PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	16/175261
Title of Invention	Stable, concentrated radionuclide complex solutions	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	16/175261
Title of Invention	Stable, concentrated radionuclide complex solutions	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Advanced Accelerator Applications (Italy) Srl

Mailing Address Information For Applicant:

Address 1	Via dell'Industria Prima Traversa		
Address 2			
City	Pozzilli	**State/Province**	
Country	IT	Postal Code	86077
Phone Number		Fax Number	
Email Address	pip_inbox.phchbs@novartis.com		

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	16/175261
Title of Invention	Stable, concentrated radionuclide complex solutions	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Lian Ouyang/			Date (YYYY-MM-DD)	2019-05-13
First Name	Lian	Last Name	Ouyang	Registration Number	69,254

Additional Signature may be generated within this form by selecting the Add button.

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	16/175261
Title of Invention	Stable, concentrated radionuclide complex solutions	

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2]	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2018081860	WO	A1	2018-05-11	Clarity Pharmaceuticals PTY LTD		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16175261
	Filing Date	2018-10-30
	First Named Inventor	de Palo, Francesco
	Art Unit	1618
	Examiner Name	Perreira, Melissa Jean
	Attorney Docket Number	PAT058197-US-CIP02

	1		

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16175261
	Filing Date	2018-10-30
	First Named Inventor	de Palo, Francesco
	Art Unit	1618
	Examiner Name	Perreira, Melissa Jean
	Attorney Docket Number	PAT058197-US-CIP02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-05-13
Name/Print	Lian Ouyang	Registration Number	69,254

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 May 2018 (11.05.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/081860 A1

(51) International Patent Classification:
A61K 51/08 (2006.01)

(21) International Application Number:
PCT/AU2017/051205

(22) International Filing Date:
02 November 2017 (02.11.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2016904515 04 November 2016 (04.11.2016) AU

(71) Applicant: **CLARITY PHARMACEUTICALS PTY LTD** [AU/AU]; National Innovation Centre, 4 Cornwallis Street, Eveleigh, New South Wales 2015 (AU).

(72) Inventors: **HARRIS, Matthew John**; 19 The Avenue, Hunters Hill, New South Wales 2110 (AU). **VAN DAM, Ellen Marianne**; 41/277-283 Canterbury Road, Canterbury, New South Wales 2193 (AU). **JEFFERY, Charmaine Marie**; 3/283 Gladstone Road, Dutton Park, Queensland 4102 (AU).

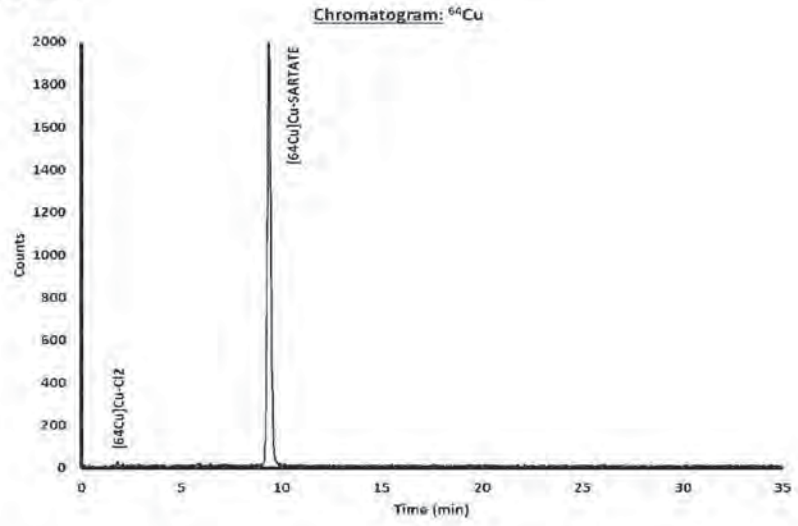
(74) Agent: **DAVIES COLLISON CAVE PTY LTD**; Level 15/1 Nicholson Street, Melbourne, Victoria 3000 (AU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: FORMULATIONS FOR RADIOTHERAPY AND DIAGNOSTIC IMAGING

Figure 1



(57) Abstract: The present invention relates to formulations of radiolabelled compounds that are of use in radiotherapy and diagnostic imaging.

[Continued on next page]

WO 2018/081860 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Formulations for Radiotherapy and Diagnostic Imaging

Field

The present invention relates to formulations of radiolabelled compounds that are of use in radiotherapy and diagnostic imaging.

Background

Radiolabelled compounds or ligands may be used as radiopharmaceuticals in applications such as radiotherapy or diagnostic imaging. Of particular use, are radiolabelled compounds that show some propensity for selectively targeting a particular site *in vivo*, (for example, a particular receptor), and subsequently delivering the radioisotope to the desired site of action. This requires that the ligand comprises a component to complex the radioisotope and a further component to target the desired site.

One of the known problems associated with such a ligand is the premature dissociation of the radioisotope prior to the arrival of the ligand-radioisotope complex at the site of action. Not only does this reduce the efficacy of the complex, but the loss of the radioisotope to areas where radiotherapeutic effects are not intended, may result in adverse consequences.

Dissociation of the radioisotope from the ligand may occur as a result of transchelation, where the radioisotope transfers to another biological ligand *in vivo*. Again, this leads to a reduced therapeutic effect and also delivery of a radioisotope to areas where treatment is not required.

The ligand to be radiolabelled and the radioisotope are usually stored and transported to the patient in separate containers to minimise the above problems relating to dissociation prior to administration. The ligand may be transported as a lyophilized powder at reduced temperatures in order to prolong stability of the compound. The radioisotope can then be combined with the ligand to form the radiopharmaceutical, just prior to administration, which can serve to minimise dissociation of the radioisotope prior to the complex reaching the site of action.

Another problem associated with radiolabelled compounds is that the use of a radioisotope may result in radiolysis, or destruction of the ligand. As a radioisotope undergoes spontaneous decay and subsequent release of radiation, this energy may be sufficient to induce cleavage of bonds and cause subsequent destruction of the ligand. In addition to the reduced efficacy of the radiopharmaceutical, release of the radioisotope also occurs, resulting in the delivery of radiation to unwanted sites.

As many radiopharmaceuticals are designed to be administered parenterally, i.e. non-orally and usually as a solution, the ligand itself must be soluble in a pharmaceutically acceptable solvent or carrier. As is known in the art, the solubility of a particular compound in any given solvent may be unpredictable. Although the solubility of a particular compound in a particular solvent may be known, the solubility of an analogue of the compound in a different solvent system may be quite different. This then presents difficulties to one seeking to develop a formulation of a compound and especially a pharmaceutically acceptable injectable formulation.

Pharmaceutical formulations typically include one or more excipients that affect the compound in some way, such as the enhancement of solubility of the compound or

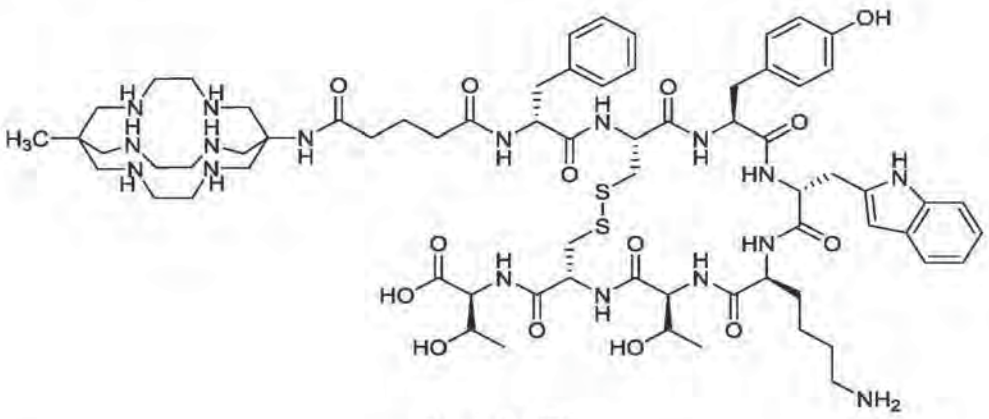
increasing stability of the compound while in solution. Alternatively, additional excipients may be used to provide other features to the formulation, such as preservatives, buffers and the like.

While many thousands of formulations of ligand-radioisotope complexes have been documented, there is no expectation that the excipients used in such formulations would provide the required solubility and bioavailability of any newly developed complex. Furthermore, one cannot expect that a particular combination of excipients would further prevent or minimise the dissociation of the radioisotope or minimise radiolysis from occurring.

Accordingly, desirable formulations of ligand-radioisotope complexes need to be tailored in order to display the requisite stability in relation to radiolysis and dissociation of the radioisotope, while also being pharmaceutically acceptable. The present invention seeks to address these problems in relation to a specific ligand complex.

Summary

In one aspect of the present invention, there is provided an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion:



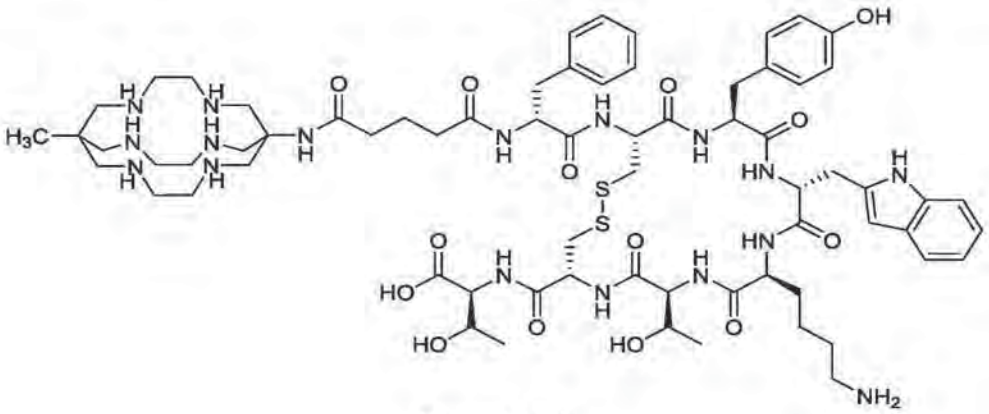
Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;
about 0.3 to about 1.2% (w/v) sodium chloride;
about 0.02 to about 0.1% (w/v) gentisic acid or a salt thereof;

wherein the formulation has a pH of between about 4 to about 8.

In another aspect of the present invention, there is provided an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion:



Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;
about 0.3 to about 1.2% (w/v) sodium chloride;
about 0.02 to about 0.1% (w/v) gentisic acid or a salt thereof; and
about 1.0 to about 4.0 mg/mL L-methionine or a salt thereof;

wherein the formulation has a pH of between about 4 to about 8.

In an embodiment and in relation to the above two aspects, the compound of Formula (I) is provided as the acetate salt.

According to a further aspect of the present invention, there is provided a process for preparing an aqueous formulation comprising a compound of Formula (I) complexed with a Cu ion, the method comprising the steps of:

i) preparing a buffering solution of an acetate salt, wherein the buffering solution further comprises ethanol and gentisic acid or a salt thereof;
ii) dissolving a compound of Formula (I), or a salt thereof, in the buffering solution obtained from step i);
iii) adding a solution of a Cu ion to the solution obtained from step ii);
iv) filtering the solution obtained from step iii) on to a stationary phase; and
v) washing the stationary phase of step iv) with ethanol and saline;

to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

According to a further aspect of the present invention, there is provided a process for preparing an aqueous formulation comprising a compound of Formula (I) complexed with a Cu ion, the method comprising the steps of:

i) preparing a buffering solution of an acetate salt, wherein the buffering solution further comprises ethanol and gentisic acid or a salt thereof;
ii) dissolving a compound of Formula (I), or a salt thereof, in the buffering solution obtained from step i);
iii) adding a solution of a Cu ion to the solution obtained from step ii);
iv) filtering the solution obtained from step iii) on to a stationary phase; and

v) washing the stationary phase of step iv) with ethanol and saline into a vial containing a solution of L-methionine or a salt thereof;

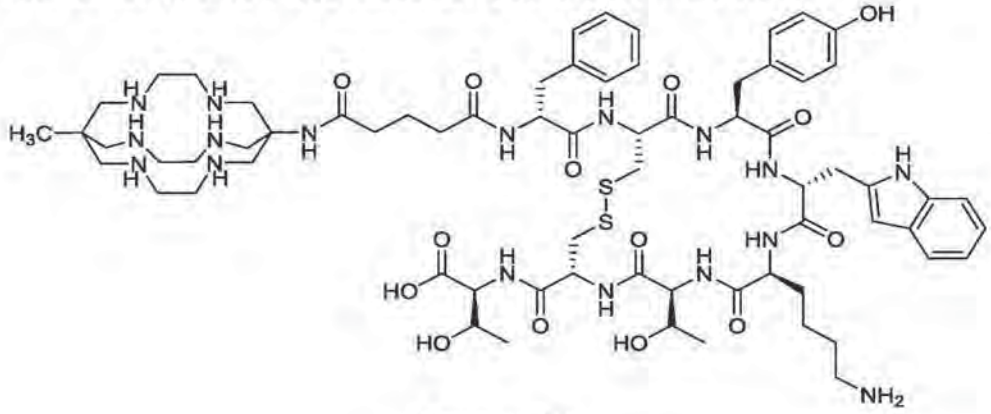
to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

According to another aspect of the present invention, there is provided an aqueous formulation prepared by a process as defined in an earlier aspect.

The aqueous formulation of the present invention may also be prepared by providing certain components of the formulation as a kit of parts, where the kit comprises at least a compound of Formula (I), or a salt thereof, and the Cu ion that is intended to be complexed with the compound of Formula (I), in which the compound of Formula (I), or a salt thereof, and the Cu ion are provided separately in the kit and may be combined to form the aforementioned complex prior to administration.

Accordingly, in another aspect the present invention provides a kit for making an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion, the kit comprising:

a container comprising a lyophilised compound of Formula (I)

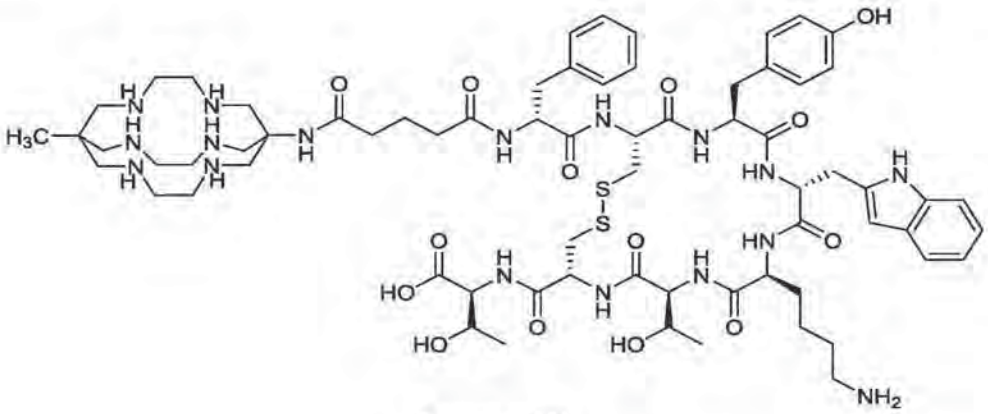


Formula (I)

or a salt thereof;
a container comprising a solution of a Cu ion; and
instructions for preparing an aqueous formulation as defined in an earlier aspect, including the addition of a buffered solution of ethanol, sodium chloride and gentisic acid, or a salt thereof.

In another aspect the present invention provides a kit for making an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion, the kit comprising:

a container comprising a lyophilised compound of Formula (I)



Formula (I)

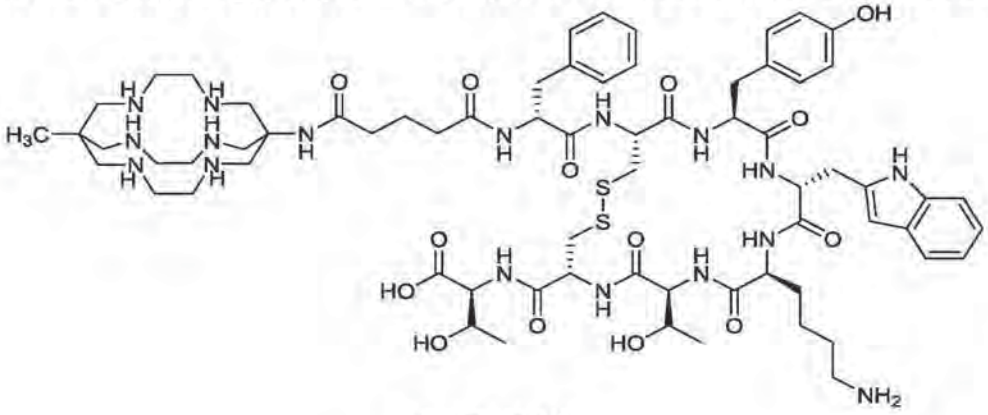
or a salt thereof;

a container comprising a solution of a Cu ion; and

instructions for preparing an aqueous formulation as aforementioned defined, including the addition of a buffered solution of ethanol, sodium chloride, gentisic acid or a salt thereof, and L-methionine or a salt thereof.

A further aspect of the present invention provides a kit for making an aqueous formulation as defined in an earlier aspect for parenteral administration, the kit comprising:

a container comprising a lyophilised compound of Formula (I), or a salt thereof;



Formula (I)

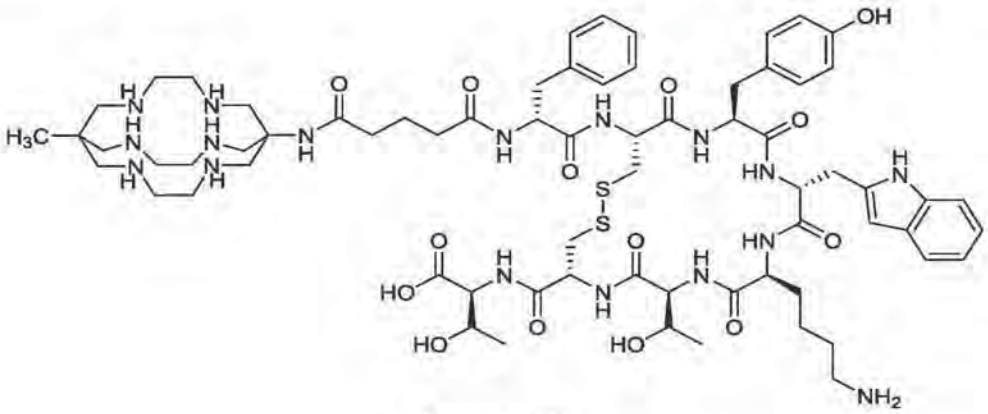
a container comprising a solution of a Cu ion;

a container comprising a buffered solution of ethanol, sodium chloride and gentisic acid, or a salt thereof; and

instructions for preparing an aqueous formulation as defined in an earlier aspect.

A further aspect of the present invention provides a kit for making an aqueous formulation as aforementioned for parenteral administration, the kit comprising:

a container comprising a lyophilised compound of Formula (I), or a salt thereof;



Formula (I)

a container comprising a solution of a Cu ion;
a container comprising a buffered solution of ethanol, sodium chloride, gentisic acid or a salt thereof, and L-methionine or a salt thereof; and
instructions for preparing an aqueous formulation as defined in an earlier aspect.

Another aspect of the present invention provides a method for radioimaging, diagnosing or treating a cancer, the method comprising administering to a subject in need thereof an aqueous formulation as defined in an earlier aspect.

Brief description of the figures

Figure 1: Area percent report, using gamma scintillation detector – High performance liquid chromatograph (HPLC) analysis of a low-dose ^{64}Cu-SARTATE formulation of Example 1 immediately after preparation (radiochemical yield = 606 MBq) representing 97.3% of ^{64}Cu detected being present as ^{64}Cu-SARTATE.

Figure 2: Graph of repeat HPLC analyses of low-dose ^{64}Cu-SARTATE formulation of Example 1 over 24 hours, using gamma scintillation detector, representing that the radiochemical purity of ^{64}Cu-SARTATE remains stable (> 90%) over time.

Figure 3: Area percent report, using gamma scintillation detector – HPLC analysis of a high-dose ^{64}Cu-SARTATE formulation of Example 2 immediately after preparation (radiochemical yield = 3500 MBq) representing 98.2% of ^{64}Cu detected being present as ^{64}Cu-SARTATE.

Figure 4: Graph of repeat HPLC analyses of high-dose ^{64}Cu-SARTATE formulation of Example 2 over 45 hours, using gamma scintillation detector, representing that the radiochemical purity of ^{64}Cu-SARTATE remains stable (>90%) over time.

Figure 5: Area percent report, using gamma scintillation detector – HPLC analysis of ^{67}Cu-SARTATE formulation of Example 3 immediately after preparation (radiochemical yield = 3922 MBq) representing 98.6% of ^{67}Cu detected being present as ^{67}Cu-SARTATE.

Figure 6: Graph of repeat HPLC analyses of ^{67}Cu-SARTATE formulation of Example 3 over 11 hours, using gamma scintillation detector, representing that the radiochemical purity of ^{67}Cu-SARTATE remains stable (>90%) over time.

Figure 7: Graph of repeat HPLC analyses of ^{64}Cu-SARTATE formulation of Example 2 over 43 hours, after incubation in fresh human serum.

Figure 8: In vitro internalization of ^{64}Cu-SARTATE in the SSTR2 over-expressing cell line A427-7 (closed symbols) and with an excess of Tyr^3-octreotate (open symbols), for increasing periods of incubation.

Figure 9: Cell-surface binding of ^{64}Cu-SARTATE in the SSTR2 over-expressing cell line A427-7 (closed symbols) and with an excess of Tyr^3-octreotate (open symbols), for increasing periods of incubation.

Figure 10: Comparison of the normalized uptake of ^{64}Cu-SARTATE in A427-7 and the A427 parental cell-line over 2 hours ($p < 0.0001$).

Figure 11: In vivo biodistribution of ^{64}Cu-SARTATE in select tissues from A427-7 tumour bearing Balb/c mice at 2 and 24 h. A blocking study was performed to confirm the specificity of ^{64}Cu-SARTATE for SSTR2 after 2 hours by co-injecting an excess of Tyr^3-octreotate.

Figure 12: In vivo PET imaging of ^{64}Cu-SARTATE using small animal PET maximum intensity projection images of A427-7 tumour-bearing Balb/c mice at 2 hours and 24 hours post-injection of ^{64}Cu-SARTATE, with and without the co-injection of an excess of Tyr^3-octreotate.

Detailed description

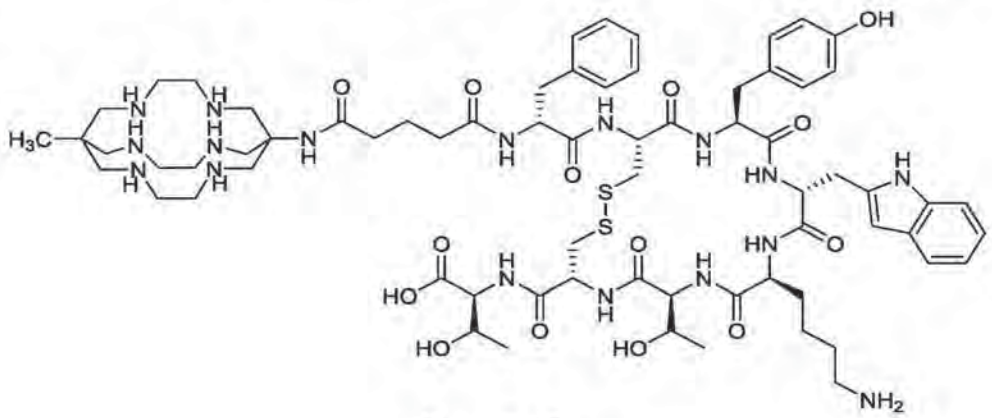
The present invention relates to stable formulations of a specific radioisotope-ligand complex. The present inventors have found that the formulations of a complex disclosed herein minimise dissociation of the radioisotope from the ligand and/or minimise radiolysis of the ligand arising from the radioisotope.

The formulations of a radioisotope-ligand complex referred to herein are stable in solution and under physiological conditions for a time. The stability of the formulation relates to the stability of the complex, where the radioisotope may undergo dissociation or the complex may undergo radiolysis. The stability of the complex can be measured by considering the radiochemical purity of the formulation. Radiochemical purity is defined as the amount of the radioisotope complexed by the sarcophagine ligand expressed as percentage of the total amount of the radioisotope present in the formulation. The radioisotope may be present in the formulation as a complex with the sarcophagine ligand, as a free radioisotope or as part of a radiolysis product.

It has previously been found that octreotate-containing ligands target somatostatin receptors, namely the type 2 (SSTR2) and type 5 (SSTR5) receptors. An example of a ligand containing octreotate is MeCOSar-octreotate, or MeCOSar-D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH, where MeCOSar is the macrocyclic sarcophagine ligand 5-[[8-amino-3,6,10,13,19-hexaazabicyclo-[6.6.6]eico-1-yl)amino]-5-oxo-pentanyl and octreotate is D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-OH. A person skilled in the art would appreciate that

octreotate is a cyclic octapeptide and is derived from the corresponding linear peptide by formation of a Cys-Cys disulphide bond. A person skilled in the art would also appreciate that a sarcophagine ("sar") is a nitrogen-containing hexadentate macrocyclic ligand, which is capable of complexing donor atoms, such as transition metal ions and in the context of the present invention Cu ions.

