

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208547Orig1s000**

**OTHER REVIEW(S)**

**505(b)(2) ASSESSMENT**

<b>Application Information</b>		
NDA # <b>208547</b>	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: <b>NETSPOT</b> Established/Proper Name: <b>Kit for the preparation of gallium Ga 68 dotatate injection</b>  Dosage Form: <b>intravenous injection</b> • Strengths: 40 mcg of dotatate		
Applicant: <b>Advanced Accelerator Applications USA, Inc.</b>		
Date of Receipt: <b>July 1, 2015</b>		
PDUFA Goal Date: <b>June 1, 2016</b>		Action Goal Date (if different):
RPM: <b>Modupe Fagbami</b>		
Proposed Indication(s): <span style="float: right;">(b) (4)</span>		
Note – DMIP is recommending a revised indication as follows based on review of the supporting information: Positron emission tomography (PET) imaging, as an adjunct to other diagnostic tests, for localization of neuroendocrine tumors (NETs) in adults and pediatric patients.		

**GENERAL INFORMATION**

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

*If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed	Information relied-upon (e.g., specific sections of the application or labeling)
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drug(s), OTC final drug monograph)	
Published Literature	Safety and Effectiveness; All sections of labeling except Sections 3 Dosage Forms and Strengths and 16 How Supplied/Storage and Handling

\*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature<sup>1</sup>. [See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.](#)

**The bridge is based on the physio-chemical characteristics of the drug product. All formulations described in the literature contain the same active moiety, 68Ga-DOTATATE, as the proposed drug product. The identity of 68Ga-DOTATATE is established by comparison to the “cold” Ga-DOTATATE reference standard. Differences in excipients between the products utilized in literature and the proposed product will not impact drug performance due to the nature and small amounts of excipients in the drug product. Furthermore, the strengths of the drug products described in the literature are in the same range as the proposed product.**

#### RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES  NO   
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
If “NO,” proceed to question #5.  
If “YES,” list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES  NO

#### RELIANCE ON LISTED DRUG(S)

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a final OTC drug monograph?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

- d) Discontinued from marketing?

YES  NO

If “**YES**”, please list which drug(s) and answer question d) i. below.  
If “**NO**”, proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?  
YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book)).*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES  NO

If “**NO**” to (a) proceed to question #11.  
If “**YES**” to (a), answer (b) and (c) then proceed to question #12.

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?  
N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES  NO   
*If "NO", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO   
N/A

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
N/A  YES  NO

*If this application relies only on non product-specific published literature, answer "N/A"  
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

**PATENT CERTIFICATION/STATEMENTS**

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

*If "NO", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

*Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

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/s/  
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MODUPE O FAGBAMI  
06/01/2016

## Division of Medical Imaging Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 208547

**Name of Drug:** NETSPOT(kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use

**Applicant:** Advanced Accelerator Applications (AAA)

#### Labeling Reviewed

**Submission Date:** July 1, and 13, 2015; May 5, 6, 20, 26, 27 and 31, 2016

**Receipt Date:** July 1, and 13, 2015; May 5, 6, 20, 26, 27 and 31, 2016

#### Background and Summary Description:

Netspot is a radioactive diagnostic agent indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult and pediatric patients.

The Applicant, Advanced Accelerator Applications (AAA) submitted NDA 208547 (b) (4) (Kit for the Preparation of <sup>68</sup>Ga- DOTATATE for Injection) as a 505(b)(2), for as a priority review on July 1, 2015. The product being a New Molecular Entity (NME) was reviewed under the “Program” with the PDUFA due date of March 1, 2016. However, the Applicant’s submission of a major amendment during the review, extended the PDUFA due date to June 1, 2016.

**NOTE:** Per review, the Proprietary name became “NETSPOT” and Established name “Kit for the preparation of gallium Ga 68 dotatate injection”.

#### Review

The labeling (Package Insert and Carton and Container) were reviewed by Cynthia Welsh, Clinical Reviewer and Alex Gorovets, Team Leader and CDTL; John Amartey, CMC Reviewer, and Eldon Leutzinger, Team Leader; and Danae Christodoulou, Branch Chief; Clinical Pharmacology Reviewer, Christy John, and Team Leader Gene Williams; DMEPA Reviewer, Michelle Rutledge, and Team Leader, Yelena Maslov; and Adam George, ODPD Reviewer. All the reviews are in DARRTS.

The FDA revised Package Insert was first communicated to the Applicant on April 29, 2016, and the Applicant revisions was received on May 6, 2016. Additional updates to the package insert

were communicated to the Applicant on May 24, and 31, 2016, and a final acceptable package insert was received from the Applicant on May 31, 2016.

The Agency's update and final labeling (carton and container) was communicated to the Applicant on May 16, and 23, 2016. The Applicant accepted Agency's revisions with their submissions of May 20, and 26, 2016.

### **Recommendations**

The entire package insert included in this review showing the FDA final revisions to the package insert. Also attached is the clean package insert agreed upon by the FDA and the Applicant.

Modupe Fagbami

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Regulatory Project Manager	Date
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Kyong Kang, PharmD.

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Chief, Project Management Staff	Date
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Cynthia Welsh, M.D. Clinical Reviewer	Date
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Nushin Todd, M.D., Clinical Team Leader	Date
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Christy John, Ph.D., Clinical Pharmacology Reviewer	Date
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Gene Williams, Ph.D., Clinical Pharmacology Team Leader	Date
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John Amartey, Ph.D, CMC Reviewer	Date
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Eldon Leutzinger, Ph.D., CMC Team Leader	Date
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Danae Christodoulou, Ph.D., CMC Branch Chief	Date
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Michele Rutledge, PharmD, DMEPA Reviewer	Date
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Yelena Maslov, PharmD, DMEPA Team Leader	Date
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Adam George, M.D., OPDP Reviewer

Date

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Nushin Todd, M.D., Associate Director, Labeling

Date

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/s/  
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MODUPE O FAGBAMI  
06/01/2016

CYNTHIA A WELSH  
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CHRISTY S JOHN  
06/01/2016

JOHN K AMARTEY  
06/01/2016

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YELENA L MASLOV  
06/01/2016

ADAM N GEORGE  
06/01/2016

NUSHIN F TODD  
06/01/2016

KYONG A KANG  
06/01/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 23, 2016

**To:** Modupe Fagbami  
Regulatory Project Manager  
Division of Medical Imaging Products (DMIP)

**From:** Adam George, Pharm.D., RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Amy Toscano, Pharm.D, RAC, CPA  
Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA 208547 NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use**

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In response to your consult request dated January 25, 2016, we have reviewed the draft prescribing information (PI) and carton and container labeling for NDA 208547 NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use (Netspot). Reference is made to the Applicant's February 12, 2016 submission of major amendments to the application which extended the user fee goal date to June 1, 2016. OPDP has reviewed the substantially complete version of the draft PI titled "NDA 208547 Labeling Review 12-9-2015" accessed via SharePoint on April 28, 2016 at 1:03 pm. We do not have any comments on the proposed PI at this time.

