

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208054Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING  
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and Composition)  
and/or Method of Use*

NDA NUMBER:

208054

NAME OF APPLICANT/NDA HOLDER:

Blue Earth Diagnostics Ltd.

*The following is provided in accordance with Section 305(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Pending

ACTIVE INGREDIENT(S)

Fluciclovine F18

STRENGTH(S)

(b)(4) fluciclovine F 18 at  
reference time and date

DOSAGE FORM

for Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

5,808,146

b. Issue Date of Patent

09/15/1998

c. Expiration Date of Patent

11/09/2015

d. Name of Patent Owner

Emory University

Address (of Patent Owner)

1599 Clifton Road, NE, 4th Floor (formerly at 2009 Ridgewood

City/State

Atlanta / GA

ZIP Code

30322

FAX Number (if available)

404-727-1271

Telephone Number

404-727-2211

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Lathrop & Gage LLP

Address (of agent or representative named in 1.e.)

4845 Pearl East Circle, Suite 201

City/State

Boulder / CO

ZIP Code

80301

FAX Number (if available)

720-931-3001

Telephone Number

720-931-3000

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**3. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed

*Jonathan Allis*  
Jonathan Allis (Sep 4, 2015)

11/09/2015

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Jonathan Allis, CEO

Address

215 Euston Road

City/State

London/London

ZIP Code

NW1 2BE

Telephone Number

+44 (0)1749 838888

FAX Number (if available)

E-Mail Address (if available)

This section applies only to requirements of the Paperwork Reduction Act of 1995.

**\*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.\***

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services  
Food and Drug Administration  
Office of Chief Information Officer  
Paperwork Reduction Act (PRA) Staff  
PRAStaff@fda.hhs.gov

*"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."*

## INFORMATION AND INSTRUCTIONS FOR FORM 3542a

### PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

#### General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/inorechoices/fdaforms/fdaforms.html>.

#### First Section

Complete all items in this section.

##### 1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) include full address of patent owner. If patent owner resides outside the U.S., indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

##### 2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

##### 3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

##### 4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approved labeling that describe with specificity the patented method of use.

##### 5. No Relevant Patents

Complete this section only if applicable.

##### 6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

## EXCLUSIVITY SUMMARY

**NDA #:** 208054

**CDER - Division of Medical Imaging Products (DMIP)**

**Trade Name:** Axumin

**Generic Name:** Fluciclovine F 18

**Applicant Name:** Blue Earth Diagnostics

**Approval Date:** May 27, 2016

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

**YES**       **NO**

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

#### **505(b)(1)**

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

**YES**       **NO**

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

(b) (4)

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(b) (4)

d) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.**

### **PART III     THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES      NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES      NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES      NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # YES  ! NO   
! Explain:



=====

**Regulatory Health Project Manager:** Thuy M. Nguyen, M.P.H.

**Name of person completing form:** Phillip Davis, M.D.

**Title:** Clinical Reviewer

**Date:** March 28, 2016

**Name of Division Director signing form:** Libero Marzella, M.D., Ph.D.

**Title:** Division Director

**Date:** May 27, 2016

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THUY M NGUYEN  
05/27/2016

LIBERO L MARZELLA  
05/27/2016

Regarding NDA 208054:

Blue Earth Diagnostics Ltd hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Food, Drug and Cosmetic Act in connection with this application.

*Jonathan Allis*  
Jonathan Allis (Aug 19, 2015)

Aug 19, 2015

Name: Jonathan Allis

Date:

Title: Chief Executive Officer

Confidential

blue earth  
LABORATORIES

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

<b>NDA #</b> 208054	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
<b>Proprietary Name:</b> Axumin <b>Established/Proper Name:</b> Fluciclovine F 18 <b>Dosage Form:</b> Injection		<b>Applicant:</b> Blue Earth Diagnostics (BED) <b>Agent for Applicant:</b> Michelle Wilson, Ph.D.
<b>RPM:</b> Thuy M. Nguyen, M.P.H.		Division: Medical Imaging Products
<b>NDA Application Type:</b> <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <b>Efficacy Supplement:</b> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <b>BLA Application Type:</b> <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) <b>Efficacy Supplement:</b> <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b>For ALL 505(b)(2) applications, two months prior to EVERY action:</b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)           <ul style="list-style-type: none"> <li><input type="checkbox"/> No changes</li> <li><input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)</li> </ul> </li> </ul> <p>Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed Action: <u>Approval</u></li> <li>User Fee Goal Date is : <u>May 28, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP - Approval
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review Priority:  Standard  Priority

Chemical Classification (new NDAs only): Type 1 - NME  
(confirm chemical classification at time of approval)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (including Approval Letter with final labeling)	05/27/16
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> <li>Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input checked="" type="checkbox"/> Included 05/26/16
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included 12/04/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included 05/11/16
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability letter</li> <li>Review</li> </ul>	12/10/15 11/20/15
❖ Labeling reviews (indicate dates of reviews)	RPM: <input checked="" type="checkbox"/> 11/24/15 DMEPA: <input checked="" type="checkbox"/> 12/15/15 OPDP: <input checked="" type="checkbox"/> 04/05/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting (indicate date of each review)	11/24/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included 05/27/16
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (indicate date)</li> <li>If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Date reviewed by PeRC: 08/05/15</li> <li>If PeRC review not necessary, explain: Full Waiver - GRANTED</li> </ul>	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) ( <i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i> )	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	08/03/15
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	01/13/16
<ul style="list-style-type: none"> <li>Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	03/22/16
<ul style="list-style-type: none"> <li>Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 05/26/16
Division Director Summary Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 05/10/16
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 04/05/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input checked="" type="checkbox"/> None
<b>Clinical</b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review: Co-signed the primary review</li> </ul>	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> <li>Clinical review (<i>indicate date for each review</i>)</li> </ul>	03/04/16

<ul style="list-style-type: none"> <li>• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i></li> </ul>	See Clinical Review, 03/04/16
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i><sup>5</sup></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i></li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>❖ Risk Management                             <ul style="list-style-type: none"> <li>• REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i></li> <li>• REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul> </li> </ul>	<input checked="" type="checkbox"/> 02/21/16
<ul style="list-style-type: none"> <li>❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i></li> </ul>	<input checked="" type="checkbox"/> None requested - N/A
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Microbiology Team Leader Review: Co-signed the primary review</li> </ul>	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 02/23/16
<b>Biostatistics</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Statistical Division Director Review: Co-signed the TL &amp; primary reviews</li> </ul>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 02/26/16
Statistical Review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 02/19/16
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology Division Director Review: Co-signed the TL &amp; primary review</li> </ul>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review: Co-signed the primary review	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> 02/18/16
<ul style="list-style-type: none"> <li>❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i></li> </ul>	<input checked="" type="checkbox"/> None requested

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

<b>Nondclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 05/24/16
• Supervisory Review: Co-signed the primary review	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review, including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 01/25/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief): Co-signed the IQA	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 02/29/16, 05/19/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	<input checked="" type="checkbox"/> 02/29/16
<input type="checkbox"/> Review & FONSI ( <i>indicate date of review</i> )	
<input type="checkbox"/> Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	N/A
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	N/A
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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THUY M NGUYEN  
05/27/2016

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**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS**

Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),

Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com) / Office: (513) 758-5671

Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling (PI) Request – May 26, 2016.

The FDA concurs with the Sponsor's proposed labeling (PI) dated May 25, 2016 (received by email, 05/25/16).

Please review in its entirety the attached FDA & Sponsor Agreed-Upon Labeling (PI).

The attached MS Word Doc & PDF versions are the same.

By 1:00 pm, US EST, today - May 26, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

BED concurrence and the CLEAN version of the Agreed-Upon Labeling (PI) (in color and PDF & MS Word Doc).

And follow-up with a formal official submission of the Agreed-Upon Labeling (PI) (in color and PDF & MS Word Doc) to the FDA by 3:00 pm, US EST, today – May 26, 2016.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER – Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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05/26/2016

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Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),

Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com) / Office: (513) 758-5671

Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling (PI) Request – May 25, 2016.

Please review the attached FDA labeling (PI) in its entirety and specifically Sections 2.1, 5.1 and 14.

The attached MS Word Doc & PDF versions are the same.

By 3:00 pm, US, EST, today – Wednesday, May 25, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

1. If BED agrees with the attached FDA labeling comments, please provide BED concurrence along with BED final concurred labeling (PI) in both Word Doc & PDF version

OR

2. If BED disagrees, please provide comments along with BED proposed labeling as an annotated version (with red-lined, track-changes) along with a clean revised version – both annotated and clean versions in MS Word Doc.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

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Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling and Label Request – May 9, 2016.

Please review the attached FDA & Sponsor Agreed-Upon Labeling (PI) & (2) Labels in its entirety.

The attached MS Word Doc & PDF versions are the same.

By 12:00 pm, US, EST, Tuesday – May 10, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

BED concurrence and BED final agreed-upon version of the labeling (PI) and labels (both in color and PDF & Word Doc).

And follow-up with a formal official submission of the final agreed-upon labeling and labels to the FDA by May 13, 2016.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

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Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling & Label Comments & Request – May 5, 2016.

Please review the attached FDA labeling (PI) & (2) labels in its entirety.

The attached MS Word Doc & PDF versions are the same.

By 9:00 am, US, EST, Monday – May 9, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

**1. If BED agrees with the attached FDA labeling, labels and comments, please provide BED concurrence and BED final acceptance version of the labeling (PI) and labels.**

**OR**

**2. If BED disagrees, please provide comments along with BED proposed labeling & labels as an annotated version (with red-lined, track-changes) along with a clean revised version – both annotated and clean versions in MS Word (for the labeling and labels).**

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
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Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find below the FDA & PK Labeling Information Request (IR) – April 22, 2016.

The attached PK Labeling IR - MS Word DocX & PDF versions are the same.

Also, as discussed at today's Labeling TCON, 04/22/16, regarding the labeling, please revise Sections 2, 6, 12 and 14, and submit the entire – revised labeling (PI).

By 9:00 am, US, EST, Tuesday - April 26, 2016, please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov).

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
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Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),

Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com) / Office: (513) 758-5671

Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling & Label Comments & Request – April 15, 2016.

Please review the attached FDA labeling & (2) labels in its entirety.

The attached MS Word Doc & PDF versions are the same.

By 9:00 am, US, EST, Tuesday - April 19, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

1. If BED agrees with the attached FDA labeling, labels and comments, please provide BED concurrence

**OR**

2. If BED disagrees, please provide comments along with BED proposed labeling & labels as an annotated version (with red-lined, track-changes) along with a clean revised version – both annotated and clean versions in MS Word (for the labeling and labels).

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

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Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),

Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com) / Office: (513) 758-5671

Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Labeling & Label Comments & Request – April 5, 2016.

Please review the attached FDA labeling & (2) labels in its entirety.

By 3:00 pm, US, EST, Wednesday – April 6, 2016, please provide via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), the following:

1. If BED agrees with the attached FDA labeling, labels and comments, please provide BED concurrence

OR

2. If BED disagrees, please provide comments along with BED proposed labeling & labels as an annotated version (with red-lined, track-changes) along with a clean revised version – both annotated and clean versions in MS Word (for the labeling and labels).

