Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	de Palo, Francesco	Nonprovisional Application Number (if known):	
Title of Invention:	Stable, concentrated radionuclide complex solutions		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.
2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.
3. The applicable box is checked below:

I. ☑ **Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)**

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ **Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)**

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature	/Lian Ouyang/	Date	10/30/2018
Name (Print/Typed)	Lian Ouyang	Practitioner Registration Number	69,254

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

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

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

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

PTO/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	
Title of Invention	Stable, concentrated radionuclide complex solutions	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Francesco		de Palo	

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

City	Country of Residence [i]
Colleretto Giacosa	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via Ribes, 5
City	Colleretto Giacosa
State/Province	
Postal Code	10010
Country [i]	IT

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Lorenza		Fugazza	

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

City	Country of Residence [i]
Colleretto Giacosa	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via Ribes, 5
City	Colleretto Giacosa
State/Province	
Postal Code	10010
Country [i]	IT

Inventor 3 Remove

Legal Name

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

Prefix	Given Name	Middle Name	Family Name	Suffix
	Donato		Barbato	

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

City	Colleretto Giacosa	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via Ribes, 5
City	Colleretto Giacosa
State/Province	
Postal Code	10010
Country [i]	IT

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Maurizio		Mariani	

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

City	Colleretto Giacosa	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via Ribes, 5
City	Colleretto Giacosa
State/Province	
Postal Code	10010
Country [i]	IT

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniela		Chicco	

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

City	Colleretto Giacosa	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via Ribes, 5
City	Colleretto Giacosa
State/Province	
Postal Code	10010
Country [i]	IT

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

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giovanni		Tesoriere	

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

City	Colleretto Giacosa	Country of Residence i	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	Via Ribes, 5		
City	Colleretto Giacosa	**State/Province**	
Postal Code	10010	**Country** i	IT

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	01095		
Email Address	pip_inbox.phchbs@novartis.com	Add Email	Remove Email

Application Information:

Title of the Invention	Stable, concentrated radionuclide complex solutions		
Attorney Docket Number	PAT058197-US-CIP02	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	**Suggested Figure for Publication (if any)**	

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

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	• Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	01095		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	16/140962	2018-09-25

PTO/AIA/14 (11-15)
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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	
Title of Invention	Stable, concentrated radionuclide complex solutions	

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/140962	Continuation in part of	16/045484	2018-07-25
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/057415	WO	2018-09-25	
			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/055575	WO	2018-07-25	
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	
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)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	
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 — Remove

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 Ribes, 5		
Address 2			
City	Colleretto Giacosa	**State/Province**	
Country	IT	Postal Code	10010
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. Add

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.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	
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.

Remove

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 i		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. Add

Signature:

Remove

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)	2018-10-30
First Name	Lian	Last Name	Ouyang	Registration Number	69,254

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

PTO/AIA/14 (11-15)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	PAT058197-US-CIP02
	Application Number	
Title of Invention	Stable, concentrated radionuclide complex solutions	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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

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

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

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

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

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

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

Abstract

Stable, concentrated radionuclide complex solutions

The present invention relates to radionuclide complex solutions of high concentration and of high chemical stability, that allows their use as drug product for diagnostic and/or therapeutic purposes. The stability of the drug product is achieved by at least one stabilizer against radiolytic degradation. The use of two stabilizers introduced during the manufacturing process at different stages was found to be of particular advantage.

Claims

1. 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 and not the second stabilizer, then the aqueous dilution solution comprises at least one stabilizer 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 mg/mL.

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

5. 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 and the solution provided in step (2.1) compries only one stabilizer which is ascorbic acid or a salt thereof.

6. The process according to claim 2, wherein the solution provided in step (1.2) comprises stabilizer/stabilizers in a total concentration of from 15 to 50 mg/mL.

7. The process according to claim 6, wherein the solution provided in step (1.2) comprises stabilizer/stabilizers in a total concentration of from 20 to 40 mg/mL

8. The process according to claim 7, wherein the solution provided in step (1.2) comprises only one stabilizer which is gentisic acid in a concentration of from 20 to 40 mg/mL.

9. The process according to claim 8, wherein the solution provided in step (1.2) comprises only one stabilizer which is gentisic acid in a concentration of from 25 to 35 mg/mL.

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

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

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

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

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

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

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

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

Stable, concentrated radionuclide complex solutions

RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. Application Serial No. 16/140,962 filed September 25, 2018, which is a continuation-in-part of U.S. Application Serial No. 16/045,484 filed July 25, 2018 and claims priority to, and the benefit of International Application No. PCT/IB2018/055575 filed July 25, 2018, the contents of each of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to radionuclide complex solutions of high concentration and of high chemical and radiochemical stability, that allows their use as commercial drug product for diagnostic and/or therapeutic purposes.

BACKGROUND OF THE INVENTION

The concept of targeted drug delivery is based on cell receptors which are overexpressed in the target cell in contrast to the not-to-be-targeted cells. If a drug has a binding site to those overexpressed cell receptors it allows the delivery of the drug after its systemic administration in high concentration to those target cells while leaving other cells, which are not of interested, unaffected. For example, if tumor cells are characterized by an overexpression of a specific cell receptor, a drug with binding affinity to said receptor will after intravenous infusion accumulate in high concentration in the tumor tissue while leaving the normal tissue unaffected.

This targeted drug delivery concept has also been used in radiomedicine to deliver radionuclides selectively to the target cells for diagnostic or therapeutic purposes.

For this radiomedicinal application the target cell receptor binding moiety is typically linked to a chelating agent which is able to form a strong complex with the metal ions of a radionuclide. This radiopharmaceutical drug is then delivered to the target cell and the decay of the radionuclide is then releasing high energy electrons, positrons or alpha particles as well as gamma rays at the target site.

One technical problem with those radiopharmaceutical drug products is that the decay of the radionuclide occurs constantly, e.g. also during the manufacturing and during storage of the drug product, and the released high energy emissions induce the cleavage of the chemical bonds of the molecules which form part of the drug product. This is often referred to as radiolysis or radiolytic degradation. The radiolytic degradation of the receptor binding moiety of the drug may lead to a decrease in its efficacy to act as a diagnostic and/or therapeutic.

The poor stability of those radiopharmaceutical drug products and their lack of any significant shelf-life required that those drugs have so far to be manufactured as an individual patient's dose unit in the laboratories at the hospital and administered immediately to the patient who had to be present at that hospital already awaiting the radiological treatment. To facilitate such drug preparation in the hospital laboratories, "cold" (i.e. non-radioactive) freeze-dried kits have been developed which comprise the cell receptor binding moiety linked to a chelating agent without the radionuclide. The freeze-dried content of those kit vials is then to be reconstituted with a solution of the radionuclide short before administration (*Das et al. J Radioanal Nucl Chem 2014, 299, 1389-1398; Das et al. Current Radiopharmaceuticals 2014, 7, 12-19; Luna-Gutierrez et al. J Radioanal Nucl Chem 2017, 314, 2181-2188*). However, those kits are not "ready-to-use" as they require the reconstitution step and in addition further processing steps (e.g. applying heat for the complexation reaction) as well as purification and sterilization steps before the drug can be finally administered.

To reduce radiolysis of radiopharmaceutical drug products and thus improve stability, various strategies have been explored with more or less success: The drug product may be stored at low temperatures, or produced in high dilution, or stabilizers may be added.

Adding stabilizers however may be problematic as those chemicals may have a negative impact on the complexation of the radionuclide into the chelating agent or may have a limited solubility and precipitate from the solution. Ethanol has been reported as stabilizer against radiolysis (*WO 2008/009444*). While ethanol might not have a negative impact on the complexation or a solubility issue, higher amounts of ethanol in an infusion solution may be physiologically problematic and may have a negative impact on the tolerability of the drug product.

Producing the drug product in high dilution has the disadvantage that large volumes of infusion solutions need to be administered to patients. For the convenience of patients and for drug tolerability reasons it would be highly desirable to provide the radiopharmaceutical drug product in a high concentration. Those highly concentrated solutions however are in particular prone to radiolysis. Therefore, there are contradictory positions between, on the one hand, avoiding radiolysis by dilution of the drug product but, on the other hand, avoiding patient discomfort during treatment by providing a concentrated drug solution. In *Mathur et al. Cancer Biotherapy and Radiopharmaceuticals, 2017, 32(7), 266-273* a product of high concentration has been reported and claimed being ready-to-use. However, that composition may be problematic with respect to tolerability as it contains high amounts of ethanol.

It remains therefore a challenge to design a ready-to-use radiopharmaceutical drug product which can be produced at commercial scale and delivered as a sufficiently stable and sterile solution in a high concentration which leads to a convenient small infusion volume for patients and which has a composition of high physiological tolerability (e.g. a composition which does not contain ethanol).

SUMMARY OF THE INVENTION

The present inventors have now found a way to design and produce a highly concentrated radionuclide complex solution which is chemically and radiochemically very stable even if stored at ambient or short term elevated temperatures so that it can be produced on commercial scale and supplied as ready-to-use radiopharmaceutical product.

The present invention is provided in various aspects as outlined in the following:

A pharmaceutical aqueous solution comprising

(a) a complex formed by

(ai) a radionuclide, and

(aii) a cell receptor binding organic moiety linked to a chelating agent; and

(b) at least one stabilizer against radiolytic degradation;

wherein
said radionuclide is present in a concentration that it provides a volumetric radioactivity of at least 100 MBq/mL, preferably of at least 250 MBq/mL.

Said stabilizer(s), component (b), is (are) present in a total concentration of at least 0.2 mg/mL, preferably at least 0.5 mg/mL, more preferably at least 1.0 mg/mL, even more preferably at least 2.7 mg/mL.

A pharmaceutical aqueous solution, comprising

(a) a complex formed by

(ai) the radionuclide ^{177}Lutetium (Lu-177), present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL , and

(aii) the chelating agent linked somatostatin receptor binding organic moiety DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide);

(bi) gentisic acid or a salt thereof as the first stabilizer against radiolytic degradation present in a concentration of from 0.5 to 1 mg/mL;

(bii) ascorbic acid or a salt thereof as the second stabilizer against radiolytic degradation present in a concentration of from 2.0 to 5.0 mg/mL.

A process for manufacturing said pharmaceutical aqueous solution as defined above, comprising the process steps:

(1) Forming a complex of the radionuclide and the chelating agent linked cell receptor binding organic moiety by

(1.1) preparing an aqueous solution comprising the radionuclide;

(1.2) preparing an aqueous solution comprising the chelating agent linked cell receptor binding organic moiety, a first stabilizer, optionally a second stabilizer; and

(1.3) mixing the solutions obtained in steps (1.1) and (1.2) and heating the resulting mixture;

(2) Diluting the complex solution obtained by step (1) by

(2.1) preparing an aqueous dilution solution optionally comprising a second stabilizer; and

(2.2.) mixing the complex solution obtained by step (1) with the dilution solution obtained by the step (2.1).

The present invention provide the following advantages:

The high concentration allows administering a high dose within a short time frame. E.g. in the case of ^{177}Lu-DOTA-TATE, the high dose of 7.4 GBq can be provided in a small volume of 20.5 to 25.0 mL which allows the IV infusion administration to be completed within about 20 to 30 minutes.

The use of suitable stabilizer(s), according to the present invention as described, herein ensures high stability, at least 95%, 96%, 97%, 98%, 99% or 100% chemical stability with respect to the chemical purity for the cell receptor-binding molecule after 72 hours at 25 °C, even if this molecule is a sensitive peptide molecule. E.g. for DOTA-TATE 100% chemical purity were found after 72 hours at 25 °C and even after 48 hours at 32 °C were found. Even under short term elevated temperature conditions (32°C for 12 h and 25° for 60 h) such high stability was found with respect to chemical purity.

Further, the use of suitable stabilizer(s), according to the present invention as described, herein ensures high stability, at least 95% radiochemical stability with respect to the radiochemical purity radionuclide complex. E.g. for ^{177}Lu-DOTA-TATE at least 95% radiochemical purity were found after 72 hours at 25 °C. Even under short term elevated temperature conditions (32°C for 12 h and 25° for 60 h) such high stability was found with respect to radiochemical purity.

While sufficient stability may be achieved already with one single stabilizer, the use of two stabilizers has been found to be of particular suitability in stabilizing sensitive radiopharmaceutical solutions. In particular, the presence of one stabilizer during complex formation and another stabilizer added after the complex formation is of advantage as it ensures that already during the complexation reaction, the cell receptor-binding molecule is protected against radiolysis and the other stabilizer enhances the protecting effect for the shelf-life period. Further, by this sequential application of the two stabilizers it is ensured, that during complexation only a relatively small amount of stabilizer is present (which minimizes the

potential interference of that stabilizer with the complexation reaction) and after complexation a large amount of a stabilizer combination is present (which strengthens the protective power of the stabilizers for the following drug product storage time period).

This sequential application of two stabilizers also reduces the overall thermal stress of those stabilizers as one of them is not present when the complexation reaction, which involves high temperatures, takes place.

Further, particularly the use of two different stabilizers is advantageous as this combination is more efficacious in reacting to the various different radicals possibly formed by the radiolysis of the cell receptor binding molecule than only one single stabilizer can do.

The composition of the radiopharmaceutical solution does not require the presence of ethanol. The solution is sufficiently stable without ethanol. The absence of ethanol is of advantage with respect to the physiological tolerability of the solution.

A shelf-life of at least 3 days is required to allow a radiopharmaceutical drug product to be manufactured from a centralized pharmaceutical production site and to commercialize it as a ready-to-use drug product.

Therefore, due to the high stability (72 h at 25°C) the present invention allows centralized pharmaceutical production at highest quality standards (e.g. cGMP) and at industrial scale, e.g. at 74 GBq or 148 GBq batch size which provides the drug product in numerous dose units, e.g. enough dose units for the treatment of 10 to 20 patients at the same time.

Further, due to the high stability, there is sufficient time for the present invention to be shipped from a centralized pharmaceutical production site to remote clinical centers.

Even further, due to the high stability, the present invention can be provided as a ready-to-use infusion solution which can be immediately administered to the patient without a need for the clinical staff to perform any preparatory work before administration.

The present invention of particular suitability for the somatotatin receptor binding peptides, here in particular for the very sensitive somatostatin analogues octreotide and octreotate which are in particular prone to degradation reactions. Further, the present invention of particular suitability for the radionuclide Lutetium-177 with its specific radioactivity characteristics.

DETAILED DESCRIPTION OF THE INVENTION

Herein after, the present invention is described in further detail and is exemplified.

In general, the present invention is concerned about a pharmaceutical aqueous solution, in particular a radiopharmaceutical aqueous solution. The solution is for intravenous (IV) use/application/administration. The solution is stable, concentrated, and ready-to-use.

The stability of the solution ascertained by the use of stabilizers against radiolytic degradation.

In general, the stabilizers used in accordance with the present inventions may be selected from gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid, vitamin C) or salts thereof (e.g. sodium ascorbate), methionine, histidine, melatonin, ethanol, and Se-methionine. Preferred stabilizers are selected from gentisic acid or salts thereof and ascorbic acid or salts thereof.

Ethanol is considered as less preferred stabilizer due to tolerability issues associated with it if present in higher concentrations. Ethanol should be ideally avoided in the solutions of the present invention (in other words: free of ethanol), 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 foreseen to be injected/infused. Even more preferably, the solution is free of ethanol.

In accordance with the present invention the following embodiments are provided:

1. A pharmaceutical aqueous solution comprising
   (a) a complex formed by
      (ai) a radionuclide, and
      (aii) a cell receptor binding organic moiety linked to a chelating agent; and
   (b) at least one stabilizer against radiolytic degradation;
   wherein

said radionuclide is present in a concentration that it provides a volumetric radioactivity of at least 100 MBq/mL, preferably of at least 250 MBq/mL.

2. The pharmaceutical aqueous solution according to embodiment 1, wherein said stabilizer(s), component (b), is (are) present in a total concentration of at least 0.2 mg/mL, preferably at least 0.5 mg/mL, more preferably at least 1.0 mg/mL, even more preferably at least 2.7 mg/mL.

3. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein said radionuclide is present in a concentration that it provides a volumetric radioactivity of from 100 to 1000 MBq/mL, preferably from 250 to 500 MBq/mL.

4. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein said stabilizer(s) is (are) present in a total concentration of from 0.2 to 20.0 mg/mL, preferably from 0.5 to 10.0 mg/mL, more preferably from 1.0 to 5.0 mg/mL, even more preferably from 2.7 to 4.1 mg/mL.

5. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the component (b) is only one stabilizers against radiolytic degradation, i.e. only a first stabilizer.

6. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the component (b) are at least two stabilizers against radiolytic degradation, i.e. at least a first and a second stabilizer, preferably only two stabilizers, i.e. only a first and a second stabilizer.

7. The pharmaceutical aqueous solution according to any one of the embodiments 5 to 6, wherein the first stabilizer is present in a concentration of from 0.2 to 5 mg/mL, preferably from 0.5 to 5 mg/mL, more preferably from 0.5 to 2 mg/mL, even more preferably from 0.5 to 1 mg/mL, even more preferably from 0.5 to 0.7 mg/mL.

8. The pharmaceutical aqueous solution according to embodiment 6 or 7, wherein the second stabilizer is present in a concentration of from 0.5 to 10 mg/mL, more preferably from 1.0 to 8.0 mg/mL, even more preferably from 2.0 to 5.0 mg/mL, even more preferably from 2.2 to 3.4 mg/mL.

9. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the stabilizer(s) is (are) selected from gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid, vitamin C) or salts thereof (e.g. sodium ascorbate), methionine, histidine, melatonin, ethanol, and Se-methionine, preferably selected from gentisic acid or salts thereof and ascorbic acid or salts thereof.

10. The pharmaceutical aqueous solution according to any one of the embodiments 5 to 9, wherein the first stabilizer is selected from gentisic acid and ascorbic acid, preferably the first stabilizer is gentisic acid.

11. The pharmaceutical aqueous solution according to any one of the embodiments 6 to 10, wherein the second stabilizer is selected from gentisic acid and ascorbic acid, preferably the second stabilizer is ascorbic acid.

12. The pharmaceutical aqueous solution according to any one of the embodiments 6 to 8, wherein the first stabilizer is gentisic acid or a salt thereof and the second stabilizer is ascorbic acid or a salt thereof, and the ratio of the concentration (in mg/mL) of the first stabilizer to the concentration (in mg/mL) of the second stabilizer is from 1:3 to 1:7, preferably from 1:4 to 1:5.

13. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the radionuclide is selected from ^{177}Lu, ^{68}Ga, ^{18}F, ^{99m}Tc, ^{211}At, ^{82}Rb, ^{166}Ho, ^{225}Ac, ^{111}In, ^{123}I, ^{131}I, ^{89}Zr, ^{90}Y, preferably selected from ^{177}Lu and ^{68}Ga, more preferably is ^{177}Lu.

14. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the cell receptor binding moiety is a somatostatin receptor binding peptide, preferably said somatostatin receptor binding peptide is selected from octreotide, octreotate, lanreotide, vapreotide and pasireotide, preferably selected from octreotide and octreotate.

15. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the chelating agent is selected from DOTA, DTPA, NTA, EDTA, DO3A, NOC and NOTA, preferably is DOTA.

16. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the cell receptor binding moiety and the chelating agent form together molecules selected from DOTA-OC, DOTA-TOC (edotreotide), DOTA-NOC, DOTA-TATE (oxodotreotide), DOTA-LAN, and DOTA-VAP, preferably selected from DOTA-TOC and DOTA-TATE, more preferably is DOTA-TATE.

17. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein the radionuclide, the cell receptor binding moiety and the chelating agent form together the complex ^{177}Lu-DOTA-TOC (^{177}Lu-edotreotide) or ^{177}Lu-DOTA-TATE (^{177}Lu-oxodotreotide), preferably ^{177}Lu-DOTA-TATE.

18. The pharmaceutical aqueous solution according to any one of the preceding embodiments, further comprising a buffer, preferably said buffer is an acetate buffer, preferably in an amount to result in a concentration of from 0.3 to 0.7 mg/mL (preferably about 0.48 mg/mL) acetic acid and from 0.4 to 0.9 mg/mL (preferably about 0.66 mg/mL) sodium acetate.

19. The pharmaceutical aqueous solution according to any one of the preceding embodiments, further comprising a sequestering agent, preferably said sequestering agent is diethylentriaminepentaacetic acid (DTPA) or a salt thereof, preferably in an amount to result in a concentration of from 0.01 to 0.10 mg/mL (preferably about 0.05 mg/mL).

20. The pharmaceutical aqueous solution according to any one of the preceding embodiments, which has a shelf life of at least 24 hours (h) at ≤ 25 °C, at least 48 h at ≤ 25 °C, at least 72 h at ≤ 25 °C, of from 24 h to 120 h at ≤ 25 °C, from 24 h to 96 h at ≤ 25 °C, from 24 h to 84 h at ≤ 25 °C, from 24 h to 72 h at ≤ 25 °C, in particular has a shelf life of 72 h at ≤ 25 °C.

21. The pharmaceutical aqueous solution according to any one of the preceding embodiments, wherein said solution is produced at commercial scale manufacturing, in particular is produced at a batch size of at least 20 GBq, at least 50 GBq, or at least 70 GBq.

22a. The pharmaceutical aqueous solution according to any one of the preceding embodiments, which is ready-to-use.

22b. The pharmaceutical aqueous solution according to any one of the preceding embodiments, which is for commercial use.

23. A pharmaceutical aqueous solution, comprising
(a) a complex formed by
(ai) the radionuclide ^{177}Lutetium (Lu-177), present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL , and
(aii) the chelating agent linked somatostatin receptor binging organic moiety DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide);
(bi) gentisic acid or a salt thereof as the first stabilizer against radiolytic degradation present in a concentration of from 0.5 to 1 mg/mL;
(bii) ascorbic acid or a salt thereof as the second stabilizer against radiolytic degradation present in a concentration of from 2.0 to 5.0 mg/mL.

24. The pharmaceutical aqueous solution according to embodiment 23, further comprising:
(c) Diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL.

25. The pharmaceutical aqueous solution according to embodiments 23 or 24, further comprising:
(d) acetic acid in a concentration of from 0.3 to 0.7 mg/mL and sodium acetate in a concentration from 0.4 to 0.9 mg/mL.

26. The pharmaceutical aqueous solution according to any one of the preceding embodiments wherein the stabilizer(s) is (are) present in the solution during the complex formation of components (ai) and (aii).

27. The pharmaceutical aqueous solution according to any one of embodiments 5 to 26 wherein only the first stabilizer is present during the complex formation of components (ai) and (aii), preferably in an amount to result in a concentration of from 0.5 to 5 mg/mL, more preferably from 0.5 to 2 mg/mL, even more preferably from 0.5 to 1 mg/mL, even more preferably from 0.5 to 0.7 mg/mL, in the final solution.

28. The pharmaceutical aqueous solution according to any one of embodiments 6 to 27 wherein a part of the amount of the second stabilizer is already present in the solution during the complex formation of components (ai) and (aii) and another part of the amount of the second stabilizer is added after the complex formation of components (ai) and (aii).

29. The pharmaceutical aqueous solution according to any one of embodiments 6 to 28 wherein the second stabilizer is added after the complex formation of components (ai) and (aii).

30. The pharmaceutical aqueous solution according to embodiment 6 or 29 wherein the second stabilizer is added after the complex formation of components (ai) and (aii), preferably in an amount to result in a concentration of from 0.5 to 10 mg/mL, more preferably from 1.0 to 8.0 mg/mL, even more preferably from 2.0 to 5.0 mg/mL, even more preferably from 2.2 to 3.4 mg/mL, in the final solution.

31. The pharmaceutical aqueous solution according to any one of the preceding embodiments, further comprising a sequestering agent, added after the complex formation

of components (ai) and (aii), for removing any uncomplexed Lu, preferably said sequestering agent is diethylentriaminepentaacetic acid (DTPA) or a salt thereof, preferably in an amount to result in a concentration of from 0.01 to 0.10 mg/mL (preferably about 0.05 mg/mL) in the final solution.

32. A process for manufacturing the pharmaceutical aqueous solution as defined in any one of the preceding embodiments, comprising the process steps:

(1) Forming a complex of the radionuclide and the chelating agent linked cell receptor binding organic moiety by

(1.1) preparing an aqueous solution comprising the radionuclide;

(1.2) preparing an aqueous solution comprising the chelating agent linked cell receptor binding organic moiety, a first stabilizer, optionally a second stabilizer; and

(1.3) mixing the solutions obtained in steps (1.1) and (1.2) and heating the resulting mixture;

(2) Diluting the complex solution obtained by step (1) by

(2.1) preparing an aqueous dilution solution optionally comprising a second stabilizer; and

(2.2.) mixing the complex solution obtained by step (1) with the dilution solution obtained by the step (2.1).

33. The process according to embodiment 32 wherein only the first stabilizer is present during the step (1.3), preferably in an amount to result in a concentration of from 0.5 to 5 mg/mL, more preferably from 0.5 to 2 mg/mL, even more preferably from 0.5 to 1 mg/mL, even more preferably from 0.5 to 0.7 mg/mL, in the final solution.

34. The process according to any one of embodiments 32 to 33 wherein a part of the amount of the second stabilizer is already present in the solution during the step (1.3) and another part of the amount of the second stabilizer is added, after the step (1.3), in step (2.1).

35. The pharmaceutical aqueous solution according to any one of embodiments 32 to 34 wherein the second stabilizer is added, after the step (1.3), in step (2.1).

36. The pharmaceutical aqueous solution according to any one of embodiments 32 to 35 wherein the second stabilizer is added, after the step (1.3), in step (2.1), preferably in an amount to result in a concentration of from 0.5 to 10 mg/mL, more preferably from 1.0 to 8.0 mg/mL, even more preferably from 2.0 to 5.0 mg/mL, even more preferably from 2.2 to 3.4 mg/mL, in the final solution.

37. The process according any one of embodiments 32 to 36, wherein the solution of step (1.2) further comprises a buffer, preferably an acetate buffer.

38. The process according to any one of embodiments 32 to 37, wherein in step (1.3) the resulting mixture is heated to a temperature of from 70 to 99 °C, preferably from 90 to 98 °C, for from 2 to 59 min.

39. The process according to any one of embodiments 32 to 38, wherein the solution of step (2.1) further comprises diethylentriaminepentaacetic acid (DTPA) or a salt thereof.

40. The process according to any one of embodiments 32 to 39, further comprising the process steps:

    (3) Filtering the solution obtained by step (2) through 0.2 µm:

    (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, preferably from 7.0 to 8.0 MBq, more preferably from 7.3 to 7.7 MBq, even more preferably from 7.4-7.5 MBq, preferably said volume is from 10 to 50 mL, more preferably from 15 to 30 mL, even more preferably from 20 to 25 mL.

41. The process according to any one of embodiments 32 to 40, wherein the solution of step (1.1) comprises $LuCl_3$ and HCl.

42. The process according to any one of embodiments 32 to 41, wherein the solution of step (1.2) comprises ^{177}Lu-DOTA-TATE or ^{177}Lu- DOTA-TOC, gentisic acid, acetic acid, and sodium acetate.

43. The process according to any one of embodiments 32 to 42, wherein the solution of step (2.1) comprises DTPA, and ascorbic acid.

44. The process according to any one of embodiments 32 to 43, wherein the dose unit containers in step (4) are stoppered vials, enclosed within a lead container.

45. The pharmaceutical aqueous solution obtained (or obtainable) by the process as defined in any one of the embodiments 32 to 44.

Further embodiments of the present invention are described in the following as "E embodiments":

E1. A pharmaceutical aqueous solution comprising:
(a) a complex formed by
(ai) the radionuclide ^{177}Lu (Lutetium-177), and
(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA; and
(b) at least two different stabilizers against radiolytic degradation;
wherein
said radionuclide is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL; and
said stabilizers are present in a total concentration of from 0.2 to 20.0 mg/mL.

The "complex formed by" may be alternatively worded: "complex of".
The "different" in "two different stabilizers" refers to a difference in the chemical entity of such stabilizers. "Two different stabilizers" has the meaning that the two stabilizers are different chemical entities, e.g. gentisic acid and ascorbic acid are two different stabilizers. "at least two" means two or more, however, preferably that just two stabilizers are present (not three or more). It is further preferred that ethanol is not one of the two stabilizers.

E2. The pharmaceutical aqueous solution according to embodiment E1,
wherein said component (b) comprises the stabilizers:

(bi) gentisic acid or a salt thereof; and

(bii) ascorbic acid or a salt thereof.

E3. The pharmaceutical aqueous solution according to embodiment E2, wherein

(bi) gentisic acid is present in a concentration of from 0.5 to 2 mg/mL, preferably from 0.5 to 1 mg/mL; and

(bii) ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL.

In a particular embodiment the present invention provides:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA; and

(b) the stabilizers against radiolytic degradation

(bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and

(bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL.

E4. The pharmaceutical aqueous solution according to embodiment E3, further comprising:

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL.

E5. The pharmaceutical aqueous solution according to embodiments E3 or E4, further comprising:

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 4.5 to 6.0, preferably from 4.7 to 6.0, more preferably from 5.0 to 6.0, even more preferably from 5.0 to 5.5.

In a particular embodiment the present invention provides:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) at least two stabilizers against radiolytic degradation comprising (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5.

In a particular embodiment the present invention provides:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) stabilizers against radiolytic degradation consisting of (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5.

The herein indicated pH values are the pH values of the final solution. However, it can also be the pH during manufacturing of the solution, e.g. the pH during the complex formation.

E6. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 wherein at least one of the stabilizers is present during the complex formation of components (ai) and (aii) and at least one of the stabilizers is added after the complex formation of components (ai) and (aii).

E7. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 wherein at least gentisic acid is present during the complex formation of components (ai) and (aii) and at least ascorbic acid is added after the complex formation of components (ai) and (aii).

E8. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and the only stabilizer added after the complex formation of components (ai) and (aii) is ascorbic acid.

In a particular embodiment the present invention provides:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA; and

(b) the stabilizers against radiolytic degradation

(bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL (in the final solution) and

(bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL (in the final solution);

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii).

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) at least two stabilizers against radiolytic degradation comprising (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii).

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) stabilizers against radiolytic degradation consisting of (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii).

E9. The pharmaceutical aqueous solution according to any one of the embodiments E6 to E8 wherein that/those stabilizer/stabilizers which is/are present during the complex formation of components (ai) and (aii) is/are present during the complex formulation in a total concentration of from 15 to 50 mg/mL, preferably from 20 to 40 mg/mL.

E10. The pharmaceutical aqueous solution according to embodiment E9 wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formulation in a concentration of from 20 to 40 mg/mL, preferably from 25 to 35 mg/mL.

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) at least two stabilizers against radiolytic degradation comprising (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii); and

wherein the only stabilizer present during the complex formation of components (ai) and

(aii) is gentisic acid and is present during the complex formulation in a concentration of from 20 to 40 mg/mL, preferably from 25 to 35 mg/mL.

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL, and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) stabilizers against radiolytic degradation consisting of (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii); and

wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formulation in a concentration of from 20 to 40 mg/mL, preferably from 25 to 35 mg/mL.

Embodiments E6 to E10 may be alternatively defined by the following wording:

E6. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 produced by having at least one of the stabilizers present during the complex formation of components (ai) and (aii) and at least one of the stabilizers added after the complex formation of components (ai) and (aii).

E7. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 produced by having at least gentisic acid present during the complex formation of components (ai) and (aii) and at least ascorbic acid added after the complex formation of components (ai) and (aii).

E8. The pharmaceutical aqueous solution according to any one of the embodiments E1 to E5 produced by having gentisic acid as the only stabilizer present during the complex formation of components (ai) and (aii) ascorbic acid as the only stabilizer added after the complex formation of components (ai) and (aii).

E9. The pharmaceutical aqueous solution according to any one of the embodiments E6 to E8 produced by having that/those stabilizer/stabilizers present during the complex formation of components (ai) and (aii) present during the complex formation in a total concentration of from 15 to 50 mg/mL, preferably from 20 to 40 mg/mL.

E10. The pharmaceutical aqueous solution according to embodiment E9 produced by having gentisic acid as the only stabilizer present during the complex formation of components (ai) and (aii) and present during the complex formulation in a concentration of from 20 to 40 mg/mL, preferably from 25 to 35 mg/mL.

In the embodiments of the present invention, in particular in embdodiments E9 and E10, the radionuclide may be present during the complex formation in a concentration that it provides a volumetric radioactivity of up to 20 GBq/mL, preferably up to 15 GBq/mL, or from 5 to 20 GBq/mL, preferably from 10 to 20 GBq/mL, more preferably from 10 to 15 GBq/mL.

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (in the final solution), and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) at least two stabilizers against radiolytic degradation comprising (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii); and

wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formulation in a concentration of from 20 to 40 mg/mL;

and wherein the radionuclide is present during the complex formation in a concentration that it provides a volumetric radioactivity of from 10 to 20 GBq/mL.

