Norbert J. Pelc, Sc.D.

BRACCO
LIFE FROM INSIDE

CDX-0002C.01

Bracco Ex. 2013
Jubilant v. Bracco
IPR2018-01449

Norbert J. Pelc, Sc.D.

- 1974: B.S., University of Wisconsin, Appl. Math, Engineering & Physics
- 1979: Sc.D., Harvard University, Medical Radiological Physics
- Served on the first National Advisory Council of the National Institute of Biomedical Imaging and Bioengineering of the NIH
- Member, National Academy of Engineering
- >40 years in medical imaging (11 in industry)
- Professor of Bioengineering, Radiology, and, by courtesy, Electrical Engineering, Stanford University

Assignments

- Provide an opinion regarding Bracco's assertion of assignor estoppel
- Respond to Respondents' arguments that the asserted claims are invalid based on:
  - Anticipation
  - Obviousness
  - Prosecution laches
  - Improper inventorship

Person of Ordinary Skill in the Art

- A POSITA at the time of the inventions claimed in the Asserted Patents would generally have:
  - a graduate degree in medicine and/or in a medical related science, including physics, chemistry, biology, physiology, and/or biophysics, or a related field
  - at least some clinical, research, and/or design experience with respect to PET imaging and/or PET imaging systems.
- An individual with an undergraduate degree along with significant experience could also be sufficiently skilled.
  - Amount of experience following an undergraduate degree would depend on the level of formal education and amount of experience working with radiopharmaceuticals.
  - Such a person may be working as part of a team.

Legal Principles

Legal Principles

- **Validity**
  - Presumption of Validity
  - Assignor Estoppel
  - Anticipation
  - Non-Obviousness
  - Prosecution Laches
  - Inventorship

Legal Principles

- **Presumption of Validity**
  - Issued claims are presumed valid.
  - To overcome this presumption, Respondents must show by clear and convincing evidence that the challenged claims are invalid.

Legal Principles

- **Assignor Estoppel**
  - One who assigns a patent to another party is an assignor.
  - The assignor and those in privity with the assignor are estopped from contesting the validity or enforceability of that patent when sued for infringement.

Legal Principles

- **Anticipation**
  - A claim is anticipated when the Respondents show by clear and convincing evidence that each and every element set forth in the claim is found, either expressly or inherently, in a single prior art reference, before the priority date.

Legal Principles

- **Non-Obviousness**
  - A claim is obvious when the Respondents show by clear and convincing evidence that the differences between the patented invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a POSITA.
  - The obviousness inquiry should not be performed with the benefit of hindsight, but instead must be based on the knowledge at the time of the invention.
  - It is not enough to demonstrate that each limitation was independently known in the art, there must have been a reason to combine the element in the manner claimed and there must have been a reasonable expectation of success in doing so.
  - Objective factors bearing on the question of non-obviousness may include, commercial success; long-felt but unmet need in the art; failures of others to meet a need met by the invention; unexpected results achieved by the invention; and praise of the invention by others.

Legal Principles

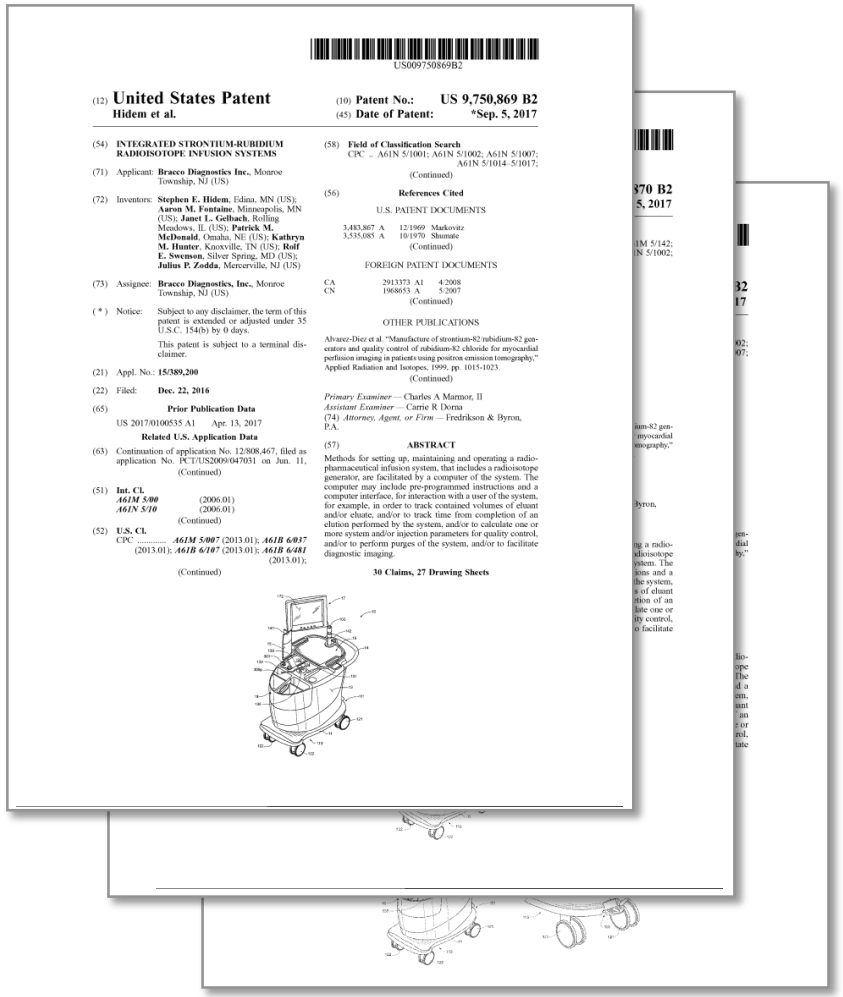
- **Prosecution Laches**
  - A patent may be unenforceable when it has issued only after an unreasonable and unexplained delay in prosecution that constitutes an egregious misuse of the statutory patent system under the totality of the circumstances.
  - The mere passage of time from a patent application filing to the issuance of the patent is insufficient, in and of itself, to constitute improper delay as a matter of law.

Legal Principles

- **Inventorship**
  - As part of the presumption of validity, the inventors as named in an issued patent are presumed to be correct.
  - To rebut this presumption, a party challenging patent validity for omission of an inventor must present clear and convincing evidence that an omitted individual actually invented the claimed invention.
  - A good faith error in designating inventorship cannot render a patent invalid, and can be corrected.

Asserted Patents

Asserted Patents



US009750869B2

(12) **United States Patent**
Hidem et al.

(10) **Patent No.: US 9,750,869 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS**

(71) Applicant: **Bracco Diagnostics Inc.**, Monroe Township, NJ (US)

(72) Inventors: **Stephen E. Hidem**, Edina, MN (US); **Aaron M. Fontaine**, Minneapolis, MN (US); **Janet L. Gelbach**, Rolling Meadows, IL (US); **Patrick M. McDonald**, Omaha, NE (US); **Kathryn M. Hunter**, Knoxville, TN (US); **Rolf E. Swenson**, Silver Spring, MD (US); **Julius P. Zodda**, Mercerville, NJ (US)

(73) Assignee: **Bracco Diagnostics, Inc.**, Monroe Township, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/389,200**

(22) Filed: **Dec. 22, 2016**

(65) **Prior Publication Data**

US 2017/0100535 A1 Apr. 13, 2017

Related U.S. Application Data

(63) Continuation of application No. 12/808,467, filed as application No. PCT/US2009/047031 on Jun. 11, (Continued)

(51) **Int. Cl.**
A61M 5/00 (2006.01)
A61N 5/10 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 5/007*** (2013.01); ***A61B 6/037*** (2013.01); ***A61B 6/107*** (2013.01); ***A61B 6/481*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC .. A61N 5/1001; A61N 5/1002; A61N 5/1007; A61N 5/1014–5/1017;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,483,867 A 12/1969 Markovitz
3,535,085 A 10/1970 Shumate
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2913373 A1 4/2008
CN 1968653 A 5/2007
(Continued)

OTHER PUBLICATIONS

Alvarez-Diez et al. "Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography," Applied Radiation and Isotopes, 1999, pp. 1015-1023.
(Continued)

Primary Examiner — Charles A Marmor, II
Assistant Examiner — Carrie R Dorna
(74) *Attorney, Agent, or Firm* — Fredrikson & Byron, P.A.

(57) **ABSTRACT**

Methods for setting up, maintaining and operating a radiopharmaceutical infusion system, that includes a radioisotope generator, are facilitated by a computer of the system. The computer may include pre-programmed instructions and a computer interface, for interaction with a user of the system, for example, in order to track contained volumes of eluant and/or eluate, and/or to track time from completion of an elution performed by the system, and/or to calculate one or more system and/or injection parameters for quality control, and/or to perform purges of the system, and/or to facilitate diagnostic imaging.

30 Claims, 27 Drawing Sheets

(12) **United States Patent**
Hidem et al.

(10) **Patent No.: US 9,750,869 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS**

(71) Applicant: **Bracco Diagnostics Inc.**, Monroe Township, NJ (US)

(72) Inventors: **Stephen E. Hidem**, Edina, MN (US); **Aaron M. Fontaine**, Minneapolis, MN (US); **Janet L. Gelbach**, Rolling Meadows, IL (US); **Patrick M. McDonald**, Omaha, NE (US); **Kathryn M. Hunter**, Knoxville, TN (US); **Rolf E. Swenson**, Silver Spring, MD (US); **Julius P. Zodda**, Mercerville, NJ (US)

(58) **Field of Classification Search**
CPC .. A61N 5/1001; A61N 5/1002; A61N 5/1007; A61N 5/1014–5/1017;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,483,867 A 12/1969 Markovitz
3,535,085 A 10/1970 Shumate
(Continued)

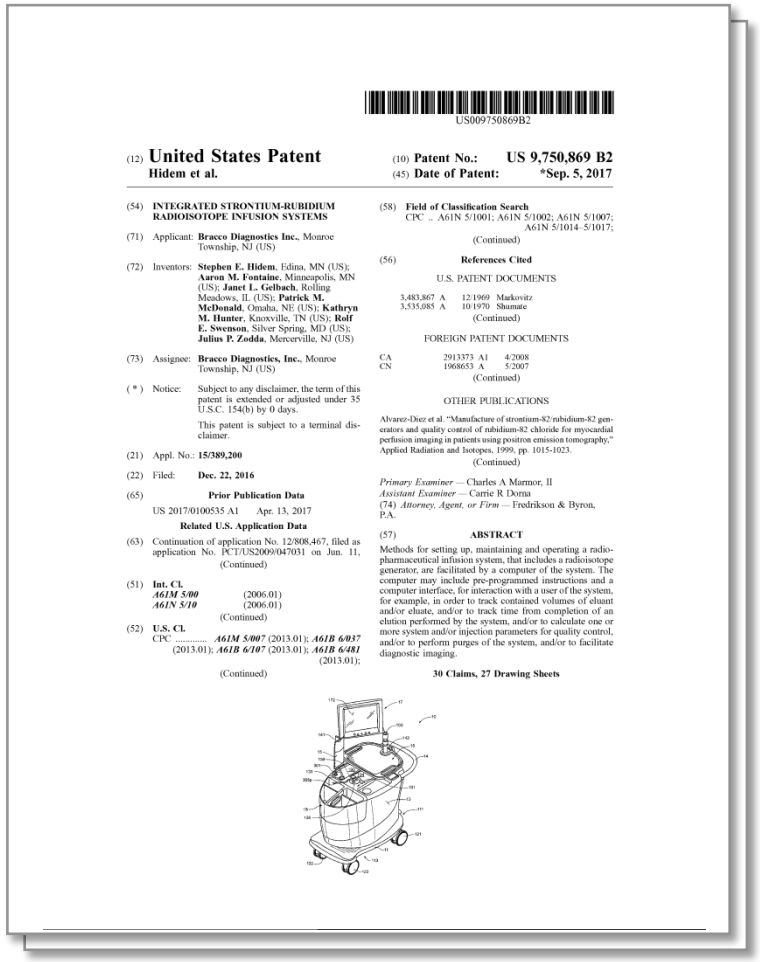
FOREIGN PATENT DOCUMENTS

- 9,750,869 (“’869 Patent”)
- 9,750,870 (“’870 Patent”)
- 9,814,826 (“’826 Patent”)

JX-0001, -0002, 0003

BRACCO
LIFE FROM INSIDE

Asserted Patents



US009750869B2

(12) **United States Patent**
Hidem et al.

(10) **Patent No.: US 9,750,869 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS**

(71) Applicant: **Bracco Diagnostics Inc.**, Monroe Township, NJ (US)

(72) Inventors: **Stephen E. Hidem**, Edina, MN (US); **Aaron M. Fontaine**, Minneapolis, MN (US); **Janet L. Gelbach**, Rolling Meadows, IL (US); **Patrick M. McDonald**, Omaha, NE (US); **Kathryn M. Hunter**, Knoxville, TN (US); **Rolf E. Swenson**, Silver Spring, MD (US); **Julius P. Zodda**, Mercerville, NJ (US)

(73) Assignee: **Bracco Diagnostics, Inc.**, Monroe Township, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/389,200**

(22) Filed: **Dec. 22, 2016**

(65) **Prior Publication Data**

US 2017/0100535 A1 Apr. 13, 2017

Related U.S. Application Data

(63) Continuation of application No. 12/808,467, filed as application No. PCT/US2009/047031 on Jun. 11, (Continued)

(51) **Int. Cl.**
A61M 5/00 (2006.01)
A61N 5/10 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 5/007*** (2013.01); ***A61B 6/037*** (2013.01); ***A61B 6/107*** (2013.01); ***A61B 6/481*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC .. A61N 5/1001; A61N 5/1002; A61N 5/1007; A61N 5/1014–5/1017;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,483,867 A 12/1969 Markovitz
3,535,085 A 10/1970 Shumate
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2913373 A1 4/2008
CN 1968653 A 5/2007
(Continued)

OTHER PUBLICATIONS

Alvarez-Diez et al. "Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography," Applied Radiation and Isotopes, 1999, pp. 1015-1023.
(Continued)

Primary Examiner — Charles A Marmor, II
Assistant Examiner — Carrie R Dorna
(74) *Attorney, Agent, or Firm* — Fredrikson & Byron, P.A.