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

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THUY M NGUYEN  
04/05/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Clinical Information Request - 03/17/16 / re: submission dated 09/28/15  
**Date:** Thursday, March 17, 2016 3:51:00 PM  
**Attachments:** [NDA 208054 CLIN IR 031716.pdf](#)

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached the FDA Clinical Information Request – March 17, 2016.

By 3:00 p.m., US, EST – March 18, 2016, please provide a response via email

to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

**Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),**

**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

**Spon Rep:** Ms. Kathy Nagle / **Email:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

**Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the FDA Clinical Information Request – March 17, 2016.**

**By 3:00 p.m., US, EST – March 18, 2016,** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

## **NDA 208054: Axumin [F-18] Fluciclovine**

### **FDA Clinical Information Request – March 17, 2016**

Regarding NDA 208054: Axumin fluciclovine F 18, submission dated September 28, 2015, we note that a number of the study reports submitted in support of your NDA appear to be from studies sponsored by entities other than Blue Earth Diagnostics (e.g., GE Healthcare, (b) (4) Emory University, Bologna University, etc.; see Table 1 of module 2.5).

In addition, your summary of clinical studies with fluciclovine F 18 makes reference to various literature publications.

For each source of information that is being relied upon for approval of your NDA, including published literature, please clarify if BED owns or has obtained Right-of-Reference to the submitted studies/data. If BED has Right-of-Reference to any of the relied upon study data/information, provide a Letter-of-Authorization (LOA) from the data-owner permitting the FDA to review those data in support of your NDA application.

If your NDA contains information necessary for approval from studies not conducted by or for BED and for which BED has not obtained a Right-of-Reference or use, then you should amend your NDA to be submitted pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. See the draft Guidance for Industry: *Applications Covered by Section 505(b)(2)* (October 1999), available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

If you rely on published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the FDA's regulations at 21 CFR 314.54. Note that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a Sponsor relies.

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/s/  
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THUY M NGUYEN  
03/17/2016



NDA 208054

INFORMATION REQUEST

Blue Earth Diagnostic Ltd.  
Attention: Michelle Wilson, Ph.D.  
Expert Regulatory Consultant  
118 Palm Springs Drive  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin™(Fluciclovine F-18), 335 to 8200 MBq/ml or 9 to 221 mCi/ml, multi-dose vial for injection.

We also refer to your January 11, 2016, January 19, 2016, and February 4, 2016 submissions in response to our December 23, 2015, January 14, 2016, and February 1, 2016 Information Request letters respectively.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by February 25, 2016, in order to continue our evaluation of your NDA.

1. Provide component drawings, composition of components and component specifications for the 30mL vial supplied by (b) (4) Also, clarify if the stopper formulation meets the USP safety criteria.

If you have any questions, please contact me, at (240) 402-2690.

Sincerely,

Thao M.  
Vu -A

Digitally signed by Thao M. Vu -A  
DN: cn=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
c=Thao M. Vu -A,  
09.2342.19.200300.100.1.1-200169941  
Z  
Date: 2016.02.23 13:25:43 -05'00'

Thao M. Vu, R.Ph

Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

## **MEMORANDUM OF TELECONFERENCE**

**NDA 208054: Axumin [F-18] Fluciclovine**

**February 12, 2016, 12:00 Noon to 1:55 PM**

### **FDA Representatives**

Anthony Mucci, Ph.D., Jyoti Zalkikar, Ph.D., Phillip Davis, M.D., Nushin Todd, M.D., Ph.D., Frank Lutterodt, M.S., and Libero Marzella, M.D., Ph.D.

### **Applicant Representatives**

Michelle Wilson, Ph.D., Expert Regulatory Strategist, Virtual Regulatory Solutions, Inc., and statistical team for Blue Earth Diagnostics.

FDA held a teleconference with the applicant, Blue Earth Diagnostics, on February 12, 2016, to obtain clarification on the statistical datasets for NDA 208054. At the teleconference, FDA informed the applicant of the difficulty in interpreting the datasets that were submitted to the NDA. During the teleconference, which lasted for one hour and 55 minutes, discussions were held regarding specific categories within the datasets.

Following the meeting, FDA submitted an information request for additional datasets that were discussed during the teleconference. The applicant agreed to provide the data as well as an e-mail confirmation of the information discussed at the meeting.

Drafted by Frank Lutterodt

Reviewed and edited by Dr. Nushin Todd

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/s/  
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FRANK A LUTTERODT  
02/22/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)  
**Subject:** Dr. Wilson (for Spon - BED): NDA 208054 / Axumin: FDA Clinical Information Request - 02/16/16 / re: submission dated 09/28/15  
**Date:** Tuesday, February 16, 2016 11:15:00 AM  
**Attachments:** [NDA 208054 Fluciclovine Data Sheets Clin IR 021616.xls](#)

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached the **Excel attachment and the following FDA Clinical Information Request – February 16, 2016:**

**Please find the attached Excel spreadsheet template created by the FDA Clinical review team.**

**We request you complete all of the spreadsheets by filling in the missing data points.**

**Please clearly explain or highlight the data points used for calculating the primary endpoint analyses presented in the NDA final clinical study reports.**

**Also, please highlight subjects which contributed multiple data points to the analyses.**

**By 9:00 a.m., US EST – Wednesday, February 17, 2016.** please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

**Emory Data BED001**

<b>Prostate Bed Region Only</b>	<b>Prostate Biopsy?</b>	<b>Biopsy Result</b>	<b>TRUS?</b>	<b>TRUS Result</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Yes=1, No=2	Pos=1, Neg=2

**Fluciclovine Scan**   **Did imaging guide biopsy?**   **Imaging test that guided biopsy**

Pos=1, Neg=2

Yes=1, No=2

(Fluciclovine, Prostatecint, CT, MRI)

**Prostascint Result** (n will be different than paper as BED001 & BED002 enrolled only histology SOT subjects)

Pos=1, Neg=2

**Emory Data BED001**

<b>Pelvic Lymph Nodes Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Scan</b>	<b>Did imaging guide biopsy?</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Yes=1, No=2

**Imaging test that guided biopsy    Proscint Result**

(Fluciclovine, Proscint, CT, MRI) Pos=1, Neg=2

**Emory Data BED001**

**Extra Prostatic Sites Only**   **Biopsy?**   **Biopsy Result**   **Fluciclovine Scan**   **Did imaging guide biopsy?**

**Subject ID**                      Yes=1, No=2   Pos=1, Neg=2   Pos=1, Neg=2      Yes=1, No=2

**Imaging test that guided biopsy      Prostatectomy Result**

(Fluciclovine, Prostatectomy, CT, MRI)      Pos=1, Neg=2

**Emory Data BED002**

<b>Prostate Bed Region Only</b>	<b>Prostate Biopsy?</b>	<b>Biopsy Result</b>	<b>TRUS?</b>	<b>TRUS Result</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Yes=1, No=2	Pos=1, Neg=2

**Fluciclovine Reader 1** **Fluciclovine Reader 2** **Fluciclovine Reader 3** **Did imaging guide biopsy?**

Pos=1, Neg=2

Pos=1, Neg=2

Pos=1, Neg=2

Yes=1, No=2

**Imaging test that guided biopsy      Prostatectomy Result**

(Fluciclovine, Prostatectomy, CT, MRI)

**Emory Data BED002**

<b>Pelvic Lymph Nodes Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Reader 1</b>	<b>Fluciclovine Reader 2</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Pos=1, Neg=2

<b>Fluciclovine Reader 3</b>	<b>Did imaging guide biopsy?</b>	<b>Imaging test that guided biopsy</b>	<b>Prostascint Result</b>
Pos=1, Neg=2	Yes=1, No=2	(Fluciclovine, Prostascint, CT, MRI)	Pos=1, Neg=2

**Emory Data BED002**

<b>Extra Prostatic Sites Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Reader 1</b>	<b>Fluciclovine Reader 2</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Pos=1, Neg=2

<b>Fluciclovine Reader 3</b>	<b>Did imaging guide biopsy?</b>	<b>Imaging test that guided biopsy</b>	<b>Prostascint Result</b>
Pos=1, Neg=2	Yes=1, No=2	(Fluciclovine, Prostascint, CT, MRI)	Pos=1, Neg=2

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THUY M NGUYEN  
02/16/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle\\_Kathy\\_\(K.Nagle@blueearthdx.com\)](mailto:Nagle_Kathy_(K.Nagle@blueearthdx.com))  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Response - Feb 16 / FDA Clinical IR, 02/16/16 / re: submission dated 09/28/15  
**Date:** Tuesday, February 16, 2016 2:57:00 PM  
**Attachments:** [NDA 208054 Fluciclovine Data Sheets Clin IR 021616.xls](#)

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Please find the FDA Responses (in red) within your email, 02/16/16 (below).

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

---

**From:** Nguyen, Thuy M  
**Sent:** Tuesday, February 16, 2016 2:34 PM  
**To:** 'VRS Secure'  
**Cc:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); Nagle, Kathy ([K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com))  
**Subject:** Dr. Wilson (for Spon - BED): NDA 208054 / Axumin: Spon's Clarification Request - Feb 16 / FDA Clinical Information Request - 02/16/16 / re: submission dated 09/28/15

Dear Dr. Wilson,

Thank you for the clarification request, 02/16.

Sincerely,  
Thuy M. Nguyen

**From:** VRS Secure [[mailto:vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)]  
**Sent:** Tuesday, February 16, 2016 1:39 PM  
**To:** Nguyen, Thuy M  
**Cc:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); Nagle, Kathy ([K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com))  
**Subject:** Re: Dr. Wilson (for Spon - BED): NDA 208054 / Axumin: FDA Clinical Information Request - 02/16/16 / re: submission dated 09/28/15

Dear Thuy,

BED would appreciate receiving some clarifications in regards to the requested dated 16 February 2016 and the associated spreadsheet.

For all the spreadsheet tabs, BED would like to confirm that each row of record would represent the results within the region of interest, for one subject (or one subject one fluciclovine administration if a subject has had more than one administration), and not a listing of the data at a lesion level.

**FDA Response – 02/16/16: Correct.**

BED did not collect information concerning which of the images collected might have 'guided' the biopsy on the CRF and thus cannot complete columns G and H of any of the requested spreadsheets. However, BED can insert the day relative to the fluciclovine scan that the biopsy was taken as a substitute for this information, if that is of assistance; BED would appreciate confirmation.

**FDA Response – 02/16/16: Yes. A column showing the timing of biopsies relative to fluciclovine scan is requested.**

Thank you very much.

Best wishes,

***Michelle***

Michelle Wilson, Ph.D.  
Expert Regulatory Strategist  
Virtual Regulatory Solutions, Inc.  
[michelle.wilson@vrsmail.com](mailto:michelle.wilson@vrsmail.com)  
[www.VirtualRegulatorySolutions.com](http://www.VirtualRegulatorySolutions.com)  
(c) 513-578-5671

On Tue, Feb 16, 2016 at 11:15 AM, Nguyen, Thuy M <[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)> wrote:

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached the **Excel attachment and the following FDA Clinical Information Request – February 16, 2016:**

**Please find the attached Excel spreadsheet template created by the FDA Clinical review team.**

**We request you complete all of the spreadsheets by filling in the missing data points.**

**Please clearly explain or highlight the data points used for calculating the primary endpoint analyses presented in the NDA final clinical study reports.**

**Also, please highlight subjects which contributed multiple data points to the analyses.**

**By 9:00 a.m., US EST – Wednesday, February 17, 2016.** please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission

to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: [\(301\) 796-1427](tel:(301)796-1427)

--

Virtual Regulatory Solutions, Inc.