In a particular embodiment the present invention is defined in the following:

A pharmaceutical aqueous solution comprising:

(a) a complex formed by

(ai) the radionuclide ^{177}Lu (Lutetium-177) in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (in the final solution), and

(aii) a somatostatin receptor binding peptide linked to the chelating agent DOTA;

(b) stabilizers against radiolytic degradation consisting of (bi) gentisic acid in a concentration of from 0.5 to 1 mg/mL and (bii) ascorbic acid in a concentration of from 2.0 to 5.0 mg/mL;

(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL; and

(d) an acetate buffer composed of:

(di) acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and

(dii) sodium acetate in a concentration from 0.4 to 0.9 mg/mL;

preferably said acetate buffer provides for a pH of from 5.0 to 5.5;

wherein gentisic acid is present during the complex formation of components (ai) and (aii) and ascorbic acid added after the complex formation of components (ai) and (aii); and wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formulation in a concentration of from 20 to 40 mg/mL;
and wherein the radionuclide is present during the complex formation in a concentration that it provides a volumetric radioactivity of from 10 to 20 GBq/mL.

E11. The pharmaceutical aqueous solution according to any one of the preceding E embodiments, which has a shelf life of at least 72 h when stored at ≤ 25 °C, in particular at least 72 h when stored at 25 °C.

"Shelf life" has herein its general meaning in the context of pharmaceutical products. The shelf life is the length of time that a pharmaceutical product may be stored while its product characteristics still comply with the product specification as defined during drug development and agreed by health authorities.

E12. The pharmaceutical aqueous solution according to any one of the preceding E embodiments, for which the radiochemical purity (determined by HPLC) is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

E13. The pharmaceutical aqueous solution according to any one of the preceding E embodiments, wherein said solution is produced at commercial manufacturing scale, in particular is produced at a batch size of at least 20 GBq, at least 50 GBq, or at least 70 GBq.

E14. The pharmaceutical aqueous solution according to any one of the preceding embodiments, which is ready-to-use.

E15. A process for manufacturing the pharmaceutical aqueous solution as defined in any one of the preceding E embodiments, comprising the process steps:

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

(1.1) preparing an aqueous solution comprising the radionuclide;

(1.2) preparing an aqueous solution comprising the a somatostatin receptor binding peptide linked to the chelating agent, and at least one stabilizer against radiolytic degradation; and

(1.3) mixing the solutions obtained in steps (1.1) and (1.2) and heating the resulting mixture;

(2) Diluting the complex solution obtained by step (1) by

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

(2.2.) mixing the complex solution obtained by step (1) with the dilution solution obtained by the step (2.1) to obtain the final solution;

wherein if the solution prepared under (1.2) comprises only one stabilizer, then the solution prepared under (2.1) comprise at least one stabilizer.

E16. The process according to embodiment E15 wherein the solution prepared in step (1.2) comprises at least one stabilizer and the solution prepared in step (2.1) comprises at least one stabilizer.

E17. The process according to embodiment E15 wherein the solution prepared in step (1.2) comprises at least the stabilizer gentisic acid and the solution prepared in step (2.1) compries at least the stabilizer ascorbic acid.

E18. The process according to embodiment E15 wherein the solution prepared in step (1.2) comprises only one stabilizer which is gentisic acid and the solution prepared in step (2.1) compries only one stabilizer which is ascorbic acid.

E19. The process according to any one of embodiments E15 to E18 wherein the solution prepared in step (1.2) comprises stabilizer/stabilizers in a total concentration of from 15 to 50 mg/mL, preferably from 20 to 40 mg/mL.

E20. The process according to any one of embodiments E15 to E18 wherein the solution prepared in step (1.2) comprises only one stabilizer which is gentisic acid in a concentration of from 20 to 40 mg/mL, preferably from 25 to 35 mg/mL.

E21. The process according any one of embodiments E15 to E20, wherein the solution of step (1.2) further comprises a buffer, preferably an acetate buffer.

E22. The process according to any one of embodiments E15 to E21, wherein in step (1.3) the resulting mixture is heated to a temperature of from 70 to 99 °C (e.g., between 80-99 °C), preferably from 90 to 98 °C (e.g., 90-95 °C), for from 2 to 59 min (e.g., 2-20 min, 2-15 min, 5-15 min, or 5-12 min) , preferably from 5-15 min or 10 to 15 min.

E23. The process according to any one of embodiments E15 to E22, wherein the solution of step (2.1) further comprises diethylentriaminepentaacetic acid (DTPA) or a salt thereof.

E24. The process according to any one of embodiments E15 to E23, further comprising the process steps:

(3) Filtering the solution obtained by step (2) through 0.2 µm:

(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, preferably from 7.0 to 8.0 MBq, more preferably from 7.3 to 7.7 MBq, even more preferably from 7.4-7.5 MBq, preferably said volume is from 10 to 50 mL, more preferably from 15 to 30 mL, even more preferably from 20 to 25 mL.

E25. The process according to any one of embodiments E15 to E24, wherein the solution of step (1.1) comprises $LuCl_3$ and HCl.

E26. The process according to any one of embodiments E15 to E25, wherein the solution of step (1.2) comprises ^{177}Lu-DOTA-TATE or ^{177}Lu- DOTA-TOC, gentisic acid, acetic acid, and sodium acetate.

E27. The process according to any one of embodiments E15 to E26, wherein the solution of step (2.1) comprises DTPA, and ascorbic acid.

E28. The process according to any one of embodiments E24 to E27, wherein the dose unit containers in step (4) are stoppered vials, enclosed within a lead container.

E29. The pharmaceutical aqueous solution obtained (or: obtainable) by the process as defined by any one of embodiments E15 to E28.

Further embodiments of the present invention are described in the following as "EE embodiments":

EE1. 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 and not the second stabilizer, then the aqueous dilution solution comprises at least one stabilizer 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 mg/mL.

For example, the first stabilizer is gentisic acid or a salt thereof and the second stabilizer, when present, is ascorbic acid or a salt thereof. For example, the at least one stabilizer in the aqueous dilution solution, when present, is ascorbic acid or a salt thereof.

EE2. The process according to embodiment EE 1, comprising the process steps:

(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.

EE3. The process according to embodiment EE1 or EE2, wherein the solution in step (1.2) comprises the first stabilizer and the solution provided in step (2.1) comprises at least one stabilizer.

EE4. The process according to any one of embodiments EE1 to EE3, wherein the solution provided in step (1.2) comprises at least gentisic acid or a salt thereof and the solution provided in step (2.1) compries at least ascorbic acid or a salt thereof.

EE5. The process according to any one of embodiments EE1 to EE4, wherein the solution provided in step (1.2) comprises only one stabilizer which is gentisic acid or a salt thereof and the solution provided in step (2.1) compries only one stabilizer which is ascorbic acid or a salt thereof.

EE6. The process according to any one of embodiments EE1 to EE5, wherein the solution provided in step (1.2) comprises stabilizer/stabilizers in a total concentration of from 15 to 50 mg/mL.

EE7. The process according to any one of embodiments EE1 to EE6, wherein the solution provided in step (1.2) comprises stabilizer/stabilizers in a total concentration of from 20 to 40 mg/mL

EE8. The process according to any one of embodiments EE1 to EE7, wherein the solution provided in step (1.2) comprises only one stabilizer which is gentisic acid in a concentration of from 20 to 40 mg/mL.

EE9. The process according to any one of embodiments EE1 to EE8, wherein the solution provided in step (1.2) comprises only one stabilizer which is gentisic acid in a concentration of from 25 to 35 mg/mL.

EE10. The process according to any one of embodiments EE1 to EE9, wherein the solution provided in step (1.2) further comprises a buffer, e.g., an acetate buffer.

EE11. The process according to any one of embodiments EE1 to EE10, wherein in step (1.3) the resulting mixture is heated to a temperature of from 70 to 99 °C (e.g., between 80-99 °C, 90-98 °C, or between 90-95 °C).

EE12. The process according to any one of embodiments EE1 to EE11, wherein in step (1.3) the resulting mixture is heated from 2 to 59 min (e.g., 2-20 min, 2-15 min, 5-15 min, 5-12 min, 5-15 min or 10 to 15 min).

EE13. The process according to any one of embodiments EE1 to EE12, wherein in step (1.3) the resulting mixture is heated to a temperature of from 90 to 98 °C for from 10 to 15 min.

EE14. The process according to any one of embodiments EE1 to EE13, wherein the solution provided in step (2.1) further comprises diethylentriaminepentaacetic acid (DTPA) or a salt thereof.

EE15. The process according to any one of embodiments EE1 to EE14, 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 about 5 to about 10 MBq (e.g., from about 7 to about 8 MBq, or from 7.3 to 7.7 MBq, or from 7.4-7.5 MBq).

For example, the volume in embodiment EE15 is from about 10 to about 50 mL, e.g., from about 15 to about 30 mL or from about 20 to about 25 mL.

EE16. The process according to any one of embodiments EE1 to EE15, wherein the solution of step (1.1) comprises $LuCl_3$ and HCl.

EE17. The process according to any one of embodiments EE1 to EE16, wherein the solution of step (1.2) comprises ^{177}Lu-DOTA-TATE or ^{177}Lu- DOTA-TOC, gentisic acid, acetic acid, and sodium acetate.

EE18. The process according to any one of embodiments EE1 to EE17, wherein the solution of step (2.1) comprises DTPA and ascorbic acid.

EE19. The process according to any one of embodiments EE15 to EE18, wherein the dose unit containers in step (4) are stoppered vials, enclosed within a lead container.

EE20. The pharmaceutical aqueous solution obtained (or: obtainable) by the process as defined by any one of embodiments EE1 to E19.

EE21. The pharmaceutical aqueous solution according to embodiment EE20, which has a shelf life of at least 72 h when stored at ≤ 25 °C, in particular at least 72 h when stored at 25 °C.

EE22. The pharmaceutical aqueous solution according to embodiment EE20 or EE21, for which the radiochemical purity (determined by HPLC) is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

EE23. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE22, wherein said solution is produced at a batch size of at least 20 GBq, at least 50 GBq, or at least 70 GBq.

EE24. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE23, which is ready to use.

EE25. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE24, free of ethanol.

EE26. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE25, wherein gentisic acid is present in a concentration of from 0.5 to 2 mg/mL, preferably from 0.5 to 1 mg/mL; and ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL.

EE27. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE26, wherein the diethylentriaminepentaacetic acid (DTPA) or a salt thereof is present in a concentration of from 0.01 to 0.10 mg/mL.

EE28. The pharmaceutical aqueous solution according to any one of embodiments EE20 to EE27, wherein the acetate buffer is composed of acetic acid in a concentration of from 0.3 to 0.7 mg/mL; and sodium acetate in a concentration from 0.4 to 0.9 mg/mL; preferably said acetate buffer provides for a pH of from 4.5 to 6.0, preferably from 5.0 to 5.5.

In all the embodiments as described herein, the somatostatin receptor binding peptide linked to the chelating agent DOTA (component (aii)) is preferably DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide), more preferably DOTA-TATE (oxodotreotide).

The present invention further provides the pharmaceutical aqueous solution as defined herein for use in the treatment of neuroendocrine tumors (NET).

Alternatively, the present invention provides a method for the treatment of NET in human patients in need of such treatment which comprises administering an effective amount of the pharmaceutical aqueous solution as defined herein.

As a further alternative the present invention provides the use of pharmaceutical aqueous solution as defined herein for the manufacture/preparation of a medicament for the treatment of NET.

As a further alternative the present invention provides a medicament for the treatment of NET comprising pharmaceutical aqueous solution as defined herein.

Neuroendocrine tumors (NET) which may be treated by the pharmaceutical aqueous solutions as defined here alone or in combinations in accordance with the present invention are selected from the group consisting of gastroenteropancreatic neuroendocrine tumor, carcinoid tumor, pheochromocytoma, paraganglioma, medullary thyroid cancer, pulmonary neuroendocrine tumor, thymic neuroendocrine tumor, a carcinoid tumor or a pancreatic neuroendocrine tumor, pituitary adenoma, adrenal gland tumors, Merkel cell carcinoma, breast cancer, Non-Hodgkin lymphoma, Hodgkin lymphoma, Head & Neck tumor, urothelial carcinoma (bladder), Renal Cell Carcinoma, Hepatocellular Carcinoma, GIST, neuroblastoma, bile duct tumor, cervix tumor, Ewing sarcoma, osteosarcoma, small cell lung cancer (SCLC), prostate cancer, melanoma, meningioma, glioma, medulloblastoma, hemangioblastoma, supratentorial primitive, neuroectodermal tumor, and esthesioneuroblastoma.

Further NET tumors which may be treated by the pharmaceutical aqueous solutions as defined here alone or in combinations in accordance with the present invention may be selected from the group consisting of functional carcinoid tumor, insulinoma, gastrinoma, vasoactive

intestinal peptide (VIP) oma, glucagonoma, serotoninoma, histaminoma, ACTHoma, pheocromocytoma, and somatostatinoma.

The present invention further provides the combination or combination therapy of the complex formed by the radionuclide ^{177}Lu (Lutetium-177), and a somatostatin receptor binding peptide linked to the chelating agent as defined herein, or the combination or combination therapy of the pharmaceutical aqueous solution as defined herein, together with one of more therapeutic agents as outlined in the following:

In certain instances, pharmaceutical aqueous solution of the present invention are combined with other therapeutic agents, such as other anti-cancer agents, anti-allergic agents, anti-nausea agents (or anti-emetics), pain relievers, cytoprotective agents, and combinations thereof.

General Chemotherapeutic agents considered for use in combination therapies include anastrozole (Arimidex®), bicalutamide (Casodex®), bleomycin sulfate (Blenoxane®), busulfan (Myleran®), busulfan injection (Busulfex®), capecitabine (Xeloda®), N4-pentoxycarbonyl-5-deoxy-5-fluorocytidine, carboplatin (Paraplatin®), carmustine (BiCNU®), chlorambucil (Leukeran®), cisplatin (Platinol®), cladribine (Leustatin®), cyclophosphamide (Cytoxan® or Neosar®), cytarabine, cytosine arabinoside (Cytosar-U®), cytarabine liposome injection (DepoCyt®), dacarbazine (DTIC-Dome®), dactinomycin (Actinomycin D, Cosmegan), daunorubicin hydrochloride (Cerubidine®), daunorubicin citrate liposome injection (DaunoXome®), dexamethasone, docetaxel (Taxotere®), doxorubicin hydrochloride (Adriamycin®, Rubex®), etoposide (Vepesid®), fludarabine phosphate (Fludara®), 5-fluorouracil (Adrucil®, Efudex®), flutamide (Eulexin®), tezacitibine, Gemcitabine (difluorodeoxycitidine), hydroxyurea (Hydrea®), Idarubicin (Idamycin®), ifosfamide (IFEX®), irinotecan (Camptosar®), L-asparaginase (ELSPAR®), leucovorin calcium, melphalan (Alkeran®), 6-mercaptopurine (Purinethol®), methotrexate (Folex®), mitoxantrone (Novantrone®), mylotarg, paclitaxel (Taxol®), nab-paclitaxel (Abraxane®), phoenix (Yttrium90/MX-DTPA), pentostatin, polifeprosan 20 with carmustine implant (Gliadel®), tamoxifen citrate (Nolvadex®), teniposide (Vumon®), 6-

thioguanine, thiotepa, tirapazamine (Tirazone®), topotecan hydrochloride for injection (Hycamptin®), vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine (Navelbine®).

Anti-cancer agents of particular interest for combinations with the pharmaceutical aqueous solution of the present invention include:

Tyrosine kinase inhibitors: Erlotinib hydrochloride (Tarceva®); Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech); Sunitinib malate (Sutent®); Bosutinib (4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile, also known as SKI-606, and described in US Patent No. 6,780,996); Dasatinib (Sprycel®); Pazopanib (Votrient®); Sorafenib (Nexavar®); Zactima (ZD6474); and Imatinib or Imatinib mesylate (Gilvec® and Gleevec®).

Vascular Endothelial Growth Factor (VEGF) receptor inhibitors: Bevacizumab (Avastin®), axitinib (Inlyta®); Brivanib alaninate (BMS-582664, (*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Sorafenib (Nexavar®); Pazopanib (Votrient®); Sunitinib malate (Sutent®); Cediranib (AZD2171, CAS 288383-20-1); Vargatef (BIBF1120, CAS 928326-83-4); Foretinib (GSK1363089); Telatinib (BAY57-9352, CAS 332012-40-5); Apatinib (YN968D1, CAS 811803-05-1); Imatinib (Gleevec®); Ponatinib (AP24534, CAS 943319-70-8); Tivozanib (AV951, CAS 475108-18-0); Regorafenib (BAY73-4506, CAS 755037-03-7); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); Brivanib (BMS-540215, CAS 649735-46-6); Vandetanib (Caprelsa® or AZD6474); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); Linfanib (ABT869, CAS 796967-16-3); Cabozantinib (XL184, CAS 849217-68-1); Lestaurtinib (CAS 111358-88-4); N-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS38703, CAS 345627-80-7); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); 4-Methyl-3-[[1-methyl-6-(3-pyridinyl)-1*H*-

pyrazolo[3,4-*d*]pyrimidin-4-yl]amino]-*N*-[3-(trifluoromethyl)phenyl]-benzamide (BHG712, CAS 940310-85-0); . and Aflibercept (Eylea®), sulfatinib, surufatinib.

