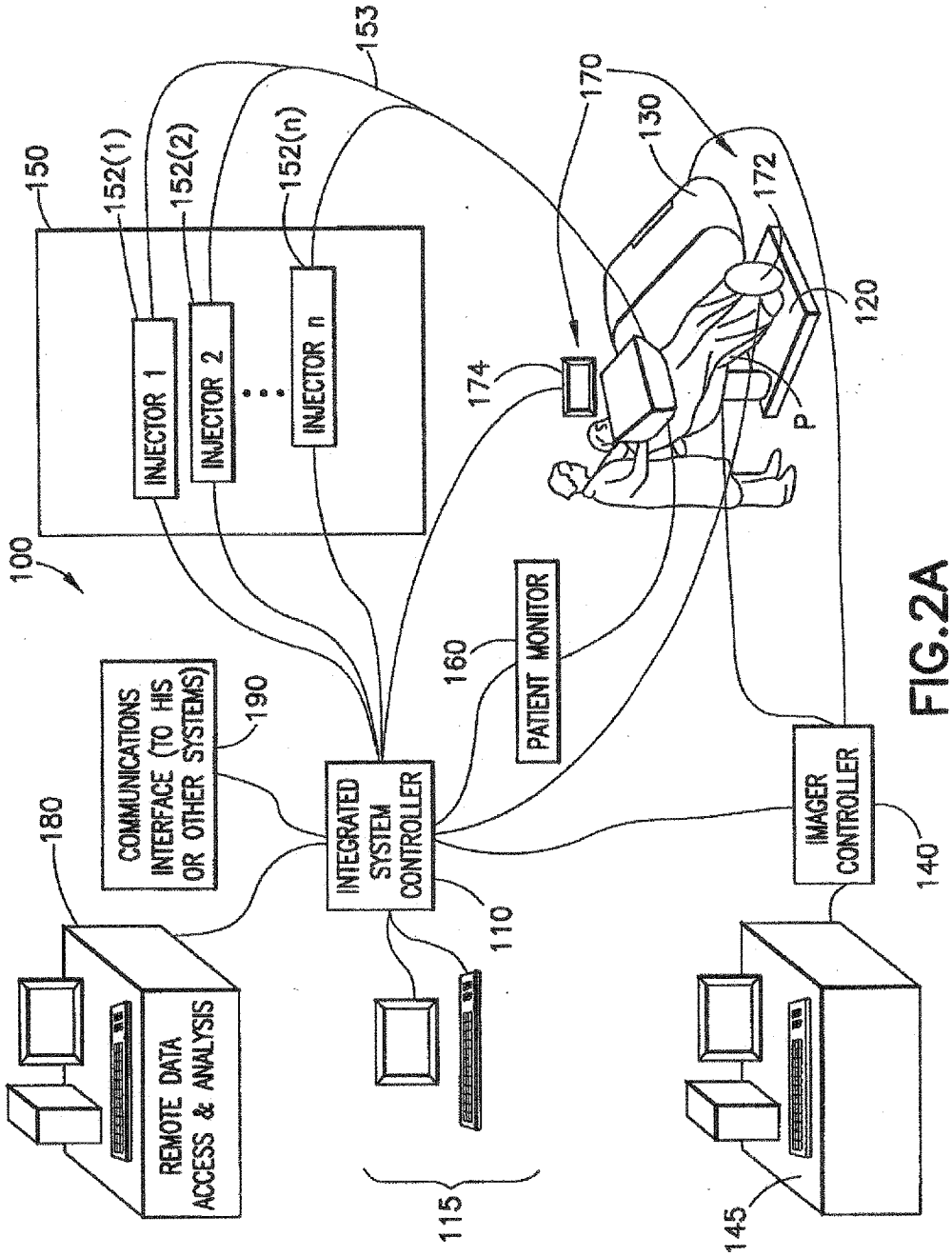

150
152(1)
152(2)
152(n)
153
170
130
172
120
174
P
INJECTOR 1
INJECTOR 2
INJECTOR n
100
160
PATIENT MONITOR
190
COMMUNICATIONS INTERFACE (TO HIS OR OTHER SYSTEMS)
180
INTEGRATED SYSTEM CONTROLLER
110
IMAGER CONTROLLER
140
REMOTE DATA ACCESS & ANALYSIS
115
145

FIG.2A

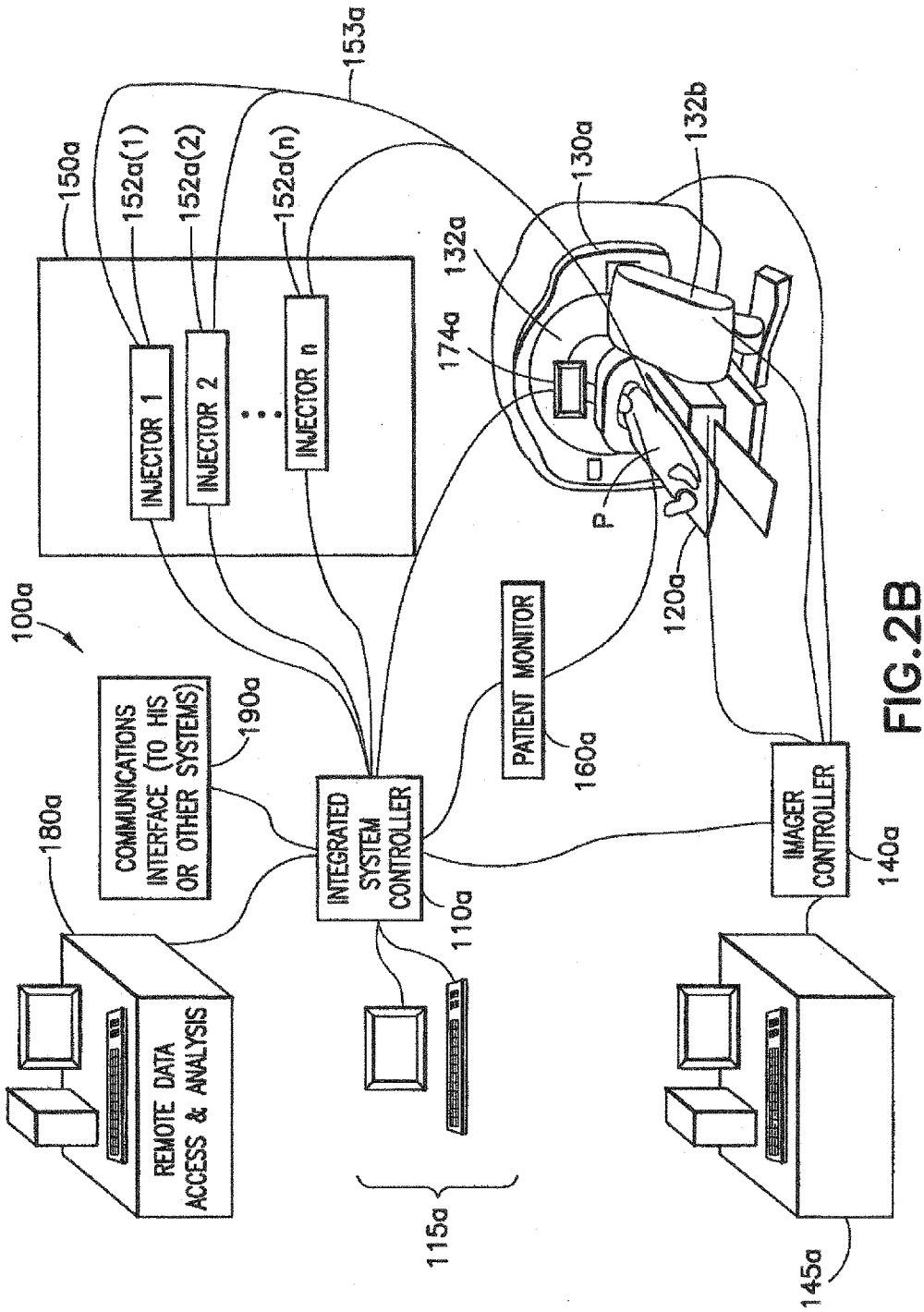

100a
150a
153a
152a(1)
152a(2)
152a(n)
INJECTOR 1
INJECTOR 2
INJECTOR n
130a
132a
132b
174a
P
120a
PATIENT MONITOR
160a
COMMUNICATIONS INTERFACE (TO HIS OR OTHER SYSTEMS)
190a
180a
INTEGRATED SYSTEM CONTROLLER
110a
IMAGER CONTROLLER
140a
REMOTE DATA ACCESS & ANALYSIS
115a
145a

FIG.2B

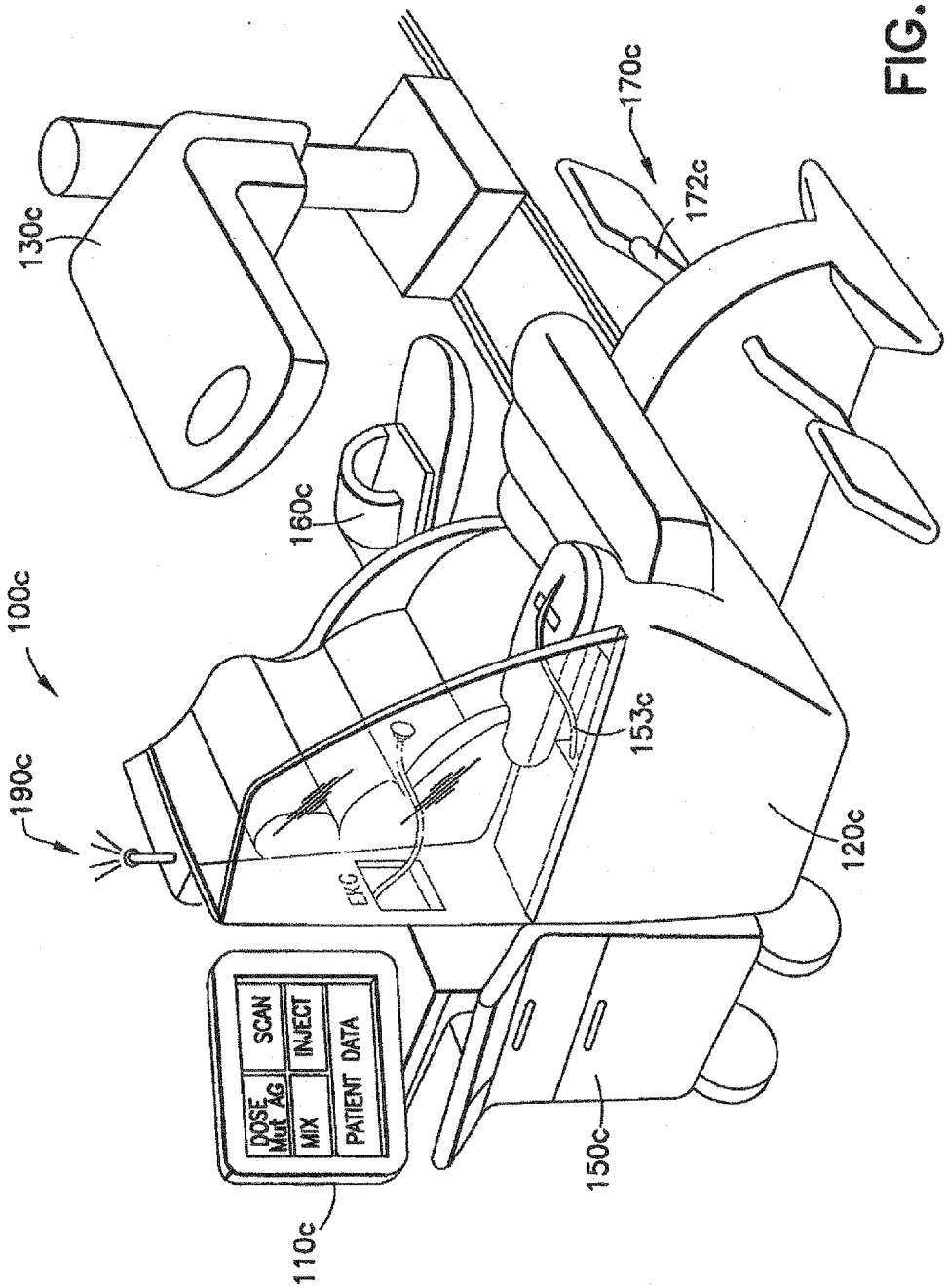

130c
170c
172c
160c
100c
153c
190c
120c
ECG
SCAN
INJECT
DOSE Mult Ag
MIX
PATIENT DATA
110c
150c

FIG.2C

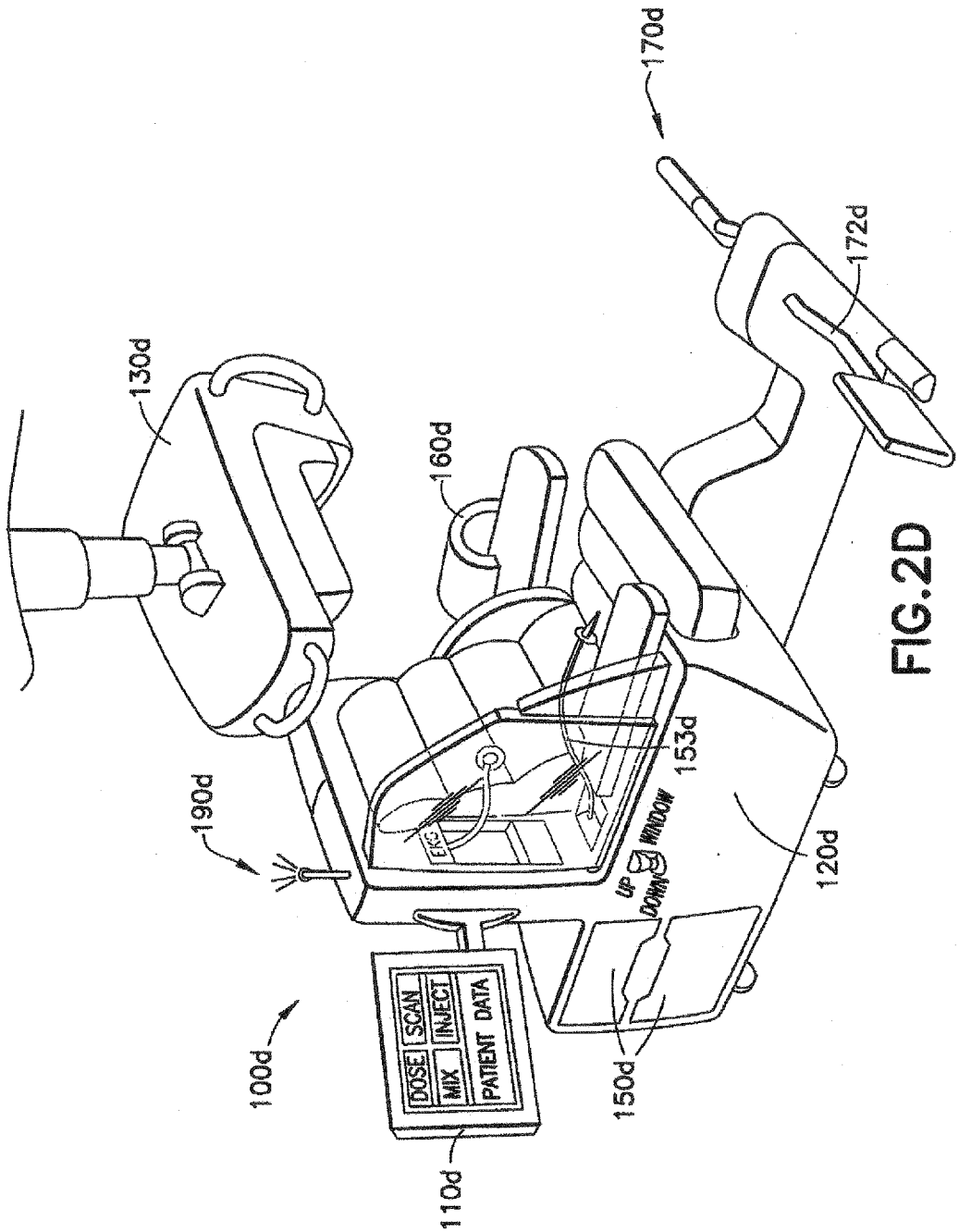

170d
172d
130d
160d
153d
190d
120d
100d
150d
110d
DOSE
SCAN
MIX
INJECT
PATIENT DATA
UP
DOWN
WINDOW

