CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208054Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

Date: May 19, 2016

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
OPQ/ONDP/DNDP-II/Branch VI

Ravindra K. Kasliwal -S

Digitally signed by Ravindra K. Kasliwal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.05.19 11:26:44 -04'00'

Through: Danae D. Christodoulou, Ph.D.
Branch Chief, Branch VI, DNDP-II, ONDP/OPQ

Subject: Amendment to NDA 208054 CMC review.

This memorandum is to amend the CMC review #1 (date 29-Feb-2016) of NDA 208054 for Axumin, (fluciclovine F18) Injection for the following:

1. To clarify that the CMC commitment (dated 11-Jan-2011) that the applicant has made (to investigate the feasibility of reducing the amount of (b) (4) impurity in the drug product. Preliminary work will start soon and the company will aim to report the results of the development work to the Agency, and discuss and agree future steps, within 12 months of NDA approval) is not to be considered as a "PMC" as defined under 506B of the Act. This is because the currently approved limits for (b) (4) impurity have been assessed to be acceptable from a safety and efficacy perspective. However, since this impurity does not add any value to the drug product quality and is present in substantially large amounts relative to the mass of the radioactive drug substance, we would like the sponsor to either further reduce the amount of this impurity or to eliminate this impurity from the drug product. Based on relative risk to the patient we do not believe this should be categorized as a "PMC". The CMC team would track the commitment upon receipt of the Applicant's "Annual Report" submission.

2. To record that the following final labeling and labels are acceptable from a CMC perspective:

- Label for product made at Huntsman Cancer Institute:

(b) (4)

- Label for product made at PETNET:

(b) (4)

- CMC sections in Package Insert:

11 DESCRIPTION

11.1 Chemical Characteristics

Axumin contains the fluorine 18 (F 18) labeled synthetic amino acid analog fluciclovine. Fluciclovine F 18 is a radioactive diagnostic agent used with PET imaging. Chemically, fluciclovine F 18 is (1r, 3r)-1-amino-3[^{18}F]fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is:

Axumin is a sterile, non-pyrogenic, clear, colorless, hyperosmolal (approximately 500 - 540 mOsm/kg) injection for intravenous use. Each milliliter contains up to 2 micrograms of fluciclovine, 335 to 8200 MBq (9 to 221 mCi) fluciclovine F 18 at calibration time and date, and 20 mg trisodium citrate in water for injection. The solution also contains hydrochloric acid, sodium hydroxide and has a pH between 4 and 6.

11.2 Physical Characteristics

Fluorine 18 (F 18) is a cyclotron produced radionuclide that decays by positron emission (ß+ decay, 96.7%) and orbital electron capture (3.3%) to stable oxygen 18 with a physical half-life of 109.7 minutes. The positron can undergo annihilation with an electron to produce two gamma rays; the energy of each gamma ray is 511 keV (Table 3).

Table 2: Principal Radiation Produced from Decay of Fluorine 18 Radiation

	Energy (keV)	Abundance (%)
Positron	249.8	96.7
Gamma	511.0	193.5

11.3 External Radiation

The point source air-kerma coefficient for F 18 is 3.75 x 10^{-17} Gy m^2/(Bq s). The first half-value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thicknesses of lead shielding is shown in Table 4. The use of 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

Table 3: Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Axumin is supplied as a clear, colorless injection in a 30 mL multiple-dose glass vial containing approximately 26 mL solution of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date.

30 mL sterile multiple-dose vial: NDC 69932-001-030

16.2 Storage and Handling

Store Axumin at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Axumin does not contain a preservative. Store Axumin within the original container in radiation shielding.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

MEMORANDUM

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

Date: March 31, 2016

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
OPQ/ONDP/DNDP-II/Branch VI

Ravindra K. Kasliwal -S
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DN: c=US, o=U S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.03.31 13:41:29 -04'00'

Through: Danae D. Christodoulou, Ph.D.
Branch Chief, Branch VI, DNDP-II, ONDP/OPQ

Danae D. Christodoulou -S
Digitally signed by Danae D Christodoulou S
DN: c US o U S Government ou HHS ou FDA ou People 0.9 2342 19200300 100 1 1 1300132624 cn Danae D Christodoulou S
Date: 2016 03 31 15:05 03 04'00'

Subject: Amendment to NDA 208054 CMC review.

This memorandum is to amend the CMC review #1 (date 29-Feb-2016) of NDA 208054 for Axumin [(fluciclovine F18) Injection for the following:

1. The final CMC recommendation in the review was "Approval (pending acceptable status for the manufacturing facilities)". At the time of the review, a final recommendation for the facilities was not available regarding the cGMP status of the facilities listed in the NDA from the FDA district (s) through the Office of Process and Facilities. A final recommendation of that "the facilities are adequate for the operations proposed in the submission" (NDA) has now been received (see attached facility review 30-Mar-2016). On that basis, the **final recommendation is now changed to "Approval"** under section 505(d) of the Act for chemistry, manufacturing and controls.

2. **To revise the date that the firm committed to the CMC agreement to reduce the process impurity (** (b) (4) A typographical error was made regarding the date in the "Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable" section of the executive summary. In CMC review # 1, the amendment date was noted as 11-Jan-2011, while it should have been 11-Jan-2016, as submitted in the application. The review is amended to indicate that the date was 11-Jan-2016 for the amendment with the fulfilment date of 12 months from the date of approval of the NDA.