OPDP has also reviewed the substantially complete version of the draft carton and container labeling submitted by the Sponsor to EDR May 20, 2016. We do not have any comments on the proposed carton and container labeling at this time. Copies of the reviewed PI and carton and container labeling are attached to this consult response for your reference.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions or concerns, please contact Adam George at 301-796-7607 or [adam.george@fda.hhs.gov](mailto:adam.george@fda.hhs.gov).

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ADAM N GEORGE  
05/23/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** May 23, 2016

**To:** Modupe Fagbami  
Regulatory Project Manager  
Division of Medical Imaging Products (DMIP)

**From:** Adam George, Pharm.D., RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Through:** Amy Toscano, Pharm.D, RAC, CPA  
Team Leader  
Office of Prescription Drug Promotion (OPDP)

**Subject:** **NDA 208547 NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection), for intravenous use**

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/s/  
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ADAM N GEORGE  
05/23/2016

# NDA 208547

## CARTON AND CONTAINER LABELS

### Carton Label for the kit

#### Front panel

- Change [REDACTED] (b) (4) to NETSPOT (kit for reparation of Ga 68 dotatate injection)
- Delete [REDACTED] (b) (4) per DMEPA's recommendation
- Change all DOTATATE to dotatate
- Move "For Intravenous Use Only" under the strength and increase the font or bold it per DMEPA's recommendation

First bullet: Remove [REDACTED] (b) (4) from contents of Vial

Third bullet : "Porous" should read "porous" no capital P

Add fifth bullet: 1 drug product label for radiopharmacy use

Add sixth bullet: 1 drug product syringe label for the radiopharmacy use

#### Left panel:

Remove [REDACTED] (b) (4)

Right panel: No edits.



### Container Label

**Vial 1 (Reaction vial with lyophilized powder):** Should be on vial 1.

- Change all (b) (4) to NETSPOT
- Change all Octreotate to dotatate, 40 mcg
- Ensure proprietary name and established name and strength is displayed prominently e.g.  
Netspot  
  
40 mcg dotatate per vial
- CFR reference to established name N/A here, we are not using established name
- Unbold (b) (4)
- Revise (b) (4)  
(b) (4). For intravenous Use Only After reconstitution with Ga 68 chloride and pH adjustment with Reaction Buffer prior to use.
- Unbold the storage statement: Do not agree with DMEPA's recommendation, storage statement should be prominent (because of the leaded container and the within 4h use.)  
(b) (4) Revise to "Single dose vial".

**Vial 2 (Buffer):** Should be on vial 2

- Change (b) (4) to "1 mL in 10 mL Vial"
- Delete (b) (4) and replace with "Reaction Buffer for preparation of Ga 68 dotatate injection"
- Revise (b) (4) to read such as: "For Adjusting pH of Ga 68 dotatate injection" to ensure that the Reaction Buffer will not be used alone instead of Ga 68 dotatate injection
- Directly under the above statement, add a sentence to read such as: For pH adjustment of radiolabeled Netspot only
- Add the statement "Not for Direct administration"
- Revise (b) (4) To read such as: See package insert for preparation and administration instructions.
- Revise (b) (4) information to read such as "Single Dose Vial". Discard Unused Portion

- Unbold the storage information to help improve the prominence of the most important information on the display panel.

#### Accessory Cartridge Label

- Revise [REDACTED] (b) (4) information to read such as “Cartridge for preparation of Ga 68 dotatate injection” to ensure that the accessory cartridge will be used appropriately in the preparation of Ga 68 dotatate.
- Revise “single –Use Vial” to read such as “Single Use Cartridge” Discard after Use.

#### Drug Product Label (Ga 68 dotatate) for the radiopharmacy

- Revise [REDACTED] (b) (4) to “Ga 68 dotatate injection”
- Revise [REDACTED] (b) (4) to “EOS” =End of synthesis



#### Syringe Label for Drug Product

This was requested by CMC drug product during review – the firm agreed but did not include here. The syringe label should be included in the box for the kit.

- Add radioactive symbol to the syringe label
- Revise [REDACTED] (b) (4) to “NETSPOT (Kit for preparation of Ga 68 dotatate injection”
- Add Ga 68 dotatate injection

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/s/  
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JOHN K AMARTEY  
05/16/2016

DANAE D CHRISTODOULOU  
05/16/2016  
CMC labeling review for carton and container labels

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY (CIS)  
AMENDMENT**

DATE: April 15, 2016

TO: Modupe Fagbami, Regulatory Project Manager  
Cindy Welsh, M.D., Medical Officer  
Alex Gorovets, M.D., Deputy Division Director  
Division of Medical Imaging Products (**DMIP**)

FROM: John Lee M.D., Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation (**DCCE**)  
Office of Scientific Investigations (**OSI**)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader  
Kassa Ayalew, M.D., M.P.H., Branch Chief  
Good Clinical Practice Assessment Branch, DCCE/OSI

SUBJECT: Evaluation of Clinical Inspection

APPLICATIONS: NDA 208547

APPLICANT: Advanced Accelerator Applications USA, Inc.  
Victor G. Paulus, Ph.D.  
Head, Regulatory Affairs  
350 Fifth Avenue, Suite 6902  
New York, NY 10118

DRUG: (b) (4) ®  
Commercial kit for the on-site preparation of <sup>68</sup>Ga-dotatate for injection

NME: No

INDICATION: For use with positron emission tomography as a diagnostic imaging agent in evaluating neuroendocrine tumors expressing somatostatin receptor type 2

REVIEW CLASSIFICATION: Priority review original NDA

DARRTS CONSULTATION DATE: November 19, 2015

ORIGINAL CIS DATE: February 18, 2016

REGULATORY ACTION GOAL DATE: May 4, 2016 (extended\* from March 4, 2016)

PDUFA DUE DATE: May 4, 2016 (extended\* from March 4, 2016)

\*Dates extended after receipt of major NDA amendment

## I. BACKGROUND

Advanced Accelerator Applications USA, Inc. (AAA) submitted this NDA 208547 for (b) (4)® as a 505(b)(2) application supported by the literature and by a limited amount of new clinical data collected at Vanderbilt University Medical Center (VUMC), data collected to support expanded access (EA) to an unapproved radiopharmaceutical for use with diagnostic imaging. AAA retrospectively partnered with VUMC and currently seeks the marketing approval of a commercial kit for the on-site end-user preparation of the radiopharmaceutical used in the EA study, (b) (4)® (pending trade name) for the preparation of <sup>68</sup>Ga-dotatate (GD) for intravenous injection. AAA proposes GD as a gallium-radiolabeled imaging agent for use with positron emission tomography (PET) in the evaluation of neuroendocrine tumors (NETs) expressing the somatostatin receptor type 2 (SSR2). In support of this NDA review, the EA study was audited at good clinical practice (GCP) inspection of VUMC.

NOTE: This GCP inspection (Dr. Ronald Walker, VUMC) has been completed and the findings were reported to the review division (February 18, 2016). At that time, the establishment inspection report (EIR) had not been received from the field office and the final inspection outcome remained pending. This amendment to the clinical inspection summary (CIS) presents the updated results after EIR receipt and review, noteworthy for the inspection outcome classification upgraded (VAI changed to OAI, see Section II below) from that reported in the original CIS.