FIG.2D

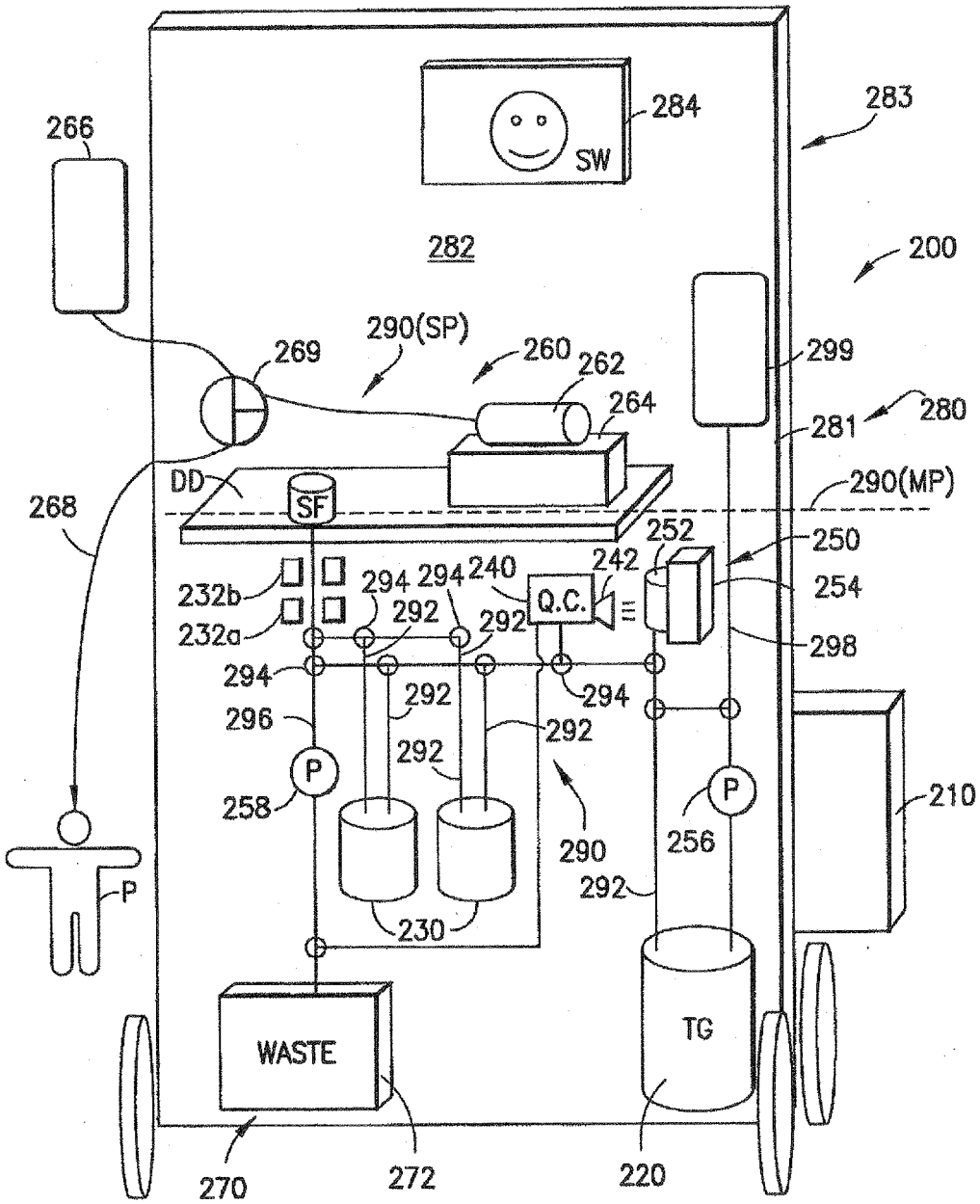

266
284
SW
283
282
200
290(SP)
269
260
262
264
299
281
280
290(MP)
268
DD
SF
252
250
254
232b
232a
294
292
240
242
Q.C.
298
296
258
P
230
290
256
210
WASTE
TG
270
272
220

