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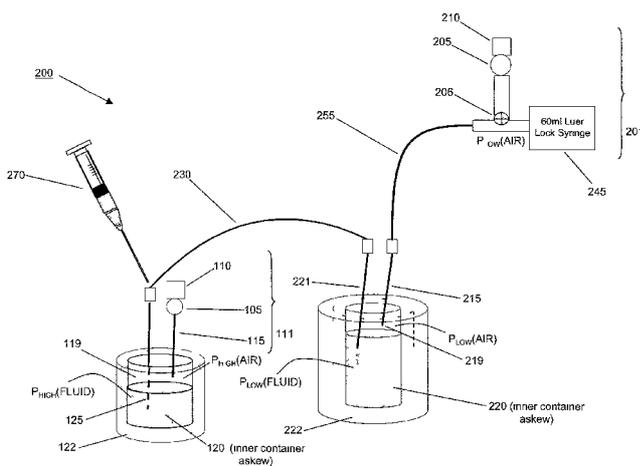


FIG 2

(57) Abstract: Described herein are infusion systems and methods for delivering a radiopharmaceutical agent to a subject without exposing an administering health care professional to a potentially deleterious amount of radiation.

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INFUSION AND TRANSFER SYSTEM FOR USE WITH RADIOACTIVE AGENTS

BACKGROUND

5 Radiopharmacology is the study and preparation of radiopharmaceuticals, *i.e.*, radioactive pharmaceuticals. Radiopharmaceuticals are used in the field of nuclear medicine as tracers in the diagnosis and treatment of many diseases.

 Radiotherapy can also be delivered through infusion (into the bloodstream) or ingestion. Examples are the infusion of metaiodobenzylguanidine (MIBG) to
10 treat neuroblastoma, of oral iodine-131 to treat thyroid cancer or thyrotoxicosis, and of hormone-bound lutetium-177 and yttrium-90 to treat neuroendocrine tumors (peptide receptor radionuclide therapy). Another example is the injection of radioactive glass or resin microspheres into the hepatic artery to radioembolize liver tumors or liver metastases.

15 Radiolabeled macromolecules have also been and are being developed. Radioimmunotherapeutic agents, for example, FDA-approved Ibritumomab tiuxetan (Zevalin), which is a monoclonal antibody anti-CD20 conjugated to a molecule of Yttrium-90, Tositumomab Iodine-131 (Bexxar), which conjugates a molecule of Iodine-131 to the monoclonal antibody anti-CD20, were the first
20 radioimmunotherapy agents approved for the treatment of refractory non-Hodgkin's lymphoma.

 Although radiolabeled agents are being developed and are increasingly more effective at treating particular diseases and disorders, they involve certain risks, especially to health care professionals, and especially when required in large doses.
25 Improved methods and devices are needed for the delivery of radiolabeled therapeutics.

SUMMARY

 Described herein are infusion systems and methods for delivering a radiopharmaceutical agent to a subject, such that an administering health care
30 professional does not get exposed to a potentially deleterious amount of radiation.

The systems and methods described herein allow for combined, *i.e.*, increased radiation doses to be delivered to the subject. The infusion and transfer systems of the present invention can be used to deliver any radiopharmaceutical agent that has a potentially deleterious amount of radiation.

5 One embodiment is directed to a dose delivery infusion system, comprising: at least one first reservoir containing a radiopharmaceutical agent with a cannula inserted into the reservoir and a airtight connector that connects the cannula to a second reservoir; and a radiation shield surrounding the at least one first reservoir. In one embodiment, the at least one first reservoir is a vial containing the
10 radiopharmaceutical agent. In one embodiment, the vial comprises a slanted bottom. In one embodiment, the system further comprises a filtered vent connected to the at least one first reservoir. In one embodiment, the radiation shield is lead. In one embodiment, the second reservoir is attached to an infusion pump. In one embodiment, the agent is a radiopharmacological agent labeled with an isotope
15 selected from the group consisting of: Technetium-99m (technetium-99m), Iodine-123 and 131, Thallium-201, Gallium-67, Yttrium-90, Samarium-153, Strontium-89, Phosphorous-32, Rhenium- 186, Fluorine- 18 and Indium- 111. In one embodiment, the radiopharmaceutical agent is selected from the group consisting of: Bexxar[®] (Iodine 1-131 Tositumomab), Zevalin[®] (Yttrium Y-90 fbritumomab Tiuxetan),
20 Quadramet[®] (Samarium Sm-153 Lexidronam), Strontium-89 chloride, Phosphorous-32, Rhenium- 186 hydroxyethylidene, Samarium-153 lexidronam, 1-131 Iobenguane (Azedra[®]), Y-90 edotreotide (Onalta[®]) and an 1-131 labeled benzamide (Solazed[®]).