### **VUMC IRB Protocol 110588**

*Use of <sup>68</sup>Ga-DOTATATE PET scanning for diagnosis and treatment of metastatic neuroendocrine tumors*

This prospective, Phase I/II, EA study was conducted at VUMC in 97 subjects with NETs. All subjects received a single administration of GD immediately before PET imaging. The study was conducted open-label, as an extension of standard clinical care at VUMC, but the overall design included a blinded component limited to GD-PET image interpretation by independent readers. The primary study objective was to demonstrate: (1) the safety and efficacy of GD-PET, and (2) the impact of GD-PET on clinical treatment plan. Study features important to the major inspectional findings were limited to subject safety monitoring, which included: (1) at baseline -- oxygen saturation (pulse oximeter), ECG, and laboratory tests; (2) at completion of imaging -- clinical adverse events (AEs) and laboratory tests; (3) for three hours after GD injection -- observation for AEs on-site; (4) next morning -- telephone interview; and (5) within one month -- AEs, ECG, vital signs, and laboratory tests.

## II. INSPECTIONS

VUMC Study 110588 (IRB Protocol 110588) was conducted as an open-label study in which the unapproved GD product was made available to patients with NETs as part of institution-specific standard of care. This study was audited on-site with emphasis on (blinded) PET image interpretation and overall internal study monitoring. For this EA study, NDA data verification (against source records on-site) was limited to Appendix 2.3 (*Individual efficacy data*), which included the 17 read results noted to be discordant between PET using GD (GD-PET) in conjunction with computed tomography (CT) versus single photon emission CT (SPECT) with or without other conventional imaging techniques (CITs). Subject records were reviewed as follows:

- *All subjects*: Confirmation that GD-PET/CTs were indeed performed as reported for all 97 subjects in the study (results evaluable for efficacy for 78, including discordant results for 17).
- *Ten subjects (selected at random)*: Verification that GD-PET/CT read results and the treatment shown on data collection forms (DCFs) are consistent with those on source records and NDA data listings.
- *Five subjects (selected for major treatment impact by GD-PET/CT, otherwise at random)*: Review of subject case records in detail to detect any serious GCP deficiency, particularly those relevant to the oncology surgeon's decision to change to a different treatment modality.

No special concerns were identified at NDA review. The audit was to be expanded as indicated to investigate further any serious concern, to include detailed case records review and/or data verification for all subjects. The final inspection outcome (after completion of EIR review) is shown below.

Clinical Investigator Site	Subjects	Inspection Outcome
Ronald C. Walker, M.D. Vanderbilt University Medical Center Vanderbilt-Ingram Cancer Center 1161 21 <sup>st</sup> Medical Center Drive Nashville, Tennessee	Total enrollment: 97 Efficacy: 78 Discordant: 17	January 19 - 27, 2016 OAI

OAI = official action indicated (significant GCP violations)

### Ronald C. Walker, M.D.

a. What was inspected:

**General records:** study conduct including institutional review board (**IRB**), drug accountability and disposition, and subject records

**Subject records and data verification:** subject eligibility, informed consent, AEs and safety monitoring, primary endpoint, and protocol deviations

b. General observations and comments:

Case records were reviewed for all 97 subjects enrolled in the study, including detailed review for 22 subjects (17 with discordant PET results and five others selected at random). A Form FDA 483 was issued for not completing study evaluations according to the study protocol, as evidenced by the following findings at detailed records review for the 22 subjects:

- Incomplete laboratory testing: apparently not tested for serum creatinine and/or hepatic enzymes prior to enrollment (screening evaluation, two subjects), or for tumor markers within seven days prior to study medication receipt (baseline evaluation, 14 subjects)
- Day 1 safety monitoring (clinical and laboratory evaluation): not performed (13 subjects); lacking physical examination (**PE**), complete blood count (**CBC**), comprehensive metabolic panel (**CMP**), pulse oximetry (**PO**), electrocardiogram (**ECG**), or AEs; or completed at an outside facility not identified on Form FDA 1572 (8 subjects)
- No documentation of phone follow up for AEs: within 24 hours of study medication receipt (19 subjects), or at Week 4 (20 subjects)

This EA study was conducted to meet the standard of care at VUMC (under an IND) and not to support an NDA. Much of the protocol-specified safety data were not collected. All audited data (Appendix 2.3, *Individual efficacy data*) were adequately verifiable against source records and DCFs.

c. Assessment of data integrity: The efficacy data from this study site reported in the NDA appear reliable. However, some of the protocol-specified safety assessments required under this investigator's IND were not collected or documented. The review division will need to determine the potential impact of the missing data on any conclusions reached regarding the safety of this product.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

AAA submitted this NDA 208547 for (b) (4)®, a commercial kit for the on-site end-user preparation of the imaging agent GD for use with PET in evaluating SSR2-positive NETs. As a 505(b)(2) application, the NDA is supported by the literature and by a limited amount of new data collected in an EA study conducted at VUMC.

This EA study was audited at an on-site GCP inspection of VUMC, with emphasis on PET image interpretation and internal (IRB) study monitoring. Verification of NDA data included the 17 read results discordant between GD-PET/CT and CIT/SPECT. All audited data were adequately verifiable among source records, DCFs, and NDA data listings. A Form FDA 483 was issued for many protocol deviations related to safety monitoring required under the IND. For the overall study outcome, the significance of the missing (per-protocol) safety data is unclear. The efficacy data from this study/site reported in the NDA appear reliable; however, because of incomplete collection of safety data (i.e., no documentation that subjects were adequately evaluated for post-procedure AEs by telephone interview, physical examination, and/or laboratory studies), the review division will need to determine the potential impact of the missing data on any conclusions regarding the safety of this product.

{See appended electronic signature page}

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Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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/s/  
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JONG HOON LEE  
04/15/2016

JANICE K POHLMAN  
04/18/2016

KASSA AYALEW  
04/18/2016

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: February 17, 2016

TO: Modupe Fagbami, Regulatory Project Manager  
Cindy Welsh, M.D., Medical Officer  
Alex Gorovets, M.D., Deputy Division Director  
Division of Medical Imaging Products (**DMIP**)

FROM: John Lee M.D., Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation (**DCCE**)  
Office of Scientific Investigations (**OSI**)

THROUGH: Janice Pohlman, M.D., M.P.H., Team Leader  
Kassa Ayalew, M.D., M.P.H., Branch Chief  
Good Clinical Practice Assessment Branch, DCCE/OSI

SUBJECT: Evaluation of Clinical Inspection

APPLICATIONS: NDA 208547

APPLICANT: Advanced Accelerator Applications USA, Inc.  
Victor G. Paulus, Ph.D.,  
Head, Regulatory Affairs  
350 Fifth Avenue, Suite 6902  
New York, NY 10118

DRUG: (b) (4) ®  
Commercial kit for the on-site preparation of <sup>68</sup>Ga-dotatate for injection

NME: No

INDICATION: For use with positron emission tomography as a diagnostic imaging agent in evaluating neuroendocrine tumors expressing somatostatin receptor type 2

REVIEW CLASSIFICATION: Priority review original NDA

DARRTS CONSULTATION DATE: November 19, 2015

REGULATORY ACTION GOAL DATE: March 4, 2016

PDUFA DUE DATE: March 4, 2016

## I. BACKGROUND

Advanced Accelerator Applications USA, Inc. (AAA) submitted this NDA 208547 for (b) (4)® as a 505(b)(2) application supported by the literature and by a limited amount of new clinical data collected at Vanderbilt University Medical Center (VUMC), data collected to support expanded access (EA) to an unapproved radiopharmaceutical for use with diagnostic imaging, and not to support new drug development for marketing approval. AAA retrospectively partnered with VUMC and currently seeks the marketing approval of a commercial kit for the on-site end-user preparation of the radiopharmaceutical used in the EA study, (b) (4)® (pending trade name) for the preparation of <sup>68</sup>Ga-dotatate (GD) for intravenous (IV) injection. AAA proposes GD as a gallium-radiolabeled imaging agent for use with positron emission tomography (PET) in the diagnosis, clinical staging, and follow up of neuroendocrine tumors (NETs) expressing the somatostatin receptor type 2 (SSRT2).