(57) **ABSTRACT**

Methods for setting up, maintaining and operating a radiopharmaceutical infusion system, that includes a radioisotope generator, are facilitated by a computer of the system. The computer may include pre-programmed instructions and a computer interface, for interaction with a user of the system, for example, in order to track contained volumes of eluant and/or eluate, and/or to track time from completion of an elution performed by the system, and/or to calculate one or more system and/or injection parameters for quality control, and/or to perform purges of the system, and/or to facilitate diagnostic imaging.

30 Claims, 27 Drawing Sheets

Fig. 1A

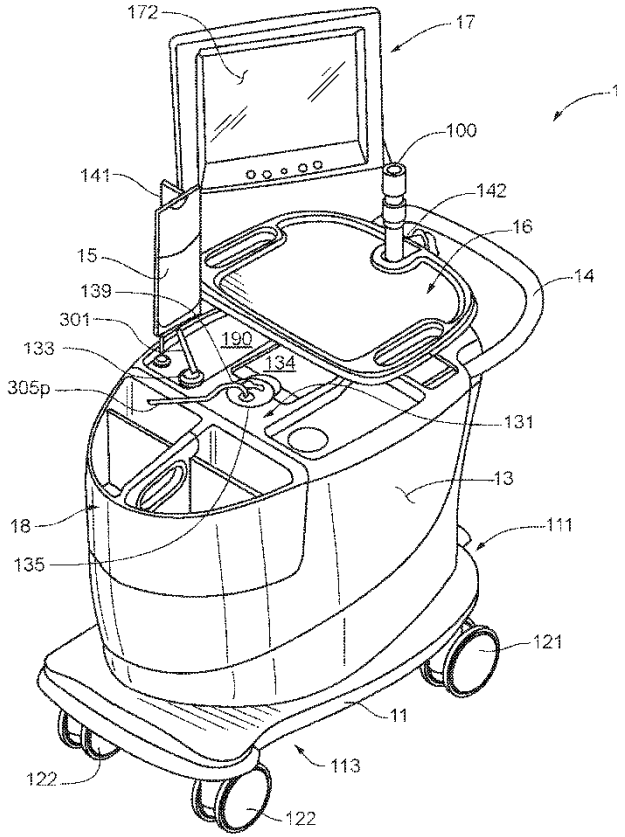
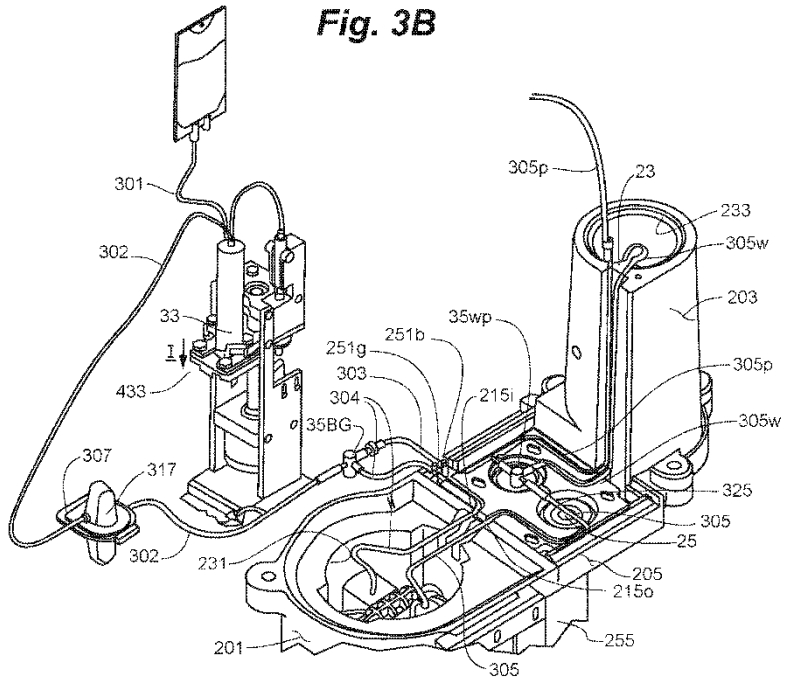


Fig. 3B



JX-0002

BRACCO
LIFE FROM INSIDE

CDX-0002C.15

Asserted Claims

Asserted Patents	Asserted Claims
9,750,869	**1-5, 8, 14, 24,** and **29-30**
9,750,870	**1-2, 8, 10-12, 16-17,** and **27**
9,814,826	**1-3, 5, 9, 11-14,** and **17-19**

BRACCO
LIFE FROM INSIDE

Claim construction

Claim Term	Agreed Construction
"rubidium radioactive eluate"	An eluate that contains radioactive rubidium
"strontium-rubidium radioisotope generator"	A radioisotope generator that contains a radioisotope of strontium, which decays to a radioisotope of rubidium
"strontium breakthrough test result"	Test result representing the amount of a radioisotope of strontium in the test sample relative to the amount of a radioisotope of rubidium in the test sample

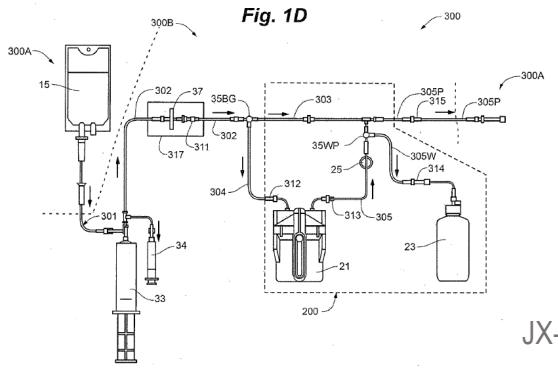
Otherwise, "all limitations in the asserted claims should be given their plain and ordinary meaning." (CX-0125)

Claims are not limited to figures

1. An infusion system on-board a cart comprising:
a cabinet structure that comprises:
a platform,
an exterior shell that extends upwardly above the platform and has a front side; a rear side; two sidewalls connecting the front side to the rear side; and a top surface; wherein the platform and the exterior shell collectively define an interior space of the cabinet structure and wherein the interior space of the cabinet structure is configured to receive a strontium-rubidium radioisotope generator having an inlet tubing port configured to receive saline and an outlet tubing port configured to discharge a rubidium radioactive eluate,
an opening through the exterior shell configured to provide access to the strontium-rubidium radioisotope generator within the interior space of the cabinet structure, and
an opening through the top surface of the exterior shell configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure;
a computer with a touch screen display configured to receive an input from a user for controlling operation of the infusion system, wherein the touch screen display is mounted on a vertical post having a top end extending above the cabinet structure;
a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment;
a first door accessible via the opening through the exterior shell, the first door being configured to provide access to the first shielding compartment and to close over the first opening;
a second shielding compartment having a second opening facing vertically upwardly through which the waste bottle can be inserted into and removed from the second shielding compartment;
a second door accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening;

wherein the first opening is located at a lower elevation than the second opening;
a radioactivity detector positioned to measure radioactivity of the rubidium radioactive eluate flowing through an eluate tubing line in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator;
a shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample; and
wherein the computer of the infusion system is configured to:
provide a stop button on the touch screen display to abort a function of the infusion system in response to a user input activating the stop button,
pump saline from a saline reservoir positioned outside of the interior space of the cabinet structure into the strontium-rubidium radioisotope generator through the inlet tubing port of the strontium-rubidium radioisotope generator thereby generating the rubidium radioactive eluate that is discharged through the outlet tubing port,
fill the eluate reservoir in the shielded well on-board the cart with the test sample of the rubidium radioactive eluate,
determine a strontium breakthrough test result on the test sample filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, and
not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.

'869 Patent (JX-0002.043-44)



JX-0002.008

It should be noted that, according to alternate embodiments, system **10** includes an 'on board' dose calibrator for quality control tests, and circuit **300** is expanded to include elements for an automated collection of eluate samples for activity measurements, via the on board dose calibrator. According to a first set of these alternate embodiments, a sample collection reservoir is integrated into circuit **300**, downstream of divergence valve **35**WP and in communication with tubing line **305**P, in order to receive quality control test samples of eluate, via tubing line **305**P, and both the reservoir and the dose calibrator are located in a separate shielded well. According to a second set of these alternate embodiments, waste bottle **23** is configured to receive the quality control test samples of eluate, via tubing line **305**W, and a dose calibrator is integrated into shielding assembly **200**. Quality control procedures will be described in greater detail below, in conjunction with FIGS. **6-8**B.

'869 Patent (JX-0002.035); 8:12-23

BRACCO
LIFE FROM INSIDE

Claims of the Asserted Patents go beyond mere automation

1. An infusion system on-board a cart comprising:
a cabinet structure that comprises:
a platform,
an exterior shell that extends upwardly above the platform and has a front side; a rear side; two sidewalls connecting the front side to the rear side; and a top surface; wherein the platform and the exterior shell collectively define an interior space of the cabinet structure and wherein the interior space of the cabinet structure is configured to receive a strontium-rubidium radioisotope generator having an inlet tubing port configured to receive saline and an outlet tubing port configured to discharge a rubidium radioactive eluate,
an opening through the exterior shell configured to provide access to the strontium-rubidium radioisotope generator within the interior space of the cabinet structure, and
an opening through the top surface of the exterior shell configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure;
a computer with a touch screen display configured to receive an input from a user for controlling operation of the infusion system, wherein the touch screen display is mounted on a vertical post having a top end extending above the cabinet structure;
a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment;
a first door accessible via the opening through the exterior shell, the first door being configured to provide access to the first shielding compartment and to close over the first opening;
a second shielding compartment having a second opening facing vertically upwardly through which the waste bottle can be inserted into and removed from the second shielding compartment;
a second door accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening;

wherein the first opening is located at a lower elevation than the second opening;
a radioactivity detector positioned to measure radioactivity of the rubidium radioactive eluate flowing through an eluate tubing line in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator;
a shielded well on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample; and
wherein the computer of the infusion system is configured to:
provide a stop button on the touch screen display to abort a function of the infusion system in response to a user input activating the stop button,
pump saline from a saline reservoir positioned outside of the interior space of the cabinet structure into the strontium-rubidium radioisotope generator through the inlet tubing port of the strontium-rubidium radioisotope generator thereby generating the rubidium radioactive eluate that is discharged through the outlet tubing port,
fill the eluate reservoir in the shielded well on-board the cart with the test sample of the rubidium radioactive eluate,
determine a strontium breakthrough test result on the test sample filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, and
not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.

'869 Patent (JX-0002.043-44)

The invention claimed is:
1. A method of building an infusion system to deliver a rubidium radioactive eluate comprising:
installing a first shielding compartment, a second shielding compartment, and a shielded well on a platform of a cart, wherein:
the first shielding compartment has a first opening facing vertically upwardly,
the first opening is configured for a strontium-rubidium radioisotope generator to be inserted into and removed from the first shielding compartment,
the second shielding compartment has a second opening facing vertically upwardly,
the second opening is configured for a waste bottle to be inserted into and removed from the second shielding compartment,
the first opening is located at a lower elevation than the second opening, and
the shielded well is configured to receive an eluate reservoir that is configured to receive a sample of the rubidium radioactive eluate;
configuring a computer with a touch screen display for the infusion system to:
fill the eluate reservoir in the shielded well on-board the cart with the sample of the rubidium radioactive eluate by pumping saline from a saline reservoir into the strontium-rubidium radioisotope generator via a saline tubing line thereby generating the rubidium radioactive eluate that is discharged through an eluate tubing line,
determine a strontium breakthrough test result on the sample of the rubidium radioactive eluate filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, and
not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.

'826 Patent (JX-0001.043)

BRACCO
LIFE FROM INSIDE

Claims of the Asserted Patents go beyond mere automation

The invention claimed is:

1. A method of using an infusion system on-board a cart to deliver a rubidium radioactive eluate comprising:

installing a saline reservoir on the infusion system, wherein the infusion system comprises a platform and an exterior shell extending upwardly above the platform, and wherein the platform and the exterior shell collectively define an interior space of a cabinet structure;

placing the saline reservoir in fluid communication through a saline tubing line with an inlet tubing port of a strontium-rubidium radioisotope generator located in a first shielding compartment in the interior space of the cabinet structure, wherein the strontium-rubidium radioisotope generator further comprises an outlet tubing port configured to discharge the rubidium radioactive eluate, and wherein the first shielding compartment has a first opening facing vertically upwardly;

inserting a waste bottle into a second shielding compartment on-board the cart, wherein the second shielding compartment on-board the cart has a second opening facing vertically upwardly and being at a higher elevation than the first opening;

placing the waste bottle in fluid communication with the outlet tubing port of the strontium-rubidium radioisotope generator through an eluate tubing line, wherein a computer on-board the cart is configured to control the fluid communication between the waste bottle and the outlet tubing port, and wherein the computer has a touch screen display mounted on a vertical post with a top end extending above the cabinet structure;

inserting an eluate reservoir in a shielded well on-board the cart;

placing the eluate reservoir in fluid communication with the eluate tubing line, wherein the computer is further configured to control the fluid communication between the eluate reservoir and the eluate tubing line;

pumping a sample of the rubidium radioactive eluate into the eluate reservoir in the shielded well on-board the cart;

measuring a radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line with a radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line;

measuring a calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart;

comparing the radioactivity of the sample of the rubidium radioactive eluate flowing through the eluate tubing line measured by the radioactivity detector on-board the cart while the sample of the rubidium radioactive eluate is flowing through the eluate tubing line with the calibration radioactivity of the sample pumped into the eluate reservoir in the shielded well on-board the cart; and