One embodiment is directed to a method for delivering an effective dose of a
25 radiopharmaceutical agent, comprising, infusing the radiopharmaceutical agent using a system comprising: at least one first reservoir containing a radiopharmaceutical agent with a cannula inserted into the reservoir and a airtight connector that connects the cannula to a second reservoir; and a radiation shield surrounding the at least one first reservoir. In one embodiment, the at least one first
30 reservoir is a vial containing the radiopharmaceutical agent. In one embodiment, the vial comprises a slanted bottom. In one embodiment, the system used in the method further comprises a filtered vent connected to the at least one first reservoir. In one

embodiment, the radiation shield is lead. In one embodiment, the second reservoir is attached to an infusion pump. In one embodiment, the radiopharmaceutical agent is selected from the group consisting of: Bexxar[®] (Iodine 1—131 Tositumomab), Zevalin[®] (Yttrium Y-90 Ibritumomab Tiuxetan), Quadramet[®] (Samarium Sm-153 Lexidronam), Strontium-89 chloride, phosphorous-32, rhenium-186 hydroxyethylidene, samarium-153 lexidronam, 1-131 Iobenguane, Y-90 edotreotide and an 1-131 labeled benzamide.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a schematic of an 1-131 Iobenguane (MIBG) therapeutic infusion system in accordance with an embodiment of the present invention.

FIG. 2 shows a schematic of an 1-131 Iobenguane (MIBG) therapeutic dose transfer system in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

Described herein are apparatus systems and methods for administering radiolabeled compounds to a subject such that, for example, greater than about 700 mCi can be delivered in a manner that does not expose health care professionals to a hazardous radiation dose. As used herein, the term "subject" refers to an animal. The animal can be a mammal, *e.g.*, either human or non-human. A subject can be, for example, primates (*e.g.*, monkeys, apes and humans), cows, pigs, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. As used herein, the term "dose" refers to an effective amount of a therapeutic agent. Doses can be measured in, for example, any measure of quantity including, for example, a unit for measuring radioactive dose. Doses are known for known therapeutic agents, and, if not known, one of skill in the art would be able to determine an effective amount of a therapeutic agent. As used herein, the term "efficacy" refers to the degree to which a desired effect is obtained, and an "effective amount" is an amount sufficient to produce a desired therapeutic effect.

Background

Nuclear medicine is a branch of medicine and medical imaging that uses the nuclear properties of matter in diagnosis and therapy. It produces images that reflect biological processes that take place at the cellular and subcellular level.

Nuclear medicine procedures use pharmaceuticals that have been labeled with radionuclides (radiopharmaceuticals). In diagnosis, radioactive substances are administered to patients and the radiation emitted is detected. The diagnostic tests involve the formation of an image using a gamma camera or positron emission
5 tomography. Imaging may also be referred to as radionuclide imaging or nuclear scintigraphy. Other diagnostic tests use probes to acquire measurements from parts of the body, or counters for the measurement of samples taken from the patient.

In therapy, radionuclides are administered to treat disease or provide palliative pain relief. For example, administration of Iodine-131 is often used for the
10 treatment of thyrotoxicosis and thyroid cancer. Phosphorus-32 was formerly used in treatment of polycythemia vera. Those treatments rely on the killing of cells by high radiation exposure, as compared to diagnostics in which the exposure is kept as low as reasonably achievable (ALARA policy) so as to reduce the chance of inducing a cancer.

15 **Diagnostic testing**

Diagnostic tests in nuclear medicine exploit the way that the body handles substances differently when there is disease or pathology present. The radionuclide introduced into the body is often chemically bound to a complex that acts characteristically within the body; this is commonly known as a tracer. In the
20 presence of disease, a tracer will often be distributed around the body and/or processed differently. For example, the ligand methylene-diphosphonate (MDP) can be preferentially taken up by bone. By chemically attaching technetium-99m to MDP, radioactivity can be transported and attached to bone via the hydroxyapatite for imaging. Any increased physiological function, such as due to a fracture in the
25 bone, will usually mean increased concentration of the tracer. This often results in the appearance of a 'hot-spot', which is a focal increase in radio-accumulation, or a general increase in radio-accumulation throughout the physiological system. Some disease processes result in the exclusion of a tracer, resulting in the appearance of a 'cold-spot'. Many tracer complexes have been developed to image or treat many
30 different organs, glands, and physiological processes.

Types of studies

A typical nuclear medicine study involves administration of a radionuclide into the body by intravenous injection in liquid or aggregate form, ingestion while combined with food, inhalation as a gas or aerosol, or rarely, injection of a
5 radionuclide that has undergone micro-encapsulation. Some studies require the labeling of a patient's own blood cells with a radionuclide (leukocyte scintigraphy and red blood cell scintigraphy). Most diagnostic radionuclides emit gamma rays, while the cell-damaging properties of beta particles are used in therapeutic applications. Refined radionuclides for use in nuclear medicine are derived from
10 fission or fusion processes in nuclear reactors, which produce radioisotopes with longer half-lives, or cyclotrons, which produce radioisotopes with shorter half-lives, or take advantage of natural decay processes in dedicated generators, *i.e.*, molybdenum/technetium or strontium/rubidium. Commonly used intravenous radionuclides include, but are not limited to:

- 15 Technetium-99m (technetium-99m)
- Iodine- 123 and 131
- Thallium-201
- Gallium-67
- Fluorine- 18
- 20 Indium-111

Radiation dose

A patient undergoing a nuclear medicine procedure will receive a radiation dose. Under present international guidelines, it is assumed that any radiation dose, however small, presents a risk. The radiation doses delivered to a patient in a
25 nuclear medicine investigation present a very small risk of inducing cancer. In this respect, it is similar to the risk from X-ray investigations except that the dose is delivered internally rather than from an external source such as an X-ray machine. As discussed above, health care professionals, although exposed to much lower radiation doses, are also at risk because of their exposure to the multiple
30 administrations of radiation to numerous patients.

