CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216023Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 216023

Integrated Quality Assessment Template

Table of Contents

NDA Executive Summary

1. Application/Product Information

NDA Number.	216023 (resubmission)		
Applicant Name	Blue Earth Diagnostics, Ltd Oxford Science Park, Oxford, Oxforshire, UK OX4 4GA		
Drug Product Name	POSLUMA (Flotufolastat F 18 gallium) injection		
Dosage Form.	Injectable		
Proposed Strength(s)	296 – 5846 MBq/mL (8 – 158 mCi/mL) @ TOC		
Route of Administration	Intravenous		
Maximum Daily Dose	296 MBq (8 mCi)		
Rx/OTC Dispensed	Rx		
Proposed Indication	For positron emission tomography (PET) (b) (4) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer (b) (4)		
Drug Product Description	Clear, colorless solution in a 50 mL multiple-dose vial containing 296 MBq/mL to 5846 MBq/mL (8 mCi/mL to 158 mCi/mL) (b) (4)		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	25 °C		
Review Team	**Discipline**	**Primary**	**Secondary**
	*Drug Substance** (b) (4)	Joseph Leginus	Zhengfu Wang

	Drug Product/ Labeling	John Amartey	Danae Christodoulou
	Manufacturing	Krishna Ghosh	Vidya Pai
	Biopharmaceutics	N/A	N/A
	Microbiology	Yarery Smith	Marley-Stevens Riley
	Other (specify):	N/A	
	RBPM	Anika Lamansingh	
	ATL	Eldon E. Leutzinger	
Consults	N/A		

* See 4a (Summary of Assessments - Introduction)

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: 10 hours at controlled room temperature (USP) 20ºC to 25ºC (68ºF to 77ºF). POSLUMA does not contain any preservative and should be stored in the original container and in the radiation shield.

b. Additional Comments for Action: None

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Summarizing over all components (drug substance, drug product, manufacturing and facilities, microbiology, and labeling), all deficiencies identified are resolved and there is nothing left pending. All manufacturing facilities (31 of PETNET within the USA) that will produce Posluma under NDA 216023 (resubmission) have been found acceptable and approved for (b) (4) final PET Drug.

Summary of Assessments (Product Quality):

Introduction:

Production of Flotufolastat F 18 drug product is a (b) (4)

(b) (4)

- **Summary of Assessments** (b) (4)

(b) (4)

Resolved (response of 9/06/2022).

- **Summary of Assessments (Drug Substance, [^{18}F]rhPSMA-7.3C):**

(b) (4)

[redacted]

(b) (4)

All issues for drug substance are **Resolved**.

The applicant has also stated that specifically (b) (4) provided in the NDA

- **Summary of Assessments (Drug Product):**

An important CMC issue within the scope of product quality identifies with the analytical methods. The specific issue is (b) (4) to ensure all manufacturing sites are complying. The remainder of the CMC issues were largely in labeling (see Summary of Assessments under Labeling).

Methods validation is the practice of demonstrating that an analytical procedure is suitable for its intended use. In this instance, the objective is to establish/verify (b) (4)

(b) (4)

Method development and its validation are a synchronous exercise, working together like hand in glove to get the optimal performance in the analytical method. The less robust the method, the more intricate validation must be, with its outcome proportional to these intricacies. The more robust a given method, the more realistically will the validation results predict or establish its expected performance in the real world of routine QC.

Even though a product may continue to meet the established release specifications, there can be a plethora of undefined and subtle variations in product composition between productions (run-to-run) and other influences directly on the analytical methodology (b) (4)

(b) (4)

There is no issue with the quality of the data in the executed batch records and the strength of the expectations drawn from it. That this holds up in future routine use will depend not only on previous history, but also its continuance under the assumption that any perturbations encountered such as those described in the foregoing will remain solely within the scope of statistical fluctuations and any significant deviations can be readily detected, identified and corrected prior to release of production batches.

To boot, the comment for annual validation (b) (4) is a recommendation. As a recommendation it is not (of course) required but is made as advice in the service of future maintenance of product quality (based on sound analytical practice). Within the context of the foregoing assumptions, the applicant's response is being considered **Acceptable**.

Summary of Assessments (Manufacturing):
In short, all manufacturing facilities (31 of PETNET within the USA) that will produce Posluma under NDA 216023 (resubmission) have been found acceptable and approved for (b) (4) final PET Drug.

And the following is a High Level Facility Review Summary prepared by Dr. Krishna Ghosh for NDA 216023 (resubmission), 5/12/2023. The final facilities assessment (5/15/2023) is in Panorama.

Posluma will be produced at 31 of the PETNET facilities within USA. The Corporate PETNET facility in Knoxville will not be manufacturing the drug product but performing several critical GMP quality functions supporting commercial batches manufactured at all the 31 sites submitted in the application.