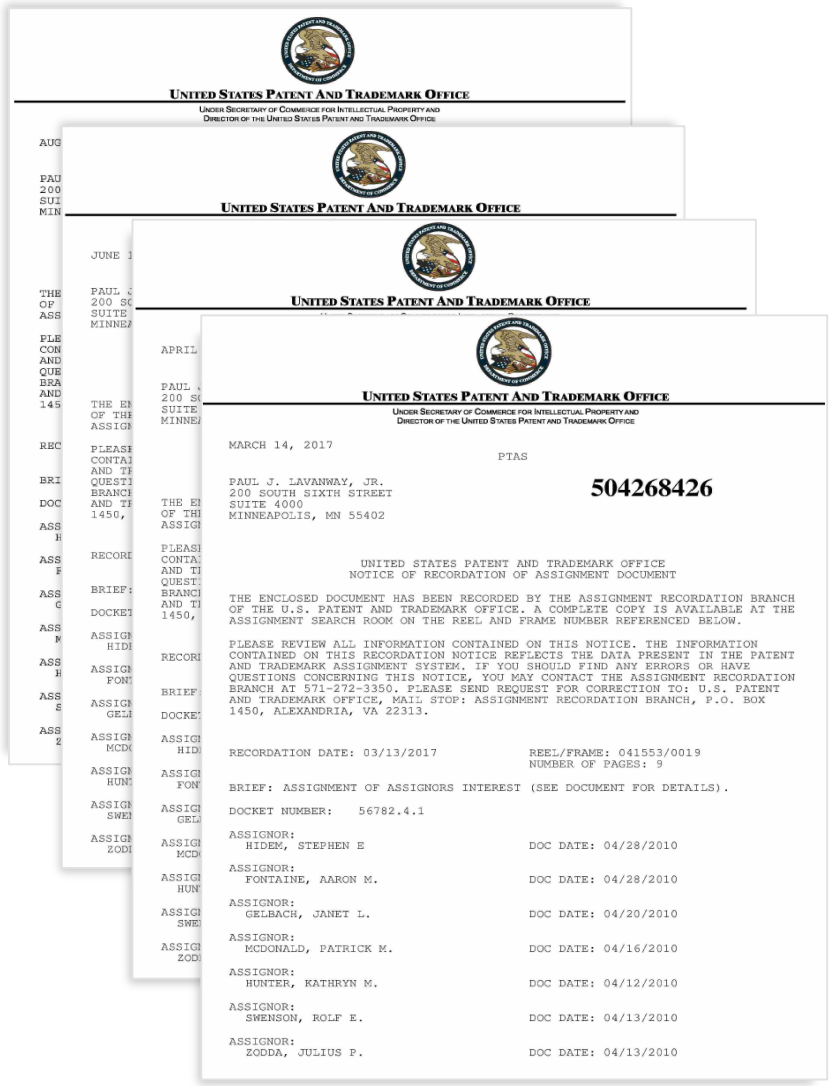
determining a strontium breakthrough test result on the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart, wherein the computer of the infusion system is further configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit.

'870 Patent (JX-0003.043-44)

BRACCO
LIFE FROM INSIDE

Assignor Estoppel

Inventor Janet Gelbach assigned her rights in the Asserted Patents to Bracco



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MARCH 14, 2017

PTAS

PAUL J. LAVANWAY, JR.
200 SOUTH SIXTH STREET
SUITE 4000
MINNEAPOLIS, MN 55402

504268426

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 03/13/2017 REEL/FRAME: 041553/0019
NUMBER OF PAGES: 9

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 56782.4.1

ASSIGNOR: HIDEM, STEPHEN E	DOC DATE: 04/28/2010
ASSIGNOR: FONTAINE, AARON M.	DOC DATE: 04/28/2010
ASSIGNOR: GELBACH, JANET L.	DOC DATE: 04/20/2010
ASSIGNOR: MCDONALD, PATRICK M.	DOC DATE: 04/16/2010
ASSIGNOR: HUNTER, KATHRYN M.	DOC DATE: 04/12/2010
ASSIGNOR: SWENSON, ROLF E.	DOC DATE: 04/13/2010
ASSIGNOR: ZODDA, JULIUS P.	DOC DATE: 04/13/2010

CX-0147, -0148, -0149, -0150

ASSIGNMENT

We, Stephen E. Hidem, residing at 4710 Juneau Lane North, Plymouth, Minnesota 55446, Aaron M. Fontaine, residing at 5663 West Bavarian Pass, Fridley, Minnesota 55432, Janet L. Gelbach, residing at 4204 Shetland Court, New Albany, Indiana 47150, Patrick M. McDonald, residing at 15395 Nicholas Street, Omaha, Nebraska 68154, Kathryn M. Hunter, residing at 1312 Judy Reagan Lane, Knoxville, Tennessee 37931, Rolf E. Swenson, residing at 35 Fieldston Road, Princeton, New Jersey 08540 and Julius P. Zodda, residing at 3 Tigers Court, Mercerville, New Jersey 08619 ("Assignor"), have made invention(s) for which United States and foreign patents and patent applications have been filed and are identified on the attached Schedule 1;

Whereas, Bracco Diagnostics Inc., a Delaware corporation having a place of business at 107 College Road East, Princeton, NJ 08540 ("Assignee"), desires to acquire the entire right, title and interest in and to the United States and foreign patents and patent applications identified on the attached Schedule 1 and in and to the inventions described and claimed therein (the "Patents"); and

NOW, THEREFORE, in exchange for good and valuable consideration, the receipt of which is hereby acknowledged, Assignor hereby assigns to Assignee, and its successors and assigns the following:

(1) The entire right, title and interest to the Patents including the inventions described or claimed therein, and to each U.S. and foreign patent application and patent from which the Patents claim priority to, in whole or in part, and to which the Patents claim priority; and

(2) The entire right, title and interest to any United States or foreign patents that may issue with respect to the inventions described or claimed in the Patents;

(3) The entire right, title and interest to any renewals, reissues, extensions, substitutions, continuations, continuations-in-part, or divisions of the Patents, and all foreign applications based thereon;

(4) The right to apply for patents in foreign countries in its own name and to claim any priority rights to which such foreign applications are entitled under international conventions, treaties or otherwise; and

(5) The right to enforce patent rights to such Patents as fully and entirely as the same would have been held and enjoyed by the Assignors if this assignment had not been made; together with all claims by Assignors for damages by reason of past infringement or for provisional rights and including the right to sue for, and collect the same for its own use and benefit, and for the use and benefit of its successors, assigns, and other legal representatives.

Date: 4-20-2010 Janet L. Gelbach

Janet L. Gelbach

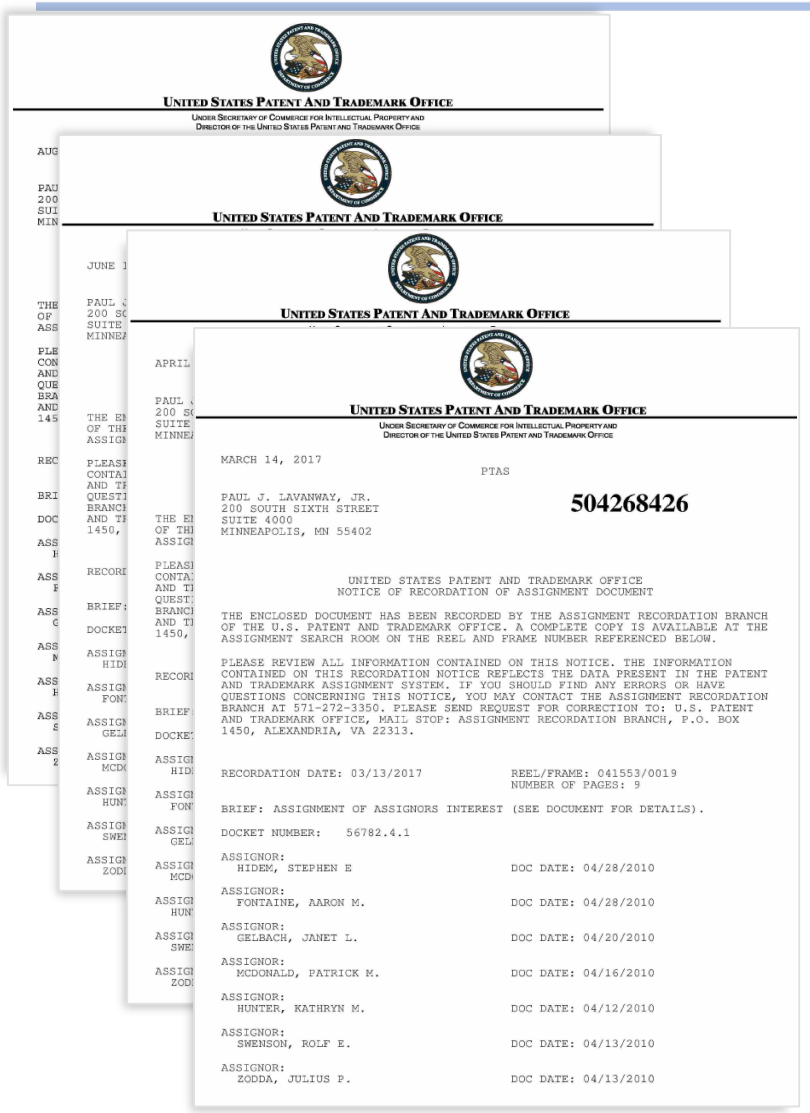
Witnessed by: Esther B. Paris (Signature) on 4-20-10 (Date)

Esther B. Paris (Name)

4204 Shetland Ct. New Albany, IN 47150 (Address)

BRACCO
LIFE FROM INSIDE

Inventor Janet Gelbach assigned her rights in the Asserted Patents to Bracco



UNITED STATES PATENT AND TRADEMARK OFFICE

UNDER SECRETARY OF COMMERCE FOR INTELLECTUAL PROPERTY AND DIRECTOR OF THE UNITED STATES PATENT AND TRADEMARK OFFICE

MARCH 14, 2017

PTAS

PAUL J. LAVANWAY, JR.
200 SOUTH SIXTH STREET
SUITE 4000
MINNEAPOLIS, MN 55402

504268426

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT RECORDATION BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT AND TRADEMARK ASSIGNMENT SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR HAVE QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE ASSIGNMENT RECORDATION BRANCH AT 571-272-3350. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, MAIL STOP: ASSIGNMENT RECORDATION BRANCH, P.O. BOX 1450, ALEXANDRIA, VA 22313.

RECORDATION DATE: 03/13/2017 REEL/FRAME: 041553/0019
NUMBER OF PAGES: 9

BRIEF: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

DOCKET NUMBER: 56782.4.1

ASSIGNOR: HIDEM, STEPHEN E — DOC DATE: 04/28/2010
ASSIGNOR: FONTAINE, AARON M. — DOC DATE: 04/28/2010
ASSIGNOR: GELBACH, JANET L. — DOC DATE: 04/20/2010
ASSIGNOR: MCDONALD, PATRICK M. — DOC DATE: 04/16/2010
ASSIGNOR: HUNTER, KATHRYN M. — DOC DATE: 04/12/2010
ASSIGNOR: SWENSON, ROLF E. — DOC DATE: 04/13/2010
ASSIGNOR: ZODDA, JULIUS P. — DOC DATE: 04/13/2010

SCHEDULE 1

US Patent Applications

Patent App. No.	Date Filed	Title	Attorney Docket No.
12/137,356	6/11/2008	SHIELDING ASSEMBLIES FOR INFUSION SYSTEMS	56782.1.5
12/137,363	6/11/2008	INFUSION SYSTEM CONFIGURATIONS	56782.1.6
12/137,364	6/11/2008	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION AND METHODS OF USE	56782.1.7
12/137,377	6/11/2008	CABINET STRUCTURE CONFIGURATIONS FOR INFUSION SYSTEMS	56782.1.8
12/808,467	6/16/2010	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION AND METHODS OF USE	56782.1.7.2
15/389,200	12/22/2016	INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS	56782.4.1

US Patents

Patent No.	Date Issued	Title

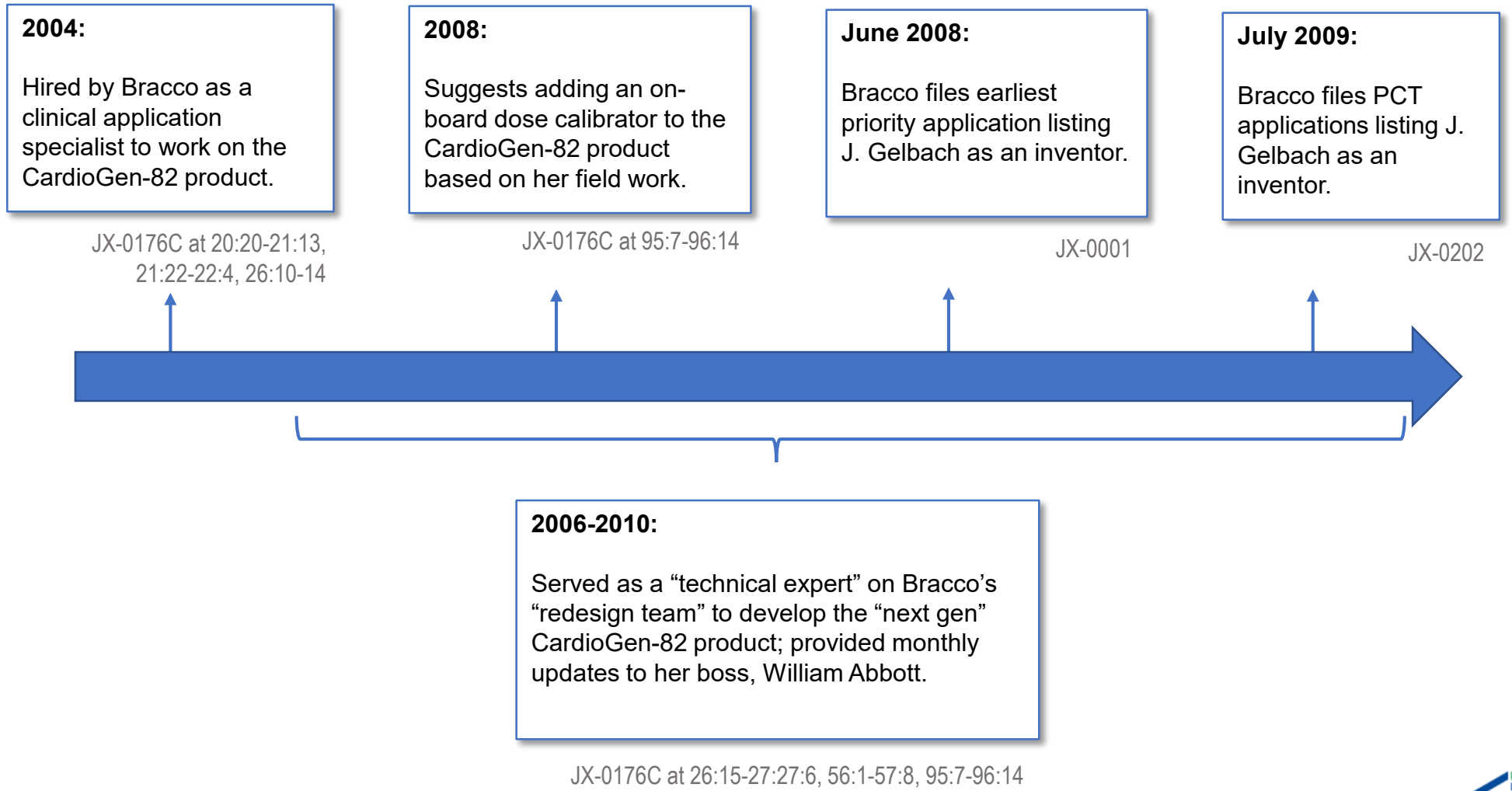
Foreign and International Patent Applications