The radiation dose from a nuclear medicine investigation is expressed as an effective dose with units of sieverts (usually given in millisieverts, mSv). The effective dose resulting from an investigation is influenced by the amount of radioactivity administered in megabecquerels (MBq), the physical properties of the radiopharmaceutical used, its distribution in the body and its rate of clearance from the body.

Effective doses can range from 6 μ Sv (0.006 mSv) for a 3 MBq chromium-51 EDTA measurement of glomerular filtration rate to 37 mSv for a 150 MBq thallium-201 non-specific tumor imaging procedure. The common bone scan with 600 MBq of technetium-99m-MDP has an effective dose of 3 mSv.

Other units of measurement include the Curie (Ci), being 3.7×10^{10} Bq, and also 1.0 grams of Radium (Ra-226); the Rad (radiation absorbed dose), now replaced by the Gray; and the Rem (Rad Equivalent Man), now replaced with the Sievert. The Rad and Rem are essentially equivalent for almost all nuclear medicine procedures, and only alpha radiation will produce a higher Rem or Sv value, due to its much higher Relative Biological Effectiveness (RBE).

Radiopharmaceutical Agents

A radiopharmaceutical agent can be any agent that requires infusion for administration to a subject for a diagnostic or therapeutic purpose. A radiopharmaceutical dose is measured in the amount of radiation delivered, *e.g.*, mCi. The system and methods described herein can deliver a dose of, for example, >700 mCi, about 200 mCi to about 700 mCi, about 250 mCi to about 500 mCi, or about 300 mCi to more than about 700 mCi.

The systems and methods described herein can be used to deliver any radiopharmaceutical agent to a subject, including, but not limited to, a radiopharmacological agent labeled with an isotope selected from the group consisting of: Technetium-99m (technetium-99m), Iodine-123 and 131, Thallium-201, Gallium-67, Yttrium-90, Samarium-153, Strontium-89, Phosphorous-32, Rhenium-186, Fluorine-18 and Indium-111. Examples of radiopharmaceutical agents that can be delivered using the present invention include, but are not limited to, Bexxar[®] (Iodine 1-131 Tositumomab), Zevalin[®] (Yttrium Y-90 Ibritumomab Tiuxetan), Quadramet[®] (Samarium Sm-153 Lexidronam), Strontium-89 chloride,

phosphorous-32, rhenium-186 hydroxyethylidene, samarium-153 lexidronam, 1-131 Iobenguane, Y-90 edotreotide or an 1-131 labeled benzamide. The systems and methods described herein are infusion systems and methods that reduce the amount of potentially deleterious radiation exposure otherwise experienced by, for example, a health care professional or patient.

The infusion systems and methods described herein allow for the combination of one or more vials containing a radiopharmaceutical agent, thereby allowing for the infusion delivery of an increased dose to the patient, without exposing a health care professional to a harmful level of radiation.

10 **Dosage Delivery and Infusion System**

FIG. 1 shows a schematic of a radiopharmaceutical agent, *e.g.*, 1-131 Iobenguane (MIBG), infusion system in accordance with an embodiment of the present invention. In some embodiments, the therapeutic infusion system 100 includes a 0.22 μm syringe filter 105 that is attached to a charcoal filter unit 110 and to a 20G x 1" Luer Lock needle 115 at the opposite end of the charcoal filter unit 110. The unit, including the 0.22 μm syringe filter 105, the charcoal filter unit 110, and the 20G x 1" Luer Lock needle 115, make up a venting unit 111. The venting unit 111 is inserted into a patient dose vial 120. In some embodiments, the patient dose vial 120 includes a 100 mL sterile vial. In some embodiments, there can be more than one dose vial, thereby allowing for multiplying the dose for the infusion system. In some embodiments, the patient dose vial(s) 120 includes a slanted bottom, and is askew to a lead (Pb) shield 122. The lead shield 122 prevents one or more radioactive elements contained in the patient dose vial 120 from contaminating one or more of operators and a patient.

In some embodiments, a 19G x 3.5" aspirating needle 125 is attached to a secondary line 130 and to a Luer Lock cannula 135 at the opposite end of the 19G x 5" aspirating needle 125. In some embodiments, the secondary line 130 is a 24" male-male (M-M) arterial pressure tubing. In some embodiments, an A-clamp 140 is clamped to the secondary line 130, initially inhibiting fluid flow between the 19G x 5" aspirating needle 125 and the Luer Lock cannula 135. The Luer Lock cannula 135 is inserted into a primary tubing injection site above a single channel infusion

pump 145. In some embodiments, the A-clamp 140 is flushed prior to clamping the secondary line 130.