Platelet-derived Growth Factor (PDGF) receptor inhibitors: Imatinib (Gleevec®); Linifanib (N-[4-(3-amino-1H-indazol-4-yl)phenyl]-N'-(2-fluoro-5-methylphenyl)urea, also known as ABT 869, available from Genentech); Sunitinib malate (Sutent®); Quizartinib (AC220, CAS 950769-58-1); Pazopanib (Votrient®); Axitinib (Inlyta®); Sorafenib (Nexavar®); Vargatef (BIBF1120, CAS 928326-83-4); Telatinib (BAY57-9352, CAS 332012-40-5); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); and Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470).

Fibroblast Growth Factor Receptor (FGFR) Inhibitors: Brivanib alaninate (BMS-582664, (*S*)-((*R*)-1-(4-(4-Fluoro-2-methyl-1*H*-indol-5-yloxy)-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); Vargatef (BIBF1120, CAS 928326-83-4); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-methyl-urea (BGJ398, CAS 872511-34-7); Danusertib (PHA-739358); and N-[2-[[4-(Diethylamino)butyl]amino]-6-(3,5-dimethoxyphenyl)pyrido[2,3-d]pyrimidin-7-yl]-N'-(1,1-dimethylethyl)-urea (PD173074, CAS 219580-11-7). sulfatinib, surufatinib.

Aurora kinase inhibitors: Danusertib (PHA-739358); *N*-[4-[[6-Methoxy-7-[3-(4-morpholinyl)propoxy]-4-quinazolinyl]amino]phenyl]benzamide (ZM447439, CAS 331771-20-1); 4-(2-Amino-4 -methyl-5-thiazolyl)-N-[4-(4-morpholinyl)phenyl]-2-pyrimidinamine (CYC116, CAS 693228-63-6); Tozasertib (VX680 or MK-0457, CAS 639089-54-6); Alisertib (MLN8237); (N-{2-[6-(4-Cyclobutylamino-5-trifluoromethyl-pyrimidine-2-ylamino)-(1S,4R)-1,2,3,4-tetrahydro-1,4-epiazano-naphthalen-9-yl]-2-oxo-ethyl}-acetamide) (PF-03814735); 4-[[9-Chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino]-benzoic acid (MLN8054, CAS 869363-13-3); Cenisertib (R-763); Barasertib (AZD1152); and N-cyclopropyl-N'-[3-[6-(4-morpholinylmethyl)-1H-benzimidazol-2-yl]-1H-pyrazol-4-yl]-urea (AT9283).

Cyclin-Dependent Kinase (CDK) inhibitors: Aloisine A; Alvocidib (also known as flavopiridol or HMR-1275, 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone, and described in US Patent No. 5,621,002); Crizotinib (PF-02341066, CAS 877399-52-5); 2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(2*R*,3*S*)-2-(hydroxymethyl)-1-methyl-3-pyrrolidinyl]- 4*H*-1-benzopyran-4-one, hydrochloride (P276-00, CAS 920113-03-7); Indisulam

(E7070); Roscovitine (CYC202); 6-Acetyl-8-cyclopentyl-5-methyl-2-(5-piperazin-1-yl-pyridin-2-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one, hydrochloride (PD0332991); Dinaciclib (SCH727965); N-[5-[[(5-*tert*-Butyloxazol-2-yl)methyl]thio]thiazol-2-yl]piperidine-4-carboxamide (BMS 387032, CAS 345627-80-7); 4-[[9-Chloro-7-(2,6-difluorophenyl)-5*H*-pyrimido[5,4-*d*][2]benzazepin-2-yl]amino]-benzoic acid (MLN8054, CAS 869363-13-3); 5-[3-(4,6-Difluoro-1H-benzimidazol-2-yl)-1H-indazol-5-yl]-N-ethyl-4-methyl-3-pyridinemethanamine (AG-024322, CAS 837364-57-5); 4-(2,6-Dichlorobenzoylamino)-1H-pyrazole-3-carboxylic acid N-(piperidin-4-yl)amide (AT7519, CAS 844442-38-2); 4-[2-Methyl-1-(1-methylethyl)-1*H*-imidazol-5-yl]-*N*-[4-(methylsulfonyl)phenyl]- 2-pyrimidinamine (AZD5438,CAS 602306-29-6); Palbociclib (PD-0332991); and (2R,3R)-3-[[2-[[3-[[S(R)]-S-cyclopropylsulfonimidoyl]-phenyl]amino]-5-(trifluoromethyl)-4-pyrimidinyl]oxy]-2-butanol (BAY 10000394), ribociclib.

Checkpoint Kinase (CHK) inhibitors: 7-Hydroxystaurosporine (UCN-01); 6-Bromo-3-(1-methyl-1*H*-pyrazol-4-yl)-5-(3*R*)-3-piperidinyl-pyrazolo[1,5-*a*]pyrimidin-7-amine (SCH900776, CAS 891494-63-6); 5-(3-Fluorophenyl)-3-ureidothiophene-2-carboxylic acid N-[(S)-piperidin-3-yl]amide (AZD7762, CAS 860352-01-8); 4-[((3S)-1-Azabicyclo[2.2.2]oct-3-yl)amino]-3-(1H-benzimidazol-2-yl)-6-chloroquinolin-2(1H)-one (CHIR 124, CAS 405168-58-3); 7-Aminodactinomycin (7-AAD), Isogranulatimide, debromohymenialdisine; N-[5-Bromo-4-methyl-2-[(2S)-2-morpholinylmethoxy]-phenyl]-N'-(5-methyl-2-pyrazinyl)urea (LY2603618, CAS 911222-45-2); Sulforaphane (CAS 4478-93-7, 4-Methylsulfinylbutyl isothiocyanate); 9,10,11,12-Tetrahydro- 9,12-epoxy-1*H*-diindolo[1,2,3-*fg*:3',2',1'-*kl*]pyrrolo[3,4-*i*][1,6]benzodiazocine-1,3(2*H*)-dione (SB-218078, CAS 135897-06-2); and TAT-S216A (YGRKKRRQRRRLYRSPAMPENL), and CBP501 ((d-Bpa)sws(d-Phe-F5)(d-Cha)rrrqrr); and (αR)-α-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1H-pyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-Cyclohexaneacetamide (PF-0477736).

3-Phosphoinositide-dependent kinase-1 (PDK1 or PDPK1) inhibitors: 7-2-Amino-*N*-[4-[5-(2-phenanthrenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]phenyl]-acetamide (OSU-03012, CAS 742112-33-0); Pyrrolidine-1-carboxylic acid (3-{5-bromo-4-[2-(1H-imidazol-4-yl)-ethylamino]-pyrimidin-2-ylamino}-phenyl)-amide (BX912, CAS 702674-56-4); and 4-Dodecyl-*N*-1,3,4-thiadiazol-2-yl-benzenesulfonamide (PHT-427, CAS 1191951-57-1).

Protein Kinase C (PKC) activators: Bryostatin I (bryo-1) and Sotrastaurin (AEB071).

B-RAF inhibitors: Regorafenib (BAY73-4506, CAS 755037-03-7); Tuvizanib (AV951, CAS 475108-18-0); Vemurafenib (Zelboraf®, PLX-4032, CAS 918504-65-1); 5-[1-(2-Hydroxyethyl)-

3-(pyridin-4-yl)-1H-pyrazol-4-yl]-2,3-dihydroinden-1-one oxime (GDC-0879, CAS 905281-76-7); 5-[2-[4-[2-(Dimethylamino)ethoxy]phenyl]-5-(4-pyridinyl)-1*H*-imidazol-4-yl]-2,3-dihydro-1*H*-Inden-1-one oxime (GSK2118436 or SB590885); (+/-)-Methyl (5-(2-(5-chloro-2-methylphenyl)-1-hydroxy-3-oxo-2,3-dihydro-1H-isoindol-1-yl)-1H-benzimidazol-2-yl)carbamate (also known as XL-281 and BMS908662) and N-(3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (also known as PLX4720).

C-RAF Inhibitors: Sorafenib (Nexavar®); 3-(Dimethylamino)-*N*-[3-[(4-hydroxybenzoyl)amino]-4-methylphenyl]-benzamide (ZM336372, CAS 208260-29-1); and 3-(1-cyano-1-methylethyl)-*N*-[3-[(3,4-dihydro-3-methyl-4-oxo-6-quinazolinyl)amino]-4-methylphenyl]-benzamide (AZ628, CAS 1007871-84-2).

Human Granulocyte colony-stimulating factor (G-CSF) modulators: Filgrastim (Neupogen®); Sunitinib malate (Sutent®); Pegilgrastim (Neulasta®) and Quizartinib (AC220, CAS 950769-58-1).

RET Inhibitors: Sunitinib malate (Sutent®); Vandetanib (Caprelsa®); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Sorafenib (BAY 43-9006); Regorafenib (BAY73-4506, CAS 755037-03-7); and Danusertib (PHA-739358).

FMS-like Tyrosine kinase 3 (FLT3) Inhibitors or CD135: Sunitinib malate (Sutent®); Quizartinib (AC220, CAS 950769-58-1); *N*-[(1-Methyl-4-piperidinyl)methyl]-3-[3-(trifluoromethoxy)phenyl]- Imidazo[1,2-*b*]pyridazin-6-amine sulfate (SGI-1776, CAS 1173928-26-1); and Vargatef (BIBF1120, CAS 928326-83-4).

c-KIT Inhibitors: Pazopanib (Votrient®); Dovitinib dilactic acid (TKI258, CAS 852433-84-2); Motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide, described in PCT Publication No. WO 02/066470); Masitinib (Masivet®); Regorafenib (BAY73-4506, CAS 755037-03-7); Tivozanib (AV951, CAS 475108-18-0); Vatalanib dihydrochloride (PTK787, CAS 212141-51-0); Telatinib (BAY57-9352, CAS 332012-40-5); Foretinib (GSK1363089, formerly XL880, CAS 849217-64-7); Sunitinib malate (Sutent®); Quizartinib (AC220, CAS 950769-58-1); Axitinib (Inlyta®); Dasatinib (BMS-345825); and Sorafenib (Nexavar®).

Bcr/Abl kinase inhibitors: Imatinib (Gleevec®); Inilotinib hydrochloride; Nilotinib (Tasigna®); Dasatinib (BMS-345825); Bosutinib (SKI-606); Ponatinib (AP24534); Bafetinib (INNO406);

Danusertib (PHA-739358), AT9283 (CAS 1133385-83-7); Saracatinib (AZD0530); and *N*-[2-[(1*S*,4*R*)-6-[[4-(Cyclobutylamino)-5-(trifluoromethyl)-2-pyrimidinyl]amino]-1,2,3,4-tetrahydronaphthalen-1,4-imin-9-yl]-2-oxoethyl]-acetamide (PF-03814735, CAS 942487-16-3).

IGF-1R inhibitors: Linsitnib (OSI-906); [7-[*trans*-3-[(Azetidin-1-yl)methyl]cyclobutyl]-5-(3-benzyloxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine (AEW541, CAS 475488-34-7); [5-(3-Benzyloxyphenyl)-7-[*trans*-3-[(pyrrolidin-1-yl)methyl]cyclobutyl]-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine (ADW742 or GSK552602A, CAS 475488-23-4); (2-[[3-Bromo-5-(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-propanedinitrile (Tyrphostin AG1024, CAS 65678-07-1); 4-[[(2*S*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-3-[7-methyl-5-(4-morpholinyl)-1*H*-benzimidazol-2-yl]-2(1*H*)-pyridinone (BMS536924, CAS 468740-43-4); 4-[2-[4-[[(2*S*)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-1,2-dihydro-2-oxo-3-pyridinyl]-7-methyl-1*H*-benzimidazol-5-yl]- 1-piperazinepropanenitrile (BMS554417, CAS 468741-42-6); (2*S*)-1-[4-[(5-Cyclopropyl-1*H*-pyrazol-3-yl)amino]pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-*N*-(6-fluoro-3-pyridinyl)-2-methyl-2-pyrrolidinecarboxamide (BMS754807, CAS 1001350-96-4); Picropodophyllotoxin (AXL1717); and Nordihydroguareacetic acid.

IGF-1R antibodies: Figitumumab (CP751871); Cixutumumab (IMC-A12); Ganitumab (AMG-479); Robatumumab (SCH-717454); Dalotuzumab (MK0646); R1507 (available from Roche); BIIB022 (available from Biogen); and MEDI-573 (available from MedImmune).

MET inhibitors: Cabozantinib (XL184, CAS 849217-68-1); Foretinib (GSK1363089, formerly XL880, CAS 849217-64-7); Tivantinib (ARQ197, CAS 1000873-98-2); 1-(2-Hydroxy-2-methylpropyl)-*N*-(5-(7-methoxyquinolin-4-yloxy)pyridin-2-yl)-5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxamide (AMG 458); Cryzotinib (Xalkori®, PF-02341066); (3Z)-5-(2,3-Dihydro-1H-indol-1-ylsulfonyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-1,3-dihydro-2H-indol-2-one (SU11271); (3Z)-N-(3-Chlorophenyl)-3-({3,5-dimethyl-4-[(4-methylpiperazin-1-yl)carbonyl]-1H-pyrrol-2-yl}methylene)-N-methyl-2-oxoindoline-5-sulfonamide (SU11274); (3Z)-N-(3-Chlorophenyl)-3-{[3,5-dimethyl-4-(3-morpholin-4-ylpropyl)-1H-pyrrol-2-yl]methylene}-N-methyl-2-oxoindoline-5-sulfonamide (SU11606); 6-[Difluoro[6-(1-methyl-1H-pyrazol-4-yl)-1,2,4-triazolo[4,3-b]pyridazin-3-yl]methyl]-quinoline (JNJ38877605, CAS 943540-75-8); 2-[4-[1-(Quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl]-1H-pyrazol-1-yl]ethanol (PF04217903, CAS 956905-27-4); N-((2R)-1,4-Dioxan-2-ylmethyl)-N-methyl-N'-[3-(1-methyl-1H-pyrazol-4-yl)-5-oxo-5H-benzo[4,5]cyclohepta[1,2-b]pyridin-7-yl]sulfamide

(MK2461, CAS 917879-39-1); 6-[[6-(1-Methyl-1*H*-pyrazol-4-yl)-1,2,4-triazolo[4,3-*b*]pyridazin-3-yl]thio]-quinoline (SGX523, CAS 1022150-57-7); and (3*Z*)-5-[[(2,6-Dichlorophenyl)methyl]sulfonyl]-3-[[3,5-dimethyl-4-[[(2*R*)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-1*H*-pyrrol-2-yl]methylene]-1,3-dihydro-2*H*-indol-2-one (PHA665752, CAS 477575-56-7).

Epidermal growth factor receptor (EGFR) inhibitors: Erlotinib hydrochloride (Tarceva®), Gefitnib (Iressa®); N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3"S")-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamide, Tovok®); Vandetanib (Caprelsa®); Lapatinib (Tykerb®); (3R,4R)-4-Amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); Canertinib dihydrochloride (CI-1033); 6-[4-[(4-Ethyl-1-piperazinyl)methyl]phenyl]-*N*-[(1*R*)-1-phenylethyl]- 7*H*-Pyrrolo[2,3-*d*]pyrimidin-4-amine (AEE788, CAS 497839-62-0); Mubritinib (TAK165); Pelitinib (EKB569); Afatinib (BIBW2992); Neratinib (HKI-272); *N*-[4-[[1-[(3-Fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester (BMS599626); *N*-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[*c*]pyrrol-5-yl]methoxy]- 4-quinazolinamine (XL647, CAS 781613-23-8); and 4-[4-[[(1*R*)-1-Phenylethyl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidin-6-yl]-phenol (PKI166, CAS 187724-61-4).