MeCOSar-octreotate (also referred to herein as "SARTATE") is also as shown in Formula (I):



Formula (I)

The compound of Formula (I) may be produced via a coupling reaction between a sarcophagine ligand and the octreotate cyclic peptide, where the macrocyclic sarcophagine and the octreotate fragments are synthesised individually prior to coupling. The sarcophagine of Formula (I) is itself derived from an amino-capped macrocyclic ligand coupled with an aliphatic carboxylate group. The synthetic route to access the compound of Formula (I), and the component sarcophagine and octreotate fragments, has been previously disclosed in *Dalton Trans.*, 2015, **43**, 1386.

The present invention also contemplates the use of pharmaceutically acceptable salts of the compound of Formula (I), as part of the claimed formulations. Examples of pharmaceutically acceptable salts of compounds of Formula (I) may include the corresponding acetate salt, sodium salt, hydrochloride salt, potassium salt, magnesium salt, calcium salt or ammonium salt. In an embodiment, the compound of Formula (I) is provided as the acetate salt.

The administrable formulations of the present invention comprise a complex of a compound of Formula (I), or a salt thereof, and a radioisotope. The radioisotope, may also be referred to as a radionuclide, and may be a metal or a metal ion. The ligand of the present specification has been found to be particularly successful in complexing copper ions, especially Cu^{2+} ions. The complex of the Formula (I), comprising a copper ion radioisotope has been previously disclosed in *Dalton Trans.*, 2015, **43**, 1386. A person skilled in the art would also appreciate that a complex of Formula (I) and a radioisotope may be achieved by contacting the compound of Formula (I), or a salt thereof, with the radioisotope that is to be complexed, such that the compound of Formula (I), or a salt thereof, is complexed with the radioisotope. This may involve the mixing of the compound of Formula (I), or a salt thereof, and the radioisotope in a suitable solvent system (such as that specifically described herein).

In an embodiment, the ligand is complexed with a Cu ion. The copper ion may be radioactive, and thus a radionuclide or radioisotope of copper. In an embodiment, the ligand is complexed with ^{60}Cu. In another embodiment, the ligand is complexed with ^{61}Cu. In another embodiment, the ligand is complexed with ^{64}Cu. In another embodiment, the ligand is complexed with ^{67}Cu. In a preferred embodiment, the ligand is complexed with ^{64}Cu. In another preferred embodiment, the ligand is complexed with ^{67}Cu.

The formulations of the present invention comprise ethanol as a component. The ethanol used in the formulation may be anhydrous ethanol. Alternatively, the ethanol used in the formulation may not have been subject to drying processes and may be hydrated. The ethanol is preferably pharmaceutical grade ethanol. The ethanol present in the formulation may further assist in preventing radiolysis of the radiolabelled complex of Formula (I).

In an embodiment, ethanol is present in the formulation in an amount of about 7% to about 13% (v/v). In an embodiment, ethanol is present in the formulation in an amount of about 7% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 8% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 9% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 10% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 11% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 12% (v/v). In another embodiment, ethanol is present in the formulation in an amount of about 13% (v/v). In a preferred embodiment, ethanol is present in the formulation in an amount of about 10% (v/v). In other embodiments, the present invention also contemplates ethanol in ranges between the aforementioned amounts.

The formulations of the present invention also comprise sodium chloride as a component. The sodium chloride in the formulations of the present invention may be provided as a saline solution. A saline solution is defined as an aqueous solution of sodium chloride. For example, normal saline is defined as an aqueous solution of sodium chloride at a concentration of 0.9% (w/v). In an embodiment of the present invention, the sodium chloride of a formulation is provided by a saline solution.

In an embodiment, sodium chloride is present in the formulation in an amount of about 0.6% to 1.2% (w/v). In an embodiment, sodium chloride is present in an amount of about 0.6% (w/v). In another embodiment, sodium chloride is present in an amount of about 0.7% (w/v). In another embodiment, sodium chloride is present in an amount of about 0.8% (w/v). In another embodiment, sodium chloride is present in an amount of about 0.9% (w/v). In another embodiment, sodium chloride is present in an amount of about 1.0% (w/v). In another embodiment, sodium chloride is present in an amount of about 1.1% (w/v). In another embodiment, sodium chloride is present in an amount of about 1.2% (w/v). In a preferred embodiment, sodium chloride is present in the formulation in an amount of about 0.9% (w/v). In other embodiments, the present invention also contemplates sodium chloride in ranges between the aforementioned amounts.

The formulations of the present invention comprise gentisic acid, or pharmaceutically acceptable salts and/or hydrates thereof, as a component. Gentisic acid is also known as 2,5-dihydroxybenzoic acid, 5-hydroxysalicylic acid or hydroquinonecarboxylic acid. Salts of gentisic acid may include the sodium salt and the sodium salt hydrate. Any reference to gentisic acid may include a reference to salts thereof, where relevant. It has been identified

by the present inventors that the gentisic acid, or salt thereof, within the present formulations assists in preventing or minimising radiolysis of the radiolabelled complex of Formula (I).

In an embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.02% to about 0.1% (w/v). In an embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.02% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.025% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.03% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.035% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.04% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.045% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.05% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.055% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.6% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.065% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.07% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.075% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.08% (w/v).). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.085% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.09% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.095% (w/v). In another embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of about 0.1% (w/v). In other embodiments, the present invention also contemplates gentisic acid, or a salt thereof, in ranges between the aforementioned amounts. In a preferred embodiment, gentisic acid, or a salt thereof, is present in the formulation in an amount of not more than 0.056% (w/v).

The formulations of the present invention have a pH of about 4 to about 8. A person skilled in the art would understand that the pH of the formulation is an inherent characteristic of the formulation, attributed to the combination of the compound of Formula (I) or a complex thereof, and the remaining excipients of the formulation. The present inventors have found that this pH range provides for optimal radiolabelling efficiency.

In an embodiment, the pH of the formulation is from about 4 to about 8. In an embodiment, the pH of the formulation is about 4. In another embodiment, the pH of the formulation is about 4.5. In another embodiment, the pH of the formulation is about 5.0. In an embodiment, the pH of the formulation is about 5.5. In another embodiment, the pH of the formulation is about 5.6. In another embodiment, the pH of the formulation is about 5.7. In another embodiment, the pH of the formulation is about 5.8. In another embodiment, the pH of the formulation is about 5.9. In another embodiment, the pH of the formulation is about 6.0. In another embodiment, the pH of the formulation is about 6.1. In another embodiment, the pH of the formulation is about 6.2. In another embodiment, the pH of the formulation is about 6.3. In another embodiment, the pH of the formulation is about 6.4. In another embodiment, the pH of the formulation is about 6.5. In another embodiment, the

pH of the formulation is about 7.0. In another embodiment, the pH of the formulation is about 7.5. In another embodiment, the pH of the formulation is about 8.0. In a preferred embodiment, the pH of the formulation is about 6.0.

In a preferred embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride and about 0.06% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride and 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. One skilled in the art would appreciate that the amount of the Formula (I)-Cu ion complex present in the aqueous formulation can be modified to suit varying needs.

In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.06% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride and 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0.

In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.06% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride and 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0.

In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.06% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of

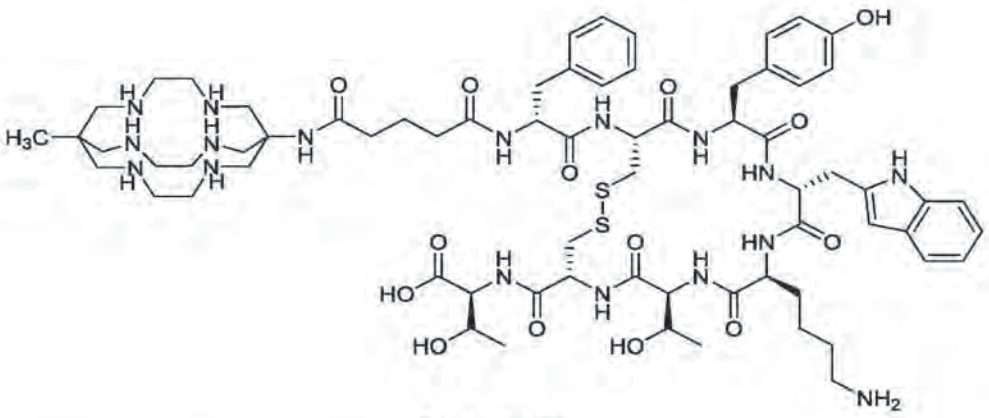
Formula (I) as the acetate, salt, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0.

In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.06% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and about 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate, salt, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0.

The aqueous formulation of the present invention may also comprise an acetate salt as a buffering salt. The acetate salt may be ammonium acetate or sodium acetate.

The present inventors have also found that the formulation may be further stabilised with the addition of L-methionine, or a salt thereof. The addition of L-methionine to a formulation comprising a compound of Formula (I), ethanol, sodium chloride and gentisic acid or a salt thereof, further enhances the stability of the formulation by preventing or minimising radiolysis of a radiolabelled complex of Formula (I). The present inventors have also found that the addition of L-methionine to a formulation comprising a compound of Formula (I) and a Cu ion allows for a formulation with a higher starting radioactivity to be obtained, where the Cu ion is a radioisotope of Cu.

Accordingly, the present invention also provides an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion:



Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;

about 0.3 to about 1.2% (w/v) sodium chloride;
about 0.02 to about 0.1% (w/v) gentisic acid or a salt thereof; and
about 1 to about 4 mg/mL L-methionine or a salt thereof;

wherein the formulation has a pH of between about 4 to about 8.

In an embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 1 mg/mL to about 4 mg/mL. In an embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 1.0 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 1.5 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 2.0 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 2.5 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 3.0 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 3.5 mg/mL. In another embodiment, L-methionine, or a salt thereof, is present in the formulation in an amount of about 4.0 mg/mL.

In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.06% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. One skilled in the art would appreciate that the amount of the Formula (I)-Cu ion complex present in the aqueous formulation can be modified to suit varying needs.

In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.06% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, not more than 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0.

In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% (v/v)

ethanol, about 0.9% (w/v) sodium chloride, about 0.06% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In an embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, not more than 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I), or a salt thereof, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0.

In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.06% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{64}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate, salt, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0.

In a further embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.06% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate salt, complexed with a ^{67}Cu ion, about 10% (v/v) ethanol, about 0.9% (w/v) sodium chloride, about 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0. In another embodiment, the aqueous formulation of the present invention comprises a compound of Formula (I) as the acetate, salt, complexed with a ^{67}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride, not more than 0.056% gentisic acid, or a salt thereof, and about 2.5 mg/mL L-methionine, or a salt thereof, wherein the formulation has a pH of about 6.0.

According to the present invention, a formulation of a complex of ^{64}Cu and a compound of Formula (I) may have a radiochemical purity of at least about 90% for a time of at least 45 hours. This means that at least about 90% of the ^{64}Cu radioisotope present in the formulation is complexed with the compound of Formula (I), or a salt thereof, for at least 45 hours after preparation of the formulation. Where the ^{64}Cu radioisotope present in the

formulation is not complexed with the compound of Formula (I), or a salt thereof, the ^{64}Cu radioisotope may be present as a free ^{64}Cu ion, or as part of a radiolysis product.

In an embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 90% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 91% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 92% at a time of about 45 hours after preparation of the formulation.

In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 93% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 94% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 95% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 96% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 97% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 98% at a time of about 45 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% at a time of about 45 hours after preparation of the formulation.

In an embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% immediately after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 1 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 3 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 6 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 9 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 12 h after preparation of the formulation. In another

embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 15 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 18 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 21 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{64}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 24 h after preparation of the formulation.

According to the present invention, a formulation of a complex of ^{67}Cu and a compound of Formula (I) may also have a radiochemical purity of at least 90% for a time of at least 11 hours. This means that at least about 90% of the ^{67}Cu radioisotope present in the formulation is complexed with the compound of Formula (I), or a salt thereof, for at least 11 hours after preparation of the formulation. Where the ^{67}Cu radioisotope present in the formulation is not complexed with the compound of Formula (I), or a salt thereof, the ^{67}Cu radioisotope may be present as a free ^{67}Cu ion, or as part of a radiolysis product.

In an embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 90% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 91% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 92% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 93% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 94% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 95% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 96% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 97% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 98% at a time of about 11 hours after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% at a time of about 11 hours after preparation of the formulation.

In an embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% immediately after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 1 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 3 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 6 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 9 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 12 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 15 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 18 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 21 h after preparation of the formulation. In another embodiment, the radiochemical purity of a formulation of the present invention comprising a complex of ^{67}Cu and a compound of Formula (I), or a salt thereof is about 99% after about 24 h after preparation of the formulation.

Preparation of an aqueous formulation of the present invention

The compound of Formula (I), or a salt thereof, complexed with a Cu ion may be provided by mixing a compound of Formula (I), or a salt thereof, with a solution of a Cu ion in the presence of a buffering solution. The solution may then be filtered and subsequently washed to provide the formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion. Accordingly, the present invention provides a process for preparing an aqueous formulation comprising a compound of Formula (I) complexed with a Cu ion, the method comprising the steps of:

i) preparing a buffering solution of an acetate salt, wherein the buffering solution further comprises ethanol and gentisic acid or a salt thereof;
ii) dissolving a compound of Formula (I), or a salt thereof, in the buffering solution obtained from step i);
iii) adding a solution of a Cu ion to the solution obtained from step ii);
iv) filtering the solution obtained from step iii) on to a stationary phase; and
v) washing the stationary phase of step iv) with ethanol and saline;

to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

The buffering solution may be a solution of ammonium acetate. Alternatively, the buffering solution may be a solution of sodium acetate. A buffering solution employing an acetate salt is used to maintain the pH in a range that allows for maximum and rapid complexation of a compound of Formula (I), or a salt thereof, with a Cu ion. The buffering solution may

comprise an aqueous solution of ammonium acetate at a concentration of between about 0.08 to about 0.12 mol/L. In an embodiment, the buffering solution comprises an aqueous solution of ammonium acetate at a concentration of about 0.08 mol/L. In another embodiment, the buffering solution comprises an aqueous solution of ammonium acetate at a concentration of about 0.09 mol/L. In another embodiment, the buffering solution comprises an aqueous solution of ammonium acetate at a concentration of about 0.1 mol/L. In another embodiment, the buffering solution comprises an aqueous solution of ammonium acetate at a concentration of about 0.11 mol/L. In another embodiment, the buffering solution comprises an aqueous solution of ammonium acetate at a concentration of about 0.12 mol/L. In a preferred embodiment, the buffering solution comprises an aqueous solution of 0.1 mol/L.

The buffering solution also comprises ethanol as a component. As previously described, the ethanol may be anhydrous or may be previously subjected to drying procedures known in the art. The buffering solution may comprise ethanol at a concentration of between about 3 to about 11% (v/v). In an embodiment, the buffering solution comprises ethanol at a concentration of about 3% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 3.5% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 4% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 4.5% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 5% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 6% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 7% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 8% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 9% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 10% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 10% (v/v). In another embodiment, the buffering solution comprises ethanol at a concentration of about 11% (v/v). In a preferred embodiment, the buffering solution comprises ethanol at a concentration of about 10% (v/v).

The buffering solution also comprises gentisic acid, or a salt thereof, as a component. As previously described, salts of gentisic acid may include the sodium salt or the sodium salt hydrate. Other salts of gentisic acid are also contemplated. The buffering solution may comprise sodium gentisate at a concentration of between about 0.1 to about 0.55% (w/v). In an embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.1% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.15% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.2% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.25% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.3% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.35% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.4% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.45% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.5% (w/v). In another embodiment, the buffering solution comprises sodium gentisate at a concentration of about

0.55% (w/v). In a preferred embodiment, the buffering solution comprises sodium gentisate at a concentration of about 0.228% (w/v).

According to an embodiment of the present invention, the buffering solution may be prepared by mixing ethanol and gentisic acid, or a salt thereof, with an aqueous solution of ammonium acetate. The buffering solution may be prepared by sequentially adding ethanol and gentisic acid, or a salt thereof, to the aqueous solution of ammonium acetate, or alternatively, the ethanol and gentisic acid, or a salt thereof, may be added to the solution of ammonium acetate together. In an embodiment of the present invention, the buffering solution comprises ammonium acetate at a concentration of about 0.1 M, with ethanol at a concentration of about 4-11% (v/v) and gentisic acid, or a salt thereof, at a concentration of about 0.5% (w/v).

According to an embodiment of the present invention, a compound of Formula (I), or a salt thereof, is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. The compound of Formula (I) or a salt thereof, may be obtained as a solid. In an embodiment, the compound of Formula (I) or a salt thereof, is obtained as a lyophilised powder. In an embodiment, the compound of Formula (I) or a salt thereof, obtained as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid or a salt thereof. In an embodiment, about 15 µg to about 65 µg of the compound of Formula (I) or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid or a salt thereof. In another embodiment, about 15 µg of the compound of Formula (I) or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid or a salt thereof. In another embodiment, about 20 µg of the compound of Formula (I) or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 25 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 30 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 35 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 40 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 45 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 50 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 55 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 60 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof. In another embodiment, about 65 µg of the compound of Formula (I), or a salt thereof, as a lyophilised powder is mixed with a

buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof.

A solution of a Cu ion is added to the mixture of a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof, and is allowed to stand for a time.

In an embodiment, the solution of a Cu ion is a solution of a Cu salt. In another embodiment, the solution of a Cu ion is a solution of a chloride salt containing copper. In another embodiment, the solution of a Cu ion is a solution of a copper(II) chloride salt. In another embodiment, the solution of a Cu ion is a solution of a copper salt containing a ^{60}Cu radioisotope. In another embodiment, the solution of a Cu ion is a solution of a chloride salt containing a ^{61}Cu radioisotope. In another embodiment, the solution of a Cu ion is a solution of a chloride salt containing a ^{64}Cu radioisotope. In another embodiment, the solution of a Cu ion is a solution of a chloride salt containing a ^{67}Cu radioisotope. In another embodiment, the solution of a Cu ion is a solution of a radioactive copper(II) chloride salt. In another embodiment, the solution of a Cu ion is a solution of a copper(II) chloride salt, wherein the copper is the ^{61}Cu isotope. In another embodiment, the solution of a Cu ion is a solution of a copper(II) chloride salt, wherein the copper is the ^{64}Cu isotope. In another embodiment, the solution of a Cu ion is a solution of a copper(II) chloride salt, wherein the copper is the ^{67}Cu isotope. In another embodiment, the solution of Cu ion is a solution of $[^{61}Cu]CuCl_2$. In another embodiment, the solution of a Cu ion is a solution of $[^{64}Cu]CuCl_2$. In another embodiment, the solution of Cu ion is a solution of $[^{67}Cu]CuCl_2$.

The solution of a Cu ion is provided as an aqueous solution. The Cu ion may be provided in an aqueous solution of hydrochloric acid. In an embodiment, the Cu ion is provided in a solution of between about 0.01 to about 0.1 mol/L hydrochloric acid. In an embodiment, the Cu ion is provided in a solution of about 0.01 mol/L hydrochloric acid. In another embodiment, the Cu ion is provided in a solution of about 0.02 mol/L hydrochloric acid. In another embodiment, the Cu ion is provided in a solution of about 0.05 mol/L hydrochloric acid. In another embodiment, the Cu ion is provided in a solution of about 0.075 mol/L hydrochloric acid. In another embodiment, the Cu ion is provided in a solution of about 0.1 mol/L hydrochloric acid. In a preferred embodiment, the Cu ion is provided as $[^{64}Cu]CuCl_2$ in a solution of about 0.05 mol/L hydrochloric acid. In another preferred embodiment, the Cu ion is provided as $[^{67}Cu]CuCl_2$ in a solution of about 0.05 mol/L hydrochloric acid.

The solution of a ^{64}Cu-radioisotope is provided as an aqueous solution with a radioactivity of between about 750 to about 3500 MBq. In an embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 750 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 1000 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 1250 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 1500 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 1750 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 2000 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 2250 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 2500 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 2750 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is about 3000 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope solution is

about 3250 MBq. In another embodiment, the radioactivity of the ^{64}Cu-radioisotope is about 3500 MBq.

The solution of a ^{67}Cu-radioisotope is provided as an aqueous solution with a radioactivity of between about 1000 to about 5000 MBq. In an embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 1000 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 1500 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 2000 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 2500 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 3000 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 3500 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 4000 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 4500 MBq. In another embodiment, the radioactivity of the ^{67}Cu-radioisotope is about 5000 MBq.

A mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof, may be allowed to stand at room temperature. The mixture may be allowed to stand with stirring, alternatively, the mixture is allowed to stand without stirring. The mixture may be allowed to stand for a time between about 5 to about 25 minutes. In an embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 5 minutes. In another embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 10 minutes. In another embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 15 minutes. In another embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 20 minutes. In another embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 25 minutes. In a preferred embodiment, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 15 minutes. In another preferred embodiment, the mixture of a ^{64}Cu-radioisotope, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid is allowed to stand without stirring for about 20 minutes.

According to another embodiment of the present invention, the mixture of a Cu ion, a compound of Formula (I), or a salt thereof, and the buffering solution of aqueous ammonium acetate comprising ethanol and gentisic acid, or a salt thereof, is filtered. The mixture may be filtered to remove the acetate salt that may remain in the solution. The mixture may be filtered through a solid phase extraction process. The mixture may be filtered through a solid phase extraction process, where the stationary phase of the solid phase extraction cartridge retains the compound of Formula (I), or a salt thereof, complexed with a Cu ion, any compound of Formula (I), or a salt thereof, that is not complexed and some gentisic acid in the form of a salt that is present, such as sodium

gentisate. As used herein, the term "stationary phase" refers to a resin-like material that is held within the solid phase extraction cartridge and allows for the separation of compounds based on their polarity.

The solid phase extraction process as described herein may use a reverse-phase stationary phase. As used herein, the term "reverse-phase" in relation to a stationary phase refers to a stationary phase that is hydrophobic in nature, such that the stationary phase has an affinity for hydrophobic or uncharged molecules. Examples of a reverse-phase stationary phase may include Phenomenex Strata-X 33u Polymeric Reversed Phase, Waters tC18 or Waters C18. Other similar stationary phases may be used. As the solid phase extraction process uses a reverse-phase stationary phase, the ammonium acetate from the buffering solution, any free Cu ions and the majority of the remaining gentisic acid or its salt is not retained by the stationary phase and these components are discarded.

In an embodiment, the mixture of a Cu ion, a compound of Formula (I) and the buffering solution of aqueous ammonium acetate is filtered through a solid phase extraction cartridge. In an embodiment, the mixture of a Cu ion, a compound of Formula (I) and the buffering solution of aqueous ammonium acetate, is filtered through a solid phase extraction cartridge with a reverse-phase stationary phase. In an embodiment, the ammonium acetate and gentisic acid from the buffering solution is removed by a solid phase extraction cartridge with a reverse-phase stationary phase. In an embodiment, the compound of Formula (I) complexed with a Cu ion is retained by a solid phase extraction cartridge with a reverse-phase stationary phase. In a preferred embodiment, the mixture of a ^{64}Cu-radioisotope, a compound of Formula (I) and the buffering solution of aqueous ammonium acetate is filtered through a solid phase extraction cartridge with a reverse-phase stationary phase. In a preferred embodiment, the compound of Formula (I) complexed with a ^{64}Cu ion is retained by a solid phase extraction cartridge with a reverse-phase stationary phase. In another preferred embodiment, the mixture of a ^{67}Cu-radioisotope, a compound of Formula (I) and the buffering solution of aqueous ammonium acetate is filtered through a solid phase extraction cartridge with reverse-phase stationary phase. In another preferred embodiment, the compound of Formula (I) complexed with a ^{67}Cu ion is retained by a solid phase extraction cartridge with a reverse-phase stationary phase.

The compound of Formula (I) complexed with a Cu ion is eluted from the solid phase extraction cartridge containing the stationary phase by washing with a solvent. As the solid phase extraction cartridge contains a reverse-phase stationary phase, eluting the compound of Formula (I) complexed with a Cu ion requires washing of the stationary phase with ethanol, saline and/or another solvent. In an embodiment, the solid phase extraction cartridge is washed with ethanol to elute the compound of Formula (I) complexed with a Cu ion. In another embodiment, the solid phase extraction cartridge is washed with saline to elute the compound of Formula (I) complexed with a Cu ion. In another embodiment, the solid phase extraction cartridge is washed with ethanol and saline to elute the compound of Formula (I) complexed with a Cu ion. In a preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to elute the compound of Formula (I) complexed with a Cu ion. In a preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to provide the formulation of the present invention. In a preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to elute the compound of Formula (I) complexed with a Cu ion and any retained components, such as gentisic acid or its salt.

As discussed above, the present inventors have found that formulations of Formula (I) complexed with a Cu ion further comprising L-methionine show even greater stability towards radiolysis. In another preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to elute the compound of Formula (I) complexed with a Cu ion and gentisic acid, or a salt thereof, into a solution of L-methionine in saline. In another preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to elute the compound of Formula (I) complexed with a Cu ion, ammonium acetate and gentisic acid, or a salt thereof, into a solution of L-methionine in saline. In another preferred embodiment, the concentration of L-methionine in the saline solution into which the solid phase extraction cartridge is washed is about 2.5 mg/mL. In another preferred embodiment, the solid phase extraction cartridge is washed with ethanol and saline sequentially to provide a formulation of the present invention.