Country	Patent App. No.	Date Filed	Title	Attorney Docket No.
WO	PCT/US09/47031	6/11/2009	INFUSION SYSTEMS INCLUDING COMPUTER-FACILITATED MAINTENANCE AND/OR OPERATION AND METHODS OF USE	56782.1.7.1

CX-0147, -0148, -0149, -0150

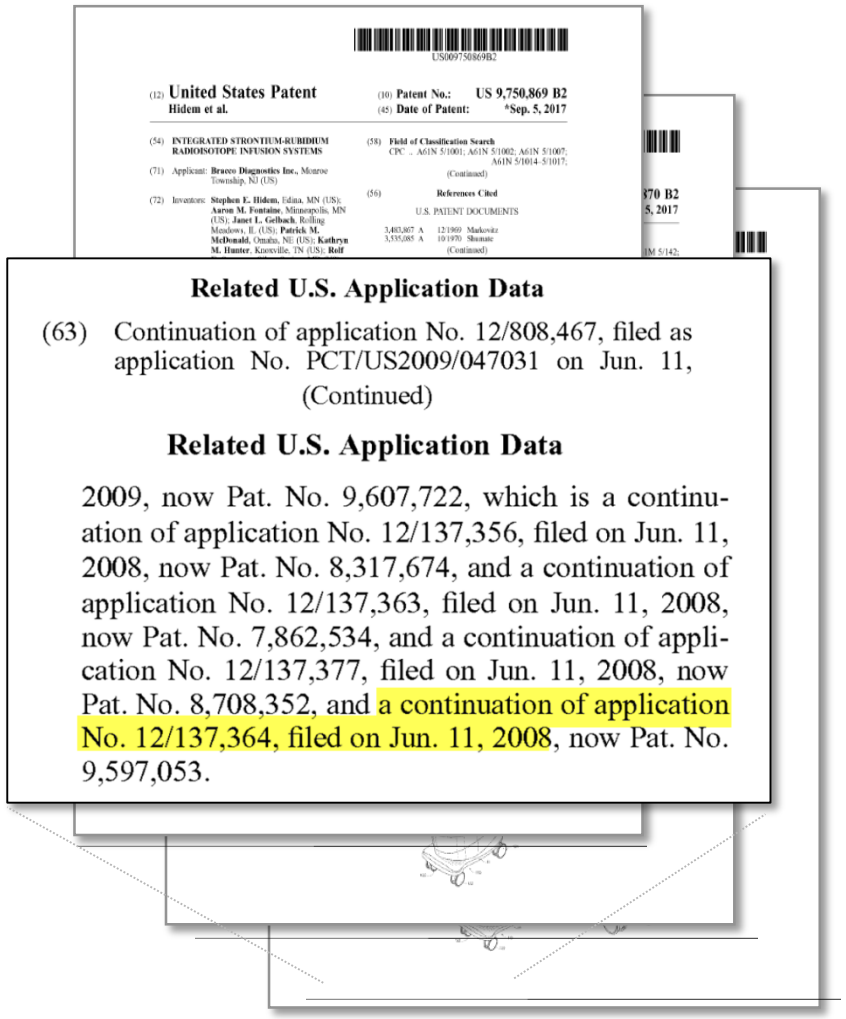
BRACCO
LIFE FROM INSIDE

Janet Gelbach's inventive work for Bracco



Anticipation Rebuttal

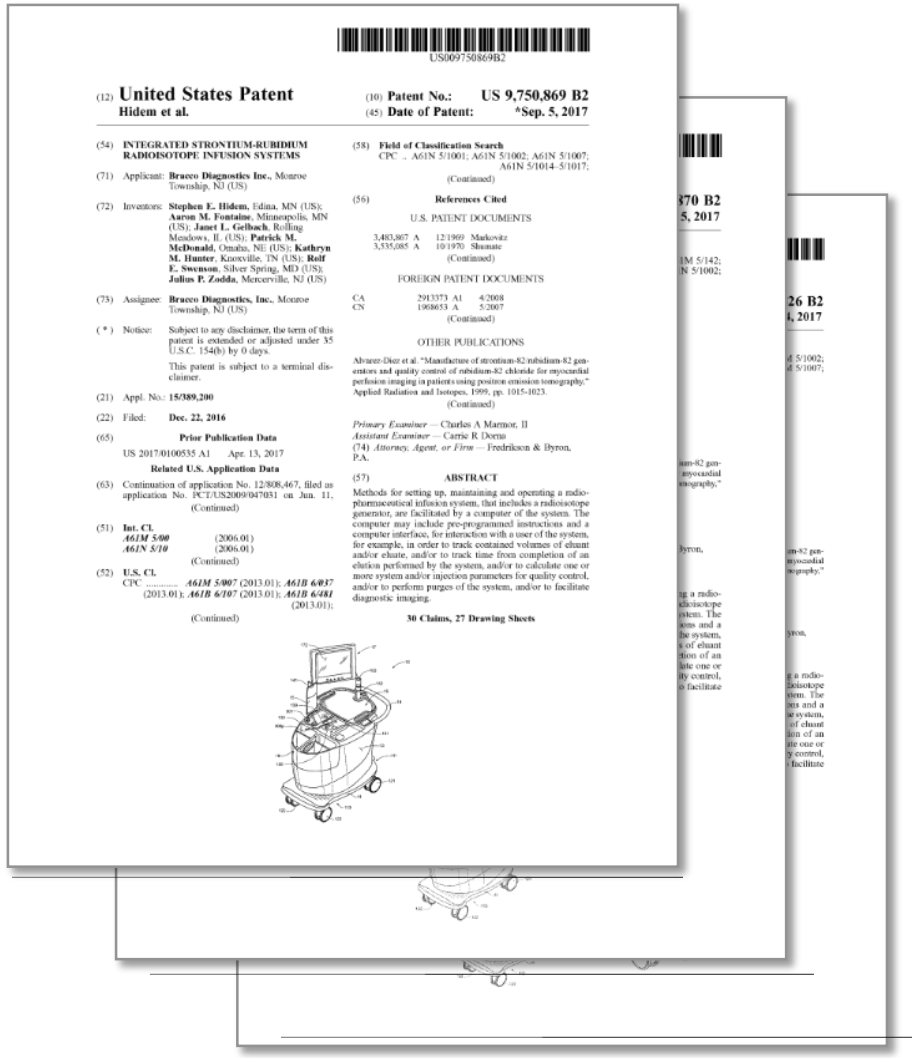
Only alleged anticipating reference is not prior art



- Respondents concede that the priority date of the asserted patents is at least as early as June 2009
- Respondents' only alleged anticipating reference – the 2016 Ruby Manual – is not prior art

Obviousness Rebuttal

Respondents' main alleged prior art references were considered during prosecution of the Asserted Patents



US009750869B2

(12) **United States Patent**
Hidem et al.

(10) **Patent No.: US 9,750,869 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS**

(71) Applicant: **Bracco Diagnostics Inc.**, Monroe Township, NJ (US)

(72) Inventors: **Stephen E. Hidem**, Edina, MN (US); **Aaron M. Fontaine**, Minneapolis, MN (US); **Janet L. Gelbach**, Rolling Meadows, IL (US); **Patrick M. McDonald**, Omaha, NE (US); **Kathryn M. Hunter**, Knoxville, TN (US); **Rolf E. Swenson**, Silver Spring, MD (US); **Julius P. Zodda**, Mercerville, NJ (US)

(73) Assignee: **Bracco Diagnostics, Inc.**, Monroe Township, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/389,200**

(22) Filed: **Dec. 22, 2016**

(65) **Prior Publication Data**

US 2017/0100535 A1 Apr. 13, 2017

Related U.S. Application Data

(63) Continuation of application No. 12/808,467, filed as application No. PCT/US2009/047031 on Jun. 11, (Continued)

(51) **Int. Cl.**
A61M 5/00 (2006.01)
A61N 5/10 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 5/007*** (2013.01); ***A61B 6/037*** (2013.01); ***A61B 6/107*** (2013.01); ***A61B 6/481*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC .. A61N 5/1001; A61N 5/1002; A61N 5/1007; A61N 5/1014-5/1017;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,483,867 A 12/1969 Markovitz
3,535,085 A 10/1970 Shonate
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2913373 A1 4/2008
CN 1983653 A 5/2007
(Continued)

OTHER PUBLICATIONS

Alvarez-Diez et al. "Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography." Applied Radiation and Isotopes, 1999, pp. 1015-1023.
(Continued)

Primary Examiner — Charles A Marmor, II
Assistant Examiner — Carrie R Dorna
(74) *Attorney, Agent, or Firm* — Fredrikson & Byron, P.A.

(57) **ABSTRACT**

Methods for setting up, maintaining and operating a radiopharmaceutical infusion system, that includes a radioisotope generator, are facilitated by a computer of the system. The computer may include pre-programmed instructions and a computer interface, for interaction with a user of the system, for example, in order to track contained volumes of eluant and/or eluate, and/or to track time from completion of an elution performed by the system, and/or to calculate one or more system and/or injection parameters for quality control, and/or to perform purges of the system, and/or to facilitate diagnostic imaging.

30 Claims, 27 Drawing Sheets

JX-0001, -0002, -0003

(56) **References Cited**

OTHER PUBLICATIONS

Lemer Pax, Posijet® Integrated FDG dispensing and infusion system, www.lemerpax.com (copyright date May 2008).

R. Klein, "Precise 82RB infusion system for cardiac perfusion measurement using 3D positron emission tomography", Ottawa-Carleton Institute for Electrical and Computer Engineering School of Information Technology and Engineering (Electrical & Computer Engineering), Feb. 2005, 147 pages.

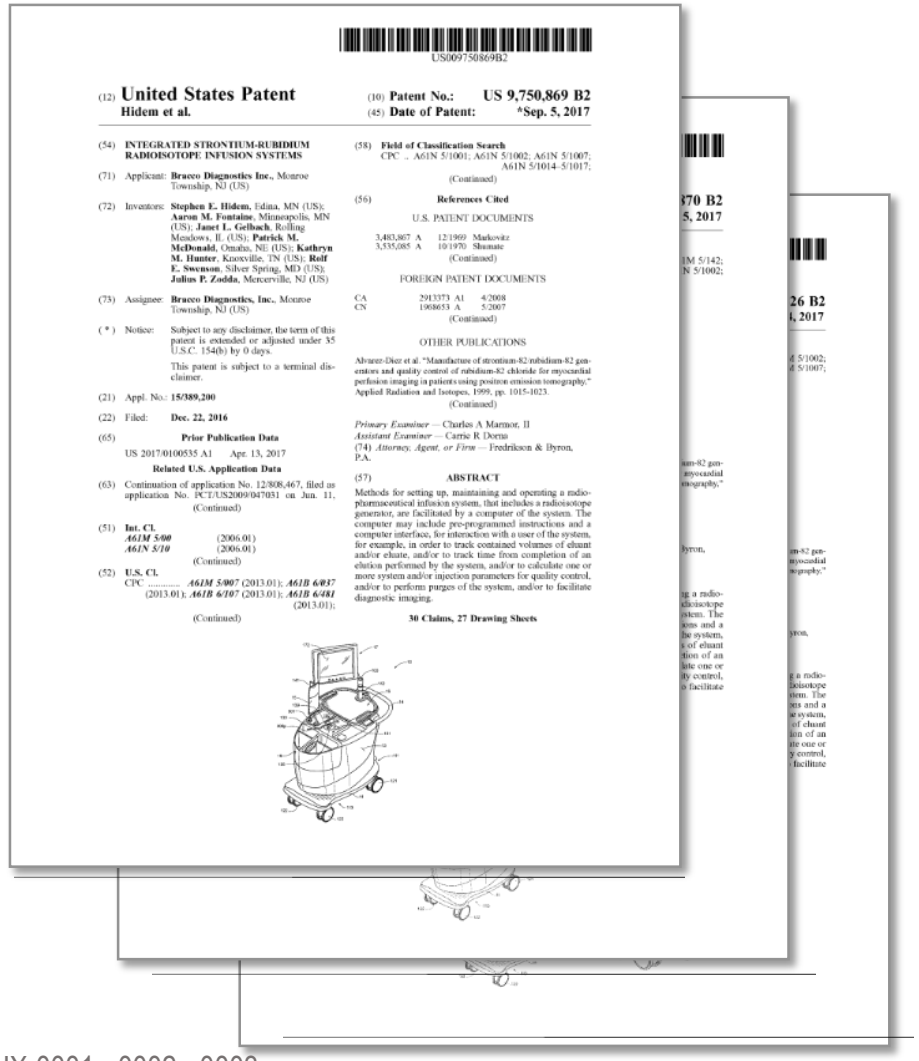
R. Klein, "Precision control of eluted Activity from a Sr/Rb generator for cardiac positron emission tomography", Proceedings of the 26th Annual International Conference of the IEEE EMBS San

"Klein Thesis"

2008/0093564	A1	4/2008	Tartaglia et al.
2008/0166292	A1	7/2008	Levin et al.
2008/0177126	A1	7/2008	Tate et al.
2008/0191148	A1	8/2008	Gibson
2008/0200747	A1	8/2008	Wagner et al.

BRACCO
LIFE FROM INSIDE

Respondents' main alleged prior art references were considered during prosecution of the Asserted Patents



US009750869B2

(12) **United States Patent**
Hidem et al.

