

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208547Orig1s000**

**CHEMISTRY REVIEW(S)**



**NDA 208547**  
**OPQ N208547 Integrated Quality Assessment**  
**Final**  
**Review Date: 4/28/2016**

<b>Drug Name/Dosage Form</b>	NETSPOT (kit for preparation of gallium Ga 68 dotatate injection)
<b>Strength</b>	(b) (4) MBq/mL; 40 ug of DOTA <sup>0</sup> -Tyr3-Octreotate in 5 (b) (4) mL (max)
<b>Route of Administration</b>	Intravenous
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Advanced Accelerator Application, Inc.
<b>US agent, if applicable</b>	N/A

**Quality Review Data Sheet**

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
2. RELATED/SUPPORTING DOCUMENTS:
  - A. DMFs:

**Table 1 Drug Master Files (DMFs)**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETE	REVIEWER
(b) (4)	Type II	(b) (4)	(b) (4)	CMC (adequate) Microbiology (adequate)	CMC (04/26/2016) Microbiology (04/26/2016)	John Amartey, PhD (CMC); Helen Ngai, Ph.D. (Microbiology)
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	07/15/1998 <sup>1</sup>	William Adams, Ph.D., CMC
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	06/25/2015	Denise Miller, Ph.D., Microbiology
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	10/23/2015	Martin Haber, Ph.D.
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	Adequate	(2)
(b) (4)	Type IV	(b) (4)	(b) (4)	Adequate	02/25/2015	David Bateman, Ph.D.
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	12/04/2015	Helen Ngai, Ph.D., Microbiology
(b) (4)	Type III	(b) (4)	(b) (4)	Adequate	02/05/2015	Martin Haber, Ph.D.

<sup>1</sup>The DMF # [REDACTED] <sup>(b) (4)</sup> was converted from paper, non-CTD to eCTD format and communicated to the Agency on 08/04/2015. The information presented in the original submission according to the holder has not changed. There was a table of administrative changes and references to updated USP and JP methods included.

<sup>2</sup>Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:** *IND, RLD, or sister applications*  
IND 111972 (Vanderbilt University Medical Center)

**3. CONSULTS: N/A**

**Quality Review Team**

<b>DISCIPLINE</b>	<b>REVIEWER</b>	<b>BRANCH/DIVISION</b>
Drug Substance	Martin Haber	ONDP/DNDAPI
Drug Product	John Amartey	ONDP/Branch VI/Division II
Process	Dhanalakshmi Kasi	OPQ/OPF/Process
Microbiology	Helen Ngai	OPQ/OPF/Microbiology
Facility	Krishna Ghosh	OPQ/OPF?DIA/B1
Biopharmaceutics	Vidula Kohatkar	OPQ/ONDP/DBP/Branch 3
Project/Manager (R.Ph)	Thao Vu	OMPT/CDER/OPQ/OPRO/OR DPMI/RBPMBI
Application Technical Lead	Eldon Leutzinger	ONDP/Branch VII/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
<u>Environmental Assessment</u> (EA)	John Amartey (claimed exclusion -21 CFR 25.31(b); acceptable)	ONDP/Branch VI/Division II

**Table 2 Documents**

<b>DOCUMENT</b>	<b>RECEIPT DATE</b>	<b>DESCRIPTION</b>	<b>Section/reviewer</b>
Original NDA	07/01/2015	NETSPOT	<u>Drug Substance</u> (2.3.S) / Martin Haber, Ph.D. <u>Drug Product</u> (2.3.P) / John Amartey, Ph.D. (2.3.P.1, P.3, P.5, P.7, P.8, R.1, R.2) / Helen Ngai, Ph.D. – see microbiology review for documents reviewed  (process, biopharm)
Responses to IR1	10/07/2015	CMC product and process information	2.3.P / John Amartey, Ph.D., Dhanalakshmi Kasi, Ph.D.
Responses to IR2	10/20/2015	CMC product controls information; LOA to IND 111972	3.2.P.6 / John Amartey, Ph.D.

Table 2 Documents Continued

Table 2 Documents			
DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
Responses to IR3	11/12/2015	(b) (4) labels – lot number; syringe labels	Labeling / John Amartey, Ph.D.
Responses to IR4	12/07/2015	CMC product controls information	3.2.P.5-6 / John Amartey, Ph.D./Dhanalakshmi Kasi

## Executive Summary

### I. Recommendations APPROVAL

#### A. Recommendation and Conclusion on Approvability

##### 1. Summary of Complete Response issues

The INTRODUCTION (Section II) describes the fundamental considerations upon which the Critical Quality Attributes (CQA's) are based and serves as the foundation upon which the array of issues stem from, drawn out of the several discipline reviews (CMC, Microbiology Product Quality, Process) of NDA 208547. These issues and their resolution are summarized in the following table. Biopharmaceutics granted a waiver – see Section II.D., and attached review.