NETs are a heterogeneous group of pulmonary and gastrointestinal neoplasms with diverse, often hormone-mediated clinical presentations. The incidence of NETs appears to have increased over the last three decades and NETs may not be as rare as previously thought (worldwide prevalence < 5/100,000 population). NETs are well-known for their endocrine syndromes; morbidity from hormonal symptoms may be severe, protracted (often years), and debilitating. However, up to one-half of NETs are hormonally inactive and the associated morbidity and mortality are caused primarily by mechanical tumor burden. No standard of care has emerged for the many different NET types other than recognizing surgery as the only therapy with favorable expectations for long-term remission and/or cure. NET patients often present with advanced unresectable (often metastatic) disease, and the five-year survival rate ranges between 5-97% depending on the tumor type. Overall survival is dictated by the completeness of surgical resection, for which radiographic imaging (for accurate clinical staging) is critical.

Conventional imaging techniques (CITs) including computed tomography (CT) and magnetic resonance imaging (MRI) are often considered inadequate for evaluating NETs, particularly for clinical staging. Since the SSRT2 is expressed on most NETs, two SSRT-based techniques using a radiolabeled somatostatin analogue (for tumor localization) are receiving increasing attention, each touted as the emerging technique of choice for NET staging: (1) single photon emission CT (SPECT) using 111-indium as the tracer radioisotope, and (2) PET using 68-gallium as the tracer radioisotope. The major differences between the two techniques are driven by the final radiation signal (for tumor visualization) from the chosen radioactive isotope, either positron emission from 68-gallium (PET) or photon emission from 111-indium (SPECT).

Relative to SPECT, AAA claims that PET using GD (GD-PET) is more sensitive, more convenient, and similarly specific for evaluating NETs. AAA further notes that GD-PET is not new, yet commercially not available in the United States (US). For this NDA, AAA partnered with VUMC where an EA study was previously conducted (without commercial sponsorship) to make GD-PET available for clinical care at VUMC (and elsewhere in the US). This EA study is considered critical to this NDA (to augment AAA's literature review) and was identified for on-site audit at good clinical practice (GCP) inspection of VUMC, the sole clinical investigator (CI) site for the study. This EA study is described briefly below, as background context for interpreting inspectional findings.

### **VUMC IRB Protocol 110588**

*Use of <sup>68</sup>Ga-DOTATATE PET scanning for diagnosis and treatment of metastatic neuroendocrine tumors*

This prospective, Phase I/II, EA study was conducted at VUMC in 97 subjects with NETs. All subjects received a single administration of GD immediately before PET (and CT) imaging. The study was conducted open-label, as an extension of standard clinical care at VUMC, but the overall design included a blinded component limited to GD-PET image interpretation by independent readers. The primary study objective was to demonstrate: (1) the safety and efficacy of GD-PET, and (2) the impact of GD-PET on clinical treatment plan.

### Subject Selection

- Adult patients (age  $\geq$  18 years) at VUMC receiving standard clinical care for a suspected or known metastatic NET, typically one of the following:
  - Pancreatic NET (insulinoma, glucagonoma, and VIPoma); non-pancreatic gastrointestinal NET
  - Typical or atypical bronchial/thymic carcinoid; medullary thyroid carcinoma
  - Unknown primary: NET marker-positive carcinoid or neuroendocrine metastases
- Karnofsky performance score  $\geq$  50 (0-100 scale): cannot work, lives at home with much assistance
- GD-PET scheduled within seven days of baseline evaluation
- Negative pregnancy test for women of childbearing potential

### Exclusion Criteria

- Active infection; (other) cancer treatment within two years; hypersensitivity to IV contrast
- Serum creatinine  $>$  3.0 mg/dL; liver enzymes  $>$  5-fold upper limit of normal (ULN)
- Body weight  $\geq$  400 pounds or otherwise technically difficult/unable PET/CT scanning
- Dosimetry criterion: urinary drainage/diversion (any reason for variable elimination)
- Use of any (other) investigational product/device within 30 days
- Requirement for any (other) investigational medication
- Any condition/circumstance that may compromise study compliance (CI judgment)

### Reader Selection

- Board-certified nuclear medicine physician with  $>$  five years of experience with PET and CT
- Each image/case interpreted by two readers, and by a third to adjudicate if the two disagree

### GD PET and CT Scanning

- PET and CT scanning combined in the same imaging machine/procedure to generate matching images that are interpreted together (for this study, GD-PET synonymous with GD-PET/CT)
  - CT added for correction of PET signal attenuation
  - Allows 1:1 matching of PET and CT for tumor localization against background anatomy
  - Routine use of oral contrast to maximize CT sensitivity for gastrointestinal NETs
- IV Injection of GD and GD-PET/CT Scanning
  - (b)(4)® kit: dotatate and  $^{68}\text{GaCl}_3$  vials for preparing one dose of GD
  - Radiolabeled GD solution storage:  $<$  25 °C,  $<$  four hours, shielded (radiation safety)
  - Reconstituted/radiolabeled GD: completely bioavailable immediately after IV injection
  - Dotatate 50  $\mu\text{g}$  at 5 / 6 / 7 mCi for  $\leq$  200 / 201-300 /  $>$  300 lbs body weight, respectively
  - Voiding immediately before GD injection, then no voiding until completion of GD-PET/CT
  - GD-PET/CT from vertex to mid-thigh at least two time points: 30, 60, and/or 90 minutes

### Image Interpretation

- Tumor localization, lesion size measurements, and determination of the standardized uptake value (SUV) for up to five (sentinel) lesions:
  - No more than three lesions in any given organ
  - For each lesion, cross-sectional measurements in long and short axes
  - Mean maximum (peak) SUV normalized to lean body mass (SUL)
- Two independent readers blinded only to the other reader's interpretation (not blinded otherwise)
- Read discrepancies resolved by consensus (or by adjudication by third reader, if needed)
- Three-way discrepancies/disagreement permitted

### Major (Co-Primary) Efficacy Endpoints and Analyses

**Clinical Efficacy:** Impact of GD-PET/CT on clinical care, as determined by change in treatment plan (intended surgery) before and after GD-PET/CT