3. The technical information regarding the drug product container closure system from (b) (4) was not provided and the applicant was asked to provide the technical and safety information regarding the container closure from (b) (4) (see page # DP-79 in CMC review # 1). In the amendment submitted on 26-Feb-2016, the company (b) (4) will send the information directly to FDA (Thao Vu, RBPM) on behalf of BED (NDA 208054) as they consider this information to be confidential. In an e-mail dated 10-Mar-2016, (b) (4) submitted the necessary information, which shows that the (b) (4) container closure is acceptable for use.

The following information is not to be released under FOI or to the Applicant (Blue Earth Diagnostics):

The (b) (4) container closure consists of following components:

(b) (4)

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Recommendation:
NDA: Approval (pending acceptable status for the manufacturing facilities)

NDA 208054
Review # 1

Drug Name/Dosage Form	AUXIMIN (Fluciclovine F 18 Injection)
Strength	335-820 MBq/ml or 9-221mCi/ml at calibration date and time
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Blue Earth Diagnostic Ltd. 215 Euston Road London NW1 2BE, UK
US agent, if applicable	Michelle Wilson, Ph.D., Expert Regulatory Strategist Virtual Regulatory Solutions U.S. Agent for Blue Earth Diagnostics Mobile: 513 578 5671 Email: vrs_secure@vrsmail.com

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	28-Sept-2015	All
Amendment	01-Oct-2015	All
Amendment	21-Oct-2015	EA
Amendment	25-Nov-2015	DP, ATL
Amendment	04-Dec-2015	DP
Amendment	11-Dec-2015	DS, DP, M, Facility
Amendment	15-Jan-2016	All
Amendment	19-Jan-2016	DS, M
Amendment	04-Feb-2016	M

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance (DS)	Benjamin D. Stevens, Ph.D., M.P.H.	CDER/OPQ/ONDP/DNDAPI/NDBII
Drug Product (DP)	Ravindra K. Kasliwal, Ph.D.	CDER/OPQ/ONDP/DNDPII/NDPBVI
Process (MP)	(Ravindra K. Kasliwal, Ph.D. as part of the drug product)	
Microbiology (M)	Eric K. Adeeku, Ph.D.	CDER/OPQ/OPF/DMA/MABI
Facility	Tony A. Wilson	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Thao M. Vu, R.Ph.	CDER/OPQ/OPRO/DRBPMI/RBPMBI
Application Technical Lead (ATL)	Ravindra K. Kasliwal, Ph.D.	CDER/OPQ/ONDP/DNDPII/NDPBVI
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	OGROP/ORA/OO/OMPTO/DMPTPO/ MDTP
Environmental Assessment (EA)	James P. Laurenson, Ph.D.	CDER/OPQ/ONDP

Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type V		(b) (4)	NA	NA	There was sufficient sterility assurance information in the NDA – See micro review.
	Type V			Not Reviewed	N/A	There is sufficient information for (b) (4) in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107707	The IND to develop Fluciclovine F18 Injection was submitted by GE Healthcare on 01-Apr-2010. The IND was transferred to BED on 21-Apr-2014.

2. CONSULTS:

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH	NA			
Clinical	NA			
Other	NA			

Executive Summary

I. Recommendations

The application may be approved from chemistry, manufacturing and controls (CMC) perspective, once the final acceptable recommendation is received regarding the manufacturing facilities.

A. Recommendation and Conclusion on Approvability

The various quality aspects, i.e., the drug substance, the drug product, the manufacturing process, the microbiological aspects and the environmental assessment have been reviewed by the review team and are adequate to support approval of the application. The review of the manufacturing facilities is not complete at the time of this review and the application may only be approved once the final acceptable recommendation is received regarding the manufacturing facility. The drug product, Axumin, is granted a 10 hour shelf-life (from the end of synthesis or manufacture) under controlled room temperature (USP) storage conditions.

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

The applicant has made a commitment (11-Jan-2011 amendment) to investigate the feasibility of reducing the amount of (b) (4) impurity in the drug product. Preliminary work will start soon and the company will aim to report the results of the development work to the Agency, and discuss and agree future steps, within 12 months of NDA approval.

II. Summary of Quality Assessments

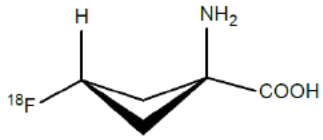
The proposed proprietary name for the product is Axumin. Fluciclovine (^{18}F) is the International Non-proprietary Name (INN) for the active substance *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid. Fluciclovine F 18 is the proposed United States Approved Name (USAN).

The drug substance, fluciclovine (^{18}F), is produced as an aqueous solution (b) (4) The quality of radioactive fluciclovine (F) drug substance is controlled during the manufacture and testing of the drug product. Due to the short half-life of the 18F-fluorine radioisotope, each batch is prepared on the day of clinical use.