	ISSUE	STATUS
DOTATATE	As identified in (b) (4) DMF (b) (4) (reviewed under separate cover) (CMC)	<b>Resolved</b> – all issues
NETSPOT	Lack of sufficient characterization of <sup>nat</sup> Ga-DOTATATE reference standard (CMC)	<b>Resolved</b> – applicant added Mass Spectral analysis to panel of characterization methods
	Lack of information to support suitability of the ITLC method for determination of RCP in nuclear pharmacy (CMC)	<b>Resolved</b> – validation data provided for ITLC method for use in radiopharmacy, and found acceptable
	Suitability of 5 µg of 1,10-phenanthroline (b) (4) in drug product (CMC)	<b>Resolved</b> - data in responses demonstrates that (b) (4)

	ISSUE	STATUS
NETSPOT	Effect of gentisic acid (b)(4) (CMC)	<b>Resolved</b> - data provided (b)(4) with gentisic acid up to (b)(4). In absence of gentisic acid, (b)(4)  (John Amartey, Ph.D., CMC, )
	Low labeling yields after delay of 10 to 20 min to add buffer to reaction vial (following radiolabeling) (CMC)	<b>Resolved</b> – procedure changed to add buffer immediately following addition of <sup>68</sup> GaCl <sub>3</sub> to NETSPOT; but, note included stating that a delay can be tolerated up to 10 min without degradation (John Amartey, Ph.D., CMC,)
	Lack of validation data for: •Container closure integrity testing and for stoppers with (b)(4) •Telstar 80 lyophilizer sterilization in place •Sterilization test for accessory cartridge (microbiology)	<b>Resolved</b> – data provided and deemed acceptable (Helen Ngai, Ph.D., microbiology, 4/26/2016)
	Lack of information on: •Environmental monitoring procedures • (b)(4) study (microbiology)	<b>Resolved</b> – data provided and deemed acceptable (Helen Ngai, Ph.D., microbiology, 4/26/2016)
	Lack of English translations for (b)(4) (microbiology)	<b>Resolved</b> – translations provided and determined to be acceptable (Helen Ngai, Ph.D., microbiology, 4/26/2016)
	Sterilization of the accessory cartridge by (b)(4) – bioburden determination study	<b>Resolved</b> (Helen Ngai, Ph.D., microbiology, 4/26/2016)
	Media fill simulations performed on Filling (b)(4) (microbiology)	<b>Resolved</b> (Helen Ngai, Ph.D., microbiology, 4/26/2016)
	Revision of endotoxin limit (microbiology)	<b>Resolved</b> (Helen Ngai, Ph.D., microbiology, 4/26/2016)
<sup>68</sup> Ge/ <sup>68</sup> Ga Generator (Eckert & Ziegler)	As identified in DMF (b)(4) for CMC	<b>Resolved</b> – all issues – see CMC review of DMF
	As identified in DMF (b)(4) for microbiology	<b>Resolved</b> – all issues – see microbiology review

