Notice of References Cited	Application/Control No. 16/175,239	Applicant(s)/Patent Under Reexamination	
	Examiner MELISSA J PERREIRA	Art Unit 1618	Page 1 of 1

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*		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					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Maus et al. (Int. J. Diagnost. Imaging 2014, 1, 5-12)
	V	
	W	
	X	

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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	01/18/2019								
	1	✓								
	2	✓								
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	19	✓								
	20	✓								
	21	✓								
	22	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

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Search Notes		
Search Notes	Date	Examiner
EAST	01/18/2019	MP
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inventor search	01/18/2019	MP
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Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1629
Examiner Name	
Attorney Docket Number	PAT058197-US-CNT02

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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.	
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	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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	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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	8	200210192	WO	A2	2002-02-07	Novartis AG et al.		
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	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.	
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	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
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	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
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	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.
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	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	01/18/2019

*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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Art Unit	1629
Examiner Name	
Attorney Docket Number	PAT058197-US-CNT02

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).

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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

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	406	"177" adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/01/18 14:46
S2	14630	DOTA	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/01/18 14:47
S3	159	S1 and S2	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/01/18 14:47
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

1095 7590 02/15/2019

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
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16/175,239	10/30/2018	de Palo et al.	PAT058197-US-CNT0

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NOVARTIS PHARMACEUTICAL CORPORATION INTELLECTUAL PROPERTY DEPARTMENT ONE HEALTH PLAZA 433/2 EAST HANOVER, NJ 07936-1080	MELISSA J PERREIRA	
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Supervisory Patent Examiner, Art Unit 1618

PTO-90C (Rev.04-03)

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

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Approved for use through 11/30/2020. OMB 0651-0031
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EFS Web 2.1.18

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

no references provided

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16175239
	Filing Date	2018-10-30
	First Named Inventor	de Palo, Francesco
	Art Unit	1629
	Examiner Name	
	Attorney Docket Number	PAT058197-US-CNT02

	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	02/14/2019

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[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.

no references provided

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(Not for submission under 37 CFR 1.99)

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Art Unit	1629
Examiner Name	
Attorney Docket Number	PAT058197-US-CNT02

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 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.

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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.

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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 16/175239 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:

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LEGAL NAME OF INVENTOR

Inventor: Donato Barbato Date (Optional): 2nd November 2018

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.

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LEGAL NAME OF INVENTOR

Inventor: Clementina Brambati Date (Optional): 19 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.

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LEGAL NAME OF INVENTOR

Inventor: Daniela Chicco Date (Optional): 31st Jan 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.

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LEGAL NAME OF INVENTOR

Inventor: Francesco de Palo Date (Optional): _____

Signature: _____

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LEGAL NAME OF INVENTOR

Inventor: Lorenza Fugazza Date (Optional): _____

Signature: Lorenza Fugazza

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.

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LEGAL NAME OF INVENTOR

Inventor: Maurizio Mariani Date (Optional): 14 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.

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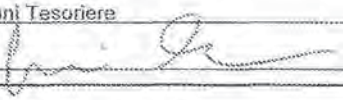
LEGAL NAME OF INVENTOR

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

Signature: 

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EFS ID:	35375463
Application Number:	16175239
International Application Number:	
Confirmation Number:	1061
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-CNT02
Receipt Date:	12-MAR-2019
Filing Date:	30-OCT-2018
Time Stamp:	16:22:24
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_CNT02_Barbato_Signed.pdf	329083 ba1ee97c23c1fdc2965da5b846fb6482c9fb75f2e	no	1

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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: 16/175,239
FILED: October 30, 2018
FOR: Stable, Concentrated radionuclide complex solutions

Art Unit: 1618
Examiner: Perreira, Melissa Jean
Conf. No.: 1061

VIS 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 January 25, 2019 (the "Office Action") in the above referenced application. With no extension of time, this response is due on or before April 25, 2019.

Applicant believes no additional fee is due. The Commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-4409, Reference No. PAT058197-US-CNT02.

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

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

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims

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

Listing of Claims:

1. (Currently Amended) A 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 comprising
      (bi) gentisic acid or a salt thereof; and
      (bii) ascorbic acid or a salt thereof;
   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~~ 1.0 to 5.0 mg/mL.

2. (Currently Amended) The pharmaceutical aqueous solution according to claim 1,
   wherein said component (b) ~~comprises the~~ consists essentially of two stabilizers:
   (bi) gentisic acid or a salt thereof as a first stabilizer; and
   (bii) ascorbic acid or a salt thereof as a second stabilizer.

3. (Currently Amended) The pharmaceutical aqueous solution according to claim [[2]] 1, wherein
   (bi) gentisic acid is present in a concentration of from 0.5 to 2 mg/mL; and
   (bii) ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL.

4. (Original) The pharmaceutical aqueous solution according to claim 3, wherein gentisic acid is present in a concentration of from 0.5 to 1 mg/mL.

5. (Original) The pharmaceutical aqueous solution according to claim 3, further comprising:
   (c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL.

6. (Original) The pharmaceutical aqueous solution according to claim 5, 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.

7. (Original) The pharmaceutical aqueous solution according to claim 6, wherein said acetate buffer provides for a pH of from 4.5 to 6.0.

8. (Original) The pharmaceutical aqueous solution according to claim 6, wherein said acetate buffer provides a pH of from 5.0 to 5.5.

9. (Original) The pharmaceutical aqueous solution according to claim 1, 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).

10. (Original) The pharmaceutical aqueous solution according to claim 1, 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).

11. (Original) The pharmaceutical aqueous solution according to claim 1, 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.

12. (Original) The pharmaceutical aqueous solution according to claim 9, 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.

13. (Original) The pharmaceutical aqueous solution according to claim 9, 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 20 to 40 mg/mL.

14. (Original) The pharmaceutical aqueous solution according to claim 12, wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formation in a concentration of from 20 to 40 mg/mL.

15. (Original) The pharmaceutical aqueous solution according to claim 11, wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formation in a concentration of from 25 to 35 mg/mL.

16. (Original) The pharmaceutical aqueous solution according to claim 1, which has a shelf life of at least 72 h when stored at ≤ 25 °C.

17. (Original) The pharmaceutical aqueous solution according to claim 1, for which the radiochemical purity (determined by HPLC) is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

18. (Original) The pharmaceutical aqueous solution according to claim 1, wherein said solution is produced at a batch size of at least 20 GBq, at least 50 GBq, or at least 70 GBq.

19. (Original) The pharmaceutical aqueous solution according to claim 1, which is free of ethanol.

20. (Original) The pharmaceutical aqueous solution according to claim 1, wherein the somatostatin receptor binding peptide linked to the chelating agent DOTA is DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide).

21. (Currently Amended) 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) DOTA-TATE or DOTA-TOC;

(b) the 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.

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

23. (New) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TATE.

24. (New) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TOC.

25. (New) The pharmaceutical aqueous solution according to claim 21, wherein said component (b) consists essentially of two stabilizers:

(bi) gentisic acid or a salt thereof as a first stabilizer; and

(bii) ascorbic acid or a salt thereof as a second stabilizer.

26. (New) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TATE with a volumetric radioactivity of about 370 MBq/mL, and said component (b) comprises gentisic acid in a concentration of about 0.63 mg/mL and ascorbic acid in a concentration of about 2.80 mg/mL.

Remarks/Arguments

Upon entry of the amendments herein, claims 1-26 are pending. Claims 1-3, and 21 have been amended. New claims 23-26 have been added. Support of the amendments and new claim appears in the original application as filed, at e.g., page 8, lines 23-27 and Examples 1 and 2 at pages 44-46. No new matter has been introduced.

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

Interview Summary

Initially, Applicant would like to thank the Examiner for conducting a telephone conference with Applicant's counsel on April 24, 2019. Claims and the 103 rejection raised in the Office Action were discussed. A part of the present document serves as a summary of the interview.

Claim Rejections-35 U.S.C. § 103

Original claims 1-22 are rejected under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375, "Chen") in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, 1, 5-12, "Maus"). *See* the Office Action at pages 2-4.

Each of the independent claims 1 and 21 is directed to a pharmaceutical aqueous solution that comprises, *inter alia*, (a) a complex of ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA (e.g., DOTA-TATE or DOTA-TOC in claim 21); and (b) at least two different stabilizers against radiolytic degradation, which include gentisic acid or a salt thereof and ascorbic acid or a salt thereof; wherein the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (i.e., **6.8-13.5 mCi/mL**). It is further recited, respectively, in claim 1 that the **stabilizers** are present in a total concentration of from **1.0 to 5.0 mg/mL**, or in claim 21 that gentisic acid is in a concentration of from **0.5 to 1 mg/mL** and ascorbic acid is in a concentration of from **2.0 to 5.0 mg/mL**.

According to the Examiner, Chen discloses stabilized radiopharmaceutical formulations comprising a radiometal (e.g. ^{177}Lu, etc.); metal chelator (e.g. DTPA, DOTA, etc.); stabilizers (e.g. gentisic acid, ascorbic acid, etc.); and buffers (e.g. acetate buffer, etc.), and that the unit dose of the ^{177}Lu-labelled complexes to be administered typically ranges from about 10 mCi to about 200 mCi and about 3.5 mCi of ^{177}Lu was used in each reaction. *Id.*, pages 2-3. The Examiner acknowledges that Chen **fails to teach at least the following four features**: (i) the concentration of DTPA, (ii) concentration of acetic acid, (iii) adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation or (iv) DOTA-TATE, DOTA-TOC. *Id.*

The Examiner further asserts that Maus teaches ^{177}Lu-DOTA-TATE which is vulnerable to radiolysis and the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis as well as use of DTPA solution to complex any non-incorporated ^{177}Lu. *Id.* The Examiner then concludes that it would have been obvious for one of skill in the art to combine the teachings of the two references and to substitute the peptide hormone such as somatostatin in the ^{177}Lu complex taught by Chen for TATE taught by Maus to arrive at the claimed invention, 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." *Id.*, page 4. Applicant respectfully disagrees. A skilled artisan, after reading Chen as a whole, would not have been motivated to combine it with the teachings in Maus, and even if Chen and Maus were combined, a skilled artisan would not have arrived at the claimed invention with a reasonable expectation of success.

Initially, contrary to the Examiner's assertion, it would not have been obvious to a skilled artisan before the effective filing date of the claimed invention to substitute the peptide hormone such as somatostatin in the ^{177}Lu complex taught by Chen for TATE taught by Maus. Chen merely mentions somatostatin and analogs thereof generally as possible examples of targeting molecules, and yet the majority of Chen's teachings and all of the examples in Chen are targeted radiodiagnostic and radiotherapeutic compounds, e.g., ^{177}Lu-A or ^{177}Lu-B, that are targeted to the Gastrin Releasing Peptide Receptor (GRPR) and stabilizers useful in preparation and stabilization of these compounds targeted to GRPR. *See, e.g.*, the Abstract, Figures 1-2, paragraphs [0002], [0017]-[0045], [0127]-[0132] and Examples 1-24, including Tables 3-25. Also, as noted by the Examiner, nowhere in Chen teaches or suggests DOTA-TATE or DOTA-TOC. Differently, Maus describes a very different ^{177}Lu complex targeted to somatostatin receptor, *i.e.*, ^{177}Lu-DOTA-TATE. More importantly, the problems that the two references aim to solve are markedly different, and naturally, the solutions that Chen and Maus reached are distinctly different. Thus, a skilled artisan, in view of Chen as a whole, would not have bene motivated to turn to Maus to look for modification for improvement. Specifically, the problem Chen aims to solve is to reduce radiolytic damage to methionine (Met) residue in the peptides that specifically target GRPR (*see* paragraphs [0018], [0021], [0024]-[0025]), and as a consequence, Chen finds that benzyl alcohol is a key component in such formulations (*see* paragraphs [0027] and [0168]). On the other hand, Maus notes a very different problem from Chen's, *i.e.*, decreased radiochemical purity (RCP) of the radio peptides due to removal of gentisic acid and ascorbic acid by the tC18 sold phase extraction (SPE) purification that is included as default in the cassette-based automated labeling procedure. Consequently, Maus reaches a conclusion that re-addition of ascorbic acid post tC18 SPE purification is required

to maintain RCP. Accordingly, there is no reason or motivation for a skilled artisan to combine the teachings of Chen and Maus.

Secondly, even if the teachings of Chen and Maus were combined, a skilled artisan would not have arrived at the invention of claims 1 and 21 with a reasonable expectation of success. Chen in many places has stressed the **unpredictability** in selecting stabilizers and in when and how much the stabilizers are added. For example, in Example 3, Chen evaluated eight stabilizers, including ascorbic acid and gentisic acid sodium salts, and found that **none** of the eight reagents **provided adequate radiostability** for 48 hours. *See* paragraph [0265]. Chen further states that this result is "**unexpected** as gentisic acid, ascorbic acid, HSA and 3,4-pyridinedicarboxylic acid have all been reported by others to provide satisfactory protection against radiolysis for other radiopharmaceuticals.... The reagent 3,4-pyridinedicarboxylic acid, previously reported as an effective radiostabilizer, was found to **interfere badly** with the labeling reaction." *Id.*; emphases added. Chen further discusses the unpredictable nature of combining various stabilizers for stabilizing ^{177}Lu-A or ^{177}Lu-B (*see, e.g.*, paragraphs [0269], [0271], [0273], [0299], and [0313]). Chen also refers to the unpredictable outcomes caused either by the sequence of adding various stabilizers (*i.e.*, adding them at or after the labeling reaction) or by the amounts of the stabilizers added. *See, e.g.*, Examples 9-14 and paragraphs [0287]-[0290], [0296], and [0298]. In addition, in Examples 4-6 of Chen, a Radiolysis Protecting Solution comprising gentisic acid, ascorbic acid, and 3 other stabilizers is immediately added after the labeling reaction (i.e., after forming of the complex ^{177}Lu-A or ^{177}Lu-B) to arrive at a final concentration of **5 mg/mL** gentisic acid and **25 mg/mL** ascorbic acid sodium salt, **1 mg/mL** HSA, **0.05 mg/mL** benzyl alcohol, and **1-2 mg/mL** amino acid when the volumetric radioactivity of ^{177}Lu is 50 mCi/2 mL, *i.e.*, **25 mCi/mL**. In other words, Chen teaches a total concentration of stabilizers being about **32-33 mg/mL** at a volumetric radioactivity of **25 mCi/mL** ^{177}Lu, which is equivalent to about from ***8.7 to 17.8 mg/mL*** total concentration of stabilizers at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu. In comparison, the total concentration of the stabilizers recited in independent claim 1 is **much lower** than that of Chen (***1.0 to 5.0 mg/mL*** total concentration of stabilizers at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu). As is independent claim 21 (gentisic acid in a concentration of **0.5-1 mg/mL** and ascorbic acid in a concentration of **2.0-5.0 mg/mL** at a volumetric radioactivity of **6.8-13.5 mCi/mL** ^{177}Lu). Noticeably, Chen **teaches away** from using such low concentration of stabilizers in the final radiopharmaceutical formulations disclosed thereof. *See, e.g.*, Table 4 and paragraph [0250]. Specifically, Chen states that while methionine at a concentration of 2.5 mg/mL was able to stabilize 3.5 mCi of ^{177}Lu-A against radiolysis for 5 days, the same concentration of 2.5 mg/mL of the same stabilizer is **unable** to stabilized the same complex when the radioactivity is increased to

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

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

Accordingly, in view of the unpredictable nature of stabilizers (e.g., their types, timing of adding them, and their amounts) taught by the primary reference, Chen, as well as the teachings away from both Chen and Maus, a skilled artisan would not have reasonably expected that the low concentrations of stabilizers recited in claim 1 or 21 would sufficiently stabilize the claimed aqueous solution. Instead, a skilled artisan would have been discouraged from arriving at the claimed invention in view of Chen and Maus. Accordingly, the pharmaceutical aqueous solution of claim 1 or 21 is nonobvious over Chen and Maus.

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

"Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. *See, e.g., In re Albrecht,* 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)." *See* MPEP § 2145. Accordingly, independent claim 1 or 21 is also patentable over Chen and Maus for unexpected stability even with the low concentrations of gentisic acid and ascorbic acid or salts thereof recited in the claims. For at least the same reasons stated above, claims 2-20, each of which depends directly or indirectly from claim 1, and claims 22-23, each of which depends from claim 21, are also patentable over Chen and Maus. Applicant respectfully requests reconsideration and withdrawal of the rejection.