FIG.3

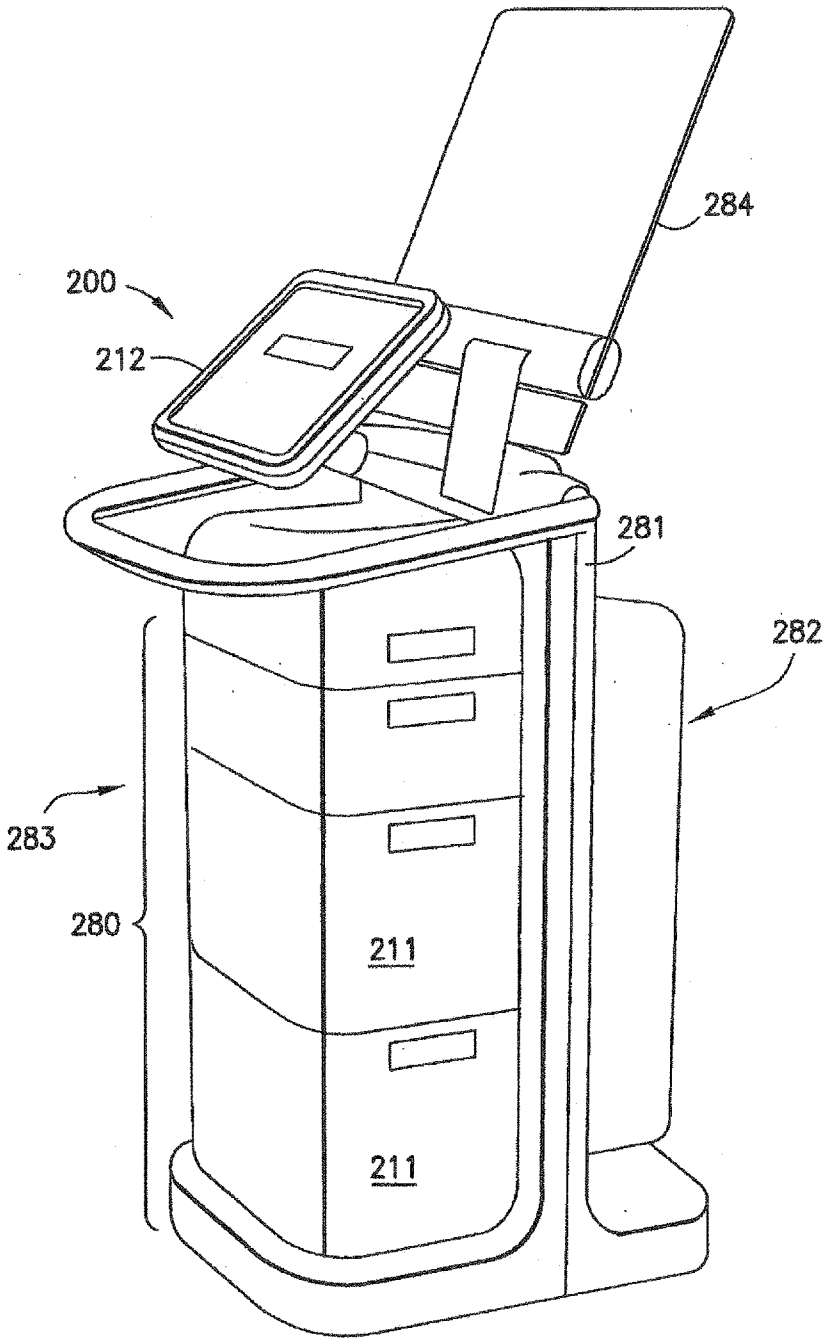


FIG.4A

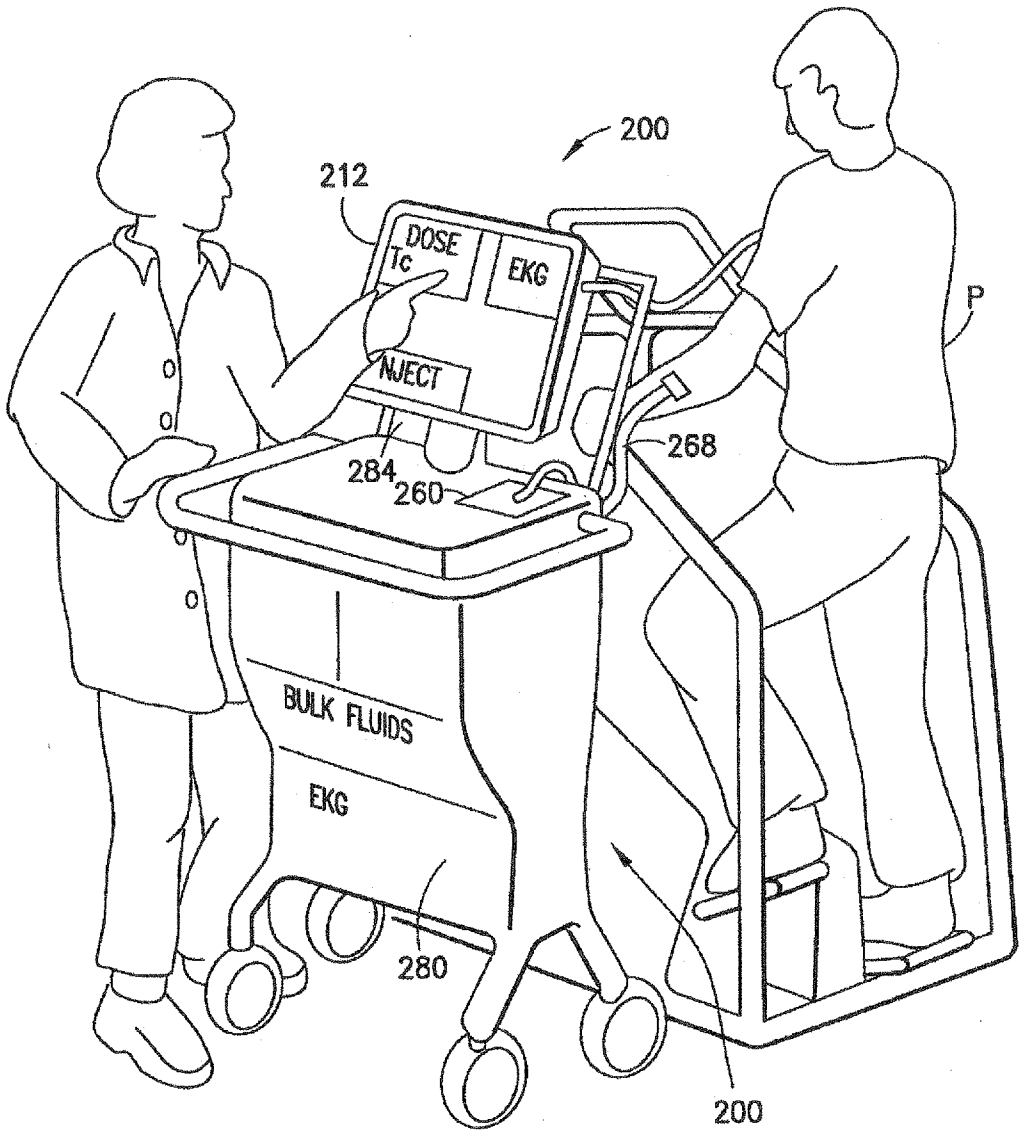

200
212
DOSE
Tc
EKG
INJECT
P
268
284
260
BULK FLUIDS
EKG
280
200

FIG.4B

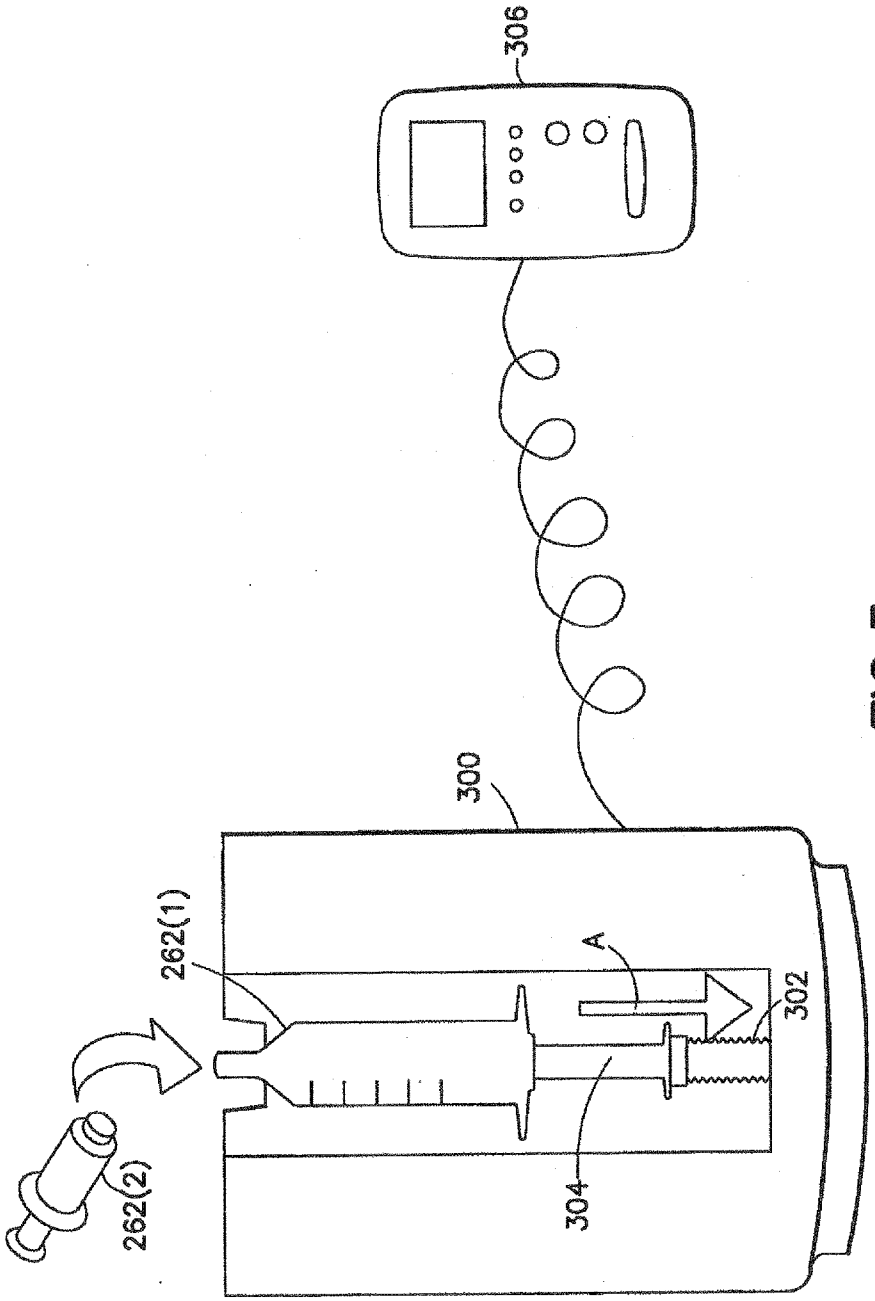


FIG.5

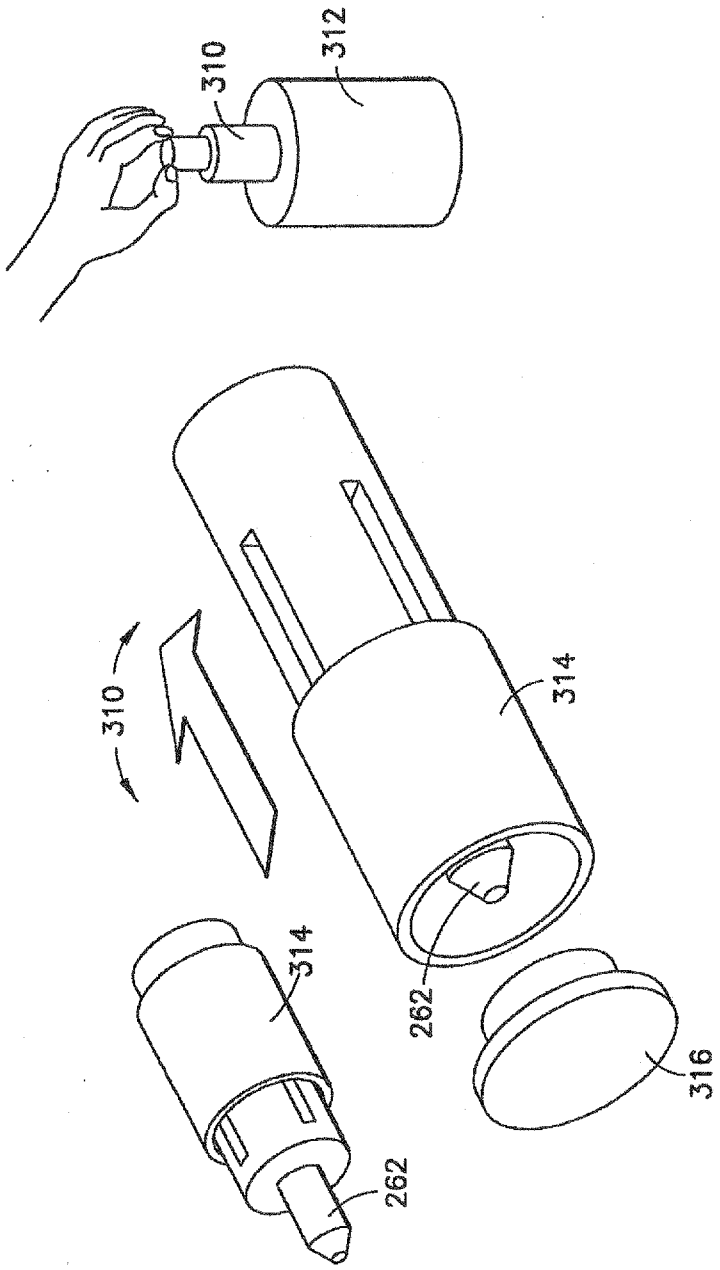


FIG.6

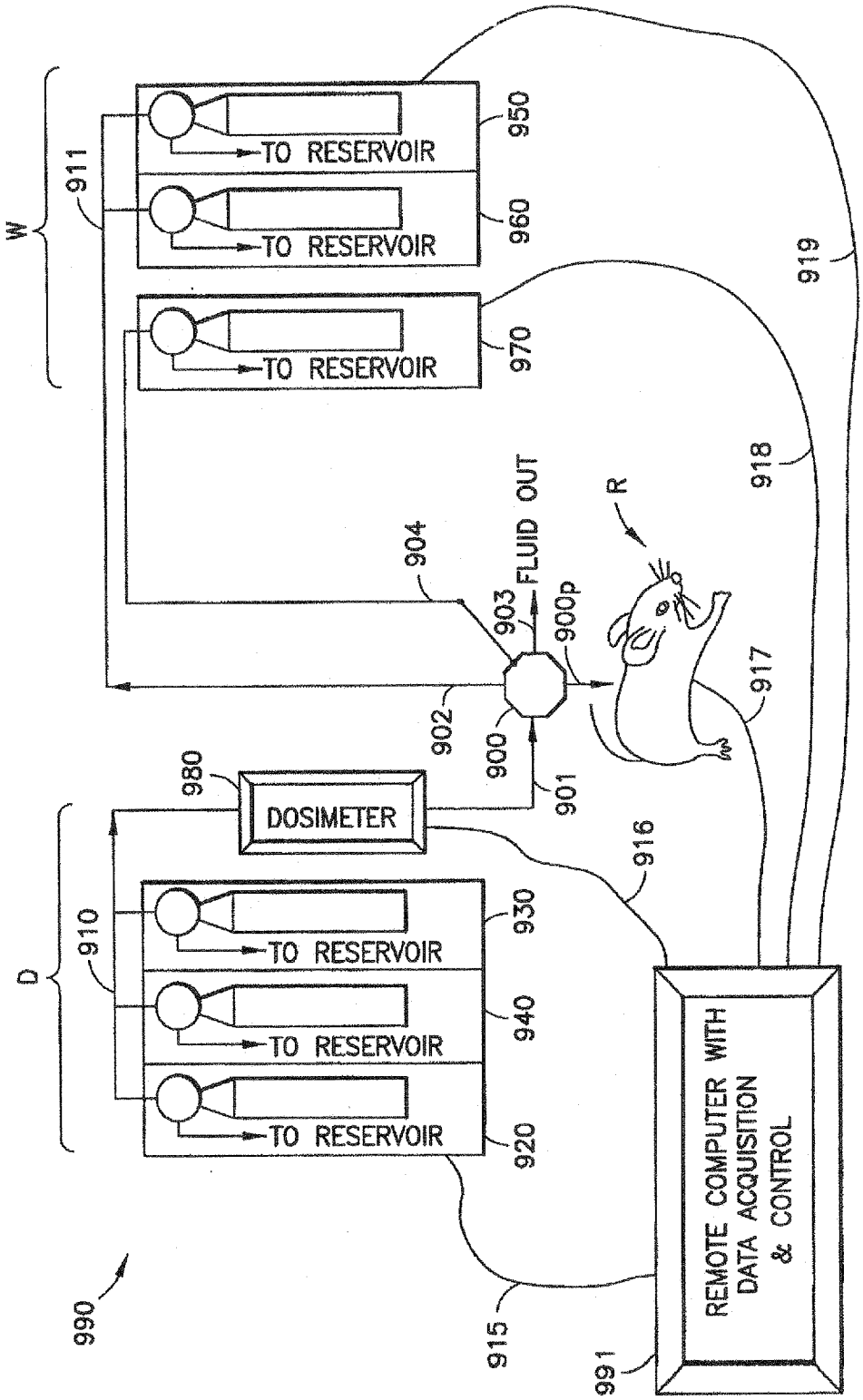

W
911
TO RESERVOIR
950
TO RESERVOIR
960
TO RESERVOIR
970
919
918
FLUID OUT
904
903
900p
R
917
902
900
901
980
DOSIMETER
916
D
910
TO RESERVOIR
930
TO RESERVOIR
940
TO RESERVOIR
920
990
915
991
REMOTE COMPUTER WITH DATA ACQUISITION & CONTROL

FIG.7

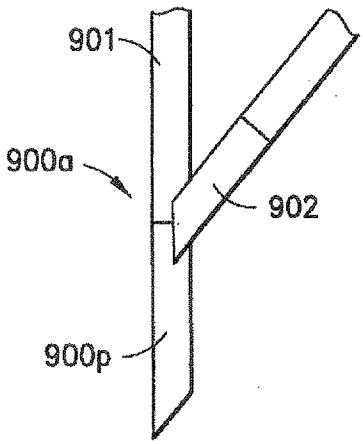


FIG.8

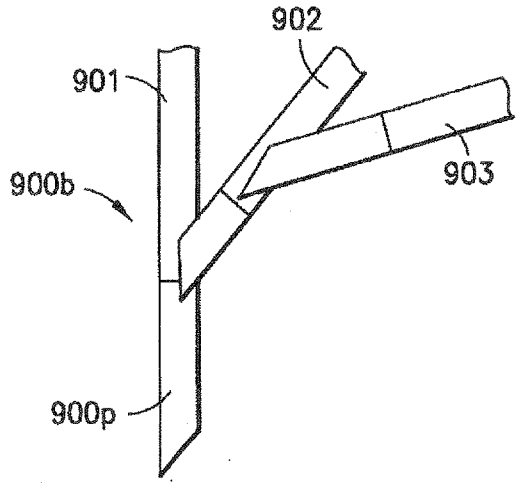


FIG.9

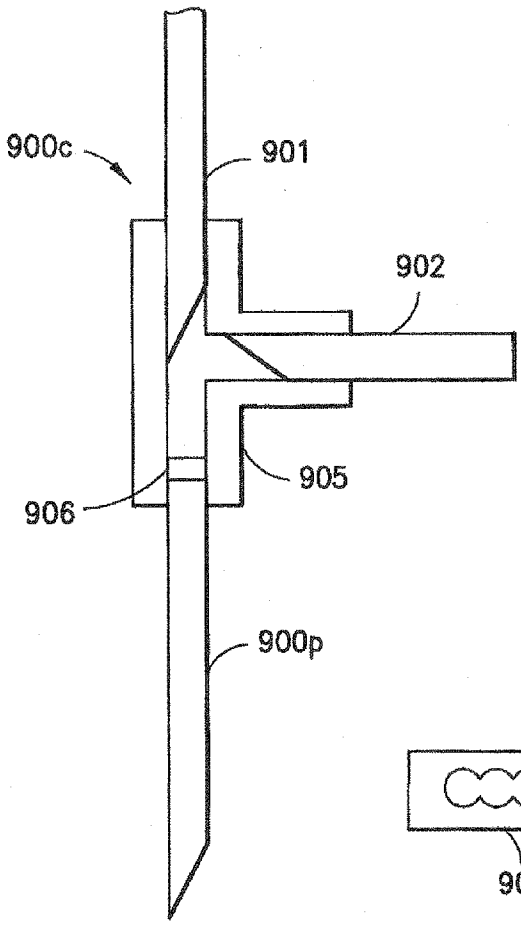


FIG.10

FIG.12

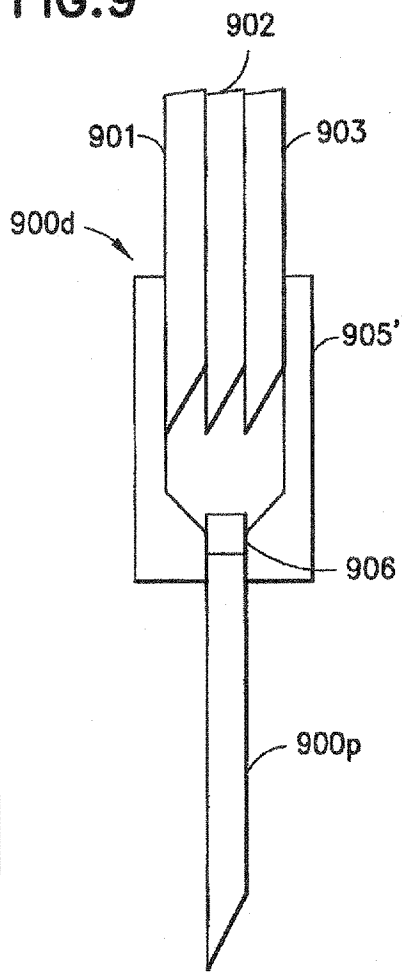


FIG.11

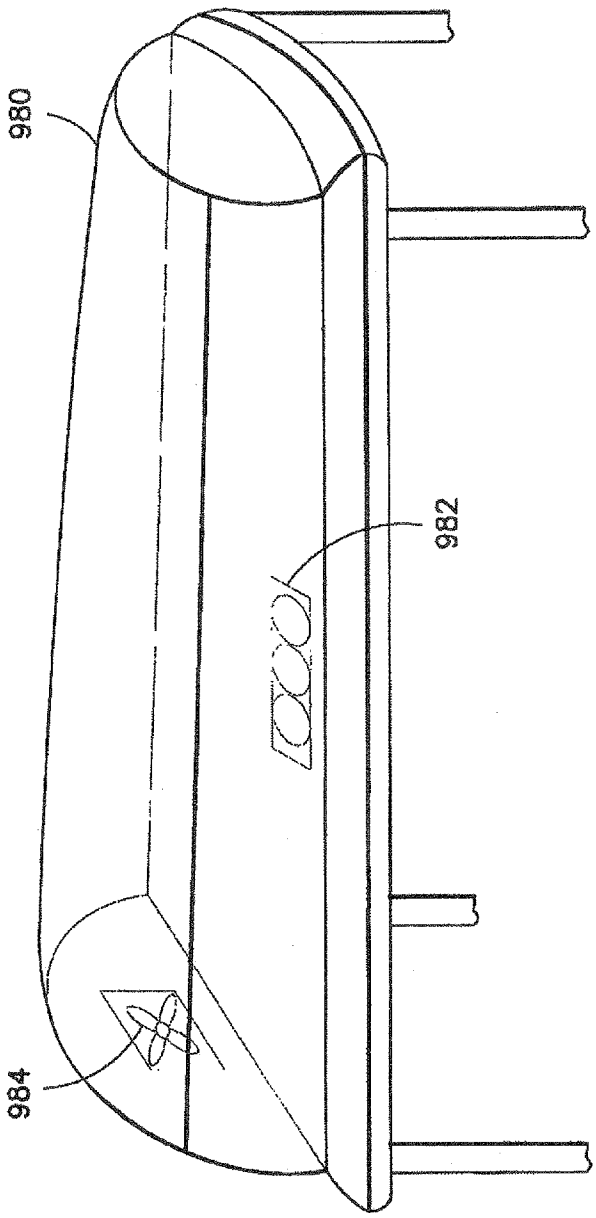


FIG. 13

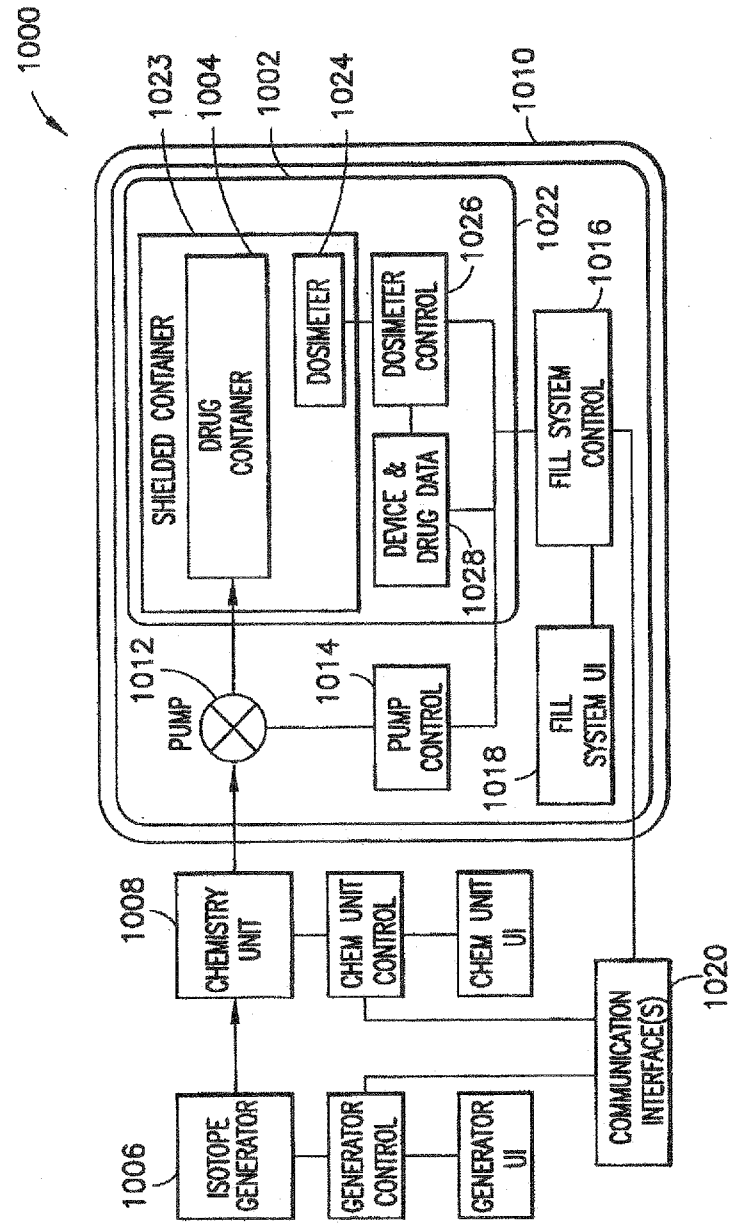

1000
1023
1004
1002
1024
1010
SHIELDED CONTAINER
DRUG CONTAINER
DOSIMETER
DOSIMETER CONTROL
1026
1022
1016
FILL SYSTEM CONTROL
DEVICE & DRUG DATA
1028
1012
PUMP
1014
PUMP CONTROL
FILL SYSTEM UI
1018
1008
CHEMISTRY UNIT
CHEM UNIT CONTROL
CHEM UNIT UI
1020
COMMUNICATION INTERFACE(S)
1006
ISOTOPE GENERATOR
GENERATOR CONTROL
GENERATOR UI