(10) **Patent No.: US 9,750,869 B2**
(45) **Date of Patent: *Sep. 5, 2017**

(54) **INTEGRATED STRONTIUM-RUBIDIUM RADIOISOTOPE INFUSION SYSTEMS**

(71) Applicant: **Bracco Diagnostics Inc.**, Monroe Township, NJ (US)

(72) Inventors: **Stephen E. Hidem**, Edina, MN (US); **Aaron M. Fontaine**, Minneapolis, MN (US); **Janet L. Gelbach**, Rolling Meadows, IL (US); **Patrick M. McDonald**, Omaha, NE (US); **Kathryn M. Hunter**, Knoxville, TN (US); **Rolf E. Swenson**, Silver Spring, MD (US); **Julius P. Zodda**, Mercerville, NJ (US)

(73) Assignee: **Bracco Diagnostics, Inc.**, Monroe Township, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/389,200**

(22) Filed: **Dec. 22, 2016**

(65) **Prior Publication Data**

US 2017/0100535 A1 Apr. 13, 2017

Related U.S. Application Data

(63) Continuation of application No. 12/808,467, filed as application No. PCT/US2009/047031 on Jun. 11, (Continued)

(51) **Int. Cl.**
A61M 5/00 (2006.01)
A61N 5/10 (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ***A61M 5/007*** (2013.01); ***A61B 6/037*** (2013.01); ***A61B 6/107*** (2013.01); ***A61B 6/481*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC ... A61N 5/1001; A61N 5/1002; A61N 5/1007; A61N 5/1014-5/1017;
(Continued)

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,480,807 A 12/1969 Markovitz
3,535,085 A 10/1970 Shunate
(Continued)

FOREIGN PATENT DOCUMENTS

CA 2913373 A1 4/2008
CN 1969653 A 5/2007
(Continued)

OTHER PUBLICATIONS

Alvarez-Diez et al. "Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography." Applied Radiation and Isotopes, 1999, pp. 1015-1023.
(Continued)

Primary Examiner — Charles A Marmor, II
Assistant Examiner — Carrie R Dorna
(74) *Attorney, Agent, or Firm* — Fredrikson & Byron, P.A.

(57) **ABSTRACT**

Methods for setting up, maintaining and operating a radiopharmaceutical infusion system, that includes a radioisotope generator, are facilitated by a computer of the system. The computer may include pre-programmed instructions and a computer interface, for interaction with a user of the system, for example, in order to track contained volumes of eluant and/or eluate, and/or to track time from completion of an elution performed by the system, and/or to calculate one or more system and/or injection parameters for quality control, and/or to perform purges of the system, and/or to facilitate diagnostic imaging.

30 Claims, 27 Drawing Sheets

JX-0001, -0002, -0003

OTHER PUBLICATIONS

Brochure, "IV and Liquid Filters: Speedflow Adult 0.2 um Positive", http://www.gvs.it/flex/FixedPages/UK/LiquidFilters.php/L/UK/ID/Speedflow%20Adjust% . . . Retrieved from URL on Nov. 11, 2008.

Bracco Brochure, "Rubidium 82 Infusion System, Easy to Operate . . . Automated . . . Complete", © Bracco Diagnostics, Inc., 0605-002NA, Jun. 2001, (2 pages).

"CardioGen-82 Infusion System User's Guide," Medical Product Service GmbH, Jul. 3, 2007, 53 pages.

BRACCO
LIFE FROM INSIDE

Bracco overcame the examiner's rejections based on Tate during prosecution of parent application

This is because the system of Tate does not generate radiopharmaceuticals but rather merely stores and deliveries a pharmaceutical manufactured elsewhere during a patient procedure. For example, to generate radiopharmaceuticals for use in the Tate system, the reference explains that "the radiopharmaceuticals are typically delivered to a nuclear medicine hospital suite or other medical facility from a radiopharmaceutical synthesis facility (within or outside the hospital or medical facility) equipped with a cyclotron in, for example, a lead-shielded container (often called a "PIG"). Often, the radiopharmaceutical is manually drawn from such containers into a shielded syringe."[11]

11/7/12 Resp. to Office Action

CX-0169.2223

Response to Arguments

13. Applicant's arguments, see pages 2-5 and 8-9 of the Response, filed November 7, 2012, with respect to the qualification of prior art in view of Applicant's priority claims to U.S. applications have been fully considered and are persuasive. The rejection of claims 1 and 38 under 35 U.S.C. § 102(b) over deKemp et al. US '848 and the rejection of claims 37-38, 40-42, and 47 under 35 U.S.C. § 103(a) over Tate in view of Quirico has been withdrawn. However, upon further consideration, new grounds of rejection are made herein.

1/4/13 Office Action

CX-0169.2243

Bracco overcame the examiner's rejections based on Tate during prosecution of parent application

Indeed, Tate does not and cannot disclose a computer pre-programmed to execute a method according to independent claim 1 because Tate does not relate to a system that generates and infuses radiopharmaceuticals via elution within a generator whatsoever. The system of Tate operation, an operator uses a vial carrying system 500 to transport a vial shield 554 containing a vial or container of pharmaceutical to the fluid delivery system.[5] This is because the system of Tate does not generate radiopharmaceuticals but rather merely stores and delivers a pharmaceutical manufactured elsewhere during a patient procedure. For example, to generate

* * *

3/29/13 Resp. to Office Action CX-0169.2498

16. Applicant's arguments, see pages 2-8 of the Remarks, filed March 29, 2013, with respect to the rejections of claims 1-5 and 37-48 under 35 U.S.C. § 103(a) have been fully considered and are persuasive. In particular, Applicant's arguments that Tate cannot provide indications of a time lapse since each elution was completed since Tate does not teach a system that generates radiopharmaceuticals via elution is persuasive. Therefore, the rejection has been withdrawn.

10/2/13 Office Action CX-0169.2686

At least 15 elements of the Asserted Claims are missing from the Klein Thesis

Respondents concede that at least 6 elements of the asserted claims are not disclosed in the Klein Thesis:

1. "first door" / "second door"
2. elevations of "first opening" and "second opening"
3. "shielded well" on the cart
4. "determine/determining a strontium breakthrough test result" in the "eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart" / dose calibrator on-board the cart
5. "two tubing passageways formed in a perimeter surface of the first opening" where "each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a/the first door is closed"
6. computer is configured to (1) "track a volume of saline remaining in the saline reservoir" and (2) provide an alert "via the touch screen display when the volume of saline remaining in the saline reservoir is below a predetermined volume threshold"

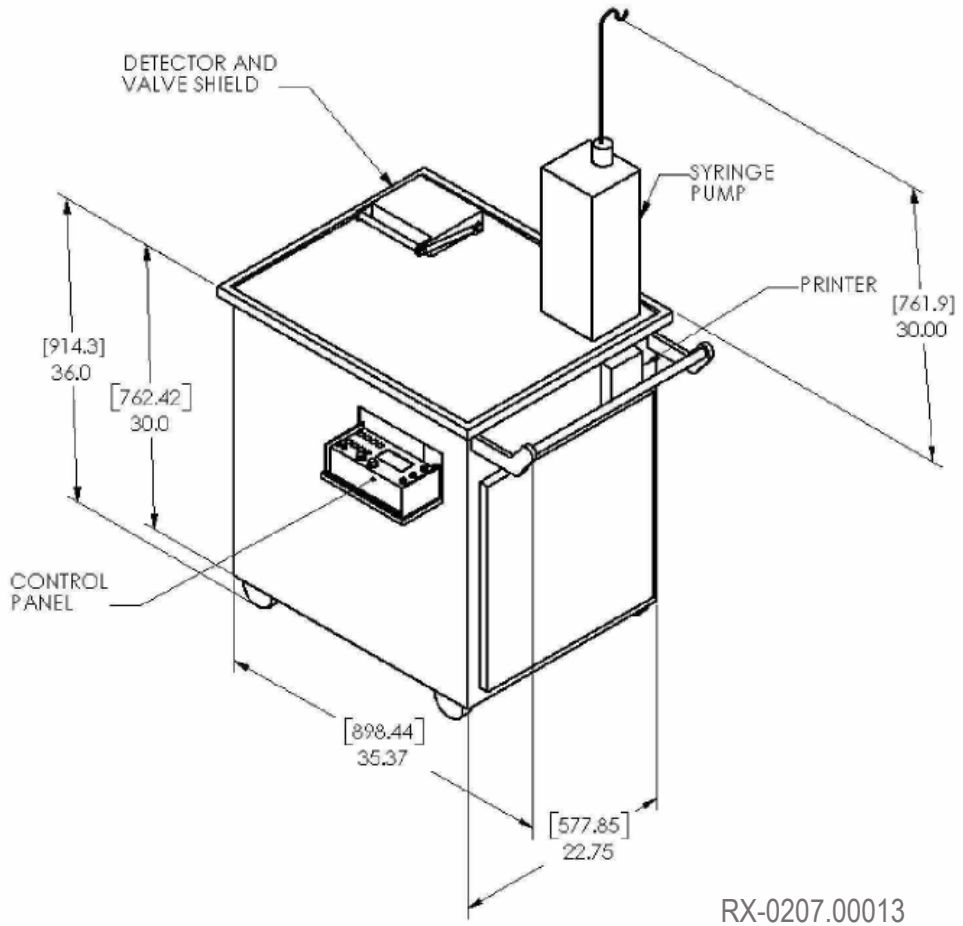
At least 9 more elements are not disclosed in the Klein Thesis:

1. "exterior shell" and "interior space of the cabinet structure"
2. "first shielding compartment" having "a first opening facing vertically upwardly"
3. "opening through the top surface"
4. configuring a computer / a computer configured "to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit"
5. "present on the touch screen display a screen reminding a user to insert the eluate reservoir in the shielded well on-board the cart"
6. "present on the touch screen a screen indicating that the patient infusion is in process"
7. "present on the touch screen display the strontium breakthrough test result"
8. configuring a computer / a computer configured to "track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to measuring the strontium breakthrough test result"
9. "a printer configured to print a document concerning a patient infusion or a quality control test result generated by the infusion system"

BRACCO
LIFE FROM INSIDE

Elements of the Asserted Claims missing from the Bracco Manual & CardioGen-82 Images

- **Respondents concede that there is no disclosure of:**
  - computer or touch screen
    - ➢Respondents revert to relying on the Klein Thesis for these elements
  - shielded well or dose calibrator on-board the cart
  - first door / second door and “opening through the top surface”
  - “two tubing passageways formed in a perimeter surface of the first opening” where “each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a/the first door is closed”



RX-0207.00013

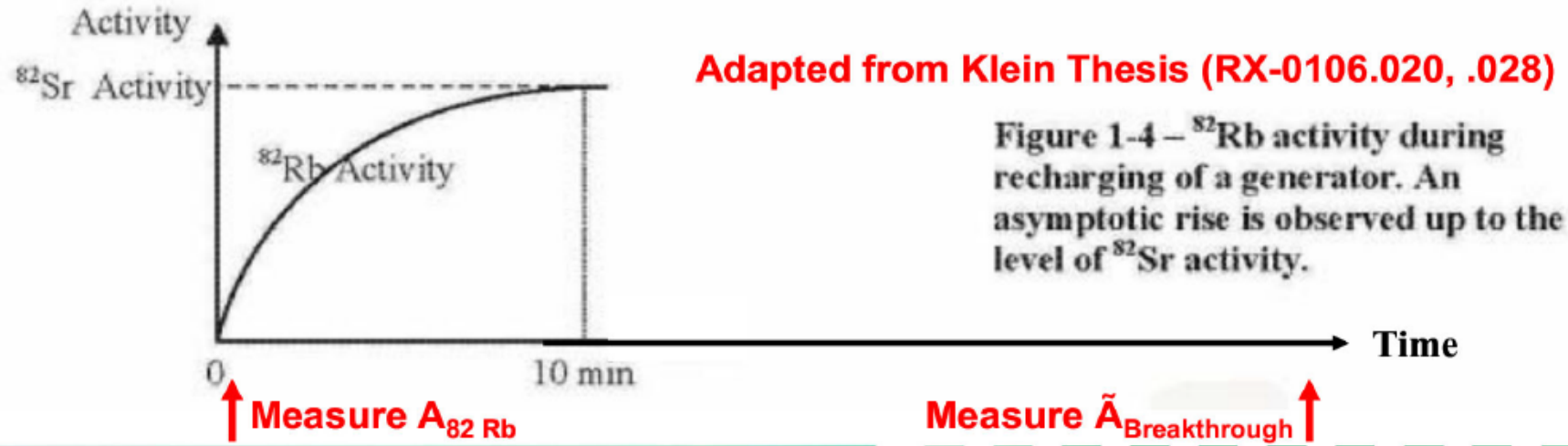
^{82}Rb and ^{18}F systems differ significantly, thus a POSITA would not combine them

	Klein Thesis or Bracco Manual	[redacted] or Tate '126 Application
Radiopharmaceutical	^{82}Rb Cl (RX-0106.00017-18)	^{18}F FDG ([redacted])
Radiopharmaceutical half-life	1.27 minutes (76 seconds) (RX-0106.0017; RX-0207.00012)	109.7 minutes (1.8 hours) ([redacted] [redacted])
Radiopharmaceutical production	Parent-daughter system for on cart elution of Sr-Rb generator (RX-0106.00017-18)	Cyclotron and radiochemistry hot cells (no generator) ([redacted])
Time from production to administration	Very rushed (RX-0106.00018)	Not rushed ([redacted])
Supply half-life	36,792 minutes (25.5 days) (RX-0106.00018)	109.7 minutes ([redacted])
Supply delivery	1 to 2 months (RX-0106.00019)	At least once a day
Two radioisotopes present, requiring breakthrough test	Yes (RX-0106.00028; RX-0207.00045-46)	No
Potential for harm (absorbed dose over time)	High (many orders of magnitude higher than ^{18}F FDG)	Lower
Determination of radioactivity in material to go to patient	On-board, in-line positron counter (RX-0106.00032; RX-207.00024)	On-board, ionization chamber ([redacted] [redacted])
Timing of radioactivity determination	On-the-fly, while flowing to patient (RX-0106.00042; RX-207.00024)	Flow is stationary ([redacted])
Radioactive waste half-life	1.27 minutes	109.7 minutes ([redacted])

BRACCO
LIFE FROM INSIDE

Key differences relating to the "dose calibrator" in ^{82}Rb and ^{18}F systems

	Klein Thesis or Bracco Manual	[Redacted] or Tate '126 Application
Used to measure radioactivity to be delivered to patient?	No (RX-0106.00026, .00033; RX-207.00024)	Yes ([Redacted])
Used to measure breakthrough?	Yes (RX-0106.00028)	No
Frequency of use	Once a day (RX-0106.00028)	Every patient ([Redacted] [Redacted])
Background radiation on cart during measurement	Very variable	~Constant ([Redacted])
Location	Off-cart (RX-0106.00034)	On-cart ([Redacted])



Adapted from Klein Thesis (RX-0106.020, .028)

Figure 1-4 – ^{82}Rb activity during recharging of a generator. An asymptotic rise is observed up to the level of ^{82}Sr activity.