This email is for the sole use of the intended recipient and contains information that may be privileged and/or confidential. If you are not an intended recipient, please notify the sender by return email and delete this email and any attachments.

**Emory Data BED001**

<b>Prostate Bed Region Only</b>	<b>Prostate Biopsy?</b>	<b>Biopsy Result</b>	<b>TRUS?</b>	<b>TRUS Result</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Yes=1, No=2	Pos=1, Neg=2

**Fluciclovine Scan**   **Did imaging guide biopsy?**   **Imaging test that guided biopsy**

Pos=1, Neg=2

Yes=1, No=2

(Fluciclovine, Prostatecint, CT, MRI)

**Prostascint Result** (n will be different than paper as BED001 & BED002 enrolled only histology SOT subjects)

Pos=1, Neg=2

**Emory Data BED001**

<b>Pelvic Lymph Nodes Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Scan</b>	<b>Did imaging guide biopsy?</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Yes=1, No=2

**Imaging test that guided biopsy    Proscint Result**

(Fluciclovine, Proscint, CT, MRI) Pos=1, Neg=2

**Emory Data BED001**

**Extra Prostatic Sites Only**   **Biopsy?**   **Biopsy Result**   **Fluciclovine Scan**   **Did imaging guide biopsy?**

**Subject ID**                      Yes=1, No=2   Pos=1, Neg=2   Pos=1, Neg=2      Yes=1, No=2

**Imaging test that guided biopsy      Prostatecint Result**

(Fluciclovine, Prostatecint, CT, MRI)      Pos=1, Neg=2

**Emory Data BED002**

<b>Prostate Bed Region Only</b>	<b>Prostate Biopsy?</b>	<b>Biopsy Result</b>	<b>TRUS?</b>	<b>TRUS Result</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Yes=1, No=2	Pos=1, Neg=2

**Fluciclovine Reader 1** **Fluciclovine Reader 2** **Fluciclovine Reader 3** **Did imaging guide biopsy?**

Pos=1, Neg=2

Pos=1, Neg=2

Pos=1, Neg=2

Yes=1, No=2

**Imaging test that guided biopsy      Prostatectomy Result**

(Fluciclovine, Prostatectomy, CT, MRI)

**Emory Data BED002**

<b>Pelvic Lymph Nodes Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Reader 1</b>	<b>Fluciclovine Reader 2</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Pos=1, Neg=2

<b>Fluciclovine Reader 3</b>	<b>Did imaging guide biopsy?</b>	<b>Imaging test that guided biopsy</b>	<b>Prostascint Result</b>
Pos=1, Neg=2	Yes=1, No=2	(Fluciclovine, Prostascint, CT, MRI)	Pos=1, Neg=2

**Emory Data BED002**

<b>Extra Prostatic Sites Only</b>	<b>Biopsy?</b>	<b>Biopsy Result</b>	<b>Fluciclovine Reader 1</b>	<b>Fluciclovine Reader 2</b>
<b>Subject ID</b>	Yes=1, No=2	Pos=1, Neg=2	Pos=1, Neg=2	Pos=1, Neg=2

<b>Fluciclovine Reader 3</b>	<b>Did imaging guide biopsy?</b>	<b>Imaging test that guided biopsy</b>	<b>Prostascint Result</b>
Pos=1, Neg=2	Yes=1, No=2	(Fluciclovine, Prostascint, CT, MRI)	Pos=1, Neg=2

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/s/  
-----

THUY M NGUYEN  
02/16/2016

**From:** Lutterodt, Frank A  
**To:** "[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)"; [vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)  
**Cc:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com); [Nguyen.Thuy.M](mailto:Nguyen.Thuy.M)  
**Subject:** Revised Data Set Request ( 2/12/16) For NDA208054 Axumin [F-18] Fluciclovine  
**Date:** Friday, February 12, 2016 5:02:00 PM  
**Attachments:** [Detailed Data Set.pdf](#)

---

Dear Dr. Wilson (for Applicant – Blue Earth Diagnostics [BED]),  
Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,  
thanks for your team’s availability for the teleconference this afternoon.

Please find attached below the [FDA Statistical Information Request dated February 12, 2016](#).

We request that you provide response by close of business Tuesday, February 16, 2016. Provide  
your response via email to Ms. Thuy Nguyen’s attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) and  
follow-up with a formal official response submission to the FDA via electronic submission  
Gateway.

Sincerely,

-

*Frank*

On behalf of Thuy Nguyen

---

-----  
Frank Lutterodt, M.S. | Regulatory Health Project Manager | Division of Medical Imaging Products  
Office of Drug Evaluation IV | Center for Drug Evaluation and Research | Food and Drug Administration  
10903 New Hampshire Avenue, Room 5483 | Silver Spring, MD 20993  
Phone: (301) 796.4251 • Fax: (301) 796.9849 | [Frank.Lutterodt@fda.hhs.gov](mailto:Frank.Lutterodt@fda.hhs.gov)

## **Revised Data Set Request ( 2/12/16)**

The Reviewer has repeated his earlier Data Set description on p 2 below.

A new data set is requested directly below, before the p2 description of the Original. This new data set should set the stage for understanding of the meaning of the Original Data Set. If the Revised Original can be forwarded faster than both itself and the Detailed Data Set together, please do so.

Further Note: The data sets should not include Secondary Truth. All Truth should be based strictly on **Detections**, as defined below.

### **Requested Detailed Data Set**

#### **Preliminary Comment:**

Each row of data is dedicated to a unique “Detection”.

A Detection is a specimen with a definitive histology result (Pos/Neg) which was found on an Image, excised, and sent for histopathology. That is, a Detection is an excised specimen with histology. ( Lesion with histology would be equivalent.) The Image could be Fluciclovine or some other modality ( Ultrasound, Prostatecint, etc.) There may be a handful of cases where a biopsy was conducted independently of images; if histology is available, this “Detection” can be part of the data set. (See Column#6 below.)

**Columns(Variables):** Only six columns.

**Column#1:** Subject ID

#### **Column#2: Detection ID**

If a subject has 5 detections, then 5 rows will be dedicated to this subject. The numbering is not important; what is critical is that each row be dedicated to a single detection, and that each Subject be assigned to the number of rows that cover all detections for that subject.

#### **Column#3: Region for the Detection in Column#2**

Either B = Prostate/Bed or E = Outside Prostate/Bed

**Column#4:** Histology result for the Detection (Pos/Neg)

**Column#5:** =1 if Fluciclovine Image made the Detection; = 0 if Fluciclovine did not make the detection. Note, as an Example: If Histology = Negative, and Column#5 =1 , then Fluciclovine is a False Positive for this Detection, but it’s still a Detection.

**Column#6:** =1 if some other Modality made the Detection; = 0 if not. It should be understood that Column#6 =1 is compatible with Column#5 =1. This simply means that both Fluciclovine and some other Modality(Image) made the detection. However, there should be a result = 1 in at least one of these two columns. If the Detection was made independently of images, say by some random biopsy with a histology result, then Column#6=1 also. Hopefully, there are few such cases.

**Example**

<b>SUB</b>	<b>DETECTION</b>	<b>REGION</b>	<b>HIST</b>	<b>Flucic</b>	<b>Other</b>
1	Detection#1	B	Neg	1	0
1	Detection#2	B	Pos	0	1
1	Detection#3	B	Pos	1	1
1	Detection#4	E	Neg	1	1
1	Detection#5	E	Pos	0	1

Then, for the Data Set below, for **SUB#1**

**BH = 3 ; BHP = 2 ; BF = 2 ; BFP = 1 ; EH = 2 ; EHP = 1 ; EF = 1 ; EFP = 0**

**Revised Requested Data Set for NDA 208054 Fluciclovine**

**Data from BED001 (Emory Data for Recurrence Subjects Only)**

**First: Identifier Variables**

**SUB** = Subject Identifier

**RACE; AGE** = Race and Age variables

**TREAT**: Treatment for original disease occurrence. This could be Prostatectomy, Radiation, etc.

The Sponsor can decide on the categories, but the fewer the better.

**Next: Diagnostic Variables**

Here the variables will be per Subject. That is, each subject will determine a single line of entries. The notation for each variable will begin with a "Region" identifier:

B for the Prostate/Prostate Bed ; E for everything else

**Variables:**

**For B**

**BH** = # B Region lesions detected by any Modality and which have Histology (+/-)

**BHP** = # Among the BH that are Histology Positive

**BF** = # Lesions among the BH that were detected by Fluciclovine

**BFP** = # Among the BF that are Histology Positive

**For E**

**EH** = # E Region Lesions detected by any Modality and which have Histology (+/-)

**EHP** = # Among the EH that are Histology Positive

**EF** = # Lesions among the EH that were detected by Fluciclovine

**EFP** = # Lesions among the EF that were detected by Fluciclovine

**Note:** Eliminate **DF, DS, DR**, etc

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

FRANK A LUTTERODT  
02/12/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle_Kathy_(K.Nagle@blueearthdx.com))  
**Subject:** Dr. Wilson (for Spon - BED): NDA 208054 / Axumin: FDA Statistical Information Request - 02/04/16 / re: submission dated 09/28/15  
**Date:** Thursday, February 04, 2016 9:38:00 AM  
**Attachments:** [NDA\\_208054\\_STAT\\_IR\\_020416.pdf](#)

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached below the **FDA Statistical Information Request – February 4, 2016.**

**By 12:00 p.m., US EST – Friday, February 5, 2016.** please provide a response via email to

my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission

to the FDA via electronic submission ESG / Gateway.

**Also, submit the revised data set by 12:00 p.m., US EST, February 5, 2016.**

And the FDA may request a teleconference (TCON) with the Sponsor.

Note: All amended / revised protocol, consent form or other revised document should be

submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

Dr. Anthony Mucci, FDA Statistical Reviewer, is available for a teleconference or email discussion regarding statistical-only.

If needed, please contact directly Dr. Mucci to schedule a statistical-only teleconference:

Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov) / Office: (301) 796-1720.

Following each statistical TCON / email discussion(s) that BED may have with Dr. Mucci,

please email to Dr. Mucci (Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov)) and to my attention

(Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)) a summary / meeting minutes of the TCON / email discussion(s)

and follow up with formal official submissions to the FDA.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

**Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),**

**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

**Spon Rep:** Ms. Kathy Nagle / **Email:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – February 4, 2016.**

**By 12:00 p.m., US EST – Friday, February 5, 2016,** please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

**Also, submit the revised data set by 12:00 p.m., US EST, February 5, 2016.**

And the FDA may request a teleconference (TCON) with the Sponsor.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

Dr. Anthony Mucci, FDA Statistical Reviewer, is available for a teleconference or email discussion regarding statistical-only.

If needed, please contact directly Dr. Mucci to schedule a statistical-only teleconference:  
Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov) / Office: (301) 796-1720.

Following each statistical TCON / email discussion(s) that BED may have with Dr. Mucci, please email to Dr. Mucci (Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov)) and to my attention (Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)) a summary / meeting minutes of the TCON / email discussion(s) and follow up with formal official submissions to the FDA.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – February 4, 2016:**

The FDA Statistical Reviewer requested several tables in addition to the requested data set. The data set provided by the Sponsor in a previous communication did not reflect the request, and, conditional on recent communications with the Sponsor’s team, a new, corrected data set is expected, but has not yet been received.