FIG.14A

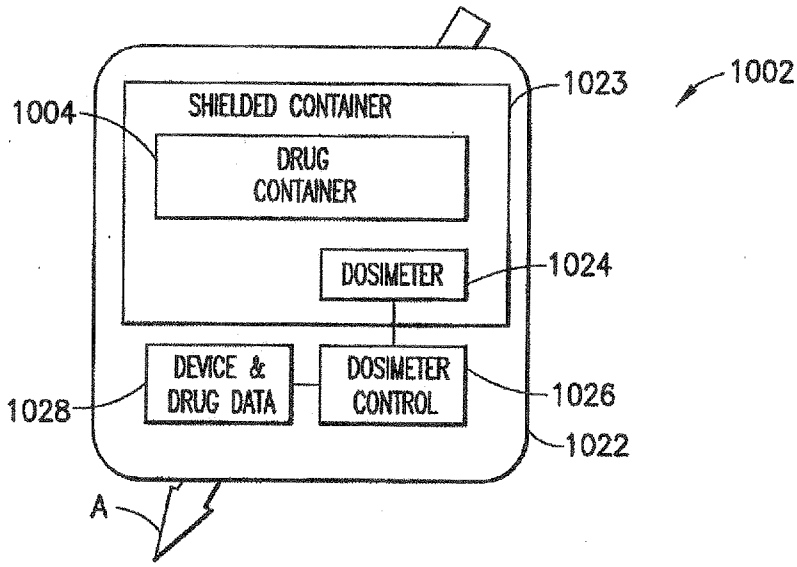

1002
1004
SHIELDED CONTAINER
1023
DRUG CONTAINER
DOSIMETER
1024
DEVICE & DRUG DATA
DOSIMETER CONTROL
1026
1028
1022
A

FIG.14B

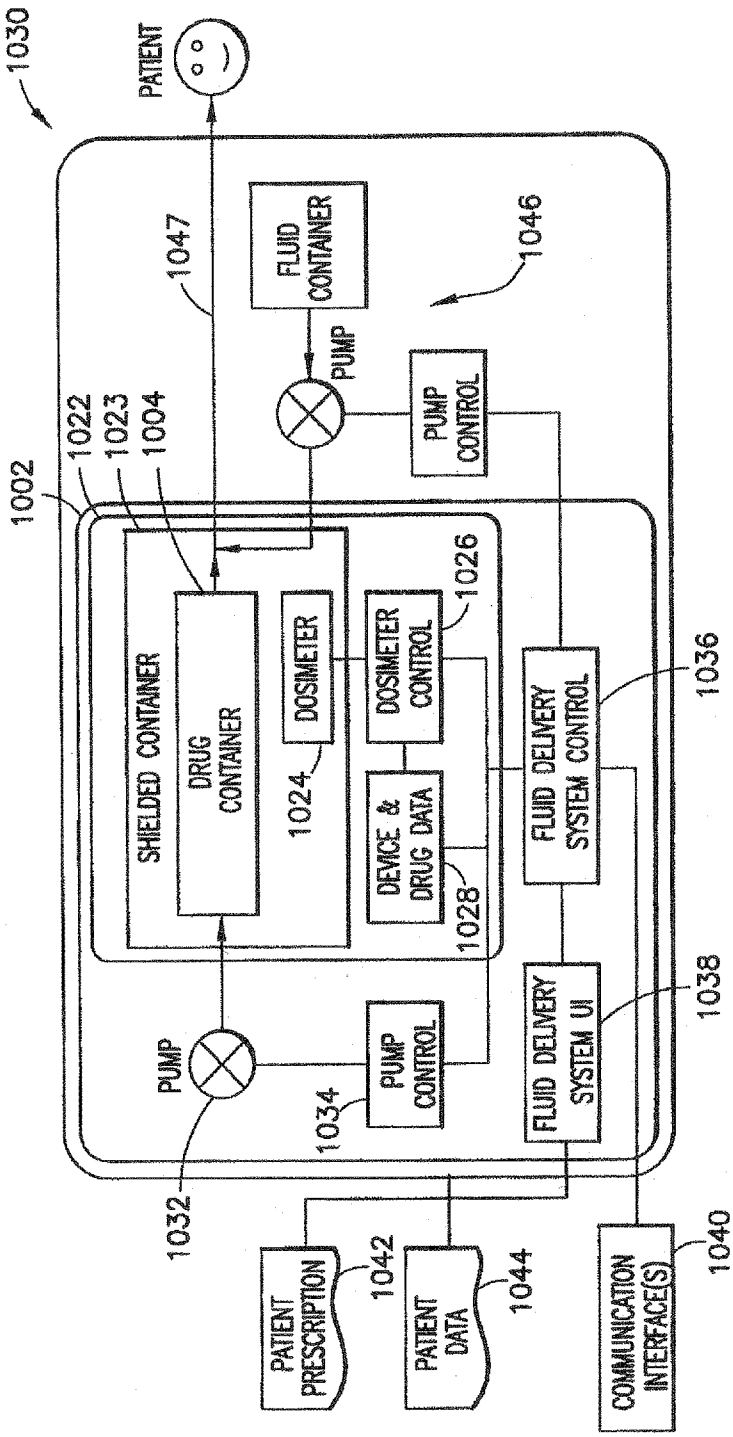

1030
PATIENT
1047
FLUID CONTAINER
1046
PUMP
PUMP CONTROL
1022
1023
1004
1002
SHIELDED CONTAINER
DRUG CONTAINER
DOSIMETER
DOSIMETER CONTROL
1026
1024
DEVICE & DRUG DATA
1028
FLUID DELIVERY SYSTEM CONTROL
1036
PUMP
PUMP CONTROL
1034
FLUID DELIVERY SYSTEM UI
1038
1032
PATIENT PRESCRIPTION
1042
PATIENT DATA
1044
COMMUNICATION INTERFACE(S)
1040

FIG.14C

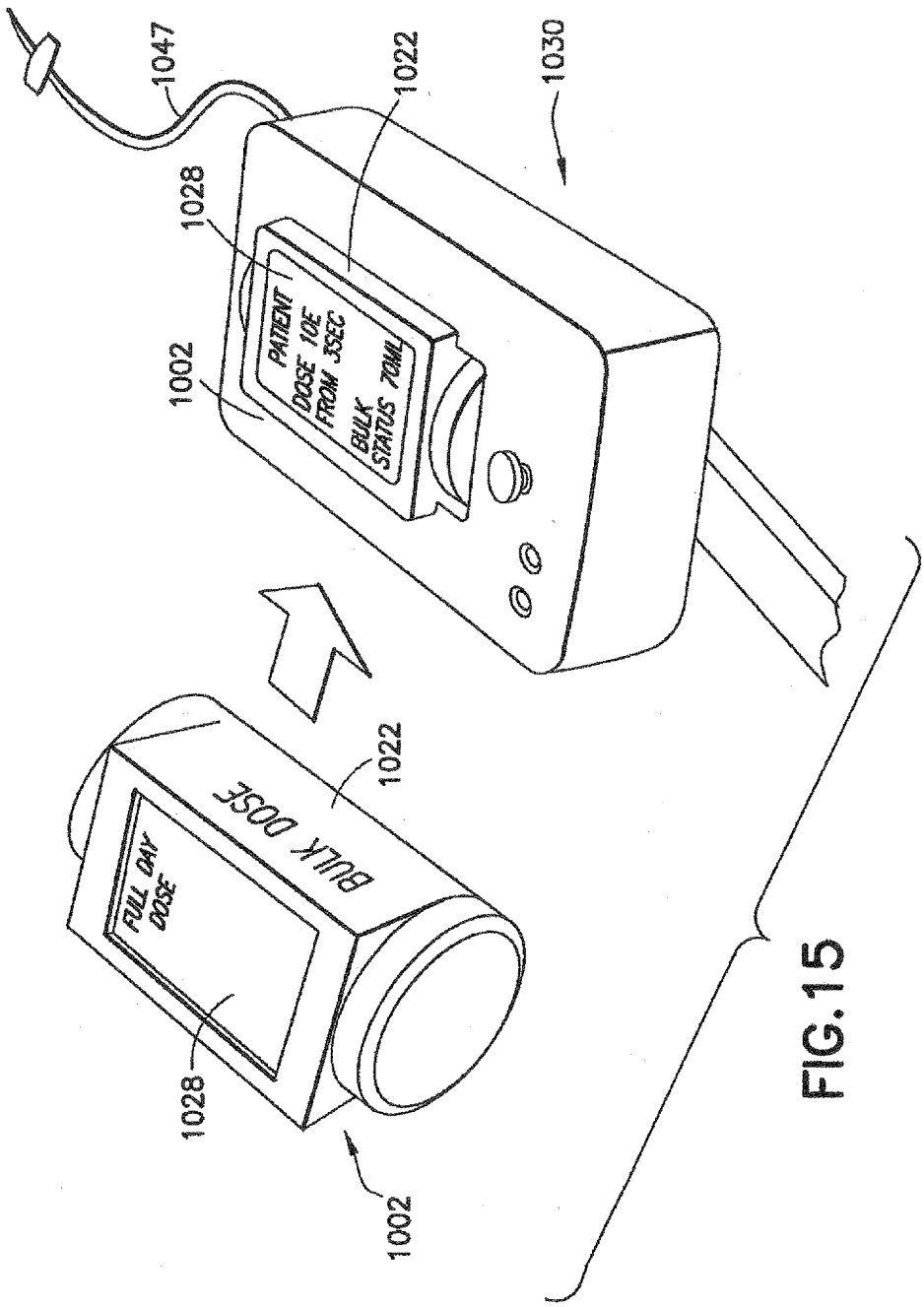

1047
1022
1030
1028
PATIENT
DOSE 10E
FROM 3SEC
BULK
STATUS 70ML
1002
BULK DOSE
FULL DAY
DOSE
1022
1028
1002

FIG.15

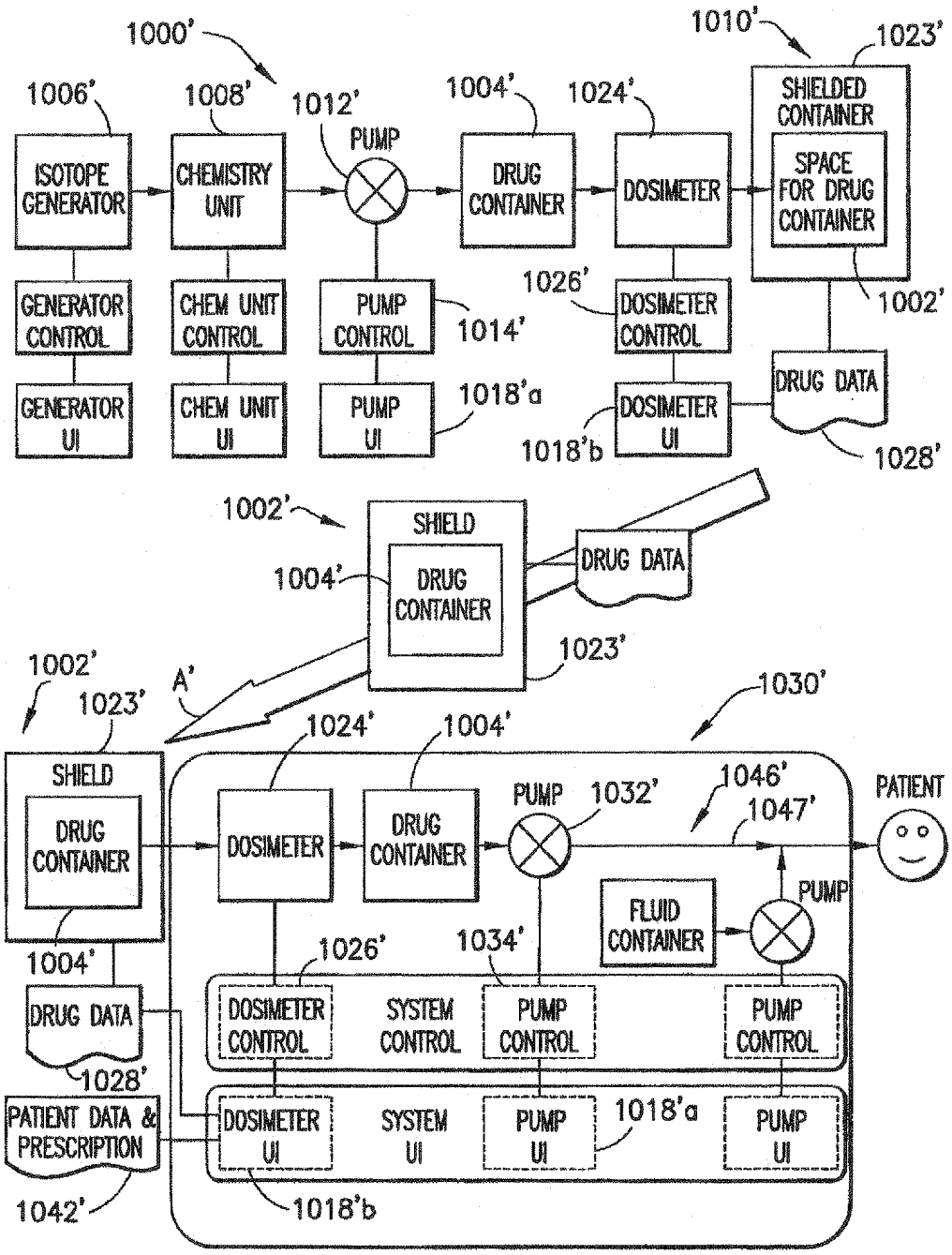

1000'
1010'
1023'
1006'
1008'
1012'
1004'
1024'
SHIELDED CONTAINER
ISOTOPE GENERATOR
CHEMISTRY UNIT
PUMP
DRUG CONTAINER
DOSIMETER
SPACE FOR DRUG CONTAINER
GENERATOR CONTROL
CHEM UNIT CONTROL
PUMP CONTROL
1014'
1026'
DOSIMETER CONTROL
1002'
GENERATOR UI
CHEM UNIT UI
PUMP UI
1018'a
1018'b
DOSIMETER UI
DRUG DATA
1028'
1002'
SHIELD
1004'
DRUG CONTAINER
DRUG DATA
1023'
1002'
1023'
A'
1030'
1024'
1004'
SHIELD
DRUG CONTAINER
DOSIMETER
DRUG CONTAINER
PUMP
1032'
1046'
1047'
PATIENT
FLUID CONTAINER
PUMP
1004'
1026'
1034'
DRUG DATA
1028'
DOSIMETER CONTROL
SYSTEM CONTROL
PUMP CONTROL
PUMP CONTROL
PATIENT DATA & PRESCRIPTION
DOSIMETER UI
SYSTEM UI
PUMP UI
1018'a
PUMP UI
1042'
1018'b

FIG.16

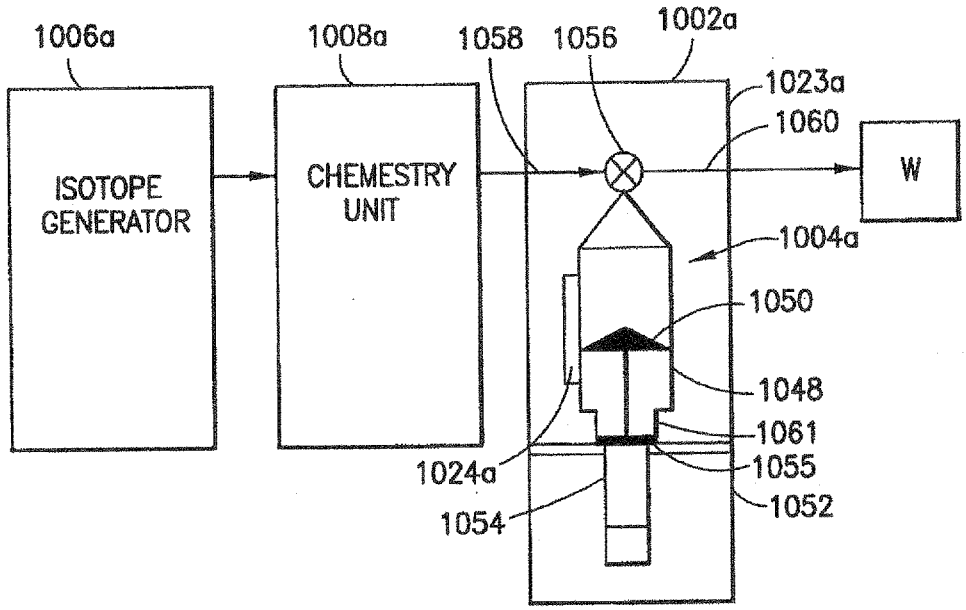

1006a
1008a
1058
1056
1002a
1023a
1060
W
ISOTOPE GENERATOR
CHEMESTRY UNIT
1004a
1050
1048
1061
1055
1052
1024a
1054

FIG.17

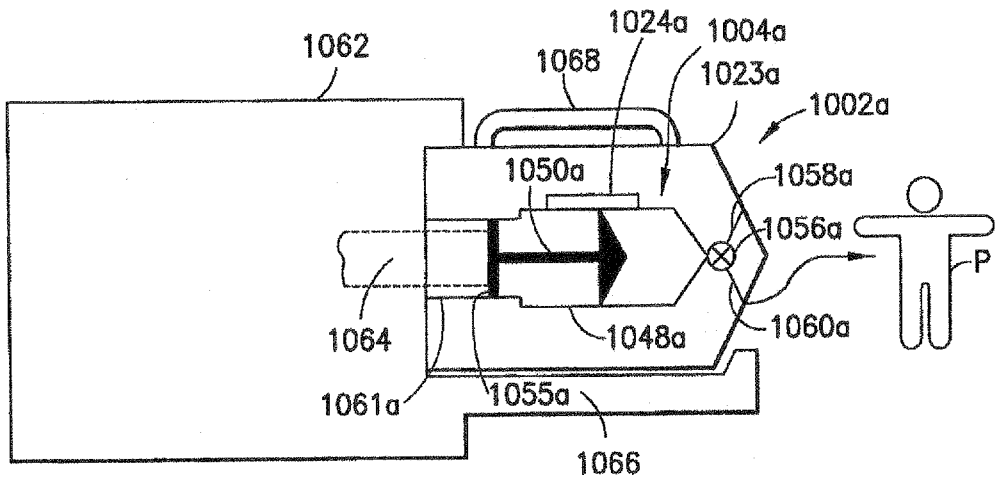

1062
1024a
1004a
1068
1023a
1002a
1050a
1058a
1056a
P
1064
1048a
1060a
1061a
1055a
1066