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

Claim 12 is also patentable over the cited references on an additional ground. It is further noted that Chen **teaches away** from presenting higher than 5 mg/mL gentisic acid or ascorbic acid at the radiolabeling reaction as at the concentration of 5 mg/mL, gentisic acid or ascorbic acid either interferes with the labeling reaction or provides less stability during the reaction. *See*, *e.g.*, paragraph [0290]. In contrast, claim 12 recites that during the complex formation (i.e., the labeling reaction), at least one of the stabilizers is present in a total concentration of from **15 to 50 mg/mL**. *See also* Example 2 of the instant application. Maus does not correct this defect of Chen, at least because Maus does not address the impact of concentrations of gentisic acid or ascorbic acid to the radiolabeling reaction. As increasing the concentration to greater than 5 mg/mL of gentisic acid or ascorbic acid at the radiolabeling reaction would render decreased stability in the formulations of Chen, it teaches away from the invention of claim 12 which recites stabilizers present in the radiolabeling reaction at a total concentration of from **15 to 50 mg/mL**. Accordingly, the pharmaceutical aqueous solution of claim 12 is nonobvious over Chen and Maus on this additional ground. As is claim 14, which depends from claim 12.

In summary, the Examiner has failed to present a proper *prima facie* case of obviousness for claims 1-22 for at least the reasons set forth above. Instead, it is clear that the Examiner's obviousness rejection is based solely on impermissible hindsight in which Applicant's specification and claims were used as a blueprint to piece together the invention of the pending claims. This is contrary to the MPEP and long standing case law that requires that any judgment on obviousness must "not include knowledge gleaned only from applicant's disclosure." *See*, *In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). The invention of the pending claims is also non-obvious in view of the combined teachings of the cited references for unexpected results set forth herein. Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

Claims 1, 9, 10, 12, 13, and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20-21 of copending U.S. Application No. 16/175,261; and claims 1-22 are provisionally rejected over claims 1-31 of copending U.S. Application No. 16/045,484. *See* the Office Action at pages 5-6.

Without arguing the propriety of this rejection, Applicant respectfully requests that the provisional nonstatutory double patenting rejections over copending U.S. Application Nos. 16/175,261 and 16/045,484 be held in abeyance until allowable subject matter in the present application has been determined.

In view of the above remarks, Applicant submits that the pending application is in condition for allowance. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith, to our Deposit Account No. 50-4409, under Docket No. PAT058197-US-CNT02.

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

Respectfully submitted,

/ Lian Ouyang /
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Date: April 24, 2019

Electronic Patent Application Fee Transmittal

Application Number:	16175239
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-CNT02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	1202	4	100	400
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	240	240
		Total in USD ($)		**640**

Electronic Acknowledgement Receipt

EFS ID:	35823274
Application Number:	16175239
International Application Number:	
Confirmation Number:	1061
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-CNT02
Receipt Date:	24-APR-2019
Filing Date:	30-OCT-2018
Time Stamp:	19:01:54
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$640
RAM confirmation Number	042519INTEFSW00005661504409
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	Power of Attorney	PAT058197_US_CNT02_POATransmittal_AIA82A_signed.pdf	201482 f26706d3da34fae3a3db686f428884ea513e37aca	no	2
Warnings:					
Information:					
2	Power of Attorney	PAT058197_US_CNT02_POA_AIA82B_signed.pdf	48757 3ca8ffcf5bd4b95b49a7b8ec0fc7d01da92db5ae	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					
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3	Information Disclosure Statement (IDS) Form (SB08)	PAT058197_US_CNT02_IDS_signed.pdf	1034301 d20cf0934dc8aa1dc3115893d94928f063854af3	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
4	Foreign Reference	WO2018081860.pdf	2439951 5e01bf889a646f015514770297de8869955575d	no	47
Warnings:					
Information:					
5		PAT058197-US-CNT02-response-to-OA-As-Filed-Signed.pdf	203595 c913d4a15067ed7b6956849e9654051452fbd2b3	yes	11
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	

	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	5	
	Applicant Arguments/Remarks Made in an Amendment		6	11	
Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	32318 7e15c902d1c0e4ec524a52cec7794bb88e52a0c7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3960404		

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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.

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

PTO/AIA/82A (07-13)
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Application Number	16/175,239
Filing Date	October 30, 2018
First Named Inventor	de Palo, Francesco
Title	Stable, concentrated radionuclide complex solutions
Art Unit	1618
Examiner Name	PERREIRA, MELISSA JEAN
Attorney Docket Number	PAT058197-US-CNT02

SIGNATURE of Applicant or Patent Practitioner

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

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

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Signature		Date (Optional)	08/04/2019
Name	GIOVANNI TESORIERE		
Title	Authorized Signatory, Advanced Accelerator Applications (Italy) Srl		

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CNT02

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	16175239
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	Examiner Name	Perreira, Melissa Jean
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Application Number	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CNT02

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Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-04-24
Name/Print	Lian Ouyang	Registration Number	69,254

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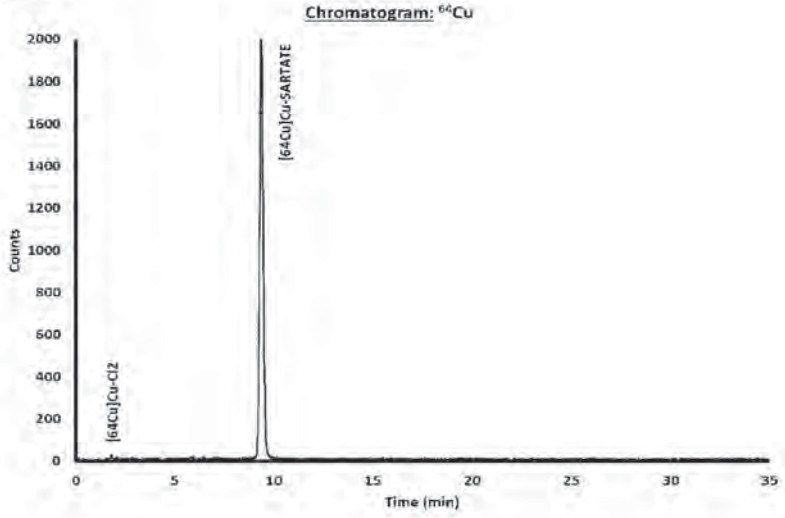
(54) Title: FORMULATIONS FOR RADIOTHERAPY AND DIAGNOSTIC IMAGING

Figure 1



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

[Continued on next page]

WO 2018/081860 A1

Published:

— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Formulations for Radiotherapy and Diagnostic Imaging

Field

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

Background

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

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

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

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

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

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

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

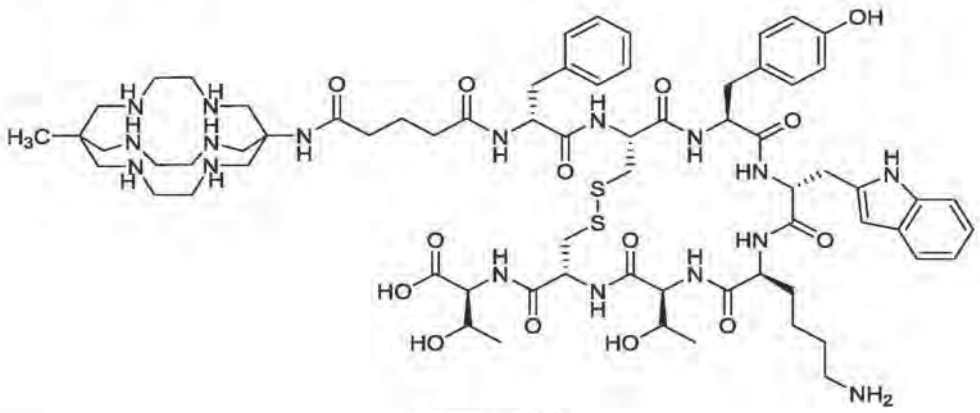
increasing stability of the compound while in solution. Alternatively, additional excipients may be used to provide other features to the formulation, such as preservatives, buffers and the like.

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

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

Summary

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

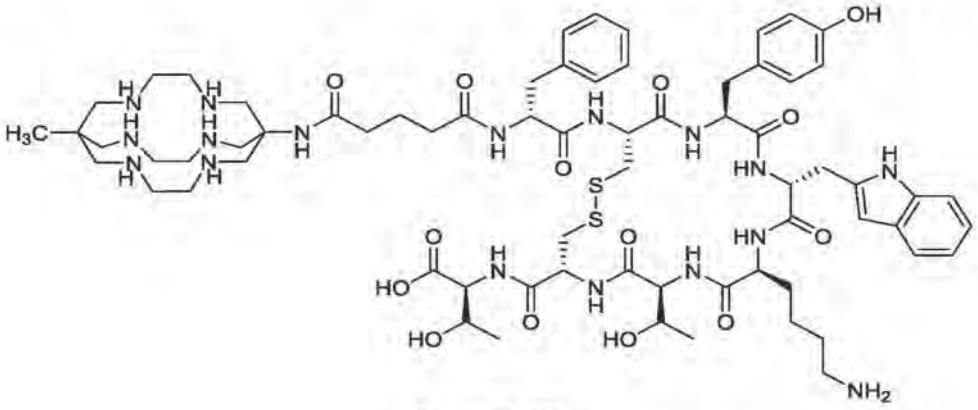


Formula (I)

the formulation further comprising:

about 7 to about 13% (v/v) ethanol;
about 0.3 to about 1.2% (w/v) sodium chloride;
about 0.02 to about 0.1% (w/v) gentisic acid or a salt thereof;
wherein the formulation has a pH of between about 4 to about 8.

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



Formula (I)

the formulation further comprising:

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

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

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

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

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

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

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

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

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

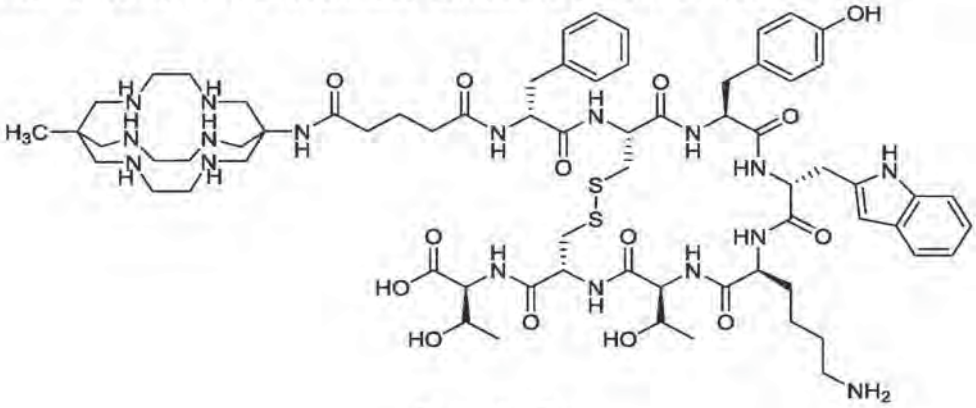
to recover an aqueous formulation comprising a compound of Formula (I), or a salt thereof, complexed with a Cu ion.

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

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

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

a container comprising a lyophilised compound of Formula (I)

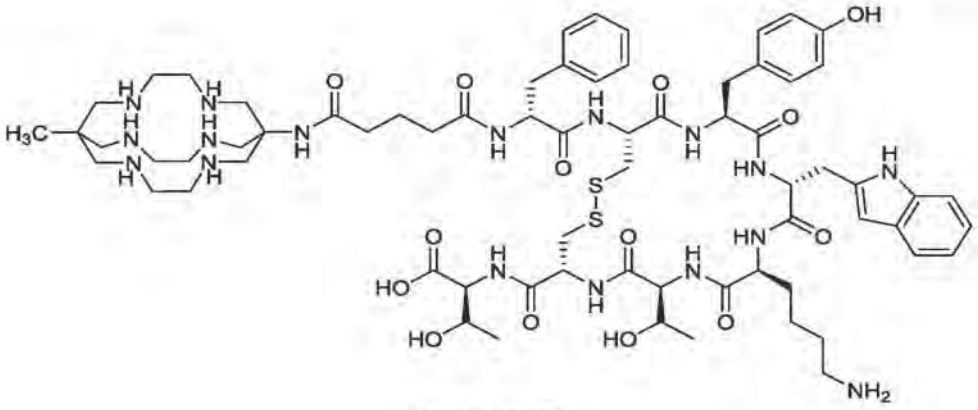


Formula (I)

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

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

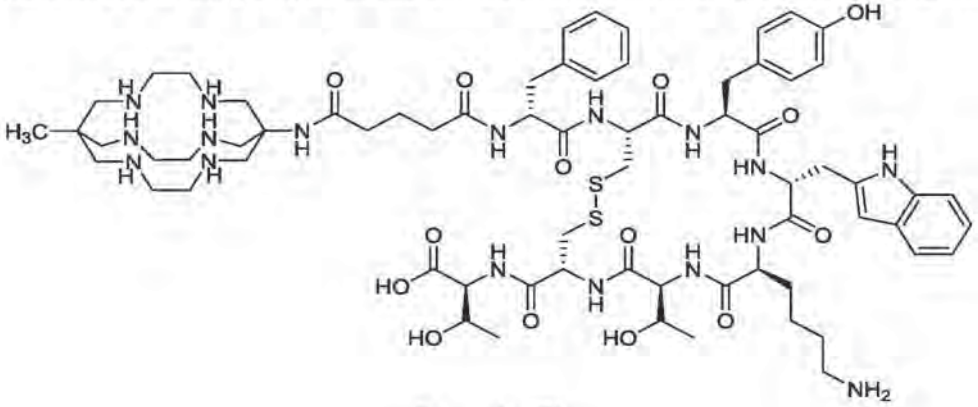
a container comprising a lyophilised compound of Formula (I)



Formula (I)

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

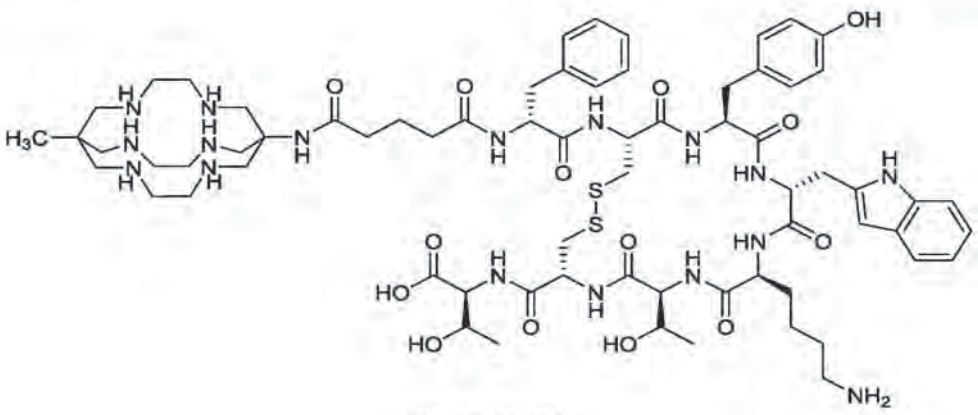
A further aspect of the present invention provides a kit for making an aqueous formulation as defined in an earlier aspect for parenteral administration, the kit comprising:
a container comprising a lyophilised compound of Formula (I), or a salt thereof;



Formula (I)

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

A further aspect of the present invention provides a kit for making an aqueous formulation as aforementioned for parenteral administration, the kit comprising:
a container comprising a lyophilised compound of Formula (I), or a salt thereof;



Formula (I)

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

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

Brief description of the figures

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

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

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

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

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

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

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

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

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

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

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

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

Detailed description

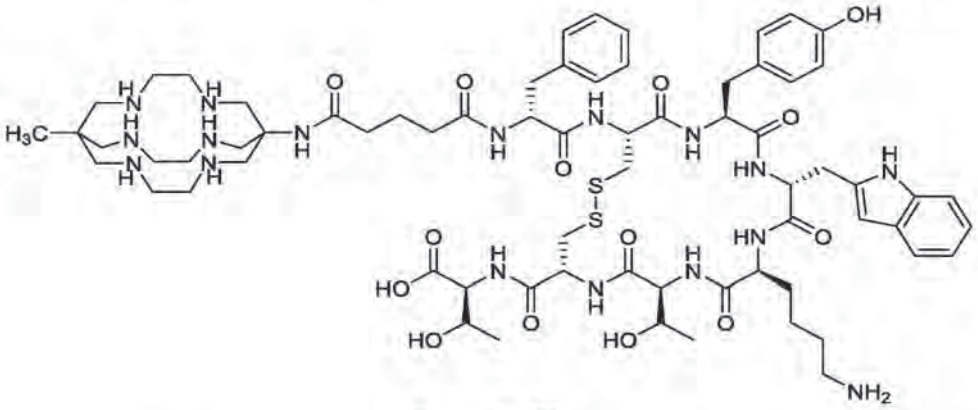
The present invention relates to stable formulations of a specific radioisotope-ligand complex. The present inventors have found that the formulations of a complex disclosed herein minimise dissociation of the radioisotope from the ligand and/or minimise radiolysis of the ligand arising from the radioisotope.