The requested tables present a similar problem. Table 1 from the Sponsor looks as follows: (Only a part of the table is reproduced below):

	<b>Lesions with Histology</b>		<b>Lesions with Histology = +</b>	
	<b>All Images</b>	<b>F Images</b>	<b>All Images</b>	<b>F Images</b>
<b>B =0, E = 0</b>	<b>13</b>	<b>16</b>		
<b>B =0, E = 1</b>	<b>5</b>	<b>6</b>		
<b>B =0, E&gt;1</b>				

The entries should reflect the number of subjects within the category. Thus,

(1):Under *Lesions with histology, All Images:*

(B=0 ; E = 1 ) should list the number of subjects for whom at least one Image type found no such lesions in the Bed, and exactly one lesion outside the Bed.

Result = 5 in Table

(2):Under *Lesions with histology, Fluciclovine Images:*

(B=0 ; E = 1 ) should list the number of subjects for whom Fluciclovine found no such lesions in the Bed, and exactly one lesion outside the Bed.

Result = 6 in Table.

But Fluciclovine Images are one among several image types, so the result in (2) can’t be larger than the result in (1).

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – February 4, 2016 (cont.):**

Let's next look at the results provided for the following requested Table:

**Table(3) (Lesions with Positive Histology/Prostate/Prostatic Bed)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>	<b>39</b>	<b>5</b>	
<b>OTHER = N</b>	<b>54</b>	<b>177</b>	
			<b>275</b>

This is a Lesion-Level Table, and should contain only histology Positive lesions.

Module 2.7.3 Summary of Clinical Efficacy presents ( Table 3, p 14 of 44) a total of 158 Positive lesions, while the entries above list 275 Positive lesions. Further, the Table above presents 177 Positive histology lesions that were not detected by either Fluciclovine or other means. But this entry should be zero, since only lesions detected by some type of Image can enter the Table. The Reviewer has no idea as to what this Table provides.

A possible source of the problems is:

Confusion between detections of lesions and classifications of lesions. The Reviewer intends a detection to mean the finding of a lesion, regardless of its subsequent histology classification.

In the interests of time, the Reviewer's Table 2 will not be discussed here. The overall concern is that the Tables provided do not reflect the Tables requested, and, additionally, these tables present entries that the Reviewer can't interpret under any alternative scenarios.

The tables, as originally requested, are present below for convenience of reference. The more critical tables are those discussed above. The FDA Statistical Reviewer is available for a TCON to discuss the interpretations, if these remain equivocal, but there is an urgent need for correct tables and data sets.

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – February 4, 2016 (cont.):**

**Requested Tables**

**Table#1**

**Distribution of Profile of Lesion Detections ( Entries are # Subjects)**

The intention here is to gather Subject Level profiles of distributions of lesion detections both for all image types and for Fluciclovine Images in particular, under restrictions on the lesion status with respect to Histology

“Lesions With Histology” means only lesions that have Histology results

“Lesions with Histology = +” means only lesions with Positive Histology

	Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images
<b>B =0, E = 0</b>				
<b>B =0, E = 1</b>				
<b>B =0, E&gt;1</b>				
<b>B =1, E = 0</b>				
<b>B =1, E = 1</b>				
<b>B =1, E&gt;1</b>	<b>NH(1, &gt;1)</b>			<b>NF+(1, &gt;1)</b>
<b>B &gt;1, E = 0</b>				
<b>B &gt;1, E = 1</b>				
<b>B &gt;1, E&gt;1</b>				

**Note: B = Prostate/Prostate Bed ; E = All other Regions**

**Meaning of Categories and Entries**

**NH(1, >1`)**: Number of Subjects with exactly one detection in B and more than one detection in E (over all histology lesions, all Image types)

**NF+(1, >1)**: Number of subjects with exactly one detection in B, but at least two detections in E ( restricted to lesions with Positive Histology, and restricted to Fluciclovine Image reads)

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – February 4, 2016 (cont.):**

**Table#2:Statistical Profile on # Detected Lesions by Location/Image Type/Histology**

	Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images
<b>B</b>				
Mean		<b>( B, F )</b>		
Sigma				
Median				
Max				
Min				
<b>E</b>				
Mean			<b>(E, All)</b>	
Sigma				
Median				
Max				
Min				

Note: B = Prostate/Prostate Bed ; E = All other Regions

$$( \mathbf{B}, \mathbf{F} ) = ( \mathbf{1}/\mathbf{N} ) \sum_1^{\mathbf{N}} \mathbf{S}_{\mathbf{K}} \text{ where } \mathbf{S}_{\mathbf{K}} = \# \text{ Lesions in Subject K ( among N Subjects )}$$

when the Region is B, and the Image Type is Fluciclovine

$$( \mathbf{All}, \mathbf{E}, + ) = ( \mathbf{1}/\mathbf{N} ) \sum_1^{\mathbf{N}} \mathbf{S}_{\mathbf{K}} \text{ where } \mathbf{S}_{\mathbf{K}} = \# \text{ Lesions with Positive Histology in Subject K}$$

(among N Subjects ) when the Region is E, and the Image Type is All

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – February 4, 2016 (cont.):**

**Tables for Lesion Detections Fluciclovine versus Other Images  
( Six Tables) Lesion Level**

**Meaning of Entries: ( Holds for all Tables)**

**L(Y,Y) = # Lesions detected by both OTHER and Fluciclovine**

**L(N,Y) = # Lesions not detected by OTHER, but by Fluciclovine**

**L(Y,N) = # Lesions detected by OTHER, but not by Fluciclovine**

**Table(1) (Lesions with Histology/Prostate/Prostatic Bed)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>	<b>L(Y,Y)</b>	<b>L(Y,N)</b>	
<b>OTHER = N</b>	<b>L(N,Y)</b>		

**Table(2) (Lesions with Histology/Elsewhere)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

**Table(3) (Lesions with Positive Histology/Prostate/Prostatic Bed)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

**Table(4) (Lesions with Positive Histology/Elsewhere)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

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/s/  
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THUY M NGUYEN  
02/04/2016

**CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)**

**TYPE C MID-CYCLE TELECONFERENCE MINUTES**

**NDA:** 208054  
**DRUG NAME:** Axumin [F-18] Fluciclovine  
**SPONSOR:** Blue Earth Diagnostics, LTD (BED)  
**DATE:** Wednesday, January 13, 2016

**SPONSOR PARTICIPANTS:**

Jonathan Allis, Ph.D., Chief Executive Officer, BED  
David Gauden, Ph.D., Head of Development, BED  
Caroline Hardwicke, Head of Clinical Operations, BED  
Mike Heslop, President, BED  
Lisa Jenkins, Ph.D., Vice President, Regulatory Strategy and Content Development, VRS  
Matthew Miller, Ph.D. Head of Imaging, BED

(b) (4)

Katharine Nagle, Ph.D., Head of CMC & QA, BED  
Penny Ward, MBBS, FFPM, Chief Medical Officer, BED  
Michelle Wilson, Ph.D., Expert Regulatory Strategist, VRS

**FDA PARTICIPANTS:**

Danae Christodoulou, Ph.D., Chemistry Branch Chief  
Phillip Davis, M.D., Clinical Reviewer  
Charles Ganley, M.D., Office Director  
Marc Goldstein, PDUFA Contractor, Eastern Research Group  
Alex Gorovets, M.D., Deputy Division Director  
Jagjit Grewal, Office Associate Director of Regulatory Affairs  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Kaye Kang, Pharm.D., Chief, Project Management Staff  
Ravi Kasliwal, Ph.D., Chemistry Reviewer  
Ira Krefting, M.D., Safety Associate Director  
Eldon Leutzinger, Ph.D., Chemistry Team Leader  
Lou Marzella, M.D., Ph.D., Division Director  
Tony Mucci, Ph.D., Statistical Reviewer  
Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager  
Yanli Ouyang, Ph.D., Pharm/Tox Reviewer  
Benjamin Stevens, Ph.D., CMC – Drug Substance Reviewer  
Nushin Todd, M.D., Clinical Team Leader  
Thao Vu, R.Ph., CMC Project Manager  
Jesse Wells, Ph.D., Microbiology Team Leader  
Gene Williams, Ph.D., Clinical Pharmacology Reviewer  
Tony Wilson, Ph.D., CMC – Facility Reviewer

**CONFIDENTIAL**

**NDA 208054: Axumin [F-18] Fluciclovine**

**Page 2**

**AGENDA: Regarding the NDA 505(b)(1) submission dated September 28, 2015, to provide the Sponsor with the FDA mid-cycle review status.**

**FDA Review Status**

**-CMC:** The FDA acknowledged the Sponsor's CMC Response to the FDA CMC Information Request (IR) dated 12/23/15. The review is ongoing.

**-Microbiology:** The review is ongoing. Forthcoming FDA IR regarding one of facility site (after further internal FDA discussion).

**-Facility:** The inspections are ongoing.

**-Pharmacology/Toxicology:** The review is ongoing. No concerns at this time.

**-Clinical Pharmacology (PK):** The review is ongoing. Forthcoming FDA IR regarding Axumin administered with high protein meal.

**-Clinical:** The review is ongoing. No significant safety issues at this time. However, the FDA stated the challenge will be on how to describe the statistical data which will not be like the data reflected in the Sponsor's proposed draft labeling (version - December 4, 2015). Forthcoming FDA IR regarding the subject deposition in Studies BED001 and BED002; clarification on scan times used in the efficacy analysis of the Emory data; how data was reported for the Bologna study vs re-analysis; and the dose-data per patient in the Emory study.

**Statistical:** Regarding the FDA Statistical Information Request dated 01/12/16, the Sponsor anticipates providing a response by the FDA requested date of January 22, 2016. Forthcoming FDA IR regarding the statistical tables.

**Upcoming Milestone Dates**

-The FDA will forward via email to the Sponsor the FDA Late-Cycle Background Package by March 7, 2016.

-The Late-Cycle Teleconference is scheduled for March 21, 2016 at 12:00 – 1:30 pm, US EST, to provide the Sponsor with the FDA review status.

-PDUFA priority 8-month due date: May 27, 2016.

**Meeting Minutes Recorded By: T.Nguyen, DMIP**

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/s/  
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THUY M NGUYEN  
02/02/2016



NDA 208054

INFORMATION REQUEST

Blue Earth Diagnostic Ltd.  
Attention: Michelle Wilson, Ph.D.  
Expert Regulatory Consultant  
118 Palm Springs Drive  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin™(Fluciclovine F-18), 335 to 8200 MBq/ml or 9 to 221 mCi/ml, multi-dose vial for injection.

We also refer to your January 11, 2016 and January 19, 2016 submissions in response to our December 23, 2015 and January 14, 2016 Information Request letters respectively.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by February 8, 2016, in order to continue our evaluation of your NDA.

1. We acknowledge that sterility testing (b) (4)  
(b) (4) as necessary for short half-life PET products; however, describe actions taken in the event that a released batch fails sterility testing. Pursuant to 21 CFR 212.70 (e), you must notify the administering physician/facility in the event of any sterility test failure of a PET drug product.