- Imaging by CITs and SPECT, then by GD-PET/CT, where CITs consists of CT, MRI, ultrasound, X-ray plain films, and/or any other imaging used as part of clinical care
  - GD-PET/CT versus CITs/SPECT: tumor seen with one and not the other
  - Change in clinical stage, treatment plan, and/or prognosis based on GD-PET/CT
- Oncology surgeon evaluation: Impact of GD-PET/CT on clinical care, by comparing intended treatment before and after GD-PET/CT
  - Minor impact: intra-modal change (e.g., extent of same surgical procedure)
  - Major impact: inter-modal change (e.g., addition of chemotherapy or cancellation of surgery)

**Sensitivity and Specificity:** (1) GD-PET/CT and SPECT, each using CITs plus any available histopathology as standard of truth (SoT); and (2) GD-PET/CT relative to SPECT

### Safety Monitoring

- Baseline: vital signs, oxygen saturation (pulse oximeter), ECG, and laboratory tests
- At completion of imaging: clinical adverse events (AEs) and laboratory tests
- For three hours after GD injection: on-site observation for AEs, then by phone next morning
- Within one month (typically one week): AEs, ECG, vital signs, and laboratory tests

### Major Sponsor-Reported Outcomes

- Relative to SPECT: GD-PET/CT was significantly more sensitive (96% vs 72%) and similarly specific, with decreased total radiation exposure (shorter half-life, 68-gallium vs 111-indium), fewer scans (one versus two), and shorter total imaging times (two vs 24-72 hours).
- Adding GD-PET/CT to CITs improved clinical decision making about NET treatment (> one-third of subjects). GD-PET/CT was well-tolerated in all subjects with no significant complications.

## II. INSPECTIONS

VUMC Study 110588 (IRB Protocol 110588) was conducted as an open-label study in which the unapproved GD product was made available to patients with NETs as part of institution-specific standard of care. This study was audited on-site with emphasis on (blinded) PET image interpretation and overall internal study monitoring. For this EA study, NDA data verification (against source records on-site) was limited to Appendix 2.3 (*Individual efficacy data*), which included the 17 read results noted to be discordant between GD-PET/CT and CIT/SPECT. Subject records were reviewed as follows:

- *All subjects:* Confirmation that GD-PET/CTs were indeed performed as reported for all 97 subjects in the study (results evaluable for efficacy for 78, including discordant results for 17).
- *Ten subjects (selected at random, or guided by audit findings):* Verification that GD-PET/CT read results and the treatment shown on data collection forms (DCFs) are consistent with those on source records and NDA data listings.
- *Five subjects (selected for major treatment impact by GD-PET/CT, otherwise at random):* Review of subject case records in detail to detect any serious GCP deficiency, particularly those relevant to the oncology surgeon's decision to change to a different treatment modality.

No special concerns were identified at preliminary NDA review. The audit was to be expanded as indicated to investigate further any serious concern, to include detailed case records review and/or data verification for all subjects. The inspection outcome is shown in the table below.

Clinical Investigator Site	Subjects	Inspection Outcome
Ronald C. Walker, M.D. Vanderbilt University Medical Center Vanderbilt-Ingram Cancer Center 1161 21 <sup>st</sup> Medical Center Drive Nashville, Tennessee	Total enrollment: 97 Efficacy: 78 Discordant: 17	January 19 - 27, 2016 VAI*

VAI = voluntary action indicated (minor GCP violations observed)

\*The final Establishment Inspection Report (**EIR**) has not been received from the field office. The inspection outcome shown is based on preliminary communication with the field investigator, pending verification at EIR receipt and review. See *Note* below, Section III.

### Ronald C. Walker, M.D.

a. What was inspected:

**General records:** study conduct including institutional review board (**IRB**), drug accountability and disposition, and subject records

**Subject records and data verification:** subject eligibility, informed consent, AEs and safety monitoring, primary endpoint, and protocol deviations

b. General observations and comments:

Case records were reviewed for all 97 subjects enrolled in the study, including detailed review for 22 subjects (17 with discordant PET results and five others selected at random). A Form FDA 483 was issued for not completing study evaluations according to the study protocol, as evidenced by the following findings at detailed records review for the 22 subjects:

- Incomplete laboratory testing: apparently not tested for serum creatinine and/or hepatic enzymes prior to enrollment (screening evaluation, two subjects), or for tumor markers within seven days prior to study medication receipt (baseline evaluation, 14 subjects)
- Week 1 safety monitoring (clinical and laboratory evaluation): not performed (13 subjects); lacking physical examination (**PE**), complete blood count (**CBC**), comprehensive metabolic panel (**CMP**), pulse oximetry (**PO**), electrocardiogram (**ECG**), or AEs; or completed at an outside facility not identified on Form FDA 1572 (8 subjects)
- No documentation of phone follow up for AEs: within 24 hours of study medication receipt (19 subjects), or at Week 4 (20 subjects)

*OSI Comments:*

- *As discussed in Sections I and II above, this EA study was intended to meet the clinical standard of care at VUMC. At time of study conduct, the information to be obtained from the study was not prospectively intended to support a regulatory submission.*
- *The protocol is not written rigorously and lacks detailed requirements for many study procedures, including laboratory testing and AE monitoring. The cited GCP deficiencies reflect a rigorous GCP audit applicable to the typical pivotal study (prospectively intended to support a regulatory submission). The cited deficiencies appear minor and unlikely to be significant.*

Study conduct appears adequate, including IRB oversight of study conduct. All audited data (on Appendix 2.3, *Individual efficacy data*) were adequately verifiable against source records and DCFs.

c. Assessment of data integrity: The data from this study site appear reliable.

### III. OVERALL ASSESSMENT AND RECOMMENDATIONS

AAA submitted this NDA 208547 for (b) (4)® as a 505(b)(2) application supported by the literature and by a limited amount of new clinical data collected at VUMC under IRB Protocol 110588, an open-label EA study conducted to consistently deliver institution-specific standard of care. AAA seeks the marketing approval of a commercial kit for the on-site end-user preparation of the imaging agent used in the EA study, GD for use with PET in evaluating SSRT2-positive NETs.

This EA study was audited on-site with emphasis on PET image interpretation and internal (IRB) study monitoring. Verification of NDA data included the 17 read results discordant between GD-PET/CT and CIT/SPECT. A Form FDA 483 was issued for minor GCP deficiencies (protocol deviations) unlikely to be significant to the study outcome. Study conduct appeared adequate, including IRB oversight of study conduct. All audited data were adequately verifiable among source records, DCFs, and NDA data listings. The data from this study/site appear reliable as reported in the NDA.

Note: The EIR has not been received from the field office and the final inspection outcome remains pending. The inspection results presented in this Clinical Inspection Summary (CIS) are based on preliminary communication with the field investigator. Upon receipt and review of the EIR, an addendum will be forwarded to the review division if the final outcome changes from that reported in this CIS. Otherwise, close-out correspondence with the CI (copied to review division) indicates EIR review completion with no new significant findings and inspection outcome finalization without an addendum as reported in this CIS.