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

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

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

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



Formula (I)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

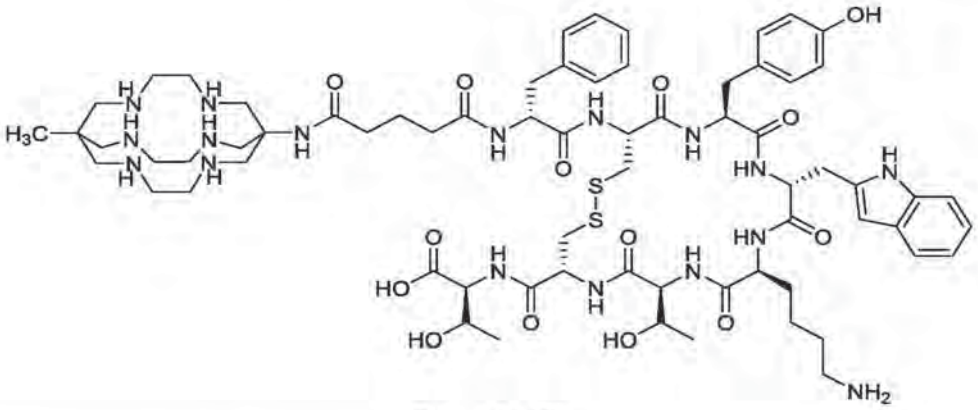
Formula (I) as the acetate, salt, complexed with a ^{64}Cu ion, about 10% ethanol, about 0.9% (w/v) sodium chloride and not more than 0.056% gentisic acid, or a salt thereof, wherein the formulation has a pH of about 6.0.

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

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

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

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



Formula (I)

the formulation further comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Preparation of an aqueous formulation of the present invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Uses of a formulation of the present invention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Examples

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Example 8 – In vivo toxicology of SARTATE

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

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

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

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

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

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

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

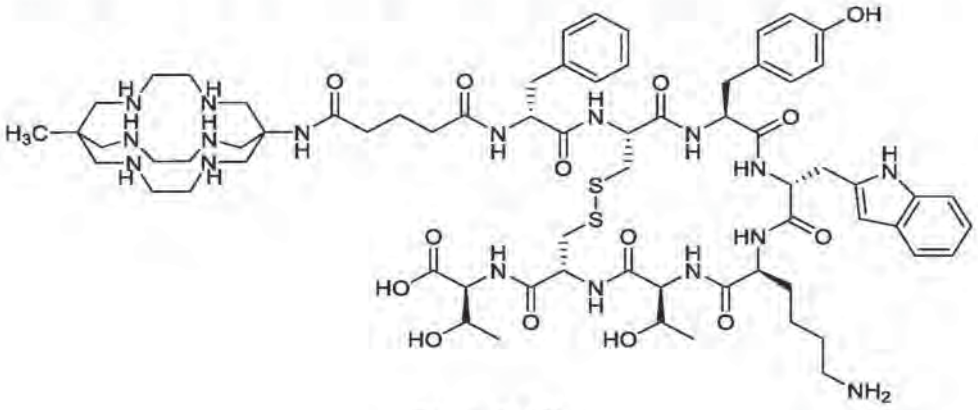
The NOAEL of 1 mg/kg in rats corresponds to a Human Equivalent Dose (HED) of 0.16 mg/kg, or a total dose of 11.2 mg in a patient with a weight of 70 kg. The maximum possible total dose in this clinical trial will be 0.02 mg (20 micrograms) per patient. The NOAEL therefore represents a safety margin of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

Example 9 – In vitro genotoxicity of SARTATE

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

What is claimed is:

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



Formula (I)

the formulation further comprising:

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

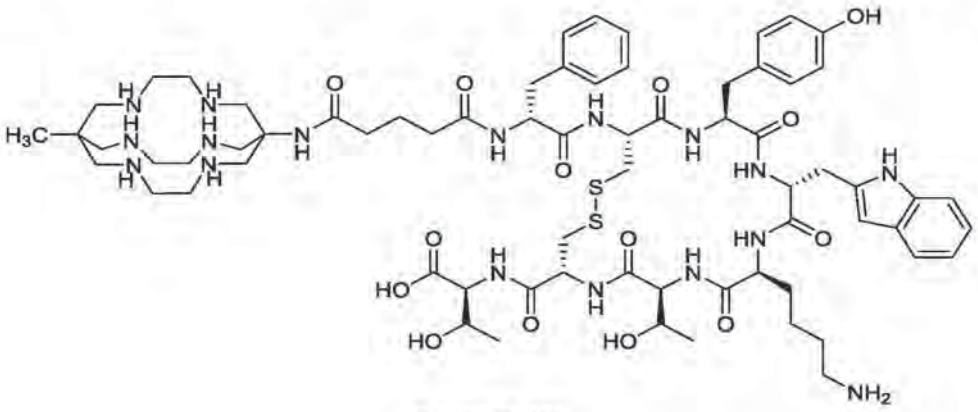
wherein the formulation has a pH of between about 4 to about 8.

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

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

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

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



Formula (I)

the formulation further comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

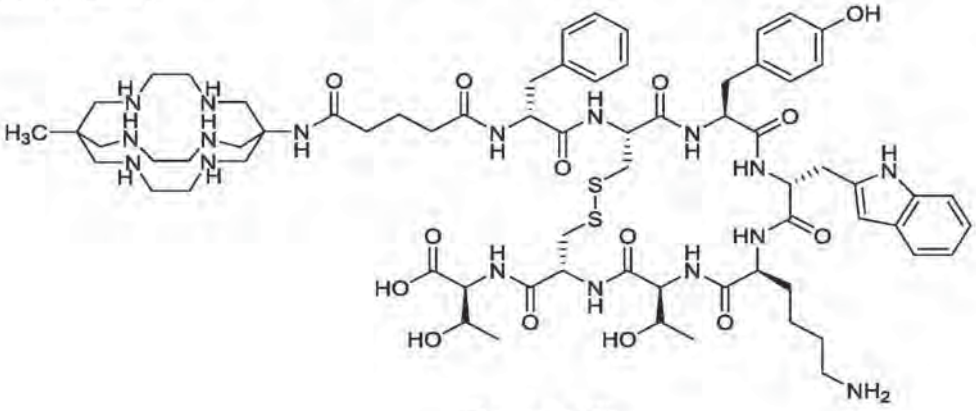
20. A process according to any one of claims 11 to 19, wherein the Cu ion is a Cu radioisotope is selected from the group consisting of ^{60}Cu, ^{61}Cu, ^{64}Cu and ^{67}Cu.

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

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

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

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

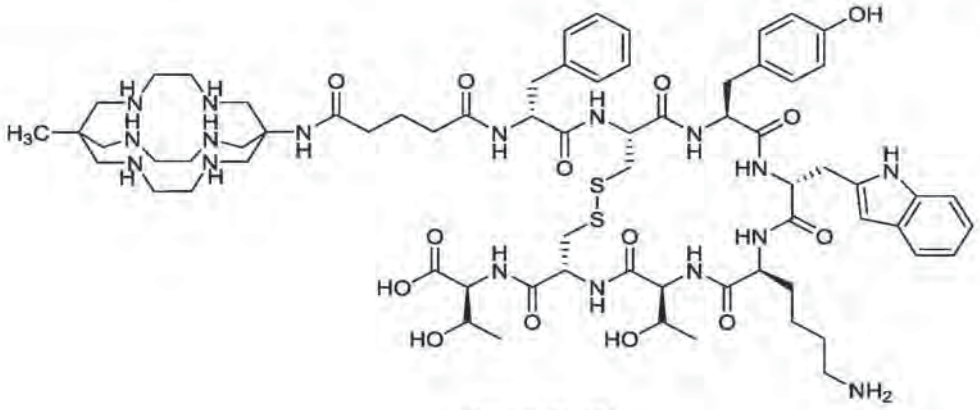


Formula (I)

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

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

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



Formula (I)

