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RESEARCH**

APPLICATION NUMBER:

208054Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

February 09, 2016

NDA: 208054

Drug Product Name

Proprietary: Axumin

Non-proprietary: Fluciclovine F 18

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
09/28/2015	09/28/2015	N/A	10/21/2015
01/11/2016	01/11/2016	N/A	01/13/2016
02/02/2016	02/02/2016	N/A	02/05/2016

Submission History (for 2nd Reviews or higher)

None

Applicant/Sponsor

Name: Blue Earth Diagnostics Ltd

Address: 215 Euston Road, London NW1 2BE, UK

Representative: Jonathan Allis, MD

Telephone: 44-0-1865-784-486

Fax: 44-0-1865-784-189

U.S. Agent

Name: Michelle Wilson, Ph.D.

Address: 118 Palm Springs Dr., Fairfield, OH 45014

Telephone: 513-578-5671

Fax: 866-369-5903

Name of Reviewer: Eric K. Adeeku, 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:** Original NDA
2. **SUBMISSION PROVIDES FOR:** Initial marketing of sterile PET drug product
3. **MANUFACTURING SITES:**
The following manufacturing facilities were identified. After approval of the NDA, other PETNET manufacturing establishments will be registered and will be brought into the NDA by supplementing the approved application under a comparability protocol.

PETNET Solutions, Inc.	PETNET Solutions, Inc.
	

The University of Utah DBA Cyclotron Radiochemistry Lab
Huntsman Cancer Institute

Salt Lake City, UT 84112

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile injection, IV, 335 – 8200 MBq/mL (9 – 221 mCi/mL), multi-dose vials
5. **METHOD(S) OF STERILIZATION:** 
6. **PHARMACOLOGICAL CATEGORY:** A radioactive diagnostic agent for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence.

B. **SUPPORTING/RELATED DOCUMENTS:**
ANDA 079086 – PETNET Solutions, Inc. – Approved for 


C. **REMARKS:** This submission is in eCTD format, and it is a 505 (b) (1) application.
The goal date is 05/28/2016.

Response to the Agency’s 12/23/2015 and 02/01/2016 information requests were provided on 01/11/2016 and 02/02/2016 respectively.

Filename: 208054.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 drug product is manufactured using (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	Severity of Effect (S)	Detect. (D)	Risk Priority Number ² (RPN)	Additional Review Emphasis based on Risk (in addition to normal review process)
Ster.	Aseptic Open Process ¹	10		5	5	250	Simulations and interventions conducted during media fills, Environmental monitoring
Endo						(b) (4)	

¹ = (b) (4)

² = RPN = O(after modification when applicable)×S×D = 314

RPN >120 = **High Risk**

B. Final Risk Assessment - None; sufficient sterility assurance information is provided.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist: Eric K. Adeeku, Ph.D.

Microbiology Secondary Reviewer: Jesse Wells, Ph.D.

Microbiology Division Director (Acting): Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

The Agency’s 12/23/2015 and 02/01/2016 information requests are addressed in the body of the review as comments (in italics) and these were responded to in the applicant’s 01/11/2016 and 02/02/2016 submissions respectively.

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

Drug product composition –
(section 3.2.P.1.1).

Component	Quantity per mL	Quantity per 5 mL
Fluciclovine (¹⁸ F)	Up to 8200 MBq (221 mCi)	Up to 41 GBq (1.105 Ci) total
Tri-sodium citrate, Ph. Eur, USP/NF	(b)(4)20 (b)(4)mg	(b)(4)100 (b)(4)mg
Hydrochloric acid	(b)(4)	
Sodium hydroxide		
Water for injection		
(b)(4)	q.s. to 1 mL	q.s. to 5 mL

Description of container closure system –

The drug product is packaged in a 30 mL/ (b)(4) multiple-dose Type I glass vial with 20 mm (b)(4) stopper and aluminum crimp seal (b)(4) type I glass vial.

Vial and stoppers are (b)(4)

(b)(4)

Manufacturer	Catalog #	Supplier/Cat. #	Description
(b)(4)			

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container-Closure and Package integrity -

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

A. PACKAGE INSERT

(section 1.14.1.2).

The drug product is supplied in 30 mL multidose vials containing 26 mL of a clear, colorless solution at a strength of 335 – 8200 MBq/mL (9 – 221 mCi/mL) Fluciclovine F 18 at calibration time and date.

Store at 20 – 25°C (68 – 77 °F), (b) (4)

Expires 10 h after EOS.

Acceptable

**Eric K.
Adeeku -A**

Digitally signed by Eric K. Adeeku -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Eric K. Adeeku -
A,
0.9.2342.19200300.100.1.1=1300417839
Date: 2016.02.23 10:44:54 -05'00'

Jesse Wells -S

Digitally signed by Jesse Wells -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Jesse Wells -S,
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Date: 2016.02.23 12:48:09 -05'00'

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 208054 **Applicant:** Blue Earth Diagnostics Ltd **Letter Date:** September 28, 2015
Drug Name: Fluciclovine F 18 **NDA Type:** 505 (b) (1) **Stamp Date:** September 28, 2015
Dosage Form: Sterile Injection **Reviewer:** Eric K. Adeeku

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	√		eCTD
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	√		
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	√		
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		√	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		√	Product has expiry of 10 h post synthesis
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	√		NMT (b) (4) endotoxins and must pass sterility testing
7	Has the applicant submitted the results of analytical method verification studies?	√		Endotoxins and sterility testing

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FILING REVIEW

	Content Parameter	Yes	No	Comments
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	√		
9	If sterile, are extended post-constitution and/or post-dilution hold times in the draft labeling supported by microbiological data?		√	
10	Is this NDA fileable? If not, then describe why.	√		

Additional Comments:

This NDA is fileable. This is a sterile PET product with an expiry date of 10 h after synthesis. No antimicrobial effectiveness test is required.

For radiopharmaceutical products that are not administered intrathecally, the endotoxins specification is NMT 175 EU/V; where V is the maximum recommended dose in mL. Therefore, since the proposed drug product specification is NMT (b)(4) if the maximum dose of NMT 5 mL is administered to a patient, the endotoxin dose at the proposed endotoxins specification and maximum dose will be within the USP limit of NMT 175 EU/dose. Testing method and validation data was provided.

Sterility testing validation is also provided.

Eric Adeeku, Ph.D.

Microbiologist

Jesse Wells, Ph.D.

Microbiology Secondary Reviewer