EGFR antibodies: Cetuximab (Erbitux®); Panitumumab (Vectibix®); Matuzumab (EMD-72000); Trastuzumab (Herceptin®); Nimotuzumab (hR3); Zalutumumab; TheraCIM h-R3; MDX0447 (CAS 339151-96-1); and ch806 (mAb-806, CAS 946414-09-1).

mTOR inhibitors: Temsirolimus (Torisel®); Ridaforolimus (formally known as deferolimus, (1*R*,2*R*,4*S*)-4-[(2*R*)-2 [(1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*, 23*S*,24*E*,26*E*,28*Z*,30*S*,32*S*,35*R*)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23, 29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$] hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate, also known as AP23573 and MK8669, and described in PCT Publication No. WO 03/064383); Everolimus (Afinitor® or RAD001); Rapamycin (AY22989, Sirolimus®); Simapimod (CAS 164301-51-3); (5-{2,4-Bis[(3*S*)-3-methylmorpholin-4-yl]pyrido[2,3-*d*]pyrimidin-7-yl}-2-methoxyphenyl)methanol (AZD8055); 2-Amino-8-[*trans*-4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxy-3-pyridinyl)-4-methyl-pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (PF04691502, CAS 1013101-36-4); N^2-[1,4-dioxo-4-[[4-(4-oxo-8-phenyl-4*H*-1-benzopyran-2-yl)morpholinium-4-yl]methoxy]butyl]-L-arginylglycyl-L-α-aspartylL-serine-, inner salt (SF1126, CAS 936487-67-1); and N-[4-[[[3-[(3,5-dimethoxyphenyl)amino]-2-

quinoxalinyl]amino]sulfonyl]phenyl]-3-methoxy-4-methyl-benzamide (XL765, also known as SAR245409); and (1r,4r)-4-(4-amino-5-(7-methoxy-1H-indol-2-yl)imidazo[1,5-f][1,2,4]triazin-7-yl)cyclohexanecarboxylic acid (OSI-027).

Mitogen-activated protein kinase (*MEK) inhibitors:* XL-518 (also known as GDC-0973, Cas No. 1029872-29-4, available from ACC Corp.); Selumetinib (5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide, also known as AZD6244 or ARRY 142886, described in PCT Publication No. WO2003077914); 2-[(2-Chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluoro-benzamide (also known as CI-1040 or PD184352 and described in PCT Publication No. WO2000035436); N-[(2R)-2,3-Dihydroxypropoxy]-3,4-difluoro-2-[(2-fluoro-4-iodophenyl)amino]- benzamide (also known as PD0325901 and described in PCT Publication No. WO2002006213); 2,3-Bis[amino[(2-aminophenyl)thio]methylene]-butanedinitrile (also known as U0126 and described in US Patent No. 2,779,780); N-[3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-6-methoxyphenyl]-1-[(2R)-2,3-dihydroxypropyl]- cyclopropanesulfonamide (also known as RDEA119 or BAY869766 and described in PCT Publication No. WO2007014011); (3S,4R,5Z,8S,9S,11E)-14-(Ethylamino)-8,9,16-trihydroxy-3,4-dimethyl-3,4,9, 19-tetrahydro-1H-2-benzoxacyclotetradecine-1,7(8H)-dione] (also known as E6201 and described in PCT Publication No. WO2003076424); 2'-Amino-3'-methoxyflavone (also known as PD98059 available from Biaffin GmbH & Co., KG, Germany); Vemurafenib (PLX-4032, CAS 918504-65-1); (R)-3-(2,3-Dihydroxypropyl)-6-fluoro-5-(2-fluoro-4-iodophenylamino)-8-methylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (TAK-733, CAS 1035555-63-5); Pimasertib (AS-703026, CAS 1204531-26-9); Trametinib dimethyl sulfoxide (GSK-1120212, CAS 1204531-25-80); 2-(2-Fluoro-4-iodophenylamino)-N-(2-hydroxyethoxy)-1,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (AZD 8330); and 3,4-Difluoro-2-[(2-fluoro-4-iodophenyl)amino]-N-(2-hydroxyethoxy)-5-[(3-oxo-[1,2]oxazinan-2-yl) methyl]benzamide (CH 4987655 or Ro 4987655).

Alkylating agents: Oxaliplatin (Eloxatin®); Temozolomide (Temodar® and Temodal®); Dactinomycin (also known as actinomycin-D, Cosmegen®); Melphalan (also known as L-PAM, L-sarcolysin, and phenylalanine mustard, Alkeran®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Carmustine (BiCNU®); Bendamustine (Treanda®); Busulfan (Busulfex® and Myleran®); Carboplatin (Paraplatin®); Lomustine (also known as CCNU, CeeNU®); Cisplatin (also known as CDDP, Platinol® and Platinol®-AQ); Chlorambucil (Leukeran®); Cyclophosphamide (Cytoxan® and Neosar®); Dacarbazine (also known as DTIC,

DIC and imidazole carboxamide, DTIC-Dome®); Altretamine (also known as hexamethylmelamine (HMM), Hexalen®); Ifosfamide (Ifex®); Prednumustine; Procarbazine (Matulane®); Mechlorethamine (also known as nitrogen mustard, mustine and mechloroethamine hydrochloride, Mustargen®); Streptozocin (Zanosar®); Thiotepa (also known as thiophosphoamide, TESPA and TSPA, Thioplex®); Cyclophosphamide (Endoxan®, Cytoxan®, Neosar®, Procytox®, Revimmune®); and Bendamustine HCl (Treanda®).

Aromatase inhibitors: Exemestane (Aromasin®); Letrozole (Femara®); and Anastrozole (Arimidex®).

Topoisomerase I inhibitors: Irinotecan (Camptosar®); Topotecan hydrochloride (Hycamtin®); and 7-Ethyl-10-hydroxycampothecin (SN38).

Topoisomerase II inhibitors: Etoposide (VP-16 and Etoposide phosphate, Toposar®, VePesid® and Etopophos®); Teniposide (VM-26, Vumon®); and Tafluposide .

DNA Synthesis inhibitors: Capecitabine (Xeloda®); Gemcitabine hydrochloride (Gemzar®); Nelarabine ((2*R*,3*S*,4*R*,5*R*)-2-(2-amino-6-methoxy-purin-9-yl)-5-(hydroxymethyl)oxolane-3,4-diol, Arranon® and Atriance®); and Sapacitabine (1-(2-cyano-2-deoxy-β-D-arabinofuranosyl)-4-(palmitoylamino)pyrimidin-2(1*H*)-one).

Folate Antagonists or Antifolates: Trimetrexate glucuronate (Neutrexin®); Piritrexim isethionate (BW201U); Pemetrexed (LY231514); Raltitrexed (Tomudex®); and Methotrexate (Rheumatrex®, Trexal®).

Immunomodulators: Afutuzumab (available from Roche®); Pegfilgrastim (Neulasta®); Lenalidomide (CC-5013, Revlimid®); Thalidomide (Thalomid®), Actimid (CC4047); and IRX-2 (mixture of human cytokines including interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

G-Protein-coupled Somatostain receptors Inhibitors: Octreotide (also known as octreotide acetate, Sandostatin® and Sandostatin LAR®); Lanreotide acetate (CAS 127984-74-1); Seglitide (MK678); Vapreotide acetate (Sanvar®); and Cyclo(D-Trp-Lys-Abu-Phe-MeAla-Tyr)(BIM23027).

Interleukin-11 and Synthetic Interleukin-11 (IL-11): Oprelvekin (Neumega®).

Erythropoietin and Synthetic erythropoietin: Erythropoietin (Epogen® and Procrit®); Darbepoetin alfa (Aranesp®); Peginesatide (Hematide®); and EPO covalently linked to polyethylene glycol (Micera®).

Histone deacetylase (HDAC) inhibitors: Voninostat (Zolinza®); Romidepsin (Istodax®); Treichostatin A (TSA); Oxamflatin; Vorinostat (Zolinza®, Suberoylanilide hydroxamic acid); Pyroxamide (syberoyl-3-aminopyridineamide hydroxamic acid); Trapoxin A (RF-1023A); Trapoxin B (RF-10238); Cyclo[(α*S*,2*S*)-α-amino-η-oxo-2-oxiraneoctanoyl-*O*-methyl-D-tyrosyl-L-isoleucyl-L-prolyl] (Cyl-1); Cyclo[(α*S*,2*S*)-α-amino-η-oxo-2-oxiraneoctanoyl-*O*-methyl-D-tyrosyl-L-isoleucyl-(2*S*)-2-piperidinecarbonyl] (Cyl-2); Cyclic[L-alanyl-D-alanyl-(2S)-η-oxo-L-α-aminooxiraneoctanoyl-D-prolyl] (HC-toxin); Cyclo[(α*S*,2*S*)-α-amino-η-oxo-2-oxiraneoctanoyl-D-phenylalanyl-L-leucyl-(2*S*)-2-piperidinecarbonyl] (WF-3161); Chlamydocin ((S)-Cyclic(2-methylalanyl-L-phenylalanyl-D-prolyl-η-oxo-L-α-aminooxiraneoctanoyl); Apicidin (Cyclo(8-oxo-L-2-aminodecanoyl-1-methoxy-L-tryptophyl-L-isoleucyl-D-2-piperidinecarbonyl); Romidepsin (Istodax®, FR-901228); 4-Phenylbutyrate; Spiruchostatin A; Mylproin (Valproic acid); Entinostat (MS-275, N-(2-Aminophenyl)-4-[N-(pyridine-3-yl-methoxycarbonyl)-amino-methyl]-benzamide); and Depudecin (4,5:8,9-dianhydro-1,2,6,7,11-pentadeoxy- D-*threo*-D-*ido*-Undeca-1,6-dienitol).

Biologic response modifiers: Include therapeutics such as interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines (therapeutic and prophylactic), gene therapy, and nonspecific immunomodulating agents. Interferon alpha (Intron®, Roferson®-A); Interferon beta; Interferon gamma; Interleukin-2 (IL-2 or aldesleukin, Proleukin®); Filgrastim (Neupogen®); Sargramostim (Leukine®); Erythropoietin (epoetin); Interleukin-11 (oprelvekin); Imiquimod (Aldara®); Lenalidomide (Revlimid®); Rituximab (Rituxan®); Trastuzumab (Herceptin®); Bacillus calmette-guerin (theraCys® and TICE® BCG); Levamisole (Ergamisol®); and Denileukin diftitox (Ontak®).

Plant Alkaloids: Paclitaxel (Taxol and Onxal™); Paclitaxel protein-bound (Abraxane®); Vinblastine (also known as vinblastine sulfate, vincaleukoblastine and VLB, Alkaban-AQ® and Velban®); Vincristine (also known as vincristine sulfate, LCR, and VCR, Oncovin® and Vincasar Pfs®); and Vinorelbine (Navelbine®).

Taxane anti-neoplastic agents: Paclitaxel (Taxol®); Docetaxel (Taxotere®); Cabazitaxel (Jevtana®, 1-hydroxy-7β,10β-dimethoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl-4-acetate-2-benzoate-13-[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate); and Larotaxel ((2α,3ξ,4α,5β,7α,10β,13α)-4,10-bis(acetyloxy)-13-({(2*R*,3*S*)-3- [(*tert*-butoxycarbonyl) amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1- hydroxy-9-oxo-5,20-epoxy-7,19-cyclotax-11-en-2-yl benzoate).

Heat Shock Protein (HSP) inhibitors: Tanespimycin (17-allylamino-17-demethoxygeldanamycin, also known as KOS-953 and 17-AAG, available from SIGMA, and described in US Patent No. 4,261,989); Retaspimycin (IPI504), Ganetespib (STA-9090); [6-Chloro-9-(4-methoxy-3,5-dimethylpyridin-2-ylmethyl)-9H-purin-2-yl]amine (BIIB021 or CNF2024, CAS 848695-25-0); *trans*-4-[[2-(Aminocarbonyl)-5-[4,5,6,7-tetrahydro-6,6-dimethyl-4-oxo-3-(trifluoromethyl)-1*H*-indazol-1-yl]phenyl]amino]cyclohexyl glycine ester (SNX5422 or PF04929113, CAS 908115-27-5); and 17-Dimethylaminoethylamino-17-demethoxygeldanamycin (17-DMAG).

Thrombopoietin (TpoR) agonists: Eltrombopag (SB497115, Promacta® and Revolade®); and Romiplostim (Nplate®).

Demethylating agents: 5-Azacitidine (Vidaza®); and Decitabine (Dacogen®).

Cytokines: Interleukin-2 (also known as aldesleukin and IL-2, Proleukin®); Interleukin-11 (also known as oprevelkin, Neumega®); and Alpha interferon alfa (also known as IFN-alpha, Intron® A, and Roferon-A®).

17 α-hydroxylase/C17,20 lyase (CYP17A1) inhibitors: Abiraterone acetate (Zyitga®).

Miscellaneous cytotoxic agents: Arsenic trioxide (Trisenox®); Asparaginase (also known as L-asparaginase, Erwinia L-asparaginase, Elspar® and Kidrolase®); and Asparaginase Erwinia Chrysanthemi (Erwinaze®).

C-C Chemokine receptor 4 (CCR4) Antibody: Mogamulizumab (Potelligent®)

CD20 antibodies: Rituximab (Riuxan® and MabThera®); and Tositumomab (Bexxar®); and Ofatumumab (Arzerra®).

CD20 Antibody Drug Conjugates: Ibritumomab tiuxetan (Zevalin®); and Tositumomab,

CD22 Antibody Drug Conjugates: Inotuzumab ozogamicin (also referred to as CMC-544 and WAY-207294, available from Hangzhou Sage Chemical Co., Ltd.)

CD30 mAb-cytotoxin Conjugates: Brentuximab vedotin (Adcetrix®);

CD33 Antibody Drug Conjugates: Gemtuzumab ozogamicin (Mylotarg®),

CD40 antibodies: Dacetuzumab (also known as SGN-40 or huS2C6, available from Seattle Genetics, Inc),

CD52 antibodies: Alemtuzumab (Campath®),

Anti-CS1 antibodies: Elotuzumab (HuLuc63, CAS No. 915296-00-3)

CTLA-4 inhibitor antibodies: Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9).

TPH inhibitors: telotristat

PARP (poly ADP ribose polymerase) inhibitors: olaparib (Lynparza), rucaparib (Rubraca), Niraparib (Zeluja), Talazoparib, Veliparib.

PD-1 Inhibitors : Spartalizumab (PDR001, Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech), MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesaro), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune).

PD-L1 inhibitors: Durvalumab, Atezolizumab, Avelumab

In particular, the present invention provides the combination or combination therapy of the complex formed by the radionuclide ^{177}Lu (Lutetium-177), and a somatostatin receptor binding peptide linked to the chelating agent as defined herein, or the combination or combination therapy of the pharmaceutical aqueous solution as defined herein, together with one of more therapeutic agents selected from the group consisting of octreotide, lanreotide, vaproreotide, pasireotide, satoreotide, everolimus, temozolomide, telotristat, sunitinib, sulfatinib, ribociclib, entinostat, and pazopanib. In particular embodiments, those combinations are for use in the treatment of NET tumors, e.g. GEP-NET, pulmonary NET, pNET, lung NET, Carcinoid syndrome, SCLC. In particular embodiments, the invention provides a method of treating a patient with NET tumors, e.g. GEP-NET, pulmonary NET, pNET, lung NET, Carcinoid syndrome, SCLC, by administering a therapeutically effective amount of the components of those combinations.

In particular embodiments, the present invention provides the combination or combination therapy of the complex formed by the radionuclide ^{177}Lu (Lutetium-177), and a somatostatin receptor binding peptide linked to the chelating agent as defined herein, or the combination or combination therapy of the pharmaceutical aqueous solution as defined herein, together with one of more immuno-oncology therapeutic agents selected from the group consisting of PD-1, PD-L1 and CTLA-4 inhibitors, in particular the I-O therapeutic agents selected from Spartalizumab, Nivolumab, Pembrolizumab, Pidilizumab, Durvalumab, Atezolizumab, Avelumab,

Ipilimumab, and Tremelimumab. In particular embodiments, those combinations are for use in the treatment of NET tumors, e.g. GEP-NET, pulmonary NET, pNET, lung NET, Carcinoid syndrome, SCLC. In particular embodiments, the invention provides a method of treating a patient with NET tumors, e.g. GEP-NET, pulmonary NET, pNET, lung NET, Carcinoid syndrome, SCLC, by administering a therapeutically effective amount of the components of those combinations.

DEFINITIONS

In the following, terms as used herein are defined in their meaning.

The use of the articles "a", "an", and "the" in both the description and claims are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising", "having", "being of" as in e.g., a complex "of a radionuclide and a cell receptor binding organic moiety linked to a chelating agent", "including", and "containing" are to be construed as open terms (i.e., meaning "including but not limited to") unless otherwise noted. Additionally, whenever "comprising" or another open-ended term is used in an embodiment, it is to be understood that the same embodiment can be more narrowly claimed using the intermediate term "consisting essentially of" or the closed term "consisting of".