**OVERALL CONCLUSION:** All issues for CMC (IR 1, IR2), microbiology, process and facilities have been resolved.

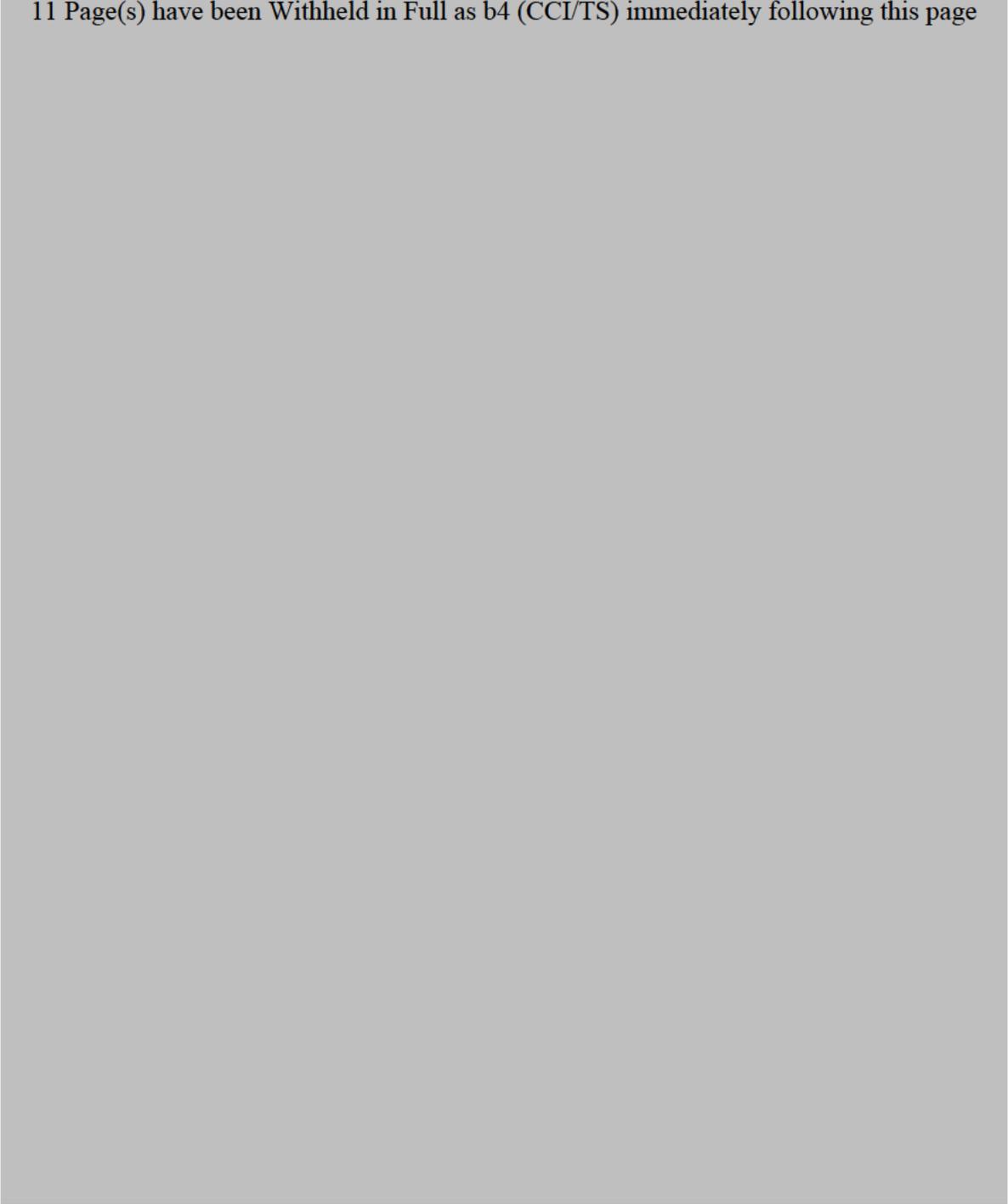
RECOMMENDATION: Approval

2. Action letter language, related to critical issues such as expiration date: N/A
3. Benefit/Risk Considerations: see Risk Assessment at end of executive summary.

**B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

N/A

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Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Eldon E.  
Leutzinger  
-A

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Leutzinger -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
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054329, cn=Eldon E. Leutzinger -  
A  
Date: 2016.05.02 08:39:15 -04'00'

**Recommendation: Approval**  
**NDA: Approval**

## NDA 208547 Review # 1

**NDA 208547: SomaKit TATE Review of referenced DMFs**

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	ADEQUATE	07/15/1998 <sup>#</sup>	ADEQUATE by Dr. Adams R.C.
	III		ADEQUATE	06/25/2015	ADEQUATE by Dr. Miller, Denise A	
	II		ADEQUATE	10/15/2015	ADEQUATE	
	III		ADEQUATE	12/23/2002	ADEQUATE	
	V		ADEQUATE	06/29/2015	ADEQUATE by Dr. Bateman, David A	
	V		ADEQUATE	12/02/2015	ADEQUATE by Dr. Helen Ngai	
	III		ADEQUATE	02/05/2015	ADEQUATE by Dr. Haber M	

<sup>1</sup>Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

<sup>#</sup>The DMF # (b) (4) was converted from paper, non-CTD to the eCTD format (communicated to the Agency on 08/04/2015). The information presented in the original submission according to holder has not changed. A table of the administrative changes and the reference of updated USP and JP methods were submitted. This is adequate.

### ASSESSMENT OF THE DRUG PRODUCT

**General Introduction:**

NETspot is a lyophilized kit formulation for the manufacture of [<sup>68</sup>Ga]-DOTATATE Injection for intravenous use. The commercial formulation in this application has not been used in any human clinical studies. However a solution clinical formulation was used by Vanderbilt University Medical Center (UMC) in IND 111972 clinical studies. The identity of the drug product of the two formulations has been established by physiochemical methods referenced to a characterized “cold” [<sup>nat</sup>Ga]-DOTATATE. The two drug products (b) (4)