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

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

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

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

Figure 1

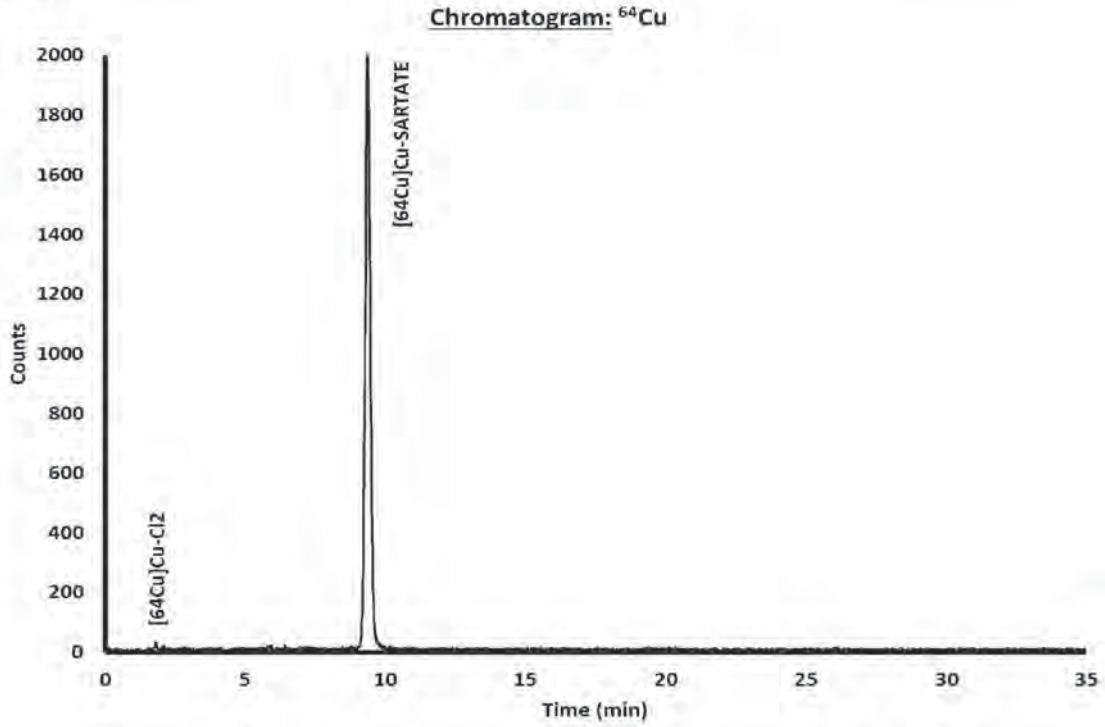


Figure 2

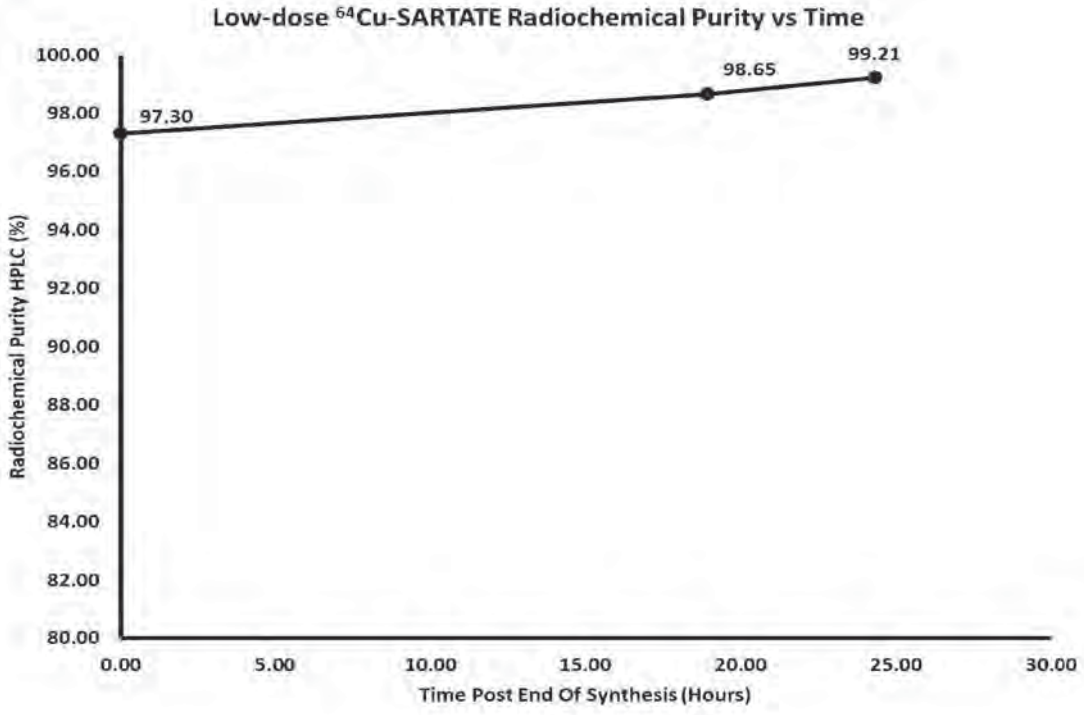


Figure 3

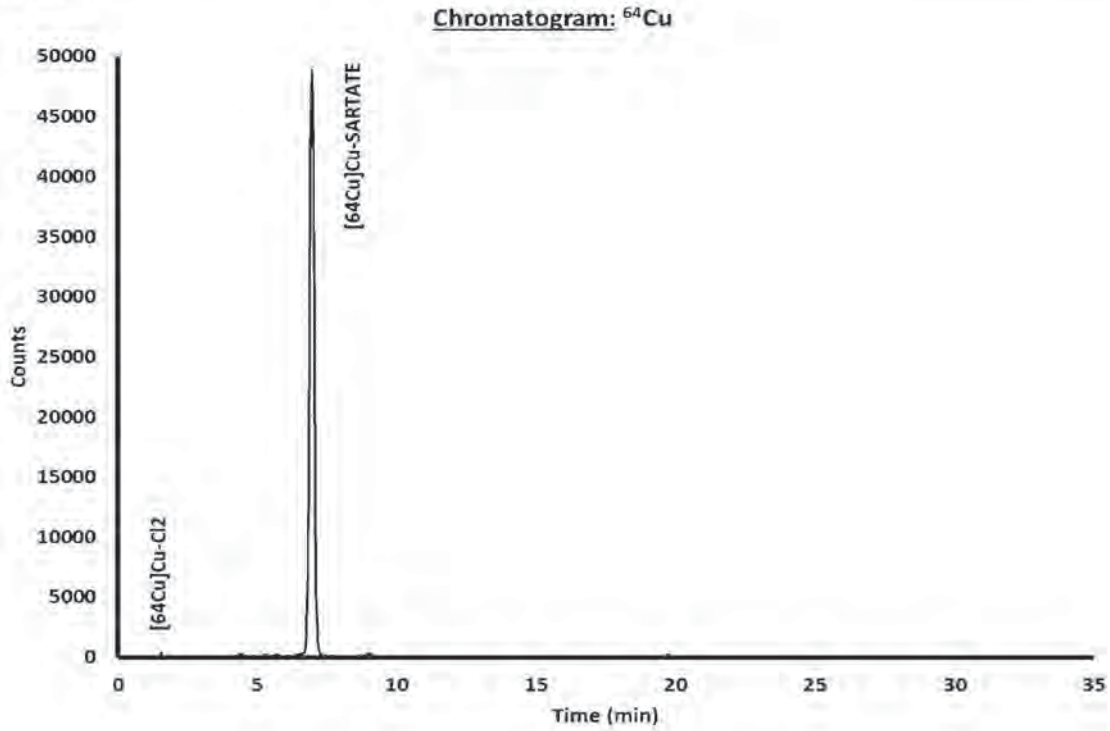


Figure 4

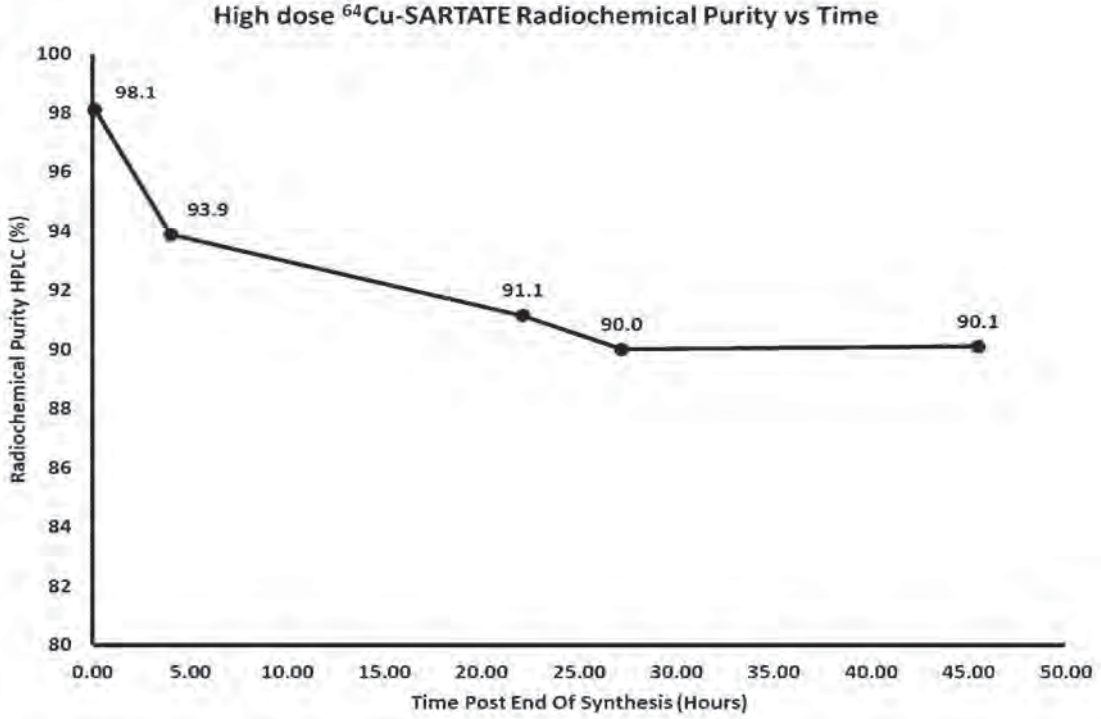


Figure 5

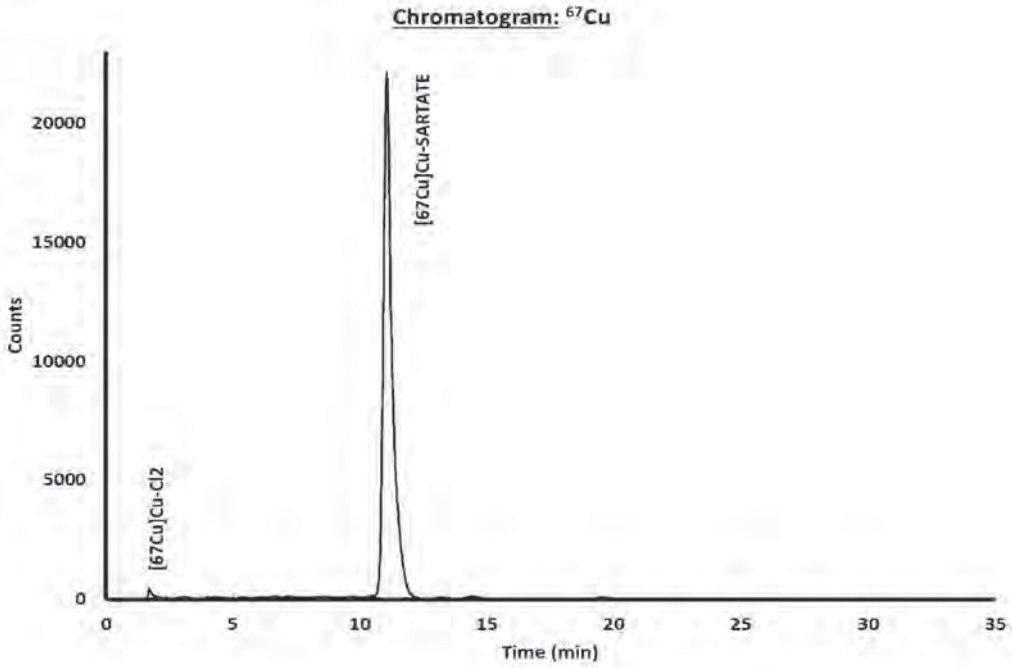


Figure 6

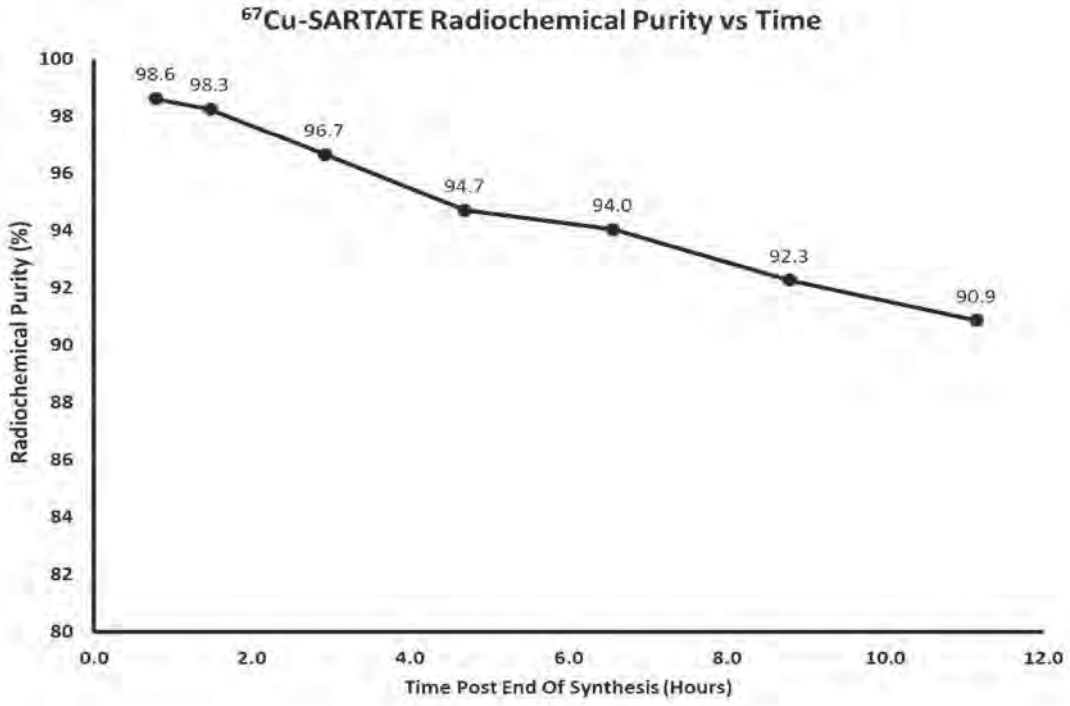


Figure 7

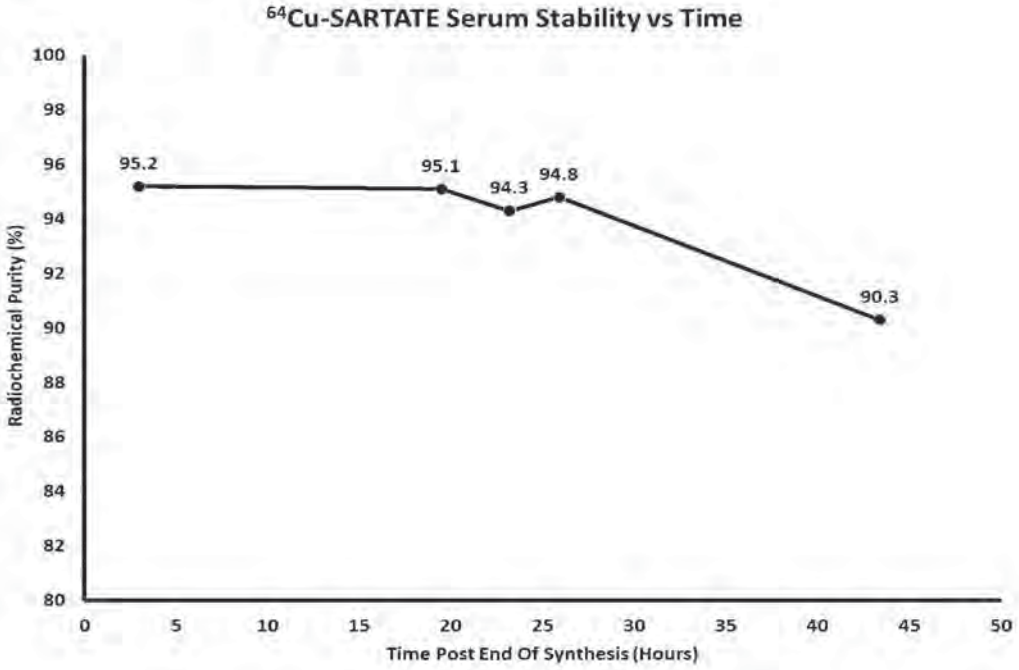


Figure 8

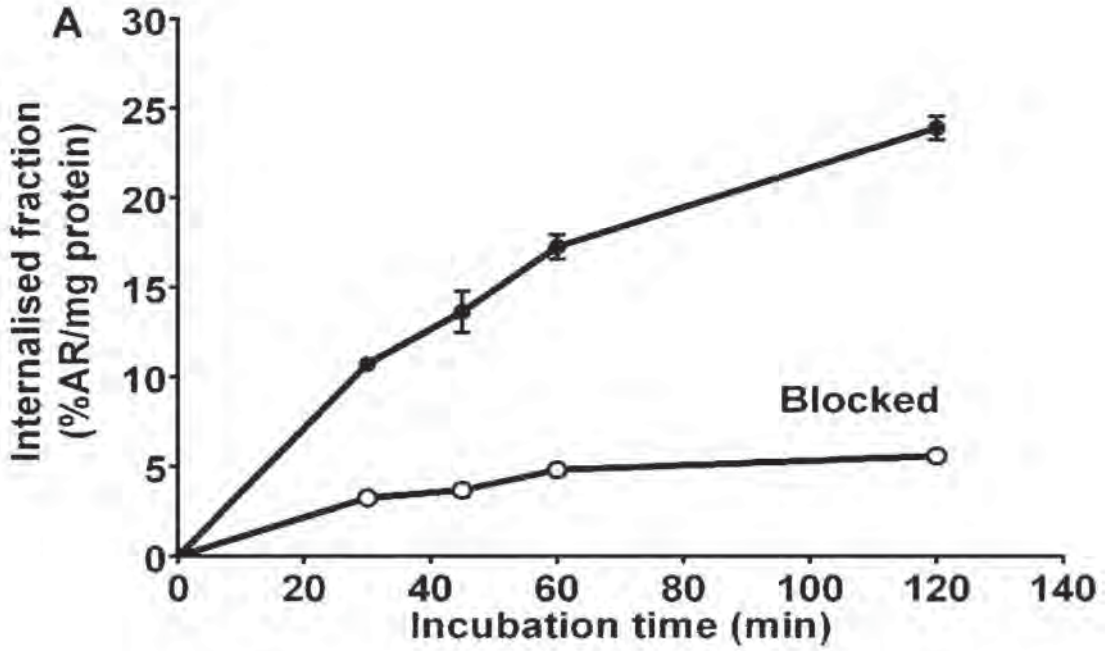


Figure 9

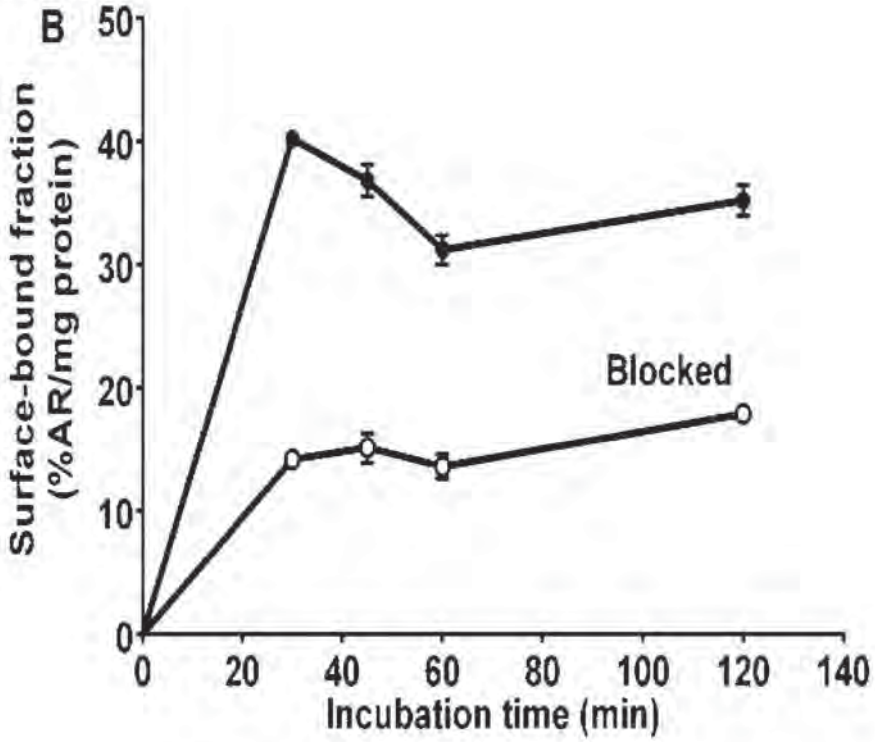


Figure 10

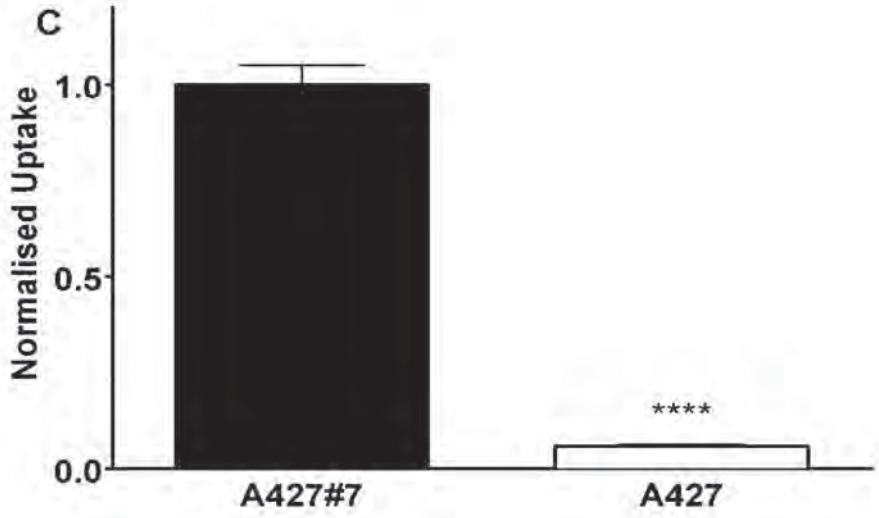


Figure 11

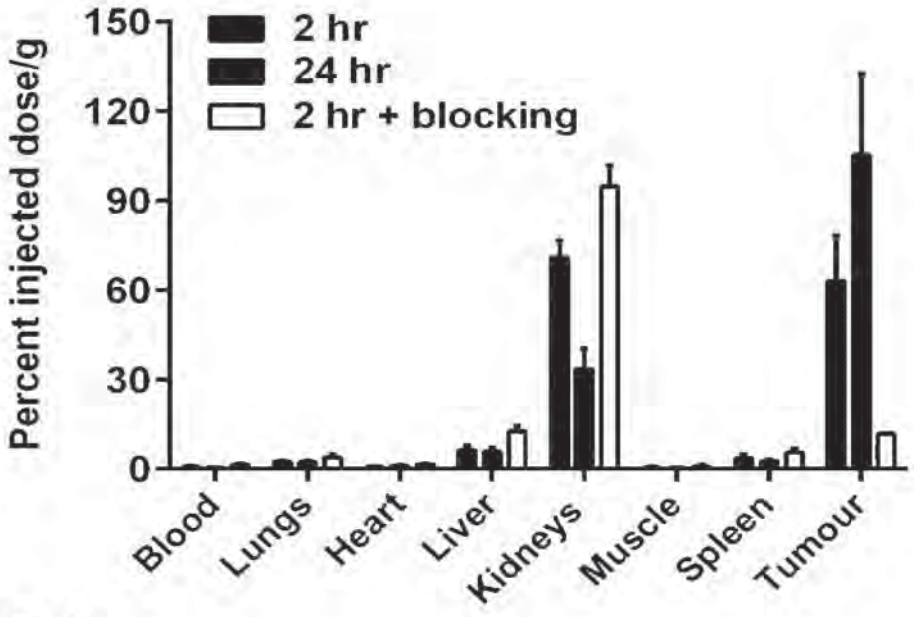
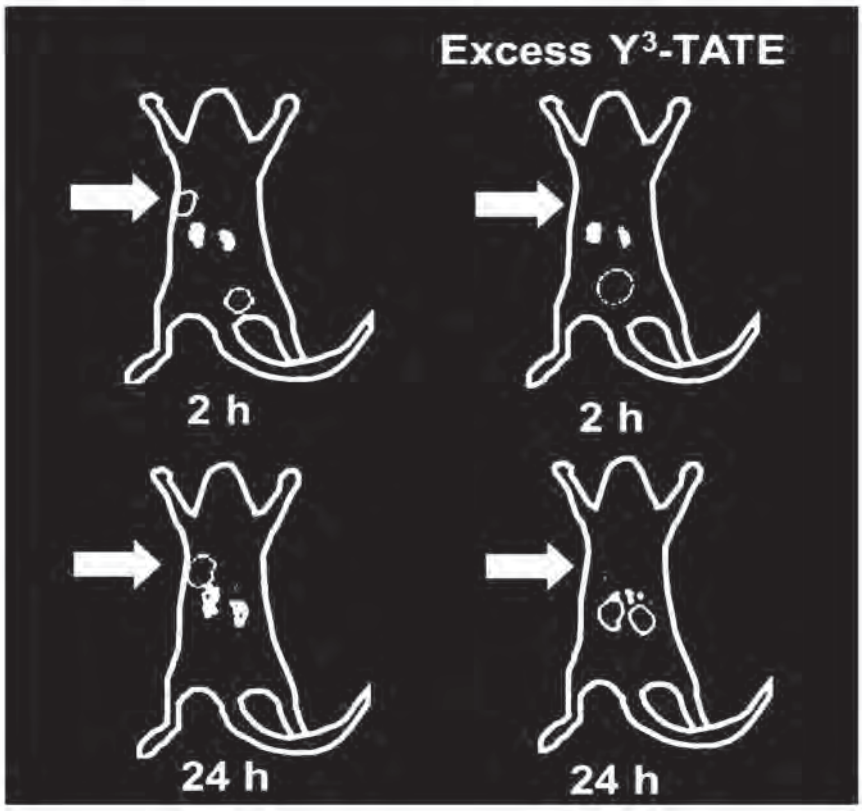


Figure 12



INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2017/051205

A. CLASSIFICATION OF SUBJECT MATTER

A61K 51/08 (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

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

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

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

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

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

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

End of Annex

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/175,239	Filing Date 10/30/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

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

APPLICATION AS AMENDED - PART II

AMENDMENT	04/24/2019	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 22	= 4		x $100 =	400
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	400

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

1095 7590 04/29/2019

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
04/29/2019	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):

php.patents@novartis.com

Applicant-Initiated Interview Summary	Application No. 16/175,239	Applicant(s) de Palo et al.		
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (First Inventor to File) Status Yes	Page 1 of 2

All participants (applicant, applicants representative, PTO personnel):

1. MELISSA J PERREIRA (Examiner); Telephonic 2. Lian Ouyang (Attorney of Record); Telephonic

Date of Interview: 24 April 2019

Claims Discussed: 1

Prior Art Discussed: Chen

Brief Description of the main topic(s) of discussion: Applicant asserts that Chen teaches of the unpredictability of the stabilizers when it comes to which stabilizer to use in a reaction scheme and when to use it in a reaction scheme.

Applicant asserts that the total concentration of the stabilizers in the final solution of Chen is much higher than the total concentration of the final solution of the instant claims.

Applicant asserts that Chen teaches that at 5 mg/ml concentration gentisic acid, ascorbic acid either interfere with the labeling reaction or provide less stability during the reaction.

Issues Discussed:

Item(s) under 35 U.S.C. 103:
The total concentration of final solution of Chen is higher than the total concentration of final solution of the instant claims.

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02

CONFIRMATION NO. 1061

POA ACCEPTANCE LETTER

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

Date Mailed: 04/29/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/24/2019.

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

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

/zabraha/

UNITED STATES PATENT AND TRADEMARK OFFICE

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
16/175,239	10/30/2018	1618	2480	PAT058197-US-CNT02	22	2

CONFIRMATION NO. 1061

UPDATED FILING RECEIPT

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

OC000000108536819

Date Mailed: 05/30/2019

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

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

Inventor(s)

Francesco de Palo, Ivrea, ITALY;
Lorenza Fugazza, Ivrea, ITALY;
Donato Barbato, Ivrea, ITALY;
Maurizio Mariani, Ivrea, ITALY;
Daniela Chicco, Albiano d'Ivrea, ITALY;
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Applicant(s)

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

Domestic Priority data as claimed by applicant

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

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

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

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

Projected Publication Date: 01/30/2020

Non-Publication Request: No

Early Publication Request: No

Title

Stable, concentrated radionuclide complex solutions

Preliminary Class

424

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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

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

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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

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02

CONFIRMATION NO. 1061

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

37 CFR 1.48 ACKNOWLEDGEMENT LETTER

OC000000108536620

Date Mailed: 05/30/2019

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

This is in response to the applicant's request under 37 CFR 1.48(a) submitted on 01/19/2019.

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

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

/ctuazon/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

1095 7590 06/05/2019

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

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
06/05/2019	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. 16/175,239	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 4/24/19.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1-26 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) 1-26 is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claims and Previous Objections/Rejections Status

Claims 1-26 are pending in the application. Claims 23-26 were newly added in the amendment filed 4/29/19.

The rejection of claims 1-22 under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375A1) in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) is withdrawn.

The rejection of claims 1,9,10,12,13 and 19 on the ground of nonstatutory double patenting as being unpatentable over claims 20 and 21 of copending Application No. 16/175,261 (reference application) is maintained.

The rejection of claims 1-22 on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of copending Application No. 16/045,484 (reference application) is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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

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

Claims 1,9,10,12,13 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20 and 21 of copending Application No. 16/175,261 (reference application) as stated in the office action mailed 1/25/19. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of copending Application No. 16/045,484 (reference application) as

stated in the office action mailed 1/25/19. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments

Applicant's arguments, see Remarks/Arguments, filed 4/24/19, with respect to 35 U.S.C. 103 have been fully considered and are persuasive. The rejection of claims 1-22 has been withdrawn.

Applicant's arguments, see Remarks/Arguments, filed 4/24/19, with respect to the rejection(s) of claim(s) 1-22 under 35 U.S.C. 103 have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) and Frilling et al. (*Surgery* **2006**, *140*, 968-977).

New Grounds of Rejection

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

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

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

claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-26 is/are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) Frilling et al. (*Surgery* **2006**, *140*, 968-977).

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