FIG.18

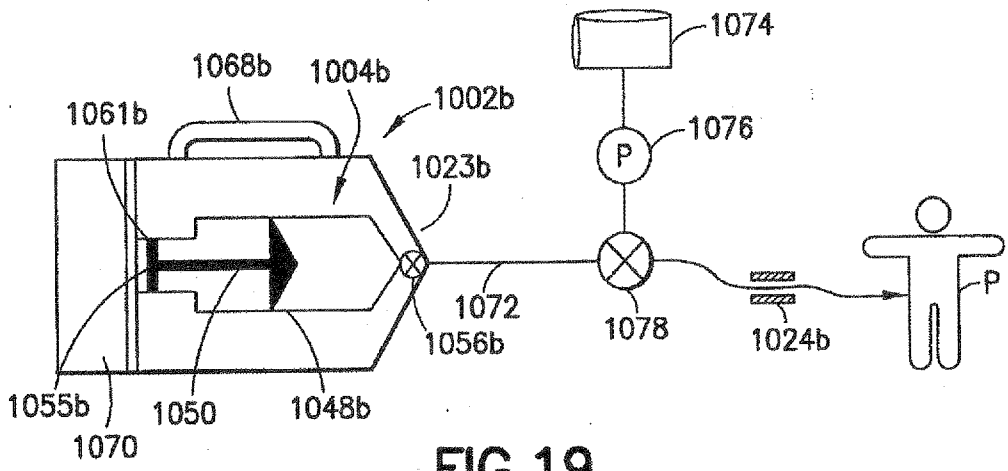

1074
1068b
1004b
1002b
1061b
1076
P
1023b
1072
1056b
1078
1024b
P
1055b
1070
1050
1048b

FIG.19

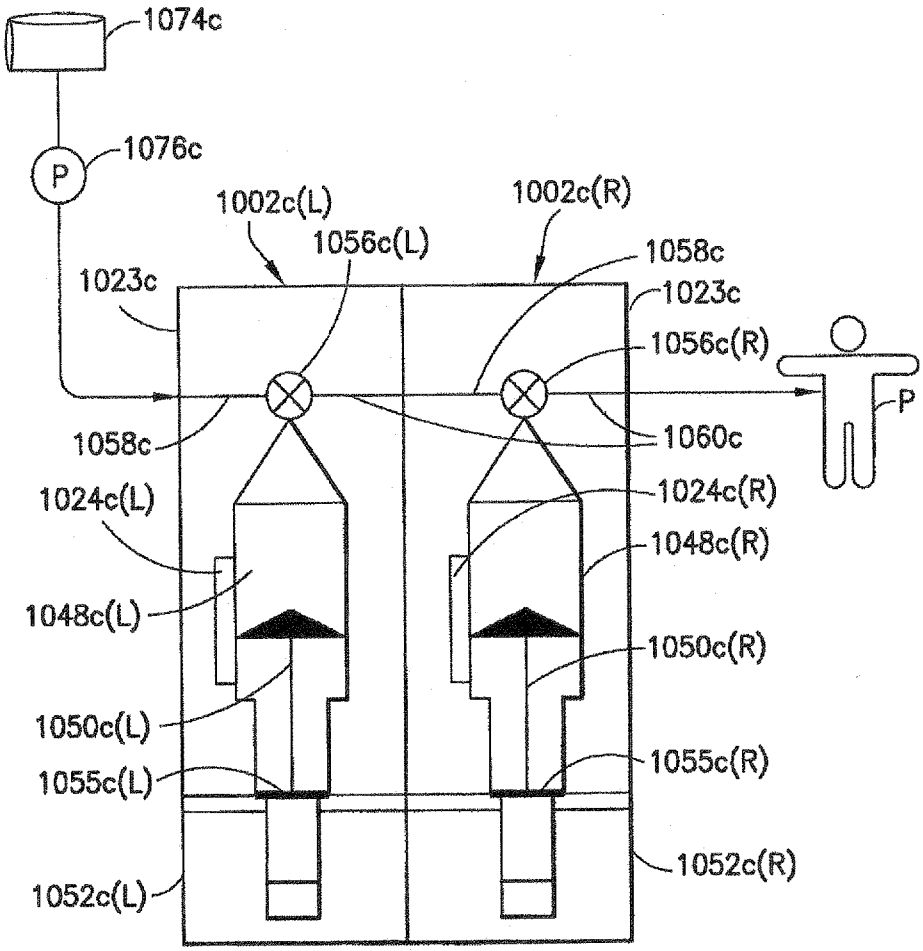

1074c
1076c
P
1002c(L)
1002c(R)
1056c(L)
1058c
1023c
1023c
1056c(R)
P
1058c
1060c
1024c(L)
1024c(R)
1048c(R)
1048c(L)
1050c(R)
1050c(L)
1055c(L)
1055c(R)
1052c(L)
1052c(R)

FIG.20

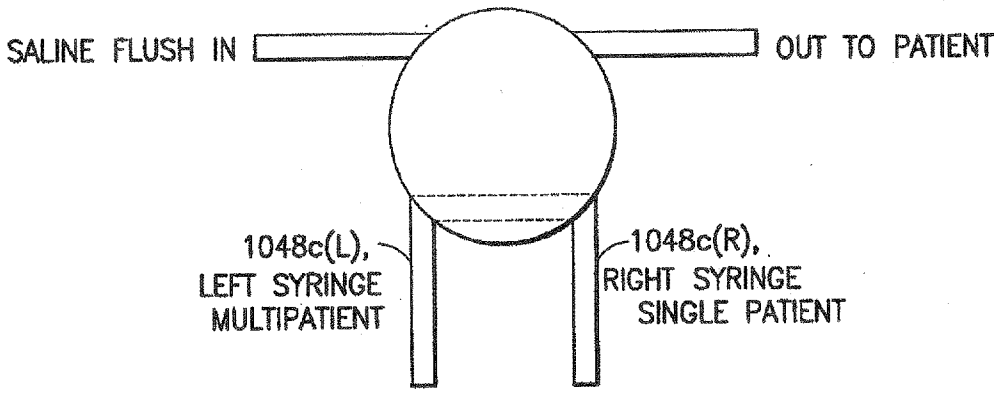


FIG.21

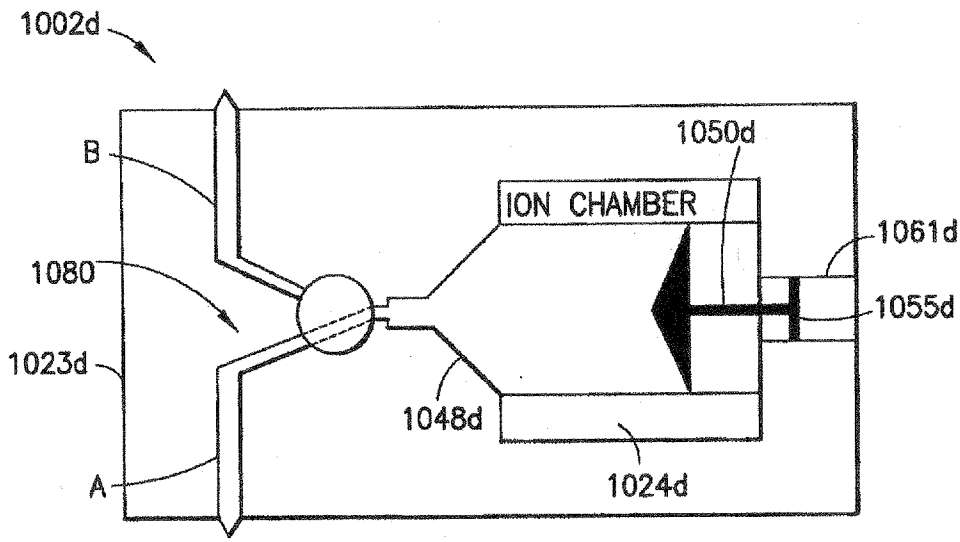


FIG.22A

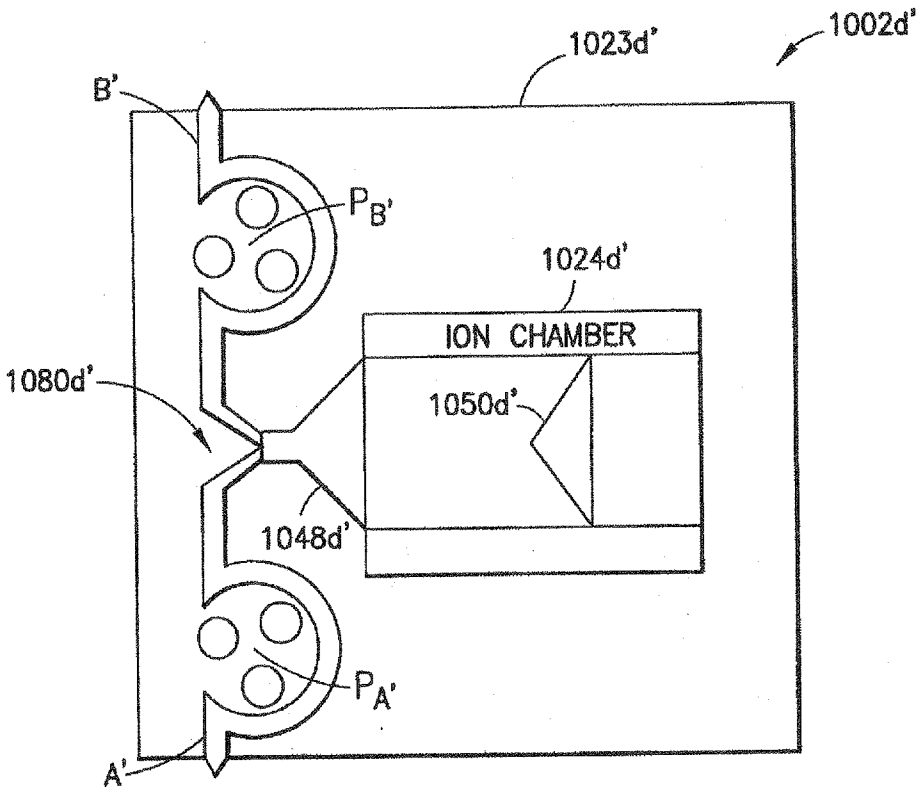


FIG.22B

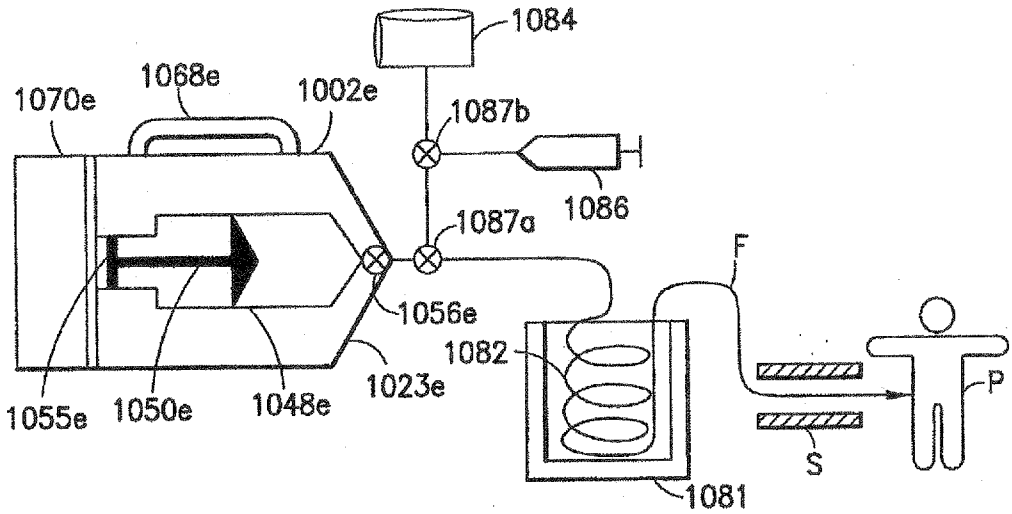

1084
1068e
1070e
1002e
1087b
1086
1087a
F
1056e
1082
P
1055e
1050e
1048e
1023e
S
1081

FIG.23

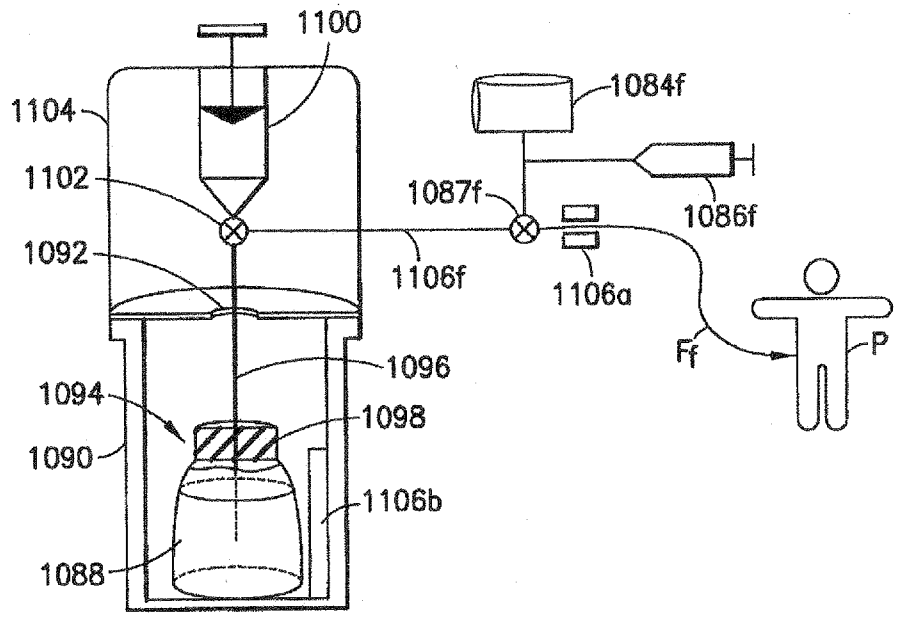

1100
1104
1084f
1102
1087f
1086f
1092
1106f
1106a
Ff
P
1096
1094
1098
1090
1106b
1088