A person skilled in the art would understand that the excipients of the formulation include the solvent that is used to elute the compound of Formula (I) complexed with a Cu ion from the stationary phase, and that the amount of each solvent used is related to the amount of each excipient in the formulations of the present invention.

A person skilled in the art would understand that the present disclosure provides a manual process for producing a formulation according to the present invention. A person skilled in the art would understand that the steps described herein may be automated, by using a suitable automated radiosynthesis module, in order to obtain a formulation according to the present invention.

The present inventors have found that the formulations disclosed herein have greater stability and show reduced radiolysis in light of the higher starting radioactivity. This enhanced stability may be attributed to the increased radiochemical purity of the formulation at a given radioactivity. The stability of the formulations of the present invention may be observed for a time of up to 45 hours post-manufacture for a formulation of ^{64}Cu-SARTATE and up to 11 hours post-manufacture for a formulation of ^{67}Cu-SARTATE. Where the formulations of the present invention are used for the purposes of treatment or therapy, the greater stability may mean that doses for multiple patients at multiple remote locations can be prepared at the same time at a single facility. This may mean that resources for manufacture are required at a single facility, rather than at multiple facilities, and greater efficiency in production of the formulations may be achieved. Where the formulations of the present invention are used for imaging purposes, further advantages may be provided since the clinical imaging sites can receive a dosage form that is ready to inject. This may be particularly advantageous for clinical sites where dedicated radiopharmaceutical production facilities do not exist.

The formulations of the present invention comprise a ligand-radioisotope complex, where the ligand is a compound of Formula (I), or a salt thereof. The compound of Formula (I), or a salt thereof, and the radioisotope may be supplied in separate containers. Alternatively, the compound of Formula (I), or a salt thereof, and the radioisotope may be supplied together as a ligand-radioisotope complex.

The container consisting of the compound of Formula (I), or a salt thereof, may provide the compound of Formula (I), or a salt thereof, as a lyophilised powder. The container may be provided at a temperature of between -20 °C and 20 °C.

The formulations may be provided as a kit comprising a container of the radioisotope and a separate container with the ligand and instructions for making the aqueous formulation of the present invention. In an embodiment, the kit of the present invention comprises a container providing a solution of a ^{64}Cu radioisotope and a separate container providing a compound of Formula (I), or a salt thereof. The container providing the radioisotope may contain a solution of a metal salt where the metal is a radionuclide.

In an embodiment, a kit of the present invention comprises a container with a solution of a ^{64}Cu radioisotope. In a further embodiment, a kit of the present invention comprises a container with a solution of a copper salt containing a ^{64}Cu radioisotope. In another embodiment, a kit of the present invention comprises a container with a solution of a chloride salt containing a ^{64}Cu radioisotope. In another embodiment, a kit of the present invention comprises a container with a solution of a radioactive copper(II) chloride salt. In another embodiment, a kit of the present invention comprises a container with a solution of a copper(II) chloride salt, wherein the copper ion is the ^{64}Cu isotope. In another embodiment, a kit of the present invention comprises a container with a solution of $[^{64}Cu]CuCl_2$.

In an embodiment, a kit of the present invention comprises a container with a solution of ^{67}Cu radioisotope. In another embodiment, a kit of the present invention comprises a container with a solution of a copper salt containing a ^{67}Cu radioisotope. In another embodiment, a kit of the present invention comprises a container with a solution of a chloride salt containing a ^{67}Cu radioisotope. In another embodiment, a kit of the present invention comprises a container with a solution of a radioactive copper(II) chloride salt. In another embodiment, a kit of the present invention comprises a container with a solution of a copper(II) chloride salt, wherein the copper ion is the ^{67}Cu isotope. In another embodiment, a kit of the present invention comprises a container with a solution of $[^{67}Cu]CuCl_2$.

The solution of the radioisotope is typically provided as an aqueous solution. In an embodiment, a kit of the present invention provides a radioisotope in the form of an aqueous solution. In a further embodiment, a kit of the present invention provides a radioisotope in the form of an acidic aqueous solution. In another embodiment, a kit of the present invention provides a radioisotope as a solution in hydrochloric acid. The radioisotope may be provided as a solution in hydrochloric acid at a concentration of between about 0.01 and about 0.1 mol/L.

In an embodiment, a kit of the present invention comprises a container with a solution of $[^{64}Cu]CuCl_2$ in hydrochloric acid. In an embodiment, a kit of the present invention comprises a container with a solution of $[^{64}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.02 mol/L. In an embodiment, a kit of the present invention comprises a container with a solution of $[^{64}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.05 mol/L. In an embodiment, a kit of the present invention comprises a container with a solution of $[^{64}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.1 mol/L.

In an embodiment, a kit of the present invention comprises a container with a solution of $[^{67}Cu]CuCl_2$ in hydrochloric acid. In another embodiment, a kit of the present invention comprises a container with a solution of $[^{67}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.02 mol/L. In another embodiment, a kit of

the present invention comprises a container with a solution of $[^{67}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.05 mol/L. In another embodiment, a kit of the present invention comprises a container with a solution of $[^{67}Cu]CuCl_2$ in hydrochloric acid, wherein the hydrochloric acid is at a concentration of about 0.1 mol/L.

The kit may further comprise a container consisting of ethanol, sodium chloride and gentisic acid in a buffered solution. This container may provide ethanol, sodium chloride and gentisic acid in an aqueous solution, or alternatively, the container may consist only of ethanol, sodium chloride and gentisic acid. In an embodiment, the kit comprises a container consisting of ethanol, sodium chloride and gentisic acid, or a salt thereof, in an ammonium acetate buffering solution.

The kit may also comprise a container consisting of ethanol, sodium chloride, gentisic acid, or a salt thereof, and L-methionine, or a salt thereof, in a buffered solution. The container of the kit may provide ethanol, sodium chloride, gentisic acid or a salt thereof, and L-methionine or a salt thereof in an aqueous solution, or alternatively, the container may consist only of ethanol, sodium chloride, gentisic acid or a salt thereof and L-methionine or a salt thereof. In an embodiment, the kit comprises a container consisting of ethanol, sodium chloride, gentisic acid, or a salt thereof, and L-methionine, or a salt thereof. In an embodiment, the kit comprises a container consisting of ethanol, sodium chloride, gentisic acid, or a salt thereof, and L-methionine, or a salt thereof, in an ammonium acetate buffering solution.

Uses of a formulation of the present invention

Formulations of the present invention may be particularly useful for the purposes of diagnosis and treatment in medicine. Complexes with a ligand bearing an appropriate targeting fragment can be used to locate specific tissue types. For such complexes to be considered suitable for use in *in vivo* diagnosis and treatment, the complex must display appropriate kinetic, stability and clearance properties under physiological conditions, in addition to the requisite solubility and stability properties of the complex in solution. As used herein, the term "complex" may relate to a ligand-metal ion complex, where the metal ion is a radioactive isotope or alternatively, the metal ion is a non-radioactive isotope.

Accordingly, the present invention provides a method for radioimaging, a method for diagnosing a disease in a subject or a method for therapy of a disease in a subject, comprising administering to the subject an effective amount of a formulation as defined herein. The present inventors have found that the formulations of the present invention may be used in a method for radioimaging, a method for diagnosing or a method for therapy of a cancer.

As used herein the term "cancer" broadly encompasses a class of neoplastic diseases characterised with abnormal cell growth with the potential to invade or spread to other parts of the body. These are to be contrasted with benign tumours, which do not spread to other parts of the body and therefore the definition as used herein includes all malignant (cancerous) disease states. The term therefore encompasses the treatment of tumours.

Accordingly, the term "tumour" is used generally to define any malignant cancerous or pre-cancerous cell growth, and may include leukemias, but is particularly directed to solid

tumours or carcinomas such as melanomas, colon, lung, ovarian, skin, breast, pancreas, pharynx, brain, prostate, CNS, and renal cancers (as well as other cancers).

Somatostatin receptors, especially SSTR2, are also highly expressed at the plasma membrane of certain tumours and cancers, including pancreatic, gastrointestinal and pulmonary neuroendocrine tumours (NETs), pituitary adenomas, breast carcinomas, meningiomas, neuroblastomas, medulloblastomas, phaeochromocytomas and paragangliomas. The presence of somatostatin receptors on such tumours has led to the development and clinical application of stable somatostatin receptors, e.g. compounds bearing an octreotate motif. The present inventors have found that a complex of a compound of Formula (I) and a Cu ion, as found in the formulations of the present invention, has shown particular utility in binding to somatostatin receptors and in particular, somatostatin receptors of subtype 2 and subtype 5. In certain embodiments, the formulation may be used in the radioimaging, the diagnosis or the treatment of a cancer where the somatostatin receptor is expressed or highly expressed.

The formulations of the present invention comprise a compound of Formula (I) containing an octreotate motif, which is analogous to octreotide, a clinically useful analogue of somatostatin. Somatostatin is released by neuroendocrine cells of the gastrointestinal tract and acts through 5 somatostatin receptor subtypes (SSTR1 to 5). Given the analogous nature of the octreotate motif to octreotide, the compounds of formula (I) may localise at and bind to particular sites where somatostatin receptors are present. Similarly, a compound of Formula (I) complexed with a Cu ion may also localise and bind to the same sites.

The radioisotope-ligand complex of the present invention may comprise a radioisotope such as ^{64}Cu. The ^{64}Cu isotope has a half-life of approximately 12.7 hours and decays by both positron emission and beta decay, which makes the use of a ^{64}Cu-labelled complex suitable for use in various modes of radioimaging. In particular, the decay characteristics and half-life of ^{64}Cu make this radioisotope a favourable choice for use in positron emission tomography (PET) and single-photon emission computed tomography (SPECT). The radioisotope-ligand complex of the present invention may comprise a radioisotope such as ^{61}Cu. The ^{61}Cu isotope has a half-life of approximately 3 hours and decays by positron emission, which makes the use of a ^{61}Cu-labelled complex suitable for use in various modes of radioimaging. The radioisotope-ligand complex of the present invention may also comprise a radioisotope such as ^{67}Cu. The ^{67}Cu isotope has a half-life of approximately 61.8 hours and decays by beta emission, which makes the use of a ^{67}Cu-labelled complex suitable for use in SPECT imaging. The ^{67}Cu-labelled complex may also be suitable for use as a radiotherapy treatment.

The administration of an effective amount of a formulation comprising a compound of Formula (I) and a Cu radioisotope, such as ^{60}Cu, ^{61}Cu, ^{64}Cu or ^{67}Cu, may lead to the binding of the complex of the compound of Formula (I) and the Cu radioisotope to somatostatin receptors. Where the somatostatin receptors are expressed on the surface of a tumour, the complex of a compound of Formula (I) and a Cu ion may bind to the somatostatin receptors. In an embodiment, the present invention provides a method for radioimaging, comprising administering to the subject a formulation comprising a compound of Formula (I) and a Cu ion. In an embodiment, a formulation comprising a compound of Formula (I) and a ^{64}Cu or ^{67}Cu ion may be used in a method for radioimaging. Monitoring of a subject to which a formulation comprising a compound of Formula (I) and a Cu radioisotope was administered

by PET or SPECT, for example, allows for the visualisation and subsequent detection of tumour sites. The visualisation information obtained by radioimaging may provide information in relation to the location of any such tumour sites. Monitoring of the subject to which the radiolabelled complex was administered by SPECT, for example, allows for the visualisation and subsequent detection of tumour sites. This provides information in relation to the location of the tumours, where present. Repeated imaging at later timepoints allows for monitoring clearance of the radioisotope-ligand complex, which enables dosimetry estimates to be calculated. A person skilled in the art would understand that the amount to be administered in order to facilitate radioimaging may vary and will subsequently depend on the nature of the subject and the intended site of imaging.

In order for the complex to be suitable for radioimaging purposes, the radioisotope-ligand complex must display sufficient metabolic stability, i.e. that the complex remains intact with the radioisotope bound to the ligand, for a requisite time. The present invention provides a complex of a compound of Formula (I) and ^{64}Cu that remains intact for up to 45 hours, as evidenced by the absence of radioisotope loss and metabolic decomposition.

The formulations of the present invention may be administered to a subject for the purposes of radioimaging, diagnosis or therapy. Administration is by a parenteral route, with administration by intravenous injection preferred. Alternatively, the formulations of the present invention may be given by intraarterial or other routes, for delivery into the systemic circulation. The subject to which the formulation is administered is then placed into a PET scanner and images showing the localisation of the radioisotope-ligand complex, and subsequently location of any tumours, are obtained. This then allows for diagnosis and detection of tumours. Alternatively, a sample (for example, a blood or a tissue sample) that has been exposed to a formulation of the present invention may be analysed by gamma spectroscopy, gamma counting, liquid scintillation counting, autoradiography or beta probe in order to obtain radioimages.

In an embodiment, the present invention provides the use of a formulation comprising a compound of Formula (I) in a method for the radioimaging of a tumour or cancer. One skilled in the art would understand that the information obtained from radioimaging of a subject may be used in the diagnosis of a tumour or cancer in the subject. In an embodiment, the present invention provides a method for the diagnosis of a tumour or cancer. In a further embodiment, the tumour or cancer may be a somatostatin-receptor expressing tumour or cancer. In an embodiment, the tumour or cancer is a neuroendocrine tumour. In another embodiment, the tumour or cancer is a pituitary adenoma. In another embodiment, tumour or cancer is a neuroblastoma. In another embodiment, the tumour or cancer is a meningioma. In another embodiment, the tumour or cancer is a medulloblastoma. In another embodiment, the tumour or cancer is a breast carcinoma. In another embodiment, the tumour or cancer is a phaeochromocytoma. In another embodiment, the tumour or cancer is a paraganglioma. In another embodiment, the tumour is a pancreatic tumour. In another embodiment, the tumour is a gastrointestinal tumour.

Where the formulation of the present invention comprises a compound of Formula (I) and a Cu radioisotope, the administration of the formulation may treat a tumour or cancer. As discussed above, the compound of Formula (I) may bind somatostatin receptors on the surface of a tumour or cancer site, such the binding of the compound to locations with somatostatin receptors also brings the Cu radioisotope into close proximity of this location. As the Cu radioisotope undergoes radioactive decay, with the mode of decay dependent on

the exact radioisotope chosen, the products of decay may be useful in the treatment of a tumour or cancer due to the proximity of the tumour or cancer to the compound of Formula (I) and Cu radioisotope.

In an embodiment, the present invention provides the use of a formulation comprising a compound of Formula (I) and a Cu radioisotope in a method for treatment of a tumour or cancer. In an embodiment, the tumour or cancer is a neuroendocrine tumour. In another embodiment, the tumour or cancer is a pituitary adenoma. In another embodiment, tumour or cancer is a neuroblastoma. In another embodiment, the tumour or cancer is a meningioma. In another embodiment, the tumour or cancer is a medulloblastoma. In another embodiment, the tumour or cancer is a breast carcinoma. In another embodiment, the tumour or cancer is a phaeochromocytoma. In another embodiment, the tumour or cancer is a paraganglioma. In another embodiment, the tumour is a pancreatic tumour. In another embodiment, the tumour is a gastrointestinal tumour.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Examples

Example 1 – Preparation of a low-dose ^{64}Cu-SARTATE formulation, incorporating ethanol and sodium gentisate as excipients to reduce radiolysis

A buffer solution of 0.1 M ammonium acetate is prepared, where the buffer solution also contains ethanol at a concentration of 4-10% (v/v). The buffer solution also contains sodium gentisate, where a 5 mL volume of the buffer solution contains 38 mg of sodium gentisate.

The compound of Formula (I) is obtained as a lyophilised powder. 20 µg of the compound of Formula (I) in its lyophilised form is dissolved in 5 mL of the prepared buffer solution.

A solution of [^{64}Cu]$CuCl_2$ in 0.05 M hydrochloric acid is prepared, where a 300 µL volume of this solution contains 1500 MBq of [^{64}Cu]. A 300 µL volume of this [^{64}Cu]$CuCl_2$ solution is added to the solution containing the compound of Formula (I) and sodium gentisate in ammonium acetate buffer. This combined solution is allowed to stand, without stirring, at room temperature for 15 minutes.

The solution is then filtered through a solid phase extraction cartridge. The cartridge is then eluted with 1.0 mL ethanol and then 9.0 mL saline solution into a sterile product vial, to give ^{64}Cu-SARTATE in a volume of 10 mL ethanol/saline solution. HPLC analysis of the solution obtained can be seen in Figure 1, showing over 97% radiochemical purity. Further HPLC analysis of the same product solution obtained over multiple time points can be seen in Figure 2, showing that the radiochemical purity remains > 90% for more than 11 hours.

Example 2 - Preparation of a high-dose ^{64}Cu-SARTATE formulation, incorporating ethanol, sodium gentisate and L-methionine as excipients to reduce radiolysis

A buffer solution of 0.1 M ammonium acetate is prepared, where the buffer solution also contains ethanol at a concentration of 4-10% (v/v). The buffer solution also contains sodium gentisate, where a 5 mL volume of the buffer solution contains 114 mg of sodium gentisate.

The compound of Formula (I) is obtained as a lyophilised powder. 20 µg of the compound of Formula (I) in its lyophilised form is dissolved in 5 mL of the prepared buffer solution.

A solution of [^{64}Cu]$CuCl_2$ in 0.05 M hydrochloric acid is prepared, where a 300 µL volume of this solution contains 4650 MBq of [^{64}Cu]. A 300 µL volume of this [^{64}Cu]$CuCl_2$ solution is added to the solution containing the compound of Formula (I) and sodium gentisate in ammonium acetate buffer. This combined solution is allowed to stand, without stirring, at room temperature for 15 minutes.

The solution is then filtered through a solid phase extraction cartridge. The cartridge is then eluted with 1.0 mL ethanol and then 16.0 mL saline solution, to give ^{64}Cu-SARTATE in a volume of 20 mL ethanol/saline solution. HPLC analysis of the solution obtained can be seen in Figure 3, showing over 98% radiochemical purity. Further HPLC analysis of the same product solution obtained over multiple time points can be seen in Figure 4, showing that the radiochemical purity remains > 90% for more than 45 hours.

Example 3 – Preparation of a ^{67}Cu-SARTATE formulation, incorporating ethanol, sodium gentisate and L-methionine as excipients to reduce radiolysis

A buffer solution of 0.1 M ammonium acetate is prepared, where the buffer solution also contains ethanol at a concentration of 4-10% (v/v). The buffer solution also contains sodium gentisate, where a 5 mL volume of the buffer solution contains 114 mg of sodium gentisate.

The compound of Formula (I) is obtained as a lyophilised powder. 60 µg of the compound of Formula (I) in its lyophilised form is dissolved in 5 mL of the prepared buffer solution.

A solution of [^{67}Cu]$CuCl_2$ in 0.05 M hydrochloric acid is prepared, where a 300 µL volume of this solution contains 4650 MBq of [^{64}Cu]. A 300 µL volume of this [^{67}Cu]$CuCl_2$ solution is added to the solution containing the compound of Formula (I) and sodium gentisate in ammonium acetate buffer. This combined solution is allowed to stand, without stirring, at room temperature for 15 minutes.

The solution is then filtered through a solid phase extraction cartridge. The cartridge is then eluted with 1.0 mL ethanol and then 16.0 mL saline solution into a sterile product vial containing a solution of L-methionine (50 mg in 3 mL saline solution), to give ^{67}Cu-SARTATE in a volume of 20 mL ethanol/saline solution. HPLC analysis of the solution obtained can be seen in Figure 5, showing over 98% radiochemical purity. Further HPLC analysis of the same product solution obtained over multiple time points can be seen in Figure 6, showing that the radiochemical purity remains > 90% for more than 11 hours.

Example 4 – In vitro serum stability of ^{64}Cu-SARTATE

Incubation of ^{64}Cu-SARTATE (radiochemical purity >99%) with fresh human serum demonstrated high metabolic stability. HPLC analysis of the serum incubated with ^{64}Cu-SARTATE obtained can be seen in Figure 7, indicating that >90% radioactivity in the non-

protein bound fraction at 3 hrs, 20 hrs, 23 hrs, 26 hrs and 34 hrs was still chelator-bound representing intact radiopeptide and indicating no loss of copper or appreciable metabolic decomposition was detected for up to 43 hours.

Example 5 – In vitro internalisation and cell-surface binding of ^{64}Cu-SARTATE

^{64}Cu-SARTATE internalisation and cell-surface binding studies were performed using A427-7 cells bearing somatostatin receptor 2. The percentage of total added radioactivity per mg of protein (%AR/mg protein) that was internalized increased with time, reaching 23.9 ± 0.7 at 120 min (Figure 8). Within 30 min, 40.2 ± 0.7 %AR/mg protein is bound to the cell surface (Figure 9). This value decreased to 31.2 ± 1.2 at 60 min and 35.2 ± 1.3 at 120 min. Both receptor-mediated internalization and cell-surface binding was partially inhibited by the addition of cold Tyr_3-octreotate to the medium. Normalized uptake of ^{64}Cu-SARTATE in the parental A427 cells was notably less than in the SSTR2 expressing A427-7 cells demonstrating the significance of receptor-specific accumulation (Figure 10).

Example 6 – In vivo biodistribution of ^{64}Cu-SARTATE

The biodistribution of Cu-SARTATE was investigated using ^{64}Cu-SARTATE in A427-7 tumour-bearing Balb/c nude mice (Figure 11). ^{64}Cu-SARTATE had effective blood clearance at 2 hours (0.4 ± 0.2 %ID/g, where %ID/g is the percentage of the injected dose per gram of tissue) with further clearance at 24 hours (0.1 ± 0.02 %ID/g). Uptake of ^{64}Cu-SARTATE by the liver (3.1 ± 1.3 %ID/g) and kidneys (35.2 ± 5.4 %ID/g) was highest at 2 hours after dosing. By 24 hours after dosing, kidney uptake of ^{64}Cu SARTATE had fallen by 71% to 10.1 ± 3.5 %ID/g, suggesting effective renal clearance of ^{64}Cu-SARTATE. At 24 hours after dosing, uptake of ^{64}Cu-SARTATE in lungs and spleen (i.e., non-target organs) was 0.6 ± 0.3 %ID/g and 0.8 ± 0.2 %ID/g, respectively, while muscle accumulation was 0.1 ± 0.01 %ID/g at 24 hours. Tumour uptake of ^{64}Cu-SARTATE at 2 hours after administration was high at 31.2 ± 13.1 %ID/g and remained high at 24 hours to 31.4 ± 14.0 %ID/g. Co-administration of excess Tyr^3-octreotate (XS Y^3-TATE) to block the receptors significantly reduced tumour uptake of ^{64}Cu-SARTATE at 2 hours by 81% to 5.9 ± 0.3 %ID/g while increasing the non-target tissue uptake, as shown by a 135% increase in the kidneys to 47.7 ± 6.3 %ID/g.

Example 7 – In vivo PET imaging of ^{64}Cu-SARTATE

Small animal PET images of A427-7 tumour-bearing Balb/c mice at 2 and 24 hours, with and without blocking with an excess of Tyr_3-octreotate are presented in Figure 12. The tumour is clearly visible at 2 hours post-injection of ^{64}Cu-SARTATE with an average tumour to background ratio of 48. The tumour to background ratio at 24 hours remained constant at 45, which indicates a high degree of specific binding and stability of the complex. The co-administration of an excess of Tyr^3-octreotate effectively blocked the tumour uptake, with tumour to background ratio of 3.1 at 2 hours and to below the limit of quantitation at 24 h. The blocking experiment further suggests the specificity for SSTR2 and the low level of non-specific binding of ^{64}Cu-SARTATE. Substantial uptake in the kidneys and bladder was evident in all animals suggesting renal clearance was the major excretion route. The tumour to kidneys ratio at 2 hours was 1.6 and increased to 2.8 at 24 hours.

Example 8 – In vivo toxicology of SARTATE

A single dose preclinical toxicology study in Sprague Dawley rats was conducted to evaluate the potential toxicity of SARTATE when administered via intravenous injection. Testing was performed on solutions of SARTATE-copper-complex (SCC) and unlabeled SARTATE ligand

(SL) at a 1:1 ratio. The study was conducted according to the requirements of OECD GLP Principles.

The test item was administered once to six groups of 10 rats (5/sex) at three doses of 50, 250 and 1000 µg/kg in the vehicle at a volume of 3mL/kg. Two vehicle control groups of 10 rats (5/sex) were administered the vehicle only (10% ethanol in 0.9% sodium chloride and 0.056% gentisic acid) at the same volumetric dose.

Four groups of rats (one vehicle and three test item treated 50, 250 and 1000 µg/kg) from the main study were sacrificed on Day 2. The remaining four groups of 10 rats (one vehicle and three test item treated 50, 250 and 1000 µg/kg) from the recovery study were observed for a treatment-free period of 14 days and sacrificed on Day 15 to assess reversibility of any toxicity.

The following parameters were evaluated: mortality, daily clinical observations, weekly body weights, weekly food consumption, haematology, biochemistry, urinalysis, organ weights and gross necropsy on day of sacrifice. Extensive histopathology was performed on all animals.

No mortalities related to treatment were observed in either the vehicle or the treated groups during both treatment and recovery periods. The test item produced no clinical abnormalities related to treatment in any animal during the 2-day and 15-day experimental periods. Treated and vehicle control groups displayed comparable body weights gains over the 2-day and 15-day experimental periods. Feed intake was similar in control and treated groups for the 2-day and 15-day experimental periods. Haematology, blood biochemistry and urine analysis revealed no test item-related effects. No macroscopic abnormalities were identified during the necropsy of all animals. There was no evidence of any test item-related effect on organ weight and all the tissues examined histopathologically in this study.