# QUALITY ASSESSMENT

**Recommendation:****NDA: CMC Process Review: Adequate**

## NDA 208547 Review # 1 Review Date

<b>Drug Name/Dosage Form</b>	(b) (4) kit for preparation of Ga <sup>68</sup> -DOTATATe
<b>Strength</b>	40 ug of DOTA0-Tyr3 Octreotate
<b>Route of Administration</b>	Intravenous
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Advanced Accelerator Application, Inc.
<b>US agent, if applicable</b>	Victor G. Paulus, PhD; Head of Regulatory Affairs 350 Fifth Avenue, Suite 6902 New York, NY, 10118

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	07/01/2015

### Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	
Drug Product	John Amartey	
Process	Dhanalakshmi Kasi	
Microbiology	Helen Ngai	
Facility	Krishna Ghosh	
Biopharmaceutics	Vidula Kohatkar	
Project/Business Process Manager	Thao Vu	
Application Technical Lead	Eldon Leutizinger	
Laboratory (OTR)		
ORA Lead		
Environmental Assessment (EA)		



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## Quality Review Data Sheet

### ASSESSMENT OF THE PROCESS

#### 2.3.P DRUG PRODUCT

##### 2.3.P.2.3 Manufacturing Process Development

1. Does the information described in the pharmaceutical development section support the proposed drug product manufacturing process?

#### Applicant's Response:

(b) (4)

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QUALITY ASSESSMENT



**Martin Haber**

**Chemist**

**CDER/OPQ/ONDP/DAPI**

**Martin T. Haber**  
**-S**

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DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300093899,  
cn=Martin T. Haber -S  
Date: 2015.10.23 19:17:27 -04'00'

**Supervisor Comments and Concurrence:**

**Donna F.**  
**Christner -S**

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ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300180419,  
cn=Donna F. Christner -S  
Date: 2015.10.23 20:39:17 -04'00'

**3.2.P DRUG PRODUCT**

The drug product consists of a two-vial kit formulation. Vial-1 is a lyophilized kit of the drug product precursor (DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate; abbreviated as DOTATATE) and excipients. Vial-2 is a buffer solution to be added to the reconstituted Vial-1. DOTATATE is a peptide conjugate manufactured by (b) (4) (referenced DMF (b) (4)). The vial-1 is reconstituted with a <sup>68</sup>Ga-eluate in dilute HCl, followed by addition of the required amount of the buffer in Vial-2. After heating at a preset temperature the drug product, [<sup>68</sup>Ga]-DOTATATE is produced. [<sup>68</sup>Ga]-DOTATATE injection is a diagnostic radiopharmaceutical indicated for (b) (4) neuroendocrine tumors.

**3.2.P.1 Description and Composition of the Drug Product**

The Drug product is a two-vial kit and consists of:

**Vial-1:** containing a lyophilized active drug substance precursor (40 µg of DOTATATE) and excipients to be reconstituted with <sup>68</sup>GaCl<sub>3</sub> aqueous solution from a <sup>68</sup>Ge/<sup>68</sup>Ga-generator (such as the Eckert and Ziegler E&Z generator).

**Vial-2:** contains a reaction buffer to be added to the reconstituted Vial-1. Additionally, there is one accessory cartridge (b) (4)

Table 3.2.P.1-1 and table 3.2.P.1-2 reproduced below show the components, composition and function of Vial-1 and Vial-2 respectively.

**Table 3.2.P.1-1: Components of Vial-1**

**Table 1. Composition of the kit Vial-1 lyophilized formulation**

Component	Composition (per vial)	Function
DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate	40 µg	Drug Substance
1,10-phenanthroline	5 µg	(b) (4)
Gentisic acid	6 µg	(b) (4)
(b) (4) Mannitol	20 mg	(b) (4)

Note that in the table above, reproduced from the application, the applicant refers to DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate; abbreviated as DOTATATE as “drug substance”. As discussed, the peptide conjugate is a drug product precursor.

**Table 3.2.P.1-2: Components of Vial-2**

**Table 2. Composition of the kit Vial-2 reaction buffer**

Component	Composition (1 ml)	Function
Formic acid	60 mg	(b) (4)
Sodium hydroxide	56.5 mg	
Water for injection	qs	

Table 3.2.P.1-3 and 3.2.P.1-4 present the composition of the drug product and the physical characteristics of <sup>68</sup>Ga respectively.