A. Drug Substance fluciclovine (^{18}F) Quality Summary

1. Chemical Name or IUPAC Name/Structure:
   - Fluciclovine (^{18}F) drug substance:

- (1*r*,3*r*)-1-Amino-3[^{18}F]fluorocyclobutane-1-carboxylic acid.
- Other Name: *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid
- CAS #: CAS-222727-39-1



Molecular Formula: $C_5H_8{}^{18}FNO_2$
Molecular Weight: 132.1 (b) (4)

(b) (4)

2. Properties/CQAs Relevant to Drug Product Quality

Fluciclovine is not chiral but does exist in two geometrical forms. (b) (4)

(b) (4)

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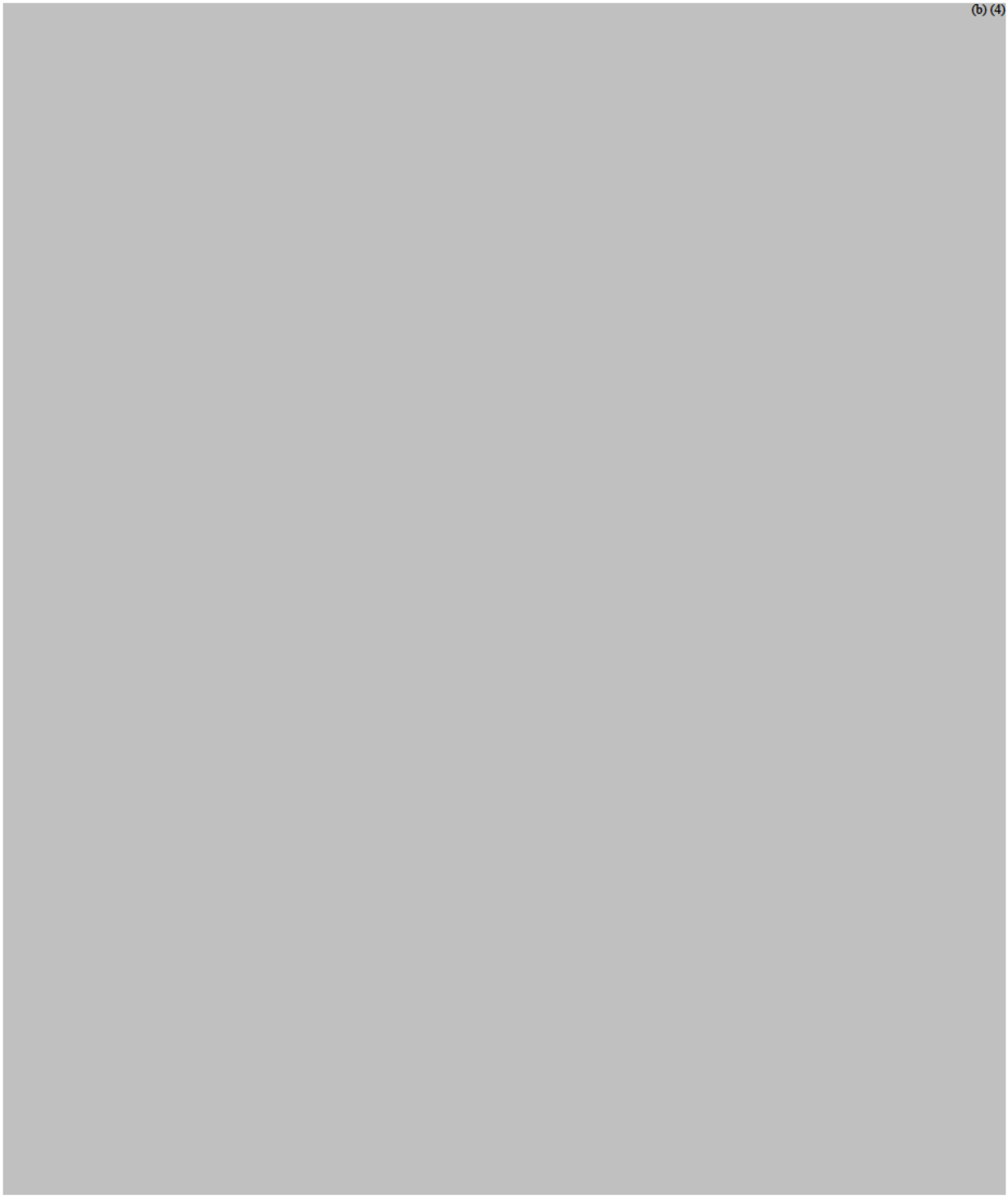
(b) (4)



B. Drug Product Axumin (Fluciclovine F 18 Injection) Quality Summary

1. Strength

Axumin is provided as a solution for injection in a multidose vial with strength of 335 to 8200 MBq/mL (9 to 221 mCi/mL) at calibration time and date, which is end of synthesis (EOS) / manufacture for a multidose vial.

2. Description/Commercial product

Fluciclovine F18 injection is presented in a multi-dose vial of capacity 30 mL containing approximately 26 mL of product. The maximum recommended injection volume of undiluted product is 5 mL. The content of fluciclovine is not more than 2 µg/mL. The pH of the solution is between 4.0 and 6.0.

Each milliliter of the drug product solution contains 20 mg. of trisodium citrate, hydrochloric acid, sodium hydroxide in water for injection. There are no co-packaged components in the drug product.

The drug product may be diluted with 0.9% sodium chloride solution for injection.
A sample of Fluciclovine F 18 Injection (b) (4) The pH was still well within the drug product specification of 4 to 6.