{See appended electronic signature page}

John Lee, M.D.  
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Division of Clinical Compliance Evaluation  
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CONCURRENCE:

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Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JONG HOON LEE  
02/17/2016

JANICE K POHLMAN  
02/17/2016

KASSA AYALEW  
02/18/2016

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** February 12, 2016  
**Requesting Office or Division:** Division of Imaging Products (DMIP)  
**Application Type and Number:** NDA 208547  
**Product Name and Strength:** Netspot (<sup>68</sup>Ga-DOTATATE)Injection  
40 mcg/vial  
**Product Type:** Single  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Advanced Accelerator Applications  
**Submission Date:** July 1, 2015  
**OSE RCM #:** 2015-1640  
**DMEPA Primary Reviewer:** Michelle Rutledge, PharmD  
**DMEPA Team Leader:** Yelena Maslov, PharmD  
**DMEPA Deputy Division:** Lubna Merchant, PharmD, MS

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## 1 REASON FOR REVIEW

This review responds to a request from DMIP to evaluate the proposed prescribing information, container label for lyophilized powder, container label for the reaction buffer, container label for the cartridge, reconstituted label, syringe label and carton labeling for Netspot (<sup>68</sup>Ga-DOTATATE) Injection. The applicant is proposing a product indicated (b) (4)

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Advanced Accelerator Applications is seeking approval of Netspot (<sup>68</sup>Ga-DOTATATE) Injection, β+ emitting radionuclide, for (b) (4)

We performed a risk assessment of the prescribing information, container label for lyophilized powder, container label for the reaction buffer, container label for the cartridge, reconstituted label for <sup>68</sup>Ga-DOTATATE, syringe label and carton labeling, submitted by the Applicant to identify areas that may lead to medication errors.

We identified areas of improvement in the prescribing information, label, and labeling.

We provide recommendations below in section 4.1 to improve the readability and prominence of important product information such as strength, statement and route of administration on the label, and provide for adequate differentiation between vials included in the kit. We recommend revising the PI to delete dangerous abbreviations, symbols, dose designation, and use of new terminology.

#### **4 CONCLUSION & RECOMMENDATIONS**

We reviewed the prescribing information, container label for lyophilized powder, container label for the reaction buffer, container label for the cartridge, reconstituted label for <sup>68</sup>Ga-DOTATATE, syringe label and carton labeling and identified that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

##### **4.1 RECOMMENDATIONS FOR THE DIVISION**

Based on this review, DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

###### **A. PRESCRIBING INFORMATION**

###### **I. HIGHLIGHTS AND SECTION 3, DOSAGE FORMS AND STRENGTHS**

- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone symbols in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
  - i. Spell out all µg symbols appearing in the Dosage Forms and Strength section to instead read such as, microgram or mcg.

###### **II. HIGHLIGHTS AND SECTION 3 DOSAGE FORMS AND STRENGTHS, SECTION 2.3 DRUG PREPARATION, SECTION 16 HOW SUPPLIED/STORAGE AND HANDLING**

- a. Remove Vial-1 and Vial-2 terminology from the prescribing information to help minimize confusion and the risk of medication errors with the use of this product. Currently, there is no corresponding "Vial-1" and "Vial-2" designation on the lyophilized powder and reaction buffer on container and carton labels and labeling. Additionally, these designations introduce new terminology to the labeling of the product, which may introduce confusion.

### III. SECTION 2.3 DRUG PREPARATION FIGURE 1. RELABELING AND RECONSTITUTION PROCEDURE

- a. Ensure the colors of the vials used in the figure correspond with the actual color of the vials to help increase correct preparation of this product.

#### 4.2 RECOMMENDATIONS FOR THE ADVANCED ACCELERATOR APPLICATIONS

We recommend the following be implemented prior to approval of this NDA:

##### A. CARTON LABELING

1. Revise the presentation of the strength statement as follows to ensure consistent strength presentation throughout the labels and labeling of the product:

40 mcg/vial or 40 mcg per vial

2. The middle panel that notes what each kit contains appears to be principal display panel as it is the widest and most prominent panel; thus, the product will be stored with this panel facing the user. However, the most important information regarding the product is stated on the left side panel. We recommend you place the information from the left side panel to the middle panel and vice versa to ensure that the important information regarding the use of the product is easily identified.
3. Relocate the route of administration information, "For Intravenous Use Only" under the strength of the product and increase its font size or bold it. We recommend this change to ensure the product is administered by the correct route.

##### B. CONTAINER LABEL FOR LYOPHILIZED POWDER of <sup>68</sup>Ga-DOTATATE

1. See A1 and revise label accordingly. Delete the statement (b) (4).
2. Ensure proprietary name and established name strength is displayed prominently on the label, for example:

Netspot  
(<sup>68</sup>Ga-DOTATATE) injection  
40 mcg DOTATATE per vial

3. Revise the non-proprietary name information from (b) (4) to <sup>68</sup>Ga-DOTATATE, as (b) (4) is not consistent with the remainder of the product labeling.

4. Ensure that the font size of established name to at least ½ the size of the proprietary name per 21 CFR 201.10(g)(2) to increase readability of this important information on the principal display panel (PDP)<sup>1</sup>.

5. Unbold the Usual dosage statement to help increase prominence of important product information.

6. Revise, [REDACTED] (b) (4)  
information such as:

For Intravenous Use Only

“After reconstitution, adjust pH with Reaction Buffer prior to Use”.

Ensure that each statement is prominent as this is important information to help with the correct use of this product.

7. Ensure this vial is well differentiated from the reaction buffer and cartridge included in the kit to ensure sufficient differentiation among the <sup>68</sup>Ga-DOTATATE versus reaction buffer versus cartridge.

8. Unbold the storage statement to help increase prominence of the most important product information.

### C. CONTAINER LABEL FOR REACTION BUFFER

1. Revise [REDACTED] (b) (4) information to read, such as: “For Adjusting pH of <sup>68</sup>Ga-DOTATATE” to ensure that Reaction Buffer will not be used alone without or instead of <sup>68</sup>Ga-Dotatate.

2. Directly underneath add a sentence to read such as: For pH adjustment of radiolabeled Netspot only.

3. Add the statement “Not for Direct administration” to the principal display panel to ensure Reaction Buffer is not administered by itself.

3. Delete [REDACTED] (b) (4) from the principal display panel as it is confusing next to 1 mcg. The statement of strength should be expressed as “1 mcg/10 mL”.

---

<sup>1</sup> Labeling, 21 CFR 201.10(g)(2), 2015

4. Remove [REDACTED] <sup>(b) (4)</sup> entirely since this is not the active ingredient, but a reaction buffer to help prepare the product for administration.

5. Revise [REDACTED] <sup>(b) (4)</sup> to read such as: See package insert for preparation and administration instructions.

6. Ensure this vial is well differentiated from the active ingredient vial and cartridge included in the kit to ensure sufficient differentiation among the active ingredient versus reaction buffer versus cartridge.

7. Revise current [REDACTED] <sup>(b) (4)</sup> information to read such as: “Single Dose Vial. Discard Unused Portion”.

8. Unbold the storage information to help increase prominence of the most important information on the principal display panel.

#### **D. CARTRIDGE CONTAINER LABEL**

1. Ensure this vial is well differentiated from the active ingredient vial and reaction buffer included in the kit to ensure sufficient differentiation among the active ingredient versus reaction buffer versus cartridge.