**Table 3.2.P.1-3: The composition of the drug product <sup>68</sup>Ga-DOTATATE injection**

**Table 3. Composition of the final <sup>68</sup>Ga-DOTA<sup>0</sup>-Tyr<sup>3</sup>-Octreotate for injection solution**

Component	<sup>68</sup> Ge/ <sup>68</sup> Ga generator elution conditions	
	Column 1: 5 ml of HCl 0.1 N (e.g. E&Z generator)	(b) (4)
	<b>Final composition</b>	
DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate (mass)	40 µg	(b) (4)
<sup>68</sup> Ga-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate (radioactivity)	1110 MBq	(b) (4)
<sup>68</sup> Ga-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate (mass)		(b) (4)
Volume		(b) (4)
Specific Activity (GBq/Total peptide)		(b) (4)
Radioconcentration		(b) (4)
Other Excipients	mg/vial	(b) (4)
1,10-phenanthroline	0.005	(b) (4)
Gentisic acid	0.006	(b) (4)
Mannitol	20	(b) (4)
Formic Acid		(b) (4)
Sodium Hydroxide		(b) (4)
Hydrochloric acid		(b) (4)
Water for Injection		(b) (4)

**Question to the applicant:** We note that 1110 MBq of <sup>68</sup>Ga radioactivity is used in the pharmaceutical development (section 3.2.P.2.2). Is 1110 MBq the maximum radioactivity for reconstitution of the (b) (4)? Explain with justification.

**Response: ADEQUATE**

The explanation and representative HPLC and summary data table are reproduced below.

**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1**

**Labeling & Package Insert**

**1. Package Insert**

**(a) "Highlights" Section (21CFR 201.57(a))**

(b) (4)

(b) (4) a radioactive diagnostic agent indicated for

(b) (4)

(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: Pending (NETspot) Established Name:[ <sup>68</sup> Ga]-DOTATATE	USAN pending Applicant was advised to apply for USAN
Dosage form, route of administration	Dosage: Sterile Solution Route: Intravenous Injection (bolus)	Adequate
Controlled drug substance symbol (if applicable)	N/A	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	Sterile intravenous injection solution. The recommended radioactivity to be administered is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) (b) (4) not more than 200 MBq (5.4 mCi).	Adequate

**Conclusion:** The information provided in this section is adequate. However, the proprietary name has not been finalized.

**(b) "Full Prescribing Information" Section**

**# 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))**

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Sterile Intravenous Injection	Adequate
Strengths: in metric system	Adult dose of 2 MBq/kg of body weight (0.054 mCi/kg). (b) (4) not more than 200 MBq (5.4 mCi). DOTATATE (40 µg)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	N/A	N/A

**Conclusion:** The information provided in this section is adequate

**#11: Description (21CFR 201.57(c)(12))**

(b) (4) NETspot) is supplied as a kit (b) (4)  
 (b) (4) nrenparation of <sup>68</sup>Ga- (b) (4)  
 (b) (4)

**Comments:**

1. In the description of method of preparation in the package insert, the applicant has (b) (4)
2. (b) (4)
3. (b) (4)

**Assessment:** The above comments were communicated to the applicant and the responses are **ADEQUATE** (see appendix page 62)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	(b) (4) NETspot); [ <sup>68</sup> Ga]-DOTATATE	
Dosage form and route of administration	Sterile Solution; Intravenous injection	Adequate
Active moiety expression of strength with equivalence statement for salt (if applicable)	N/A	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	1,10-Phenanthroline = (b) (4) mg; Gentisic acid = (b) (4) mg; Mannitol = 20 mg; Formic acid = (b) (4) mg; Sodium Hydroxide = (b) (4) mg; Hydrochloric acid = (b) (4) mg; Water for Injection	Adequate
Statement of being sterile (if applicable)	Applicant indicated that product is sterile	Adequate
Pharmacological/ therapeutic class	Diagnostic imaging agent for somatostatin receptor sub-type 2 (sstr2) expressing tumors	Adequate
Chemical name, structural formula, molecular weight	[ <sup>68</sup> Ga]-DOTATATE or [ <sup>68</sup> Ga]-DOTA <sup>0</sup> -Tyr <sup>3</sup> -Octreotate; [ <sup>68</sup> Ga]-DOTA-D-Phe-Cys-Tyr-D-Trp-Lys-	Acceptable

	Thr-Cys-Thr (cyclo 2,7) disulfide; Molecular Mass: (b)(4) g/mol (calculated)	
If radioactive, statement of important nuclear characteristics.	Gallium-68( <sup>68</sup> Ga) is produced in (b)(4)	Adequate
Other important chemical or physical properties (such as pKa, solubility, or pH)	N/A	Adequate

**Conclusion:**

The information provided is acceptable. The proprietary name NETspot was accepted.