If you have any questions, please contact me, at (240) 402-2690.

Sincerely,

Thao M.  
Vu -A

Digitally signed by Thao M. Vu -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Thao M. Vu -A,  
0.9.2342.19200300.100.1.1=20016  
09412  
Date: 2016.02.01 10:59:44 -0500

Thao M. Vu, R.Ph

Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**From:** Nguyen, Thuy M  
**To:** "[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)"; "[VRS Secure](#)"  
**Cc:** "[Nagle.Kathy.K.Nagle@blueearthdx.com](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)"  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Statistical Information Request - 01/28/16 / Spon"s REVISED - Stat Response - Jan 27 / FDA Stat IR, 01/12/16 / re: submission dated 09/28/15  
**Date:** Thursday, January 28, 2016 1:06:00 PM  
**Attachments:** [1-11-3\\_001X\\_Stats\\_v4\\_FINAL.pdf](#)  
[BED001\\_FDA\\_Dataset\\_Request\\_Tables\\_1\\_2.xpt](#)  
[BED001\\_FDA\\_Dataset\\_Request\\_Tables\\_3ad.xpt](#)  
[BED001\\_FDA\\_Dataset\\_Request\\_\(Tables\\_1-2\).xlsx](#)  
[BED001\\_FDA\\_Dataset\\_Request\\_\(Tables\\_3a-d\).xlsx](#)  
[NDA\\_208054\\_STAT\\_IR\\_011216.pdf](#)

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Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin, Sponsor's Statistical Response dated 01/27/16, please find below the **FDA Statistical Clarification Information Request (IR) – January 28, 2016**

**Dr. Anthony Mucci, the FDA Statistical Reviewer has a problem with the Sponsor's data set ADLES3 (this is what the Sponsor has sent per FDA Statistical Request).**

**The NDA submission (Study Report for R01 page 54 of 74, among other places) lists 371 lesions with histology.**

**But, the data set ADLES3 lists only 210 lesions (105 for the variable BH, 105 for the variable EH).**

**The FDA Statistical Information Request, 01/12/16, specified that BH should cover all prostate/bed lesions with histology, while EH should cover all other lesions with histology.**

**It is possible that EH was interpreted as strictly extra-prostatic instead of all other lesions, although the FDA Statistical Information Request clearly specified that EH include all lesions with histology outside the prostate/bed.**

**For the above request, if needed, the Sponsor may contact directly Dr. Mucci: Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov) / Office: (301) 796-1720.**

**By 12:00 p.m., EST – Friday, January 29, 2016. please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.**

**Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.**

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

---

**From:** Nguyen, Thuy M

**Sent:** Wednesday, January 27, 2016 1:56 PM

**To:** Michelle.Wilson@vrsmail.com; 'VRS Secure'

**Cc:** Nagle, Kathy (K.Nagle@blueearthdx.com)

**Subject:** Dr. Wilson: NDA 208054 / Axumin: Spon's REVISED - Stat Response - Jan 27 / FDA Statistical Information Request - 01/12/16 / re: submission dated 09/28/15

Dear Dr. Wilson,

Thank you for the attached – “REVISED” Stat Response, 01/27/16.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: 301-796-1427

**From:** VRS Secure [[mailto:vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)]

**Sent:** Wednesday, January 27, 2016 1:51 PM

**To:** Nguyen, Thuy M

**Cc:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); Nagle, Kathy ([K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com))

**Subject:** Re: Dr. Wilson: NDA 208054 / Axumin: Spon's Stat Response - 01/27/16 / FDA Statistical Information Request - 01/12/16 / re: submission dated 09/28/15

Dear Thuy,

We discovered that the previous SAS file didn't open properly. Attached please find a revised SAS file for Tables 1-2, a SAS file for Tables 3a-3d, 2 Excel Sheets that match the 2 SAS files and a slightly revised 1.11.3 Clinical Information Amendment that contains BED's responses. All the attached documents except for the Excel Sheets will be submitted to NDA 208054 as amendment 0016.

Our apologies for any confusion and inconvenience.

Best wishes,

**Michelle**

Michelle Wilson, Ph.D.

Expert Regulatory Strategist

Virtual Regulatory Solutions, Inc.

[michelle.wilson@vrsmail.com](mailto:michelle.wilson@vrsmail.com)

[www.VirtualRegulatorySolutions.com](http://www.VirtualRegulatorySolutions.com)

(c) 513-578-5671

On Wed, Jan 27, 2016 at 9:44 AM, Nguyen, Thuy M <[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)> wrote:

Dear Dr. Wilson (for Sponsor – BED),

Thank you for the attached Sponsor's Statistical Response – 01/27/16.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: [301-796-1427](tel:301-796-1427)

**From:** VRS Secure [mailto:[vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)]  
**Sent:** Wednesday, January 27, 2016 6:48 AM  
**To:** Nguyen, Thuy M  
**Cc:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); Nagle, Kathy ([K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com))  
**Subject:** Re: Dr. Wilson: NDA 208054 / Axumin: re - your email, 01/22/16 / FDA Statistical Information Request - 01/12/16 / re: submission dated 09/28/15

Dear Thuy,

Please find attached BED's responses to the Stats IR dated 22 January 2016. Except for the Excel sheet, the attached responses will be formally submitted to NDA 208054. Please let me know what questions you have.

Best wishes,

***Michelle***

Michelle Wilson, Ph.D.  
Expert Regulatory Strategist  
Virtual Regulatory Solutions, Inc.  
[michelle.wilson@vrsmail.com](mailto:michelle.wilson@vrsmail.com)  
[www.VirtualRegulatorySolutions.com](http://www.VirtualRegulatorySolutions.com)  
(c) [513-578-5671](tel:513-578-5671)

On Fri, Jan 22, 2016 at 2:08 PM, Nguyen, Thuy M <[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)> wrote:  
Dear Dr. Wilson (for Sponsor – BED),

Thank you for your email, 01/22/16, which I will convey to the FDA review team regarding BED delayed / pending statistical response by January 28, 2016 (instead of the original response expected date of 01/22/16).

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: [\(301\) 796-1427](tel:301-796-1427)

**From:** VRS Secure [[mailto:vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)]  
**Sent:** Friday, January 22, 2016 1:19 PM  
**To:** Nguyen, Thuy M  
**Cc:** Nagle, Kathy  
**Subject:** NDA 208054 12 January 2016 Stats IR

Dear Thuy,

Despite BED's best efforts, the response to the Stats IR dated 12 January 2016 expected 22 January 2016, will instead be emailed to FDA on Thursday, 28 January 2016 and then submitted formally to NDA 208054. BED is appreciative of the clarifications received today from Dr. Mucci.

Thank you very much. And stay safe in the pending blizzard!

Best wishes,

**Michelle**

Michelle Wilson, Ph.D.  
Expert Regulatory Strategist  
Virtual Regulatory Solutions, Inc.  
[michelle.wilson@vrsmail.com](mailto:michelle.wilson@vrsmail.com)  
[www.VirtualRegulatorySolutions.com](http://www.VirtualRegulatorySolutions.com)  
(c) [513-578-5671](tel:513-578-5671)

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Virtual Regulatory Solutions, Inc.



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**From:** Nguyen, Thuy M  
**Sent:** Tuesday, January 12, 2016 3:47 PM  
**To:** '[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)'; 'VRS Secure'  
**Cc:** 'Nagle, Kathy ([K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com))'  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Statistical Information Request - 01/12/16 / re: submission dated 09/28/15

Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – January 12, 2016.**

Dr. Anthony (Tony) Mucci, FDA Statistical Reviewer, has modified the FDA Statistical Information Request, 01/12/16 (attached), to reflect and clarify points raised during yesterday's teleconference (TCON), 01/11/16.

Dr. Mucci is available for a teleconference or email discussion regarding statistical-only.

If needed, please contact directly Dr. Mucci to schedule a statistical-only teleconference:  
Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov) / Office: [\(301\) 796-1720](tel:(301)796-1720).

Following each statistical TCON / email discussion(s) that BED may have with Dr. Mucci, please email to Dr. Mucci (Email: [Anthony.Mucci@fda.hhs.gov](mailto:Anthony.Mucci@fda.hhs.gov)) and to my attention (Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)) a summary / meeting minutes of the TCON / email discussion(s) and follow up with formal official submissions to the FDA.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

**By 12:00 p.m., EST – Friday, January 22, 2016.** please provide a response via email to my attention at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: [\(301\) 796-1427](tel:(301)796-1427)

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/s/  
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THUY M NGUYEN  
01/28/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Clinical & PK Information Request - 01/15/16 / re: submission dated 09/28/15  
**Date:** Friday, January 15, 2016 4:54:00 PM  
**Attachments:** [NDA 208054 CLIN and PK IR 011516.pdf](#)

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached the **FDA Clinical and Clinical Pharmacology (PK) Information Request – January 15, 2016.**

**By 12:00 p.m., US EST – Tuesday, January 19, 2016.** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

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If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

Office: (513) 758-5671

Spon Rep: Ms. Kathy Nagle / Email: [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

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If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**Page 2**

**FDA Clinical Information Request – January 15, 2016:**

1. We note in the original Emory paper, 93 out of 115 subjects met study inclusion criteria and were included in the analysis. In the BED001 study, 99 subjects (105 scans) out of the 115 were included in the analysis. Please clarify the source of the additional 6 subjects in the BED001 analysis. Did the additional 6 subjects in the BED001 analysis include the 5 subjects from the original study who did not undergo Prostatecint scanning?
2. In the BED001 study, 99 subjects provided 105 scan results. Please clarify the timing of the repeat Fluciclovine PET scans in these 6 subjects who underwent two scans.
3. The study report states that to be enrolled in study BED001, subjects had to have previous negative bone scans. Please clarify if other conventional imaging results were also negative in these subjects when performed prior to Fluciclovine PET scans (not as a part of follow up).
4. For subjects who underwent prostate bed biopsies, please clarify when the biopsies were performed with respect to Fluciclovine scanning.
5. The original Emory paper states that PET/CT scanning was performed at three different time points: early, delay 1 and delay 2. Please clarify which scanning time point was used for the primary analysis in both the original Emory paper and the BED001 study.
6. In the original Bologna study paper, it is stated that “No patients had a positive 11C-Choline scan with a negative 18F-Fluciclovine scan”. However, in the BED001 and BED002 analyses, there appear to be five and eight subjects, respectively, positive for 11C-Choline and negative for 18F-Fluciclovine. Please clarify this discrepancy.
7. In the Emory study publication, the radioactive dose of Fluciclovine is stated as 161.7 to 484.7 MBq (approximately 4.3 to 13.1 mCi). Please provide the average and median dose, as well as the radioactive dose for each enrolled subject if available.

**FDA Clinical Pharmacology (PK) Information Request – January 15, 2016:**

8. In your response of December 4, 2015 to the FDA Filing Letter of November 25, 2015, you wrote, “ ... attempted to collect data on administered chemical dose during the study, but as it was a retrospective data collection, information was not uniformly available for all patients. Note that, for Emory University, the chemical concentration of the drug product was not measured, and therefore, although the volume of fluciclovine administration was specified in the CRF, the equivalent chemical dose cannot be determined.” While mass dose would be of value, our request had the primary intent of obtaining radioactivity doses.