2. Revise “TBD (Kit for preparation of <sup>68</sup>Ga-DOTATATE for Injection)” information to read, such as: “Cartridge for preparation of <sup>68</sup>Ga-DOTATATE” to ensure that the accessory cartridge will be used appropriately in the preparation of <sup>68</sup>Ga-DOTATATE.

#### **E. SYRINGE LABEL**

1. Add radioactive symbol to this syringe label to increase prominence of warning information associated with this product.

2. If this syringe will be used with reconstituted product, revise the syringe label to state “<sup>68</sup>Ga-DOTATATE”.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Netspot (Kit for preparation of <sup>68</sup>Ga-DOTATATE for Injection) that Advanced Accelerator Application submitted on July 1, 2015.

<b>Table 2. Relevant Product Information for Netspot (<sup>68</sup>Ga-DOTATATE) Injection</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	<sup>68</sup> Ga-DOTATATE Injection
<b>Indication</b>	(b) (4)
<b>Route of Administration</b>	Intravenous injection (bolus)
<b>Dosage Form</b>	Powder for Injection
<b>Strength</b>	40 mcg/vial
<b>Dose and Frequency</b>	The recommended radioactivity to be administered is 2 MBq/kg of body weight (0.054 mCi/kg), (b) (4) and not more than 200 MBq (5.4 mCi)
<b>How Supplied</b>	Single-use kit containing: <ul style="list-style-type: none"> <li>• Vial-1 (10-mL Ultra inert Type I Plus glass vial, light-blue flip-off cap): lyophilized formulation</li> <li>• Vial-2 (10-mL cyclic olefin polymer vial, with a yellow flip-off cap): reaction buffer solution               <ul style="list-style-type: none"> <li>• One accessory cartridge able to reduce the amount of germanium-68 potentially present in generator eluate</li> </ul> </li> </ul>
<b>Storage</b>	For prolonged storage, (b) (4) should be stored in its original packaging at room temperature below 25°C (do not freeze). After reconstitution and radiolabelling with activities of up to 1110 MBq (30 mCi), the <sup>68</sup> Ga-DOTATATE solution must be kept upright with an appropriate shielding to protect from radiation, at a temperature below 25 °C (do not freeze), and for a maximum of 4 hours. The storage of the radiolabelled product must comply with regulatory requirements for radioactive materials.

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On November 12, 2015, we searched the L:drive using the terms, <sup>68</sup>Ga-DOTATATE, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified no previous label and labeling reviews.

## APPENDIX D. ISMP NEWSLETTERS

### D.1 Methods

On November 12, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

<b>ISMP Newsletters Search Strategy</b>	
<b>ISMP Newsletter(s)</b>	Acute Care, Community, Nursing, Canada Safety, PA Patient Safety
<b>Search Strategy and Terms</b>	Match Exact Word or Phrase: 68Ga-DOTATATE

### D.2 Results

No newsletters were identified.

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with postmarket medication error data, we reviewed the following Netspot (Kit for preparation of <sup>68</sup>Ga-DOTATATE for Injection) labels and labeling submitted by Advanced Accelerator Applications on July 1, 2015 and November 12, 2015.

- Container label for lyophilized powder
- Container label for reaction buffer
- Container label for cartridge
- Carton labeling
- Reconstituted label for <sup>68</sup>Ga-DOTATATE
- Syringe label
- Prescribing Information (not listed)

### G.2 Label and Labeling Images

#### *Carton Labeling*



#### *Container label for lyophilized powder*



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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MICHELLE K RUTLEDGE  
02/12/2016

YELENA L MASLOV  
02/17/2016

LUBNA A MERCHANT  
02/17/2016

# REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208547

**Application Type:** NDA 208547- (b) (4) (Kit for the Preparation of <sup>68</sup>Ga-DOTATATE for Injection)

**Drug Name/Dosage Form:** 40µg of DOT A0-Tyr3-Octreotate

**Applicant:** Advanced Accelerator Applications (AAA)

**Receipt Date:** July 1, 2015

**Goal Date:** March 1, 2016

## Regulatory History and Applicant's Main Proposals

(b) (4) Kit for the Preparation of <sup>68</sup>Ga-DOTATATE for Injection is a somatostatin-receptor imaging drug submitted by Advanced Accelerator Applications (AAA). The FDA granted orphan drug status for <sup>68</sup>Ga-DOTATATE in December 2013 (designation 13-4136) (b) (4)

This orphan product is intended to diagnose a serious and life-threatening disease. The Applicant is ascertaining that there is a critical unmet medical need that is widely recognized in the medical community and among regulatory authorities. Gallium imaging represents an improvement over the current standard of care, provides more accurate imaging for diagnosis, staging and monitoring of patient response to therapy.

## Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

## Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

### 1. Highlight General Format

- (b) (4)  
Also, the length of HL is beyond the one-half page or less requirement.
- Reference is missing in Dosage and Administration section

### 2. Recent Major Changes (RMC) in Highlights

## RPM PLR Format Review of the Prescribing Information

- Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI: *This section is not applicable for this product* (b) (4)

### 3. Dosage Forms and Strengths in Highlights:

- *Remove bullets as there is only one dosage form (injection)*

### 4. Contraindications in Highlights:

- *Remove bullet as there is only one item*

### 5. Adverse Reactions in Highlights:

- (b) (4)

### 6. Contents: Table of Contents (TOC):

- *Subsections should not be bolded*

### 7. FULL PRESCRIBING INFORMATION DETAILS: CONTRAINDICATIONS Section in the FPI:

- *Remove bullet as there is only one item in this section*

#### ADVERSE REACTIONS Section in the FPI:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

- *Clinical Trials Experience with preamble statement discussing varying test conditions is missing*

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## 4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

### Highlights

See Appendix for a sample tool illustrating Highlights format.

#### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

**Comment:**

*Also, the length of HL is beyond the one-half page or less requirement.*

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
  - TOC from the Full Prescribing Information (FPI).

**Comment:**

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

**Comment:**

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

**Comment:**

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:** *Reference is missing in Dosage and Administration section*

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
---------	-------------------

## Selected Requirements of Prescribing Information

• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

*Comment:*

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

*Comment:*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

*Comment:*

**N/A**

## Selected Requirements of Prescribing Information

13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

**Comment:**

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

**Comment:**

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

**Comment:**

### Recent Major Changes (RMC) in Highlights

- NO** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

**Comment:** *This section is not applicable for this product* [REDACTED] (b) (4)

- NO** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

**Comment:** *See comment for item 16*

- NO** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

**Comment:** *see comment for item 16*

### Dosage Forms and Strengths in Highlights

- NO** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

**Comment:** *Remove bullets as there is only one dosage form (injection)*

### Contraindications in Highlights

- NO** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

**Comment:** *Remove bullet as there is only one item*

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- NO** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

*Comment:*

(b) (4)

### Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**

*Comment:*

### Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

*Comment:*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.  
*Comment:*
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- NO** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].  
*Comment: Subsections should not be bolded*
- NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment: Section and subsection headings need to match the FPI*
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS\***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

## Selected Requirements of Prescribing Information

***Comment:*** Do not use all upper case letters in cross-reference. Also, the entire cross-reference should be in italics.