**#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))**

(b)(4) NETspot) is supplied as a single-

(b)(4) kit,

(b)(4)

(b)(4)

<b>Item</b>	<b>Information Provided in NDA</b>	<b>Reviewer's Assessment</b>
Strength of dosage form	Adult dose of 2 MBq/kg of body weight (0.054 mCi/kg) <sup>(b) (4)</sup> <sup>(b) (4)</sup> not more than 200 MBq (5.4 mCi). Injection Solution and DOTATATE (40 µg)	Adequate
Available units (e.g., bottles of 100 tablets)	N/A	N/A
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC not assigned	N/A
Special handling (e.g., protect from light, do not freeze)	Keep lead-shielded and in the original packaging and do not freeze	Adequate
Storage conditions	Keep at temperature below 25°C and do not freeze	Adequate

**Manufacturer/distributor name listed at the end of PI, following Section #17**

<b>Item</b>	<b>Information Provided in NDA</b>	<b>Reviewer's Assessment</b>
Manufacturer/distributor name (21 CFR 201.1)	Manufactured by: Gipharma S.r.l., Strada Crescentino snc-1, 3040 Saluggia (Vc), Italy/ distributed by: Advanced Accelerator Applications USA, Inc., NY 10118	Adequate

**Conclusion:** The requisite information has been provided and is acceptable.

#### 4. Labels

##### 1) Immediate Container Label



**Reviewer's Assessment:**

The label is mostly in a foreign language and cannot be effectively evaluated. Most importantly there should be a label supplied by the kit manufacturer to be affixed to the reconstituted drug product [<sup>68</sup>Ga]-DOTATATE. The label should bear the radioactive symbol and other relevant information as space permits. The product information should be written in by the end user radiopharmacy staff.

The label for the end-user has been provided in response to information request. Final labeling is under review.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The proprietary name: (b)(4) NETspot) and the established name: [ <sup>68</sup> Ga]-DOTATAE and indicated on the carton label. The font size differential is satisfactory	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b)(4)	The radioactivity concentration is indicated in section 3.2.P.1 (table 3) of the application. Adequate
Net contents (21 CFR 201.51(a))	DOTATATE content is 40 µg and the calculated mass of the [ <sup>68</sup> Ga]-DOTATATE is 0.0163 µg (based on 1110 MBq of <sup>68</sup> GaCl <sub>3</sub> eluate used). 1,10-Phenanthroline = (b)(4) mg; Gentisic acid = (b)(4) mg; Mannitol = 20 mg; Formic acid = (b)(4) mg; Sodium Hydroxide = (b)(4) mg; Hydrochloric acid = (b)(4) mg; Water for Injection	Adequate
Lot number per 21 CFR 201.18	Provision for lot number is indicated on the label.	Acceptable
Expiration date per 21 CFR 201.17	Location for expiration date is provided	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement "Rx only" is indicated on the label	Adequate
Storage (not required)	Storage condition is indicated	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Location for the NDC number is indicated on the label	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	The position of the bar code is provided	Adequate
Name of manufacturer/distributor	Manufactured by: Gipharma S.r.l, Strada Crescentino snc-1, 3040 Saluggia (Vc), Italy/ distributed by: Advanced Accelerator Applications USA, Inc., NY 10118	Adequate
Others	NA	N/A

\*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

\*\*Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

**Conclusion:** The label at this stage is not finalized. The proprietary name submitted in the original application is not accepted. However, NETspot has been accepted.

**2) Cartons**



(b) (4)

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	The proprietary name: NETspot and the established name: [ <sup>68</sup> Ga]-DOTATAE are indicated on the carton label. The font size differential and the prominence are acceptable	Adequate, however the proprietary name has not been accepted.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4)	The recommended dose is acceptable provided the radiation dose to the patient is within acceptable range
Net contents (21 CFR 201.51(a))	DOTATATE content is 40 µg and the calculated mass of the [ <sup>68</sup> Ga]-DOTATATE is 0.0163 µg (based on 1110 MBq of <sup>68</sup> GaCl <sub>3</sub> eluate used).	Adequate
Lot number per 21 CFR 201.18	The lot number space is provided	Adequate
Expiration date per 21 CFR 201.17	Expiration date is indicated on the label	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables] [ 201.10(a), 21CFR201.100(b)(5)(iii)]	1,10-Phenanthroline = (b) (4) mg; Genticic acid = (b) (4) mg; Mannitol = 20 mg; Formic acid = (b) (4) mg; Sodium Hydroxide = (b) (4) mg; Hydrochloric acid = (b) (4) mg; Water for Injection	The justification for using 1,10-phenanthroline is discussed in the application and is satisfactory
Sterility Information (if applicable)	Applicant indicated that the drug product is sterile	Adequate
"Rx only" statement per 21 CFR 201.100(b)(1)	The statement "Rx only" is specified	Adequate
Storage Conditions	Keep at temperature below 25°C and do not freeze	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Space for the NDC # is indicated	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	Bar code sample is provided on the label	Adequate
Name of manufacturer/distributor	Manufactured by: Gipharma S.r.l, Strada Crescentino snc-1, 3040 Saluggia (Vc), Italy/ distributed by: Advanced Accelerator Applications USA, Inc., NY 10118	Adequate
"See package insert for dosage information" (21 CFR 201.55)	The statement "see package insert before use" is stated on the label	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A	



Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Intravenous injection (bolus)	
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**Conclusion:** The proprietary name has not been accepted. Overall the labels have not been finalized.  
 Proprietary name issue has been resolved; proposed name is (b) (4)

**II. List of Deficiencies Communicated and Resolved**

**III. Appendix: Information request-1 and responses from applicant:**

The information request was communicated to the applicant on October 6, 2015 and responses were received on October 7, 2015.