3. Summary of Product Design

Sodium citrate (b) (4) drug substance, fluciclovine (^{8}F). The volume and strength of hydrochloric acid was selected to ensure efficient conversion of the radiolabelled (b) (4) The amount of sodium hydroxide (b) (4)

4. List of Excipients:

The drug product contains (b) (4) (meeting Ph. Eur. And / or USP grade), hydrochloric acid (b) (4) Sodium hydroxide (b) (4), and water for injection (USP / Ph. Eur. Grade).

5. Process

The drug substance, fluciclovine (^{18}F), is produced as an aqueous solution (b) (4)

6. Container Closure

Two alternative container closure systems (from (b) (4)) have been proposed for use for Fluciclovine F18 Injection. Both are supplied as (b) (4)

vials comprising a 30 mL USP Type 1 glass vial, [redacted] closure and aluminum overseal.

7. Expiration Date & Storage Conditions

An expiration dating period of 10 hours is proposed and justified for Fluciclovine F18 injection, when manufactured at a radioactive concentration of up to 8200 MBq/ml. The drug product should be stored at USP controlled room temperature 20°- 25°C (68°- 77°F) in the described container closure system.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Axumin
Non Proprietary Name of the Drug Product	Fluciclovine F 18 Injection
Non Proprietary Name of the Drug Substance	Fluciclovine F18
Proposed Indication(s) including Intended Patient Population	Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging [redacted] men with suspected prostate cancer recurrence. [redacted] based [redacted] on elevated blood prostate specific antigen (PSA) levels following [redacted]
Duration of Treatment	Occasional, as needed.
Maximum Daily Dose	370 MBq (10 mCi) as a [redacted] intravenous injection.
Alternative Methods of Administration	The drug product may be diluted with 0.9% sodium chloride solution for injection.

D. Biopharmaceutics Considerations

1. BCS Classification: Not reported. The
2. Biowaivers/Biostudies: None.

E. Novel Approaches

F. Any Special Product Quality Labeling Recommendations

This is a radioactive drug. Therefore, in addition to the requirements for labeling an injection drug product, a radioactive material symbol is required on the container labels.

G. Life Cycle Knowledge Information (see Attachment a)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Ravindra K. Kasliwal -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.02.29 10:09:07 -05'00'

PRIMARY QUALITY REVIEWS ARE IN FOLLOWING PAGES:

2.3.S DRUG SUBSTANCE

2.3.S.2 Manufacture

Manufacturer(s)

1. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
(b) (4)			Acceptable (NAI)	High risk manufacturing process.	Acceptable

(b) (4)

2.3.P DRUG PRODUCT

2.3.P.3 Manufacture

Manufacturer(s)

2. Are the manufacturers in conformity with current good manufacturing practice to assure that the drug meets the requirements of the FD&C Act as to safety and has the identity and strength, and meets the quality and purity characteristics which it purports?

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
PetNet Solutions, Inc. (b) (4)	(b) (4)	Manufacture (using (b) (4) (b) (4) package, label, perform analytical QC testing and release finished product	Acceptable (VAI)	High; new manufacturing platform.	Acceptable

The University of Utah DBA Cyclotron Radiochemistry Lab, Huntsman Cancer Institute	3004010435	Manufacture (using (b) (4) (b) (4) package, label, perform analytical QC testing and release finished product. (PET)	Acceptable (NAI)	High; new manufacturing platform.	Acceptable
PetNet Solutions, (b) (4) Inc.	(b) (4)	Manufacture (using (b) (4) (b) (4) package, label, perform analytical QC testing and release finished product. (PET)	Acceptable (VAI)	High; new manufacturing platform.	Acceptable

(b) (4)

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proposed in this application.

OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Based on the review of compliance history and risk assessments, no significant risks were identified and the facilities listed are adequate for the operations proposed in this submission.

Tony A. Wilson Consumer Safety Officer, Branch 3, OPF/DIA

March 30, 2016

Tony A. Wilson -S (Affiliate)

Digitally signed by Tony A. Wilson -S (Affiliate)
DN: c=US, o=U.S. Government, ou=HHS, ou=NIH, ou=People, 0.9.2342.19200300.100.1.1=2000666232, cn=Tony A. Wilson -S (Affiliate)
Date: 2016.03.30 15:57:04 -04'00'

Supervisor Comments and Concurrence:

I concur with the review.

Krishnakali Ghosh -S

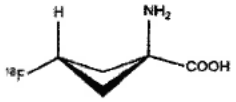
Digitally signed by Krishnakali Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000487336, cn=Krishnakali Ghosh -S
Date: 2016.03.30 15:59:31 -04'00'

Note: additional reviewers can be added, as appropriate

ASSESSMENT OF THE RADIOACTIVE DRUG SUSTANCE FLUCICLOVINE F 18

3.2.S.1. General Information (Fluciclovine (^{18}F))

- **Nomenclature (Fluciclovine (^{18}F))**
- **Company code:** FACBC
- **Chemical name:** (1*r*,3*r*)-1-Amino-3[^{18}F]fluorocyclobutane-1-carboxylic acid.
- **Other Name:** *anti*-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid.