(b) (4)

(b) (4)

Summary of Assessments (Microbiology):
There were multiple issues identified in the review by microbiology covering the broad areas of **manufacturing process and controls** (b) (4) (b) (4) **process validation** (b) (4) and **control of drug product** (b) (4) All these issues are **Resolved** (review in panorama 11/30/2022, Yarey Smith, Ph.D.). The applicant also updated the comparability protocol (b) (4) No post-approval commitments have been requested or made, and there are no remaining microbiology deficiencies.

Summary of Assessments (Labeling - CMC):
The drug product review identified three issues for labeling, (1) need for a status update on the request that FDA made for a USAN for flotufolastat F18, (2) absence of a decay chart for ^{18}F in section 11 and (3) need for inclusion of a list of excipients and their quantities in section 11. (b) (4)

For the first of these, the USANC selected ***Flotufolastat F 18 gallium*** for the USAN (decision letter to the applicant dated June 10, 2022). Hence, the drug product becomes **POSLUMA (flotufolastat F 18 gallium) injection**. The second and third are also resolved. Together, all the CMC labeling issues are **Resolved**.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

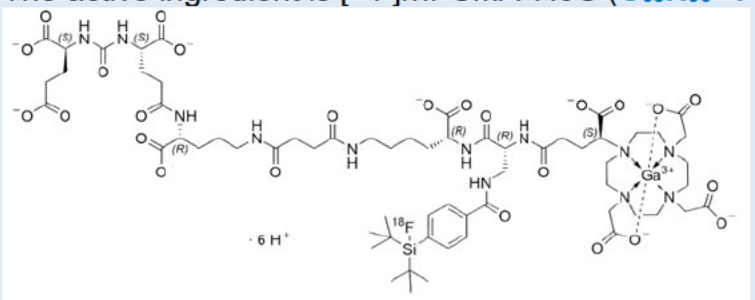
Established Conditions per ICH Q12: Yes
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

► Assessment of Chemical Type and Drug Classification Code (ATL):

The active ingredient is [^{18}F]rhPSMA-7.3C ($C_{63}H_{96}{}^{19}FGaN_{12}O_{25}Si$),



, has never been approved in another NDA submitted under section 505(b) of the FD&C Act, nor has it been marketed as a drug in the United States. Hence, by MAPP 5018.2, the active ingredient (and active moiety) is an NME, and the NDA classification is Type 1.

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NDA 216023 labeling review

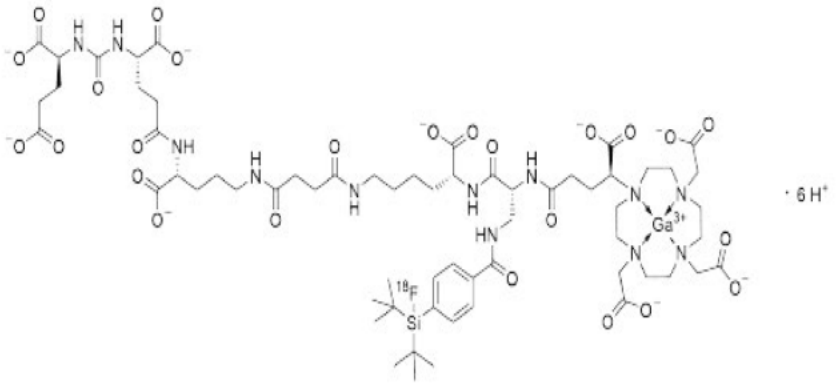
POSLUMA [redacted] injection, for intravenous use

3 Dosage form and strengths

[redacted]

11 Description

[redacted] The molecular weight is 1537.3 g/mol and the structural formula is [redacted]



POSLUMA is a sterile, non-pyrogenic, clear, colorless, isotonic, [redacted] solution [redacted] Each mL contains up to 20 mcg of flotufolastat gallium [redacted] up to 5846 MBq (158 mCi) flotufolastat F 18 gallium at [redacted]

Comment 1 (CMC-1 of 08/10, 2022): In **section 11** of the labeling document, a decay chart for F-18 is missing. Include a decay chart in the section.

Response: ADEQUATE

The applicant added the decay chart to the section (docuBridge seq# 0014 of 08/17/2022).

Comment 2 (CMC-1 of 08/10, 2022)): The excipients should be listed with the corresponding quantities in section 11.

Response: ADEQUATE

The list of excipients has been included (docuBridge seq# 0014 of 08/17/2022).

16 How Supplied/Storage and handling

POSLUMA is supplied as a clear, colorless (b) (4) in a multiple dose glass vial (NDC 69932-002-50) containing approximately (b) (4)

Store POSLUMA at (b) (4) 20ºC to 25ºC (68ºF to 77ºF).
(b) (4)

(b) (4)

(b) (4)

Carton and Container Label

1.14.1.1 Draft carton and container labels

Manufacturer: PETNET

Presentation: 50 mL vial

(b) (4)

Comment 3: The name should be consistent i.e., flotufolastat fluorine F 18 gallium.