In some embodiments, the Luer Lock cannula 135 is also attached to a normal saline reservoir 150. An infusion pump primary line 155b and 155c
5 connects the normal saline reservoir 150, supported above the patient dose vial 120 by an intravenous (IV) stand 155, to the primary tubing injection site above the single channel infusion pump 145.

In some embodiments, the A-clamp 140 is open, the primary line check valve 156 is closed, and the primary line check valve 155c is open. As such, the
10 lowered pressure at the primary tubing injection site above the single channel infusion pump 145 pulls a fluid from the patient dose vial 120 through the secondary line 130, the Luer Lock cannula 135, and an infusion pump primary line 155c and into the single channel infusion pump 145, and on to a patient through an infusion pump delivery line 160. The venting unit 111 prevents a pressure equalization
15 between the primary tubing injection site above the single channel infusion pump 145 and the patient dose vial 120, which would inhibit the fluid flow from the patient dose vial 120.

In some embodiments, a setting on the single channel infusion pump 145 can set an infusion rate for the fluid from the patient dose vial 120. In some
20 embodiments, a fill volume in the patient dose vial 120 is 50 mL, and a recommended infusion rate is 100 mL per hour. In some embodiments, the infusion will occur over a 30 minute period at the recommended infusion rate. In some embodiments, an infusion rate can be set by an in-line flow regulator valve with a locking wheel 146. In some embodiments, the in-line flow regulator valve with a
25 locking wheel 146 may be in one of the primary line 155c, the secondary line 130, and the infusion pump delivery line 160. In some embodiments, the fluid from the patient dose vial 120 is 1-131 Iobenguane.

In some embodiments, the A-clamp 140 is then closed and the primary line check valve 156 is opened. As such, the lowered pressure at the primary tubing
30 injection site above the single channel infusion pump 145 pulls a saline solution from the saline reservoir 150 through the primary lines 155b and 155c, the primary line check valves 156 and 155c, and the Luer Lock cannula 135, and into the single

channel infusion pump 145, effectively flushing the primary lines 155b and 155c of the fluid from the patient dose vial 120.

In some embodiments, the A-clamp 140 is then opened and the primary line check valve 155c is closed. As such, the height differential between the saline reservoir 150 and the patient dose vial 120 allows the saline solution from the saline reservoir 150 to flow through the primary line 155b, the Luer Lock cannula 135, and secondary line 130 into the patient dose vial 120, effectively flushing the secondary line 130 of the fluid from the patient dose vial 120. In some embodiments, the saline reservoir 150 consists of at least 50 mL of a 0.9% NaCl solution.

FIG. 2 shows a schematic of a radiopharmaceutical dose transfer system in accordance with an embodiment of the present invention. The radiopharmaceutical dose transfer system 200 allows for transferring a fluid from a shipping vial 120' to a sealed patient dose vial 220. In some embodiments, the dose transfer system 200 includes a 0.22 μm syringe filter 105', a charcoal filter unit 110', and a 20G x 1" Luer Lock needle 115', which collectively make up a venting unit 111' analogous to the venting unit 111 described previously for the radiopharmaceutical infusion system 100 given in FIG. 1. Additionally, the radiopharmaceutical dose transfer system 200 includes a shipping vial 120' and a 19G x 3.5" aspirating needle 125' analogous to the patient dose vial 120 and the 19G x 3.5" aspirating needle 125 described previously for the radiopharmaceutical infusion system 100 given in FIG. 1. The analogous elements in systems 100 and 200 represent an identical method in which the fluid is extracted from the patient dose vial 120 in system 100 and the shipping vial 120' in system 200.

The venting unit 111' is inserted into the shipping vial 120'. The venting unit 111' keeps an ambient pressure in the shipping vial head 119', resulting in an ambient fluid pressure in the shipping vial 120'. In some embodiments, the shipping vial 120' includes a 30 mL sterile vial. In some embodiments, the shipping vial 120' includes a slanted bottom, and is askew to a lead shield 122'. The lead shield 122' prevents one or more radioactive elements contained in the shipping vial 120' from contaminating one or more of operators and a patient.

In some embodiments, the radiopharmaceutical dose transfer system 200 further includes a transfer tubing set 201, which includes a 0.22 μm syringe filter 205 attached to a charcoal filter unit 210, a three-way stopcock valve 206 attached to the opposite end of the 0.22 μm syringe filter 205, and a 60 mL Luer Lock syringe 245. Drawing back the plunger of the 60 mL Luer Lock syringe 245 with the three-way stopcock valve 206 closed creates a vacuum in a primary air line 255 and a sealed patient dose vial head 219 of the sealed patient dose vial 220. In some embodiments, the sealed patient dose vial 220 seal is a 2OG x 1" Luer Lock needle 215, connected directly to the three-way stopcock valve 206 and sealed at the sealed patient dose vial 220. The reduced pressure in the sealed patient dose vial head 219 results in a reduced fluid pressure in the sealed patient dose vial 220.