FIG.24

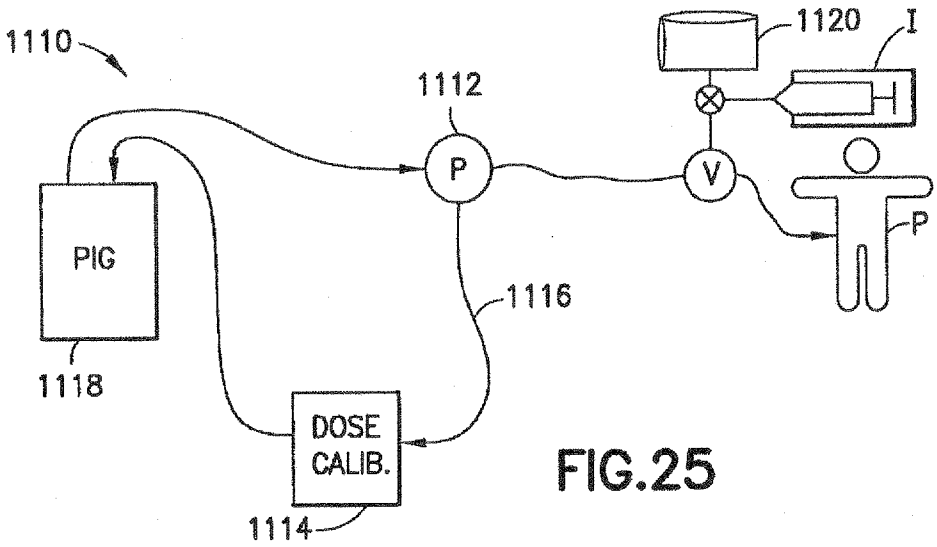

1110
1112
1120
I
P
V
P
PIG
1116
1118
DOSE
CALIB.
1114

FIG.25

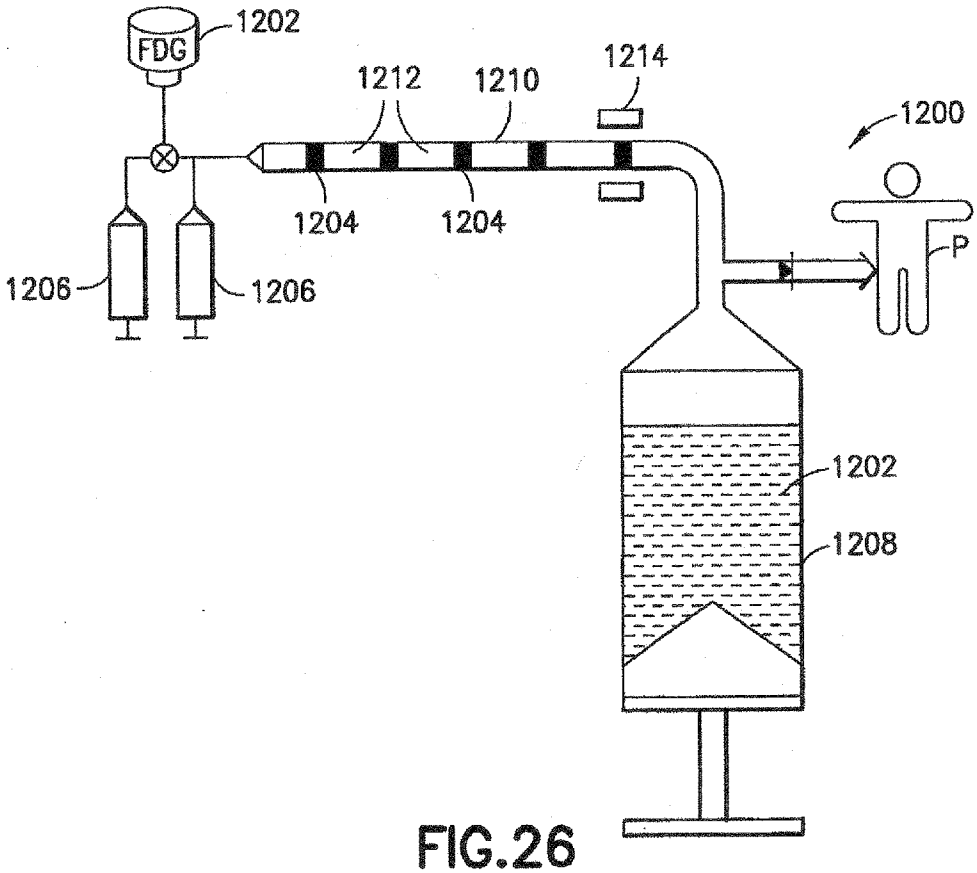

FDG
1202
1212
1210
1214
1200
1204
1204
P
1206
1206
1202
1208

FIG.26

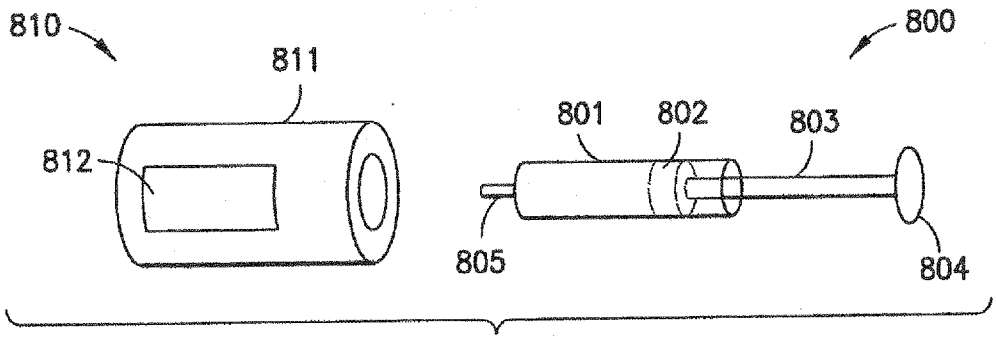


FIG.27
PRIOR ART

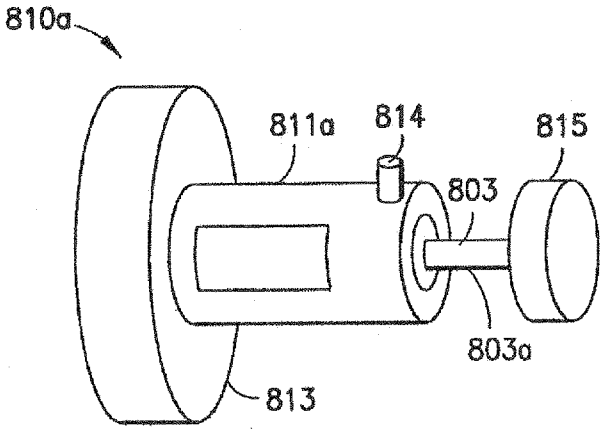


FIG.28

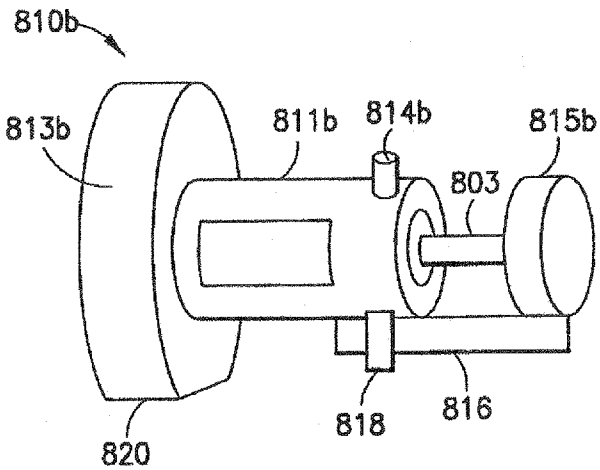


FIG.29

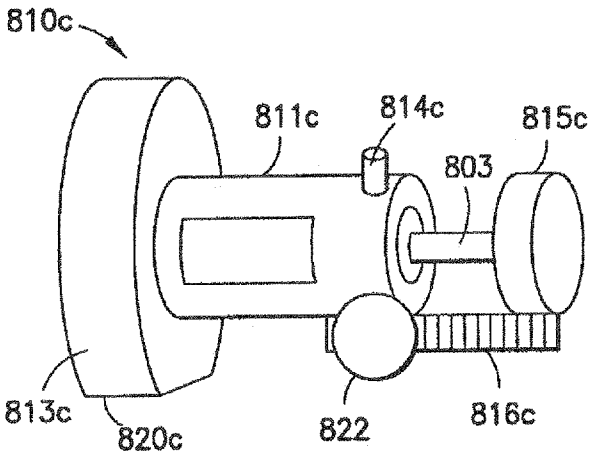


FIG.30

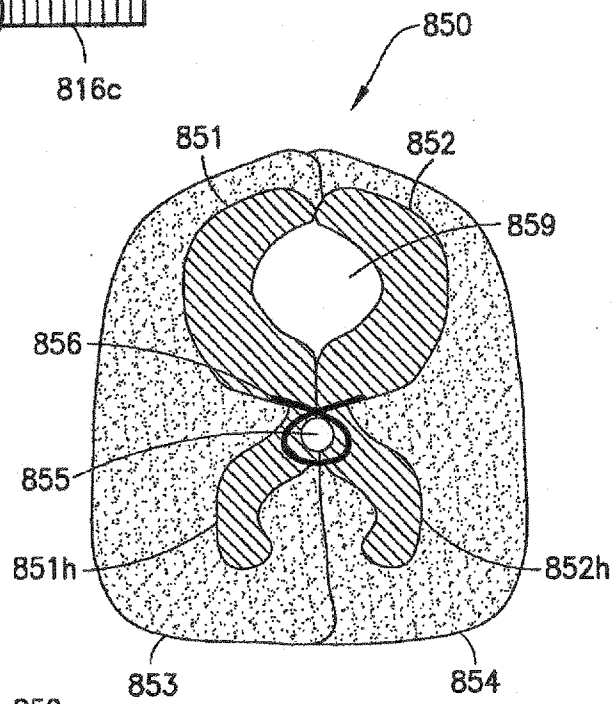


FIG.31

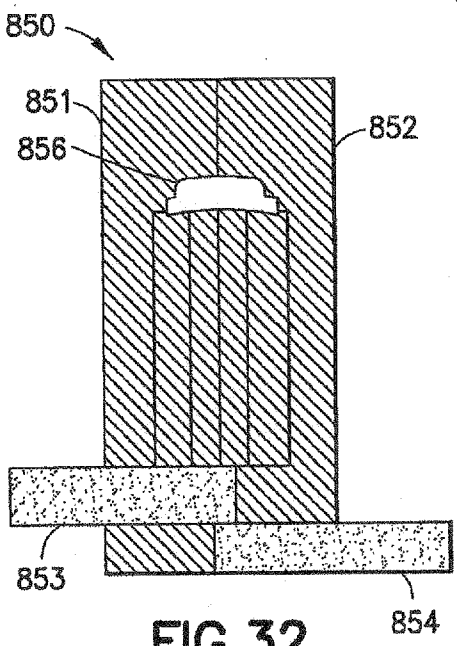


FIG.32

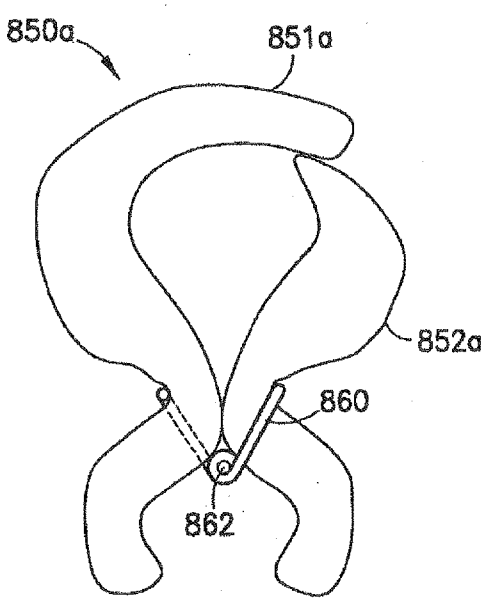


FIG.33

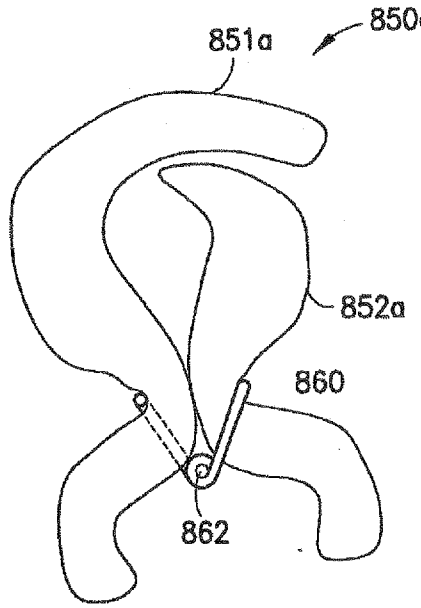