INN: fluciclovine (^{18}F)
Proposed USAN name is Fluciclovine F 18, However USAN dictionary indicates name to be fluciclovine [^{18}F]
The non-radioactive analogue of the drug substance is denoted fluciclovine.
CAS registry number: 222727-39-1 (fluciclovine (^{18}F), radioactive)
222727-43-7 (fluciclovine, non-radioactive)

(b) (4)

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ASSESSMENT OF THE DRUG PRODUCT (NDA 208054)

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition of the Drug Product

Fluciclovine F 18 Injection is formulated as a sterile solution for injection for multi-dose use containing up to 8200 MBq (221 mCi) ^{18}F-fluciclovine per milliliter at calibration date and time. Calibration date and time is equal to the end of synthesis (EOS) date and time (EOS time is the time that synthesis (b) (4) (b) (4) Fluciclovine F 18 Injection solution is presented in a multi-dose vial of capacity 30 mL containing approximately 26 mL of product. The maximum injection volume of undiluted product is 5 mL.

Table 1: Composition of fluciclovine (^{18}F) solution for injection

Component	Quantity per mL	Quantity per 5 mL	Function	Quality
Fluciclovine (^{18}F)	Up to 8200 MBq (221 mCi) at calibration date and time (b) (4)	Up to 41 GBq (1.105 Ci) total at calibration date and time (b) (4)	Drug Substance	N A
Tri-sodium citrate[2]	FL: 20 mg	FL: 100 mg (b) (4)	(b) (4)	Ph. Eur. USP NF
Hydrochloric acid			(b) (4)	ACS
Sodium hydroxide				N A
Water for injection				Ph. Eur. USP

(b) (4)

The table shows composition of fluciclovine (^{18}F) solution for injection manufactured on the (b) (4) (b) (4) The content of fluciclovine is not more than 2 µg/mL. The pH of the solution is between 4.0 and 6.0. See below comments regarding the pH range.

Reviewer's Assessment:
The table shows that the composition of fluciclovine (^{18}F) injection solution manufactured (b) (4) (b) (4) hydrochloric acid and sodium hydroxide. The differences are, however, negligible and would not have an impact on product safety or on the efficacy of the product. In the labeling the product composition may be written as containing 20 mg/ mL of trisodium citrate buffer. The amount of acid and base amounts are generally not stated and they are just mentioned by name. The product's pH is a more relevant attribute, which is controlled.

2.3.P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature: Drug product information, including control of components described under drug substance, except for the drug product container closure system supplied by (b) (4) is adequate. (b) (4)

Ravindra K. Kasliwal -S

Digitally signed by Ravindra K. Kasliwal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.02.25 14:44:57 -05'00'

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

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.02.25 16:46:16 -05'00'

ASSESSMENT OF THE MANUFACTURING PROCESS

2.3.P DRUG PRODUCT

Currently the applicant has proposed three establishments who will manufacture Fluciclovine F18 injection. Each site will manufacture, package, label, perform analytical QC testing and release finished product.

(b) (4)

PETNET Solutions, Inc.

PETNET Solutions, Inc.

(b) (4)

The University of Utah DBA Cyclotron Radiochemistry Lab
Huntsman Cancer Institute
(b) (4)
Salt Lake City, UT 84112
Establishment number: 3004010435

2.3.P.2.3 Manufacturing Process Development

(b) (4)

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(b) (4)

[redacted]

OVERALL ASSESSMENT AND SIGNATURES: PROCESS

Reviewer's Assessment and Signature: The drug product manufacturing process as well as the control of in-process intermediates and in-process parameters is adequately described.

Ravindra K. Kasliwal -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.02.25 14:46:05 -05'00'

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

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.02.25 16:47:31 -05'00'

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

Fluciclovine F 18 is a new chemical entity. Although its usage will increase over time, the expected introduction concentration (EIC) will remain well below 1 part per billion (ppb). The applicant, therefore, has claimed a categorical exclusion under 21 CFR 25.31(b). Additionally, to the best of the applicant's (BED) knowledge, no extraordinary circumstances exist, in accordance with 21 CFR 25.15(a) and (d).

Table 1: EIC values

Symbol	Definition	Fluciclovine F 18
A	kg/year produced for direct use (as active moiety)	(b) (4)
B	(b) (4) liters per day	
C	year/365 days	
D	(b) (4) kg/kg	
EIC	*Expected introduction concentration (ppb)*	

The values have been calculated for the drug substance fluciclovine F 18 (b) (4) (b) (4)

Calculation for fluciclovine F 18:
Assuming that all sites can make the maximum validated batch size

(b) (4)

(b) (4)

Both of these calculations have been based on a worse case possible production and are expected to be far in excess of the actual product potentially introduced to the environment. In both cases the EIC values are far below 1ppb.

Reviewer's Assessment:

This is a PET drug product and the mass amounts used are typically in the nanograms and microgram quantities. The applicant's amounts are calculated based on manufacture (b) (4) on the basis of analytical technologies used for mass determination. Based on these amounts the EIC (expected introduction concentration) has been calculated using the formula described in FDA environmental assessment guidance. The calculations have been based on a worse case possible production and are expected to be far in excess of the actual product potentially introduced to the environment. In both cases the EIC values are far below 1ppb. The applicant's claim for categorical exclusion acceptable.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:

Since the EIC (expected introduction concentration) values are far below 1ppb, the applicant's Claim for a categorical exclusion under 21 CFR 25.31(b) is justified and acceptable. Applicant has also stated that in accordance with 21 CFR 25.15(a) and (d), no extraordinary circumstances exist.

Ravindra K. Kasliwal -S

Digitally signed by Ravindra K. Kasliwal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.02.25 14:46:37 -05'00'

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

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.02.25 16:48:55 -05'00'

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

Labeling & Package Insert

1. Package Insert

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

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AXUMIN. See full prescribing information for AXUMIN.