The differential pressure between the fluid in the shipping vial 120' and the fluid in the sealed patient dose vial 220 pulls the fluid in the shipping vial 120' through the 19G x 3.5" aspirating needle 125', a secondary line 230, and a 2OG x 1.5" Luer Lock needle 221 into the sealed patient dose vial 220. The venting unit 111' prevents a pressure equalization between the fluid in the shipping vial 120' and the fluid in the sealed patient dose vial 220 by pinning the pressure of the fluid in the shipping vial 120' to the ambient pressure.

In some embodiments, the primary air line 255 is a 48" extension set male-female (M-F) connector. In some embodiments, the secondary line 230 is a 12" arterial pressure tubing male-male (M-M) connector.

In some embodiments, the sealed patient dose vial 220 includes a 100 mL sterile vial. In some embodiments, the sealed patient dose vial 220 includes a slanted bottom, and is askew to a lead (Pb) shield 222. The Pb shield 222 prevents one or more radioactive elements contained in the sealed patient dose vial 220 from contaminating one or more of operators and a patient.

In some embodiments, following a fluid transfer from the shipping vial 120' to the sealed patient dose vial 220, the three-way stopcock valve 206 is opened and the plunger of the 60 mL Luer Lock syringe 245 is depressed to equalize the pressure in the sealed patient dose vial head 219 to the ambient pressure and to remove excess air from the primary air line 255.

In some embodiments, the radiopharmaceutical dose transfer system 200 can provide multiple dosing levels by repeating the previously outlined steps for system 200 without replacing the sealed patient dose vial 220. In some embodiments, following completion of the previously outlined steps for the radiopharmaceutical dose transfer system 200, the dose itself may require a fine adjustment.

In some embodiments, the fine adjustment may be made to the radiopharmaceutical dose by placing the shipping vial 120' on its side inside its Pb shield 122' and, using a shielded 10 mL syringe 270 with a 20G x 1.5" needle, removing a volume from the shipping vial 120' necessary to achieve a prescribed dose, and transferring the contents of the syringe 270 volume to the sealed patient dose vial 220. In some embodiments, the pressure in the sealed patient dose vial 220 may be reduced from a positive pressure resulting from the fluid transfer to an ambient pressure by pulling back the plunger of the syringe 270 to remove an equal volume of air from the sealed patient dose vial 220.

Similarly, in some embodiments a required volume of sterile water may be added to the sealed patient dose vial 220 using the shielded 10 mL syringe 270 with the 20G x 1.5" needle, removing a volume from a sterile water vial (not shown) necessary to achieve a prescribed total volume, and transferring the sterile water contents of the syringe 270 volume to the sealed patient dose vial 220. In some embodiments, the pressure in the sealed patient dose vial 220 may be reduced from a positive pressure resulting from the fluid transfer to an ambient pressure by pulling back the plunger of the syringe 270 to remove an equal volume of air from the sealed patient dose vial 220.

Example: 1-131 Iobenguane Dosage Delivery and Infusion System

The recommended 1-131 Iobenguane (Azedra[®]) Drug Delivery System can deliver a therapeutic dose to a subject. Described herein is an 1-131 Iobenguane Drug Delivery System and procedures for use.

1-131 Iobenguane is used for the treatment of metastatic neuroendocrine tumors such as pheochromocytoma, carcinoid and neuroblastoma that are not amenable to treatment with surgery or conventional chemotherapy. The 1-131 Iobenguane Drug Product consists of an MIBG molecule radiolabeled by chemically binding to a radioactive Iodine isotope through Ultratrace[®] technology. The iodine

isotope acts either diagnostically for imaging disease or therapeutically to deliver targeted radiation to the tumor site. 1-131 Iobenguane incorporates an iodine isotope, targets specific tumor cells and does not contain unwanted carrier molecules, or cold contaminants. Cold contaminants are avoided using our
5 proprietary Ultratrace[®] technology.

Clinical Overview:

1-131 Iobenguane has received Orphan Drug status and a Fast Track designation by the FDA. A Phase I dosimetry trial was completed and was designed to evaluate the safety, tolerability and distribution of 1-131 Iobenguane in adult
10 patients with one of two forms of neuroendocrine cancer (*e.g.*, cardinal or pheochromocytoma) .

The primary objective for the 1-131 Iobenguane Phase I portion is designed to determine the maximum tolerated dose (MTD) of Ultratrace[®] Iobenguane 1-131. The Phase II portion is designed to show that Ultratrace[®] Iobenguane 1-131
15 monotherapy administered at the MTD found in the phase I study is safe and effective for refractory high-risk pheochromocytoma/neuroblastoma.

Drug Delivery System

Described herein is an overview and description of the recommended apparatus and its intended use, as well as a guideline for sites to use when
20 purchasing commercially available components and assembling the apparatus for delivery of the 1-131 Iobenguane product, although it will be appreciated that the dose delivery and infusion system can be readily applied to any radiopharmaceutical agent.

The recommended 1-131 Iobenguane Drug Delivery System consists of the
25 following configurations: 1) Therapeutic Infusion System and 2) Therapeutic Dose Transfer System, refer to attached schematics, component lists and guidelines for use.