In the submission you write, “Dosing data are in the SDTM dataset EX.XPT and ADaM dataset ADEX.XPT in BED001.” Upon opening files EX.XPT and ADEX.XPT we learned that doses administered are not present. Please include the radioactivity dose data in files EX.XPT and ADEX.XPT and re-submit them, or provide alternative files with radioactivity dose data.

9. Please provide a graph of sensitivity vs. dose (radioactivity administered) at the patient level. We envision approximately 105 data points where the y-value for each point will be the % of lesions within the patient that were detected and positive by pathology. We are open to additional presentations or analyses.

10. Please provide a table of sensitivity vs. dose at the lesion level. We envision bin-ing approximately 371 lesions according to the dose the patient received and reporting the % of lesions within the bin that were both detected and positive by pathology. We are open to additional presentations or analyses.

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/s/  
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THUY M NGUYEN  
01/15/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle_Kathy_(K.Nagle@blueearthdx.com))  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Clinical Pharm (PK) Information Request - 01/15/16 / re: submission dated 09/28/15  
**Date:** Friday, January 15, 2016 5:19:00 PM

---

Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find below the **FDA Clinical Pharmacology (PK) Information Request – January 15, 2016:**

**1. As discussed during the Mid-Cycle teleconference, 01/13/16, please provide what is known**

**regarding administration with a high protein meal. We appreciate that clinical data with administration**

**shortly after food may not be available. Thus, you may have to respond to this request based on a**

**first principle approach using existing literature and in vitro studies.**

**By 12:00 p.m., US EST – Tuesday, January 19, 2016,** please provide a response via email to

my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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/s/  
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THUY M NGUYEN  
01/15/2016



NDA 208054

INFORMATION REQUEST

Blue Earth Diagnostic Ltd.  
Attention: Michelle Wilson, Ph.D.  
Expert Regulatory Consultant  
118 Palm Springs Drive  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin™(Fluciclovine F-18), 335 to 8200 MBq/ml or 9 to 221 mCi/ml, multi-dose vial for injection.

We also refer to your January 11, 2016 submission in reponse to our December 23, 2015 Information Request letter.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by January 20, 2016, in order to continue our evaluation of your NDA.

1. Per 3.2.P.5.4 of your submission for NDA 208054 Axumin, Batch Analyses of Fluciclovine (18F), solution for injection was carried out in USP Type 1 glass vials of 30 mL and smaller volumes. However, the (b) (4) (b) (4) (b) (4) Provide your justification of not using the same vial for the leak test. Also clarify whether an identical stopper was used for the leak test. Will the (b) (4) vial be used for commercial manufacturing? If so, we expect media fill to be performed using the (b) (4) vial (b) (4) Provide the inner neck diameter specifications of both vials.
2. Provide any updated stability data for the precursor to support the proposed (b) (4) month retest period.

If you have any questions, please contact me, at (240) 402-2690.

Sincerely,

Thao M.  
Vu -A

Digitally signed by Thao M. Vu -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Thao M. Vu -A,  
0.9.2342.19200300.100.1.1=2001  
699412  
Date: 2016.01.14 12:22:45 -05'00'

Thao M. Vu, R.Ph  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

**CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)**

**TYPE C MID-CYCLE TELECONFERENCE MINUTES**

**NDA:** 208054  
**DRUG NAME:** Axumin [F-18] Fluciclovine  
**SPONSOR:** Blue Earth Diagnostics, LTD (BED)  
**DATE:** Wednesday, January 13, 2016

**SPONSOR PARTICIPANTS:**

Jonathan Allis, Ph.D., Chief Executive Officer, BED  
David Gauden, Ph.D., Head of Development, BED  
Caroline Hardwicke, Head of Clinical Operations, BED  
Mike Heslop, President, BED  
Lisa Jenkins, Ph.D., Vice President, Regulatory Strategy and Content Development, VRS  
Matthew Miller, Ph.D. Head of Imaging, BED

(b) (4)

Katharine Nagle, Ph.D., Head of CMC & QA, BED  
Penny Ward, MBBS, FFPM, Chief Medical Officer, BED  
Michelle Wilson, Ph.D., Expert Regulatory Strategist, VRS

**FDA PARTICIPANTS:**

Danae Christodoulou, Ph.D., Chemistry Branch Chief  
Phillip Davis, M.D., Clinical Reviewer  
Charles Ganley, M.D., Office Director  
Marc Goldstein, PDUFA Contractor, Eastern Research Group  
Alex Gorovets, M.D., Deputy Division Director  
Jagjit Grewal, Office Associate Director of Regulatory Affairs  
Christy John, Ph.D., Clinical Pharmacology Reviewer  
Kaye Kang, Pharm.D., Chief, Project Management Staff  
Ravi Kasliwal, Ph.D., Chemistry Reviewer  
Ira Krefting, M.D., Safety Associate Director  
Eldon Leutzinger, Ph.D., Chemistry Team Leader  
Lou Marzella, M.D., Ph.D., Division Director  
Tony Mucci, Ph.D., Statistical Reviewer  
Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager  
Yanli Ouyang, Ph.D., Pharm/Tox Reviewer  
Benjamin Stevens, Ph.D., CMC – Drug Substance Reviewer  
Nushin Todd, M.D., Clinical Team Leader  
Thao Vu, R.Ph., CMC Project Manager  
Jesse Wells, Ph.D., Microbiology Team Leader  
Gene Williams, Ph.D., Clinical Pharmacology Reviewer  
Tony Wilson, Ph.D., CMC – Facility Reviewer

**CONFIDENTIAL**

**NDA 208054: Axumin [F-18] Fluciclovine**

**Page 2**

**AGENDA: Regarding the NDA 505(b)(1) submission dated September 28, 2015, to provide the Sponsor with the FDA mid-cycle review status.**

**FDA Review Status**

**-CMC:** The FDA acknowledged the Sponsor's CMC Response to the FDA CMC Information Request (IR) dated 12/23/15. The review is ongoing.

**-Microbiology:** The review is ongoing. Forthcoming FDA IR regarding one of facility site (after further internal FDA discussion).

**-Facility:** The inspections are ongoing.

**-Pharmacology/Toxicology:** The review is ongoing. No concerns at this time.

**-Clinical Pharmacology (PK):** The review is ongoing. Forthcoming FDA IR regarding Axumin administered with high protein meal.

**-Clinical:** The review is ongoing. No significant safety issues at this time. However, the FDA stated the challenge will be on how to describe the statistical data which will not be like the data reflected in the Sponsor's proposed draft labeling (version - December 4, 2015). Forthcoming FDA IR regarding the subject deposition in Studies BED001 and BED002; clarification on scan times used in the efficacy analysis of the Emory data; how data was reported for the Bologna study vs re-analysis; and the dose-data per patient in the Emory study.

**Statistical:** Regarding the FDA Statistical Information Request dated 01/12/16, the Sponsor anticipates providing a response by the FDA requested date of January 22, 2016. Forthcoming FDA IR regarding the statistical tables.

**Upcoming Milestone Dates**

-The FDA will forward via email to the Sponsor the FDA Late-Cycle Background Package by March 7, 2016.

-The Late-Cycle Teleconference is scheduled for March 21, 2016 at 12:00 – 1:30 pm, US EST, to provide the Sponsor with the FDA review status.

-PDUFA priority 8-month due date: May 27, 2016.

**Meeting Minutes Recorded By: T.Nguyen, DMIP**

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/s/  
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THUY M NGUYEN  
02/02/2016

**From:** Nguyen, Thuy M  
**To:** "[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)"; "[VRS Secure](#)"  
**Cc:** "[Nagle.Kathy.K.Nagle@blueearthdx.com](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)"  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Statistical Information Request - 01/12/16 / re: submission dated 09/28/15  
**Date:** Tuesday, January 12, 2016 3:46:00 PM  
**Attachments:** [NDA\\_208054\\_STAT\\_IR\\_011216.pdf](#)

---

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to reflect and clarify points raised during yesterday's teleconference (TCON), 01/11/16.

Dr. Mucci is available for a teleconference or email discussion regarding statistical-only.

If needed, please contact directly Dr. Mucci to schedule a statistical-only teleconference:

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a summary / meeting minutes of the TCON / email discussion(s) and follow up with formal official submissions to the FDA.

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If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

**Spon Rep:** Ms. Kathy Nagle / **Email:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

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If you have any questions, please contact me.

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US FDA CDER - Division of Medical Imaging Products  
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Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 12, 2016:**

This FDA Statistical Information Request, 01/12/16, is an updated version of the previous FDA Statistical Information Requests (dated 12/28/15 & 01/05/16).

Dr. Anthony (Tony) Mucci, FDA Statistical Reviewer, has modified the FDA Statistical Information Request, 01/12/16 (attached below), to reflect and clarify points raised during yesterday's teleconference (TCON), 01/11/16.

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Please note that this current request focuses on BED001 Emory data only, and only on the On-Site reads and the Histology results. It is possible that the Reviewer may need additional tables later on (Tables, not data sets) related to BED002 data, especially with regard to blinded reads.

As before:

- (1): A question needs to be addressed by the Sponsor.
- (2): A user-friendly data set is required (described below in detail).
- (3): Several tables are required (described below in detail).

**Question**

The primary concern is with the meaning to be attached to Agreement at a Region Level. Note here that the Agency is in agreement that two regions suffice, namely:

Region(1): Prostate/Prostate bed

Region(2): Everything else for which data is available

To fix the concern, we'll focus on PB = Prostate/Prostate Bed, and on the On-Site versus Truth concordances.

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 12, 2016 (cont.):**

We will also focus on subjects with histology results:

So:

Let Truth, for a given subject, determine that a lesion detected in the Prostate Region has Positive Histology.

The FDA Statistical Reviewer’s understanding is that if Fluciclovine makes no detections in the Region, then Fluciclovine registers a False Negative.

However, what constitutes a True Positive?

Two possibilities:

- (a): Fluciclovine detects lesions in the Region ( could all be histology Negative)
- (b): Fluciclovine detects a histologically validated Positive lesion

**Requested Data Set for NDA 208054: Fluciclovine**

**Data from BED001 (Emory Data for Recurrence Subjects Only)**

**First: Identifier Variables**

**SUB** = Subject Identifier

**RACE; AGE** = Race and Age variables

**TREAT**: Treatment for original disease occurrence. This could be Prostatectomy, Radiation, etc.  
The Sponsor can decide on the categories, but the fewer the better.

**Next: Diagnostic Variables**

Here the variables will be per Subject. That is, each subject will determine a single line of entries. The notation for each variable will begin with a “Region” identifier:

B for the Prostate/Prostate Bed ; E for everything else.

**Variables:**

**For B**

**BH** = # B Region lesions detected by any Modality and which have Histology (+/-)

**BHP** = # Among the BH that are Histology Positive

**BF** = # Lesions among the BH that were detected by Fluciclovine

**BFP** = # Among the BF that are Histology Positive

**For E**

**EH** = # E Region Lesions detected by any Modality and which have Histology (+/-)

**EHP** = # Among the EH that are Histology Positive

**EF** = # Lesions among the EH that were detected by Fluciclovine

**EFP** = # Lesions among the EF that were detected by Fluciclovine

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 12, 2016 (cont.):**

**Final Variables:**

The Reviewer’s assumption is that all subjects are presumed Positive, so that there needs to be a Default diagnosis in the following cases:

- (a): All detected lesions are Histology Negative
- (b): No lesions are detected

Let

**DF** = 1 if (a) or (b) occurs ; = 0 otherwise

**DS** = Source of Positive Diagnosis if DF=1 ; = 0 otherwise

**DR** = Region to which the Positivity is defaulted, if DF = 1; = 0 otherwise

**Requested Tables**

**Table#1:**

**Distribution of Profile of Lesion Detections (Entries are # Subjects)**

The intention here is to gather Subject Level profiles of distributions of lesion detections both for all image types and for Fluciclovine Images in particular, under restrictions on the lesion status with respect to Histology.