The term "about" or "ca." has herein the meaning that the following value may vary for ± 20%, preferably ± 10%, more preferably ± 5%, even more preferably ± 2%, even more preferably ± 1%.

Unless otherwise defined, "%" has herein the meaning of weight percent (wt%), also refered to as weight by weight percent (w/w%).

"total concentration": sum of one or more individual concentrations.

"aqueous solution": a solution of one or more solute in water.

"complex formed by

(ai) a radionuclide, and

(aii) a cell receptor binding organic moiety linked to a chelating agent":

The radionuclide metal ion is forming a non-covalent bond with the functional groups of the chelating agent, e.g. amines or carboxylic acids. The chelating agent has at least two such complexing functional groups to be able to form a chelate complex.

The chelating agent in the context of the present invention may be
DOTA: 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid,
DTPA: Diethylentriaminepentaacetic acid,
NTA: Nitrilotriacetic acid,
EDTA: Ethylenediaminetetraacetic acid,
DO3A: 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid,
NOTA: 1,4,7-Triazacyclononane-1,4,7-triacetic acid,
Trizoxetan,
Tetraxetan
or mixtures thereof, preferably is DOTA.

"cell receptor binding moiety": a chemical molecule which binds with at least part of its molecule to a receptor molecule at the surface of a cell. A cell receptor binding moiety,for which the present invention is in particular suitable, is a somatostatin receptor binding peptide, preferably said somatostatin receptor binding peptide is selected from octreotide, octreotate, lanreotide, vapreotide, pasireotide, ilatreotide, pentetreotide, depreotide, satoreotide, veldoreotide, preferably selected from octreotide and octreotate.

"linked": the cell receptor binding organic moiety is either directly linked to the chelating agent or connected via a linker molecule, preferably it is directly linked. The linking bond(s) is (are) either covalent or non-covalent bond(s) between the cell receptor binding organic moiety (and the linker) and the chelating agent, preferably the bond(s) is (are) covalent.

"Stabilizer against radiolytic degradation": stabilizing agent which protects organic molecules against radiolytic degradation, e.g. when a gamma ray emitted from the radionuclide is cleaving a bond between the atoms of an organic molecules and radicals are formed,

those radicals are then scavenged by the stabilizer which avoids the radicals undergoing any other chemical reactions which might lead to undesired, potentially ineffective or even toxic molecules. Therefore, those stabilizers are also referred to as "free radical scavengers" or in short "radical scavengers". Other alternative terms for those stabilizers are "radiation stability enhancers", "radiolytic stabilizers", or simply "quenchers".

"stabilizer(s) is (are) present in the solution during the complex formation of components (ai) and (aii)": first stabilizer present and optionally also second stabilizer present, i.e. either first stabilizer alone or in combination with second stabilizer present

"present during the complex formation": stabilizer(s) are in either the radionuclide solution or in the chelating agent containing solution before those two solutions are added and potentially elevated temperatures are applied to facilitate the complex formation. Preferably the stabilizer(s) are in the chelating agent containing solution.

"only the first stabilizer is present during the complex formation of components (ai) and (aii)": the first stabilizer is present, the second is not present. In other words only one stabilizer is present.

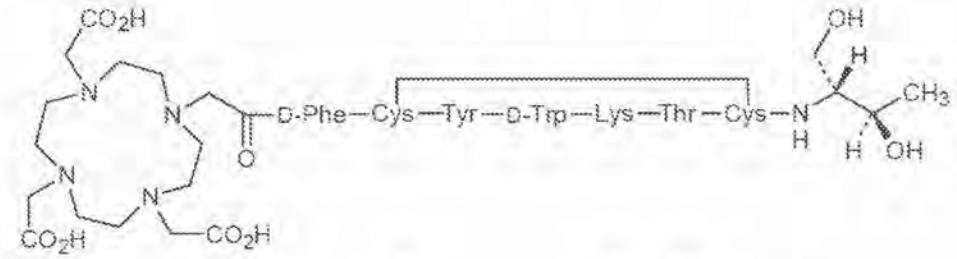
"second stabilizer is added after the complex formation of components (ai) and (aii)": Regardless of whether the second stabilizers may have been present already during the complex formation or not, the second stabilizer is added after the complex forming reaction is completed, e.g. after the reacting solution which might have been heated up to an elevated temperature is again cooled down to ambient temperature.

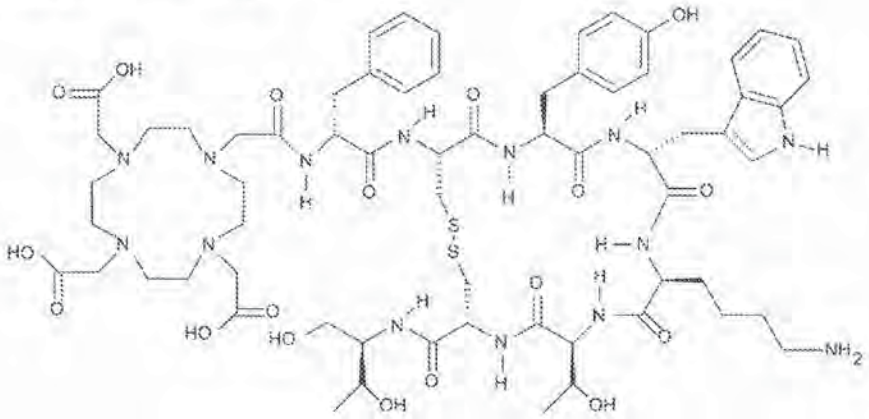
The cell receptor binding moiety and the chelating agent may form together the following molecules:

DOTA-OC: [DOTA^0,D-Phe^1]octreotide,

DOTA-TOC: [DOTA^0,D-Phe^1,Tyr^3]octreotide, edotreotide (INN),

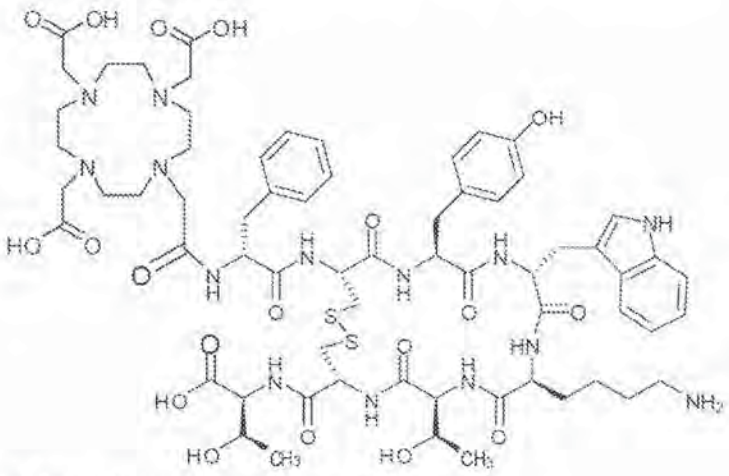
represented by the following formulas:





DOTA-NOC: [DOTA^0, D-Phe^1,1-Nal^3]octreotide,

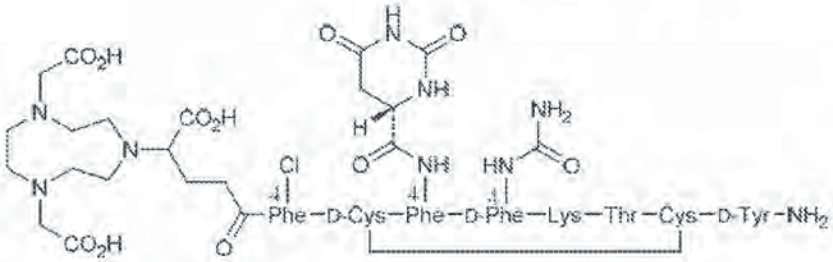
DOTA-TATE: [DOTA^0,D-Phe^1,Tyr^3]octreotate, DOTA-Tyr^3-Octreotate, DOTA-d-Phe-Cys-Tyr-d-Trp-Lys-Thr-Cys-Thr (cyclo 2,7), oxodotreotide (INN), represented by the following formula :



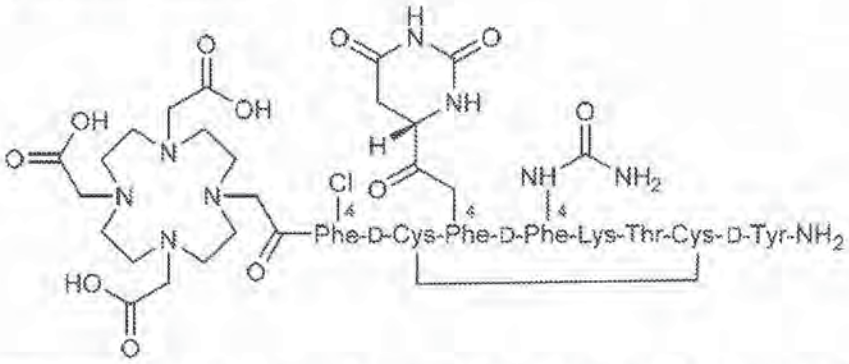
DOTA-LAN: [DOTA^0,D-β-Nal^1]lanreotide,

DOTA-VAP: [DOTA^0,D-Phe^1,Tyr^3]vapreotide.

Satoreotide trizoxetan



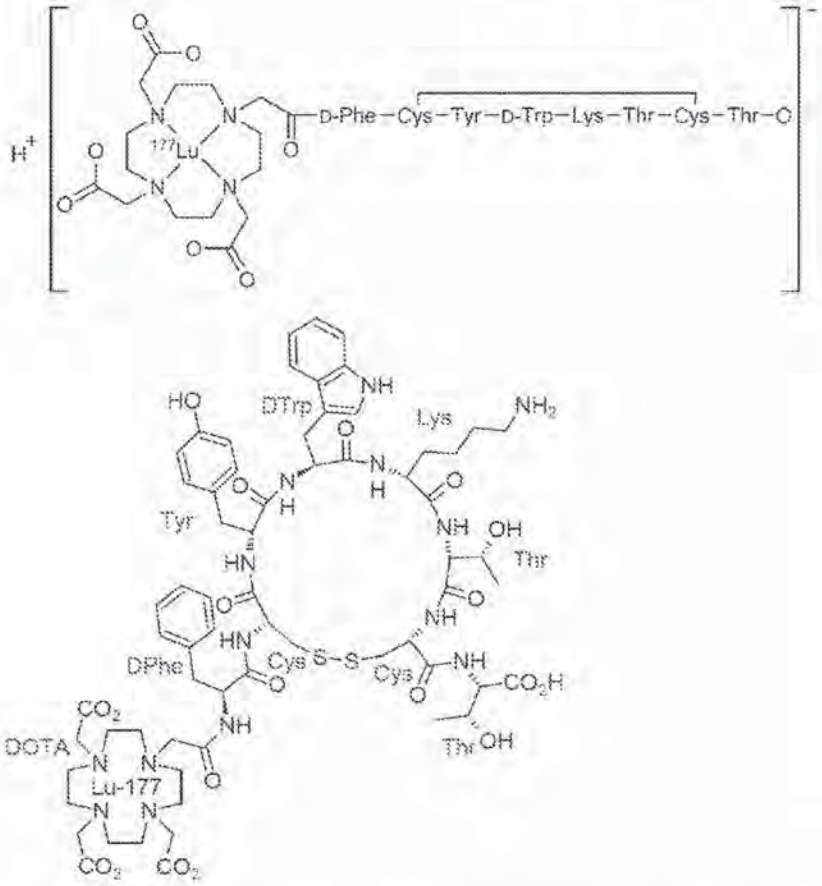
Satoreotide tetraxetan



The preferred "cell receptor binding moiety linked to the chelating agent" molecules for the present invention are DOTA-TOC, DOTA-TATE, and Satoreotide tetraxetan, more preferably the molecule is DOTA-TATE.

For the present invention, the preferred complex formed by (or the preferred complex of) the radionuclide and the cell receptor binding moiety linked to the chelating agent according to the present invention is ^{177}Lu-DOTA-TATE, which is also referred to as Lutetium (177Lu) oxodotreotide (INN), i.e. hydrogen [N-{[4,7,10-tris(carboxylato-κ*O*-methyl)-1,4,7,10-tetraazacyclododecan-1-yl-κ^{4}N^1,N^4,N^7,N^{10}]acetyl-κ*O*}-D-phenylalanyl-L-cysteinyl-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninato cyclic (2→7)-disulfide(4-)](177Lu)lutetate(1-)

and is represented by the following formulas:



"Buffer for a pH from 4.5 to 6.0": may be an acetate buffer, citrate buffer (e.g. citrate + HCl or citric acid + Disodium hydrogenphosphate) or phosphate buffer (e.g. Sodium dihydrogenphosphate + Disodium hydrogenphosphate), preferably said buffer is an acetate buffer, preferably said acetate buffer is composed of acetic acid and sodium acetate.

"Sequestering agent", a chelating agent suitable to complex the radionuclide metal ions, preferably DTPA: Diethylentriaminepentaacetic acid.

"for commercial use": the drug product, e.g. a pharmaceutical aqueous solution, is able to obtain (preferably has obtained) marketing authorization by health authorities, e.g. US-FDA or EMA, by complying with all drug product quality and stability requirements as demanded

by such health authorities, is able to be manufactured (preferably is manufactured) from or at a pharmaceutical production site at commercial scale followed by a quality control testing procedure, and is able to be supplied (preferably is supplied) to remotely located end users, e.g. hospitals or patients.

"Combination": refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present invention and a combination partner (e.g. another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term "fixed combination" means that the therapeutic agents, e.g. a compound of the present invention and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the therapeutic agents, e.g. a compound of the present invention and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more therapeutic agent.

EXAMPLES

Hereinafter, the present invention is described in more details and specifically with reference to the examples, which however are not intended to limit the present invention.

Materials:

The $^{177}LuCl_3$ may be obtained from commercial sources, e.g. I.D.B. Holland BV. The DOTA^0-Tyr^3-Octreotate may be obtained from commercial sources, e.g. by piCHEM Forschungs- und Entwicklungs GmbH, Austria. All other components of the drug product are commercially available from various sources.

Example 1: Composition of drug product

The Drug Product (^{177}Lu-DOTA^0-Tyr^3-Octreotate 370 MBq/mL solution for infusion) is designed as a sterile ready-to-use solution for infusion containing ^{177}Lu-DOTA^0-Tyr^3-Octreotate as Drug Substance with a volumetric activity of 370 MBq/mL at reference date and time (calibration time (tc)). Calibration time (tc) corresponds to the End of Production (EOP = t0) which is the time of measurement of the activity of the first QC vial. The shelf-life of Drug Product is defined as 72 hours after calibration time. Drug Product is a single dose vial, containing suitable amount of solution that allows delivery of 7.4 GBq of radioactivity at injection time.

Manufacturing site prepares single doses calibrated within the range of 7.4 GBq ± 10 % (200 mCi) after the end of production. Certificates of analysis reports both the exact activity provided and the time when this activity is reached. This value is declared as "Injection time: {DD MM YYYY} {hh:mm} UTC". Considering the variable injection time and constant decay of the radionuclide, the filling volume needed for an activity of 7.4 GBq at injection time is calculated and can range from 20.5 and 25.0 mL.

Composition of drug product per mL

Property/Component	**Quantity (Unit/mL)**	**Function**
^{177}Lu-DOTA^0-Tyr^3-Octreotate (volumetric activity)	370 MBq/mL at t_c (EOP)	Drug Substance
X-DOTA^0-Tyr^3-Octreotate	10 µg/mL	Total peptide content
Specific Activity (GBq/Total peptide)	≥ 53 GBq/µmol at EOP	NA

Excipients		
Acetic acid	0.48 mg/mL	pH adjuster
Sodium acetate	0.66 mg/mL	pH adjuster
Gentisic acid	0.63 mg/mL	RSE
Ascorbic acid	2.80 mg/mL	RSE
DTPA	0.05 mg/mL	Sequestering agent
Sodium chloride (NaCl)	6.85 mg/mL	Isotonizing agent
Sodium hydroxide (NaOH)	0.64 mg/mL	pH adjuster
Water for injection	Ad 1 mL	Solvent

EOP: End of Production=t_0=activity measurement of the first vial=calibration time t_c

RSE: Radiation Stability Enhancer

Example 2: Manufacturing of drug product

For a 74 GBq batch size (2 Ci batch size) a $^{177}LuCl_3$ solution, about 74 GBq in HCl, is mixed together with a DOTA-Tyr^3-Octreotate (about 2 mg) solution, and a Reaction Buffer solution, containing an antioxidant agent (and stabilizator against radiolytic regradation) (i.e. Gentisic acid, about 157 mg) and a buffer system (i.e. Acetate buffer system), resulting in a total of about 5.5 mL solution, which is used for radiolabelling that occurs at a temperature of about 90 to about 98°C within less than 15 minutes.