**Question 1:** The experimental method for monitoring (b) (4) gentisic acid is not described. Also, the data show that at time zero there is approximately (b) (4) % degradation. What are the degradation products and how were they measured? Provide this information.

**Question 2:** We note that 1110 MBq of <sup>68</sup>Ga radioactivity is used in the pharmaceutical development (section 3.2.P.2.2). Is 1110 MBq the maximum radioactivity for reconstitution of the (b) (4)? Explain with justification.

**Question 3:** We note that (b) (4) 1,10-phenanthroline, however (b) (4) is not listed in the components and composition of the drug product. Revise the components and composition to include (b) (4) otherwise provide data to justify its exclusion.

**Question 4:** A table is presented which shows (b) (4) gentisic acid on the stability of Ga-68-DOTATATE, but the activity level used is not indicated. In view of the generator eluate strength ranging from (b) (4) this study should be performed with the highest radioactivity level possible to observe any changes. Explain and make the correction.

**Question 5:** In the container closure section of the pharmaceutical description, (b) (4) stopper is used for vial#1. What are the levels for (b) (4) in this stopper material? Although the applicant indicated that ICP testing is performed to assess release of (b) (4) no data is presented. Provide the information.

**Question 6:** The delay in buffer addition (table 6 of 3.2.P.2.2) on the reaction yield (b) (4) minutes delay. Is the DOTATATE stable in the acidic medium used? Explain.

**Question 7:** Your application references the EZR Drug Master File (DMF) for the Ge-68/Ga-68 generator. No reference is made to the (b) (4) DMF in the application. Additionally, for lack of information on the (b) (4) generator, the composition of the finished drug product table submitted and all references to the (b) (4) generator in association with the EZ generator in the application should be corrected to include only the E&Z generator. In a post-approval supplement, you may provide information to support use of the (b) (4) generator with your product, and include a Letter of Authorization (LoA) to the pertinent DMF.

**Question 8:** The generator is eluted either manually or by a (b) (4) pump. Description of the pump elution is lacking in the application. Provide a clear description of the pump-assisted elution process, the type and location of pump in the generator and reaction set-up provided in the application.

**Question 9:** The [<sup>nat</sup>Ga]-DOTATATE (in-house standard) mass analysis figure 2 of 3.2.P.6 is presented in the application, however other structural elucidation data should be presented as well, such as HPLC chromatogram showing the purity etc. of the reference standard.

**Question 10:** In the leachable/extractable experiment for (b) (4) in section 3.2.P.2.2, the average amount detected is listed as (b) (4) μg/mL. Therefore for a 5 mL eluate the total amount of (b) (4) present in vial-2). The generator acceptance limit is (b) (4) μg/GBq. The 5 μg of phenanthroline = (b) (4) μmol; (b) (4)

**Question 11:** In section 3.2.P.5, the radiolabeling test is performed prior to batch release; HPLC and ITLC are used to test radiochemical purity. Although a sample ITLC plot is presented in the application, an HPLC chromatogram is not provided to show the radiochemical as well as the chemical purity and UV profile of the drug product. Present a representative chromatogram showing UV plot in addition to the radioactivity trace to support the claim that there are no degradation products and impurities.

The UV HPLC assay is performed as release test on the Vial-1 lyophilized formulation.

Conversely and consistently with the common practice, the UV profile is not part of the specifications of the reconstituted radiolabeled imaging product for which the following radiochemical specifications have been defined:

Free Ga (b) (4) %

GaDOTATATE (b) (4) %

Representative radiometric and UV chromatograms of <sup>68</sup>GaDOTATATE solution generated during development are provided in Attachment 3.

The UV chromatogram confirms the absence of peaks other than then the ones from the component of the formulation.

**Question 15:** Information on the container closure system for Vial-2 reaction buffer, kit vial is lacking in the application. The section presented contains information for vial-1. Provide this information for assessment.

**Question 16:** In the [<sup>68</sup>Ga]-DOTATATE release test in the radiopharmacy, visual inspection is not included. Include visual inspection of the final drug product to assure clarity and absence of visible particulates.