The typical reaction mixture for radiolabeling DOTA-TATE consisted of 60 MBq of ^{177}Lu in 0.01-0.05 M HCl with 2 nmol peptide dissolved in Milli-Q water, sodium acetate as buffer (2.5 M) and 10 µL of quenchers in a final volume of 0.14 mL (final pH 4-4.5). To inhibit oxidation and radiolysis, quenchers were added in various combinations and concentrations prior to radiolabeling. Quenchers included ascorbate, gentisic acid, ethanol and methionine. Any non-incorporated ^{177}Lu will be rapidly captured by the addition of DTPA. DOTA-TATE labelling at therapeutic level (patient's dose) was performed under the kit formulation as previously reported in a concentrated form (60GBq in 3 mL) (p29, 2.1. ^{111}In/^{177}Lu labelling of SS-analogs).

To obtain maximum protection of radiolabeled SS-analogs and minor effect in pharmaceutics, quencher concentration in reaction mixture was investigated time dependently. DOTA-TATE was radiolabeled with 60 MBq ^{177}Lu in the presence of different concentrations of quenchers and 2 nmol DOTA-TATE in a final volume of 0.14 mL. Ascorbic acid and gentisic acid were investigated with final concentrations of 1-20 mM, 1-50 mM for methionine and 2-20% (v/v) for ethanol (p29, 2.4. Optimizing

quencher concentration). Under the experimental conditions the optimal quencher concentration were 3.5 mM for ascorbic and gentisic acid (p30, 3.2. Optimizing quencher concentration; Fig. 2). For example, a reaction mixture of 60MBq ^{177}Lu, 2nmol DOTA-TATE in 0.14 mL contains ascorbic and gentisic acid (3.5 mM) (p30, 3.3. Radiolabelled SS-analogs in the presence of quencher mixtures). The calculated dose during storage is shown in different volumes (5, 50 and 100 mL) of saline containing a therapeutic amount (3.7 GBq) of ^{177}Lu (p30, left column, first paragraph; Fig. 1).

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

de Blois et al. does not disclose 250-500 MBq/mL (i.e. 6.8-13.5 mCi/mL) or about 370 MBq/mL of radionuclide.

Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) discloses the administration of a 10 mCi dose of ^{177}Lu-DOTATATE for diagnostic scanning purposes of neuroendocrine tumors wherein whole body planar images and SPECT-CT images were obtained at 4,24 and 48 hours (abstract; p136, left column, third paragraph; p136, Patients; p136, right column, paragraphs 3 and 6). The results of the pre-therapy whole body ^{177}Lu-DOTATATE diagnostic scans have been encouraging by demonstrating sensitivities comparable with the ^{68}Ge-DOTATOC PET and ^{111}Indium Octreotide scan, opening a whole new approach toward the management of neuroendocrine tumors (p138, Discussion and Conclusion).

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

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

de Blois et al. does not explicitly disclose a.) (bi) gentisic acid is present in a concentration of from 0.5 to 2 mg/mL and (bii) ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL; b.) (ai)/(aii) gentisic acid is present during complex formation in a concentration of from 20 to 40 mg/mL or of from 25 to 35 mg/mL; c.) does not explicitly disclose the absence of ethanol; d.) does not disclose the pH of from 5.0-5.5; or e.) has a shelf life of at least 72 h when stored at ≤ 25°C.

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

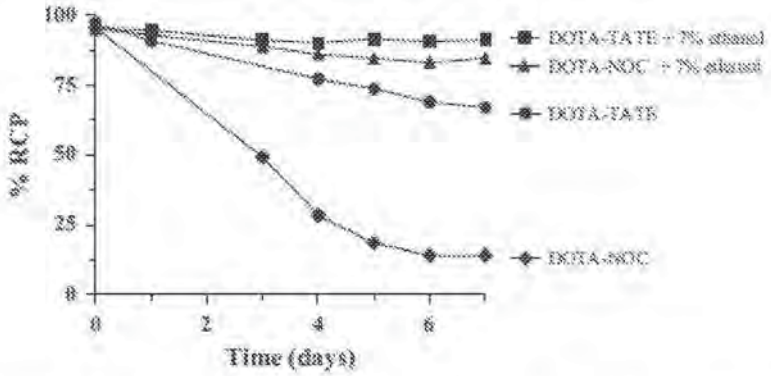
temperature, as shown in the HPLC of FIG. 7 (p86, 5. Development of DOTA-TATE cold kit for the preparation of 177Lu-DOTA-TATE for clinical applications).

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention that the gentisic acid is present in a concentration of from 0.5 to 2 mg/mL and ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL as de Blois et al. teaches that the ascorbic acid and gentisic acid can be combined to provide a final concentrations of 1-20 mM, preferably 3.5 mM for ascorbic and gentisic acid and this would require the use of the low end of the range of final concentration for each stabilizer to yield a total of 3.5 mM.

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

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

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention that the ^{177}Lu-DOTATATE formulation of de Blois et al. does not necessarily comprise ethanol as de Blois et al. specifically teaches that the addition of ethanol dramatically stabilized ^{111}In-DOTA-TATE during 7 days and [^{111}In-DTPA^{0}]octreotide (OctreoScan®) during storage and shows that the addition of ethanol does improve the stabilization of the ^{177}Lu-DOTATATE formulation upon storage over a week (Fig) and RCM meeting discloses that the ^{177}Lu-DOTA-TATE is prepared at the hospital radiopharmacy without ethanol and used after a period of 45 min-1h.



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

Also, RCM meeting discloses that the ^{177}Lu-DOTA-TATE is stable up to 4 d as it retained its radiochemical purity >98% when stored and does not require ethanol.

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention to adjust the pH of the reaction mixture for radiolabeling to pH = 5 as RCM meeting discloses that the complexation yield of ^{177}Lu-DOTA-TATE achievable is highly dependent on the pH.

It would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention that the ^{177}Lu-DOTA-TATE has a shelf life of at least 72 h when stored at ≤ 25°C as RCM meeting discloses that the ^{177}Lu-DOTA-TATE is stable up to 4 d as it retained its radiochemical purity >98% when stored at room temperature, as determined via HPLC.

de Blois et al. does not disclose a.) the concentration of DTPA, b.) concentration of acetic acid, or c.) adding one of the stabilizers during complex formation and one of the stabilizers after the complex formation.

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

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

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

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to utilize DTPA in 4 mg/mL in the stabilized radiopharmaceutical formulations of de Blois et al. for the advantage of complexing any non-incorporated ^{177}Lu, as taught by Maus et al.

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

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

de Blois et al. does not disclose DOTA-TOC.

Frilling et al. (*Surgery* **2006**, *140*, 968-977) discloses that ^{177}Lu-DOTA-TOC has been introduced for the palliative treatment of somatostatin receptor-expressing neuroendocrine tumors (NETs) (abstract; p969, left column, second paragraph). ^{177}Lu is a more favorable agent for labeling DOTATOC for use for somatostatin receptor-targeted radionuclide therapy because of their high energy and longer range (p969, left column, second paragraph).

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 TATE of de Blois et al. for the TOC of Frilling et al. as the ^{177}Lu-DOTA-TOC is analogously used for treatment of NETs and the substitution of one somatostatin targeting moiety for another analogous somatostatin targeting moiety predictably yields a stabilized radiopharmaceutical complex that targets a somatostatin receptor for treatment of NETs.

Response to Arguments

Applicant assertions with regards to Chen et al. are moot as the reference of Chen et al. is not included in the current rejection.

Applicant asserts that Maus et al. teaches away from using lower concentrations of gentisic acid and ascorbic acid.

The reference of Maus et al. was not used to teach of the lower concentrations of gentisic acid and ascorbic acid but was used to teach of the addition of the 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 add one of the stabilizers during complex formation and one of the stabilizers after the complex formation of the stabilized radiopharmaceutical formulations of de Blois et al. as Maus et al. teaches of the study examines the effect of gentisic acid and ascorbic acid as quencher during and after the radiolabeling ^{177}Lu-DOTA-TATE.

The reference of de Blois et al. was used to teach that the gentisic acid is present in a concentration of from 0.5 to 2 mg/mL and ascorbic acid is present in a concentration of from 2.0 to 5.0 mg/mL as de Blois et al. teaches that the ascorbic acid and gentisic acid can be combined to provide a final concentrations of 1-20 mM and therefore, it would have been obvious to one ordinarily skilled in the art before the effective filing date of the claimed invention to vary and optimize the concentration of ascorbic acid and gentisic acid in the ^{177}Lu-DOTA-TATE.