FIG.34

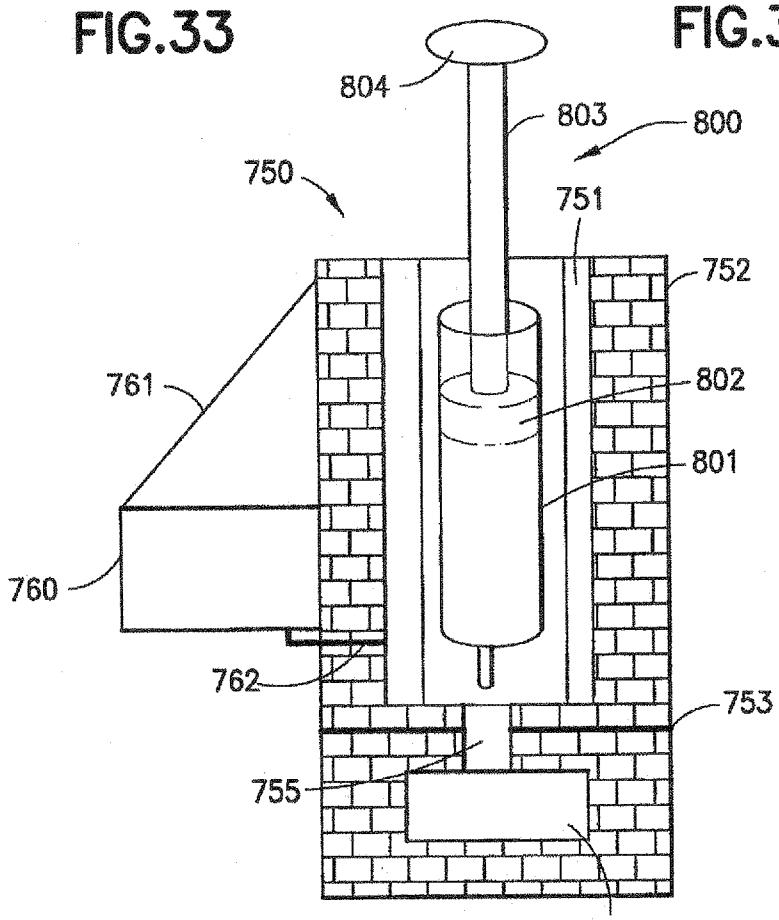


FIG.35A

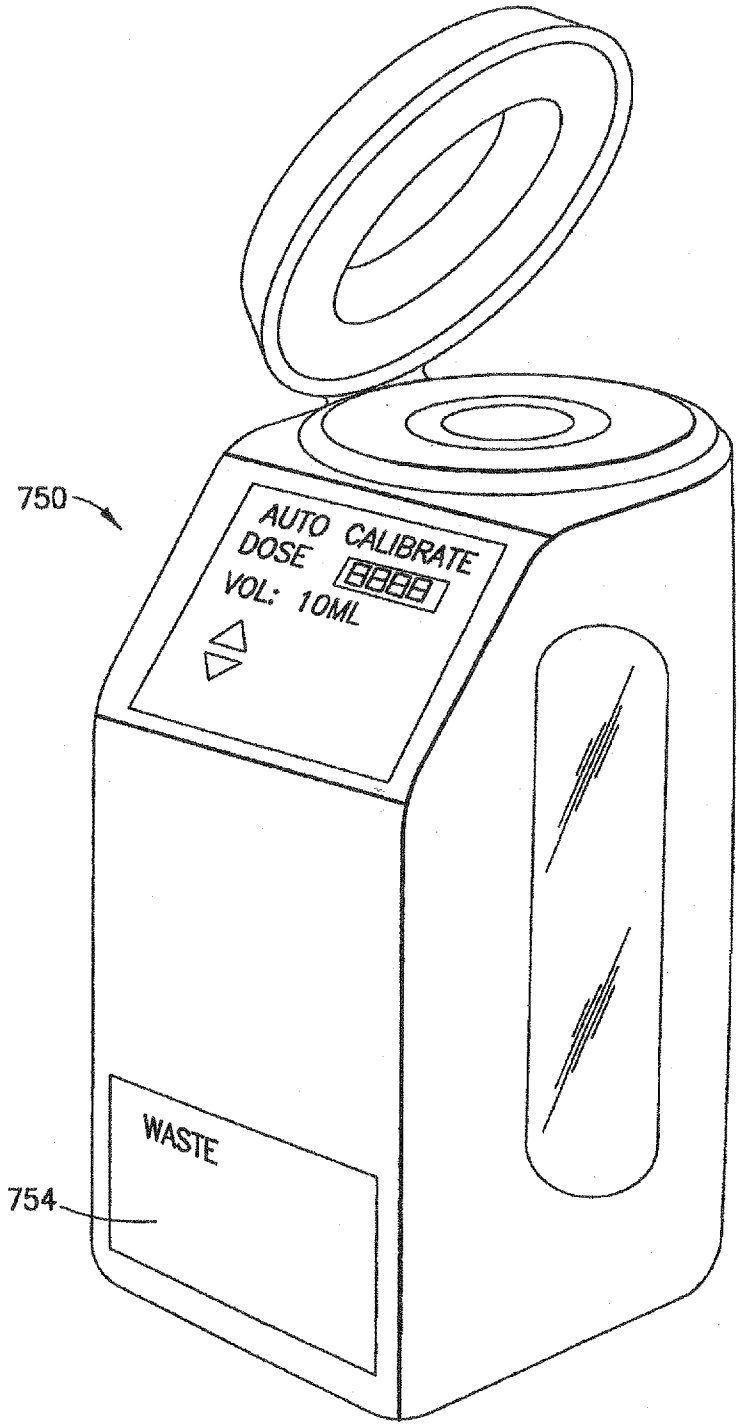


FIG.35B

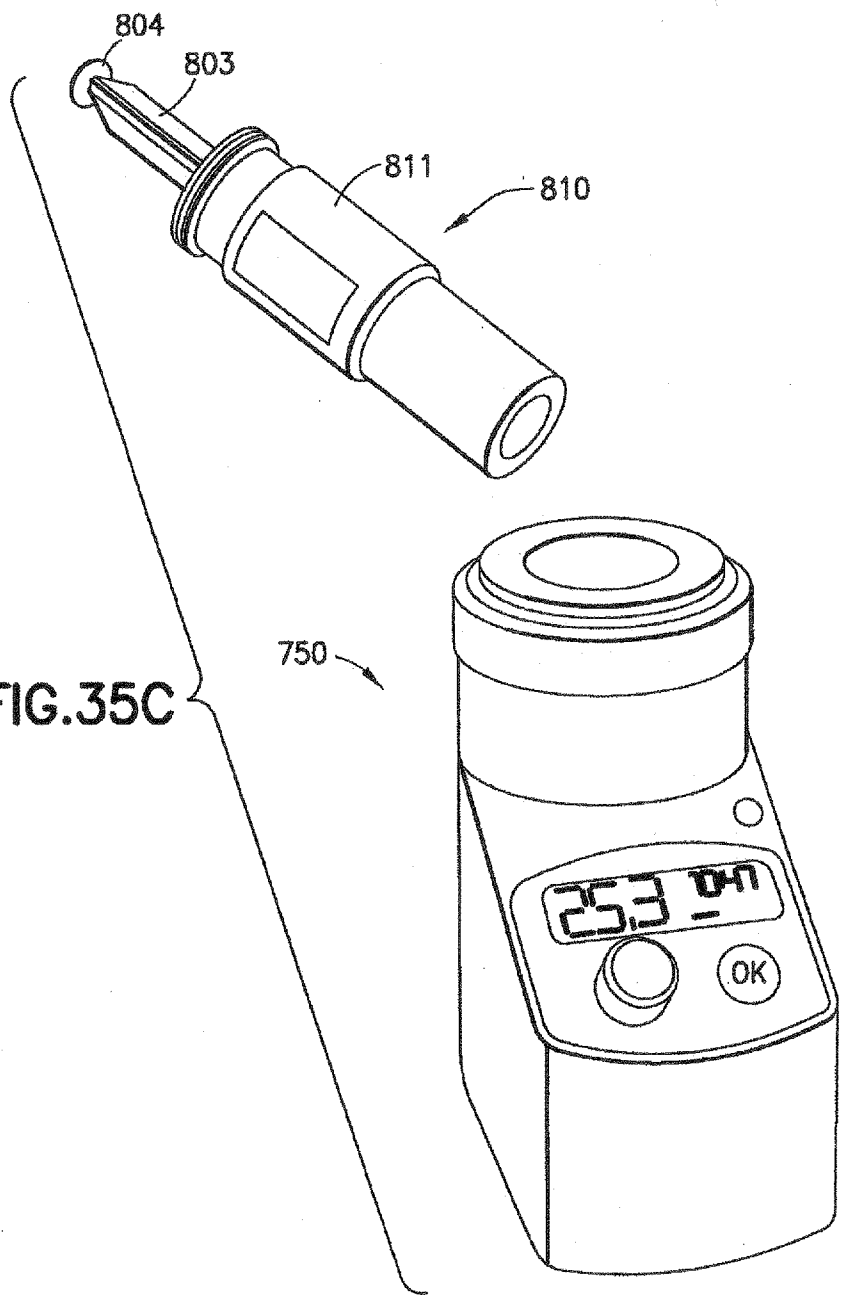


FIG.35C

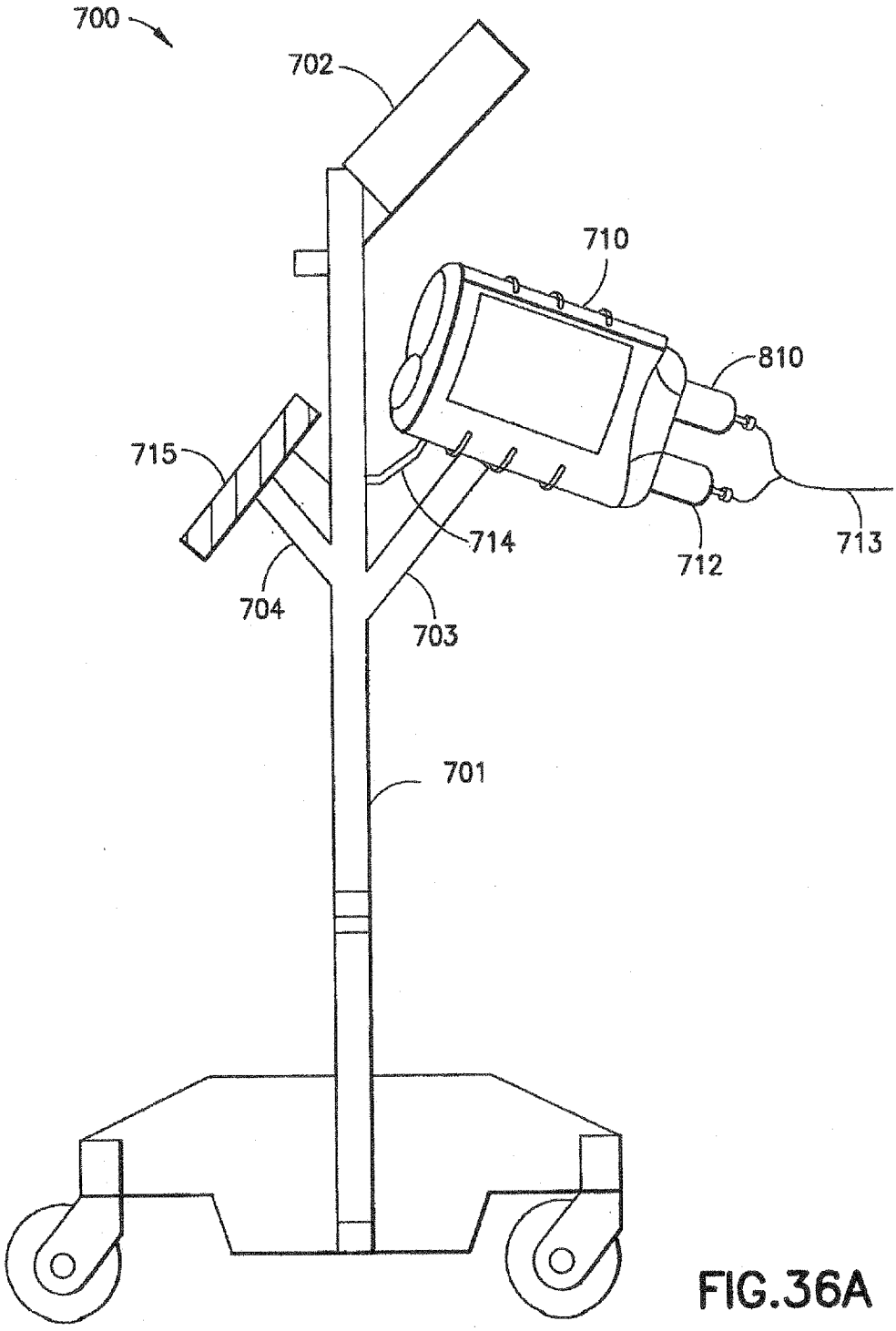


FIG.36A

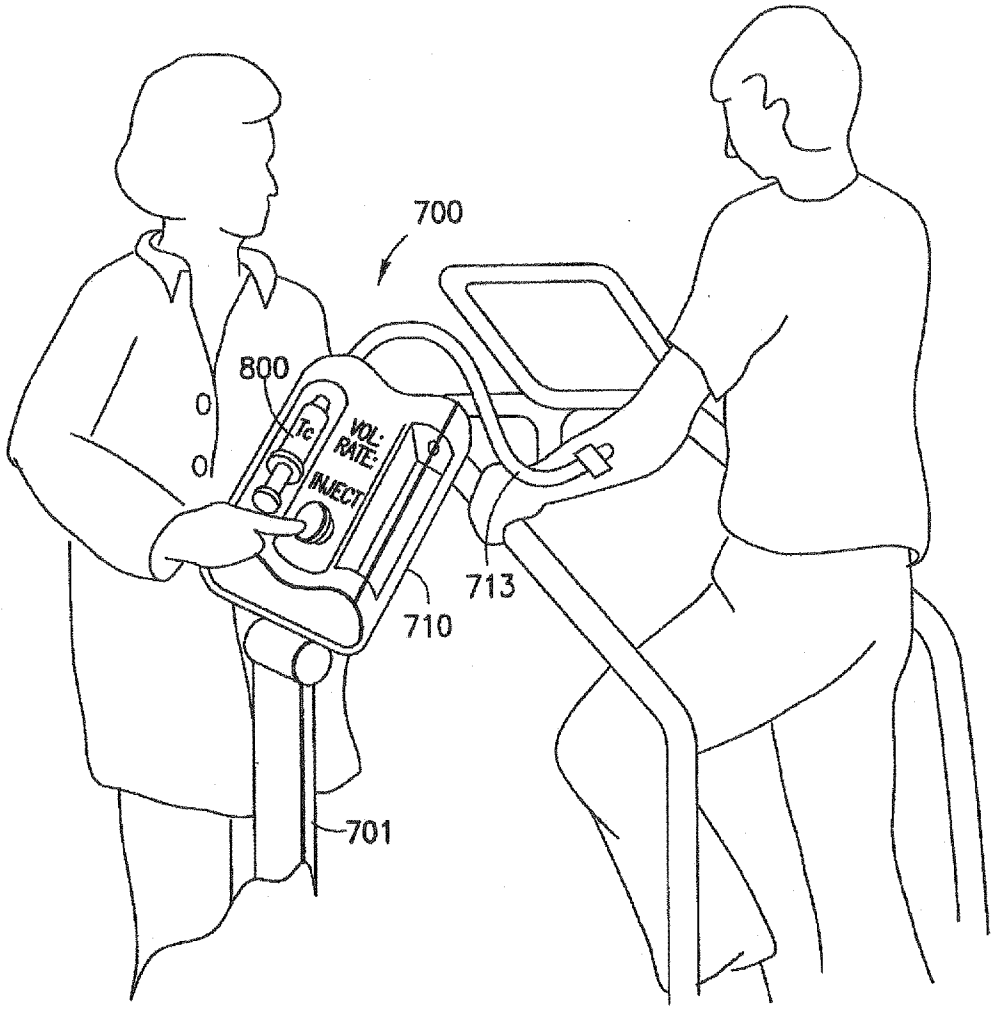


FIG.36B

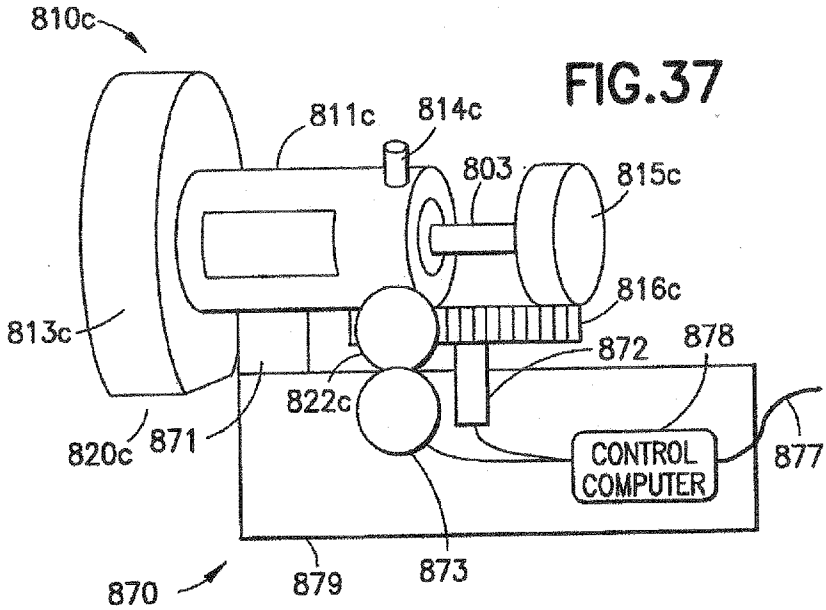

810c
811c
814c
803
815c
816c
813c
872
878
822c
820c
871
CONTROL COMPUTER
877
870
879
873

FIG.37

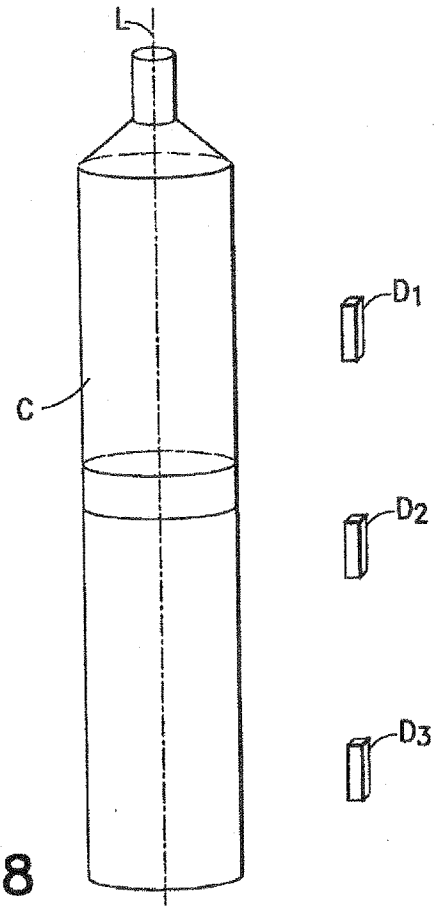

L
D1
C
D2
D3

FIG.38

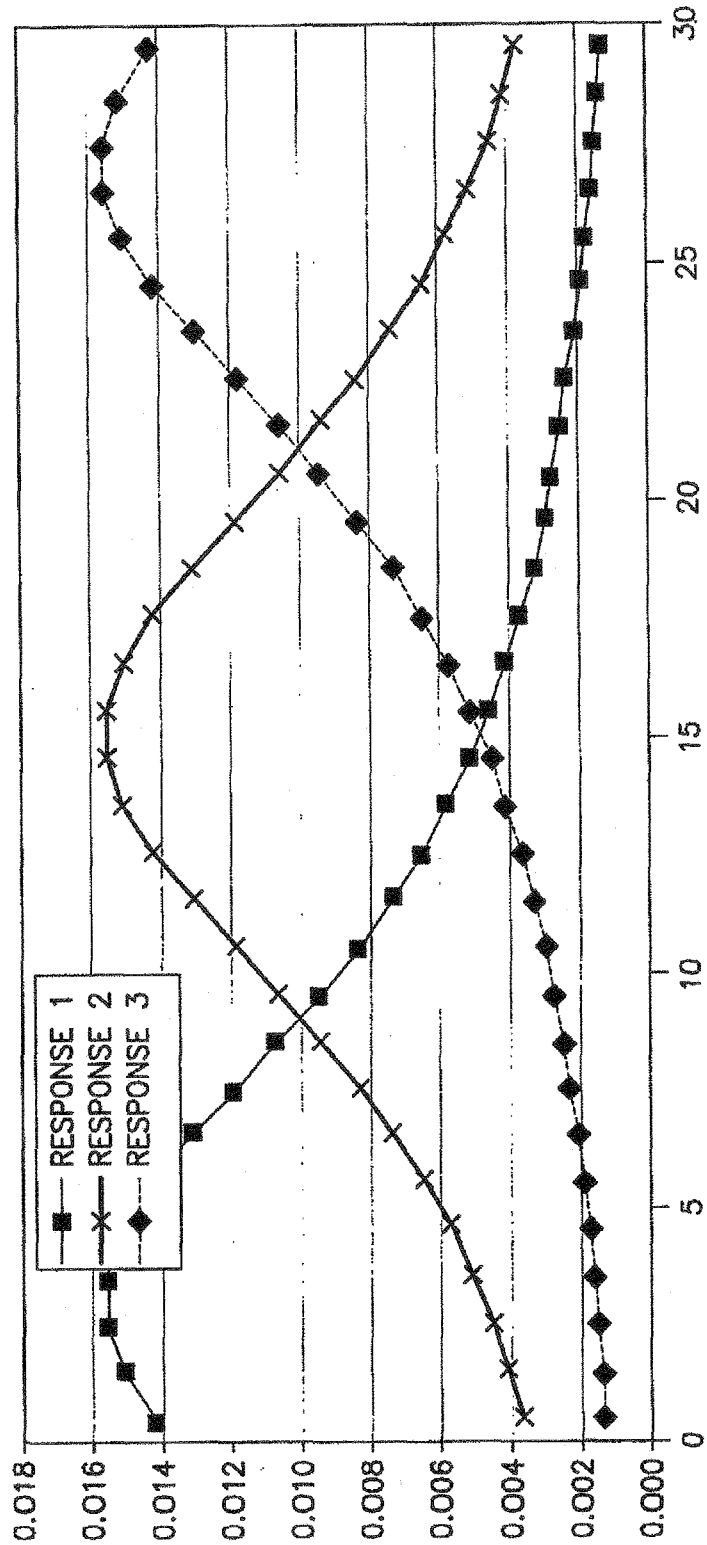

RESPONSE 1
RESPONSE 2
RESPONSE 3
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
5
10
15
20
25
30