Under the conditions of the study, the test item administered intravenously at 50, 250 and 1000 µg/kg in the Sprague Dawley rat produced no toxic effects. The No Observed Adverse Effect level (NOAEL) is therefore 1000 µg/kg (1 mg/kg).

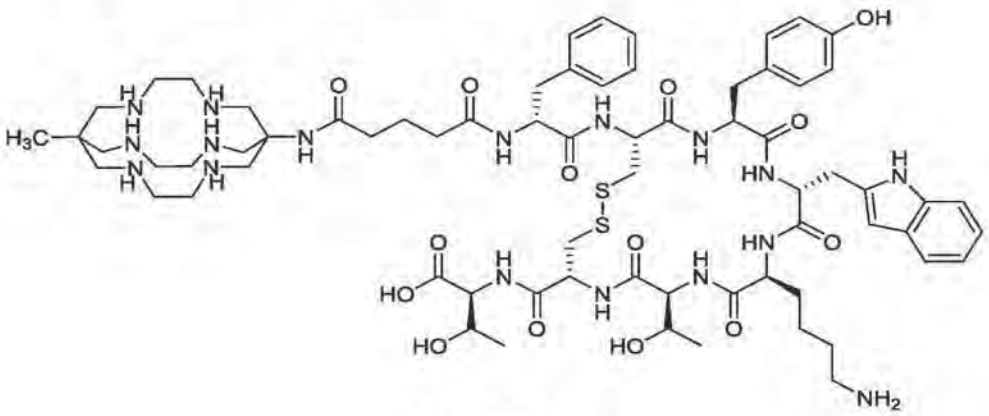
The NOAEL of 1 mg/kg in rats corresponds to a Human Equivalent Dose (HED) of 0.16 mg/kg, or a total dose of 11.2 mg in a patient with a weight of 70 kg. The maximum possible total dose in this clinical trial will be 0.02 mg (20 micrograms) per patient. The NOAEL therefore represents a safety margin of 50 times the maximum human dose of SARTATE. As the dose of ^{64}Cu-SARTATE to be administered to patients is determined by activity (200 MBq), it is expected that the likely dose of SARTATE actually injected will be a fraction of the total possible dose, which increases the safety margin substantially.

Example 9 – In vitro genotoxicity of SARTATE

To evaluate the mutagenic potential of SARTATE, GLP AMES testing was performed on solutions of SARTATE-copper-complex (SCC) and unlabeled SARTATE ligand (SL) at a 1:1 ratio. The SL:SCC solution did not induce an appropriate fold increase in the mean revertants per plate over the mean revertants per plate of the appropriate vehicle control. SL:SCC solution did not exhibit any cytotoxicity at the dose levels used with any of the 5 tester strains. The product is considered to be non-mutagenic.

What is claimed is:

1. An aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion



Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;
about 0.3 to about 1.2% (w/v) sodium chloride; and
about 0.02 to about 0.1% (w/v) gentisic acid, or a salt thereof;

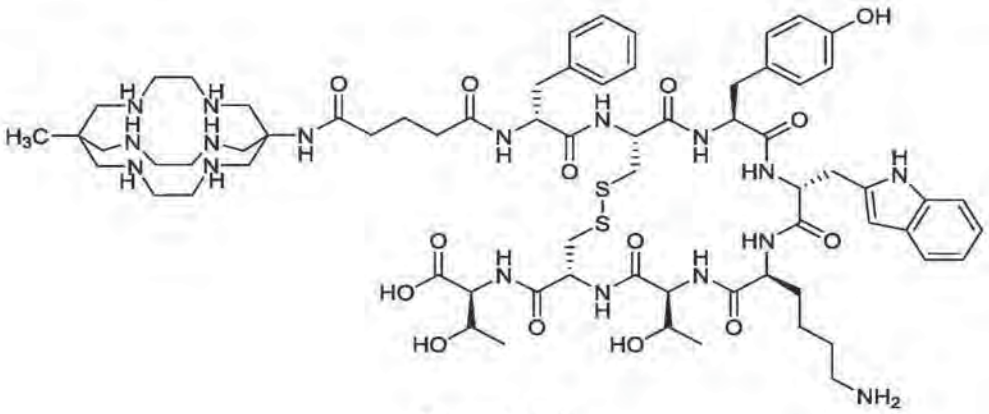
wherein the formulation has a pH of between about 4 to about 8.

2. An aqueous formulation according to claim 1, wherein the formulation comprises:

about 10% (v/v) ethanol;
about 0.9% (w/v) sodium chloride;
about 0.06% (w/v) gentisic acid, or a salt thereof;

wherein the formulation comprises an acetate salt; and
wherein the formulation has a pH of about 6.0.

3. An aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion



Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;
about 0.3 to about 1.2% (w/v) sodium chloride;
about 0.02 to about 0.1% (w/v) gentisic acid, or a salt thereof; and
about 1.0 to about 4.0 mg/mL L-methionine, or a salt thereof;

wherein the formulation has a pH of between about 4 to about 8.

4. An aqueous formulation according to claim 3, wherein the formulation comprises:

about 10% (v/v) ethanol;
about 0.9% (w/v) sodium chloride;
about 0.06% (w/v) gentisic acid, or a salt thereof; and
about 2.5 mg/mL L-methionine, or a salt thereof;

wherein the formulation comprises an acetate salt; and
wherein the formulation has a pH of about 6.0.

5. An aqueous formulation according to any one of claims 1 to 4, wherein the compound of Formula (I) is in the form of an acetate salt.

6. An aqueous formulation according to any one of claims 1 to 5, wherein the formulation comprises an acetate salt as a buffering agent.

7. An aqueous formulation according to any one of claims 1 to 6, wherein the gentisic acid salt is sodium gentisate.

8. An aqueous formulation according to any one of claims 1 to 7, wherein the concentration of gentisic acid, or a salt thereof, is no more than 0.056% (w/v).

9. An aqueous formulation according to any one of claims 1 to 7, wherein the Cu ion is a Cu radioisotope.

10. An aqueous formulation according to claim 9, wherein the Cu radioisotope is selected from the group consisting of ^{60}Cu, ^{61}Cu, ^{64}Cu and ^{67}Cu.

11. A process for preparing an aqueous formulation comprising a compound of Formula (I) complexed with a Cu ion, the method comprising the steps of:

i) preparing a buffering solution of an acetate salt, wherein the buffering solution further comprises ethanol and gentisic acid, or a salt thereof;
ii) dissolving a compound of Formula (I), or a salt thereof, in the buffering solution obtained from step i);
iii) adding a solution of a Cu ion to the solution obtained from step ii);
iv) filtering the solution obtained from step iii) on to a stationary phase; and
v) washing the stationary phase of step iv) with ethanol and saline;

to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

12. A process for preparing an aqueous formulation comprising a compound of Formula (I) complexed with a Cu ion, the method comprising the steps of:

i) preparing a buffering solution of an acetate salt, wherein the buffering solution further comprises ethanol and gentisic acid, or a salt thereof;
ii) dissolving a compound of Formula (I), or a salt thereof, in the buffering solution obtained from step i);
iii) adding a solution of a Cu ion to the solution obtained from step ii);
iv) filtering the solution obtained from step iii) on to a stationary phase; and
v) washing the stationary phase of step iv) with ethanol and saline into a solution of L-methionine;

to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

13. A process according to claim 11 or 12, wherein the acetate salt of the buffering solution is ammonium acetate.

14. A process according to any one of claims 11 to 13, wherein the concentration of the buffering solution of an acetate salt is about 0.1 mol/L.

15. A process according to any one of claims 11 to 14, wherein the ethanol is present in the buffering solution at a concentration of about 4% to about 10% (v/v).

16. A process according to any one of claims 11 to 15, wherein the buffering solution contains sodium gentisate.

17. A process according to any one of claims 11 to 16, wherein the solution of a Cu ion is a solution in hydrochloric acid.

18. A process according to claim 17, wherein the concentration of the hydrochloric acid solution is from about 0.01 to about 0.10 mol/L.

19. A process according to claim 17 or 18, wherein the concentration of the hydrochloric acid solution is about 0.02 mol/L.

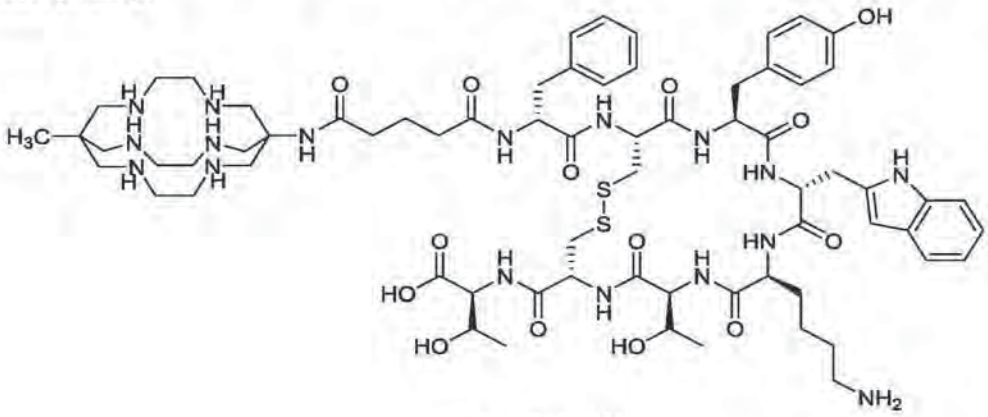
20. A process according to any one of claims 11 to 19, wherein the Cu ion is a Cu radioisotope is selected from the group consisting of ^{60}Cu, ^{61}Cu, ^{64}Cu and ^{67}Cu.

21. A process according to any one of claims 11 to 20, wherein the Cu ion is obtained from a chloride salt of the Cu ion.

22. A process according to claim 12, wherein the concentration of the solution of L-methionine is about 2.5 mg/mL.

23. An aqueous formulation prepared by a process of any one of claims 11 to 22.

24. A kit for making an aqueous formulation for parenteral administration comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion, the kit comprising:

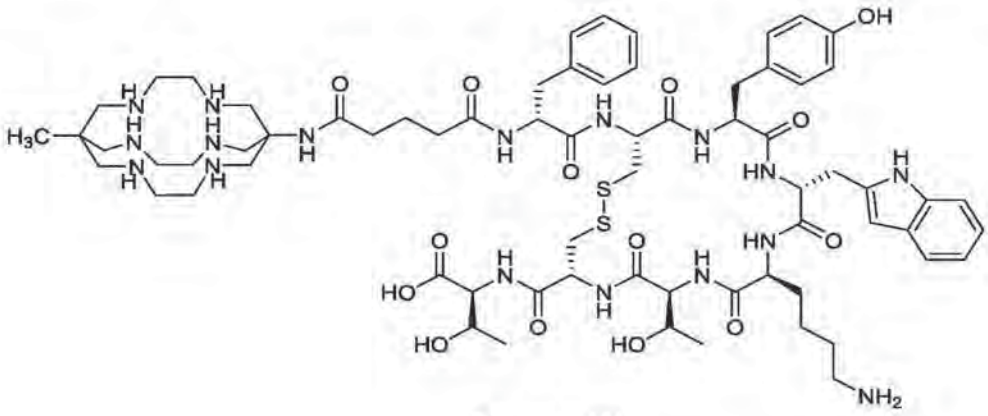


Formula (I)

a container comprising a lyophilised compound of Formula (I), or a salt thereof;
a container comprising a solution of a Cu ion; and

instructions for preparing an aqueous formulation according to any one of claims 1 to 10, including the addition of a buffered solution of ethanol, sodium chloride and gentisic acid, or a salt thereof.

25. A kit for making an aqueous formulation for parenteral administration comprising a compound of Formula (I) complexed with a Cu ion, or a salt thereof, the kit comprising:



Formula (I)

a container comprising a lyophilised compound of Formula (I), or a salt thereof;
a container comprising a solution of a Cu ion;
a container comprising a buffered solution of ethanol, sodium chloride and gentisic acid, or a salt thereof; and

instructions for preparing an aqueous formulation according to any one of claims 1 to 10, including the addition of a buffered solution of ethanol, sodium chloride and gentisic acid, or a salt thereof.

26. A kit according to claim 24 or 25, wherein the container comprising a buffered solution of ethanol, sodium chloride and gentisic acid further comprises L-methionine, or a salt thereof.

27. A method for radioimaging, diagnosing or treating a cancer, the method comprising administering to a subject in need thereof an aqueous formulation according to any one of claims 1 to 10.