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 1-18,20,21 and 23-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 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 pharmaceutical solution of the instant claims encompasses the pharmaceutical solution of the copending Application No. 16/140,962 as they comprise analogous constituents in analogous concentrations. 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. 16/175,239	Applicant(s)/Patent Under Reexamination de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
	A					
	B					
	C					
	D					
	E					
	F					
	G					
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	K					
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FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	de Blois et al. (Appl. Radiat. Isotop. 2014, 85, 28-33)
	V	Singh et al. (Ind. J. Nucl. Med. 2011, 26, 135-138)
	W	RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012)
	X	Frilling et al. (Surgery 2006, 140, 968-977)

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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	01/18/2019	05/30/2019							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
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	21	✓	✓							
	22	✓	✓							
	23		✓							
	24		✓							
	25		✓							
	26		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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
EAST	01/18/2019	MP
google scholar	01/18/2019	MP
inventor search	01/18/2019	MP
copending application search	01/18/2019	MP
EAST	05/30/2019	MP
google scholar	05/29/2019	MP

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

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	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CNT02

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	1	2018081860	WO	A1	2018-05-11	Clarity Pharmaceuticals PTY LTD		

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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	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CNT02

	1	

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EXAMINER SIGNATURE

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	05/29/2019

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

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1618
Examiner Name	Perreira, Melissa Jean
Attorney Docket Number	PAT058197-US-CNT02

CERTIFICATION STATEMENT

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

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

OR

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

See attached certification statement.

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

A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Lian Ouyang/	Date (YYYY-MM-DD)	2019-04-24
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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Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

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

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S7	40	DOTA near2 TOC	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:01
S8	421	"177" adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:02
S9	1	S8 and S7	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:02
S10	0	177sup? adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:04
S11	0	"177"?sup adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:04
S12	288	sup?177 adj Lu	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:05
S13	0	S7 and S12	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 12:05
S14	14	DOTA near2 edotreotide	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 13:00
S15	0	S14 and S12	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/05/30 13:01

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CASE PAT058197-US-CNT02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1618
Francesco de Palo et al.	Examiner: Perreira, Melissa Jean
APPLICATION NO: 16/175239	Conf. No.: 1061
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 Non-Final Office Action mailed June 5, 2019 (the "Office Action") in the above referenced application. With no extension of time, this response is due on or before September 5, 2019.

Applicant believes no additional fee is due. The Commissioner is authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-4409, Reference No. PAT058197-US-CNT02

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

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

Remarks/Arguments begin on page 6 of this paper.

Amendments to the Claims:

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

Listing of Claims:

1. (Currently Amended) A 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 comprising

(bi) gentisic acid or a salt thereof; and

(bii) ascorbic acid or a salt thereof;

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 1.0 to 5.0 mg/mL; and

the pharmaceutical aqueous solution is substantially free of ethanol, and the radiochemical purity (determined by HPLC) of the solution is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

2. (Currently Amended) [[The]] A pharmaceutical aqueous solution ~~according to claim 1, wherein said component (b),~~ 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) stabilizers against radiolytic degradation ~~consists~~ consisting essentially of two stabilizers:

(bi) gentisic acid or a salt thereof as a first stabilizer; and

(bii) ascorbic acid or a salt thereof as a second stabilizer;

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 1.0 to 5.0 mg/mL.

3. (Previously Presented) The pharmaceutical aqueous solution according to claim 1, wherein

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

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

4. (Original) The pharmaceutical aqueous solution according to claim 3, wherein gentisic acid is present in a concentration of from 0.5 to 1 mg/mL.

5. (Original) The pharmaceutical aqueous solution according to claim 3, further comprising:
(c) diethylentriaminepentaacetic acid (DTPA) or a salt thereof in a concentration of from 0.01 to 0.10 mg/mL.

6. (Original) The pharmaceutical aqueous solution according to claim 5, 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.

7. (Original) The pharmaceutical aqueous solution according to claim 6, wherein said acetate buffer provides for a pH of from 4.5 to 6.0.

8. (Original) The pharmaceutical aqueous solution according to claim 6, wherein said acetate buffer provides a pH of from 5.0 to 5.5.

9. (Original) The pharmaceutical aqueous solution according to claim 1, 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).

10. (Original) The pharmaceutical aqueous solution according to claim 1, 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).

11. (Original) The pharmaceutical aqueous solution according to claim 1, 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.

12. (Original) The pharmaceutical aqueous solution according to claim 9, 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.

13. (Original) The pharmaceutical aqueous solution according to claim 9, 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 20 to 40 mg/mL.

14. (Original) The pharmaceutical aqueous solution according to claim 12, wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formation in a concentration of from 20 to 40 mg/mL.

15. (Original) The pharmaceutical aqueous solution according to claim 11, wherein the only stabilizer present during the complex formation of components (ai) and (aii) is gentisic acid and is present during the complex formation in a concentration of from 25 to 35 mg/mL.

16. (Original) The pharmaceutical aqueous solution according to claim 1, which has a shelf life of at least 72 h when stored at ≤ 25 °C.

17. (Currently Amended) The pharmaceutical aqueous solution according to claim 1, ~~for which the radiochemical purity (determined by HPLC) is maintained at ≥ 95% for at least 72 h when stored at 25 °C~~ which is a single dose that allows delivery of 7.4 GBq ± 10 % of radioactivity at injection time.

18. (Original) The pharmaceutical aqueous solution according to claim 1, wherein said solution is produced at a batch size of at least 20 GBq, at least 50 GBq, or at least 70 GBq.

19. (Currently Amended) The pharmaceutical aqueous solution according to claim 17, which is ~~free of ethanol~~ provided in a volume of 20.5 to 25.0 mL.

20. (Original) The pharmaceutical aqueous solution according to claim 1, wherein the somatostatin receptor binding peptide linked to the chelating agent DOTA is DOTA-TATE (oxodotreotide) or DOTA-TOC (edotreotide).

21. (Currently Amended) 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) DOTA-TATE or DOTA-TOC;

(b) the 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; wherein the pharmaceutical aqueous solution is substantially free of ethanol, and the radiochemical purity (determined by HPLC) of the solution is maintained at ≥ 95% for at least 72 h when stored at 25 °C.

22. (Currently Amended) The pharmaceutical aqueous solution according to claim 21, which is ~~free of ethanol~~ a single dose that allows delivery of 7.4 GBq ± 10 % of radioactivity at injection time.

23. (Previously Presented) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TATE.

24. (Previously Presented) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TOC.

25. (Previously Presented) The pharmaceutical aqueous solution according to claim 21, wherein said component (b) consists essentially of two stabilizers:

(bi) gentisic acid or a salt thereof as a first stabilizer; and

(bii) ascorbic acid or a salt thereof as a second stabilizer.

26. (Previously Presented) The pharmaceutical aqueous solution according to claim 21, wherein said complex is formed by the radionuclide ^{177}Lu and DOTA-TATE with a volumetric radioactivity of about 370 MBq/mL, and said component (b) comprises gentisic acid in a concentration of about 0.63 mg/mL and ascorbic acid in a concentration of about 2.80 mg/mL.

Remarks/Arguments

Upon entry of the amendments herein, claims 1-26 are pending. Claims 1, 2, 17, 19, and 21-22 have been amended. Support of the amendments appears in the original application as filed, at e.g., original claims 19 and 22, page 5, lines 6-9, and page 44, lines 24-32. No new matter has been introduced.

Claim Rejections-35 U.S.C. § 103

Applicant notes that the previous rejection of original claims 1-22 under 35 U.S.C. 103 as being unpatentable over Chen et al. (US 2007/0269375, "Chen") in view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, 1, 5-12, "Maus") is withdrawn. *See* the Office Action at page 2. A new ground of rejection is made. Specifically, claims 1-26 are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (Appl. Radiat. Isotop. **2014**, 85, 28-33; "de Blois") in view of Singh et al. (Ind. J. Nucl. Med. **2011**, 26, 135-138; "Singh") and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu and 90Y-labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, **2012**; "RCM") and in further view of Maus and Frilling et al. (Surgery **2006**, 140, 968-977; "Frilling"). *See* the Office Action at pages 4-11.

Each of the independent claims 1 and 21 is directed to a pharmaceutical aqueous solution that comprises, *inter alia*, (a) a complex of ^{177}Lu (Lutetium-177) and a somatostatin receptor binding peptide linked to the chelating agent DOTA (e.g., DOTA-TATE or DOTA-TOC in claim 21); and (b) at least two different stabilizers against radiolytic degradation, which include gentisic acid or a salt thereof and ascorbic acid or a salt thereof; wherein the radionuclide ^{177}Lu is present in a concentration that it provides a volumetric radioactivity of from 250 to 500 MBq/mL (i.e., 6.8-13.5 mCi/mL), wherein the solution is substantially **free of ethanol** and the **radiochemical purity (RCP)** of the solution is maintained at **≥ 95% for at least 72 h when stored at 25 °C**.

According to the Examiner, de Blois discloses that use of **ethanol**, in combination with a mixture of gentisic and ascorbic acid, has superior effects on stabilizing radiolabeled somatostatin analogs, and as a consequence, ^{177}Lu-labelled somatostatin analogs can be stored and transported in a single vial ready to use liquid formulation up to 7 days after radiolabeling (abstract). Also, de Blois teaches a typical reaction mixture for radiolabeling DOTA-TATE consisted of 60 MBq of ^{177}Lu in a final volume of 0.14 mL, buffer, and quenchers that include ascorbate, gentisic acid, **ethanol** and methionine. *See* the Office Action at pages 5-6. Applicant would like to point out de Blois **teaches away** from the claimed solution which is substantially **free of ethanol** while maintaining a RCP of **≥ 95% for at least 72 h when stored at 25 °C**. More specifically, de Blois discloses various ^{177}Lu-DOTA-TATE solutions containing different quencher mixtures, some with ethanol and the others without. *See* de Blois p30, section 3.3 and

page 33, Figures 6-7, which are reproduced below to facilitate discussion (dashed lines added to indicate RCP of ^{177}Lu-DOTA-TATE solutions absent ethanol at 72 h, i.e., 3 days).

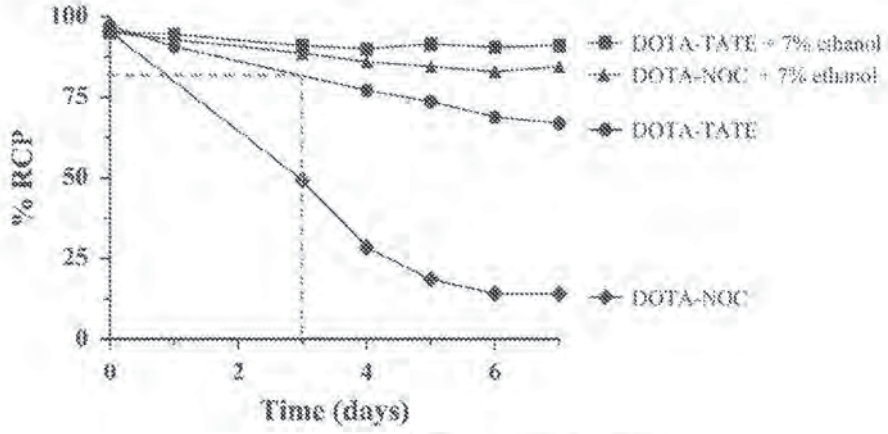

Figure 6 of de Blois

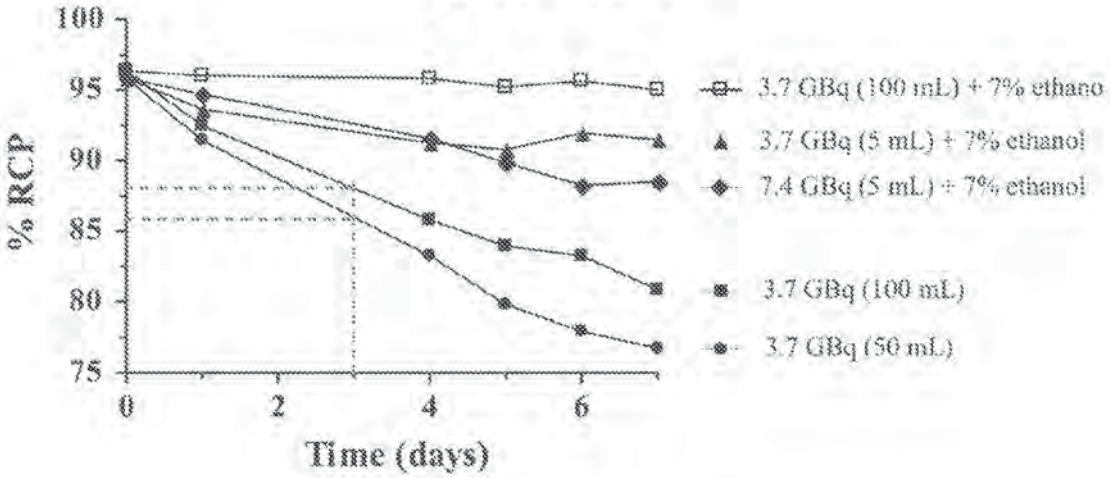

Figure 7 of de Blois

As clearly shown in the figures above, **absent ethanol**, the RCP of ^{177}Lu-DOTA-TATE solutions dropped to **less than 90%** after storing for 72 hrs. In contrast, adding ethanol helps to maintain the RCP of ^{177}Lu-DOTA-TATE solutions at 90% or above. Accordingly, de Blois **teaches away** from the claimed solution, which is substantially **free of ethanol** while maintaining a RCP of ≥ **95% for at least 72 h when stored at 25 °C**.

The Examiner further contends that the secondary reference RCM discloses that the ^{177}Lu-DOTA-TATE is stable up to 4 days as it retained its radiochemical purity >98% when stored and does not require ethanol. *See* the Office Action at page 9. Applicant notes that the ^{177}Lu-DOTA-TATE solution disclosed in RCM does not contain ascorbic acid or a salt thereof that is used in the claimed solution. In addition, nowhere does RCM teach or suggest the volume of the ^{177}Lu-DOTA-TATE solution tested for stability. Thus, RCM does not teach or

suggest the **volumetric radioactivity,** 250 to 500 MBq/mL, recited in claim 1 or 21.[1] Accordingly, even if de Blois and RCM were combined, the resulting solution would be different from the claimed solutions. Further, Maus also teaches that RCP of ^{177}Lu-DOTATATE is an essential factor for successful peptide receptor-targeted radionuclide therapy (*see* Introduction at pages 5-6). The proposed modification by the Examiner to de Blois, i.e., removing ethanol, would render the solutions in de Blois unstable for storage and transport, and thus render de Blois unsatisfactory RCP for its intended purpose for patient infusion. The Examiner is reminded that prior art must be considered in its entirety, including disclosures that teach away from the claims and that proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference. *See* MPEP §§ 2141.02 and 2143.01.

The Examiner further relies on multiple secondary references: (i) Singh for disclosing the administration of a 10 mCi (i.e., 370 MBq) dose of ^{177}Lu-DOTATATE, (ii) Maus for disclosing DTPA in 4 mg/mL and (iii) Frilling for disclosing DOTA-TOC. Initially, Applicant notes that Singh merely discloses the **absolute dose of radioactivity** of ^{177}Lu-DOTATATE, 370 MBq, without disclosing the volume of the formulation. Accordingly, a skilled artisan would not have any knowledge of **volumetric radioactivity** of the formulation used in Singh, not to mention that she or he would have been motivated in any way to arrive at the claimed solution with the specific volumetric radioactivity of 250 to 500 MBq/mL recited in claims 1 and 21. In view of de Blois and these secondary references, the Examiner contends that it is obvious to vary and/or optimize the amounts of ^{177}Lu, gentisic acid, ascorbic acid, or DTPA provided in the claimed solutions, quoting "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). *See* the Office Actin at pages 7-10. Applicant disagrees and would like to point out that optimization of the application parameters had not been within the level of ordinary skill in the art at least because of the **unpredictable** nature of stabilizers (e.g., their types, timing of adding them, and their amounts) as evidenced by the teachings in Chen cited by the Examiner in the previous office action. Specifically, Chen in many places has stressed the **unpredictability** in selecting stabilizers and in when and how much the stabilizers are added. For example, in Example 3, Chen evaluated eight stabilizers, including ascorbic acid and gentisic acid sodium salts, and found that **none** of the eight reagents **provided adequate radiostability** for 48 hours. *See* paragraph [0265]. Chen further states that this result is "**unexpected** as gentisic acid, ascorbic acid, HSA and 3,4-pyridinedicarboxylic acid have all been reported by others to provide satisfactory protection against radiolysis for other radiopharmaceuticals.... The reagent 3,4-pyridinedicarboxylic acid, previously reported as an effective radiostabilizer, was found to **interfere badly** with the labeling

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

reaction." *Id.*; emphases added. In other words, the general conditions of the pending claims are not disclosed in the prior art at least for the unpredictable nature of stabilizers. Accordingly, it is not obvious to optimize the amounts of ^{177}Lu, gentisic acid, and ascorbic acid by routine experimentation to arrive at the claimed solutions.

