

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208547Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

25 April 2016

NDA: 208547

Drug Product Name

Proprietary: (b) (4)

Non-proprietary: Kit for the preparation of 68Ga-DOTATATE

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
1/27/2016	1/27/2016	N/A	1/27/2016
2/1/2016	2/1/2016	N/A	2/1/2016
2/5/2016	2/5/2016	N/A	2/5/2016
2/12/2016	2/12/2016	N/A	2/12/2016

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
7/1/2015	1	12/2/2015
10/20/2015	1	12/2/2015
10/26/2015	1	12/2/2015
11/19/2015	1	12/2/2015

Applicant/Sponsor

Name: Advanced Accelerator Applications USA, Inc.

Address: 350 Fifth Avenue, Suite 6902, New York, NY USA 10018

Representative:

Telephone: 212-325-2391

Fax: 212-335-2381

Name of Reviewer: Helen Ngai, Ph.D.

Conclusion: The submission is recommended for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Amendments
 2. **SUBMISSION PROVIDES FOR:** Responses to Agency's complete response letter
 3. **MANUFACTURING SITE:** Gipharma S.r.l., Via Crescentino, 13040 Saluggia (Vc), Italy.
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile lyophilized powder for injection, 40 µg/ 10 mL vial. Sterile reaction buffer packaged separately as ~ 1 mL fill/ 10 mL vial. IV. Single dose.
 5. **METHOD(S) OF STERILIZATION:** [REDACTED] (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Diagnostic for [REDACTED] (b) (4) neuroendocrine tumors [REDACTED] (b) (4) NETs).

B. **SUPPORTING/RELATED DOCUMENTS:**

Type II DMF [REDACTED] (b) (4) from Eckert and Ziegler for the 68GE/68GA- generator as manufactured in Berlin, Germany. LOA date 20/April/2015. The relevant information was reviewed in [REDACTED] (b) (4) mic1a1.doc (adequate) dated 25/April/2016 by H. Ngai.

- C. **REMARKS:** eCTD/ Global submit review. Comparability protocols are N/A. A discipline review letter was sent on 12/11/2015; responses received 2/1/2016, 2/5/2016 and 2/12/2016.

Filename: 208547a1.doc

Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The kit consists of a sterile lyophilized powder manufactured by (b) (4). The reaction buffer is (b) (4). The accessory cassette is sterilized by (b) (4).

B. Brief Description of Microbiology Deficiencies – None identified

C. Contains Potential Precedent Decision(s) - Yes No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O ^(3,4,5)	Severity of Effect (S)	Detect. (D)	Risk Priority Number ⁶ (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	(b) (4)	6		5	5	150	(b) (4) sterilization
Ster.	Aseptic Open ² Process	10		5	5	250	Simulations and interventions conducted during media fills, Environmental monitoring
Endo		4		4	4	64	

1 = A Closed Aseptic Process is one that has no exposed manipulations other than filling and stoppering after the components are sterilized. (e.g., RABS, isolator, closed drying and filling process for a powder)

2 = An Open Aseptic Process is one that has one or more steps with potential to contaminate the drug product after the component sterilizing. (e.g., sterile drug substance/excipient, interaction of operators with sterile product path, traditional Class 100 filling area).

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process hold times]

4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]

5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]

6 = RPN = O(after modification when applicable)×S×D

RPN <50 = **Low Risk**; RPN 50-120 = **Moderate Risk**; RPN >120 = **High Risk**

- B. Final Risk Assessment** - No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Helen Ngai, Ph.D.

Microbiology Secondary Reviewer/Jesse Wells, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The subject drug product is a sterile 2-vial kit which consists of: a sterile lyophilized powder for reconstitution and a sterile reaction buffer. The lyophilized powder is (b) (4) while the reaction buffer is (b) (4). The reaction buffer is (b) (4). A discipline review letter was sent on 12/11/2015; responses received 2/1/2016, 2/5/2016 and 2/12/2016 are summarized below.

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/s/

HELEN NGAI
04/26/2016

JESSE WELLS
04/26/2016

Product Quality Microbiology Review

2 Dec 2015

NDA: 208547

Drug Product Name

Proprietary: (b)(4)

Non-proprietary: Kit for the preparation of 68Ga-DOTATATE

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
7/1/2015	7/1/2015	N/A	7/10/2015
10/20/2015	10/20/2015	N/A	10/20/2015
10/26/2015	10/26/2015	N/A	11/19/2015
11/19/2015	11/19/2015	N/A	11/19/2015

Submission History (for 2nd Reviews or higher)

Submit Date(s)	Microbiology Review #	Review Date(s)
None		

Applicant/Sponsor

Name: Advanced Accelerator Applications USA, Inc.