Figure 1

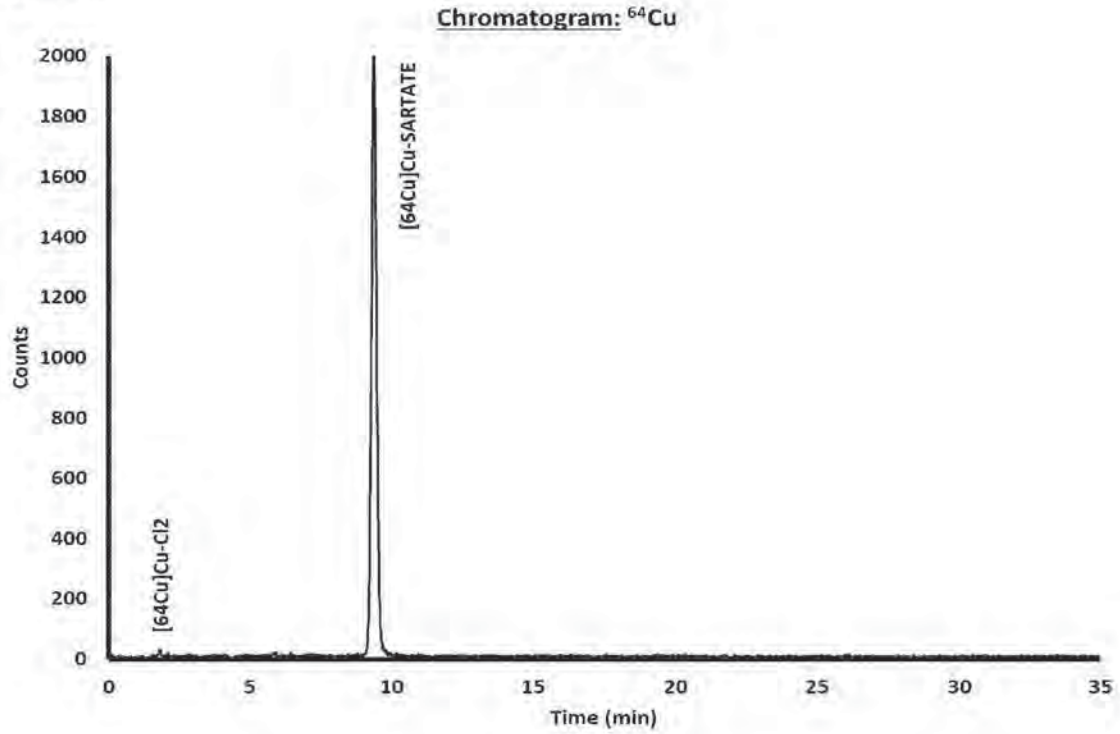


Figure 2

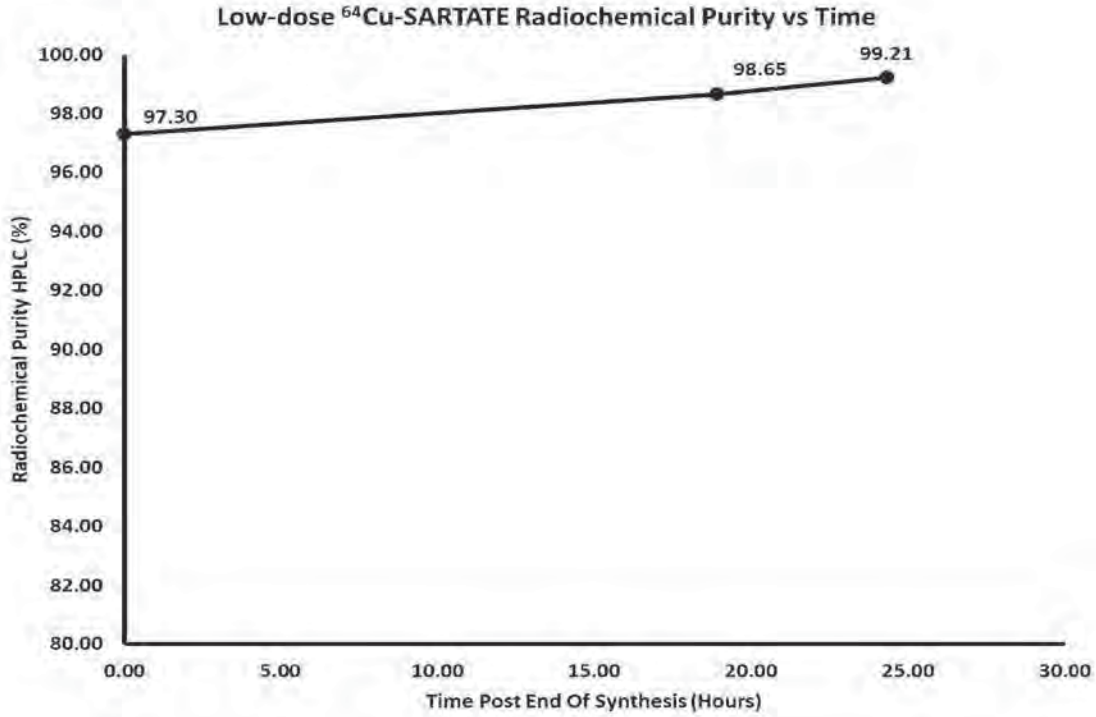


Figure 3

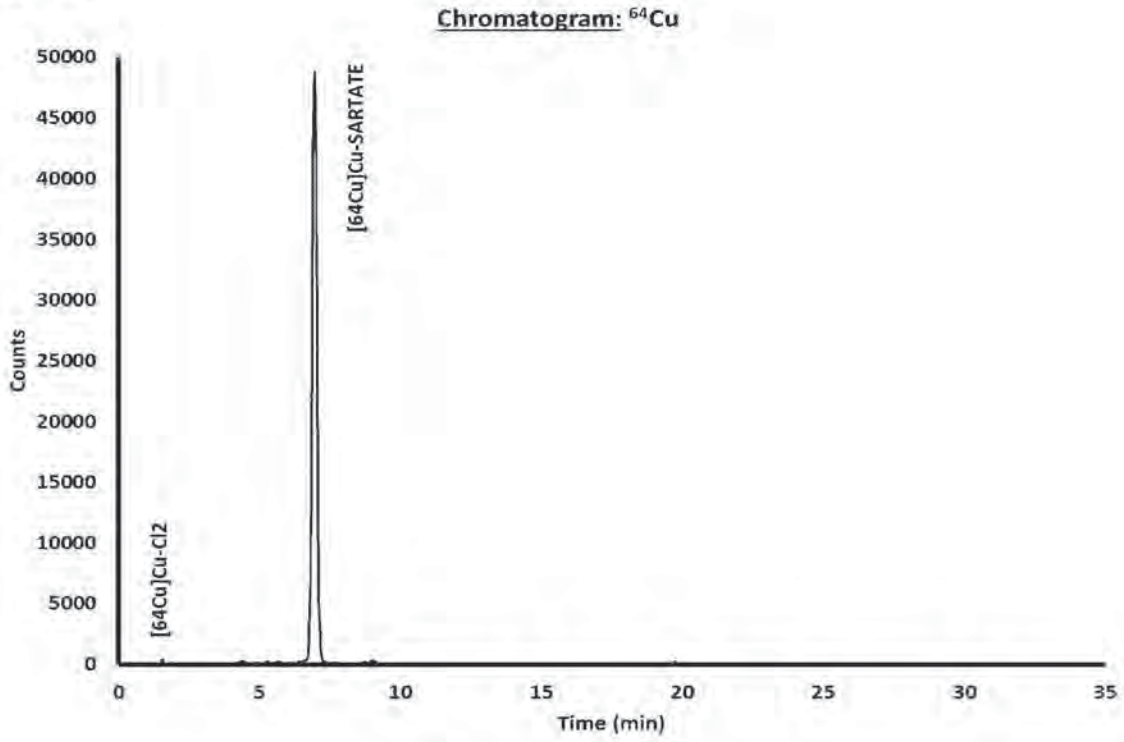


Figure 4

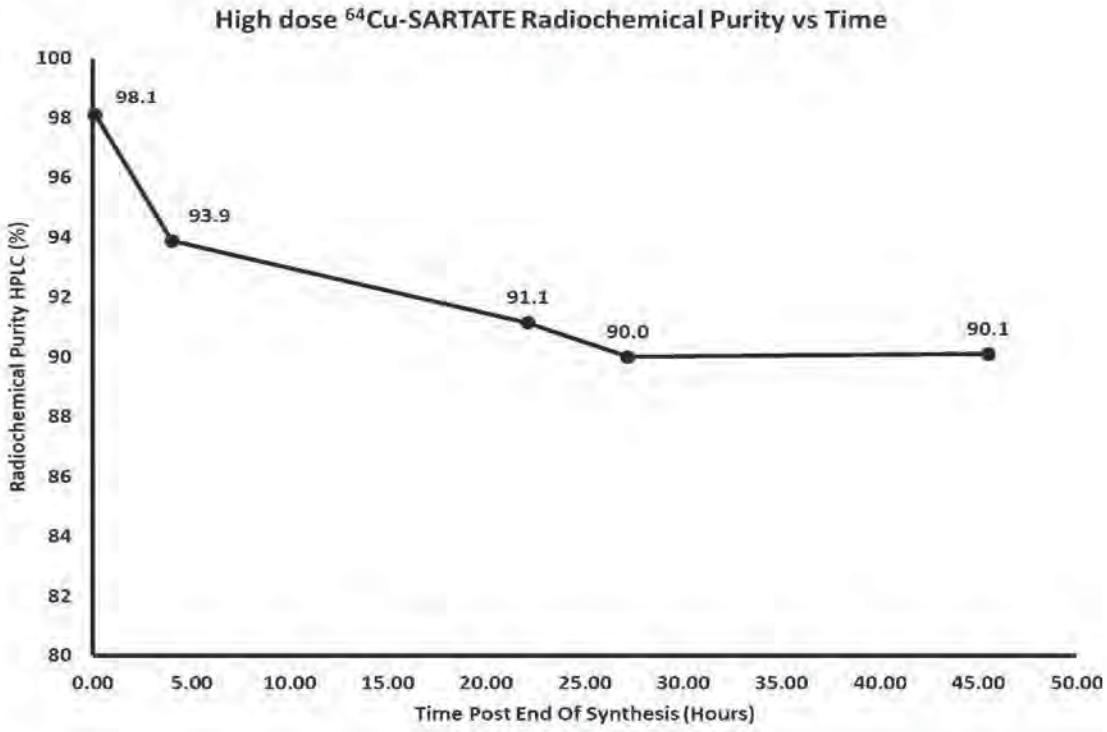


Figure 5

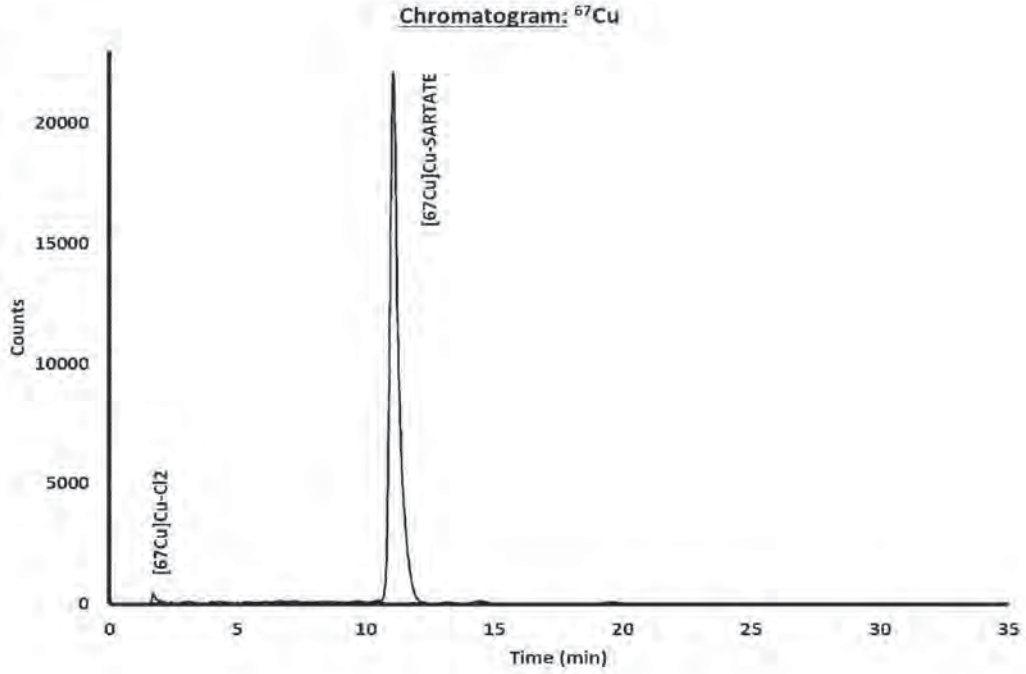


Figure 6

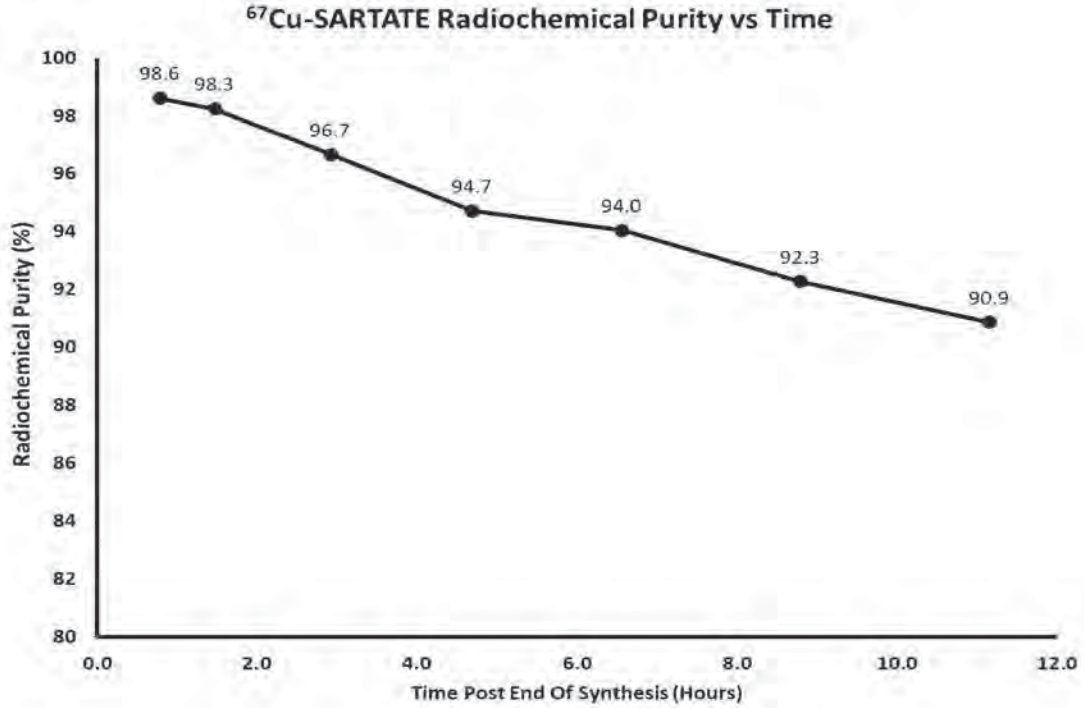


Figure 7

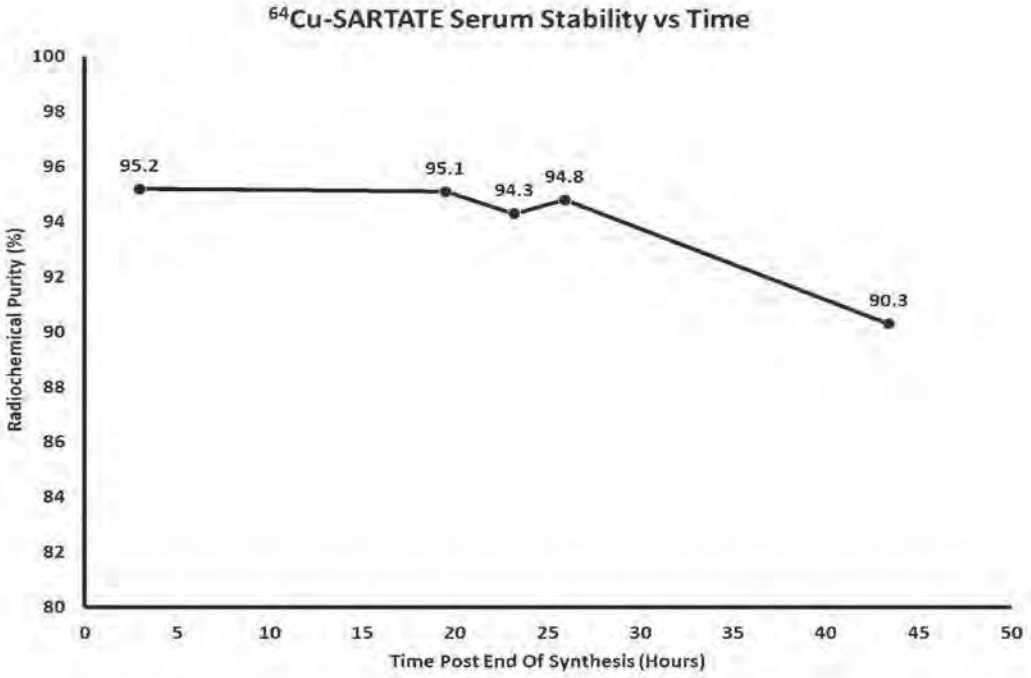


Figure 8

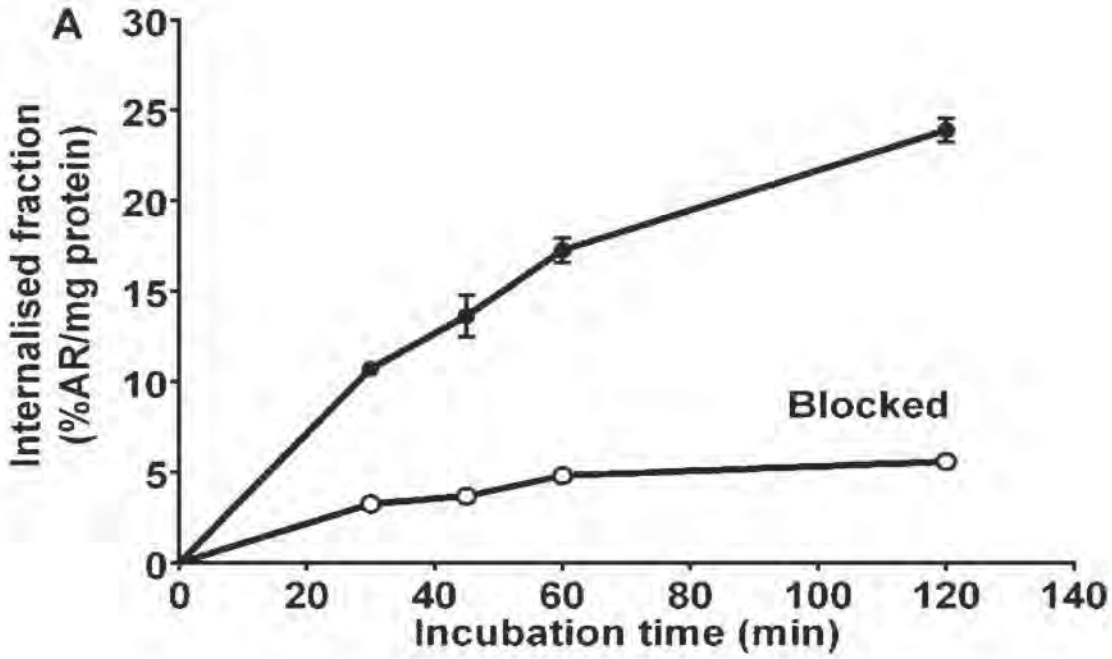


Figure 9

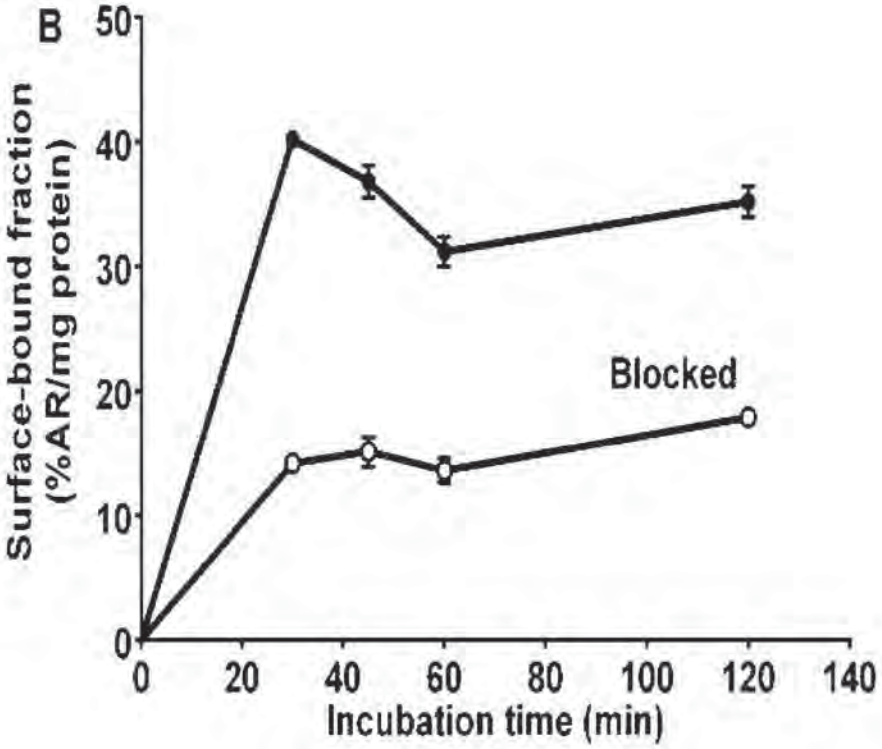


Figure 10

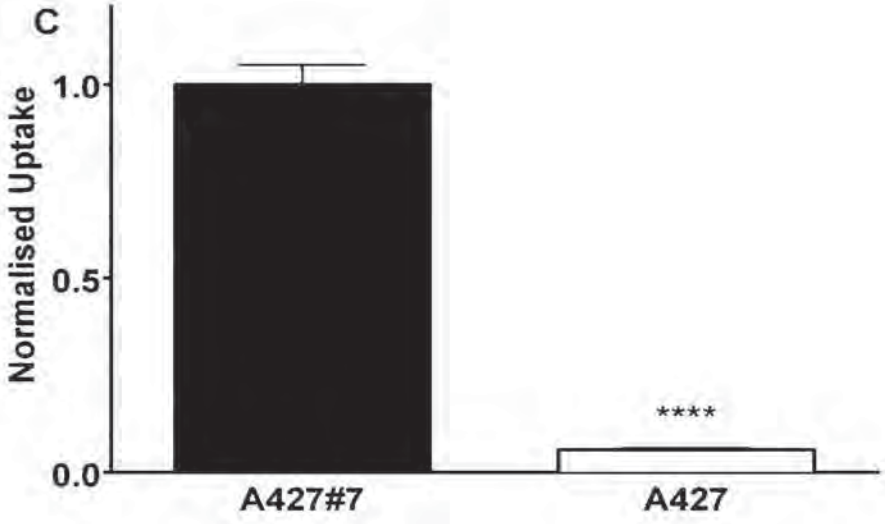


Figure 11

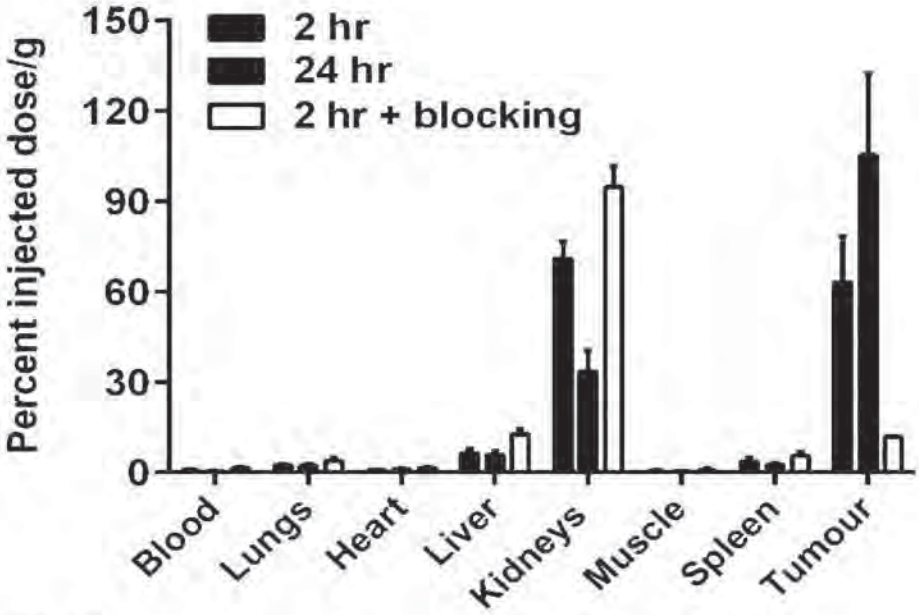
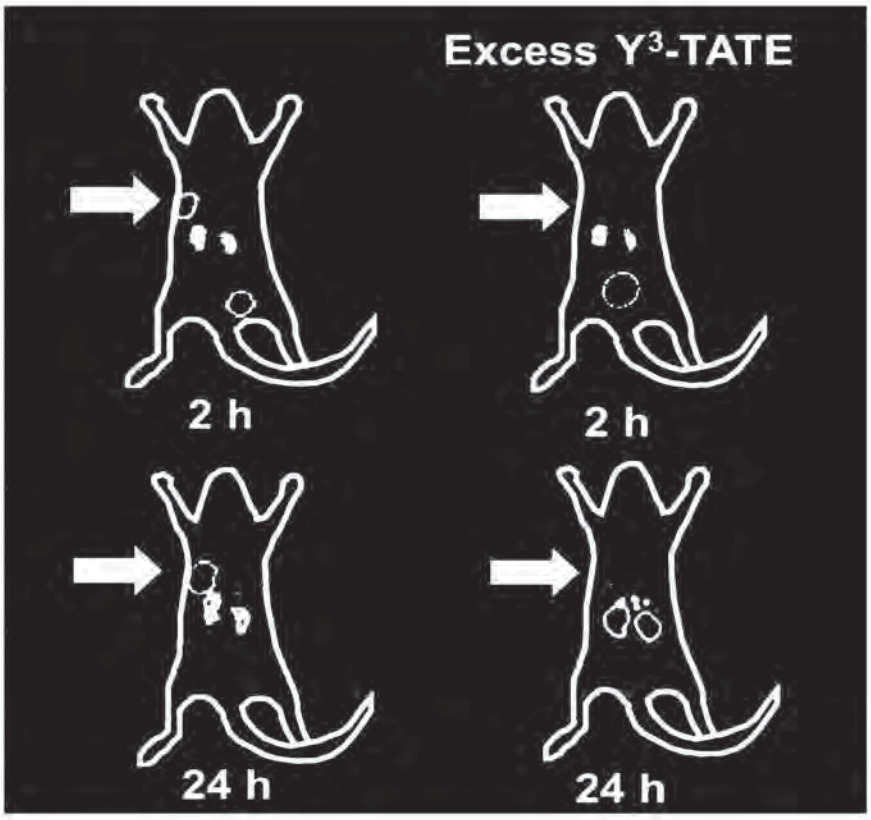


Figure 12



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2017/051205

A. CLASSIFICATION OF SUBJECT MATTER

A61K 51/08 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

PATENW (Sartate, mecosar octeride, Gentisic acid, radiolysis, radio protectant, IPC/CPC A61K 51/08, IPC/CPC A61K47/10)

MEDLINE, HCA, BIOSIS, EMBASE (Sartate, mecosar octeride, Gentisic acid, radiolysis, radio protectant, 490-79-9, 59-51-8, 63-68-3, 64-17-5, M Harris, E Van Dam, C Jeffery

Internal IP Australia databases (M Harris, E Van Dam, C Jeffery)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2018	18 April 2018
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Neal Dalton AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61399359615

Form PCT/ISA/210 (fifth sheet) (July 2009)

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/AU2017/051205
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Paterson, B. M. et al. "PET imaging of tumours with a 64Cu labeled macrobicyclic cage amine ligand tethered to Tyr3-octreotate" Dalton Trans., 2014, Vol.43, 1pages 386-1396 see page 1393 SarTATE, page 1393 Preparation of 64CuSarTATE, page 1394 Small animal PET imaging	1-27
A	WO 2008/009444 A1 (Adrianus A. Vandulmen) 24 January 2008 see page 7 lines 5-15	1-23, 25-27
A	Hicks. R, et al. "First-Time-in-Human Trial of Cu-64 MeCOSAR-octreotate (CuSARTATE) for Imaging and Dosimetry Estimation in Neuroendocrine Tumor (NET)" J Nucl Med May 1, 2016 vol. 57 no. supplement 2, abstract 26	1-27
A	**Eleni Gourni** et al. "Copper-64 Labeled Macrobicyclic Sarcophagine Coupled to a GRP Receptor Antagonist Shows Great Promise for PET Imaging of Prostate Cancer" Mol. Pharmaceutics, 2015, vol. 12 No. 8, pages 2781–2790	1-27
A	Paterson, B. M. et al. "Bifunctional ^{64}Cu-labelled macrobicyclic cage amine isothiocyanates for immuno-positron emission tomography" Dalton Trans., 2015, Vol. 44, pages 4901-4909.	1-27

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2017/051205**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2008/009444 A1	24 January 2008	WO 2008009444 A1	24 Jan 2008

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82A (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	16/175,261
Filing Date	October 30, 2018
First Named Inventor	de Palo, Francesco
Title	Stable, concentrated radionuclide complex solutions
Art Unit	1618
Examiner Name	PERREIRA, MELISSA JEAN
Attorney Docket Number	PAT058197-US-CIP02

SIGNATURE of Applicant or Patent Practitioner

Signature	/Lian Ouyang/	Date (Optional)	
Name	Lian Ouyang	Registration Number	69,254
Title (if Applicant is a juristic entity)	Authorized Signatory for Applicant		
Applicant Name (if Applicant is a juristic entity)	Advanced Accelerator Applications (Italy) Srl		

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: PA..
Document Description: Power of Attorney

PTO/AIA/82B (07-13)
Approved for use through 01/31/2018. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 01095

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Advanced Accelerator Applications (Italy) Srl

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	08/06/2019
Name	GIOVANNI TESORIERE		
Title	Authorized Signatory, Advanced Accelerator Applications (Italy) Srl		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	16175261
Filing Date:	30-Oct-2018
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	2	100	200
Miscellaneous-Filing:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**580**

Electronic Acknowledgement Receipt

EFS ID:	35994535
Application Number:	16175261
International Application Number:	
Confirmation Number:	8183
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Amy Olinger
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	13-MAY-2019
Filing Date:	30-OCT-2018
Time Stamp:	18:41:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$580
RAM confirmation Number	051419INTEFSW00006511504409
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PAT058197-US-CIP02-Amendment_Signed.pdf	213281 f63cbc82d0b254b9df482ce3c9b63401de21a24e	yes	11

Multipart Description/PDF files in .zip description

Document Description	Start	End
Applicant Arguments/Remarks Made in an Amendment	6	11
Claims	2	5
Amendment/Req. Reconsideration-After Non-Final Reject	1	1

Warnings:

Information:

2	Transmittal Letter	PAT58197-US-CIP02_Transmittal_Letter_signed.pdf	116655 681646a5d59d7062aff5406fa14182c3c046b96	no	1

Warnings:

Information:

3	Application Data Sheet	PAT058197_US_CIP02_ADS_signed_LO.pdf	227529 6cb652893f7c97a7d99c8ec528e57e6fa8b373	no	11

Warnings:

Information:

This is not an USPTO supplied ADS fillable form

4	Information Disclosure Statement (IDS) Form (SB08)	PAT058197_US_CIP02_IDS_signed.pdf	1034293 928775f311888da79063d4be285a4dac747e6bb9	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available

within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

5	Foreign Reference	WO2018081860.pdf	2439951 5e01bf889a6466015514770297de8869955f75d	no	47
Warnings:					
Information:					
6	Power of Attorney	PAT058197_US_CIP02_POATransmittal_AIA82Asigned.pdf	206663 dc6e577bbc2a29564ef13743454160 90a6f20486	no	2
Warnings:					
Information:					
7	Power of Attorney	PAT058197_US_CIP02_POA_AIA82B_signed.pdf	48757 3cb4a438c2e5d2511073ccca46fbde6879132876	no	1
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	33989 e20538ef3cc9dde92482429be2dce26b73366130	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4321118		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Remarks/Arguments

Upon entry of the amendments herein, claims 1-23 are pending. Claims 1 and 4-9 have been amended. New claims 22 and 23 have been added. Support of the amendments and new claims appears in the original application as filed, at e.g., page 8, lines 13-16; page 20, lines 10-13; page 45, lines 17-24, and Examples 1-2 at pages 52-54. No new matter has been introduced.

Applicant also submits herewith a supplemental Information Disclosure Statement for the Examiner's consideration.

Claim Rejections-35 U.S.C. § 112

Original claims 6-9 are rejected under 35 U.S.C. 112(d) as being of improper dependent form. *See* the Office Action at page 2. Specifically, the Examiner points out that original claim 1 teaches a total concentration of the stabilizers being 0.2-20 mg/mL and dependent claims 6-9 each teach a total concentration of stabilizers being 15-50 mg/mL, 20-40 mg/mL, or 25-35 mg/mL respectively, which does not further limit the concentration of claim 1. *Id.*

Applicant would like to point out that the stabilizers' concentration in claim 1 is that in the obtained pharmaceutical aqueous solution after a dilution step while the concentrations in claims 6-9 are those of stabilizer(s) present during the complex formation and before a dilution step. Applicant submits that claims 6-9, each of which depends from claim 1 indirectly, further limit claim 1 by providing additional features for various steps of the claimed process. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. 112(d) be withdrawn.

Claim Rejections-35 U.S.C. § 103

Original claims 1-21 are rejected under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375, "Chen") in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, 1, 5-12, "Maus"). *See* the Office Action at pages 2-5.

Independent claim 1 is directed to a process for manufacturing a pharmaceutical aqueous solution that comprises, *inter alia*, (a) a complex of ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA; and (b) at least two different stabilizers against radiolytic degradation; wherein the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (i.e., **6.8-13.5 mCi/mL**) and the **stabilizers** are present in a total concentration of from **1.0 to 5.0 mg/mL**. It is further recited in claim 1 that, if the solution comprising the complex ("the complex solution" hereinafter) comprises **only the first stabilizer** as an stabilizer against radiolytic degradation and not the second stabilizer, then the aqueous dilution solution comprises at least one stabilizer against radiolytic degradation that is **different** from the first stabilizer.

According to the Examiner, Chen discloses stabilized radiopharmaceutical formulations and methods of making and using the formulations which comprise a radiometal (e.g., ^{177}Lu, etc.); metal chelator (DOTA); stabilizers gentisic acid, ascorbic acid; and that the unit dose of the ^{177}Lu-labelled complexes to be administered typically ranges from about 10 mCi to about 200 mCi. *Id.*, pages 3-4. The Examiner acknowledges that Chen **fails to teach at least the following three features**: (i) further addition of DTPA, (ii) adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation or (iii) DOTA-TATE, DOTA-TOC. *Id.*

The Examiner further asserts that Maus teaches the radiolabeling involving mixing DOTA-TATE with 7.5 GBq $^{177}LuCl_3$, examining effects of gentisic acid and ascorbic acid as quencher during and after the radiolabeling procedure, and addition of 0.25 mL DTPA solution to complex any on-incorporated ^{177}Lu. *Id.*, pages 4-5. The Examiner then concludes that it would have been obvious for one of skill in the art to combine the teachings of the two references and to substitute the peptide hormone such as somatostatin in the ^{177}Lu complex taught by Chen for TATE taught by Maus, utilize DTPA taught by Maus, and add one of the stabilizers during complex formation and the other after the complex formation to arrive at the claimed invention. *Id.*, page 5. Applicant respectfully disagrees. A skilled artisan, after reading Chen as a whole, would not have been motivated to combine it with the teachings in Maus. Even if Chen and Maus were combined, a skilled artisan would not have arrived at the claimed invention with a reasonable expectation of success.

Initially, contrary to the Examiner's assertion, it would not have been obvious to a skilled artisan before the effective filing date of the claimed invention to substitute the peptide hormone such as somatostatin in the ^{177}Lu complex taught by Chen for TATE taught by Maus. Chen merely mentions somatostatin and analogs thereof generally as possible examples of targeting molecules, and yet the majority of Chen's teachings and all of the examples in Chen are targeted radiodiagnostic and radiotherapeutic compounds, e.g., ^{177}Lu-A or ^{177}Lu-B, that are targeted to the Gastrin Releasing Peptide Receptor (GRPR) and stabilizers useful in preparation and stabilization of these compounds targeted to GRPR. *See, e.g.*, the Abstract, Figures 1-2, paragraphs [0002], [0017]-[0045], [0127]-[0132] and Examples 1-24, including Tables 3-25. Also, as noted by the Examiner, nowhere in Chen teaches or suggests DOTA-TATE or DOTA-TOC. Differently, Maus describes a very different ^{177}Lu complex targeted to somatostatin receptor, *i.e.*, ^{177}Lu-DOTA-TATE. More importantly, the problems that the two references aim to solve are markedly different, and naturally, the solutions that Chen and Maus reached are distinctly different. Thus, a skilled artisan, in view of Chen as a whole, would not have been motivated to turn to Maus to look for modification for improvement. Specifically, the problem Chen aims to solve is to reduce radiolytic damage to methionine (Met) residue in the peptides that specifically target GRPR (*see* paragraphs [0018], [0021], [0024]-[0025]), and as a consequence, Chen finds that benzyl alcohol is a key component in such formulations (*see*

paragraphs [0027] and [0168]). On the other hand, Maus notes a very different problem from Chen's, *i.e.*, decreased radiochemical purity (RCP) of the radio peptides due to removal of gentisic acid and ascorbic acid by the tC18 sold phase extraction (SPE) purification that is included as default in the cassette-based automated labeling procedure. Consequently, Maus reaches a conclusion that re-addition of ascorbic acid post tC18 SPE purification is required to maintain RCP. Accordingly, there is no reason or motivation for a skilled artisan to combine the teachings of Chen and Maus.