In summary, the Examiner has failed to present a proper *prima facie* case of obviousness for claims 1-26 for at least the reasons set forth above. Instead, it is clear that the Examiner's obviousness rejection is based solely on impermissible hindsight in which Applicant's specification and claims were used as a blueprint to cherry pick elements from as many as **five** prior art references and piece together the invention of the pending claims. This is contrary to the MPEP 2141.02 that requires a prior art reference be "considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention" (emphasis original) and the long standing case law that requires that any judgment on obviousness must "not include knowledge gleaned only from applicant's disclosure." *See*, *In re McLaughlin*, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971).

Further, the invention of the pending claims is also non-obvious in view of the combined teachings of the cited references for unexpected results set forth herein. The instant application provides sufficient evidence to demonstrate that the claimed **ethanol-free** pharmaceutical aqueous solution, with the recited concentrations of gentisic acid and ascorbic acid or salts thereof, are stable (e.g., RCP as determined by HPLC being maintained at ≥ 95%) for at least 72 hours when stored at 25 °C. *See e.g.*, Example 3 of the instant application. This effect was not present in the teachings of any of the cited references, and would not have been expected or predicted by a skilled artisan. For example, as taught by de Blois, **absent ethanol**, the RCP of ^{177}Lu-DOTA-TATE solutions dropped to **less than 90%** after storing for 72 hrs. Even considering de Blois' higher concentrated solution with ethanol (3.7 GBq/5mL, i.e., 740 MBq/mL), the RCP at 72 hrs has dropped to lower than 95% (see Fig. 7 of de Blois).

"Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness. *See*, *e.g.*, *In re Albrecht,* 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)." *See* MPEP § 2145. Accordingly, independent claim 1 or 21 is also patentable over de Blois in combination with all secondary references for unexpected stability. For at least the same reasons stated above, claims 2-20, each of which depends directly or indirectly from claim 1, and claims 22-23, each of which depends from claim 21, are also patentable over cited references, taken alone or in combination. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 2 has been rewritten as an independent claim and is patentable over the cited references on a similar ground. Claim 2 recites that component (b) **consists essentially** of two stabilizers: (bi) gentisic acid or a salt thereof as a first stabilizer, and (bii) ascorbic acid or a salt thereof as a second stabilizer. In contrast, the stable formulations taught in de Blois contains at

least four stabilizers, ascorbic acid, gentisic acid, **methionine** and **ethanol**. Given the **unpredictable** nature of stabilizers as discussed above and teaching away by de Blois, a skilled artisan would not have been motivated to modify the teachings in de Blois in view of the other cited references to get rid of methionine and ethanol to arrive at the stable pharmaceutical aqueous solution in claim 2 with a reasonable expectation of success. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Claim 12 is also patentable over the cited references on an additional ground. It is further noted that de Blois, in view of Chen, **teaches away** from presenting higher than 5 mg/mL gentisic acid or ascorbic acid at the radiolabeling reaction. de Blois teaches that the concentration of ascorbic acid and gentisic acid at the radiolabeling reaction is optimized to 3.5 mM or 3.5 millimoles per liter, which is equal to **0.5-0.6 mg/mL** ascorbic acid and gentisic acid, much lower than the total concentration of from **15 to 50 mg/mL** recited in claim 12. *See* de Blois p29, section 2.5. This low concentration of stabilizers at the radiolabeling reaction is consistent with the teachings in Chen, which state that, at the concentration of 5 mg/mL, gentisic acid or ascorbic acid either **interferes** with the labeling reaction or provides **less stability** during the reaction. *See, e.g.*, paragraph [0290] of Chen. In contrast, claim 12 recites that during the complex formation (i.e., the labeling reaction), at least one of the stabilizers is present in a total concentration of from **15 to 50 mg/mL**. *See also* Example 2 of the instant application. None of Singh, RCM, Maus and Frilling corrects this defect of de Blois, at least because none of these references addresses the impact of concentrations of gentisic acid or ascorbic acid to the radiolabeling reaction. As increasing the concentration to greater than 5 mg/mL of gentisic acid or ascorbic acid at the radiolabeling reaction would render decreased stability in the formulations as indicated by de Blois in view of Chen, it teaches away from the invention of claim 12 which recites stabilizers present in the radiolabeling reaction at a total concentration of from **15 to 50 mg/mL**. Accordingly, the pharmaceutical aqueous solution of claim 12 is nonobvious over de Blois, either taken alone or in combination with other references cited by the Examiner on this additional ground. As is claim 14, which depends from claim 12. Applicant respectfully requests reconsideration and withdrawal of the rejection.

Double Patenting

Claims 1, 9, 10, 12, 13, and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20-21 of copending U.S. Application No. 16/175,261; claims 1-22 are provisionally rejected over claims 1-31 of copending U.S. Application No. 16/045,484; and claims 1-18,20,21 and 23-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 29 of copending Application No. 16/140,962. *See* the Office Action at pages 2 and 13.

Without arguing the propriety of this rejection, Applicant respectfully requests that the provisional nonstatutory double patenting rejections over copending U.S. Application Nos. 16/175,261, 16/045,484 and 16/140,962 be held in abeyance until allowable subject matter in the present application has been determined.

In view of the above remarks, Applicant submits that the pending application is in condition for allowance. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith, to our Deposit Account No. 50-4409, under Docket No. PAT058197-US-CNT02.

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

Respectfully submitted,

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

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+1 617 871 3880

Date: September 5, 2019

Electronic Acknowledgement Receipt

EFS ID:	37078329
Application Number:	16175239
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CNT02
Receipt Date:	05-SEP-2019
Filing Date:	30-OCT-2018
Time Stamp:	17:07:08
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PAT058197_US_CNT02_Nonfinal_Sept5_2019_Signed.pdf	676168 3fc86c1a88257ec3494b1718fd585f6919aa630c	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	11
Warnings:			
Information:			
	Total Files Size (in bytes):	676168	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 16/175,239	Filing Date 10/30/2018	☐ To be Mailed

ENTITY: ☑ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

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

APPLICATION AS AMENDED - PART II

AMENDMENT	09/05/2019	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 26	= 0		x $100 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	*** 3	= 0		x $460 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

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

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

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

1095 7590 11/04/2019

NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
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EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
11/04/2019	ELECTRONIC

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

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

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

phip.patents@novartis.com

Office Action Summary	Application No. 16/175,239	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

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

Period for Reply

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

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

Status

1)☑ Responsive to communication(s) filed on 9/5/19.

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

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

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

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

Disposition of Claims*

5) ☑ Claim(s) 1-26 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) 1-26 is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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

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

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

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

Attachment(s)

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

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

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

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

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

Claims and Previous Objections/Rejections Status

Claims 1-26 are pending in the application.

The rejection of claims 1-26 under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) Frilling et al. (*Surgery* **2006**, *140*, 968-977) is maintained.

The rejection of claims 1,9,10,12,13 and 19 on the ground of nonstatutory double patenting as being unpatentable over claims 20 and 21 of copending Application No. 16/175,261 (reference application) is maintained.

The rejection of claims 1-26 on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of copending Application No. 16/045,484 (reference application) is maintained.

The rejection of claims 1-18,20,21 and 23-26 on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 29 of copending Application No. 16/140,962 (reference application) is maintained.

Response to Arguments

Applicant's arguments filed 9/5/19 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

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

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

Claims 1-26 is/are rejected under 35 U.S.C. 103 as being unpatentable over de Blois et al. (*Appl. Radiat. Isotop.* **2014**, 85, 28-33) in view of Singh et al. (*Ind. J. Nucl. Med.* **2011**, *26*, 135-138) and RCM meeting (Development and preclinical evaluation of therapeutic radiopharmaceuticals based on 177Lu- and 90Y- labelled monoclonal antibodies and peptides: Stip, Republic of Macedonia October 01-05, 2012) and in further view of Maus et al. (*Int. J. Diagnost. Imaging* **2014**, *1*, 5-12) Frilling et al. (*Surgery* **2006**, *140*, 968-977) as stated in the office action mailed 6/5/19.

Applicant's assertions with regard to Chen are moot as it is not included in the instant rejection.

Applicant asserts that de Blois discloses the use of ethanol, in combination with a mixture of gentisic and ascorbic acid which teaches away from the claimed solution which is substantially free of ethanol while remaining a RCP of ≥ 95% for at least 72 h when stored at 25°C. Absent ethanol, the RCP of ^{177}Lu-DOTA-TATE solution dropped to less than 90% after storing for 72 hrs. In contrast, adding ethanol helps to maintain the RCP of ^{177}Lu-DOTA-TATE solutions at 90% or above.

The specification recites that "at least the amount of ethanol in the solutions of the present invention should be limited, e.g. less than 5%, preferably less than 2%, more preferably less than 1% in the final solution" which is being understood to define the limitation "substantially free of ethanol" as recited in the instant claim.

The reference of de Blois et al. teaches that concentration of ethanol is 2-20% (v/v) for ethanol. Therefore, it would have been obvious to one ordinarily skilled in the art to reduce the amount of ethanol to about 2% which encompasses the "substantially free of ethanol" amount of the instant claims.

Applicant asserts that in RCM the ^{177}Lu-DOTA-TATE does not contain ascorbic acid or a salt thereof that is used in the claimed solution. In addition, nowhere does RCM teach or suggest the volume of the ^{177}Lu-DOTA-TATE solution tested for stability. Thus, RCM does not suggest the volumetric radioactivity, 250 to 500 MBq/mL.

The reference of RCM teaches of stability studies after labeling DOTA-SP (Nle) with 33 MBq of ^{177}Lu with the addition of ascorbic acid or gentisic acid as stabilizers immediate after labeling. The RCP was determined to be 98.0 ± 0.1 with ascorbic acid and 97.8 ± 0.3 with gentisic acid after 24 hours. The acceptance limit for RCP is ≥ 95% (p12, 5.2.2 Quality control).

The reference of de Blois et al. teaches that the combination of gentisic acid, ascorbic acid and 2% ethanol can be used for stabilization.

Therefore, it would have been obvious to modify the amount of each stabilizer to provide for an acceptance limit for RCP of ≥ 95%.

Applicant asserts that Maus teaches that RCP of ^{177}Lu-DOTA-TATE is an essential factor for successful peptide receptor-targeted radionuclide therapy. The proposed modification to de Blois, removing ethanol, would render the solution in de Blois unstable for storage and transport, and thus render de Blois unsatisfactory RCP for its intended purpose for patient infusion.

The reference of Maus was used to teach that the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis of the ^{177}Lu-DOTA-TATE. The removal of gentisic acid and ascorbic acid decrease RCP <95% but reintroduction of ascorbic acid resulted in a RCP ≥ 95% at 72h.

Therefore, it would have been obvious to modify the amount of each stabilizer to provide for an acceptance limit for RCP of ≥ 95% wherein the stabilizers do not necessarily include ethanol or is substantially free of ethanol and provide an RCP ≥ 95% at 72h.

Applicant asserts that optimization of the application parameters had not been within the level of ordinary skill in the art at least because of the unpredictable nature of stabilizers (e.g. their types, timing of adding them, and their amounts).

The reference of Maus was used to teach that the use of gentisic acid and ascorbic acid to reduce the effects of radiolysis of the ^{177}Lu-DOTA-TATE. The removal of gentisic acid and ascorbic acid decrease RCP <95% but reintroduction of ascorbic acid resulted in a RCP ≥ 95% at 72h. The ^{177}Lu-DOTA-TATE without tC18 purification post-radiolabeling remained stable RCP ≥ 95% at 72h but with tC18 purification resulted in 95% RCP after ~35h and 92% at 72h post radiolabeling. Therefore, the RCP does not vary greatly, such as from 95% to 92%.

The reference of de Blois et al. teaches that the combination of gentisic acid, ascorbic acid and 2% ethanol can be used for stabilization.

Therefore, it would have been predictable that ^{177}Lu-DOTA-TATE has an RCP of 95% ~35h and that addition of gentisic acid, ascorbic acid or a combination post radiolabeling helps to maintain the RCP to ≥ 95% at 72h.

Applicant asserts that Singh merely discloses the absolute dose of radioactivity of ^{177}Lu-DOTA-TATE, 370 MBq, without disclosing the volume of the formulation. Accordingly, a skilled artisan would not have any knowledge of volumetric radioactivity of the formulation, not to mention that she or he

would have been motivated in any way to arrive at the claimed solution with the specific volumetric radioactivity of 250 to 500 MBq/mL.

The reference of Singh teaches of a ten millicuries administered as a slow intravenous injection and therefore, it would have been predictable to provide a constant ten millicuries over the course of an intravenous injection which necessarily is included in a large volume of solution to provide for images at 4, 24 and 48 hours post injection.

Also, the instant claims are product claims drawn to a pharmaceutical aqueous solution and therefore, it would have been predictable to one ordinarily skilled in the art to provide a concentration of a radiolabeled complex in a volume of solution within a vial/container and to vary the amount of radiolabeled complex and/or volume of liquid for storage, transportation, etc. for use in a hospital wherein the whole complex or a portion of the complex is used in a medical procedure.

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 1,9,10,12,13 and 19 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 20 and 21 of copending Application No. 16/175,261 (reference application) as stated in the office action mailed 6/5/19. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-31 of copending Application No. 16/045,484 (reference application) as stated in the office action mailed 6/5/19. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-18,20,21 and 23-26 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 and 29 of copending Application No. 16/140,962 (reference application) as stated in the office action mailed 6/5/19. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Applicant asserts that the provisional nonstatutory double patenting rejections be held in abeyance until allowable subject matter in the present application has been determined.

The rejections are maintained as the claims are not allowable.

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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

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

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

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

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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
EAST	01/18/2019	MP
google scholar	01/18/2019	MP
inventor search	01/18/2019	MP
copending application search	01/18/2019	MP
EAST	05/30/2019	MP
google scholar	05/29/2019	MP
EAST	10/25/2019	MP

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

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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	01/18/2019	05/30/2019	10/25/2019						
	1	✓	✓	✓						
	2	✓	✓	✓						
	3	✓	✓	✓						
	4	✓	✓	✓						
	5	✓	✓	✓						
	6	✓	✓	✓						
	7	✓	✓	✓						
	8	✓	✓	✓						
	9	✓	✓	✓						
	10	✓	✓	✓						
	11	✓	✓	✓						
	12	✓	✓	✓						
	13	✓	✓	✓						
	14	✓	✓	✓						
	15	✓	✓	✓						
	16	✓	✓	✓						
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	18	✓	✓	✓						
	19	✓	✓	✓						
	20	✓	✓	✓						
	21	✓	✓	✓						
	22	✓	✓	✓						
	23		✓	✓						
	24		✓	✓						
	25		✓	✓						
	26		✓	✓						

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S16	74	DOTA same TATE	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	ON	2019/10/25 14:38

10/ 28/ 2019 2:15:52 PM
C:\ Users\ mperreira\ Documents\ EAST\ Workspaces\ 16175239.wsp

UNITED STATES PATENT AND TRADEMARK OFFICE

USPTO Automated Interview Request (AIR)

Jan 15 2020

This paper requesting to schedule and/or conduct an interview is appropriate because:

This submission is requested to be accepted as an authorization for this interview to communicate via the internet. Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned concerning scheduling of the interview via video conference, instant messaging, or electronic mail, and to conduct the interview in accordance with office practice including video conferencing.