The synthesis is carried out using a single use disposable kit cassette installed on the front of the synthesis module which contains the fluid pathway (tubing), reactor vial and sealed reagent vials.

The obtained mother solution is diluted with a solution containing a chelating agent (i.e. DTPA), an antioxidant agent (i.e. Ascorbic acid) sodium hydroxide, and sodium chloride and, then sterile filtered through 0.2 µm to give the ready-to-use solution as described in Example 1 with a pH of 4.5-6.0, in particular 5.2-5.3. Finally, the solution is dispensed in volumes of from 20.5 to 25.0 mL into sterile vials. The stoppered vials are enclosed within lead containers for protective shielding.

Manufacturing Process can also be implemented for batch sizes higher than 74GBq. In this case the amount of the raw materials (Lutetium, peptide and Reaction Buffer) are multiplied to guarantee the same raw materials ratio.

Example 3: Stability study results after storage at various temperature conditions.

The following table provides the stability test data for a batch produced at 74 GBq batch size according to the process described in Example 2.

"n.d." = not determined; "LOD" = limit of detection

Time points		**t(0)**	**t(0+24h)**	**t(0+48h)**	**t(0+72h)**
Stability at 5 ± 2 °C		***CQ1***			***11 mL*** ***21.8 mL***
pH		5.3	n.d.	n.d.	5.3 5.3
Chemical purity (RP-UV-HPLC)	Peptide purity (%)	100.0	n.d.	n.d.	100.0 100.0
Radiochemical purity (RP-γβ-HPLC)	^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate (%)	98.37	n.d.	n.d.	96.09 96.40
Time points		**t(0)**	**t(0+24h)**	**t(0+48h)**	**t(0+72h)**
Stability at 25 ± 2 °C		***CQ1***	***5 mL***	***5mL***	***5 mL*** ***24.7 mL***
pH		5.3	5.3	5.2	5.2 5.3
Chemical purity (RP-UV-HPLC)	Peptide purity (%)	100.0	100.0	100.0	100.0
Radiochemical purity (RP-γβ-HPLC)	^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate (%)	98.28	96.99	96.29	95.02 95.62
Time points		**t(0)**	**t(0+24h)**	**t(0+48h)**	**t(0+72h)**
Stability at 32 ± 2 °C		***CQ1***	***5.6 mL*** ***22.2 mL***	***5.6 mL*** ***22.2 mL***	
pH		5.3	n.d.	5.3 5.3	n.d.
Chemical purity (RP-UV-HPLC)	Peptide purity (%)	100.0	100.0 100.0	100.0 100.0	n.d.
Radiochemical	^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate (%)	98.37	96.03	94.45	n.d.

purity (RP-γβ-HPLC)			96.51	95.45	
Time points		**t(0)**	**t(0+24h)**	**t(0+48h)**	**t(0+72h)**
Stability at 32 ± 2 °C per 12h and at 25 ± 2 °C per 60h		***CQ1***			***11 mL***
Chemical purity (RP-UV-HPLC)	Peptide purity (%)	100.0	n.d.	n.d.	100.0
Radiochemical purity (RP-γβ-HPLC)	^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate (%)	98.28	n.d.	n.d.	95.01

Very similar good stability results were obtained for batches produced at 148 GBq batch size.

Electronic Patent Application Fee Transmittal

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

Filed as Large Entity

Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
REQUEST FOR PRIORITIZED EXAMINATION	1817	1	4000	4000
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	1	100	100
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**5960**

Electronic Acknowledgement Receipt

EFS ID:	34160959
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
Filer Authorized By:	
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	30-OCT-2018
Filing Date:	
Time Stamp:	16:41:09
Application Type:	Utility under 35 USC 111(a)

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Warnings:					
Information:					
2	Application Data Sheet	PAT058197_US_CIP02_ADS-signed.pdf	1823433 cc110f3e89291b6b7e0f4c6bf0253597d7f223a7	no	10
Warnings:					
Information:					
3		PAT058197_US_CIP02_Appln_to_be_filed_FINAL.pdf	554735 0d08d329ab93a7ca6504758460bfce6d2cd2d4c	yes	59

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Document Description	Start	End
Abstract	59	59
Claims	56	58
Specification	1	55

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

PTO/SB/08a (02-18)
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(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

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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	5804157		1998-09-08	Mallinckrodt Medical, Inc.	
	2	5830431		1998-11-03	Mallinckrodt Medical, Inc.	
	3	5776894		1998-07-07	Novartis AG	
	4	5753627		1998-05-19	Novartis AG	
	5	6183721	B1	2001-02-06	Novartis AG	
	6	6277356	B1	2001-08-21	Novartis AG	
	7	6123916		2000-09-26	Novartis AG	

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Attorney Docket Number	PAT058197-US-CIP02

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	1	2008009444	WO	A1	2008-01-24	Van Dulmen, A.		
	2	2013167130	WO	A1	2013-11-14	Rigshospitalet		
	3	2015063746	WO	A1	2015-05-07	The South African Nuclear Energy Corporation Ltd.		
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	6	2018074918	WO	A1	2018-04-26	Technische Universiteit Delft		
	7	0515313	EP	B1	2000-08-09	Novartis AG		

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	First Named Inventor	de Palo, Francesco
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	Examiner Name	
	Attorney Docket Number	PAT058197-US-CIP02

	8	200210192	WO	A2	2002-02-07	Novartis AG et al.		
	9	199701579	WO	A2	1997-01-16	Sandoz Ltd et al.		

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	6	BANERJEE et al., Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications, Chem Rev, (2015), 115, 2934-2974.	
	7	Declaration for Grace Period filed in PCT/IB2018/057415, September 25, 2018	

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	Art Unit	1618
	Examiner Name	
	Attorney Docket Number	PAT058197-US-CIP02

	8	Declaration for Grace Period filed in PCT/IB2018/055575, July 25, 2018
	9	ASLANI et al., Lutetium-177 DOTATATE Production with and Automated Radio-pharmaceutical Synthesis System, Asia Oceania Journal of Nuclear Medicine & Biology, (2015), 3, 107-115.
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	First Named Inventor	de Palo, Francesco
	Art Unit	1618
	Examiner Name	
	Attorney Docket Number	PAT058197-US-CIP02

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	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

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)	2018-11-01
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.**

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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 Acknowledgement Receipt

EFS ID:	34182379
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:	01-NOV-2018
Filing Date:	
Time Stamp:	11:26:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PAT058197-US-CIP02_IDS_Stmt-rev_and_signed.pdf	64809 6a1a8e6bdc859d3c433bf216261bae0d268b573e	no	1

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PAT058197-US-CIP02_IDS-signed.pdf	1036947 6dd0320c695598108a7eea9c61582c2168d37e32	no	7
Warnings:					
Information:					
		Total Files Size (in bytes):	1101756		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
de PALO, Francesco et al.
APPLICATION NO: 16/175261
FILED: October 30, 2018
FOR: Stable, concentrated radionuclide complex solutions

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

INFORMATION DISCLOSURE STATEMENT

Sir:

This paper is being filed:

☒ within three months of the filing date of the application. Therefore, no fees are required.

☒ before the mailing date of a first Office Action on the merits, and so under 37 C.F.R. §1.97(b)(3) no fees are required.

If a fee is deemed to be required, the Commissioner is hereby authorized to charge such fee to Deposit Account No. 50-4409 in the name of Novartis.

In accordance with 37 C.F.R. §1.56, Applicant wishes to call the Examiner's attention to the references cited on the attached form(s) PTO/SB/08A/B.

☒ The references are of record in parent Application No. 16/045484 filed July 25, 2018, and copies are available therein.

The Examiner is requested to consider the foregoing information in relation to this application and indicate that each reference was considered by returning a copy of the initialed PTO/SB/08A/B form(s). Applicant would also like to bring to the Examiner's attention a co-pending application with Application No. 16/175239 filed October 30, 2018.

Respectfully submitted,

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

c/o Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 433
East Hanover, NJ 07936
+18627785816

Date: November 1, 2018

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	1820	PAT058197-US-CIP02	21	1

CONFIRMATION NO. 8183

FILING RECEIPT

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

OC000000103944437

Date Mailed: 11/21/2018

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

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;

Applicant(s)

Advanced Accelerator Applications (Italy) Srl, Colleretto Giacosa, ITALY;

Power of Attorney: None

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: 11/20/2018

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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/175,261

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	* 1			OR	x 100 =	100
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	0.00
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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

AMENDMENT A

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

AMENDMENT B

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** 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 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

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

FORMALITIES LETTER

Date Mailed: 11/21/2018

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing.

Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- Surcharge as set forth in 37 CFR 1.16(f) must be submitted.
  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required within **TWO MONTHS** from the date of this Notice to avoid abandonment is/are itemized below. No entity status discount is in effect. If applicant is qualified for small entity status, a written assertion of small entity status must be submitted to establish small entity status. (See 37 CFR 1.27). If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $ **160** surcharge.
- $(**0**) previous unapplied payment amount.
- $ **160** TOTAL FEE BALANCE DUE.

Items Required To Avoid Processing Delays:

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

• A properly executed inventor's oath or declaration has not been received for the following inventor(s):
Francesco de Palo
Lorenza Fugazza
Donato Barbato
Maurizio Mariani
Daniela Chicco
Giovanni Tesoriere

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web, including a copy of this Notice and selecting the document description "Applicant response to Pre-Exam Formalities Notice". https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at 1-866-217-9197 or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

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**.

/jmilani/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
de Palo, Francesco et al.
APPLICATION NO: 16/175,261
FILED: October 30, 2018
FOR: **Stable, concentrated radionuclide complex solutions**

Confirm. No. 8183

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

REPLY TO NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION FILED UNDER 37 CFR 1.53 (B)

Sir:

The Notice mailed on November 21, 2018 has a shortened statutory time set to expire on January 21, 2019. In response, the applicants now submit payment for the surcharge as set forth in 37 CFR1.16 (f). Please charge Deposit Account No. 50-4409 in the name of Novartis in the amount of $160 for payment of the Surcharge fee.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §§ 1.16 and 1.17 which may be required, or credit any overpayment, to Account No. 50-4409 in the name of Novartis.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 433
East Hanover, NJ 07936
+1 617 871 3880

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

Date: December 3, 2018

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/Amy Olinger
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:				
LATE FILING FEE FOR OATH OR DECLARATION	1051	1	160	160
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

Electronic Acknowledgement Receipt

EFS ID:	34466966
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/Safiya Watson
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CIP02
Receipt Date:	03-DEC-2018
Filing Date:	30-OCT-2018
Time Stamp:	16:28:24
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	120418INTEFSW00003400504409
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	Transmittal Letter	PAT058197-US-CIP02_Surcharge_Payment_Signed.pdf	63832 3d84c7c744065e5f563f03e1e52a5c167acdf3c5	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30402 d744c43d56175d65361653d9cc03bd31269a522a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	94234		

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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 16/175,261

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	* 1			OR	x 100 =	100
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 460 =	0.00
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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1820

APPLICATION AS AMENDED - PART II

AMENDMENT A

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

AMENDMENT B

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** 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 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
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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

INFORMAL NOTICE

OC000000104250227

Date Mailed: 12/06/2018

INFORMATIONAL NOTICE TO APPLICANT

Applicant is notified that the above-identified application contains the deficiencies noted below. No period for reply is set forth in this notice for correction of these deficiencies. However, if a deficiency relates to the inventor's oath or declaration, the applicant must file an oath or declaration in compliance with 37 CFR 1.63, or a substitute statement in compliance with 37 CFR 1.64, executed by or with respect to each actual inventor no later than the expiration of the time period set in the "Notice of Allowability" to avoid abandonment. See 37 CFR 1.53(f).

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

- A properly executed inventor's oath or declaration has not been received for the following inventor(s):
  - Francesco de Palo
  - Lorenza Fugazza
  - Donato Barbato
  - Maurizio Mariani
  - Daniela Chicco
  - Giovanni Tesoriere

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**.

/fasrat/

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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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	1980	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

OC000000104250226

Date Mailed: 12/06/2018

Receipt is acknowledged of this non-provisional 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 APPLICANT, 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 Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections 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**

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;

Applicant(s)

Advanced Accelerator Applications (Italy) Srl, Colleretto Giacosa, ITALY;

Power of Attorney: None

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: 11/20/2018

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).

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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

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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 12/13/2018

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
12/13/2018	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

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 16/175,261	**Applicant(s)** de Palo et al.	
	Examiner BRIAN W BROWN	**Art Unit** OPET	**AIA (First Inventor to File) Status** Yes

1. THE REQUEST FILED 30 October 2018 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to BRIAN BROWN at (571)272-5338.

In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/BRIAN W BROWN/ Petitions Examiner, OPET	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
de Palo, Francesco et al.
APPLICATION NO: 16/175261
FILED: October 30, 2018
FOR: **Stable, concentrated radionuclide complex solutions**

Confirm. No. 8183

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

COMMUNICATION

Applicant requests that the following name be added as an inventor to this application:

Clementina Brambati

Applicant has also enclosed a corrected Application Data Sheet to reflect such change and submits herewith the requisite processing fee set forth in 37 CFR 1.17(i) for the application.

The Application Data Sheet submitted on October 30, 2018 erroneously lists the address of each of the Applicant and the Inventors. The corrected Application Data Sheet enclosed also shows the changes to the addresses. Applicant also requests that an Updated Official Filing Receipt be issued to reflect the changes.

No other fee is believed to be due with this request. However, the commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-4409.

Respectfully submitted,

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

Novartis Pharmaceuticals Corporation
One Health Plaza, Bldg. 433
East Hanover, NJ 07936
+1 617 871 3880

Date: January 15, 2019

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	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Francesco		de Palo	

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

City	~~Colleretto Giacosa~~ Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Lorenza		Fugazza	

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

City	~~Colleretto Giacosa~~ Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

Inventor 3 Remove

Legal Name

PTO/AIA/14 (11-15)
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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	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Donato		Barbato	

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

City	~~Colleretto Giacosa~~ Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Maurizio		Mariani	

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

City	~~Colleretto Giacosa~~ Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniela		Chicco	

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

City	~~Colleretto Giacosa~~ Albiano d'Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

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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	

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giovanni		Tesoriere	

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

City	~~Colleretto Giacosa~~ Noicattaro	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	~~Via Ribes, 5~~ Via dell'Industria Prima Traversa		
City	~~Colleretto Giacosa~~ Pozzilli	State/Province	
Postal Code	~~10010~~ 86077	Country [i]	IT

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Clemintina		Brambati	

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

City	Torino	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Advanced Accelerator Applications (Italy) S.R.L.		
Address 2	Via dell'Industria Prima Traversa		
City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	01095		
Email Address	pip_inbox.phchbs@novartis.com	Add Email	Remove Email

PTO/AIA/14 (11-15)
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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	

Application Information:

Title of the Invention	Stable, concentrated radionuclide complex solutions		
Attorney Docket Number	PAT058197-US-CIP02	**Small Entity Status Claimed** ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	01095		

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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	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	16/140962	2018-09-25
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/140962	Continuation in part of	16/045484	2018-07-25

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/057415	WO	2018-09-25	
			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/055575	WO	2018-07-25	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

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	

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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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
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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 Ribes, 5~~ Via dell'industria Prima Traversa		
Address 2			
City	~~Colleretto Giacosa~~ Pozzilli	**State/Province**	
Country IT		Postal Code	~~10010~~ 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
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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)	2019-01-15
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.

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/Amy Olinger
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:				
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	140

Electronic Acknowledgement Receipt

EFS ID:	34859458
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:	15-JAN-2019
Filing Date:	30-OCT-2018
Time Stamp:	15:43:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$140
RAM confirmation Number	011619INTEFSW00003002504409
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	Transmittal Letter	PAT58197-US-CIP02_Transmittal_Letter_signed.pdf	62297 69bf13d3b128abab1d3f8527051187 9fcd70904c	no	1
Warnings:					
Information:					
2	Application Data Sheet	PAT058197_US_CIP02_ADS_signed.pdf	809976 cf82d84fe51258c3e8c9d60ded6f6099d4b2a8b8	no	11
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
3	Fee Worksheet (SB06)	fee-info.pdf	30462 63f9e1daeecbf21ae3d5fcee66a5c86bcc9625ec	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	902735		

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
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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 02/12/2019

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
02/12/2019	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 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 10/30/18.

☐ 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) 1-21 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) 1-21 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: _____.

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 Status

Claims 1-21 are pending in the application.

Claim Rejections - 35 USC § 112

Claims 6-9 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 1 teaches that the total concentration of the stabilizers is 0.2 to 20 mg/mL and the claims 6-9 teach of the total concentration of the stabilizers is 15-50 mg/mL, 20 to 40 mg/mL and 25 to 35 mg/mL which doesn't further limit the concentration of claim 1. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

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 1-21 is/are rejected 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).