AXUMIN (Fluciclovine F 18) (b) (4)
Initial U.S. Approval: 20xx

----------INDICATIONS AND USAGE----------
Axumin is a radioactive diagnostic agent for positron emission tomography (PET) imaging (b) men with suspected prostate cancer recurrence (b) (4) (b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4) (1)

----------DOSAGE AND ADMINISTRATION----------
Use appropriate radiation safety handling measures (2.1).
- Aseptically withdraw Axumin from its container and administer 370 MBq (10 mCi) as a (b) (4) intravenous injection. (2.2).
- Initiate imaging 3-5 minutes after administration. Scanning should start from mid-thigh and proceed to base of skull, with a total scan time of approximately 20-30 minutes (2.4).
- The effective radiation (b) (4) dose (b) (4) 370 MBq (10 mCi) (b) (4) of Axumin is approximately 8 mSv (0.8 rem) in an adult (2.6).

(b) (4)

----------DOSAGE FORMS AND STRENGTHS----------
(b) (4) in 30 mL (b) (4) dose vials containing a (b) (4) 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date (3).

----------CONTRAINDICATIONS----------
(b) (4)

----------WARNINGS AND PRECAUTIONS----------
- Image interpretation errors can occur with (b) (4) imaging (5.1).
- Radiation risk: Axumin (b) (4) (b) (4) contributes to a patient's long-term cumulative radiation exposure. Ensure safe handling to protect patients and health care workers from unintentional radiation exposure (2.1, 5.3).

----------ADVERSE REACTIONS----------
Most commonly reported adverse reactions (b) (4) injection site pain (b) erythema (b) (4) and dysguesia (6.1)

See 17 for PATIENT COUNSELING INFORMATION (b) (4)

Revised: M/20XX

Assessment:

- The proprietary name "Axumin" is acceptable (Per DMEPA).
- The established name should be consistent with how the radioactive products are described in USP. It should be "Fluciclovine F 18 (b) (4)". It should be placed below the Proprietary name "Axumin".
- (b) (4)
- The route of administration is "intravenous" and it should be indicated in the highlight section along with the established name.
- Following "Dosage form and Strengths" statement is recommended.
  - Axumin is supplied as a colorless injectable solution in a 30 mL multidose vial containing 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at the time and date of calibration (3).

(b) "Full Prescribing Information" Section

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

3 DOSAGE FORMS AND STRENGTHS

(b) (4) supplied in 30 mL (b) (4) dose vials containing (b) (4) 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date.

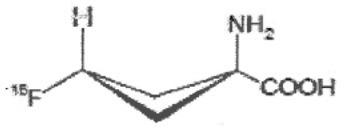
Assessment: The proposed statement does not mention dosage form, which is injection. I recommend that the statement be revised in following manner:

(b) (4) supplied (b) (4) in a 30 mL (b) (4) dose vial containing 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at the time and date of calibration.

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

11 DESCRIPTION

Axumin contains (b) (4) F 18, a synthetic amino acid analog (b) (4) (b) (4) Chemically, fluciclovine F 18 is (b) (4) (b) (4)-1-amino-3-fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is:



Axumin is a sterile, non-pyrogenic, clear, colorless (b) (4) Each milliliter (b) (4) (b) (4) contains up to 2 micrograms of fluciclovine (b) (4) 335 to 8200 MBq (9 to 221 mCi) fluciclovine F 18 at calibration time and date, (b) (4) mg trisodium citrate (b) (4) hydrochloric acid (b) (4) sodium hydroxide (b) (4) pH (b) (4) between (b) (4) and 6.0.

Assessment: The two paragraphs in the description section should be revised as follows:

- Axumin, (b) (4) F 18 Iniection (b) (4) (b) (4) (b) (4) Chemically, fluciclovine [^{18}F] is (b) (4) (1*r*,3*r*)-1-Amino-3[^{18}F]fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is:

- Axumin is a sterile, non-pyrogenic, clear, colorless (b) (4) Each milliliter (b) (4) contains up to 2 micrograms of fluciclovine and 335 to 8200 MBq (9 to 221 mCi) fluciclovine [^{18}F] at calibration time and date, 20 mg trisodium citrate (b) (4) hydrochloric acid (b) (4) (b) (4) sodium hydroxide (b) (4) pH (b) (4) between 4.0 and 6.0.

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Axumin is supplied in 30 mL (b) (4) dose vials containing approximately 26 mL of (b) (4) solution (b) (4) of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine 18 F at calibration time and date.

30 mL sterile (b) (4) dose vial: NDC 69932-001-030

16.2 Storage and Handling
Store Axumin at 20°C to 25°C (68°F to 77°F) (b) (4) (b) (4) does not contain a preservative. Store Axumin within the original container (b) (4) radiation shielding. (b) (4)

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Assessment:
- How supplied section is accurate.
- Following revised statement is recommended.

Store Axumin at controlled room temperature (USP) 20°- 25°C (68°- 77°F). (b) (4) does not contain a preservative. Store Axumin within the original container (b) (4) radiation shielding. Do not use Axumin after the expiry date and time stated on the label.

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

The manufacturer's / distributor's name is not provided in the package insert.