Secondly, even if the teachings of Chen and Maus were combined, a skilled artisan would not have arrived at the invention of claim 1 with a reasonable expectation of success. Chen in many places has stressed the **unpredictability** in selecting stabilizers and in when and how much the stabilizers are added. For example, in Example 3, Chen evaluated eight stabilizers, including ascorbic acid and gentisic acid sodium salts, and found that **none** of the eight reagents **provided adequate radiostability** for 48 hours. *See* paragraph [0265]. Chen further states that this result is "**unexpected** as gentisic acid, ascorbic acid, HSA and 3,4-pyridinedicarboxylic acid have all been reported by others to provide satisfactory protection against radiolysis for other radiopharmaceuticals.... The reagent 3,4-pyridinedicarboxylic acid, previously reported as an effective radiostabilizer, was found to **interfere badly** with the labeling reaction." *Id.*; emphases added. Chen further discusses the unpredictable nature of combining various stabilizers for stabilizing ^{177}Lu-A or ^{177}Lu-B (*see, e.g.*, paragraphs [0269], [0271], [0273], [0299], and [0313]). Chen also refers to the unpredictable outcomes caused either by the sequence of adding various stabilizers (*i.e.*, adding them at or after the labeling reaction) or by the amounts of the stabilizers added. *See, e.g.*, Examples 9-14 and paragraphs [0287]-[0290], [0296], and [0298]. In addition, in Examples 4-6 of Chen, a Radiolysis Protecting Solution comprising gentisic acid, ascorbic acid, and 3 other stabilizers is immediately added after the labeling reaction (i.e., after forming of the complex ^{177}Lu-A or ^{177}Lu-B) to arrive at a final concentration of **5 mg/mL** gentisic acid and **25 mg/mL** ascorbic acid sodium salt, **1 mg/mL** HSA, **0.05 mg/mL** benzyl alcohol, and **1-2 mg/mL** amino acid when the volumetric radioactivity of ^{177}Lu is 50 mCi/2 mL, *i.e.*, **25 mCi/mL**. In other words, Chen teaches a total concentration of stabilizers being about **32-33 mg/mL** at a volumetric radioactivity of **25 mCi/mL** ^{177}Lu, which is equivalent to about from ***8.7 to 17.8 mg/mL*** total concentration of stabilizers at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu. In comparison, the total concentration of the stabilizers recited in independent claim 1 is **much lower** than that of Chen (***1.0 to 5.0 mg/mL*** total concentration of stabilizers at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu). Noticeably, Chen **teaches away** from using such low concentration of stabilizers in the final radiopharmaceutical formulations disclosed thereof. *See, e.g.*, Table 4 and paragraph [0250]. Specifically, Chen states that while methionine at a concentration of 2.5 mg/mL was able to stabilize 3.5 mCi of ^{177}Lu-A against radiolysis for 5 days, the same concentration of 2.5 mg/mL of the same stabilizer is **unable** to stabilized the same complex when the radioactivity is

increased to 50 mCi/2 mL, which is equivalent to about ***0.7-1.4 mg/mL*** stabilizer at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu.

Maus, the secondary reference, does not make the unpredictability go away, at least because it also refers to a noticeably **higher** total concentration of gentisic acid and ascorbic acid (equivalent to ***5-10 mg/mL*** at a volumetric radioactivity of 6.8-13.5 mCi/mL ^{177}Lu and up to ***15.4 mg/mL*** gentisic acid or ***17.6 mg/mL*** ascorbic acid sodium salt at a volumetric radioactivity of 13.5 mCi/mL ^{177}Lu).[1] More importantly, Maus also **teaches away** from using lower concentrations of gentisic acid and ascorbic acid. Specifically, according to Maus, decreased concentrations of gentisic acid and ascorbic acid by the tC18 purification lead to decreased radiochemical purity (RCP), e.g., <95% after 5 hr in 20 mL. *See, e.g.*, Abstract of Maus.

Accordingly, in view of the unpredictable nature of stabilizers (e.g., their types, timing of adding them, and their amounts) taught by the primary reference, Chen, as well as the teachings away from both Chen and Maus, a skilled artisan would not have reasonably expected that the low total concentration of stabilizers recited in claim 1 would sufficiently stabilize the pharmaceutical aqueous solution obtained via the claimed process. Instead, a skilled artisan would have been discouraged from arriving at the claimed invention in view of Chen and Maus. Accordingly, the claimed process of making such pharmaceutical aqueous solution recited in claim 1 is nonobvious over Chen and Maus.

Further, the instant application provides sufficient evidence to demonstrate that the claimed process procedures stable pharmaceutical aqueous solutions with the low total concentration of stabilizers (e.g., RCP as determined by HPLC being maintained at ≥ 95%) for at least 72 hours when stored at 25 °C. *See e.g.*, Example 3 of the instant application. This effect was not present in the teachings of any of the cited references, and would not have been expected or predicted by a skilled artisan.

"Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. *See, e.g., In re Albrecht,* 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)." *See* MPEP § 2145. Accordingly, independent claim 1 is also patentable over Chen and Maus for unexpected stability of the pharmaceutical solution produced by the claimed method, even when the obtained solution has the low total concentration of stabilizers recited in claim 1. For at least the same reasons stated above, claims 2-21, each of which depends directly or indirectly from claim 1, are also patentable over Chen and Maus. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 6 is also patentable over the cited references on an additional ground. It is further noted that Chen **teaches away** from presenting higher than 5 mg/mL gentisic acid or ascorbic

[1] Maus refers to ref. 13 for the DOTA-TATE kit formulation, in which the final concentration of gentisic acid in the final solution is **15 mg/mL** and that of ascorbic acid is **70 mg/mL** at a volumetric radioactivity of 4.44 GBq/mL or **120 mCi/mL** ^{177}Lu. *See* ref. 13 cited in Maus at page 1320, left column, in "Methods" section. Maus also teaches re-addition of ascorbic acid or gentisic acid to reach a final concentration of 100 mmol/L with a volumetric radioactivity of 0.5 GBq/mL, i.e., **15.4 mg/mL** gentisic acid or **17.6 mg/mL** ascorbic acid with a volumetric radioactivity of **13.5 mCi/mL** ^{177}Lu. *See, e.g.*, Table 1 and page 10 "Discussion" section.

acid at the radiolabeling reaction as at the concentration of 5 mg/mL, gentisic acid or ascorbic acid either interferes with the labeling reaction or provides less stability during the reaction. *See, e.g.*, paragraph [0290]. In contrast, claim 6 recites that during the complex formation (i.e., the labeling reaction), at least one of the stabilizers is present in a total concentration of from **15 to 50 mg/mL**. *See also* Example 2 of the instant application. Maus does not correct this defect of Chen, at least because Maus does not address the impact of concentrations of gentisic acid or ascorbic acid to the radiolabeling reaction. As increasing the concentration to greater than 5 mg/mL of gentisic acid or ascorbic acid at the radiolabeling reaction would render decreased stability in the formulations of Chen, it teaches away from the invention of claim 6, which recites stabilizers present in the radiolabeling reaction at a total concentration of from **15 to 50 mg/mL**. Accordingly, the process of claim 6 is nonobvious over Chen and Maus on this additional ground. As are claim 7-11, each of which depends directly or indirectly from claim 6.

In summary, the Examiner has failed to present a proper *prima facie* case of obviousness for claims 1-21 for at least the reasons set forth above. Instead, it is clear that the Examiner's obviousness rejection is based solely on impermissible hindsight in which Applicant's specification and claims were used as a blueprint to piece together the invention of the pending claims. This is contrary to the MPEP and long standing case law that requires that any judgment on obviousness must "not include knowledge gleaned only from applicant's disclosure." *See, In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). The invention of the pending claims is also non-obvious in view of the combined teachings of the cited references for unexpected results set forth herein. Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 2, 4-10, 13, and 15-29 of copending U.S. Application No. 16/140,962 or over claims 1-11, 13-19 and 23-44 of copending U.S. Application No. 16/045,484. In addition, claims 1-11, 14, 15, 17, 18, 20 and 21 are provisionally rejected over claims 1-11, 14, 15, 17, 18, 20 and 21 of U.S. Application No. 16/175,239. *See* the Office Action at pages 6-7.

Without arguing the propriety of this rejection, Applicant respectfully requests that the provisional nonstatutory double patenting rejections over copending U.S. Application Nos. 16/140,962, 16/045,484 and 16/175,239 be held in abeyance until allowable subject matter in the present application has been determined.

In view of the above remarks, Applicant submits that the pending application is in condition for allowance. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith, to our Deposit Account No. 50-4409, under Docket No. PAT058197-US-CIP02.

Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

/ Lian Ouyang /
Lian Ouyang
Attorney for Applicant
Reg. No. 69,254

Novartis Institutes for BioMedical Research, Inc.
700 Main Street, 427Q
Cambridge, MA 02139
USA
+1 617 871 3880

Date: May 13, 2019

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A process for manufacturing a pharmaceutical aqueous solution, comprising:

providing a solution comprising a complex of the radionuclide ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA; a first stabilizer against radiolytic degradation, and optionally a second stabilizer against radiolytic degradation different from the first stabilizer; and

diluting the solution comprising the complex with an aqueous dilution solution optionally comprising at least one stabilizer against radiolytic degradation to obtain the pharmaceutical aqueous solution;

wherein if the solution comprising the complex comprises only the first stabilizer as an stabilizer against radiolytic degradation and not the second stabilizer, then the aqueous dilution solution comprises at least one stabilizer against radiolytic degradation that is different from the first stabilizer, and in the obtained pharmaceutical aqueous solution, the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL and the stabilizers are present in a total concentration of from ~~0.2 to 20.0~~ 1.0 to 5.0 mg/mL.

2. (Original) The process according to claim 1, comprising:

(1) forming a complex of the radionuclide ^{177}Lu and a somatostatin receptor binding peptide linked to the chelating agent DOTA by

(1.1) providing an aqueous solution comprising the radionuclide;

(1.2) providing an aqueous solution comprising the a somatostatin receptor binding peptide linked to the chelating agent, and a first stabilizer against radiolytic degradation and optionally a second stabilizer against radiolytic degradation different from the first stabilizer; and

(1.3) mixing the solutions provided in steps (1.1) and (1.2) and heating the resulting mixture to form a solution comprising the complex;

(2) diluting the solution comprising the complex obtained by step (1) by

(2.1) providing an aqueous dilution solution optionally comprising at least one stabilizer against radiolytic degradation; and

(2.2.) mixing the solution comprising the complex obtained by step (1) with the dilution solution provided in step (2.1) to obtain the pharmaceutical aqueous solution;

wherein if the solution in step (1.2) comprises only one stabilizer that is the first stabilizer, then the solution in step (2.1) comprise at least one stabilizer that is different from the first stabilizer.

3. (Original) The process according to claim 2, wherein the solution in step (1.2) comprises the first stabilizer and the solution provided in step (2.1) comprises at least one stabilizer.

4. (Currently amended) The process according to claim 2, wherein ~~the solution provided in step (1.2) comprises~~ at least gentisic acid or a salt thereof is provided in step (1.2) and the solution provided in step (2.1) ~~compries~~ comprises at least ascorbic acid or a salt thereof.

5. (Currently amended) The process according to claim 2, wherein ~~the solution provided in step (1.2) comprises~~ only one stabilizer which is gentisic acid or a salt thereof is provided in step (1.2) and the solution provided in step (2.1) ~~compries~~ comprises only one stabilizer which is ascorbic acid or a salt thereof.

6. (Currently amended) The process according to claim 2, wherein the ~~solution provided in step (1.2) comprises~~ stabilizer/stabilizers provided in step (1.2) is/are present during the complex formation in step (1.3) in a total concentration of from 15 to 50 mg/mL.

7. (Currently amended) The process according to claim 6, wherein the ~~solution provided in step (1.2) comprises~~ stabilizer/stabilizers provided in step (1.2) is/are present during the complex formation in step (1.3) in a total concentration of from 20 to 40 mg/mL

8. (Currently amended) The process according to claim 7, wherein the ~~solution provided in step (1.2) comprises~~ only one stabilizer provided in step (1.2) ~~which~~ is gentisic acid and the stabilizer is present during the complex formation in step (1.3) in a concentration of from 20 to 40 mg/mL.

9. (Currently amended) The process according to claim 8, wherein the ~~solution provided in step (1.2) comprises~~ only one stabilizer provided in step (1.2) ~~which~~ is gentisic acid and the stabilizer is present during the complex formation in step (1.3) in a concentration of from 25 to 35 mg/mL.

10. (Original) The process according to claim 9, wherein the solution provided in step (1.2) further comprises a buffer.

11. (Original) The process according to claim 10, wherein the buffer is an acetate buffer.

12. (Original) The process according to claim 2, wherein in step (1.3) the resulting mixture is heated to a temperature of from 70 to 99 °C, for from 2 to 59 min.

13. (Original) The process according to claim 12, wherein in step (1.3) the resulting mixture is heated to a temperature of from 90 to 98 °C for from 5 to 15 min.

14. (Original) The process according to claim 2, wherein the solution provided in step (2.1) further comprises diethylentriaminepentaacetic acid (DTPA) or a salt thereof.

15. (Original) The process according to claim 2, further comprising the process steps:

(3) filtering the solution obtained by step (2) through 0.2 µm; and

(4) dispensing the filtered solution obtained by step (3) into dose unit containers in a volume required to deliver the radioactive dose of from 5.0 to 10 MBq.

16. (Original) The process according to claim 2, wherein the solution of step (1.1) comprises $LuCl_3$ and HCl.

17. (Original) The process according to claim 2, wherein the solution of step (1.2) comprises ^{177}Lu-DOTA-TATE or ^{177}Lu- DOTA-TOC, gentisic acid, acetic acid, and sodium acetate.

18. (Original) The process according to claim 2, wherein the solution of step (2.1) comprises DTPA and ascorbic acid.

19. (Original) The process according to claim 15, wherein the dose unit containers in step (4) are stoppered vials, enclosed within a lead container.

20. (Original) The pharmaceutical aqueous solution obtained by the process of claim 1.

21. (Original) The pharmaceutical aqueous solution according to claim 20, which is free of ethanol.

22. (New) The pharmaceutical aqueous solution according to claim 20, wherein the stabilizers in the obtained pharmaceutical aqueous solution consists essentially of gentisic acid or a salt thereof and ascorbic acid or a salt thereof.

23. (New) The pharmaceutical aqueous solution according to claim 22, wherein the stabilizers are present in a total concentration of from about 2.7 to about 4.1 mg/mL.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/175,261	Filing Date 10/30/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	05/13/2019	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 23	Minus	** 21	= 2		x $100 =	200
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	200

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/CAROL A BARNES/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02

CONFIRMATION NO. 8183

POA ACCEPTANCE LETTER

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

OC000000108204593

Date Mailed: 05/16/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/13/2019.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/dtdinh/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02

CONFIRMATION NO. 8183

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000108260984

Date Mailed: 05/20/2019

NOTICE OF ACCEPTANCE OF REQUEST UNDER 37 CFR 1.48(a)

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 01/15/2019.

The request under 37 CFR 1.48(a) to correct the inventorship, to correct or update the name of an inventor, or to correct the order of names of joint inventors is accepted.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/rmohamed/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/175,261	10/30/2018	1618	2180	PAT058197-US-CIP02	21	1

CONFIRMATION NO. 8183

UPDATED FILING RECEIPT

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

OC000000108260983

Date Mailed: 05/20/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Francesco de Palo, Colleretto Giacosa, ITALY;
Lorenza Fugazza, Colleretto Giacosa, ITALY;
Donato Barbato, Colleretto Giacosa, ITALY;
Maurizio Mariani, Colleretto Giacosa, ITALY;
Daniela Chicco, Colleretto Giacosa, ITALY;
Giovanni Tesoriere, Colleretto Giacosa, ITALY;
Clementina Brambati, Torino, ITALY;

Applicant(s)

Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY;

Power of Attorney: The patent practitioners associated with Customer Number 01095

Domestic Priority data as claimed by applicant

This application is a CIP of 16/140,962 09/25/2018
which is a CIP of 16/045,484 07/25/2018

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/057415 09/25/2018 No Access Code Provided
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/055575 07/25/2018 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

Projected Publication Date: 01/30/2020

Non-Publication Request: No

Early Publication Request: No

Title

Stable, concentrated radionuclide complex solutions

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/175,261	10/30/2018	1618	2180	PAT058197-US-CIP02	21	1

CONFIRMATION NO. 8183

CORRECTED FILING RECEIPT

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

OC000000108540179

Date Mailed: 05/30/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Francesco de Palo, Colleretto Giacosa, ITALY;
Lorenza Fugazza, Colleretto Giacosa, ITALY;
Donato Barbato, Colleretto Giacosa, ITALY;
Maurizio Mariani, Colleretto Giacosa, ITALY;
Daniela Chicco, Colleretto Giacosa, ITALY;
Giovanni Tesoriere, Noicattaro, ITALY;
Clementina Brambati, Torino, ITALY;

Applicant(s)

Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY;

Power of Attorney: The patent practitioners associated with Customer Number 01095

Domestic Priority data as claimed by applicant

This application is a CIP of 16/140,962 09/25/2018
which is a CIP of 16/045,484 07/25/2018

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/057415 09/25/2018 No Access Code Provided
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/055575 07/25/2018 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/29/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/175,261**

Projected Publication Date: 01/30/2020

Non-Publication Request: No

Early Publication Request: No

Title

Stable, concentrated radionuclide complex solutions

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

1095 7590 06/06/2019

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/06/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 16/175,261	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 5/13/19.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-23 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-23 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims and Previous Objections/Rejections Status

Claims 1-23 are pending in the application. Claims 22 and 23 were newly added in the amendment filed 5/13/19.

The rejection of claims 6-9 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph is withdrawn due to the amendment.

The rejection of claims 1-21 under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375A1) in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) is withdrawn.

The rejection of claims 1-20,22 and 23 on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,4-10,13 and 15-29 of copending Application No. 16/140,962 (reference application) is maintained.

The rejection of claims 1-20,22 and 23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,13-19 and 23-44 of copending Application No. 16/045,484 (reference application) is maintained.

The rejection of claims 1-11,14,15,17,18 and 20-23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,14,15,17,18,20 and 21 of copending Application No. 16/175,239 (reference application) is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise

extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,4-10,13 and 15-29 of copending Application No. 16/140,962 as stated in the office action mailed 2/12/19.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,13-19 and 23-44 of copending Application No. 16/045,484 as stated in the office action mailed 2/12/19.

Claims 1-11,14,15,17,18,20 and 21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,14,15,17,18,20 and 21 of copending Application No. 16/175,239 as stated in the office action mailed 2/12/19.

Response to Arguments

Applicant's arguments, see Remarks/Arguments, filed 5/13/19, with respect to the rejection(s) of claim(s) 1-20 under 35 U.S.C. 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) and Chen et al. (US 2007/0269375A1).

New Grounds of Rejection

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory

basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-23 is/are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) and Chen et al. (US 2007/0269375A1).

de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) discloses that ^{177}Lu-labelled somatostatin analogs can be stored and transported in a single vial ready to use liquid formulation up to 7 days after radiolabeling. The use of ethanol, in combination with a mixture of gentisic and ascorbic acid, has superior effects on stabilizing radiolabeled somatostatin analogs (abstract).

The typical reaction mixture for radiolabeling DOTA-TATE consisted of 60 MBq of ^{177}Lu in 0.01-0.05 M HCl with 2 nmol peptide dissolved in Milli-Q water, sodium acetate as buffer (2.5 M) and 10 µL of quenchers in a final volume of 0.14 mL (final pH 4-4.5). To inhibit oxidation and radiolysis, quenchers were added in various combinations and concentrations prior to radiolabeling. Quenchers included ascorbate, gentisic acid, ethanol and methionine. Radiolabelling of DOTA-TATE and other DOTA-conjugated SS-analogs with ^{177}Lu requires heating for 15 mins at 80°C (p29, 2.1. ^{111}In/^{177}Lu labelling of SS-analogs).

Any non-incorporated ^{177}Lu will be rapidly captured by the addition of DTPA. DOTA-TATE labelling at therapeutic level (patient's dose) was performed under the kit formulation as previously reported in a concentrated form (60GBq in 3 mL) (p29, 2.1. ^{111}In/^{177}Lu labelling of SS-analogs).

To obtain maximum protection of radiolabeled SS-analogs and minor effect in pharmaceutics, quencher concentration in reaction mixture was investigated time dependently. DOTA-TATE was radiolabeled with 60 MBq ^{177}Lu in the presence of different concentrations of quenchers and 2 nmol DOTA-TATE in a final volume of 0.14 mL. Ascorbic acid and gentisic acid were investigated with final concentrations of 1-20 mM, 1-50 mM for methionine and 2-20% (v/v) for ethanol (p29, 2.4. Optimizing quencher concentration). Under the experimental conditions the optimal quencher concentration were 3.5 mM for ascorbic and gentisic acid (p30, 3.2. Optimizing quencher concentration; Fig. 2) which encompasses the total concentration of from 1.0 to 5.0 mg/mL of the instant claim 1 and the total concentration of from about 2.7 to about 4.1 mg/mL of the instant claim 23. For example, a reaction mixture of 60MBq ^{177}Lu, 2nmol DOTA-TATE in 0.14 mL contains ascorbic and gentisic acid (3.5 mM) (p30, 3.3. Radiolabelled SS-analogs in the presence of quencher mixtures). The calculated dose during storage is shown in different volumes (5, 50 and 100 mL) of saline containing a therapeutic amount (3.7 GBq) of ^{177}Lu (p30, left column, first paragraph; Fig. 1).

The addition of ethanol clearly stabilized ^{111}In-DOTA-TATE during 7 days and [^{111}In-DTPA^{0}]octreotide (OctreoScan®) during storage (p30, 3.3. Radiolabelled SS-analogs in the presence of quencher mixtures; Figs. 3 and 4). Intravenous administration of a ^{177}Lu-labelled SS-analogs mixture containing ethanol could lead to carcinoid syndrome (p31, 4.2. Addition of ethanol as a quencher).

de Blois et al. does not disclose 250-500 MBq/mL (i.e. 6.8-13.5 mCi/mL) of radionuclide.

Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) discloses the administration of a 10 mCi dose of ^{177}Lu-DOTATATE for diagnostic scanning purposes of neuroendocrine tumors wherein whole body planar images and SPECT-CT images were obtained at 4,24 and 48 hours (abstract; p136, left column,

third paragraph; p136, Patients; p136, right column, paragraphs 3 and 6). The results of the pre-therapy whole body ^{177}Lu-DOTATATE diagnostic scans have been encouraging by demonstrating sensitivities comparable with the ^{68}Ge-DOTATOC PET and ^{111}Indium Octreotide scan, opening a whole new approach toward the management of neuroendocrine tumors (p138, Discussion and Conclusion).

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention to utilize a 10 mCi dose of ^{177}Lu-DOTATATE of de Blois et al. for diagnostic scanning purposes of neuroendocrine tumors in a subject as Singh et al. teaches that a 10 mCi dose of ^{177}Lu-DOTATATE is comparable to ^{68}Ge-DOTATOC PET and ^{111}Indium Octreotide scan but is cost effective and provide a greater lesion uptake.

Furthermore, it is obvious to vary and/or optimize the amount of ^{177}Lu provided in the composition, according to the guidance provided by de Blois et al. and Singh et al., to provide a composition having the desired properties such as the desired radioactivity. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

de Blois et al. does not explicitly disclose gentisic acid is present during complex formation in a concentration of from 20 to 40 mg/mL, of from 25 to 35 mg/mL or of from 15 to 50 mg/mL.

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention that the gentisic acid can provided in a concentration of from 20 to 40 mg/mL, of from 25 to 35 mg/mL or of from 15 to 50 mg/mL as de Blois et al. can be provided in a concentration of 1-20 mM.

Furthermore, it is obvious to vary and/or optimize the amount of gentisic acid provided in the composition, according to the guidance provided by de Blois et al., to provide a composition having the

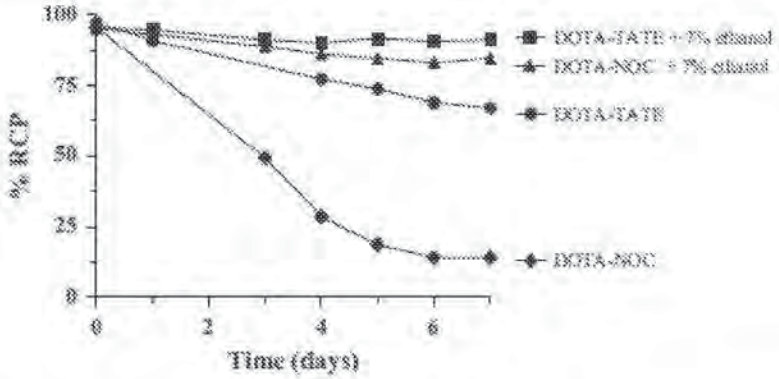
desired properties such as the desired radiolytic stability during complex formation. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

de Blois et al. does not explicitly disclose the absence of ethanol.

RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) discloses that ^{177}Lu-DOTA-TATE is prepared at the hospital radiopharmacy from a cold kit by a simple and single step. Careful adjustment of the pH of the radioactive reaction mixture prior to incubation is required, as the complexation yield of ^{177}Lu-DOTA-TATE achievable is highly dependent on the pH. The cold kit was prepared by adding DOTA-TATE dissolved in supra-pure water to a solution of ammonium acetate (pH ~5) containing gentisic acid and subsequently freeze-drying the mixtures after adjusting the pH to 5. The therapeutic dose of ^{177}Lu-DOTA-TATE could be prepared by adding the required volume of $^{177}LuCl_3$ with the lyophilized kit in 1 mL of water for injection and subsequently incubating the reaction mixture at 85-90°C for a period of 45 min-1h. It was observed that the preparation is stable up to 4 d as it retained its radiochemical purity >98% when stored at room temperature, as shown in the HPLC of FIG. 7 (p86, 5. Development of DOTA-TATE cold kit for the preparation of 177Lu-DOTA-TATE for clinical applications).

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention that the ^{177}Lu-DOTATATE formulation of de Blois et al. does not necessarily comprise ethanol as de Blois et al. specifically teaches that the addition of ethanol dramatically stabilized for ^{111}In-DOTA-TATE during 7 days and [^{111}In-DTPA^0]octreotide (OctreoScan®) during storage and shows that the addition of ethanol does improve the stabilization of the ^{177}Lu-DOTATATE

formulation upon storage over a week (Fig below) but does not dramatically stabilize the ^{177}Lu-DOTATATE and RCM meeting discloses that the ^{177}Lu-DOTA-TATE is prepared at the hospital radiopharmacy without ethanol and used after a period of 45 min-1h.



It would have been predictable to one ordinarily skilled in the art that the ^{177}Lu-DOTATATE formulation of de Blois et al. does not necessarily require ethanol if is it to be mixed at the medical facility and to be used after preparation as the ethanol could lead to carcinoid syndrome and therefore should be avoided and its addition was essential only for the ^{111}In-DOTA-TATE during 7 days and [^{111}In-DTPA^{0}]octreotide (OctreoScan®).

de Blois et al. does not disclose adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation.

Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) discloses ^{177}Lu-DOTA-TATE which is vulnerable to radiolysis and the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis (abstract). The degree of radiolysis is influenced by several factors like the amount of DOTA-TATE, temperature, time, the total activity, the volumic activity, quenchers, etc. (p6, first paragraph). The study examines the effect of gentisic acid and ascorbic acid as quencher during and after the radiolabeling ^{177}Lu-DOTA-TATE (p6, first and second paragraph).

The radiolabeling involves mixing DOTA-TATE with 7.5 GBq $^{177}LuCl_3$ for 30 mins at 80°C. Addition of 0.25 mL DTPA-solution (4 mg/mL) was used to complex any non-incorporated ^{177}Lu (p7, 2.2. Manual radiolabeling procedure). The total activity of the formulation is 0.5 GBq/mL (table 1).

The radiochemical purity (RCP) of ^{177}Lu-DOTA-TATE was measured by HPLC. RCP ≥95% at 72h post radiolabeling (p8, 5.2 Radiolabeling without tC18 Purification).

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to add one of the stabilizers during complex formation and one of the stabilizers after the complex formation of the stabilized radiopharmaceutical formulations of de Blois et al. as Maus et al. teaches of the study examines the effect of gentisic acid and ascorbic acid as quencher during and after the radiolabeling ^{177}Lu-DOTA-TATE.

de Blois et al. does not disclose that the dose unit containers are stoppered vials, enclosed within a lead container.

Chen et al. (US 2007/0269375A1) discloses stabilized radiopharmaceutical formulations comprising a radiometal (e.g. ^{177}Lu, etc.); metal chelator (e.g. DTPA, DOTA, etc.); stabilizers (e.g. gentisic acid, ascorbic acid, etc.); buffers (e.g. acetate buffer, etc.) (abstract; p2, [0026]; p3, [0027]; p4, [0051]; p6, [0058]; p13, [0155],[0164]).

To lead-shielded 4-mL vials were added the individual stabilizer solutions, $^{177}LuCl_3$ and COMPOUND A (dissolved in water) (p26, [0289],[0292]; p28, [0303]; claim 189). The formulation was stored in the lead-shielded vials wherein the lead-shielded vials encompass the lead container of the instant claims. The radiopharmaceutical formulation was transferred to individual vials which encompasses the single dose unit container of the instant claims.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to store the ^{177}Lu-DOTA-TATE of de Blois et al. to reduce exposure to the ^{177}Lu, as Chen et al. teaches of storing the formulation in lead-shielded vials.

Applicant asserts that Chen et al. does not teach of DOTA-TATE or DOTA-TOC or the addition of benzyl alcohol is a key component in the formulations but teaches of the unpredictability in selecting stabilizers and in when and how much of the stabilizers are added. The concentration of the stabilizers of the instant claims is much lower than that of Chen et al. and Chen et al. teaches away from using such low concentration of stabilizers in the final radiopharmaceutical formulations.

The reference of Chen et al. was not used to teach of the DOTA-TATE or DOTA-TOC, the addition of benzyl alcohol or the low concentration of stabilizers in the final radiopharmaceutical formulations.

The reference of Chen et al. was used to teach of storing the formulation in lead-shielded vials to reduce exposure to the ^{177}Lu.

Applicant asserts that Maus et al. refers to a noticeably higher total concentration of gentisic acid and ascorbic acid. Maus et al. teaches away from using lower concentrations of gentisic acid and ascorbic acid.

The reference of Maus et al. was not used to teach of using lower concentrations of gentisic acid and ascorbic acid but was used to teach of adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to add one of the stabilizers during complex formation and one of the stabilizers after the complex formation of the stabilized radiopharmaceutical formulations of de Blois et al. as Maus et al. teaches of the examination of the effect of gentisic acid and ascorbic acid as quencher during and after the radiolabeling ^{177}Lu-DOTA-TATE.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on M9-2, T9-3, W9-3, Th9-3, F9-2.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 517-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 16/175,261	Applicant(s)/Patent Under Reexamination de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	de Blois et al. (Appl. Radiat. Isotop. 2014, 85, 28-33)
	V	of Singh et al. (Ind. J. Nucl. Med. 2011, 26, 135-138)
	W	RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012)
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/06/2019	05/31/2019							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20	✓	✓							
	21	✓	✓							
	22		✓							
	23		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
google scholar	02/05/2019	MP
inventor search	02/05/2019	MP
copending application search	02/05/2019	MP
EAST	02/06/2019	MP
google scholar	05/30/2019	MP

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2018081860	WO	A1	2018-05-11	Clarity Pharmaceuticals PTY LTD		

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

	1	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	05/30/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-05-13
Name/Print	Lian Ouyang	Registration Number	69,254

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
16/175,261	10/30/2018	1618	2180	PAT058197-US-CIP02	21	1

CONFIRMATION NO. 8183

CORRECTED FILING RECEIPT

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

OC000000109921948

Date Mailed: 07/26/2019

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Francesco de Palo, Ivrea, ITALY;
Lorenza Fugazza, Ivrea, ITALY;
Donato Barbato, Ivrea, ITALY;
Maurizio Mariani, Ivrea, ITALY;
Daniela Chicco, Albiano d'Ivrea, ITALY;
Giovanni Tesoriere, Noicattaro, ITALY;
Clementina Brambati, Torino, ITALY;

Applicant(s)

Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY;

Power of Attorney: The patent practitioners associated with Customer Number 01095

Domestic Priority data as claimed by applicant

This application is a CIP of 16/140,962 09/25/2018
which is a CIP of 16/045,484 07/25/2018

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/057415 09/25/2018 No Access Code Provided
INTERNATIONAL BUREAU OF THE WORLD INTELL PCT/IB2018/055575 07/25/2018 No Access Code Provided

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/29/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/175,261**

Projected Publication Date: 01/30/2020

Non-Publication Request: No

Early Publication Request: No

Title

Stable, concentrated radionuclide complex solutions

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor

community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

CASE PAT058197-US-CIP02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1618
Francesco de Palo et al.	Examiner: Perreira, Melissa Jean
APPLICATION NO: 16/175261	Conf. No.: 8183
FILED: October 30, 2018	
FOR: Stable, Concentrated radionuclide complex solutions	

VIA EFS
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND REPLY TO NON-FINAL OFFICE ACTION

This Reply is submitted in response to the Office Action mailed June 6, 2019 (the "Office Action" in the above referenced application. With no extension of time, this response is due on or before September 6, 2019.

Applicant believes no additional fee is due. The Commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-4409, Reference No. PAT058197-US-CIP02.

Reconsideration of the present rejections and withdrawal of the present rejections are respectfully requested.

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Currently amended) A process for manufacturing a pharmaceutical aqueous solution, comprising:

providing a solution comprising a complex of the radionuclide ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA; a first stabilizer against radiolytic degradation, and optionally a second stabilizer against radiolytic degradation different from the first stabilizer; and

diluting the solution comprising the complex with an aqueous dilution solution ~~optionally~~ comprising at least one stabilizer against radiolytic degradation to obtain the pharmaceutical aqueous solution;

wherein if the solution comprising the complex comprises only the first stabilizer as an stabilizer against radiolytic degradation and not the second stabilizer, then the aqueous dilution solution comprises at least one stabilizer against radiolytic degradation that is different from the first stabilizer, and in the obtained pharmaceutical aqueous solution, the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL and the stabilizers are present in a total concentration of from 1.0 to 5.0 mg/mL.

2. (Currently amended) The process according to claim 1, comprising:

(1) forming a complex of the radionuclide ^{177}Lu and a somatostatin receptor binding peptide linked to the chelating agent DOTA by

(1.1) providing an aqueous solution comprising the radionuclide;

(1.2) providing an aqueous solution comprising the a somatostatin receptor binding peptide linked to the chelating agent, and a first stabilizer against radiolytic degradation and optionally a second stabilizer against radiolytic degradation different from the first stabilizer; and

(1.3) mixing the solutions provided in steps (1.1) and (1.2) and heating the resulting mixture to form a solution comprising the complex;

(2) diluting the solution comprising the complex obtained by step (1) by

(2.1) providing an aqueous dilution solution ~~optionally~~ comprising at least one stabilizer against radiolytic degradation; and

(2.2.) mixing the solution comprising the complex obtained by step (1) with the dilution solution provided in step (2.1) to obtain the pharmaceutical aqueous solution;

wherein if the solution in step (1.2) comprises only one stabilizer that is the first stabilizer, then the solution in step (2.1) comprise at least one stabilizer that is different from the first stabilizer.

3. (Original) The process according to claim 2, wherein the solution in step (1.2) comprises the first stabilizer and the solution provided in step (2.1) comprises at least one stabilizer.

4. (Previously Presented) The process according to claim 2, wherein at least gentisic acid or a salt thereof is provided in step (1.2) and the solution provided in step (2.1) comprises at least ascorbic acid or a salt thereof.

5. (Previously Presented) The process according to claim 2, wherein only one stabilizer which is gentisic acid or a salt thereof is provided in step (1.2) and the solution provided in step (2.1) comprises only one stabilizer which is ascorbic acid or a salt thereof.

6. (Previously Presented) The process according to claim 2, wherein the stabilizer/stabilizers provided in step (1.2) is/are present during the complex formation in step (1.3) in a total concentration of from 15 to 50 mg/mL.

7. (Previously Presented) The process according to claim 6, wherein the stabilizer/stabilizers provided in step (1.2) is/are present during the complex formation in step (1.3) in a total concentration of from 20 to 40 mg/mL

8. (Previously Presented) The process according to claim 7, wherein the only one stabilizer provided in step (1.2) is gentisic acid and the stabilizer is present during the complex formation in step (1.3) in a concentration of from 20 to 40 mg/mL.

9. (Previously Presented) The process according to claim 8, wherein the only one stabilizer provided in step (1.2) is gentisic acid and the stabilizer is present during the complex formation in step (1.3) in a concentration of from 25 to 35 mg/mL.

10. (Original) The process according to claim 9, wherein the solution provided in step (1.2) further comprises a buffer.

11. (Original) The process according to claim 10, wherein the buffer is an acetate buffer.

12. (Original) The process according to claim 2, wherein in step (1.3) the resulting mixture is heated to a temperature of from 70 to 99 °C, for from 2 to 59 min.

13. (Original) The process according to claim 12, wherein in step (1.3) the resulting mixture is heated to a temperature of from 90 to 98 °C for from 5 to 15 min.

14. (Original) The process according to claim 2, wherein the solution provided in step (2.1) further comprises diethylentriaminepentaacetic acid (DTPA) or a salt thereof.

15. (Currently amended) The process according to claim 2, further comprising the process steps:

(3) filtering the solution obtained by step (2) through 0.2 µm; and

(4) dispensing the filtered solution obtained by step (3) into dose unit containers in a volume required to deliver the radioactive dose of ~~from 5.0 to 10 MBq~~ 7.4 GBq ± 10 %.

16. (Original) The process according to claim 2, wherein the solution of step (1.1) comprises $LuCl_3$ and HCl.

17. (Original) The process according to claim 2, wherein the solution of step (1.2) comprises ^{177}Lu-DOTA-TATE or ^{177}Lu- DOTA-TOC, gentisic acid, acetic acid, and sodium acetate.

18. (Original) The process according to claim 2, wherein the solution of step (2.1) comprises DTPA and ascorbic acid.

19. (Original) The process according to claim 15, wherein the dose unit containers in step (4) are stoppered vials, enclosed within a lead container.

20. (Original) The pharmaceutical aqueous solution obtained by the process of claim 1.

21. (Currently amended) The pharmaceutical aqueous solution according to claim 20, which is substantially free of ethanol.

22. (Previously Presented) The pharmaceutical aqueous solution according to claim 20, wherein the stabilizers in the obtained pharmaceutical aqueous solution consists essentially of gentisic acid or a salt thereof and ascorbic acid or a salt thereof.

23. (Previously Presented) The pharmaceutical aqueous solution according to claim 22, wherein the stabilizers are present in a total concentration of from about 2.7 to about 4.1 mg/mL.

24. (New) The pharmaceutical aqueous solution according to claim 22, for which the radiochemical purity (determined by HPLC) is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

Remarks/Arguments

Upon entry of the amendments herein, claims 1-24 are pending. Claims 1, 2, 15 and 21 have been amended. New claim 24 has been added. Support of the amendments and new claim appears in the original claims and application as filed, at e.g., page 5, lines 6-9 and 19-24, page 7, lines 18-23, page 31, lines 7-10, page 52, lines 24-31, and page 54, lines 1-6. No new matter has been introduced.

Applicant also submits herewith a supplemental Information Disclosure Statement for the Examiner's consideration.

Claim Rejections-35 U.S.C. § 103

Applicant notes that the previous rejection of original claims 1-21 under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375, "Chen") in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, 1, 5-12, "Maus") is withdrawn. *See* the Office Action at page 2. A new ground of rejection is made. Specifically, claims 1-23 are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (Appl. Radiat. Isotop. **2014**, 85, 28-33; "de Blois") in view of Singh et al. (Ind. J. Nucl. Med. **2011**, 26, 135-138; "Singh") and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu and 90Y-labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, **2012**; "RCM") and in further view of Maus and Chen. *See* the Office Action at pages 4-11. Applicant disagrees.

Independent claim 1, as amended, is directed to a process for manufacturing a pharmaceutical aqueous solution that comprises, *inter alia*, (a) a complex of ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA; and (b) at least two different stabilizers against radiolytic degradation; wherein the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (i.e., **6.8-13.5 mCi/mL**) and the **stabilizers** are present in a total concentration of from **1.0 to 5.0 mg/mL**. It is further recited in claim 1 that, (i) the solution comprising the complex ("the complex solution" hereinafter) comprises a first stabilizer and optionally a second stabilizer different from the first stabilizer; and (ii) **diluting** the complex solution with an aqueous dilution solution comprising **at least one stabilizer**.

According to the Examiner, the primary reference de Blois discloses a typical reaction mixture for radiolabeling DOTA-TATE consisted of 60 MBq of ^{177}Lu in a final volume of 0.14 mL, buffer, and quenchers that include ascorbate, gentisic acid, ethanol and methionine. *See* the Office Action at page 5. The Examiner further contends that the optimal quencher concentration, i.e., 3.5 mM for ascorbic and gentisic acid taught by de Blois encompasses the total stabilizer concentration of 1.0-5.0 mg/mL recited in claim 1 and that of about 2.7-4.1 mg/mL recited in claim 23. *Id.*, page 6. It seems that the Examiner has mistakenly deems the unit "mM"

to be the same as "mg/mL". The unit "mM" is millimole per liter and "mg/mL" is milligram per milliliter. 1 liter is 1000 milliliter and 1 millimole of ascorbic acid or gentisic acid is about 176 mg or 154 mg respectively. Accordingly, **3.5 mM** ascorbic acid and gentisic acid is equal to **0.5-0.6 mg/mL** ascorbic acid and gentisic acid, which is **not** encompassed by the stabilizer concentration recited in claim 1 or 23 as asserted by the Examiner.

The Examiner further contends that de Blois does not disclose 250-500 MBq/mL (i.e., 6.8-13.5 mCi/mL) of radionuclide but Singh teaches administration of a 10 mCi dose of ^{177}Lu-DOTATATE. *Id.* Applicant notes that Singh merely discloses the **absolute dose of radioactivity** of ^{177}Lu-DOTATATE without disclosing the volume of the formulation. Accordingly, a skilled artisan would not have any knowledge of **volumetric radioactivity** of the formulation used in Singh, not to mention that she or he would have been motivated in any way to arrive at the volumetric radioactivity of 250 to 500 MBq/mL recited in claim 1.

Further, de Blois fails to teach or suggest **diluting** the complex solution with an aqueous dilution solution comprising **at least one stabilizer**. de Blois only teaches use of saline, i.e., sodium chloride solution, for dilution. The secondary references Singh and RCM do not cure this defect as neither of them even teaches or suggests a dilution step. In addition, nowhere does RCM teach or suggest the volume of the ^{177}Lu-DOTA-TATE solution tested for stability. Thus, RCM does not teach or suggest the **volumetric radioactivity,** 250 to 500 MBq/mL, recited in claim 1.[1] According to the Examiner, de Blois fails to teach absence of ethanol (as recited in claim 21) or dose unit containers being stoppered vials enclosed within a lead container (as recited in claim 19). She then relies on (1) part of Maus' teachings on use of stabilizers after complex formation, (2) part of RCM's teaching on absence of ethanol and (3) part of Chen's teachings on lead-shielded vials to support the obviousness rejection. As argued in Applicant's response filed on May 13, 2019, both Maus and Chen **teach away** from using the low concentration of stabilizers (i.e., 1.0-5.0 mg/mL) for high volumetric radioactivity (i.e., 250-500 MBq/mL) recited in claim 1. While the Examiner finds that the arguments are persuasive and thus has withdrawn the previous rejection over Chen and Maus, she intentionally ignores those portions in these prior art references that would lead away from the claimed invention in the present office action. *See* the Office Action at page 11, e.g., "[t]he reference Chen et al. was not used to teach...the low concentration of stabilizers in the final radiopharmaceutical formulations. The reference of Chen et al. was used to teach of storing the formulations in lead-shielded vials to reduce exposure to the ^{177}Lu.... The reference of Maus et al. was not used to teach of using lower concentrations of gentisic acid and ascorbic acid but used to teach of adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation."

[1] 740 GBq/mg at p86 of RCM is the specific activity, i.e., 740 GBq for every milligram of ^{177}Lu, which is different from volumetric radioactivity, i.e., the radioactivity per unit volume of the solution of ^{177}Lu-DOTATATE.

The Examiner has clearly violated the requirements for establishing a proper *prima facie* case of obviousness. MPEP 2141.02 requires a prior art reference be "considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention" (emphasis original). Instead, the Examiner's obviousness rejection is based on impermissible hindsight in which Applicant's specification and claims were used as a blueprint to cherry pick elements from as many as **five** prior art references and piece together the invention of the pending claims.

Further, the instant application provides sufficient evidence to demonstrate that the claimed process produces stable pharmaceutical aqueous solutions with the low total concentration of stabilizers (e.g., RCP as determined by HPLC being maintained at ≥ 95%) for at least 72 hours when stored at 25 °C. *See e.g.*, Example 3 of the instant application. This effect was not present in the teachings of any of the cited references, and would not have been expected or predicted by a skilled artisan.

"Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. *See, e.g., In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)." *See* MPEP § 2145. Accordingly, independent claim 1 is also patentable over de Blois in view of Singh, RCM, Maus and Chen for unexpected stability of the pharmaceutical solution produced by the claimed method, even when the obtained solution has the low total concentration of stabilizers recited in claim 1. For at least the same reasons stated above, claims 2-23, each of which depends directly or indirectly from claim 1, are also patentable over the cited references. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 8 is also patentable over the cited references on an ***additional*** ground. It is further noted that de Blois, in view of Chen, **teaches away** from presenting higher than 5 mg/mL gentisic acid or ascorbic acid at the radiolabeling reaction. de Blois teaches that the concentration of ascorbic acid and gentisic acid at the radiolabeling reaction is optimized to 3.5 mM or 3.5 millimoles per liter, which is equal to **0.5-0.6 mg/mL** ascorbic acid and gentisic acid, much lower than the gentisic acid concentration of from **20 to 40 mg/mL** recited in claim 8. *See* de Blois p29, section 2.5. This low concentration of stabilizers at the radiolabeling reaction is consistent with the teachings in Chen, which state that, at the concentration of 5 mg/mL, gentisic acid or ascorbic acid either **interferes** with the labeling reaction or provides **less stability** during the reaction. *See, e.g.*, paragraph [0290] of Chen. In contrast, claim 8 recites that during the complex formation (i.e., the labeling reaction), gentisic acid is present at a concentration of from **20 to 40 mg/mL**. *See also* Example 2 of the instant application. None of Singh, RCM, and Maus corrects this defect of de Blois and Chen, at least because none of these references addresses the impact of concentrations of gentisic acid or ascorbic acid to the radiolabeling reaction. As increasing the concentration to greater than 5 mg/mL of gentisic, acid or ascorbic acid at the radiolabeling reaction would render decreased stability in the formulations as

indicated by de Blois in view of Chen, it teaches away from the invention of claim 8, which recites a concentration of gentisic acid from **20 to 40 mg/mL**. Accordingly, the process of claim 8 is nonobvious over de Blois, either taken alone or in combination with other references cited by the Examiner on this additional ground. As are claims 9-11, each of which depends directly or indirectly from claim 8. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 21 is also patentable over the cited references on an ***additional*** ground. Claim 21 is directed to a substantially **ethanol-free** stable pharmaceutical aqueous solution obtained by the process of claim 1 that provides a volumetric radioactivity of from 250 to 500 MBq/mL and low concentration of stabilizers, i.e., 1.0-5.0 mg/mL. Applicant would like to point out de Blois **teaches away** from the claimed solution which is substantially **free of ethanol**. More specifically, de Blois discloses various ^{177}Lu-DOTA-TATE solutions containing different quencher mixtures, some with ethanol and the others without. *See* de Blois p30, section 3.3 and page 33, Figures 6-7. As clearly shown in the two figures, **absent ethanol**, the RCP of ^{177}Lu-DOTA-TATE solutions dropped to **less than 90%** after storing for 72 hrs. In contrast, adding ethanol helps to maintain the RCP of ^{177}Lu-DOTA-TATE solutions at 90% or above. Accordingly, de Blois **teaches away** from the claimed solution that is substantially **free of ethanol** while maintaining a RCP of ≥ 95% for at least 72 h when stored at 25 °C. As noted above, while the ^{177}Lu-DOTA-TATE solution disclosed in RCM does not contain ethanol, nowhere does RCM teach or suggest the volume of the ^{177}Lu-DOTA-TATE solution tested for stability. Thus, RCM does not teach or suggest the **volumetric radioactivity,** 250 to 500 MBq/mL, recited in claim 21. Accordingly, even if de Blois and RCM were combined, the resulting solution would be different from the claimed solution. Further, Maus also teaches that RCP of ^{177}Lu-DOTATATE is an essential factor for successful peptide receptor-targeted radionuclide therapy (*see* Introduction at pages 5-6). The proposed modification by the Examiner to de Blois, i.e., removing ethanol, would render the solutions in de Blois unstable for storage and transport, and thus render de Blois unsatisfactory RCP for its intended purpose for patient infusion. The Examiner is reminded that prior art must be considered in its entirety, including disclosures that teach away from the claims and that proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference. *See* MPEP §§ 2141.02 and 2143.01. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 22 is patentable over the cited references on an ***additional*** ground. Claim 22 recites that the stabilizers in pharmaceutical aqueous solution obtained by the process of claim 1 **consist essentially** of two stabilizers: (i) gentisic acid or a salt thereof as a first stabilizer; and (ii) ascorbic acid or a salt thereof as a second stabilizer. In contrast, the stable formulations

taught in de Blois contains at least four stabilizers, ascorbic acid, gentisic acid, **methionine** and **ethanol**. Given the *unpredictable* nature of stabilizers as discussed in Chen and the **teaching away** by de Blois, a skilled artisan would not have been motivated to modify the teachings in de Blois in view of the other cited references to get rid of methionine and ethanol to arrive at the stable pharmaceutical aqueous solution in claim 22 with a reasonable expectation of success. Applicant respectfully requests reconsideration and withdrawal of the rejection. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

Claims 1-20 remain provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 2, 4-10, 13, and 15-29 of copending U.S. Application No. 16/140,962 or over claims 1-11, 13-19 and 23-44 of copending U.S. Application No. 16/045,484. In addition, claims 1-11, 14, 15, 17, 18, 20 and 21 remain provisionally rejected over claims 1-11, 14, 15, 17, 18, 20 and 21 of U.S. Application No. 16/175,239. *See* the Office Action at pages 2-4.