BRACCO
LIFE FROM INSIDE

“exterior shell” and “interior space of the cabinet structure”

’869 independent claim 1	’870 independent claim 1	’826 dependent claim 14
an **exterior shell** that extends upwardly above the platform and has a front side; a rear side; two sidewalls connecting the front side to the rear side; and a top surface; wherein the platform and the exterior shell collectively define an **interior space of the cabinet structure**	wherein infusion system comprises a platform and an **exterior shell** extending upwardly above the platform, and wherein the platform and the exterior shell collectively define an **interior space of a cabinet structure**	wherein the infusion system further comprises: an **exterior shell** extending upwardly above the platform, wherein the platform and the exterior shell collectively define an **interior space of a cabinet structure**

The Klein Thesis describes a cart with an open side

- Respondents contend:

Klein Thesis, FIG. 2-3 (annotated)

- **No "exterior shell"**
- **No "interior space of the cabinet structure"**

Stone Rpt. ¶ 896

“first shielding compartment” having “a first opening facing vertically upwardly”

’869 independent claim 1	’870 independent claim 1	’826 independent claim 1
a **first shielding compartment** in the interior space of the cabinet structure having a **first opening facing vertically upwardly** through which the strontium-rubidium radioisotope **generator** can be inserted into and removed from the first shielding compartment	a strontium-rubidium radioisotope **generator** located in a **first shielding compartment** in the interior space of the cabinet structure . . . wherein the first shielding compartment has a **first opening facing vertically upwardly**	installing a **first shielding compartment**, . . . wherein: the first shielding compartment has a **first opening facing vertically upwardly**, the first opening is configured for a strontium-rubidium radioisotope **generator** to be inserted into and removed from the first shielding compartment

“compartment” - plain and ordinary meaning

- compartment
  - any of the divisions into which a space is partitioned off
  - a separate section, part, division, or category
    - Webster's New World College Dictionary, Fifth Edition Copyright © 2014 by Houghton Mifflin Harcourt Publishing Company.

- compartment
  - 1 : a separate division or section
  - 2 : one of the parts into which an enclosed space is divided
    - https://www.merriam-webster.com/dictionary/compartment

- compartment
  - a part or space marked or partitioned off.
  - a separate room, section, etc.:
  - a baggage compartment.
    - https://www.dictionary.com/browse/compartment

The Klein Thesis does not disclose a “first shielding compartment” having “a first opening facing vertically upwardly”

Assembly

All the components are assembled in a stainless steel cart shown in Figure 2-3. The generator was placed in the cart and surrounded by lead rings to provide maximum radiation shielding. All the saline lines were mounted on a modified top cover for easy access and monitoring (Figure 2-4). A high density plastic lid covers the lines to reduce positron exposure. Finally the LCD touch screen was mounted on an adjustable support arm, so that the operators can adjust its angle for ideal height and visibility.

RX-0106.033-34.

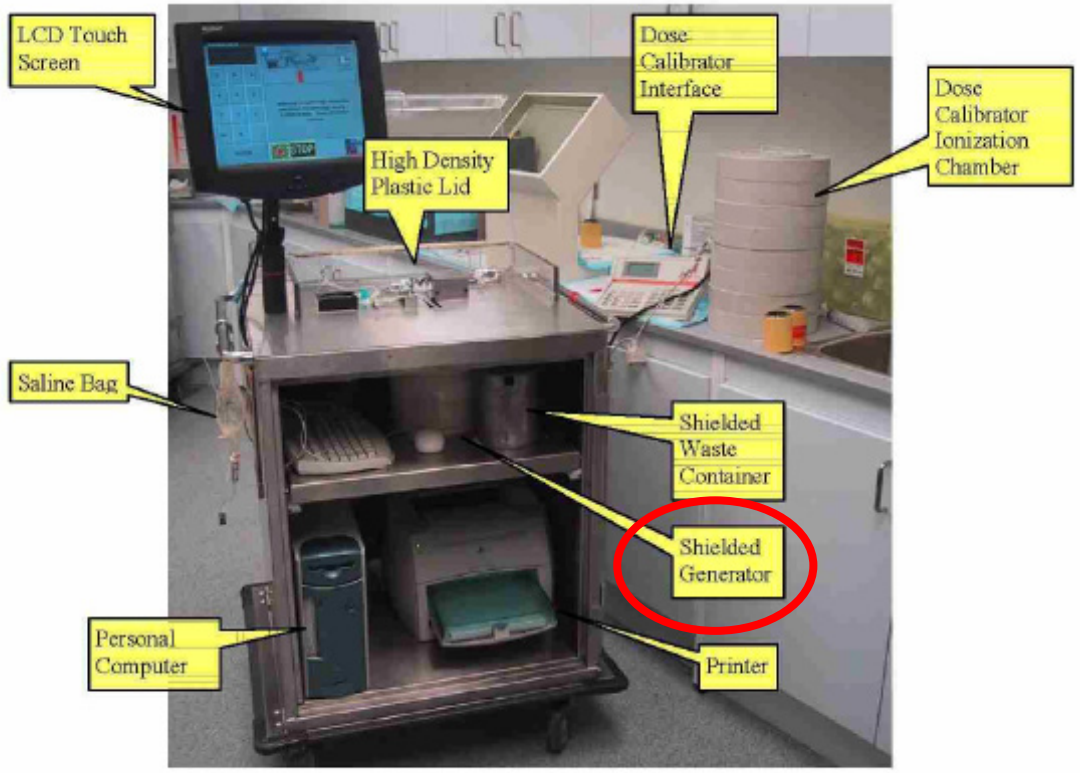


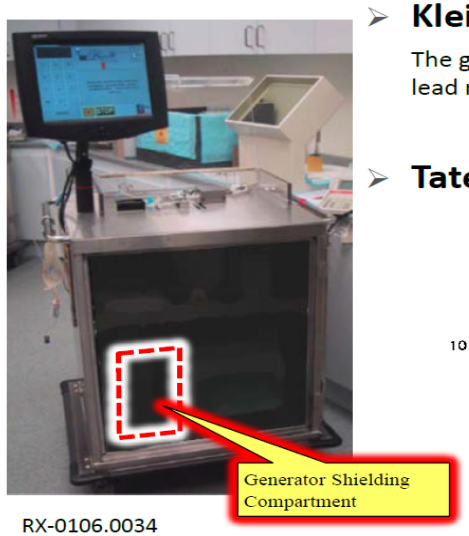
Figure 2-3 - Photograph of the assembled ^{82}Rb elution system and its components.

POSITA would not combine the Klein Thesis with Tate, which also does not disclose "first shielding compartment" having "a first opening facing vertically upwardly"

- Respondents contend:

U.S.P. 9,750,869: Claim Language

Claim 1	Prior Art
a first shielding compartment in the interior space of the cabinet structure having a first opening facing vertically upwardly through which the strontium-rubidium radioisotope generator can be inserted into and removed from the first shielding compartment;	➢ **Klein:** The generator was placed in the cart and surrounded by lead rings to provide maximum radiation shielding. RX-0106.0033 ➢ **Tate:** RX-0103.0005



RX-0106.0034

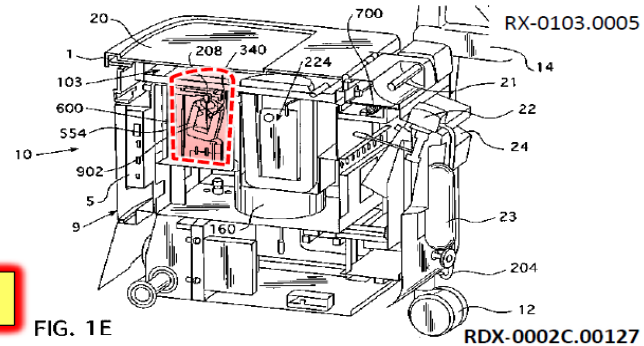


FIG. 1E

RDX-0002C.00127

- POSITA would not move the generator of the Klein Thesis as Respondents contend
- Tate has no generator, no first shielding compartment having a first opening facing vertically upwardly

BRACCO
LIFE FROM INSIDE

first / second “door” and “opening through the top surface”

’869 independent claim 1
a **first door** accessible via the opening through the exterior shell, the first door being configured to provide access to the first shielding compartment and to close over the first opening;
an **opening through the top surface of the exterior shell** configured to provide access for inserting a waste bottle into or removing the waste bottle from the interior space of the cabinet structure
a **second door** accessible via the opening through the top surface of the exterior shell, the second door being configured to provide access to the second shielding compartment and to close over the second opening;

BRACCO
LIFE FROM INSIDE

The Klein Thesis does not disclose a first/second door, and neither does Tate

[0140] The handle **682** is used by an operator or technician to insert and remove the vial access system **600** from the well **111** of the fluid delivery system **10**. The handle **682** is preferably connected to the vertical support arm **676** via a suitable pivot connection (such as a hinge or bolt connection) **680** to permit movement of the handle **682** between an extended, carrying position (see FIG. **6**D) for carrying the vial access system **600** and a horizontal or operating position (see FIGS. **6**B and **6**E) in which the handle **682** rests on top of the cap **684** (e.g., when the vial access system **600** is disposed in the well **111**), thereby allowing the cover **20** of the fluid delivery system **10** to be closed.

[0141] The cap **684** is preferably rigidly connected to the vertical support arm **676** via an arm **650** (see FIGS. **6**A and **6**D), but it may be pivotally connected to the vertical support arm **676** via, for example, a pivot connection (not shown) or adjustably connected to the vertical support arm **676** via, for example, a slot (not shown) formed in the arm **650**. As best shown in FIGS. **6**E and **6**F, when the cap **684** is lowered (by sliding the vertical support arm **676** within the housing **678**) to insert the cannula **208** into the vial **902** within the vial shield **554**, and the handle **682** is pivoted to a horizontal position atop the cap **684**, the cap **684** and the handle **682** (and thus the remainder of the vial access system **600**) lies below or flush with the upper surface **103** of the fluid delivery system **10**, thereby allowing the cover **20** to close over the upper surface **103** of the fluid delivery system **10** and the MPDS **200** installed therein. The cap **684** preferably includes or is formed with radioactive shielding material (e.g., lead) to minimize radiation exposure to personnel from the FDG or other radioactive solution contained within the vial **902** in the vial shield **554**.

BRACCO
LIFE FROM INSIDE

Respondents' combination of the Klein Thesis and Tate for first/second "door" and "opening through the top surface" fails

- No disclosure of an "opening through the top surface" in the Klein Thesis
- POSITA would not move the generator of the Klein Thesis as Respondents contend
- Tate does not disclose a first/second door
- POSITA would not combine the Klein Thesis and Tate

elevations of “first opening” and “second opening”

’869 independent claim 1	’870 independent claim 1	’826 independent claim 1
wherein the first opening is located at a **lower elevation** than the second opening	wherein the second shielding compartment on-board the cart has a second opening facing vertically upwardly and being at a **higher elevation** than the first opening	the first opening is located at a **lower elevation** than the second opening

’869 dependent claim 3	’870 dependent claim 17	’826 dependent claim 18
The infusion system of claim 2, wherein . . . , the first opening is at a first elevation, the second opening is at a second elevation, the first elevation is between approximately 1 foot and approximately 2 feet, with respect to the lowermost portion of the cabinet structure, and the second elevation is between approximately 2 feet and approximately 3 feet, with respect to the lower surface of the platform.	The method of claim 16, wherein . . . , the first opening is at a first elevation, the second opening is at a second elevation, the first elevation is between approximately 1 foot and approximately 2 feet, with respect to the lowermost portion of the cabinet structure, and the second elevation is between approximately 2 feet and approximately 3 feet, with respect to the lower surface of the platform.	The method of claim 17, wherein . . . , the first opening is at a first elevation, the second opening is at a second elevation, the first elevation is between approximately 1 foot and approximately 2 feet, with respect to the lowermost portion of the cabinet structure, and the second elevation is between approximately 2 feet and approximately 3 feet, with respect to the lower surface of the platform.