Chen et al. (US 2007/0269375A1) discloses stabilized radiopharmaceutical formulations and the method of making and using the stabilized radiopharmaceutical formulations wherein stabilizers are added to improve the radiostability of the formulations (abstract; p1, [0026]; p3, [0035]). The formulation comprises a metal radionuclide (^{177}Lu), a metal chelator (DOTA), and the stabilizers gentisic acid, ascorbic acid (p3, [0026]; p4, [0048],[0051]; p5, [0052]; p6, [0058]). The gentisic acid is used in a concentration 2-20 mg/mL and ascorbic acid is used in a concentration 10 to 100 mg/mL (p13, [0166]; Table 2) and the proper stabilizer or stabilizer combination used to stabilize the radionuclide selected will also depend on the properties of the isotope selected (p12, [0152]). For ^{177}Lu-labeled complexes, the unit dose to be administered typically ranges from about 10 mCi (~370 MBq) to about 200 mCi (p11, [0140]; p13, [0155]).

The stabilizing solution comprises gentisic acid, ascorbic acid, human serum albumin, benzyl alcohol, a physiologically acceptable buffer or salt solution at a pH of about 4.5 to about 8.5, and one or more amino acids (p3, [0026]; p13, [0164]) wherein the buffer is acetate buffer (p3, [0027]; p13, [0165]) and the solution does not comprise ethanol. The radiolysis stabilizing solution may be added to the radiolabeled compound immediately following the radiolabeling reaction (p3, [0026]).

The metal chelator may be linked to a targeting molecule (e.g. peptide, etc.) (p8, [0117]). The peptide comprises octreotide, etc. (p9, [0120]).

Each stabilizer was prepared in water and mixed with 5 mg/mL sodium acetate (NaOAc) buffer (0.2 M, pH 4.8). 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) 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.

The ^{177}Lu-A formulation was prepared via adding NaOAc-stabilizer solution in a lead-shielded vial with $^{177}LuCl_3$ and COMPOUND A. The reaction mixture was heated to 100°C for 5 minutes and then cooled. Na_2EDTA in water was added (p25, [0286]) which encompasses dilution of the instant claims.

Preparation of 177Lu-C: In a 2-mL glass vial, 200µl of 0.2 M, pH 4.8 NaOAc buffer, 30 µg Compound C in 30 µg of 0.01 N HCl and 5.6 mCi $177LuCl_3$ were added. After incubation at 85° C. for 10 min, the reaction vial was cooled to room temperature with a water bath, and then 20µl of 2% EDTA was added to challenge any free Lu-177 that remained (p31-32, [0338]) wherein the 85° C. for 10 min encompasses the temperature and time of the instant claims.

The half-life of the radionuclide is long enough to allow synthesis and purification of the radiotherapeutic construct (p7, [0059]).

Chen et al. does not explicitly disclose filtration.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to filter and purify the stabilized radiopharmaceutical formulations as Chen et al. teaches of the synthesis and purification of the radiotherapeutic construct.

Chen et al. does not disclose further a.) further addition of DTPA, b.) adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation or c.) DOTA-TATE, DOTA-TOC.

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 utilize DTPA in 4 mg/mL in the stabilized radiopharmaceutical formulations of Chen et al. for the advantage of complexing any non-incorporated ^{177}Lu, as taught by Maus et al.

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 Chen 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.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the peptide hormone, such as somatostatin of Chen et al. for the TATE of Maus et al. as the substitution of one somatostatin targeting moiety for another analogous somatostatin targeting moiety predictably yields a stabilized radiopharmaceutical complex that targets a somatostatin receptor.

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 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the solutions comprise the same constituents, such as DOTA-TATE, ^{177}Lu, stabilizers in analogous quantities wherein the first stabilizer is mixed in the chelator solution and the second stabilizer in a subsequent solution. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

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 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the solutions comprise the same constituents, such as DOTA-TATE, ^{177}Lu, stabilizers in analogous quantities wherein the first stabilizer is mixed in the chelator solution and the second stabilizer in a subsequent solution. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

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 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the solutions comprise the same constituents, such as DOTA-TATE, ^{177}Lu, stabilizers in analogous quantities wherein the first stabilizer is mixed in the chelator solution and the second stabilizer in a subsequent solution. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

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	US-20070269375-A1	11-2007	Chen; Jianqing	A61K51/088	424/1.69
	B					
	C					
	D					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
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	R					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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	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.

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

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

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								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
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	17	✓								
	18	✓								
	19	✓								
	20	✓								
	21	✓								

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	287	sup?177 adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L2	14885	DOTA	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L3	179	l1 and l2	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L4	50	l1 same l2	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L5	6689	gentisic and ascorbic	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L6	38	l3 and l5	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56
L7	16	l4 and l5	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/02/06 21:56

2/6/2019 9:56:56 PM

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
	1	5804157		1998-09-08	Mallinckrodt Medical, Inc.	
	2	5830431		1998-11-03	Mallinckrodt Medical, Inc.	
	3	5776894		1998-07-07	Novartis AG	
	4	5753627		1998-05-19	Novartis AG	
	5	6183721	B1	2001-02-06	Novartis AG	
	6	6277356	B1	2001-08-21	Novartis AG	
	7	6123916		2000-09-26	Novartis AG	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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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	2008009444	WO	A1	2008-01-24	Van Dulmen, A.		
	2	2013167130	WO	A1	2013-11-14	Rigshospitalet		
	3	2015063746	WO	A1	2015-05-07	The South African Nuclear Energy Corporation Ltd.		
	4	2015171792	WO	A1	2015-11-12	The John Hopkins University et al.		
	5	2016207732	WO	A1	2016-12-29	Advanced Accelerator Applications		
	6	2018074918	WO	A1	2018-04-26	Technische Universiteit Delft		
	7	0515313	EP	B1	2000-08-09	Novartis AG		

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Art Unit	1618
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Attorney Docket Number	PAT058197-US-CIP02

	8	200210192	WO	A2	2002-02-07	Novartis AG et al.		
	9	199701579	WO	A2	1997-01-16	Sandoz Ltd et al.		

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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.	T5
	1	BREEMAN et al., Optimising Conditions for Radiolabelling of DOTA-peptides with 90Y, 111In and 177Lu at High Specific Activities, Eur J Nucl Med Mol Imaging, (2003), 30, 917-920.	
	2	BREEMAN et al., Overview of Development and Formulation of 177Lu-DOTA-TATE for PRRT, Current Radiopharmaceuticals, (2016), 9, 8-18.	
	3	MAUS et al., Aspects on radiolabeling of 177Lu-DOTA-TATE: After C18 purification re-addition of ascorbic acid is required to maintain radiochemical purity, Int J. Diagnostic Imaging, (2014), 1, 5-12.	
	4	LIU et al., Ascorbic Acid: Useful as a Buffer Agent and Radiolytic Stabilizer for Metalloradiopharmaceuticals, Bioconjugate Chem, (2003), 14, 1052-1056.	
	5	LIU et al., Stabilization of 90Y-Labeled DOTA-Biomolecule Conjugates Using Gentisic Acid and Ascorbic Acid, Bioconjugate Chem, (2001), 12, 554-558.	
	6	BANERJEE et al., Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications, Chem Rev, (2015), 115, 2934-2974.	
	7	Declaration for Grace Period filed in PCT/IB2018/057415, September 25, 2018	

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	8	Declaration for Grace Period filed in PCT/IB2018/055575, July 25, 2018
	9	ASLANI et al., Lutetium-177 DOTATATE Production with and Automated Radio-pharmaceutical Synthesis System, Asia Oceania Journal of Nuclear Medicine & Biology, (2015), 3, 107-115.
	10	LUTATHERA, Advanced Accelerator Applications, Highlights of Prescribing Information, January 2018
	11	LUTATHERA, European Medicines Agency, EPAR Public Assessment Report, First Published January 17, 2018
	12	LUTATHERA, European Medicines Agency, EPAR Product Information, First Published January 17, 2018, last updated April 11, 2018
	13	LUTATHERA, European Medicines Agency, CHMP Summary Positive Opinion, First Published July 21, 2017
	14	LUNA-GUTIERREZ et al., Freeze-Dried multi-dose kits for the fast preparation of 177Lu-Tyr3-octreotide and 177Lu-PSMA(inhibitor) under GMP conditions, J Radioanal Nucl Chem, (2017), 314, 2181-2188.
	15	DAS et al., Preparation of DOTA-TATE and DOTA-NOC freeze-dried kits for formulation of patient doses of 177Lu-labeled agents and their comparison for peptide receptor radionuclide therapy application, J Radioanal Nucl Chem, (2014) 299, 1389-1398
	16	de BLOIS et al., Effectiveness of Quenchers to Reduce Radiolysis of 111In- or 177-Lu-Labelled Methionine-Containing Regulatory Peptides. Maintaining Radiochemical Purity as Measured by HPLC, Current Topics in Med Chem, (2012), 12, 2677-2685.
	17	WILD et al., DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals, Eur J Nucl Med Mol Imaging, (2003), 30, 1338-1347.
	18	KWEKKEBOOM et al., [177-Lu-DOTA0, Tyr3]octreotate: comparison with [111In-DTPA0]octreotide in patients, Eur J Nucl Med Mol Imaging, (2001), 28, 1319-1325.

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	
	Attorney Docket Number	PAT058197-US-CIP02

	19	DAS et al., Preparation of Therapeutic Dose of 177Lu-DOTA-TATE Using a Novel Single Vial Freeze-dried Kit: A Comparison with 'In-situ' Preparation at Hospital Radiopharmacy, Current Radiopharmaceuticals, (2014) 7, 12-19.
	20	MATHUR et al., Bulk Scale Formulation of Therapeutic Dosed of Clinical Grade Ready-to-Use 177Lu-DOTA-TATE: The Intricate Radiochemistry Aspects, Cancer Biotherapy and Radiopharmaceuticals, (2017), 32, 7, 266-273.
	21	Advanced Accelerator Applications Announces European Approval of Lutetium (177Lu) Oxodotreotide (Lutathera®) for Gastroenteropancreatic Neuroendocrine (GEP-NET) Tumors, PRESS RELEASE September 29, 2017
	22	Advanced Accelerator Applications Receives US FDA Approval for LUTATHERA® for Treatment of Gastroenteropancreatic Neuroendocrine Tumors, PRESS RELEASE January 26, 2018

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EXAMINER SIGNATURE

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	02/06/2019

*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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

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Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	
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)	2018-11-01
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.**

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

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PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of invention	Stable, concentrated radionuclide complex solutions

As the below named inventor, I hereby declare that:

This declaration is directed to:

- ☐ The attached application, or
- ☒ United States application or PCT international application number 16/175261 filed on October 30, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Donato Barbato Date (Optional): 21st December 2018

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (05-12)
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U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Clementina Brambati Date (Optional): 13 DECEMBER 2018

Signature: Clementina Brambati

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (05-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Stable, concentrated radionuclide complex solutions

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [ ] The attached application, or
- [X] United States application or PCT international application number 16/175261 filed on October 30, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Daniela Chicco Date (Optional): January 24th, 2019

Signature: Daniela Chicco

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Stable, concentrated radionuclide complex solutions

As the below named inventor, I hereby declare that:

This declaration is directed to:

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The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: Francesco de Palo Date (Optional) : _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Title of invention	Stable, concentrated radionuclide complex solutions

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This declaration is directed to:

- [ ] The attached application, or
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LEGAL NAME OF INVENTOR

Inventor: Lorenza Fugazza Date (Optional): _____

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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Title of Invention	Stable, concentrated radionuclide complex solutions

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LEGAL NAME OF INVENTOR

Inventor: Maurizio Mariani Date (Optional): 18 December 2018

Signature: Maurizio Mariani

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Stable, concentrated radionuclide complex solutions

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This declaration is directed to:

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- [X] United States application or PCT international application number 16/175261 filed on October 30, 2018.

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTOR

Inventor: Giovanni Tesoriere Date (Optional): 31/01/2019

Signature: [signature]

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

Electronic Acknowledgement Receipt

EFS ID:	35375284
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:	12-MAR-2019
Filing Date:	30-OCT-2018
Time Stamp:	16:15:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Oath or Declaration filed	PAT058197_US_CIP02_Barbato_Signed.pdf	329189 ec9fc51cd352438a4c6c2e633ba9d53d582a2c95	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:					
2	Oath or Declaration filed	PAT058197_US_CIP02_Brambati_Signed.pdf	80941 e98aec700ee134d82a0f2ae036a21353dda8ae2b	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:					
3	Oath or Declaration filed	PAT058197_US_CIP02_Chicco_Signed.pdf	138448 c3f6aaed88d7ec0250087846 7dd7aea8fe0555f0	no	1
Warnings:					
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Information:					
4	Oath or Declaration filed	PAT058197_US_CIP02_Depalo_Signed.pdf	55740 b91be3b07a08be8393c6cea3f6dac79c0aa0e86c	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:					
5	Oath or Declaration filed	PAT058197_US_CIP02_Fugazza_Signed.pdf	135915 1b194804cc028a77232b6 4ecab532bf9d020c62	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:					
6	Oath or Declaration filed	PAT058197_US_CIP02_Mariani_Signed.pdf	176230 4aafb3b7174de230edb5b7d2381f276ff56012d2	no	1
Warnings:					
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Information:					

7	Oath or Declaration filed	PAT058197_US_CIP02_Tesorier e_Signed.pdf	538963 5ba37f787029502f921986fb0fea1d83ac0d0525	no	1

Warnings:

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Information:

Total Files Size (in bytes):	1455426

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.

CASE PAT058197-US-CIP02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1618
de Palo, Francesco 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 February 12, 2019 (the "Office Action") in the above referenced application. With no extension of time, this response is due on or before May 13, 2019 as May 12, 2019 falls on a Sunday.

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT NATIONAL STAGE APPLICATION OF Confirm. No. 8183

de Palo, Francesco et al.

APPLICATION NO: 16/175261

FILED: October 30, 2018

FOR: **Stable, concentrated radionuclide complex solutions**

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

REQUEST FOR UPDATED FILING RECEIPT

Applicant requests that the spelling of the following inventor's name be corrected in this application:

Clementina Brambati

The Application Data Sheet submitted on January 15, 2019 erroneously lists the above inventor as Clemintina Brambati. The inventor's declaration filed on March 12, 2019 contained the correct spelling. Applicant has also enclosed a corrected Application Data Sheet to reflect such change and submits herewith the requisite processing fee set forth in 37 CFR 1.17(i) for the application. Applicant also requests that an Updated Official Filing Receipt be issued to reflect the changes.

No other fee is believed to be due with this request. However, the commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-4409.

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

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	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Francesco		de Palo	

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

City	Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via dell'industria Prima Traversa

City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Lorenza		Fugazza	

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

City	Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl
Address 2	Via dell'industria Prima Traversa

City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

Inventor 3 Remove

Legal Name

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	

Prefix	Given Name	Middle Name	Family Name	Suffix
	Donato		Barbato	

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

City	Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	Via dell'industria Prima Traversa		
City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Maurizio		Mariani	

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

City	Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	Via dell'industria Prima Traversa		
City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniela		Chicco	

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

City	Albiano d'Ivrea	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	Via dell'industria Prima Traversa		
City	Pozzilli	State/Province	
Postal Code	86077	Country [i]	IT

PTO/AIA/14 (11-15)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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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	

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Giovanni		Tesoriere	

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

City	Noicattaro	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	c/o Advanced Accelerator Applications (Italy) Srl		
Address 2	Via dell'Industria Prima Traversa		
City	Pozzilli	**State/Province**	
Postal Code	86077	**Country** [i]	IT

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Clemintina~~ Clementina		Brambati	

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

City	Torino	Country of Residence [i]	IT

Mailing Address of Inventor:

Address 1	Advanced Accelerator Applications (Italy) S.R.L.		
Address 2	Via dell'Industria Prima Traversa		
City	Pozzilli	**State/Province**	
Postal Code	86077	**Country** [i]	IT

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	01095		
Email Address	pip_inbox.phchbs@novartis.com	Add Email	Remove Email

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	

Application Information:

Title of the Invention	Stable, concentrated radionuclide complex solutions		
Attorney Docket Number	PAT058197-US-CIP02	**Small Entity Status Claimed** ☐	
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	0	**Suggested Figure for Publication (if any)**	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	01095		

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
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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	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation in part of	16/140962	2018-09-25
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16/140962	Continuation in part of	16/045484	2018-07-25

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/057415	WO	2018-09-25	
			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
PCT/IB2018/055575	WO	2018-07-25	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

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	

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.