Assessment: The manufacturer's / distributor's name is not listed in the package insert. The company should be asked to include manufacturer/distributor name as per 21 CFR 201.1.

2. Container and Carton Labeling

a. Immediate Container Label / Carton Label
- **For Product manufactured by PETNET:**

(b) (4)

For Product manufactured by Huntsman cancer center.

(b) (4)

[redacted]

Assessment:

- The proprietary name "Axumin" should be place on the label above the established name.
- The established name should be consistent with how the radioactive products are described in USP. It should be "Fluciclovine F 18 Injection". It should be place below the Proprietary name "Axumin".
- The composition statement should be revised as follows:
  "Each milliliter contains 0.33 GBq (9 mCi) to 8.2 GBq (221 mCi) [redacted] fluciclovine [^{18}F], 20 mg [redacted] sodium citrate".
- Revise the storage statement to: Store at controlled room temperature (USP) 20°- 25°C ([redacted]- 77°F).

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature: The labeling needs to be revised. The comments listed in labeling assessment should be sent to the applicant after the division labeling meeting.

Ravindra K. Kasliwal -S

Digitally signed by Ravindra K. Kasliwal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2016.02.25 14:47:21 -05'00'

Secondary Review Comments and Concurrence: I concur with reviewer's recommendations.

Danae D. Christodoulou -S

Digitally signed by Danae D. Christodoulou -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300132624, cn=Danae D. Christodoulou -S
Date: 2016.02.25 16:49:38 -05'00'

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 208054 **Submission Type: NDA**

Established/Proper Name: Fluciclovine F 18

Applicant: Blue Earth Diagnostics Ltd. **Letter Date:9/28/15**

Dosage Form: multi-dose; injection

Chemical Type: 1 **Stamp Date:9/28/15**

Strength: 335-8200 Mbq/ml or 9-221 mCi/ml

A. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
1.	**DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?**	X		None
2.	If the application is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			N/A
3.	Are there any **potential review** issues to be forwarded to the Applicant, not including any filing comments stated above?			Yes. See attached.

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
	Product Type			
1.	New Molecular Entity[1]	☒	☐	
2.	Botanical[1]	☐	☒	
3.	Naturally-derived Product	☐	☒	
4.	Narrow Therapeutic Index Drug	☐	☐	N/A. It is a diagnostic drug product.
5.	PET Drug	☒	☐	
6.	PEPFAR Drug	☐	☒	
7.	Sterile Drug Product	☒	☐	
8.	Transdermal[1]	☐	☒	
9.	Pediatric form/dose[1]	☐	☒	
10.	Locally acting drug[1]	☐	☒	
11.	Lyophilized product[1]	☐	☒	
12.	First generic[1]	☐	☒	
13.	Solid dispersion product[1]	☐	☒	
14.	Oral disintegrating tablet[1]	☐	☒	
15.	Modified release product[1]	☐	☒	
16.	Liposome product[1]	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

B.	NOTEWORTHY ELEMENTS OF THE APPLICATION	Yes	No	Comment
17.	Biosimiliar product[1]	☐	☒	
18.	Combination Product	☐	☒	
19.	Other	☐	☐	

	Regulatory Considerations			
20.	USAN Name Assigned	☐	☒	USAN is Submitted: fluciclovine F18 INN is assigned: fluciclovine (^{18}F)
21.	End of Phase II/Pre-NDA Agreements	☒	☐	Company held a CMC meeting with FDA on 03-Aug-2015 under IND 107707. Meeting minutes are attached.
22.	SPOTS (Special Products On-line Tracking System)	☐	☒	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	☐	☒	
24.	Comparability Protocol(s)[2]	☒	☐	A (b) (4) (b) (4) drug product manufacturing sites is provided in 3.2.R.3. This should be reviewed by drug product, microbiology and facilities reviewers.
25.	Other	☐	☐	
	Quality Considerations			
26.	Drug Substance Overage	☐	☒	N/A. This is an injectable PET drug.
27.	Design Space – Formulation	☐	☒	
28.	Design Space – Process	☐	☒	
29.	Design Space – Analytical Methods	☐	☒	
30.	Design Space – Other	☐	☒	
31.	Real Time Release Testing (RTRT)	☐	☒	
32.	Parametric Release in lieu of Sterility Testing	☒	☐	This is a PET drug (a radioactive drug). (b) (4) testing is not completed until much after the drug has been administered to a human subject. This is allowed under 21 CFR (b) (4)
33.	Alternative Microbiological Test Methods	☐	☒	
34.	Process Analytical Technology[1]	☐	☒	
35.	Non-compendial Analytical Procedures and/or specifications – Drug Product	☒	☐	
36.	Non-compendial Analytical Procedures and/or specifications – Excipients	☒	☐	Manufacture and testing of (b) (4) vial.
37.	Non-compendial Analytical Procedures and/or specifications – Microbial	☐	☒	
38.	Unique analytical methodology[1]	☐	☒	
39.	Excipients of Human or Animal Origin	☐	☒	
40.	Novel Excipients	☐	☒	
41.	Nanomaterials[1]	☐	☒	
42.	Hold Times Exceeding 30 Days	☐	☒	
43.	Genotoxic Impurities or Structural Alerts	☐	☒	This should be looked in greater detail at the time of review.
44.	Continuous Manufacturing	☐	☒	
45.	Other unique manufacturing process[1]	☐	☒	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	☐	☒	N/A. This is an injection drug product.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