Address: 350 Fifth Avenue, Suite 6902, New York, NY USA 10018

Representative:

Telephone: 212-325-2391

Fax: 212-335-2381

Name of Reviewer: Helen Ngai, Ph.D.

Conclusion: The submission is **not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** Original and information requests
 2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile drug product and responses to Agency's information requests
 3. **MANUFACTURING SITE:** Gipharma S.r.l., Via Crescentino, 13040 Saluggia (Vc), Italy.
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile lyophilized powder for injection, 40 µg/ 10 mL vial. Sterile reaction buffer packaged separately as ~ 1 mL fill/ 10 mL vial. IV. Single dose.
 5. **METHOD(S) OF STERILIZATION:**  (b) (4)
 6. **PHARMACOLOGICAL CATEGORY:** Diagnostic for  (b) (4) neuroendocrine tumors  (b) (4) NETs).

B. **SUPPORTING/RELATED DOCUMENTS:**

Type II DMF  (b) (4) from Eckert and Ziegler for the 68GE/68GA- generator as manufactured in Berlin, Germany. LOA date 20/April/2015. The relevant information was reviewed in  (b) (4) mic1.doc dated 1/Dec/2015 by H. Ngai. The DMF is not adequate.

 (b) (4)

- C. **REMARKS:** eCTD/ Global submit review. Comparability protocols are N/A. The NDA was granted expedited/ priority status. Some figures were reproduced directly from the submission. The filing date is 8/25/2015; 74 day letter comments was due 9/13/2015. The microbiology information request was not sent until 10/13/2015, responses received 10/20/2015 and 11/19/2015. PDUFA goal date is 3/1/2016. Previous NDA microbiology reviews with Gipharma could not be located.

Filename: 208547.doc

Template version: OGD modified_AP_2014v6.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –

The kit consists of a sterile lyophilized powder manufactured (b) (4). The reaction buffer is (b) (4). The accessory cassette is sterilized by (b) (4).

B. Brief Description of Microbiology Deficiencies – See the comments and deficiencies section.

C. Contains Potential Precedent Decision(s) - Yes No

III. Product Quality Microbiology Risk Assessment

A. Initial Product Quality Microbiology Risk Assessment

CQA	Risk Factor	Prob. of Occ. (O)	Modifier for O ^(3, 4, 5)	Severity of Effect (S)	Detect. (D)	Risk Priority Number ⁶ (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
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Ster.	Aseptic Open ² Process	10		5	5	250	Simulations and interventions conducted during media fills, Environmental monitoring
Endo		4		4	4	216	

1 = A Closed Aseptic Process is one that has no exposed manipulations other than filling and stoppering after the components are sterilized. (e.g., RABS, isolator, closed drying and filling process for a powder)

2 = An Open Aseptic Process is one that has one or more steps with potential to contaminate the drug product after the component sterilizing. (e.g., sterile drug substance/excipient, interaction of operators with sterile product path, traditional Class 100 filling area).

3 = Anti-Microbial Formulation (e.g., meets USP <51>), modifies O (-1) [less emphasis on in process

hold
times]

4 = Post-Constitution/-Dilution Hold Times in Labeling, modifies O (+1) [emphasize Labeling instructions for administration, dosing, storage conditions, and specified diluents. Microbial challenge studies supporting label recon/dilution/storage instructions if >4 hr RT or >24 hr refrig.]

5 = Components derived from animal sources, modifies O (+1) [emphasize Component bioburden, TSE/BSE-free documentation (TS and AP), viral inactivation studies (AP), bioburden reduction processes.]

6 = RPN = O(after modification when applicable)×S×D

RPN <50 = **Low Risk**; RPN 50-120 = **Moderate Risk**; RPN >120 = **High Risk**

B. Final Risk Assessment - The safety risk associated with the microbiology deficiencies is considered low.

IV. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist/ Helen Ngai, Ph.D.

Microbiology Secondary Reviewer/Jesse Wells, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The subject drug product is a sterile 2-vial kit which consists of: a sterile lyophilized powder for reconstitution and a sterile reaction buffer. The lyophilized powder is (b) (4) while the reaction buffer is (b) (4). The reaction buffer (b) (4). An information request was sent on 10/13/2015; amendments received 10/20/2015 and 11/19/2015. The 11/19/2015 submission contains translated documents.