- 4.1 MIP Therapeutic System Schematics
 - 4.1.1 Therapeutic Infusion System
 - 4.1.2 Therapeutic Dose Transfer System
- 4.2 Component Lists
- 4.3 MIP Working Practice Guidelines

30

4.3.1 Therapeutic Dose Transfer Process

4.3.2 Therapeutic Infusion System

1-131 Iobenguane (1-131 MIBG) Therapeutic Infusion System Working Practice Guideline

- 5 1. Obtain operating IV access. Preferred IV access sites: Bilateral forearms (non-dominant side recommended), bilateral hands (not wrists). If preferred IV access sites are unobtainable, elbow and wrist access is possible but immobilization of the extremity is strongly recommended to avoid extravasation of the site. A central line is also acceptable.
- 10 2. Hang a 250 mL bag of 0.9% Sodium Chloride Solution for Injection, USP and spike the bag using the infusion pump primary set and prime the tubing.
3. Attach the primary line to the IV access site on the patient.
4. For the primary line (0.9% Sodium Chloride) the recommended rate is 100 mL per hour. Allow the primary line to run for at least 30 minutes.
- 15 5. Attach 0.22 μ m syringe filter to the charcoal filter unit and attach a 20G x 1" needle to the opposite end of the filter. Insert the whole unit into the patient dose vial.
6. Attach the 19G x 5" aspirating needle to 24" M-M arterial pressure tubing. To the other end of the tubing attach the Luer Lock cannula.
- 20 7. Attach an A-clamp to the arterial pressure line and clamp it completely. Insert the cannula into primary tubing injection site above the pump.
8. Flush the arterial line by releasing the A-clamp. Clamp the line once it has been flushed.
9. Line up the 5" aspirating needle with the line on the pig and insert it into the patient dose vial at a slight angle. CAUTION: 5" Aspirating needle can catch side
25 of plastic vial. Ensure that 5" needle has reached the bottom of the vial.
10. Using the piggyback setting on the pump, set infusion rate of I-131 Iobenguane (1-131 MIBG). The fill volume in the patient dose vial is 50 mL, and the recommended rate is 100 mL per hour. The infusion of I-131 Iobenguane (1-131
30 MIBG) will occur over 30 minutes at the recommended rate.
11. Using an A-clamp, clamp the primary line slightly above the secondary line injection site.

12. Remove the A-clamp on the arterial pressure tubing (secondary line). Begin the infusion by watching the arterial pressure tubing to make sure 1-131 Iobenguane (1-131 MIBG) is being administered.
13. After 25 minutes, watch for air bubbles in the arterial pressure tubing. Once
5 the first air bubbles form in the arterial pressure tubing clamp off the tubing.
14. Remove the clamp from the primary line and flush the remaining volume of 1-131 Iobenguane in the primary line with at least 50 mL of 0.9% Sodium Chloride to administer residual drug.
15. Unclamp the secondary tubing and to allow the 0.9% Sodium Chloride
10 solution to flush any residual 1-131 Iobenguane (1-131 MIBG) in the in the secondary tubing back into the patient dose vial.
16. Clamp the primary tubing near the patient when the 0.9% Sodium Chloride flush is complete and detach the patient from the IV tubing.
17. Return used dose vial to radiopharmacy and measure residual activity and
15 record on CRP.

1-131 Iobenguane (1-131 MIBG) Therapeutic Dose Transfer Protocol

1. Determine the activity required for a patient dose based on the dosing protocol and patient's weight; add 5% to account for loss in administration.
2. Insert the empty 100 mL patient dose vial into a lead shield and swab the
20 septum top and the septum of the shipping vials in the warming shields with an alcohol swab.
3. Assemble the "venting unit" by attaching the male end of a charcoal filter to the female end of a 0.22 μm filter and 20G x 1" needle to the male end of the filter.
4. Insert the "venting unit" into an 1-131 Iobenguane shipping vial.
- 25 5. Assemble the "transfer tubing set" by attaching a 20G x 1" needle to the male end of the 48" M-F extension set and the female end to the 3-way stopcock.
6. To the female "T" port of the stopcock, attach a 0.22 μm filter and to the female end of the filter attach a charcoal filter.
7. To the in-line female port of the 3-way stopcock attach an empty 60 mL
30 syringe.
8. Insert the 20G x 1" needle of the "transfer tubing set" into the empty 100 mL patient dose vial.