47.	New delivery system or dosage form[1]	☐	☒	
48.	Novel BE study designs	☐	☒	
49.	New product design[1]	☐	☒	
50.	Other_____	☐	☐	

[1]Contact Office of Testing and Research for review team considerations
[2]Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	**Yes**	**No**	**N/A**	**Comment**
	GENERAL/ADMINISTRATIVE				
1.	Has an environmental assessment report or categorical exclusion been provided?	☒	☐	☐	A categorical exclusion under 21 CFR 25.31(b) is claimed.
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Drug Substance ❑ Drug Product ❑ Appendices o Facilities and Equipment o Adventitious Agents Safety Evaluation o Novel Excipients ❑ Regional Information o Executed Batch Records o Method Validation Package o Comparability Protocols	☒	☐	☐	
	FACILITY INFORMATION				
3.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: ❑ Name of facility, ❑ Full address of facility including street, city, state, country ❑ FEI number for facility (if previously registered with FDA) ❑ Full name and title, telephone, fax number and email for on-site contact person. ❑ Is the manufacturing responsibility and function identified for each facility, and ❑ DMF number (if applicable)	☒	☐	☐	The radioactive drug substance is produced [redacted (b) (4)] manufacture of the drug product. Therefore, the [redacted (b) (4)] controlled for quality before manufacture of drug substance / drug product. The following [redacted (b) (4)] There are three drug product manufacturing sites: PETNET Solutions, [redacted (b) (4)] (FEI# [redacted (b) (4)]) PETNET Solutions, [redacted (b) (4)] (FEI# [redacted (b) (4)])

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
					The University of Utah DBA Cyclotron Radiochemistry Lab, Huntsman Cancer Institute, Salt Lake city UT (FEI# 3004010435) The facility details are provided in 356H.
4.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: ❑ Is a manufacturing schedule provided? ❑ Is the schedule feasible to conduct an inspection within the review cycle?	☒	☐	☐	
DRUG SUBSTANCE INFORMATION					
5.	For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	☒	☐	☐	Type V DMF (b) (4) BB-MF (b) (4).
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ general information ❑ manufacture o Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only o Includes complete description of product lots and their uses during development – BLA only ❑ characterization of drug substance ❑ control of drug substance o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only ❑ reference standards or materials ❑ container closure system	☒	☐	☐	The radioactive drug substance is produced (b) (4) manufacture of the drug product. The drug substance section contains manufacturing and controls information on the (b) (4) The drug substance reviewer should review the information for (b) (4) Since the radioactive drug susntance fluciclovine (^{18}F) is produced (b) (4) manufacture of the drug product, it should be reviewed by the drug product reviewer as part of the drug product manufacturing.

OFFICE OF PHARMACEUTICAL QUALITY

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C. FILING CONSIDERATIONS					
	❑ stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment				
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review? ❑ Description and Composition of the Drug Product ❑ Pharmaceutical Development o Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots o Includes complete description of product lots and their uses during development ❑ Manufacture o If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? ❑ Control of Excipients ❑ Control of Drug Product o Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) o Includes data to demonstrate process consistency (i.e. data on process validation lots) o Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) o Analytical validation package for release test procedures, including dissolution ❑ Reference Standards or Materials ❑ Container Closure System o Include data outlined in container closure guidance document ❑ Stability o Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment	☒	☐	☐	A (b) (4) drug product manufacturing sites (b) (4) is provided in 3.2.R.3. This should be reviewed by drug product, microbiology and facilities reviewers. Also, see attached micro filing checklist.

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	❑ APPENDICES ❑ REGIONAL INFORMATION				
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	☐	☒	☐	
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? *(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)*	☒	☐	☐	
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	☐	☒	☐	
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	☐	☐	☒	
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	☐	☐	☒	
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	☐	☐	☒	
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	☐	☒	☐	
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	☒	☐	☐	
16.	Are the following information available in the Appendices for Biotech Products [3.2.A]? ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation, sterilization and storage o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification	☐	☐	☒	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
	○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients				
17.	Are the following information available for Biotech Products: ❑ Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: ○ LAL instead of rabbit pyrogen ○ Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those samples			☒	

CMC COMMENTS TO BE SENT TO APPLICANT:

1. We note that the limits proposed for the related impurities ((b) (4) content, greatest single unidentified impurity and sum of fluciclovine and related substances) are much higher than the amounts found in the clinical trial batches used in humans. While you justify the limits based on safety, the structurally related impurities may also compete with the drug substance molecule for the binding at the target site and could affect product performance (efficacy) as well. Provide revised specifications where the limits for the above impurities are consistent with the batch amounts (mean with reasonable deviation).

2. The lower limit of (b) (4) for the proposed pH limits of (b) (4) – 6.0 is (b) (4) for intravenous injection. Raise the lower limit to (b) (4) to make the drug product solution to be more physiologically compatible.

3. Clarify if the radiochemical purity analytical method is able to differentiate between (b) (4) (^{18}F)-fluciclovine. Also, provide data that could show that the proposed (b) (4) of (^{18}F)-fluciclovine.

Ravindra K. Kasliwal -S

Digitally signed by Ravindra K. Kasliwal -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300089677, cn=Ravindra K. Kasliwal -S
Date: 2015.11.17 10:01:26 -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

OFFICE OF PHARMACEUTICAL QUALITY

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