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

***Comment:***

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

***Comment:***

#### BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

***Comment:***

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

***Comment:***

#### CONTRAINDICATIONS Section in the FPI

- NO** 37. If no Contraindications are known, this section must state “None.”

***Comment:*** Remove bullet as there is only one item in this section

#### ADVERSE REACTIONS Section in the FPI

- NO** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

***Comment:*** *Clinical Trials Experience with preamble statement discussing varying test conditions is missing*

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

## Selected Requirements of Prescribing Information

### Comment:

#### **PATIENT COUNSELING INFORMATION Section in the FPI**

- N/A** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Comment:

- N/A** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

### Comment:

# Selected Requirements of Prescribing Information

## Appendix: Highlights and Table of Contents Format

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol  
Initial U.S. Approval: YYYY

#### WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

#### RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y  
Section Title, Subsection Title (x.x) M/201Y

#### INDICATIONS AND USAGE

**PROPRIETARY NAME** is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

#### DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

#### DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

#### CONTRAINDICATIONS

- Text (4)
- Text (4)

#### WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

#### USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

### FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: TITLE OF WARNING

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

#### 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

#### 7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\* Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MODUPE O FAGBAMI  
12/09/2015

NUSHIN F TODD  
12/09/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information	
NDA # 208547	<p>Efficacy Supplement Category:</p> <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: <span style="background-color: #cccccc; color: #000080;">(b) (4)</span> <b>(Unacceptable to DMEPA)</b> Established/Proper Name: <b>Kit for the preparation of 68Ga-DOT A TATE</b> Dosage Form: <b>Kit (one vial of lyophilizate, one vial of buffer)</b> Strengths: <b>40µg of DOT A0-Tyr3-Octreotate</b>	
Applicant: <b>Advanced Accelerator Applications USA, Inc.</b> Agent for Applicant (if applicable): <b>N/A</b>	
Date of Application: <b>July 1, 2015</b> Date of Receipt: <b>July 1, 2015</b> Date clock started after UN: <b>N/A</b>	
PDUFA Goal Date: <b>March 1, 2016</b>	Action Goal Date (if different):
Filing Date: <b>August 30, 2015</b>	Date of Filing Meeting: <b>August 25, 2015</b>
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch	
Proposed indication(s)/Proposed change(s): <b>Diagnostic for <span style="background-color: #cccccc; color: #000080;">(b) (4)</span> neuroendocrine tumors <span style="background-color: #cccccc; color: #000080;">(b) (4)</span> NETs)</b>	
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>	

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• <b>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</b></li> <li>• <b>The product is a Qualified Infectious Disease Product (QIDP)</b></li> <li>• <b>A Tropical Disease Priority Review Voucher was submitted</b></li> <li>• <b>A Pediatric Rare Disease Priority Review Voucher was submitted</b></li> </ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): **IND 122818**

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Subsequently, submission reclassified as an NME after filing and Goal date changed in DARRTS to March 1, 2016, now reviewed under the Program
Are the established/proper and applicant names correct in	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Proprietary Name

tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				found unacceptable by DMEPA
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a>  <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Priority Review
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees:  <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u>  <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>  <input type="checkbox"/> Yes <input type="checkbox"/> No			

<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes</b> , answer the bulleted questions below:		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?  <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

<b><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></b>				
<b>NDA/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes, # years requested:</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>NDA only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <b><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <b><i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i></b>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<b><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></b>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?<sup>1</sup></b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<sup>1</sup>

<b>If not</b> , explain (e.g., waiver granted).				
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If no</b> , explain.				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes</b> , BLA #				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21</i>				

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<b>CFR 54.2(g)].</b>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Even though this is an electronic submission
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b>PREA</b>				Orphan Designation granted
Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BPCA:</b>				
Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Applicant contacted and PLLR format was submitted on July 13, 2015
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL)			

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b>  <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** August 25, 2015

**BACKGROUND:**

(b) (4) Kit for the Preparation of <sup>68</sup>Ga-DOTATATE for Injection is a somatostatin-receptor imaging drug submitted by Advanced Accelerator Applications (AAA) is indicated as a diagnostic for (b) (4) Neuroendocrine tumors (b) (4) NETs).

A Type B Pre-IND 122818 meeting was held on July 1, 2014, to discuss the requirements for an IND submission to conduct a confirmatory bridging study. Also, in November 2014, the FDA Preliminary Responses were found acceptable by the Applicant for their Type C meeting request which was to obtain feedback from the division regarding the proposed literature review protocol.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Modupe Fagbami	Y
	CPMS/TL:	Kang Kyong	N
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		Y
Division Director	Libero Marzella		Y
Deputy Director	Alexander Gorovets		Y
Office Director	Charles Ganley		N
Clinical	Reviewer:	Cynthia Welsh	Y
	TL:	Alexander Gorovets	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Christy John	
	TL:	Gene Williams	
• Genomics	Reviewer:	N/A	
• Pharmacometrics	Reviewer:	N/A	
Biostatistics	Reviewer:	Satish Misra	Y
	TL:	Jyoti Zalkikar	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Sunny Awe	Y
	TL:	Adebayo Lanionu	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC) Review Team:	ATL:	Eldon Leutzinger Danae Christoboulou	Y Y
	RBPM:	Thao Vu	Y
• Drug Substance	Reviewer:	John Amartey	Y
• Drug Product	Reviewer:	John Amartey	Y
• Process	Reviewer:	Dhanalakshmi Kasi	Y
• Microbiology	Reviewer:	Helen Ngai	Y
• Facility	Reviewer:	Krishana Ghosh	N
• Biopharmaceutics	Reviewer:	Tien Mien Chen	Y
• Immunogenicity	Reviewer:	N/A	
• Labeling (BLAs only)	Reviewer:	N/A	
• Other (e.g., Branch Chiefs, EA Reviewer)	Eric Duffy		Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Michelle Rutledge	Y
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines			
<ul style="list-style-type: none"> <li>Discipline</li> </ul> <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:		
	TL:		
Other attendees			
*For additional lines, right click here and select "insert rows below"			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p>The (b)(4) and other Ga-DOTATATEs are similar. From radiochemistry standpoint they are all prepared by a common reaction involving Ga-68-chloride and the precursor-DOTATATE. The minor differences are the excipients present, which do not affect the bioavailability or bioequivalence of the product(s). Biologically, all these products bind to the sstr-2, moreover the route of administration is same (IV), and so bioavailability is not an issue.</p>
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<ul style="list-style-type: none"><li>• Electronic Submission comments</li></ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
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<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments: Awaiting comments</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> FILE  <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <p>• Is the product an NME?</p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Environmental Assessment</u></b></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p><b>If no,</b> was a complete EA submitted?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <p>• Establishment(s) ready for inspection?</p> <p><b>Comments:</b> Update from Eldon</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review (BLAs only)</u></b></p> <p><b>Comments:</b> N/A</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A Comment: Application was reclassified as an NME after filing and subsequently processed under the PROGRAM <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Libero Marzella	
<b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): <b>10/13/2015</b>	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
<b>ACTION ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MODUPE O FAGBAMI  
11/17/2015

KYONG A KANG  
11/23/2015