Comment 4: Change (b) (4) to end of synthesis (EOS).

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John Amartey

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Danae Christodoulou

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	216023
Assessment Cycle Number	01
Drug Product Name/ Strength	Posluma (flotufolastat F 18)/ 296 – 5846 MBq/mL (8 – 158 mCi/mL)
Route of Administration	IV
Applicant Name	Blue Earth Diagnostics Ltd.
Therapeutic Classification/ OND Division	(b) (4)
Manufacturing Site	Multiple sites. See Section P.3
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The subject PET drug product is (b) (4) (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Original submission (Seq. 0001)	12/22/2021
Resubmission (Seq. 0006)	05/25/2022
IR amendment (Seq. 0018)	10/11/2022
IR amendment (Seq. 0023)	11/22/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: The 12/22/2021 submission was withdrawn by the applicant on 02/17/2022. The application was resubmitted on 05/25/2022 to include full study datasets, final clinical study report, and an updated Module 2.

Concise Description of Outstanding Issues: N/A

Supporting Documents: None

S DRUG SUBSTANCE

The information pertinent to the drug substance was not included in this review as the manufacturing of drug product comprises (b) (4) (b) (4)

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Drug product composition –**

(Section P.1, 12/22/2021 submission)

Component	Quantity per mL	Quantity per 5 mL	Function	Quality reference
Flotufolastat (^{18}F) [1]	Up to 5846 MBq (158 mCi)	Up to 29230 MBq (790 mCi)	Drug Substance	in-house specification
Flotufolastat [2]	Less than 20 µg	Less than 100 µg	(b) (4)	in-house specification
Citric acid [3]	1.9 mg	9.5 mg		USP
Sodium hydroxide	0.75 mg [4]	3.8 mg		NF
Sodium chloride	7.2 mg [4]	36 mg		USP
(b) (4)				(b) (4) (b) (4)

[1] at the end of synthesis (EOS)
[2] (b) (4)
[3] calculated on anhydrous basis
[4] (b) (4)

- **Drug product description –**

(Section P.1, 12/22/2021 submission)

Flotufolastat (18F) injection is a Positron Emission Tomography (PET) imaging radiopharmaceutical formulated as a sterile isotonic solution for parenteral administration. It is presented in a multidose clear 50-mL (b) (4) glass vial closed with a synthetic rubber stopper and crimped with an aluminum overseal. The drug product is presented as a 25 mL solution in a multidose vial with a strength of 296 to 5846 MBq/mL (8 to 158 mCi/mL) (b) (4) (Module 2.3.1, page 1/1, 12/22/2021 submission).

- **Description of container closure system –**

(Section P.7, 05/25/2022 resubmission)

Configuration	Component	Description
296 – 5846 MBq/mL (8 – 158 mCi/mL)	Vial	Colorless (b) (4) glass vial, Neck diameter: 20 mm Nominal volume: 50 mL
	Stopper	20 mm rubber stopper
	Overseal	20 mm crimp seal

The applicant states that the radiopharmaceutical drug product vial is a (b) (4) (b) (4) pyrogen-free container/closure, consisting of rubber stoppers, and aluminum crimp overseal as shown above. The information regarding the vials' manufacturers is shown below. The corresponding Certificate of Analysis (CoA) for each (b) (4) vial system is provided in Section P.7 of the 12/22/2021 submission. A letter of authorization (LOA) for each of the DMFs referenced below is provided in Module 1.4.2.

Configuration	Manufacturer	DMF
296 – 5846 MBq/mL (8 – 158 mCi/mL)	(b) (4)	

No information was provided regarding the (b) (4) (b) (4) Clarification is requested in Section P.3.5 below.

Assessment: Adequate

The information provided regarding the drug product composition, the drug product description, and the description of the container closure system is deemed acceptable.

The applicant provided the CoAs for all three (b) (4) vial systems proposed for commercial manufacturing of the drug product which show that the components meet the expected microbiological specification (i.e., sterility, bacterial endotoxins). Thus, review of the DMFs pertinent to the container closure system proposed for commercial production is not needed.

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

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(b) (4)

Assessment: Adequate

The applicant adequately addressed the deficiencies. The information provided regarding the comparability protocol meets the regulatory expectations.

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

- (b) (4)

PACKAGE INSERT

The drug product is labeled as sterile, pyrogen-free, and multi-dose.

Store POSLUMA at (b) (4) 20°C to 25°C (68°F to 77°F).
(b) (4)

Assessment: Adequate

Sufficient storage conditions have been provided prior to administration of the proposed drug product.

Post-Approval Commitments: No post-approval commitments have been requested/made at this time.

MICROBIOLOGY LIST OF DEFICIENCIES: None identified

Primary Microbiology Assessor Name and Date:
Yarery Smith, Ph.D., 11/30/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Marla Stevens-Riley, Ph.D., 11/30/2022

END

Yarery Smith

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Marla Stevens-Riley

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