**Question 17:** In the description of method of preparation in the package insert the applicant has indicated

(b) (4)

(b) (4)



**Assessment:** The response is ADEQUATE

**Question 18:** You indicated in the package insert that

(b) (4)

(b) (4)



**Response 18:**

The cold kit presented in the Applicant NDA is a sterile product to be aseptically reconstituted by the local radiopharmacies with a sterile <sup>68</sup>Ga eluate. The reconstitution procedure does not require the use of an additional sterilizing filter as long as this latter condition is met.

(b) (4)



**Question 19:** There should be a label supplied by the kit manufacturer to be affixed to the reconstituted drug product [<sup>68</sup>Ga]-DOTATATE. The label should bear the radioactive symbol and other relevant information as space permits. Provide this label as part of the kit components to be supplied to the end user.

**Response 19:**

We have processed this request and are including a mock-up pending final approval of the

(b) (4)

**Assessment:** INADEQUATE, final review is still pending.

The lot number of the product is not indicated. Information request is to be sent to the applicant to revise the label. Quantitative composition of the API and all excipients should be indicated.

An individual syringe label must also be provided with the relevant information.

**IR-2 and Responses: Sent on 10/15/2015 and responses received 10/26/2015 sequence #14**

**Question:** In your response to our previous CMC information request #9, you have presented only an HPLC analysis of the [<sup>nat</sup>Ga]-DOTATATE (in-house standard). Present the mass spectrum of the reference standard to support the mass analysis in figure 2 of 3.2.P.6 presented in the application.

**Response:** The applicant has presented a mass spectrum for the reference standard (reproduced below). The ion peaks support the information in figure 2 of 3.2.P.6 of the original submission. **ADEQUATE**



**Question:** Provide a Letter of Authorization (LoA) to the IND study conducted, i.e., the VUMC protocol.

**Response:** A Letter of Authorization (LoA) from the sponsor of IND 111972 is issued to the NDA 208547 dated October 20, 2015. **ADEQUATE**

A summary table comparing the key components of the commercial and the formulation used in the VUMC protocol

Item	IND 111972	NDA208547	Comment
Generator	(b) (4)		
Buffer used			
Eluate			
Precursor (DOTATATE) Amount			

<b>Product pH</b>	(b) (4)
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**\*Reviewer created Table from data from this application and the referenced IND 111972**

**IR-3 and Responses (Seq #15 of 11/12/2015):**

**Question 1:** The shield label presented for the drug product is lacking a lot number. Revise the label to include this information.



**Assessment:** The Applicant has presented an updated label for the final drug product to be affixed the product vial in the end user radiopharmacy. Pending team review



**IR-4 and Responses (Seq #20 of 12/07/2015):**

**Question:** We remind you of your agreement during the TCON on 12/07/2015 to provide data that validates the ITLC method against the HPLC method to determine the suitability of the ITLC method for evaluation of the radiolabeling efficiency.

**Response:** The applicant presented data (01/04/2016) in a response to the information request.

**Assessment:** The data presented validated the use of the ITLC method as a quality control method at the end user radiopharmacy. As expected the % of the not complexed gallium is higher for the ITLC method as compared to the HPLC method, as the HPLC cannot detect any colloidal materials that may be present. **ADEQUATE**

**Overall summary:**

The product [NETspot] consists of a two-vial kit for the manufacture of the drug substance [<sup>68</sup>Ga]-DOTATATE. The API (DOTATATE) is lyophilized with excipients in vial-1 and the second vial-2 contains a reaction buffer. There is an additional accessory cartridge to be used with the kit. The data presented by the applicant show that the DOTATATE is stable for at least 12 months when stored at the recommended temperature and in the container closure system proposed. The identity of the reconstituted [<sup>68</sup>Ga]-DOTATATE is confirmed by comparison with a characterized "cold" non-radioactive [Ga]-DOTATATE reference standard. The product radiochemical purity is further confirmed by HPLC and ITLC analyses. The reconstituted drug product is stable for at least 4 hours when stored at 25°C. The application is approvable from the CMC perspective.

**Recommendation:** ADEQUATE - APPROVAL

**R.2 Comparability Protocols:** There is no comparability protocol in the NDA.

**OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT, EA, LABELING**

**Reviewer's Assessment and Signature: Drug product information is adequate.**

John  
Amartey -S

Digitally signed by John Amartey -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John Amartey -S,  
o=9234219200300.100.1.1=200145,  
ou=FDA  
Date: 2016.04.21 12:47:03 -04'00'

**Secondary Review Comments and Concurrence:**  
I concur with the reviewer's assessment.

Danae D.  
Christodoulou -S

Digitally signed by Danae D. Christodoulou -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, o=9234219200300.100.1.1=1300132624,  
cn=Danae D. Christodoulou -S  
Date: 2016.04.26 18:02:52 -04'00'