9. Attach a 20G x 1.5" needle to the 12" M-M arterial pressure tubing and connect the opposite end of the line to the 19G x 3.5" aspirating needle.
10. Insert the 20G x 1.5" needle into the patient dose vial and insert the 19G x 3" aspirating needle into the shipping vial to the bottom of the angled warming shield
5 (*i.e.*, tip of aspirating needle at the lowest point inside the vial)
11. Draw back the plunger of the 60 mL syringe to vacuum transfer the solution from the 1-131 Iobenguane shipping vial to the patient dose vial.
12. Close the 3-way stopcock to the patient dose vial line (open to the charcoal trap). Depress the plunger of the 60 mL syringe to push out the air. Open the
10 patient dose vial line on the 3-way stopcock.
13. If more than ONE VIAL is needed to fulfill the patient dose repeat steps 4-9.
14. Remove the needles from the patient dose vial and assay in a dose calibrator.
15. Calculate additional mL required to adjust the patient dose to the prescribed activity (add 5% for loss during administration).
- 15 16. Place the unused shipping vial inside its lead shield on its side and using a shielded 10 mL syringe with a 20G x 1.5" needle, remove the volume necessary to achieve the prescribed dose. Add the syringe contents to the patient dose vial. Pull back the plunger of the syringe to remove an equal volume of air from the patient dose vial to avoid a state of positive pressure in the vial.
- 20 17. Based on the volume (mL) of drug transferred to the patient dose vial, calculate the amount of Sterile Water for Injection, USP needed to QS the dose to a final volume of 50 mL.
18. Using an empty 60 mL syringe with a 20G x 1" needle, draw up the required volume of Sterile Water for Injection, USP and add it to the patient dose vial. Pull
25 back the plunger of the syringe to remove an equal volume of air from the patient dose vial to avoid a state of positive pressure in the vial.
19. Remove all the needles from the patient dose vial and measure the radioactivity in a radionuclide dose calibrator to verify the patient dose.
20. Record the patient dose on the case report form.

EQUIVALENTS

The present disclosure is not to be limited in terms of the particular embodiments described in this application, which are intended as illustrations of various aspects. Many modifications and variations can be made without departing
5 from the spirit and scope of the disclosure, as will be apparent to those skilled in the art. Functionally equivalent methods, systems, and apparatus within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is
10 to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments
15 only, and is not intended to be limiting. As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof.

While various aspects and embodiments have been disclosed herein, other
20 aspects and embodiments will be apparent to those skilled in the art. AU references cited herein are incorporated by reference in their entirety.

CLAIMS

What is claimed is:

1. A dose delivery infusion system, comprising:
at least one first reservoir containing a radiopharmaceutical agent with a
5 cannula inserted into the reservoir and a airtight connector that
connects the cannula to a second reservoir; and
a radiation shield surrounding the at least one first reservoir.
2. The dose delivery system of Claim 1, wherein the at least one first reservoir
is a vial containing the radiopharmaceutical agent.
- 10 3. The dose delivery system of Claim 2, wherein the vial comprises a slanted
bottom.
4. The dose delivery system of Claim 1, further comprising a filtered vent
connected to the at least one first reservoir.
5. The dose delivery system of Claim 1, wherein the radiation shield is lead.
- 15 6. The dose delivery system of Claim 1, wherein the second reservoir is
attached to an infusion pump.
7. The dose delivery system of Claim 1, wherein the radiopharmaceutical agent
is selected from the group consisting of: Bexxar® (Iodine 1-131
Tositumomab), Zevalin® (Yttrium Y-90 Ibritumomab Tiuxetan),
20 Quadramet® (Samarium Sm-153 Lexidronam), Strontium-89 chloride,
phosphorous-32, rhenium-186 hydroxyethylidene, samarium-153 lexidronam,
1-131 Iobenguane, Y-90 edotreotide and an 1-131 labeled benzamide.
8. A method for delivering an effective dose of a radiopharmaceutical agent,
comprising, infusing the radiopharmaceutical agent using a system
25 comprising:
at least one first reservoir containing a radiopharmaceutical agent with a
cannula inserted into the reservoir and a airtight connector that
connects the cannula to a second reservoir; and
a radiation shield surrounding the at least one first reservoir.

9. The method of Claim 8, wherein the at least one first reservoir is a vial containing the radiopharmaceutical agent.
10. The method of Claim 9, wherein the vial comprises a slanted bottom.
11. The method Claim 8, further comprising a filtered vent connected to the at
5 least one first reservoir.
12. The method of Claim 8, wherein the radiation shield is lead.
13. The method of Claim 8, wherein the second reservoir is attached to an infusion pump.
14. The method of Claim 8, wherein the radiopharmaceutical agent is selected
10 from the group consisting of: Bexxar[®] (Iodine 1-131 Tositumomab),
Zevalin[®] (Yttrium Y-90 Ibritumomab Tiuxetan), Quadramet[®] (Samarium
Sm-153 Lexidronam), Strontium-89 chloride, phosphorous-32, rhenium-186
hydroxyethylidene, samarium-153 lexidronam, 1-131 Iobenguane, Y-90
edotreotide and an 1-131 labeled benzamide.