“Lesions With Histology” means only lesions that have Histology results

“Lesions with Histology = +” means only lesions with Positive Histology

	<b>Lesions with Histology</b>		<b>Lesions with Histology = +</b>	
	<b>All Images</b>	<b>F Images</b>	<b>All Images</b>	<b>F Images</b>
<b>B =0, E = 0</b>				
<b>B =0, E = 1</b>				
<b>B =0, E&gt;1</b>				
<b>B =1, E = 0</b>				
<b>B =1, E = 1</b>				
<b>B =1, E&gt;1</b>	<b>NH(1, &gt;1)</b>			<b>NF+(1, &gt;1)</b>
<b>B &gt;1, E = 0</b>				
<b>B &gt;1, E = 1</b>				
<b>B &gt;1, E&gt;1</b>				

**Note: B = Prostate/Prostate Bed ; E = All other Regions**

**Meaning of Categories and Entries**

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 12, 2016 (cont.):**

**NH(1, >1):** Number of Subjects with exactly one detection in B and more than one detection in E (over all histology lesions, all Image types)

**NF+(1, >1):** Number of subjects with exactly one detection in B, but at least two detections in E ( restricted to lesions with Positive Histology, and restricted to Fluciclovine Image reads)

**Table#2: Statistical Profile on # Detected Lesions by Location/Image Type/Histology**

	Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images
<b>B</b>				
Mean		<b>( B, F )</b>		
Sigma				
Median				
Max				
Min				
<b>E</b>				
Mean			<b>(E, All)</b>	
Sigma				
Median				
Max				
Min				

Note: B = Prostate/Prostate Bed ; E = All other Regions

$$(\mathbf{B}, \mathbf{F}) = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions in Subject K ( among N Subjects )}$$

when the Region is B, and the Image Type is Fluciclovine

$$(\mathbf{All}, \mathbf{E}, +) = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions with Positive Histology in Subject K}$$

(among N Subjects ) when the Region is E, and the Image Type is All

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 12, 2016 (cont.):**

**Tables for Lesion Detections Fluciclovine versus Other Images  
(Six Tables) Lesion Level**

**Meaning of Entries: ( Holds for all Tables)**

**L(Y,Y) = # Lesions detected by both OTHER and Fluciclovine**

**L(N,Y) = # Lesions not detected by OTHER, but by Fluciclovine**

**L(Y,N) = # Lesions detected by OTHER, but not by Fluciclovine**

**Table(1) (Lesions with Histology/Prostate/Prostatic Bed)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>	<b>L(Y,Y)</b>	<b>L(Y,N)</b>	
<b>OTHER = N</b>	<b>L(N,Y)</b>		

**Table(2) (Lesions with Histology/Elsewhere)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

**Table(3) (Lesions with Positive Histology/Prostate/Prostatic Bed)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

**Table(4) (Lesions with Positive Histology/Elsewhere)**

	<b>F = Y</b>	<b>F = N</b>	
<b>OTHER = Y</b>			
<b>OTHER = N</b>			

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/s/  
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THUY M NGUYEN  
01/12/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Pharm/Tox Information Request - 01/08/16 / re: submission dated 09/28/15  
**Date:** Friday, January 08, 2016 11:10:00 AM  
**Attachments:** [NDA\\_208054\\_PT\\_IR\\_010816.pdf](#)

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Dear Dr. Wilson (for Sponsor – Blue Earth Diagnostics [BED]),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached below the FDA Pharmacology / Toxicology Information Request – January 8, 2016.

By 9:00 am, EST – Monday, January 11, 2016, please provide a response via email to

my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

**Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),**

**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

**Spon Rep:** Ms. Kathy Nagle / **Email:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find attached below the **FDA Pharmacology / Toxicology Information Request – January 8, 2016.**

**By 9:00 am, EST – Monday, January 11, 2016,** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

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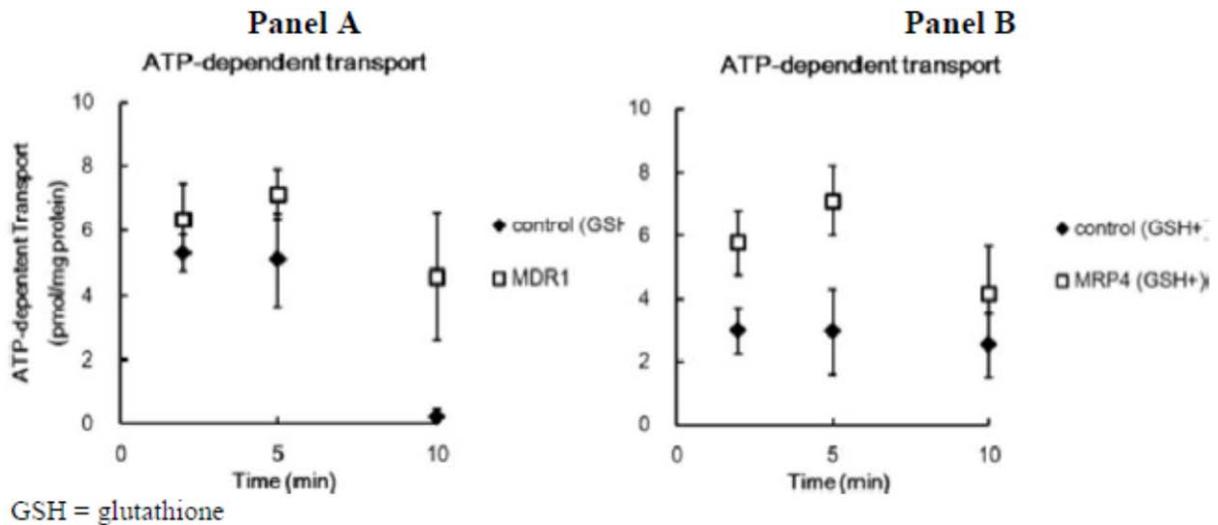
If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Pharmacology / Toxicology Information Request – January 8, 2016:**

In your study report for Study No. RPT- DEV-002, titled “To investigate potential secondary pharmacological effects of fluciclovine”, we noted an apparent discrepancy between your Figure 5.1.1.1 and text. The text stated “an MDR1-mediated uptake value of 1.1 pmol/mg protein at 2 minutes. For MRP4 a difference in the ATP-dependent uptake by MRP4- expressing vesicles compared with the negative control was observed at earlier time-points, such that the MRP4-mediated uptake was 2.8 and 4.1 pmol/mg protein at 2 and 5 minutes, respectively.” However, the values appear higher in Figure 5.1.1.1 (see below). Please explain the reason for this discrepancy and also provide the study data to clarify the discrepancy.



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/s/  
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THUY M NGUYEN  
01/08/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)  
**Subject:** Dr. Wilson: NDA 208054 /Axumin: FDA Statistical Information Request - 01/08/16 / re: submission dated 09/28/15  
**Date:** Friday, January 08, 2016 2:20:00 PM

---

Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

FDA Statistical Information Requests of December 28, 2015 and January 5, 2016, and

BED Partial Statistical Response dated January 6, 2016, below are the

**FDA Statistical Comments / Information Request – January 8, 2016:**

**The FDA Statistical Reviewer interprets the Sponsor’s partial statistical response dated 01/06/16, to the FDA Statistical Information Request of 01/05/16,**

**to mean that the expanded datasets might require more time to create than those initially proposed in December 2015**

**(the Sponsor’s proposed response date was to be January 22, 2016).**

**As this NDA is a Priority NDA with a limited review cycle, a later date is not practical.**

**Therefore, in the interests of time, the FDA Statistical Reviewer is willing to limit the request to the form originally proposed.**

**Provide a response by January 22, 2016.**

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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/s/  
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THUY M NGUYEN  
01/08/2016

**From:** Nguyen, Thuy M  
**To:** "[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)"; "[VRS Secure](#)"  
**Cc:** "[Nagle.Kathy.K.Nagle@blueearthdx.com](mailto:Nagle.Kathy.K.Nagle@blueearthdx.com)"  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Statistical Information Request - 01/05/16 / re: submission dated 09/28/15  
**Date:** Tuesday, January 05, 2016 12:18:00 PM  
**Attachments:** [NDA\\_208054\\_STAT\\_IR\\_010516.pdf](#)

---

Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find below the **FDA Statistical Information Request – January 5, 2016.**

This request is an updated version of the previous FDA Statistical Information Request dated 12/28/15.

The Sponsor stated that response on the FDA Statistical Information Request dated 12/28/15, would not begin before January 4, 2016.

In the interim, the FDA Statistical Reviewer has determined that a slightly amplified data set would be appropriate; the change consists strictly

in the addition of several variables to the data set. The FDA Statistical Reviewer is available for discussion per content and feasibility.

Note: All amended / revised protocol, consent form or other revised document should be

submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

**By 12:00 p.m., EST – January 22, 2016.** please provide a response via email to my attention:  
[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov).

and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me.

Sincerely,

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**Dear Dr. Michelle Wilson, Ph.D. (for Sponsor – Blue Earth Diagnostics [BED]),**

**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

**Spon Rep:** Ms. Kathy Nagle / **Email:** [K.Nagle@blueearthdx.com](mailto:K.Nagle@blueearthdx.com)

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – January 5, 2016.**

This request is an updated version of the previous FDA Statistical Information Request dated 12/28/15. The Sponsor stated that response on the FDA Statistical Information Request dated 12/28/15, would not begin before January 4, 2016. In the interim, the FDA Statistical Reviewer has determined that a slightly amplified data set would be appropriate; the change consists strictly in the addition of several variables to the data set. The FDA Statistical Reviewer is available for discussion per content and feasibility.

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**By 12:00 p.m., EST – January 22, 2016,** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov), and follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me.

Sincerely,  
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Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016:**

The FDA Statistical Reviewer has determined that in order to both validate and explore the data and the results provided in NDA208054:

Preliminary Comment: This note is an updated version of the previous request. The changes consist largely of additions of variables to the requested data set. The FDA Statistical Reviewer is available for any responses/questions the Sponsor may have.

Please note that this current request focuses on BED001 Emory data only. It is possible that the FDA Statistical Reviewer may need additional tables later on related to BED002 data, especially with regard to blinded reads.

To proceed:

- (1): Several questions need to be addressed by the Sponsor.
- (2): A user-friendly data set is required ( described below in detail).
- (3): Several tables are required (described below in detail).

**Questions**

The primary concern is with the meaning to be attached to Agreement at a Region Level (Three Regions: Prostate/Prostate Bed ; Lymph Node ; Extra-Prostatic )  
To fix the concern, we'll focus first on PB = Prostate/Prostate Bed, and on two Blinded readers, say R1 = Blinded Reader1 and R2 = Blinded Reader2:

(a): Let R1 have a list of detected lesions  $X_1, X_2, \dots, X_K$ , while R2 has a list  $Y_1, Y_2, \dots, Y_J$   
Do we conclude that there is Agreement between R1 and R2 at Region Level in that both detected at least one lesion in PB, or is it required that they detected at least one common lesion?