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**2. REVIEW OF COMMON TECHNICAL DOCUMENT-
QUALITY (CTD-Q)
MODULE 1**

A. PACKAGE INSERT

Pre-use storage temperature: room temperature below 25°C (do not freeze); Route of administration: IV as bolus dose; Container: Mono-dose

Reconstituted: (b) (4) HCl is injected to a generator to isolate ^{68}Ga in HCl. The solution is added to the accessory cartridge. After the cartridge, the solution is filtered again, collected in vial 1 with lyophilized powder, then the reaction buffer from vial 2 is added.

Proposed expiry for the radiolabeled finished drug product after reconstitution: 4 hours

Microbiological studies in support of the reconstituted final solution will not be requested as the radiolabeled product expiry is 4 hours.

Acceptable

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3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

NDA: 208547 APPLICANT: Advanced Accelerator Applications USA, Inc.

DRUG PRODUCT: [REDACTED] (b) (4)

Microbiology Deficiencies:

1. DMF [REDACTED] (b) (4) is not adequate. The DMF holder has been notified.
2. Provide the container closure integrity testing validation data from the studies previously stated to be subcontracted to [REDACTED] (b) (4)
3. In regard to environmental monitoring (EM), procedures are performed according to CQM023, CQM018, CQM030 and CQM112. Provide a description of the sample sites (diagrams or tables would be helpful), alert and action levels and frequency of testing. Describe actions taken when EM alert or action levels are exceeded.
4. In regard to the [REDACTED] (b) (4) validation studies for the [REDACTED] (b) (4), provide at least two recent (within the past 1-2 years) [REDACTED] (b) (4)
5. Provide the English translation of [REDACTED] (b) (4)
6. The [REDACTED] (b) (4) study provided in report no. rQP-OPQ-143 [REDACTED] (b) (4) is acknowledged. Provide at least two additional recent (within the past 1-2 years) summary reports for [REDACTED] (b) (4) addition, provide the English translation of report QP-IQ-064/QP-OQ-064/QP-PQ-064.
7. In regard to the sterilization validation studies using the [REDACTED] (b) (4) are noted. [REDACTED] (b) (4)

(b) (4) If the three consecutive studies are several years old, please provide results of one recent requalification as well.

8. In regard to the stopper validation studies using the (b) (4), (b) (4)
9. In regard to the Telstar Lyomega 80 lyophilizer sterilization in place validation study, provide two additional recent sterilization in place validation studies to demonstrate reproducibility of the sterilization cycle. Please include the following: dates of performance, validation and production cycle parameters, validation and production acceptance criteria, the number and placement of heat distribution TCs and biological indicators (a diagram would be helpful), (b) (4)
10. In regard to the sterilization of the (b) (4) (accessory cartridge) by (b) (4) report, (b) (4) report no. 4259-14, is acknowledged. Please provide a comparison of the device used in the bioburden determination study. (b) (4)
11. In regard to the media fill simulations performed on (b) (4), it is noted that detailed descriptions of procedures and specifications for media fills and results from executed media fills are available at Gipharma S.r.l and referenced to, (b) (4)
- The information requested was not provided in the report referenced. For the media fills described in the submission, provide: the dates of the media fills, vial size used, number of units filled, number of units incubated, volume filled, fill speed, duration of filling, results of growth promotion testing, environmental monitoring summaries and a summary of planned and unplanned interventions for each media fill. Please indicate which runs simulated the lyophilization process. If the maximum proposed filling duration for commercial production was not simulated in these media fills, then please provide results of an additional media fill that included simulation of the maximum proposed filling duration.

-
12. Revise the endotoxins limit based on the maximum dosage of the drug product that can be delivered within one hour based on the package insert. For medical imaging, the reviewer calculates that the endotoxin dose exceeds the USP <85> recommended limit of NMT 175 EU/ V. The reviewer calculates the maximum potential endotoxin exposure for the drug product based on the combined endotoxins specifications for the lyophilized powder, reaction buffer, elution buffer and cartridge is (b) (4) EU. Provide revised MVD calculations, Finished Product Release Specifications, and stability protocol specifications documents reflecting the change. Indicate the drug product dilution that will be used during routine endotoxins testing.
13. The sterility test validation results for the accessory cartridge referenced to report, (b) (4), ' report no. 4259-14, pg. 5/8,' is noted. Provide sterility test validation data demonstrating that the sterility test method used for the cartridge is capable of detecting a low number (10-100 CFU) of surviving microorganisms.

Helen
Ngai -S

Digitally signed by Helen Ngai
-S
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Government, ou=HHS,
ou=FDA, ou=People,
cn=Helen Ngai -S,
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Jesse
Wells -S

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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.

/s/

HELEN NGAI
12/04/2015

JESSE WELLS
12/04/2015