15

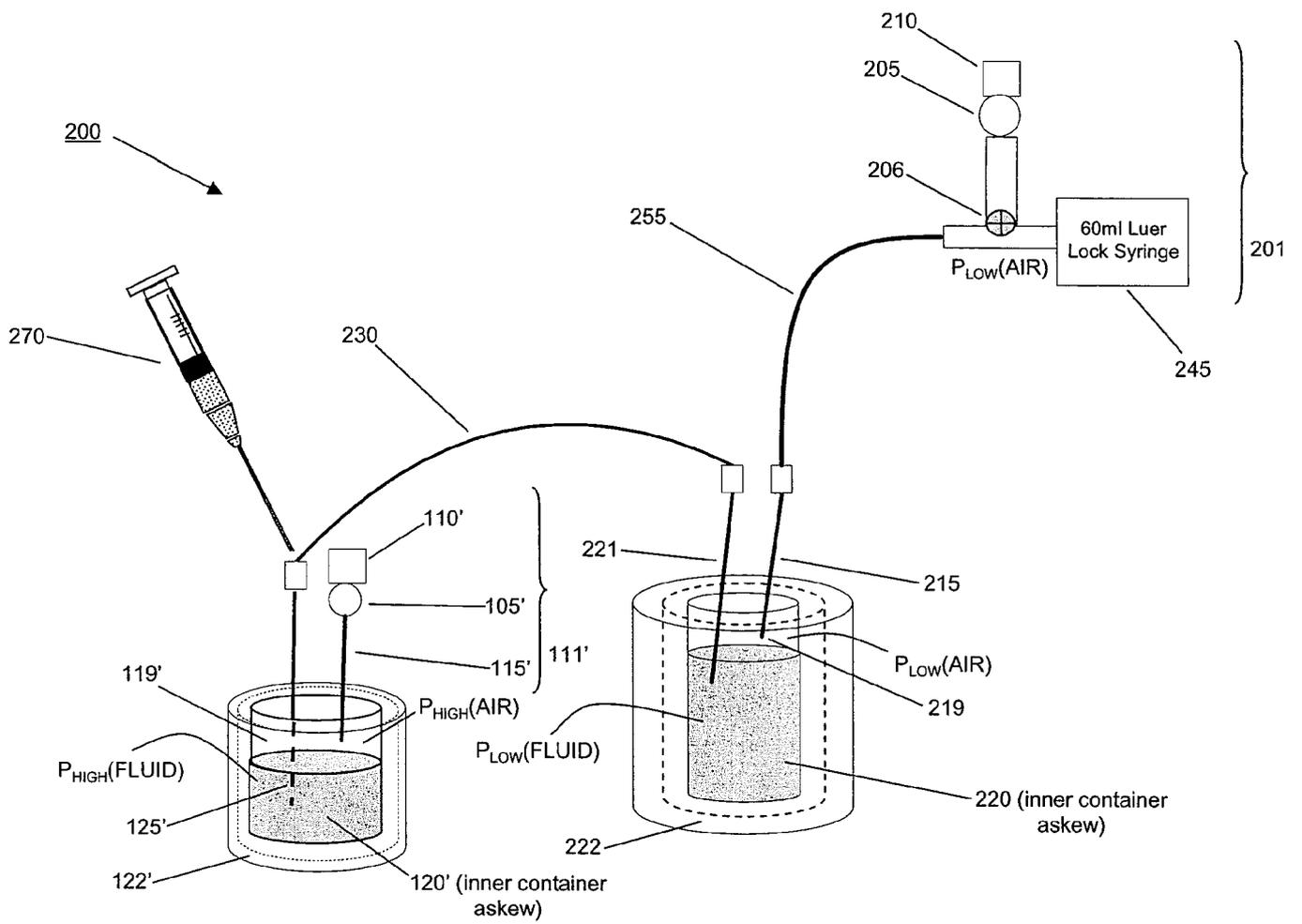


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/076426

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61M5/178 A61M5/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61M B65B

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 769 811 A (NEMOTO KYORINDO CO LTD [JP]) 4 April 2007 (2007-04-04) the whole document -----	1-7
X	US 4 401 108 A (GALKIN BENJAMIN M [US] ET AL) 30 August 1983 (1983-08-30) the whole document -----	1-7
A	EP 1 820 730 A (TEMA SINERGIE S R L [IT]) 22 August 2007 (2007-08-22) abstract -----	1
A	WO 2005/118031 A (E Z EM INC [US]; WILLIAMS ROBERT C JR [US]) 15 December 2005 (2005-12-15) abstract -----	1
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

23 December 2008

Date of mailing of the international search report

12/01/2009

Name and mailing address of the ISA/

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Authorized officer

Niel sen , Michael

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/076426

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2000 350783 A (SUMITOMO HEAVY INDUSTRIES) 19 December 2000 (2000-12-19) abstract -----	1
A	EP 1 616 587 A (UNIV ZUERICH [CH]) 18 January 2006 (2006-01-18) abstract -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/076426

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) (or the following reasons:

1. Claims Nos.: 8-14
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39. K iv) PCT- Method for treatment of the human or animal body by surgery
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the Invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No PCT/US2008/076426
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Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
EP 1769811	A	04-04-2007	WO 2005123161 A1 US 2008300483 A1	29-12-2005 04-12-2008
US 4401108	.A	30-08-1983	NONE	
EP 1820730	A	22-08-2007	AT 401245 T EP 1975065 A2 WO 2007096742 A1	15-08-2008 01-10-2008 30-08-2007
WO 2005118031	A	15-12-2005	AT 387227 T CA 2567517 A1 EP 1755704 A1 ES 2303266 T3 JP 2008500119 T US 2005277833 A1	15-03-2008 15-12-2005 28-02-2007 01-08-2008 10-01-2008 15-12-2005
OP 2000350783	A	19-12-2000	NONE	
EP 1616587	A	18-01-2006	WO 2006007750 A1 CN 1984690 A JP 2008506428 T	26-01-2006 20-06-2007 06-03-2008