Without arguing the propriety of this rejection, Applicant respectfully requests that the provisional nonstatutory double patenting rejections over copending U.S. Application Nos. 16/140,962, 16/045,484 and 16/175,239 be held in abeyance until allowable subject matter in the present application has been determined.

In view of the above remarks, Applicant submits that the pending application is in condition for allowance. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith, to our Deposit Account No. 50-4409, under Docket No. PAT058197-US-CIP02.

Should the Examiner have any questions, please contact the undersigned attorney.

Respectfully submitted,

/ Lian Ouyang/
Lian Ouyang
Attorney for Applicant
Reg. No. 69,254

Novartis Institutes for BioMedical Research, Inc.
700 Main Street, 427Q
Cambridge, MA 02139
USA
+1 617 871 3880

Date: September 6, 2019

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

U.S.PATENTS

Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS

Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS

Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16175261
	Filing Date	2018-10-30
	First Named Inventor	de Palo, Francesco
	Art Unit	1618
	Examiner Name	Perreira, Melissa Jean
	Attorney Docket Number	PAT058197-US-CIP02

	1	Frilling et al., "Treatment with 90Y- and 177Lu-DOTATOC in patients with metastatic neuroendocrine tumors", Surgery, Vol. 140, pp 968-977, 2006	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-09-06
Name/Print	Lian Ouyang	Registration Number	69,254

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	16175261
Filing Date:	30-Oct-2018
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang/Susan Dillon
Attorney Docket Number:	PAT058197-US-CIP02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	1	100	100
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**340**

Electronic Acknowledgement Receipt

EFS ID:	37084191
Application Number:	16175261
International Application Number:	
Confirmation Number:	8183
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	06-SEP-2019
Filing Date:	30-OCT-2018
Time Stamp:	10:23:35
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$340
RAM confirmation Number	E201996A24156407
Deposit Account	504409
Authorized User	Susan Dillon

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PAT058197_US_CIP02_Nonfinal_Sept6_2019_Signed.pdf	226238 d69d836ceb5ee674d8366599972e7c99bcfa2757	yes	10

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	5
Applicant Arguments/Remarks Made in an Amendment	6	10

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
2	Information Disclosure Statement (IDS) Form (SB08)	PAT058197_US_CNT02_IDS_signeddated9-6-19.pdf	1034345 94b18a21f5ab4b9bd06f5569552de30e671dea49	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
3	Non Patent Literature	Friling_2006.pdf	1191296 ed0e8337759a2216ec8f56ba7af95ff32159b3a5	no	10

Warnings:

Information:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
4	Fee Worksheet (SB06)	fee-info.pdf	32205 3ffdf931b3a4c2c5712e05f6d5f88673c9020160d	no	2

Warnings:

Information:

Total Files Size (in bytes):	2484084

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/175,261	Filing Date 10/30/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $100 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $460 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT	09/06/2019	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 24	Minus	** 23	= 1		x $100 =	100
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	100

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/LISA THOMAS/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

1095 7590 11/04/2019

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
11/04/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

phip.patents@novartis.com

Office Action Summary	Application No. 16/175,261	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 9/6/19.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-24 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-24 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims and Objections/Rejections Status

The claims 1-24 are pending in the application. Claim 24 was newly added in the amendment filed 9/6/19

The rejection of claims 1-23 under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) and Chen et al. (US 2007/0269375A1) is maintained but modified to include newly added claim 24.

The rejection of claims 1-20,22 and 23 on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,4-10,13 and 15-29 of copending Application No. 16/140,962 (reference application) is maintained.

The rejection of claims 1-20,22 and 23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,13-19 and 23-44 of copending Application No. 16/045,484 (reference application) is maintained.

The rejection of claims 1-11,14,15,17,18 and 20-23 on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,14,15,17,18,20 and 21 of copending Application No. 16/175,239 (reference application) is maintained.

Response to Arguments

Applicant's arguments filed 9/6/19 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-24 is/are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) and Chen et al. (US 2007/0269375A1) as stated in the office action mailed 6/6/19.

In regards to newly added claim 24, the reference of de Blois discloses the combination of gentisic and ascorbic acid and ethanol while remaining a RCP of $\geq$ 95% for at least 72 h when stored at 25°C. The concentration of ethanol is 2-20% (v/v).

The reference of RCM discloses stability studies of ^{177}Lu-DOTA-TATE after labeling DOTA-SP (Nle) with 33 MBq of ^{177}Lu with the addition of ascorbic acid or gentisic acid as stabilizers immediate after

labeling. The RCP was determined to be 98.0 ± 0.1 with ascorbic acid and 97.8 ± 0.3 with gentisic acid after 24 hours. The acceptance limit for RCP is ≥ 95% (p12, 5.2.2 Quality control).

The reference of Maus discloses that the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis of the ^{177}Lu-DOTA-TATE. The removal of gentisic acid and ascorbic acid decrease RCP <95% but reintroduction of ascorbic acid resulted in a RCP ≥ 95% at 72h.

Therefore, it would have been obvious to one ordinarily skilled in the art to reduce the amount of ethanol to about 2% or less which encompasses the "substantially free of ethanol" amount of the instant claims and vary the amounts of gentisic acid and ascorbic acid to maintain the acceptance limit for RCP of ≥ 95%.

Applicant asserts that de Blois discloses 3.5 mM ascorbic acid and gentisic acid which is equal to 0.5-0.6 mg/mL ascorbic acid and gentisic acid, which is not encompassed by the stabilizer concentration recited in claims 1 or 23 as asserted by the examiner.

The reference of de Blois teaches that the optimal quencher is 3.5 mM for ascorbic and gentisic acid (equal to 0.5-0.6 mg/mL, see remarks p2) but the concentrations of the combination of ascorbic and gentisic acid comprises 1-20 mM which encompasses the stabilizer concentration recited in claims 1 or 23.

Applicant asserts that du Blois fails to teach absence of ethanol or does unit containers being stoppered vials enclosed with a lead container.

The specification recites that "at least the amount of ethanol in the solutions of the present invention should be limited, e.g. less than 5%, preferably less than 2%, more preferably less than 1% in the final solution" which is being understood to define the limitation "substantially free of ethanol" as recited in the instant claim.

The reference of de Blois teaches that concentration of ethanol is 2-20% (v/v) for ethanol. Therefore, it would have been obvious to one ordinarily skilled in the art to reduce the amount of

ethanol to about 2% which encompasses the "substantially free of ethanol" amount of the instant claims.

The reference of RCM meeting teaches that the ^{177}Lu-DOTA-TATE is prepared at the hospital radiopharmacy without ethanol.

The reference of de Blois was not used to teach of does unit containers being stoppered vials enclosed with a lead container.

The reference of Chen et al. was used to teach of stabilized radiopharmaceutical formulations comprising a radiometal (e.g. ^{177}Lu, etc.); metal chelator (e.g. DTPA, DOTA, etc.); stabilizers (e.g. gentisic acid, ascorbic acid, etc.); buffers (e.g. acetate buffer, etc.). To lead-shielded 4-mL vials were added the individual stabilizer solutions, $^{177}LuCl_3$ and COMPOUND A (dissolved in water).

Applicant asserts that Singh merely discloses the absolute dose of radioactivity of ^{177}Lu-DOTA-TATE without disclosing the volume of the formulation. Accordingly, a skilled artisan would not have any knowledge of volumetric radioactivity of the formulation, not to mention that she or he would have been motivated in any way to arrive at the claimed solution with the specific volumetric radioactivity of 250 to 500 MBq/mL.

The reference of Singh teaches of a ten millicuries (370 MBq) administered as a slow intravenous injection and therefore, it would have been predictable to provide a constant ten millicuries over the course of an intravenous injection which necessarily is included in a large volume of solution to provide for images at 4, 24 and 48 hours post injection. The DOTA-TATE labelling at therapeutic level (patient's dose) was performed under the kit formulation in a concentrated form (60GBq in 3 mL). It can be diluted with saline for patient infusion.

Applicant asserts that the claimed process produces stable pharmaceutical aqueous solutions with the low total concentration of stabilizers (e.g. RCP as determined by HPLC being maintained at ≥

95%) for at least 72 hours when stored at 25°C. The effect was not present in the teachings of any of the cited references, and would not have been expected or predicted by the skilled artisan.

The reference of RCM teaches of stability studies of ^{177}Lu-DOTA-TATE after labeling DOTA-SP (Nle) with 33 MBq of ^{177}Lu with the addition of ascorbic acid or gentisic acid as stabilizers immediate after labeling. The RCP was determined to be 98.0 ± 0.1 with ascorbic acid and 97.8 ± 0.3 with gentisic acid after 24 hours. The acceptance limit for RCP is ≥ 95% (p12, 5.2.2 Quality control).

Therefore, it was not unexpected to provide ^{177}Lu-DOTA-TATE with ascorbic acid or gentisic acid stabilizers to provide for RCP is ≥ 95%.

Applicant asserts that de Blois, in view of Chen, teaches away from presenting a higher than 5 mg/mL gentisic acid or ascorbic acid at the radiolabeling reaction. de Blois teaches 3.5 mM ascorbic acid and gentisic acid, which is equal to 0.5-0.6 mg/mL ascorbic acid and gentisic acid. This low concentration of stabilizers at the radiolabeling reaction is consistent with the teachings in Chen, which states that, at the concentration of 5 mg/mL, gentisic acid or ascorbic acid either interferes with the labeling reaction or provides less stability during the reaction.

The reference of de Blois teaches that the optimal quencher is 3.5 mM for ascorbic and gentisic acid (equal to 0.5-0.6 mg/mL, see remarks p2) but the concentrations of the combination of ascorbic and gentisic acid comprises 1-20 mM.

The reference of RCM teaches of stability studies after labeling DOTA-SP (Nle) with 33 MBq of ^{177}Lu with the addition of ascorbic acid or gentisic acid as stabilizers immediate after labeling. The RCP was determined to be 98.0 ± 0.1 with ascorbic acid and 97.8 ± 0.3 with gentisic acid after 24 hours. The acceptance limit for RCP is ≥ 95% (p12, 5.2.2 Quality control).

The reference of Chen teaches of the concentration of stabilizers such as gentisic acid (2-20 mg/mL), ascorbic acid (10 to 100 mg/mL) wherein the stabilized radiopharmaceutical formulations comprise a radiometal (e.g. ^{177}Lu, etc.); metal chelator (e.g. DTPA, DOTA, etc.); stabilizers (e.g. gentisic

acid, ascorbic acid, etc.); buffers (e.g. acetate buffer, etc.). To lead-shielded 4-mL vials were added the individual stabilizer solutions, $^{177}LuCl_3$ and COMPOUND A (dissolved in water) wherein A is DOTA-Gly-ACA-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2 wherein the COMPOUND A is not identical to the TATE of the reference of de Blois.

None of the five stabilizers individually, such as gentisic acid, ascorbic acid interferes with the labeling reaction and each provides stability during the reaction at 1 mg/mL and gentisic acid does not interfere at 2.5 mg/mL but at 5 mg/mL interferes with the labeling.

The reference of Maus was used to teach that the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis of the ^{177}Lu-DOTA-TATE. The removal of gentisic acid and ascorbic acid decrease RCP <95% but reintroduction of ascorbic acid resulted in a RCP ≥ 95% at 72h.

It would have been obvious to modify the combination of stabilizers to provide for a RCP≥ 95% depending on the complex that is being stabilized as it is known by RCM that the stability of ^{177}Lu-complexes comprises an RCP 98.0 ± 0.1 with ascorbic acid and 97.8 ± 0.3 with gentisic acid after 24 hours wherein the acceptance limit for RCP is ≥ 95% and Maus teaches addition of ascorbic acid to ^{177}Lu-DOTA-TATE resulted in a RCP ≥ 95% at 72h.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,4-10,13 and 15-29 of copending Application No. 16/140,962 as stated in the office action mailed 6/6/19.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,13-19 and 23-44 of copending Application No. 16/045,484 as stated in the office action mailed 6/6/19.

Claims 1-11,14,15,17,18,20 and 21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-11,14,15,17,18,20 and 21 of copending Application No. 16/175,239 as stated in the office action mailed 6/6/19.

Applicant asserts that the provisional nonstatutory double patenting rejections be held in abeyance until allowable subject matter in the present application has been determined.

The rejections are maintained as the claims are not allowable.

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on M9-2, T9-3, W9-3, Th9-3, F9-2.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 517-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	02/06/2019	05/31/2019	10/28/2019						
	1	✓	✓	✓						
	2	✓	✓	✓						
	3	✓	✓	✓						
	4	✓	✓	✓						
	5	✓	✓	✓						
	6	✓	✓	✓						
	7	✓	✓	✓						
	8	✓	✓	✓						
	9	✓	✓	✓						
	10	✓	✓	✓						
	11	✓	✓	✓						
	12	✓	✓	✓						
	13	✓	✓	✓						
	14	✓	✓	✓						
	15	✓	✓	✓						
	16	✓	✓	✓						
	17	✓	✓	✓						
	18	✓	✓	✓						
	19	✓	✓	✓						
	20	✓	✓	✓						
	21	✓	✓	✓						
	22		✓	✓						
	23		✓	✓						
	24			✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
google scholar	02/05/2019	MP
inventor search	02/05/2019	MP
copending application search	02/05/2019	MP
EAST	02/06/2019	MP
google scholar	05/30/2019	MP
EAST	10/28/2019	MP

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	65	Dota near5 TATE	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/10/28 15:19
L2	288	sup?177 adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/10/28 15:19
L3	1	L2 and l1	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/10/28 15:19

10/ 28/ 2019 3:19:51 PM
C:\ Users\ mperreira\ Documents\ EAST\ Workspaces\ 16175261.wsp

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

U.S.PATENTS

Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS

Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS

Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS

Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

	1	Frilling et al., "Treatment with 90Y- and 177Lu-DOTATOC in patients with metastatic neuroendocrine tumors", Surgery, Vol. 140, pp 968-977, 2006

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	10/28/2019

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CIP02

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-09-06
Name/Print	Lian Ouyang	Registration Number	69,254

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Jan 27 2020

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Lian Ouyang

S-signature:
/Lian Ouyang/

Registration Number:
69254

U.S. Application Number:
16175261

Confirmation Number:
8183

E-mail Address:
lian.ouyang@novartis.com

Phone Number:
+1 6178713880

Proposed Time of Interview:
2-3-2020 9:30 AM ET

Alternative Proposed Time(s) of Interview:
2-3-2020 10:00 AM ET

Alternative Proposed Time(s) of Interview:
2-3-2020 10:30 AM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:
103 rejection and cited references

uspto UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02

CONFIRMATION NO. 8183

1095
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

PUBLICATION NOTICE

OC0000000114333410

Title: Stable, concentrated radionuclide complex solutions

Publication No.US-2020-0030464-A1
Publication Date:01/30/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16175261
Filing Date	30-Oct-2018
First Named Inventor	Francesco de Palo
Attorney Docket Number	PAT058197-US-CIP02
Title of Invention	Stable, concentrated radionuclide complex solutions

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Advanced Accelerator Applications (Italy) Srl	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16140962 filed on 09/25/2018

16045484 filed on 07/25/2018

16175239 filed on 10/30/2018

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

(•) Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request. ( ) I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ( ) Small Entity ( ) Micro Entity (•) Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: (•) An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 69254 ( ) A sole inventor ( ) A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ( ) A joint inventor; all of whom are signing this request	
Signature	/Lian Ouyang/
Name	Lian Ouyang

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16175261
Filing Date:	30-Oct-2018
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang/Susan Dillon
Attorney Docket Number:	PAT058197-US-CIP02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	160

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16175261

Filing Date: 30-Oct-2018

Applicant/Patent under Reexamination: de Palo

Electronic Terminal Disclaimer filed on January 31, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	38458688
Application Number:	16175261
International Application Number:	
Confirmation Number:	8183
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	31-JAN-2020
Filing Date:	30-OCT-2018
Time Stamp:	16:06:27
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$160
RAM confirmation Number	E20201UG06261244
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	35180 d36ffb5ea171d157a4543c8386bfe20d411764a0	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30499 4d8540fea1233ec81518684de9d454 1bf0be bf97	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65679		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 02/11/2020

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 02/11/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

TITLE OF INVENTION: STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	05/11/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 02/11/2020
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

TITLE OF INVENTION: STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	05/11/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001690

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

1095 7590 02/11/2020

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 02/11/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/175,261	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 1/31/20.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 1-24 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Lian Ouyang on 1/31/20.

The application has been amended as follows:

IN THE CLAIMS:

1.) In line 16 of the instant claim 1, please delete "mg/mL." and insert "mg/mL, and ethanol is present in a concentration of less than 1%." in its place.

2.) In line 2 of the instant claim 21, please delete "substantially"

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on M9-2, T9-3, W9-3, Th9-3, F9-2.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 517-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see https://ppair-my.uspto.gov/pair/PrivatePair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Applicant-Initiated Interview Summary	Application No. 16/175,261	Applicant(s) de Palo et al.		
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (First Inventor to File) Status Yes	Page 1 of 2

All participants (applicant, applicants representative, PTO personnel):

1. MELISSA J PERREIRA (Examiner); Telephonic 2. Lian Ouyang (Attorney of Record); Telephonic

Date of Interview: 31 January 2020

Claims Discussed: Claim 1 and 21

Amendment proposed: An amendment to the claims 1 and 21 were proposed.

Brief Description of the main topic(s) of discussion: The applicant proposed amending claim 1 to include that ethanol is present in less than 1%.
The applicant proposed amending claim 21 to include recite that no ethanol is present.

Issues Discussed:

Proposed Amendments:
The applicant proposed amending claim 1 to include that ethanol is present in less than 1%.
The applicant proposed amending claim 21 to include recite that no ethanol is present.

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

U.S. Patent and Trademark Office
PTOL-413/413b (Rev. 01/01/2015)

Interview Summary

Paper No. 20200205

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC							
Symbol						Type	Version
A61K	/	51	/	048		F	2013-01-01
C22B	/	59	/	00		I	2013-01-01
A61K	/	33	/	24		I	2013-01-01
A61K	/	51	/	0482		A	2013-01-01

CPC Combination Sets								
Symbol						Type	Set	Ranking	Version
	/		/						

/MELISSA J PERREIRA/ Examiner, Art Unit 1618 (Assistant Examiner)	05 February 2020 (Date)	Total Claims Allowed: 24	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618 (Primary Examiner)	05 February 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No.: 20200205

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	51	/	00
A61M	/	36	/	14

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
424	1.69

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/MELISSA J PERREIRA/ Examiner, Art Unit 1618 (Assistant Examiner)	05 February 2020 (Date)	Total Claims Allowed: 24	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618 (Primary Examiner)	05 February 2020 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	10	10	19	19										
2	2	11	11	20	20										
3	3	12	12	21	21										
4	4	13	13	22	22										
5	5	14	14	23	23										
6	6	15	15	24	24										
7	7	16	16												
8	8	17	17												
9	9	18	18												

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 February 2020	Total Claims Allowed:	
(Assistant Examiner)	(Date)	24	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 February 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20200205

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
google scholar	02/05/2019	MP
inventor search	02/05/2019	MP
copending application search	02/05/2019	MP
EAST	02/06/2019	MP
google scholar	05/30/2019	MP
EAST	10/28/2019	MP
EAST	02/05/2020	MP
Allowability conference (SPE Mike Hartley)	02/04/2020	MP

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,261	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	51/0482	02/05/2020	MP

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	

Bibliographic Data

Application No: 16/175,261

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MELISSA J PERREIRA/ (Examiner's Signature) | (Initials)

Title: Stable, concentrated radionuclide complex solutions

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/30/2018	424	1618	PAT058197-US-CIP02
RULE			

APPLICANTS

Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY

INVENTORS

Francesco de Palo Ivrea, ITALY

Lorenza Fugazza Ivrea, ITALY

Donato Barbato Ivrea, ITALY

Maurizio Mariani Ivrea, ITALY

Daniela Chicco Albiano d'Ivrea, ITALY

Giovanni Tesoriere Noicattaro, ITALY

Clementina Brambati Torino, ITALY

CONTINUING DATA

This application is a CIP of 16140962 09/25/2018

16140962 is a CIP of 16045484 07/25/2018

FOREIGN APPLICATIONS

PCT/IB2018/055575 07/25/2018

PCT/IB2018/057415 09/25/2018

IF REQUIRED, FOREIGN LICENSE GRANTED**

05/29/2019

STATE OR COUNTRY

ITALY

ADDRESS

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2

EAST HANOVER, NJ 07936-1080
UNITED STATES

FILING FEE RECEIVED

$5,960

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	289	sup?177 adj Lu	US-PGPUB; USPAT	OR	ON	2020/02/05 10:45
L2	7135	gentisic and ascorbic	US-PGPUB; USPAT	OR	ON	2020/02/05 10:45
L3	49	l1 and l2	US-PGPUB; USPAT	OR	ON	2020/02/05 10:45
L4	423	A61K51/0482.cpc.	US-PGPUB; USPAT	OR	ON	2020/02/05 11:00
L5	12	l3 and l4	US-PGPUB; USPAT	OR	ON	2020/02/05 11:00

2/ 5/ 2020 11:00:26 AM
C:\ Users\ mperreira\ Documents\ EAST\ Workspaces\ 16175261.wsp

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
Francesco de Palo et al.
APPLICATION NO: 16/175261
FILED: October 30, 2018
FOR: Stable, Concentrated radionuclide complex solutions

Art Unit: 1618
Examiner: Perreira, Melissa Jean
Conf. No.: 8183

VIA EFS
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

INTERVIEW SUMARY AND REPLY TO NOTICE OF ALLOWANCE

Applicant thanks Examiner Perreira for the Notice of Allowance mailed on February 11, 2020.

Interview Summary

Applicant's representative thanks Examiner Perreira for the courtesy of telephonic interview conducted on January 31, 2020. During the interview, claims 1 and 21 as well as prior art cited for the 103 rejection were discussed. Applicant proposed claim amendments, which are described on page 2 of the Notice of Allowance.

In response to the Notice of Allowance, enclosed is a completed Part B- Fee(s) Transmittal. The issue fee in the amount of $1,000 is being paid with this reply on the Electronic Filing System. Apply those fees and any other necessary charges or credits to Deposit Account No. 50-4409, referencing the above docket number.

Dated: February 11, 2020

Respectfully submitted,

Electronic signature: / Lian Ouyang /
Lian Ouyang
Registration No.: 69254
Novartis Institutes for Biomedical Research, Inc.
700 Main Street
Cambridge, Massachusetts 02139
(617) 871-3880
Attorney For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	16175261
Filing Date:	30-Oct-2018
Title of Invention:	STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang/Susan Dillon
Attorney Docket Number:	PAT058197-US-CIP02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1000

Electronic Acknowledgement Receipt

EFS ID:	38558274
Application Number:	16175261
International Application Number:	
Confirmation Number:	8183
Title of Invention:	STABLE, CONCENTRATED RADIONUCLIDE COMPLEX SOLUTIONS
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	11-FEB-2020
Filing Date:	30-OCT-2018
Time Stamp:	18:37:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E20202A138266298
Deposit Account	504409
Authorized User	Susan Dillon

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	PAT058197-US-CIP_IF.pdf	282209 8e58510f18612cb0aca486fe2917f9a16596765a	no	2
Warnings:					
Information:					
2	Applicant summary of interview with examiner	PAT058197-US-CIP02_response_interview_summary.pdf	149933 172e3bc50e096a692d63562ac9fd1d709b45f409	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30113 f95bac1f67979cb677dd7b7eee8ea23816eda3bf	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	462255		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B – FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 02/11/2020
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
16/175,261	10/30/2018	Francesco de Palo	PAT058197-US-CIP02	8183

TITLE OF INVENTION:

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1,000	05/11/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Lian Ouyang
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: ADVANCED ACCELERATOR APPLICATIONS (ITALY) S.R. L.

(B) RESIDENCE: (CITY and STATE or COUNTRY): POZZILLI (ISERNIA), ITALY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☑ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☑ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Lian Ouyang/ Date 02/11/2020

Typed or printed name Lian Ouyang Registration No. 69254

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (02-18)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175261
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	
Attorney Docket Number	PAT058197-US-CIP02

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
Change(s) applied to document. /C.C.B./ 2/19/2020	1	5804157		1998-09-08	~~Mallinckrodt Medical, Inc.~~	Srinivasan et al.
	2	5830431		1998-11-03	~~Mallinckrodt Medical, Inc.~~	Srinivasan et al.
	3	5776894		1998-07-07	~~Novartis AG~~	Albert et al.
	4	5753627		1998-05-19	~~Novartis AG~~	Albert et al.
	5	6183721	B1	2001-02-06	~~Novartis AG~~	Albert et al.
	6	6277356	B1	2001-08-21	~~Novartis AG~~	Albert et al.
	7	6123916		2000-09-26	~~Novartis AG~~	Krenning et al.

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

EFS Web 2.1.18

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,261	03/24/2020	10596276	PAT058197-US-CIP02	8183

1095 7590 03/04/2020

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Francesco de Palo, Ivrea, ITALY;
Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY;
Lorenza Fugazza, Ivrea, ITALY;
Donato Barbato, Ivrea, ITALY;
Maurizio Mariani, Ivrea, ITALY;
Daniela Chicco, Albiano d'Ivrea, ITALY;
Giovanni Tesoriere, Noicattaro, ITALY;
Clementina Brambati, Torino, ITALY;