Name(s):
Lian Ouyang

S-signature:
/Lian Ouyang/

Registration Number:
69254

U.S. Application Number:
16175239

Confirmation Number:
1061

E-mail Address:
lian.ouyang@novartis.com

Phone Number:
+1 6178713880

Proposed Time of Interview:
1-23-2020 11:00 AM ET

Alternative Proposed Time(s) of Interview:
1-24-2020 10:30 AM ET

Alternative Proposed Time(s) of Interview:
1-24-2020 11:00 AM ET

Prefered Interview Type:
Telephonic

I am the applicant or applicant's representative for this application.

Topic for Discussion:
103 rejection and cited references

uspto UNITED STATES PATENT AND TRADEMARK OFFICE

Doc Code: DIST.E.FILE Document Description: Electronic Terminal Disclaimer - Filed	PTO/SB/25 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION**
Application Number	16175239
Filing Date	30-Oct-2018
First Named Inventor	Francesco de Palo
Attorney Docket Number	PAT058197-US-CNT02
Title of Invention	Stable, concentrated radionuclide complex solutions

☒ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☒ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Advanced Accelerator Applications (Italy) Srl	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

16175261 filed on 10/30/2018

16140962 filed on 09/25/2018

16045484 filed on 07/25/2018

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

◉ Terminal disclaimer fee under 37 CFR 1.20(d) is included with Electronic Terminal Disclaimer request. ○ I certify, in accordance with 37 CFR 1.4(d)(4), that the terminal disclaimer fee under 37 CFR 1.20(d) required for this terminal disclaimer has already been paid in the above-identified application.	
Applicant claims the following fee status: ○ Small Entity ○ Micro Entity ◉ Regular Undiscounted I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.	
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application Registration Number 69254 ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this request	
Signature	/Lian Ouyang/
Name	Lian Ouyang

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner).
Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

Electronic Patent Application Fee Transmittal

Application Number:	16175239
Filing Date:	30-Oct-2018
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang/Susan Dillon
Attorney Docket Number:	PAT058197-US-CNT02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	160

Doc Code: DISQ.E.FILE
Document Description: Electronic Terminal Disclaimer – Approved

Application No.: 16175239

Filing Date: 30-Oct-2018

Applicant/Patent under Reexamination: de Palo

Electronic Terminal Disclaimer filed on January 28, 2020

☒ APPROVED

This patent is subject to a terminal disclaimer

☐ DISAPPROVED

Approved/Disapproved by: Electronic Terminal Disclaimer automatically approved by EFS-Web

U.S. Patent and Trademark Office

Electronic Acknowledgement Receipt

EFS ID:	38420031
Application Number:	16175239
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CNT02
Receipt Date:	28-JAN-2020
Filing Date:	30-OCT-2018
Time Stamp:	15:03:35
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	E20201RF03333029
Deposit Account	504409
Authorized User	Susan Dillon

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

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

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Terminal Disclaimer-Filed (Electronic)	eTerminal-Disclaimer.pdf	35181 19896ca25817e9c261830abfb78753cee52961f7	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30497 fa0e665a8e95155af17abe7e910a12f4f40ee0c2	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	65678		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02

CONFIRMATION NO. 1061

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

PUBLICATION NOTICE

Title: Stable, concentrated radionuclide complex solutions

Publication No.US-2020-0030467-A1
Publication Date:01/30/2020

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

1095 7590 02/05/2020

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

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 02/05/2020

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

TITLE OF INVENTION: Stable, concentrated radionuclide complex solutions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	05/05/2020

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 02/05/2020

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

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175,239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

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nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1000	05/05/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001690

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑ Issue Fee ❑ Publication Fee (if required) ❑ Advance Order - # of Copies _____

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via EFS-Web ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

❑ Applicant asserting small entity status. See 37 CFR 1.27

❑ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/175.239	10/30/2018	Francesco de Palo	PAT058197-US-CNT02	1061

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1618	

DATE MAILED: 02/05/2020

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

Notice of Allowability	Application No. 16/175,239	Applicant(s) de Palo et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to 1/24/20.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3. ☑ The allowed claim(s) is/are 1 and 3-26 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

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

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☑ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☑ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Notice of Pre-AIA or AIA Status

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

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Lian Ouyang on 1/28/2020.

The application has been amended as follows:

IN THE CLAIMS:

1.) In line 12 of claim 1, please delete "is substantially free of" and insert "has less than 1%" in its place.

2.) Please cancel claim 2

3.) In line 12 of claim 21, please delete "is substantially free of" and insert "has less than 1%" in its place.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the prior art does not teach of the combination of gentisic acid, ascorbic acid and less than 1% ethanol to provide stabilization of the ^{177}Lu-somatostatin complex wherein the gentisic acid and ascorbic acid are in low concentrations but the complex maintains a radiochemical purity (RCP) of $\geq$ 95% for at least 72h.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

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

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

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

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

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

Applicant-Initiated Interview Summary	Application No. 16/175,239	Applicant(s) de Palo et al.		
	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (First Inventor to File) Status Yes	Page 1 of 2

All participants (applicant, applicants representative, PTO personnel):

1. MELISSA J PERREIRA (Examiner); Telephonic 2. Lian Ouyang (Attorney of Record); Telephonic

Date of Interview: 24 January 2020

Claims Discussed: Claims 1,2 and 21

Prior Art Discussed: The prior art does not teach of the combination of gentisic acid,ascorbic acid and less than 1% ethanol to provide stabilization of the 177Lu-somatostatin complex wherein the gentisic acid and ascorbic acid are in low concentrations but the complex maintains a radiochemical purity (RCP) of ³ 95% for at least 72h.

Amendment proposed: Applicant suggested amending the claims to recite "less than 1% ethanol."

Brief Description of the main topic(s) of discussion: The applicant and examiner suggested amending the claims to recite "less than %1 ethanol." The instant claim 2 is cancelled as it does not exclude ethanol as a formulation constituent, such as solvent, etc.
SPE Mike Hartley agreed with the amendment for allowance.

Issues Discussed:

Proposed Amendments:
An amendment to the claims to recite "less than %1 ethanol."

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

U.S. Patent and Trademark Office
PTOL-413/413b (Rev. 01/01/2015)

Interview Summary

Paper No. 20200128

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	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
EAST	01/18/2019	MP
google scholar	01/18/2019	MP
inventor search	01/18/2019	MP
copending application search	01/18/2019	MP
EAST	05/30/2019	MP
google scholar	05/29/2019	MP
EAST	10/25/2019	MP
EAST	01/28/2020	MP
Allowability conference (SPE Mike Hartley)	01/27/2020	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	51/08	01/28/2020	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	de Palo et al.
	Examiner	Art Unit
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CPC								
Symbol							Type	Version
A61K	/	51	/	083			F	2013-01-01
A61K	/	47	/	12			I	2013-01-01
A61K	/	47	/	22			I	2013-01-01
A61K	/	47	/	18			I	2013-01-01
A61K	/	51	/	121			I	2013-01-01
A61K	/	51	/	08			A	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	28 January 2020	Total Claims Allowed:	
(Assistant Examiner)	(Date)	25	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	29 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20200128

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

INTERNATIONAL CLASSIFICATION					
CLAIMED					
A61K	/	51	/	00	
A61M	/	36	/	14	

NON-CLAIMED					
	/		/		

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
424	1.69

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	28 January 2020	Total Claims Allowed:	
(Assistant Examiner)	(Date)	25	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	29 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	16/175,239	de Palo et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

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

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	9	10	18	19										
	2	10	11	19	20										
2	3	11	12	20	21										
3	4	12	13	21	22										
4	5	13	14	22	23										
5	6	14	15	23	24										
6	7	15	16	24	25										
7	8	16	17	25	26										
8	9	17	18												

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	28 January 2020	Total Claims Allowed:	
(Assistant Examiner)	(Date)	25	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	29 January 2020	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

U.S. Patent and Trademark Office

Part of Paper No.: 20200128

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S17	229	DOTA same somatostatin	US-PGPUB; USPAT	OR	ON	2020/01/28 12:59
S18	289	sup?177 adj Lu	US-PGPUB; USPAT	OR	ON	2020/01/28 13:00
S19	6	S17 and S18	US-PGPUB; USPAT	OR	ON	2020/01/28 13:00
S20	834	A61K51/08.cpc.	US-PGPUB; USPAT	OR	ON	2020/01/28 13:04
S21	38	S17 and S20	US-PGPUB; USPAT	OR	ON	2020/01/28 13:04
S22	1	S19 and S20	US-PGPUB; USPAT	OR	ON	2020/01/28 13:05

1/28/2020 2:14:38 PM
C:\Users\mperreira\Documents\EAST\Workspaces\16175239.wsp

Bibliographic Data

Application No: 16/175,239

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MELISSA J PERREIRA/ (Examiner's Signature) | (Initials)

Title: Stable, concentrated radionuclide complex solutions

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/30/2018	424	1618	PAT058197-US-CNT02
RULE			

APPLICANTS

Advanced Accelerator Applications (Italy) Srl, Pozzilli, ITALY

INVENTORS

Francesco de Palo Ivrea, ITALY

Lorenza Fugazza Ivrea, ITALY

Donato Barbato Ivrea, ITALY

Maurizio Mariani Ivrea, ITALY

Daniela Chicco Albiano d'Ivrea, ITALY

Giovanni Tesoriere Noicattaro, ITALY

Clementia Brambati Torino, ITALY

CONTINUING DATA

This application is a CON of 16140962 09/25/2018

16140962 is a CIP of 16045484 07/25/2018

FOREIGN APPLICATIONS

PCT/IB2018/055575 07/25/2018

PCT/IB2018/057415 09/25/2018

IF REQUIRED, FOREIGN LICENSE GRANTED**

STATE OR COUNTRY

ITALY

ADDRESS

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

UNITED STATES

FILING FEE RECEIVED

$6,060

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF	Art Unit: 1618
Francesco de Palo et al.	Examiner: Perreira, Melissa Jean
APPLICATION NO: 16/175239	Conf. No.: 1061
FILED: October 30, 2018	
FOR: Stable, Concentrated radionuclide complex solutions	

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

INTERVIEW SUMARY, COMMENTS ON STATEMENT OF REASONS FOR ALLOWANCE, AND REPLY TO NOTICE OF ALLOWANCE

Applicant thanks Examiner Perreira for the Notice of Allowance mailed on February 5, 2020.

Interview Summary

Applicant's representative thanks Examiner Perreira for the courtesy of telephonic interviews conducted on January 24, 2020 and then on January 28, 2020. During the January 24, 2020 interview, claims 1, 2, and 21 as well as prior art cited for the 103 rejection were discussed. Applicant proposed claim amendments. During the January 28, 2020 interview, Applicant authorized the Examiner's amendments described on page 2 of the Notice of Allowance.

Comments on Statement of Reasons for Allowance

It is recognized that in accordance with M.P.E.P. § 1302.14, the Examiner's statement of reasons for allowance is not intended to necessarily state all the reasons for allowance or all the details why claims are allowed. In the application referenced above, it is not conceded that the Examiner's stated reasons for allowance are the only reasons for which the claims are allowable. The Examiner's reasons for allowance indicate that particular claim elements are not disclosed or suggested by the prior art of record, yet the claims may be patentable for other reasons as well, including the inventive combination of all of the recited claim elements. It is not conceded

that the specific limitations identified by the Examiner are necessary to distinguish the art of record or to satisfy the requirements of 35 U.S.C. § 112. Moreover, the Examiner does not assert, and it would not be conceded, that the Examiner's reasons have any bearing on the patentability of claims in any other applications directed to the disclosed subject matter.

In addition, each dependent claim stands on its own and may be allowable on its own merits. In particular, each dependent claim may be allowable on the basis of a combination of some of the features recited in the dependent claim and its base claim(s), which combination of features may not include all of the limitations identified in the Examiner's reasons for allowance.

In response to the Notice of Allowance, enclosed is a completed Part B- Fee(s) Transmittal. The issue fee in the amount of $1,000 is being paid with this reply on the Electronic Filing System. Apply those fees and any other necessary charges or credits to Deposit Account No. 50-4409, referencing the above docket number.

Dated: February 10, 2020

Respectfully submitted,

Electronic signature: / Lian Ouyang /
Lian Ouyang
Registration No.: 69254
Novartis Institutes for Biomedical Research, Inc.
700 Main Street
Cambridge, Massachusetts 02139
(617) 871-3880
Attorney For Applicant

Electronic Patent Application Fee Transmittal

Application Number:	16175239
Filing Date:	30-Oct-2018
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Filer:	Lian Ouyang/Susan Dillon
Attorney Docket Number:	PAT058197-US-CNT02

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1000

Electronic Acknowledgement Receipt

EFS ID:	38547248
Application Number:	16175239
International Application Number:	
Confirmation Number:	1061
Title of Invention:	Stable, concentrated radionuclide complex solutions
First Named Inventor/Applicant Name:	Francesco de Palo
Customer Number:	1095
Filer:	Lian Ouyang/Susan Dillon
Filer Authorized By:	Lian Ouyang
Attorney Docket Number:	PAT058197-US-CNT02
Receipt Date:	10-FEB-2020
Filing Date:	30-OCT-2018
Time Stamp:	22:29:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1000
RAM confirmation Number	E202020M31094480
Deposit Account	504409
Authorized User	Susan Dillon

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

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

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	PAT058197-US-CNT02_IF.pdf	289101 91668bbaef59c53c5943050 4c3c5f192b977 10d4	no	2
Warnings:					
Information:					
2	Applicant summary of interview with examiner	PAT058197-US-CNT02_response_interview_summary.pdf	154942 6706ab44086ad75c5be37ab2b93af80840c 77960	no	2
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30100 0fe1cdebeeeee9c886eec8046df71fc06eed 9e06	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	474143		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PART B – FEE(S) TRANSMITTAL

Complete and send this form, together with the applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

By fax, send to: (571) 273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1095 7590 02/05/2020
NOVARTIS PHARMACEUTICAL CORPORATION
INTELLECTUAL PROPERTY DEPARTMENT
ONE HEALTH PLAZA 433/2
EAST HANOVER, NJ 07936-1080

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
16/175,239	10/30/2018	Francesco de Palo	PAT0580197-US-CNT02	1061

TITLE OF INVENTION:

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1000	$0.00	$0.00	$1,000	05/05/2020

EXAMINER	ART UNIT	CLASS-SUBCLASS

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363)

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1. Lian Ouyang
2.
3.

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE or COUNTRY)

ADVANCED ACCELERATOR APPLICATIONS (ITALY) S.R. L. POZZILLI (ISERNIA), ITALY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☑ Corporation or other private group entity ☐ Government

4a. Fees Submitted: ☑ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment (*Please first reapply any previously paid fee shown above*):

☑ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change of Entity Status (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29. NOTE: Absent a valid Certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27. NOTE: If the application was previously under micro entity status, checking this box will be taken as a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status. NOTE: Checking this box will be taken as a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Lian Ouyang/ Date 02/10/2020

Typed or printed name Lian Ouyang Registration No. 69254

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

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

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

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

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
16/175,239	10/30/2018	1618	2480	PAT058197-US-CNT02	22	2

CONFIRMATION NO. 1061

CORRECTED FILING RECEIPT

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

OC000000114658882

Date Mailed: 02/12/2020

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

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

Inventor(s)

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

Applicant(s)

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

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

Domestic Priority data as claimed by applicant

This application is a CON 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: 02/11/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/175,239**

Projected Publication Date: Not Applicable

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

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

Notice of Pre-AIA or AIA Status

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

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Lian Ouyang on 1/28/2020.

The application has been amended as follows:

IN THE CLAIMS:

1.) In line 12 of claim 1, please delete "is substantially free of" and insert "has less than 1%" in its place.

2.) Please cancel claim 2

3.) In line ~~12~~ 14 of claim 21, please delete "is substantially free of" and insert "has less than 1%" in its place.

Change(s) applied to document,
/L.R./
2/11/2020

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the prior art does not teach of the combination of gentisic acid, ascorbic acid and less than 1% ethanol to provide stabilization of the ^{177}Lu-somatostatin complex wherein the gentisic acid and ascorbic acid are in low concentrations but the complex maintains a radiochemical purity (RCP) of $\geq$ 95% for at least 72h.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

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	16175239
Filing Date	2018-10-30
First Named Inventor	de Palo, Francesco
Art Unit	1629
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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
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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

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