The Klein Thesis does not disclose a first opening (for the generator) at a lower elevation than the second opening (for the waste bottle)

- Respondents contend:

Stone Rpt. ¶ 629

- **Klein Thesis does not disclose a first opening at a lower elevation than the second opening**
- **POSITA would not modify the Klein Thesis as Respondents contend**

BRACCO
LIFE FROM INSIDE

Klein Thesis: layout is crucial

3.3 Flow Hardware Layout Justification

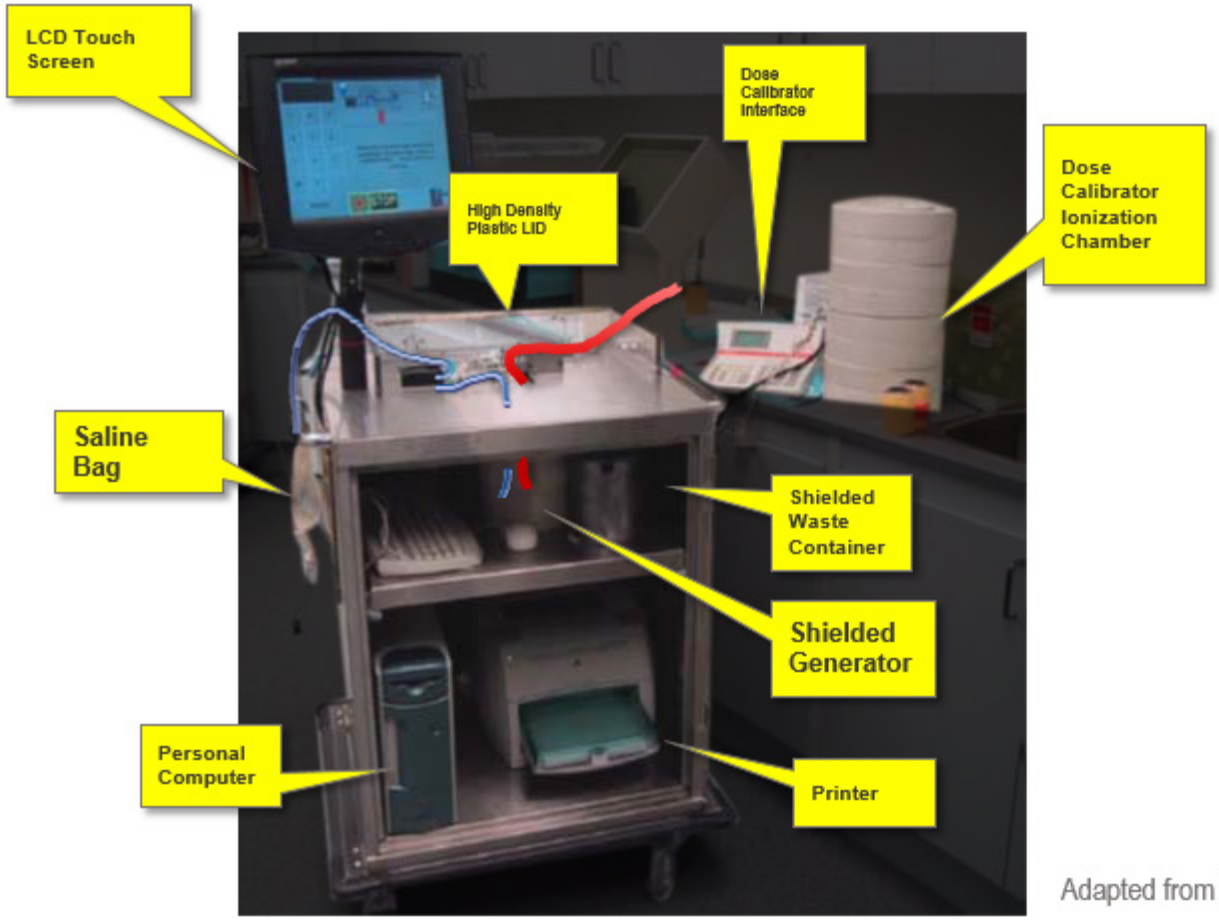
At the heart of the ^{82}Rb elution system are the saline lines that transport the activity from the generator to the patient. The layout of the saline lines, sensors and actuators is crucial to implementing a physical system that is easy to control. During flow of a radioactive volume through the lines, both a transport delay and a radioactive decay take place. Therefore the activity at the output is delayed and reduced in relation to the activity at the input. If the line volume, V, and flow rate, f, are known and fixed, one can compute the delay time, T, and the radioactive decay, D as shown below.

$$T = \frac{V}{f} \quad (3)$$

$$D = e^{-\lambda T} \quad (4)$$

RX-0106.049

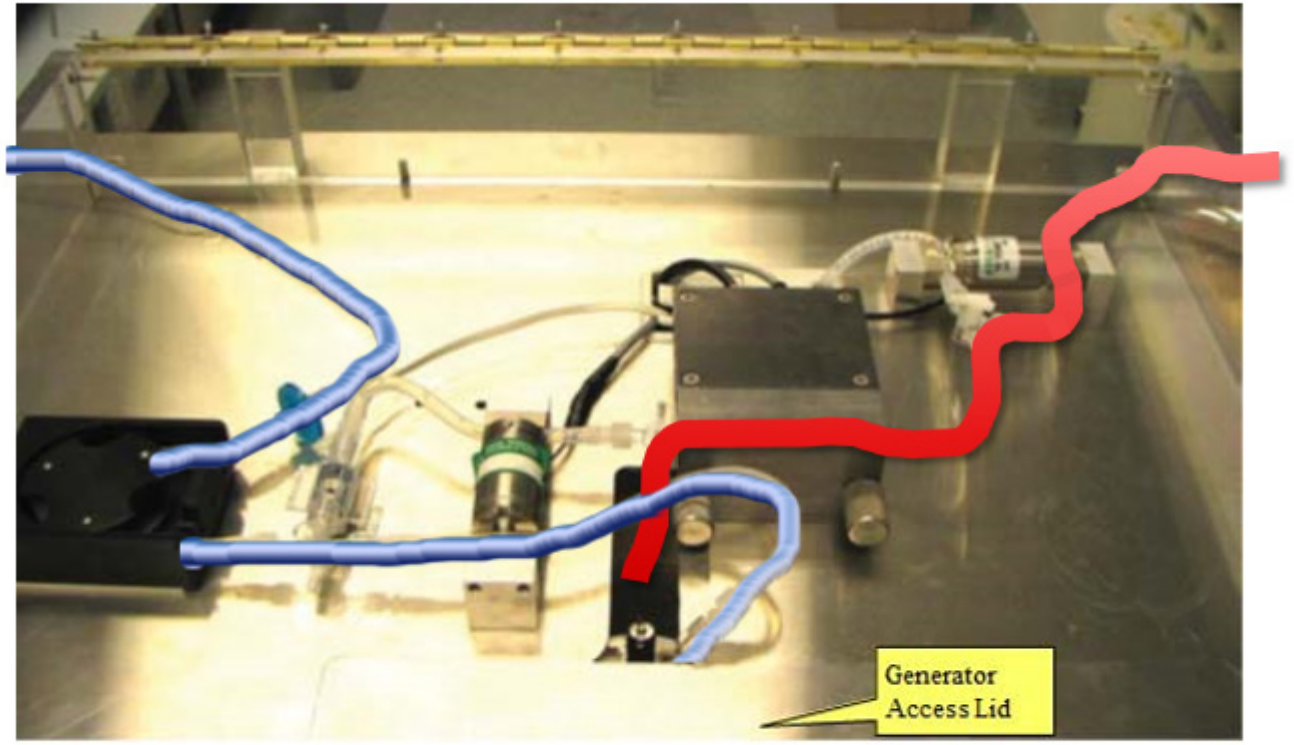
A POSITA would not make Respondents' proposed modifications to the disclosure of the Klein Thesis



Adapted from Klein Thesis, RX-0106.034

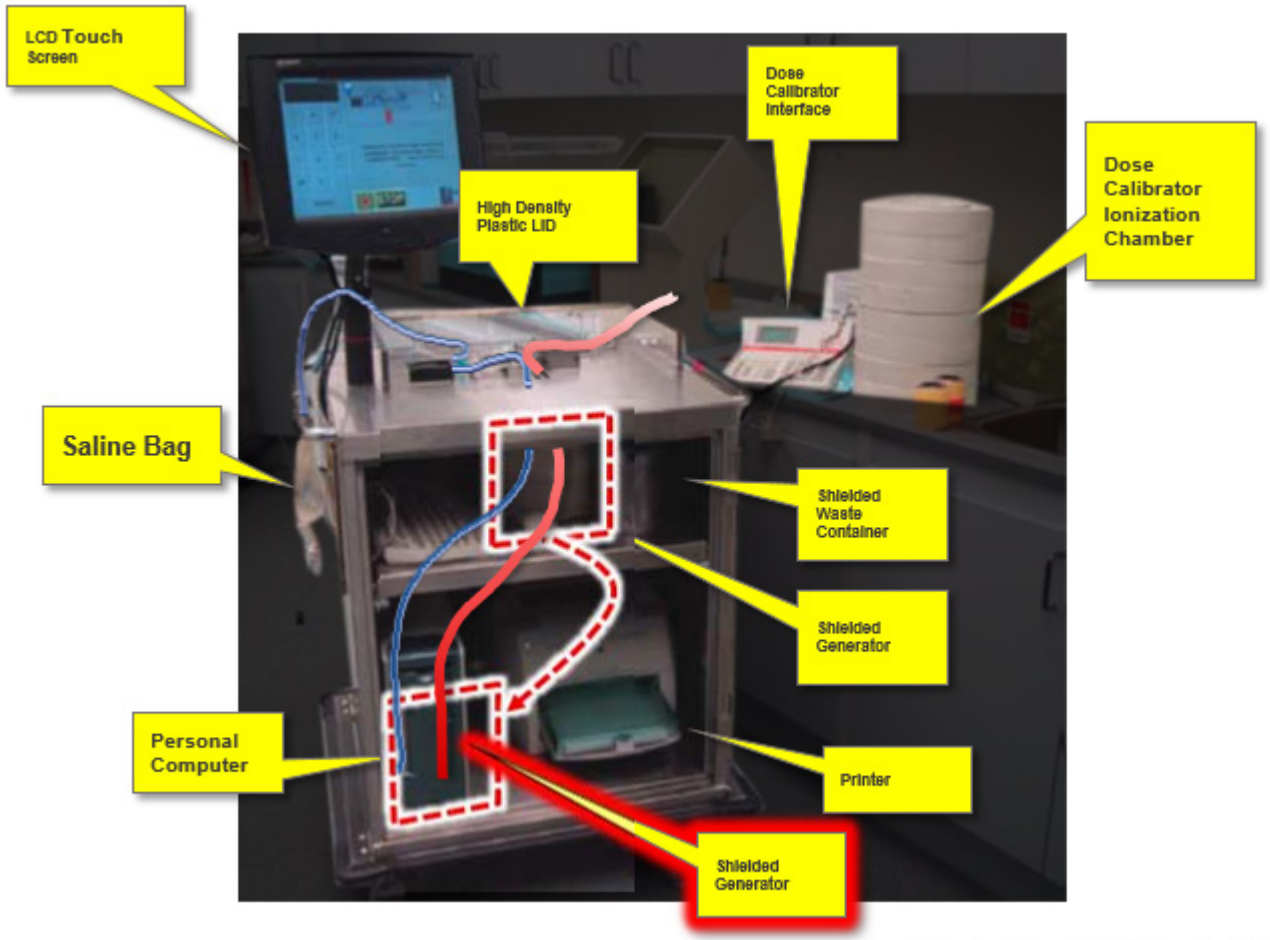
BRACCO
LIFE FROM INSIDE

A POSITA would not make Respondents' proposed modifications to the disclosure of the Klein Thesis



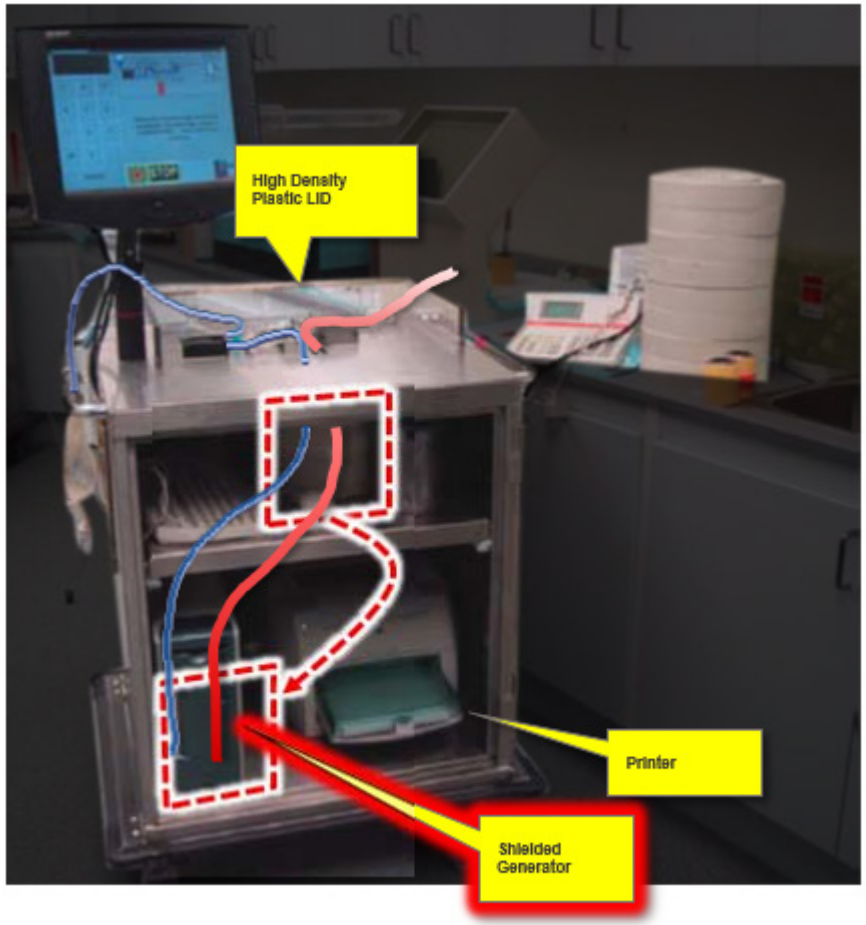
Adapted from Klein Thesis, RX-0106.034

A POSITA would not make Respondents' proposed modifications to the disclosure of the Klein Thesis



Adapted from Klein Thesis, RX-0106.034

A POSITA would not make Respondents' proposed modifications to the disclosure of the Klein Thesis



Adapted from Klein Thesis, RX-0106.034

“shielded well” on the cart

’869 independent claim 1	’870 independent claim 1	’826 independent claim 1
a **shielded well** on-board the cart configured to receive an eluate reservoir, wherein the eluate reservoir is configured to receive a test sample	inserting an eluate reservoir in a **shielded well** on-board the cart	installing . . . a **shielded well** on a platform of a cart, wherein: the shielded well is configured to receive an eluate reservoir that is configured to receive a sample of the rubidium radioactive eluate
wherein the computer of the infusion system is configured to . . . fill the eluate reservoir in the **shielded well** on-board the cart with the test sample of the rubidium radioactive eluate	placing the eluate reservoir in fluid communication with the eluate tubing line, wherein the computer is further configured to control the fluid communication between the eluate reservoir and the eluate tubing line; pumping a sample of the rubidium radioactive eluate into the eluate reservoir in the **shielded well** on-board the cart	configuring a computer with a touch screen display for the infusion system to: fill the eluate reservoir in the **shielded well** on-board the cart with the sample of rubidium radioactive eluate