FIG.39A

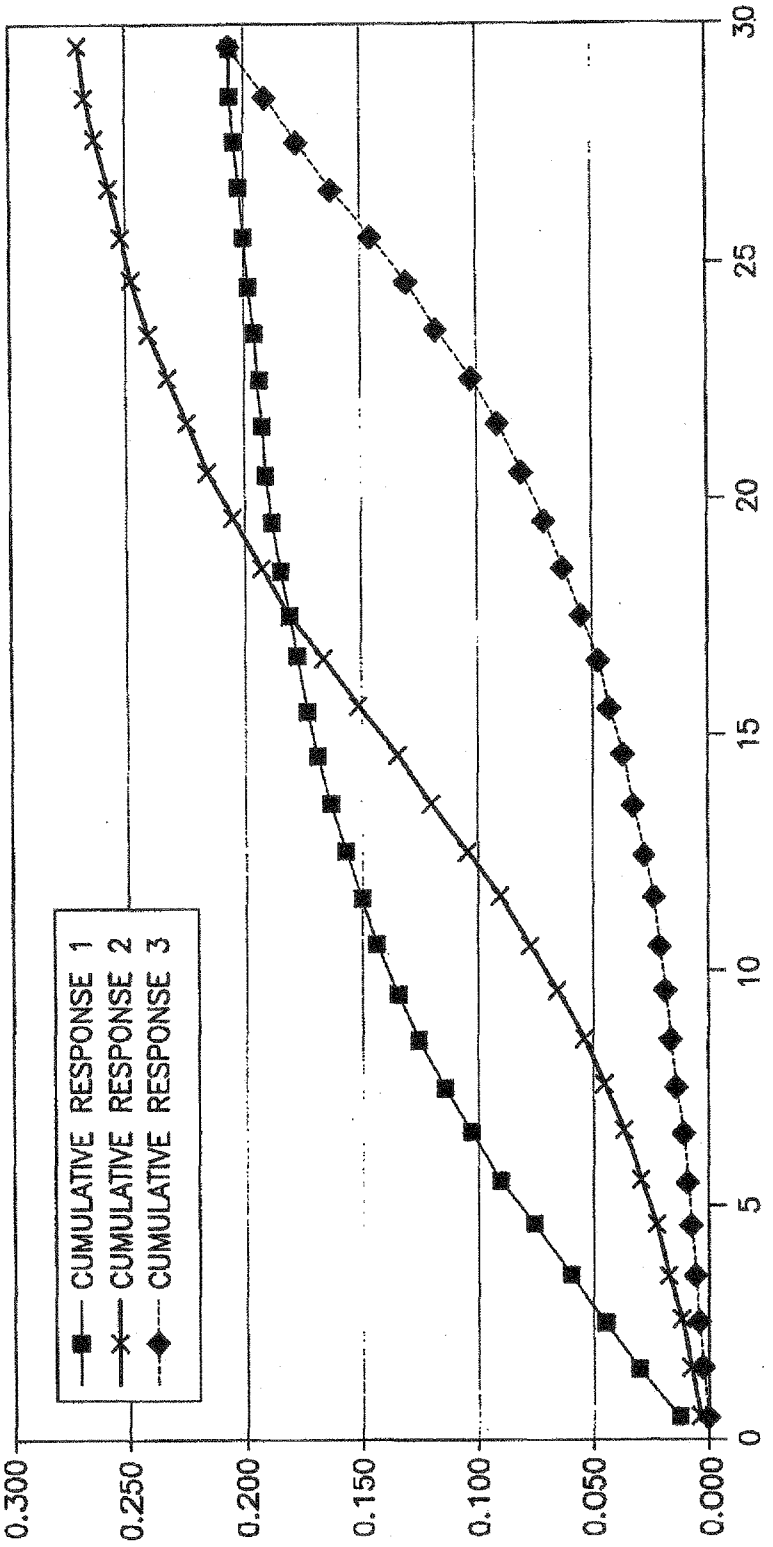

CUMULATIVE RESPONSE 1
CUMULATIVE RESPONSE 2
CUMULATIVE RESPONSE 3
0.300
0.250
0.200
0.150
0.100
0.050
0.000
0
5
10
15
20
25
30

FIG.39B

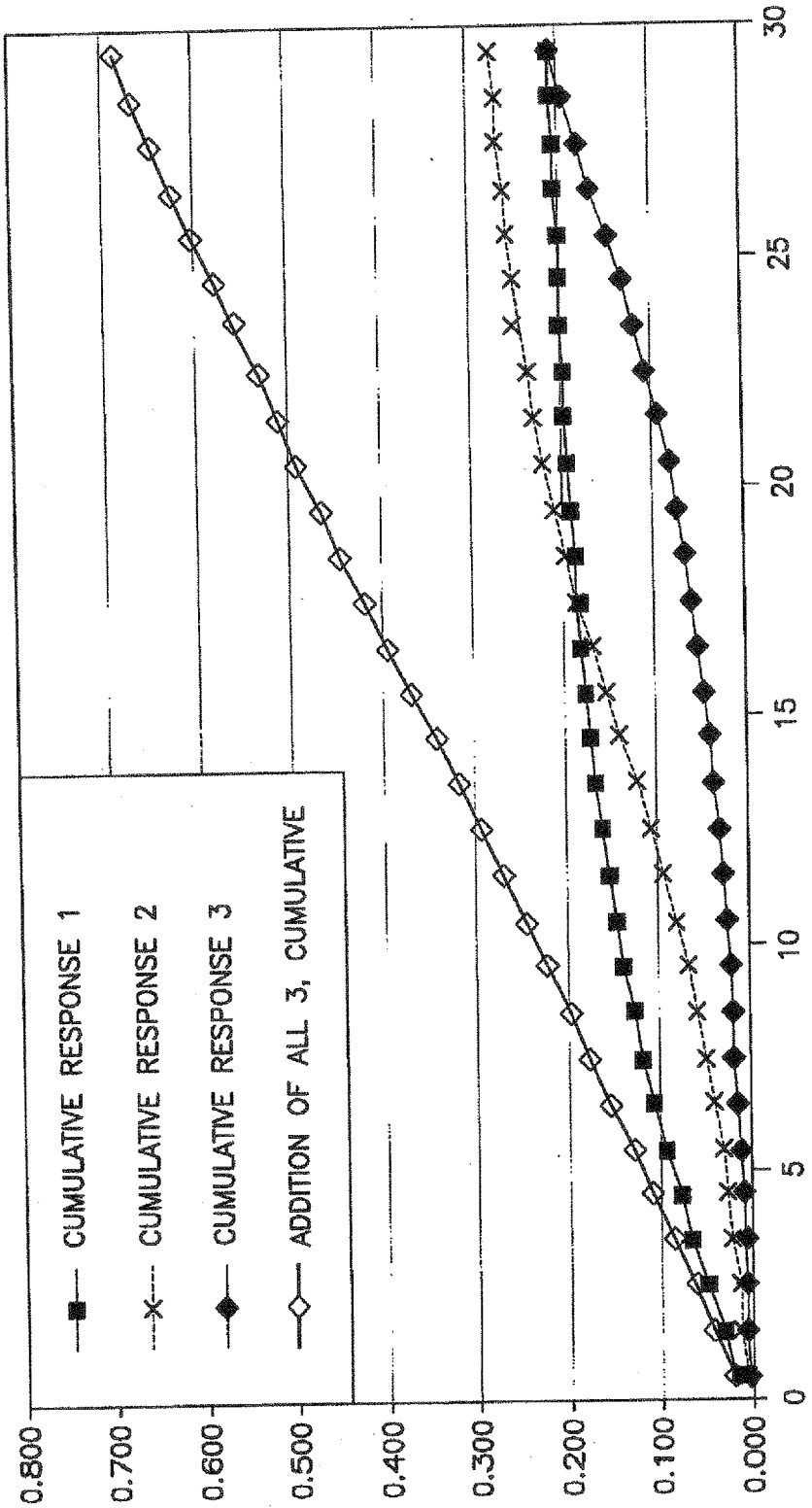

CUMULATIVE RESPONSE 1
CUMULATIVE RESPONSE 2
CUMULATIVE RESPONSE 3
ADDITION OF ALL 3, CUMULATIVE
0.800
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
5
10
15
20
25
30

FIG.39C

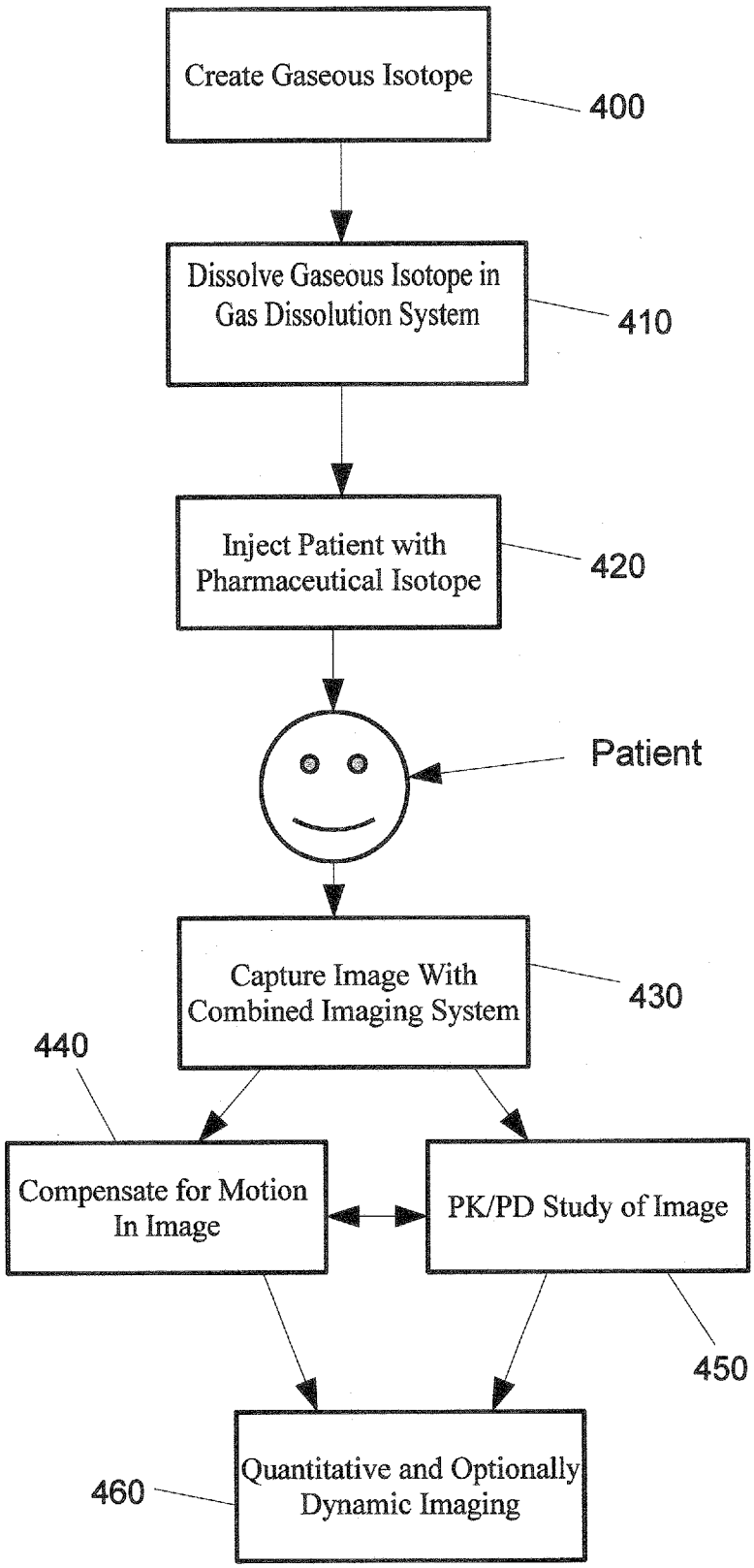

Create Gaseous Isotope
400
Dissolve Gaseous Isotope in Gas Dissolution System
410
Inject Patient with Pharmaceutical Isotope
420
Patient
Capture Image With Combined Imaging System
430
440
Compensate for Motion In Image
PK/PD Study of Image
450
Quantitative and Optionally Dynamic Imaging
460

FIG. 40A

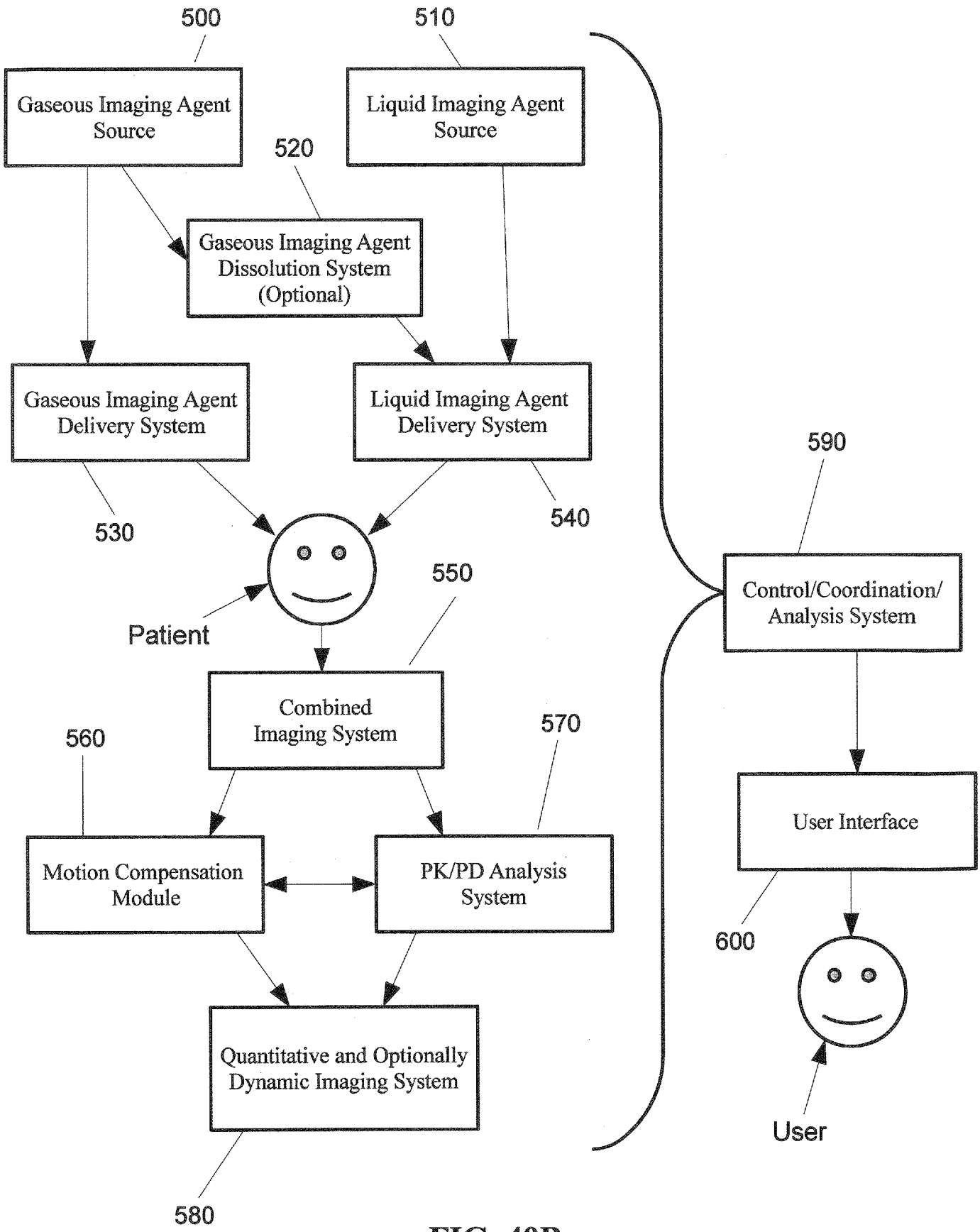

500
510
Gaseous Imaging Agent Source
Liquid Imaging Agent Source
520
Gaseous Imaging Agent Dissolution System (Optional)
Gaseous Imaging Agent Delivery System
Liquid Imaging Agent Delivery System
530
540
590
Patient
550
Control/Coordination/ Analysis System
Combined Imaging System
560
570
User Interface
Motion Compensation Module
PK/PD Analysis System
600
Quantitative and Optionally Dynamic Imaging System
User
580

FIG. 40B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/24203

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61B 6/03; G21F 5/14 (2015.01)
CPC - G06F 19/3406; A61B6/548
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)
CPC -- G06F 19/3406; A61B6/548

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)
PubWEST (USPT,PGPB,JPAB,EPAB); Google
Search Terms: Radiopharmaceutical radioisotope blurry motion compensation detection generator injection module processing automated GUI interface flush magnetic resonance positron emission tomography

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 7,734,331 B2 (Dhawale et al.) 08 June 2010 (08.06.2010), entire document especially abstract, col 3, ln 30-40, col 4, ln 50-65, col 5, ln 45-65, col 4, ln 45-65, col 6, ln 25-55; fig. 1	1-2, 5-7, 9-14, 16-17, 19 and 21-23 --- 3-4, 8, 15, 18, 20 and 24
Y	US 7,747,309 B2 (Prince) 29 June 2010 (29.06.2010), entire document especially abstract, col 6, ln 25-35, col 15, ln 30-40, col 5, ln 10-20 and col 14, ln 37-60	3-4, 8, 15, 18, 20 and 24

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

* 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
25 May 2015 (25.05.2015)	22 JUN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)