“shielded well on-board the cart”

Patent and Claim	Element
’826 dependent claim 2	measure a calibration radioactivity of the sample while the sample remains in the eluate reservoir in the **shielded well on-board the cart**
	compare the radioactivity of the sample measured while flowing through the eluate tubing line with the calibration radioactivity of the sample measured in the eluate reservoir in the **shielded well on-board the cart**
’869 dependent claim 28	the eluate reservoir located inside the **shielded well on-board the cart** and in fluid communication with the eluate tubing line
’869 dependent claim 29	measure an activity of the test sample filled into the eluate reservoir in the **shielded well on-board the cart** while the eluate reservoir remains in the shielded well on-board the cart, wherein the activity is measured with the dose calibrator in the shielded well on-board the cart

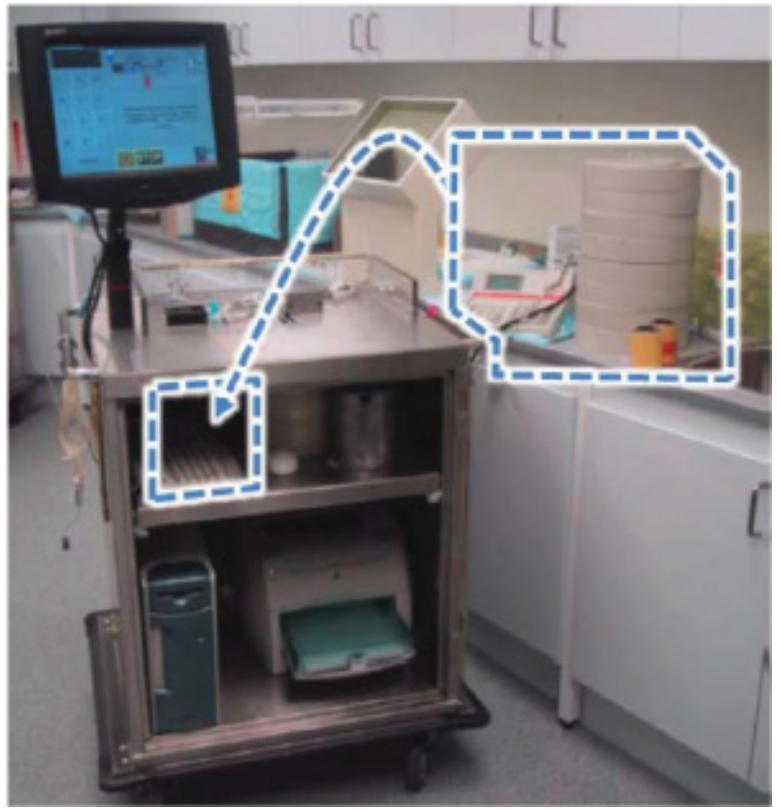
“determine/determining a strontium breakthrough test result” in the “eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart” / dose calibrator on-board the cart

’869 independent claim 1	’870 independent claim 1	’826 independent claim 1
wherein the computer of the infusion system is configured to . . . **determine a strontium breakthrough test result** on the test sample filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart	**determining a strontium breakthrough test result** on the sample pumped into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart	configuring a computer with a touch screen display for the infusion system to . . . **determine a strontium breakthrough test result** on the sample of the rubidium radioactive eluate filled into the eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart

’869 dependent claim 27	’870 dependent claim 16	’826 dependent claim 3
The infusion system of claim 24, further comprising a dose calibrator located in the shielded well on-board the cart and in communication with the computer, wherein the dose calibrator is configured to **determine the strontium breakthrough test result** . . .	The method of claim 13, wherein the infusion system further comprises a dose calibrator in the shielded well on-board the cart and in communication with the computer to **determine the strontium breakthrough test result**.	The method of claim 2, further comprising installing a dose calibrator in the shielded well on-board the cart, wherein the dose calibrator is in communication with the computer to **measure the strontium breakthrough test result** and the calibration radioactivity of the sample pumped into the eluate reservoir.

The Klein Thesis does not disclose a "shielded well" or dose calibrator on the cart

- Respondents contend:



- **Respondents concede that the Klein Thesis does not disclose a shielded well or dose calibrator on the cart**
  - **Klein Thesis does not disclose determining a strontium breakthrough test result in the "eluate reservoir in the shielded well on-board the cart while the eluate reservoir remains in the shielded well on-board the cart"**
- **POSITA would not move the dose calibrator of the Klein Thesis on-board the cart**

Stone Rpt. ¶ 594

A POSITA would not rearrange the cart described in the Klein Thesis as proposed by Respondents

- POSITA would not:
  - Move the dose calibrator on-board the cart
  - Move the generator to a lower elevation than the waste bottle

configuring a computer / a computer configured “to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit”

’869 independent claim 1	’870 independent claim 1	’826 independent claim 1
wherein the **computer of the infusion system is configured to . . . not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit**	wherein the **computer of the infusion system is** further **configured to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit**	**configuring a computer** with a touch screen display for the infusion system **to . . . not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit**

The Klein Thesis does not disclose configuring a computer “to not allow a patient infusion if the strontium breakthrough test result is greater than or equal to an allowed limit”

“present on the touch screen display a screen reminding a user to insert the eluate reservoir in the shielded well on-board the cart”

’870 patent dependent claim 8	’826 patent dependent claim 9
The method of claim 2, wherein the computer of the infusion system is further configured to: . . . **present on the touch screen display a screen reminding a user to insert the eluate reservoir in the shielded well on-board the cart** . . .	The method of claim 2, further comprising configuring the computer to: . . . **present on the touch screen display a screen reminding a user to insert the eluate reservoir in the shielded well on-board the cart** . . .

- References cited by Respondents do not disclose configuring a computer / a computer configured to “present on the touch screen display a screen reminding a user to insert the eluate reservoir in the shielded well on-board the cart”

BRACCO
LIFE FROM INSIDE

“present on the touch screen a screen indicating that the patient infusion is in process”

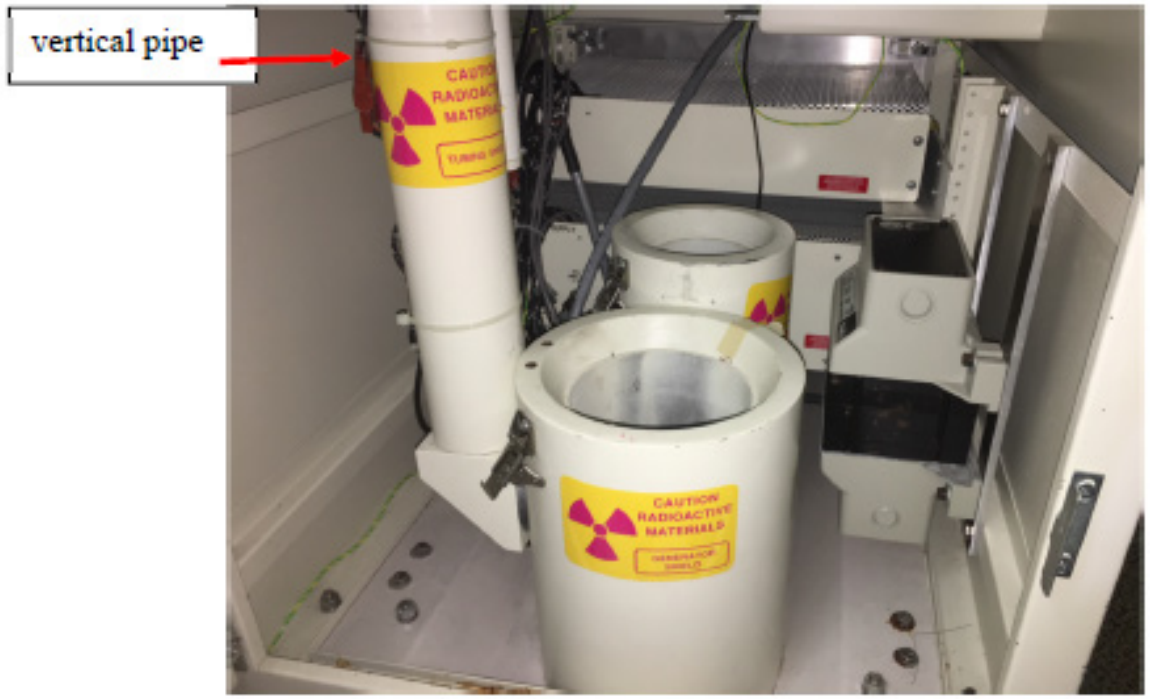
’870 patent dependent claim 8	’826 patent dependent claim 9
The method of claim 2, wherein the computer of the infusion system is further configured to: . . . **present on the touch screen display a screen indicating that the patient infusion is in process**, wherein the screen indicating that the patient infusion is in process displays a stop button to abort the patient infusion . . .	The method of claim 2, further comprising configuring the computer to: . . . **present on the touch screen display a screen indicating that the patient infusion is in process**, wherein the screen indicating that the patient infusion is in process displays a stop button to abort the patient infusion . . .

“two tubing passageways formed in a perimeter surface of the first opening” where “each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a/the first door is closed”

’869 dependent claims 4 and 24	’870 dependent claim 12	’826 dependent claim 13
The infusion system of claim 1, wherein the first shielding compartment comprises **two tubing passageways formed in a perimeter surface of the first opening, and each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when the first door is closed** thereover.	The method of claim 11, wherein . . . **two tubing passageways formed in a perimeter surface of the first opening, wherein each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a first door is closed** over the first opening.	The method of claim 12, wherein . . . **two tubing passageways formed in a perimeter surface of the first opening, wherein each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a first door is closed** over the first opening.
The infusion system of claim 1, . . . wherein: the first shielding compartment comprises **two tubing passageways formed in a perimeter surface of the first opening, each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when the first door is closed** thereover, the first door is mounted via a hinge . . .		

Tate does not disclose “two tubing passageways formed in a perimeter surface of the first opening” where “each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a/the first door is closed”

The CardioGen-82 Images do not disclose “two tubing passageways formed in a perimeter surface of the first opening” where “each of the two tubing passageways has a depth configured to prevent pinching or crushing of a corresponding tubing line routed therethrough when a/the first door is closed”



Adapted from CardioGen-82 Images, RX-0357.07

computer is configured to (1) “track a volume of saline remaining in the saline reservoir” and (2) provide an alert “via the touch screen display when the volume of saline remaining in the saline reservoir is below a predetermined volume threshold”

’869 dependent claim 14	’870 dependent claim 10	’826 dependent claim 11
The infusion system of claim 1, wherein the **computer of the infusion system is** further **configured to track a volume of the saline remaining in the saline reservoir and to alert the user via the touch screen display when the volume of the saline remaining in the saline reservoir is below a predetermined volume threshold**.	The method of claim 9, wherein the **computer of the infusion system is** further **configured to: track a volume of saline remaining in the saline reservoir, provide an alert via the touch screen display when the volume of saline remaining in the saline reservoir is below a predetermined volume threshold** . . .	The method of claim 10, further comprising **configuring the computer to: . . . track a volume of saline remaining in the saline reservoir, provide an alert via the touch screen display when the volume of saline remaining in the saline reservoir is below a predetermined volume threshold** . . .

“present on the touch screen display the strontium breakthrough test result”

’870 dependent claim 8	’826 dependent claim 9
The method of claim 2, further comprising configuring the computer to: . . . **present on the touch screen display the strontium breakthrough test result**.	The method of claim 2, wherein the computer of the infusion system is further configured to: . . . **present on the touch screen display the strontium breakthrough test result**.

- No disclosure of presenting the strontium breakthrough test result on the touch screen display

configuring a computer / a computer configured to “track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to measuring the strontium breakthrough test result”

’826 dependent claim 11	’870 dependent claim 27
The method of claim 10, further comprising configuring the computer to: **track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to measuring the strontium breakthrough test result** . . .	The method of claim 1, wherein the computer of the infusion system is further configured to **track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to determining the strontium breakthrough test result**.

The Klein Thesis does not disclose configuring a computer / a computer configured to "track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to measuring the strontium breakthrough test result"

- Respondents contend:

The breakthrough of each isotope, A_{82Sr}/A_{82Rb} and A_{85Sr}/A_{82Rb}, is calculated as a relative activity ratio of Sr activity to ^{82}Rb activity delivered as demonstrated in (11), below.

$$\frac{A_{82Sr}}{A_{82Rb}} = \frac{\frac{\hat{A}_{Breakthrough}}{1+0.48s(t)}}{A_{82Rb}} \quad \text{and} \quad \frac{A_{85Sr}}{A_{82Rb}} = s(t) \cdot A_{82Sr} \qquad (11)$$

The dose calibrator is sensitive to the radiation of ^{82}Rb decay which is a consequence of ^{82}Sr decay. The ^{82}Sr activity is not measured directly. $\hat{A}_{Breakthrough}$ is the measured breakthrough activity by the dose calibrator after sufficient time has passed for the initial ^{82}Rb activity, A_{82Rb}, to decay. The equation corrects for the dose calibrator sensitivity to the different isotopes, their decay sequence and their abundance.

RX0106.00061

A calibration run follows to recalculate the calibration constant of the activity detector and measure the activity vs. volume curve of the generator. Calibration is performed by eluting at a constant flow rate (15ml/min) over 60 seconds to an external dose calibrator, which serves as a reference. The activity in the dose calibrator is registered 30 minutes after the end of the elution to compute the breakthrough ^{82}Sr and ^{85}Sr activity. Only after a calibration run with low Sr breakthrough has been successfully completed can patient elutions be carried out. The calibration constant is a measure of the positron counter's efficiency and is therefore not expected to change significantly. Monitoring of the calibration constant can be used to detect problems in the system.

RX0106.00028

- No disclosure of configuring a computer / a computer configured to "track time passed from completion of pumping the sample of the rubidium radioactive eluate into the eluate reservoir to measuring the strontium breakthrough test result"

“a printer configured to print a document concerning a patient infusion or a quality control test result generated by the infusion system”

’869 dependent claim 24
“a printer configured to print a document concerning a patient infusion or a quality control test result generated by the infusion system”

- No disclosure of a printer configured to print a document concerning a patient infusion or a quality control test result generated by the infusion system

BRACCO
LIFE FROM INSIDE