Then, for Diagnostics:

Let R1 = Blinder Reader1, while R2 = Truth Read for PB.

Assume R2 yields outcome =1 in the sense that the some lesion detected by some modality in the Region PB was histology Positive.

What is required in order that the R1 read yield a True Positive for PB:

Is it required only that R1 make a detection in PB (not necessarily a Histology Positive lesion? )

Or:

Is it required that R1 detect a lesion that is histology Positive?

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016 (cont.):**

**Requested Data Set for NDA 208054 Fluciclovine**

**Data from BED001 (Emory Data for Recurrence Subjects Only)**

**First: Identifier Variables**

**SUB** = Subject Identifier

**RACE; AGE** = Race and Age variables

**TREAT:** Treatment for original disease occurrence. This could be Prostatectomy, Radiation, etc.  
The Sponsor can decide on the categories, but the fewer the better.

**Next: Diagnostic Variables**

Here the variables will be per Subject. That is, each subject will determine a single line of entries. The notation for each variable will begin with a “Region” identifier:

B for the Prostate/Prostate Bed ; N for the Pelvic Node area ; E for Extra-Prostatic

**Variables:**

**For B = Prostate/Prostate Bed**

**BD** = # B Region lesions detected by any Modality

**BL** = # B Region lesions detected by any Modality and which have Histology (+/-)

**BLP** = # Among the BL that are Histology Positive

**BF** = # Lesions among the BD that were detected by Fluciclovine

**BLF** = # Lesions among the BL that were detected by Fluciclovine

**BLFP** = # Among the BLF that are Histology Positive

**BC** = # Lesions among the BD that were detected by ProstaScint

**BLC** = # Lesions among the BL that were detected by ProstaScint

**BLCP** = # Among the BLC that are Histology Positive

**For N = Pelvic node Region**

**ND** = # N Region Lesions detected by any Modality

**NL** = # N Region Lesions detected by any Modality and which have Histology (+/-)

**NLP** = # Among the NL that are Histology Positive

**NF** = # Lesions among the ND that were detected by Fluciclovine

**NLF** = # Lesions among the NL that were detected by Fluciclovine

**NLFP** = # Among the NLF that are Histology Positive

**NC** = # Lesions among the ND that were detected by ProstaScint

**NLC** = # Lesions among the NL that were detected by ProstaScint

**NLCP** = # Among the NLC that are Histology Positive

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016 (cont.):**

**For E = Extra Prostatic Region**

**ED**= # E Region Lesions detected by any Modality

**EL** = # E Region Lesions detected by any Modality and which have Histology (+/-)

**ELP** = # Among the EL that are Histology Positive

**EF** = # Lesions among the ED that were detected by Fluciclovine

**ELF** = # Lesions among the EL that were detected by Fluciclovine

**ELFP** = # Among the ELF that are Histology Positive

**EC** = # Lesions among the ED that were detected by ProstaScint

**ELC** = # Lesions among the EL that were detected by ProstaScint

**ELCP** = # Among the ELC that are Histology Positive

**Final Variables:**

The final variables are dedicated to diagnoses for which the entries above are inadequate, under the assumption that each subject is recurrent for cancer:

**DF** = 1 if variables above do not clearly provide at least one diseased region ; = 0 otherwise

**DS** = Source of Positive Diagnosis when DF=1 ( Follow-Up, Rising PSA , Detection of lesion by modalities other than F-18, but without Histology verification or Histology Positivity, etc.)

**DR** = Region to which the Positivity Default is allocated

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016 (cont.):**

**Requested Tables**

**Table #1: Distribution of Profile of Lesion Detections (Entries are # Subjects)**

The intention here is to gather Subject Level profiles of distributions of lesion detections both or all image types and for Fluciclovine Images in particular, under restrictions on the lesion status with respect to Histology

“All Lesions” means with or without Histology

“Lesions With Histology” means only lesions that have Histology results

“Lesions with Histology = +” means only lesions with Positive Histology

	All Lesions		Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images	All Images	F Images
<b>B =0, E = 0</b>						
<b>B =0, E = 1</b>						
<b>B =0, E&gt;1</b>						
<b>B =1, E = 0</b>			<b>NHA(1,0)</b>			
<b>B =1, E = 1</b>						
<b>B =1, E&gt;1</b>	<b>NA(1, &gt;1)</b>					<b>NF+(1, &gt;1)</b>
<b>B &gt;1, E = 0</b>						
<b>B &gt;1, E = 1</b>						
<b>B &gt;1, E&gt;1</b>		<b>NF(&gt;1,&gt;1)</b>				

Note: B = Prostate/Prostate Bed ; E = All other Regions

**Meaning of Categories and Entries**

**NA(1, >1)**: Number of Subjects with exactly one detection in B and more than one detection in E (over all lesions, all Image types)

**NF(>1,>1)**: Number of Subjects with at least two detections in B and at least two detections in E (over all lesions, but restricted to Fluciclovine Images)

**NHA(1, 0)**: Number of Subjects with exactly one detection in B and no detections in E (restricted to lesions with histology, but over all Image types)

**NF+(1, >1)**: Number of subjects with exactly one detection in B, but at least two detections in E ( restricted to lesions with Positive Histology, and restricted to Fluciclovine Image reads)

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016 (cont.):**

**Table#2: Statistical Profile on # Detected Lesions by Location/Image Type/Histology**

	All Lesions		Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images	All Images	F Images
<b>B</b>						
Mean						
Sigma						
Median						
Max						
Min						
<b>E</b>						
Mean						
Sigma						
Median						
Max						
Min						

Note: B = Prostate/Prostate Bed ; E = All other Regions

$$\text{Mean(All, B, F)} = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions in Subject K ( among N Subjects )}$$

when the Region is B, the Image Type is Fluciclovine, and the range is over all lesions

$$\text{Mean (His=+, E, All Images)} = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions in Subject K ( among N}$$

Subjects ) when the Region is E, the Image Type is All, and the range is over all lesions with Positive Histology

**Tables for Lesion Detections Fluciclovine versus Other Images  
( Six Tables) Lesion Level**

**Meaning of Entries: ( Holds for all Tables)**

**L(Y,Y) = # Lesions detected by both OTHER and Fluciclovine**

**L(N,Y) = # Lesions not detected by OTHER, but by Fluciclovine**

**L(Y,N) = # Lesions detected by OTHER, but not by Fluciclovine**

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – January 5, 2016 (cont.):**

**Table(3,1) (All Lesions/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>	<b>L(Y,Y)</b>	<b>L(Y,N)</b>	
<b>OTHER = No</b>	<b>L(N,Y)</b>		

**Table(3,2) (All Lesions/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table(3,3) (Lesions with Histology/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table(3,4) (Lesions with Histology/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table(3,5) (Lesions with Positive Histology/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table(3,6) (Lesions with Positive Histology/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

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/s/  
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THUY M NGUYEN  
01/05/2016

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Nagle, Kathy \(K.Nagle@blueearthdx.com\)](mailto:Nagle.Kathy(K.Nagle@blueearthdx.com)); [Lutterodt, Frank A](#)  
**Subject:** Dr. Wilson: NDA 208054 / Axumin: FDA Statistical Information Request - 12/28/15 / re: submission dated 09/28/15  
**Date:** Monday, December 28, 2015 10:58:00 AM  
**Attachments:** [NDA\\_208054\\_STAT\\_IR\\_122815.pdf](#)

---

Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015,

please find attached the **FDA Statistical Information Request – December 28, 2015.**

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

**By 12:00 p.m., EST – Wednesday, December 30, 2015.** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

AND to Mr. Frank Lutterodt, Project Manager: [Frank.Lutterodt@fda.hhs.gov](mailto:Frank.Lutterodt@fda.hhs.gov) / Office: (301) 796-4251.

Mr. Lutterodt will be covering for me this week and he is included on this email.

And follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me and Mr. Lutterodt.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

Office: (301) 796-1427

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**Email:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [VRS\\_Secure@vrsmail.com](mailto:VRS_Secure@vrsmail.com)

**Office:** (513) 758-5671

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Regarding NDA 208054: Axumin [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – December 28, 2015.**

Note: All amended / revised protocol, consent form or other revised document should be submitted as an annotated version (with red-lined, track-changes) along with a clean revised version and a summary of changes.

**By 12:00 p.m., EST – Wednesday, December 30, 2015,** please provide a response via email to my attention: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) AND to Mr. Frank Lutterodt, Project Manager: [Frank.Lutterodt@fda.hhs.gov](mailto:Frank.Lutterodt@fda.hhs.gov) / Office: (301) 796-4251. Mr. Lutterodt will be covering for me this week.

And follow-up with a formal official response submission to the FDA via electronic submission ESG / Gateway.

If you have any questions, please contact me and Mr. Lutterodt.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015:**

In order to significantly expedite the priority review of NDA 208054, the FDA Statistical Reviewer is requesting a data set and several tables restricted to the Emory Study in BED001. The existing primary data sets are not user-friendly.

It is requested the information be provided **by 12:00 p.m., EST, Wednesday - December 30, 2015**; and the delivery date for the data set can be by 9:00 a.m., EST, Tuesday - January 5, 2016, if necessary.

If needed and upon your request, the FDA Statistical Reviewer will be available December 29 & 30, for a TCON to ensure that the various elements proper to the tables/data set are understood.

Additionally, the FDA Statistical Reviewer has several questions regarding the Blinded Reads from BED002:

In order to adequately determine the Performance of the blinded reads with respect to Truth, some form of co-location of lesion detections by these reads with those from the original reads would be necessary. Otherwise, there is no assurance that the blinded read detections are the same as the original detections. Were such co-locations established? If not, there would have to be some kind of default algorithm in place that would assert enough of an identity in region findings between blinded and original detections to allow for statistics involving concordances of blinded reads with Truth. Were such algorithms used? If so, what were they?

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015 (cont.):**

**Requested Data Set for NDA 208054**

**Data from BED001 (Emory Data for Recurrence Subjects Only)**

**First: Identifier Variables**

**SUB** = Subject Identifier

**RACE; AGE** = Race and Age variables

**TREAT**: Treatment for original disease occurrence. This could be Prostatectomy, Radiation, etc.  
The Sponsor can decide on the categories, but the fewer the better.

**Next: Diagnostic Variables**

Here the variables will be per Subject. That is, each subject will determine a single line of entries. The notation for each variable will begin with a “Region” identifier:

B for the Prostate/Prostate Bed; N for the Pelvic Node area; E for Extra-Prostatic

**Variables:**

**For B = Prostate/Prostate Bed**

**BL** = # B Region lesions detected by any Modality and which have Histology (+/-)

**BLP** = # Among the BL that are Histology Positive

**BLF** = # Lesions among the BL that were detected by Fluciclovine

**BLFP** = # Among the BLF that are Histology Positive

**For N = Pelvic node Region**

**NL** = # N Region Lesions detected by any Modality and which have Histology (+/-)

**NLP** = # Among the NL that are Histology Positive

**NLF** = # Lesions among the NL that were detected by Fluciclovine

**NLFP** = # Among the NLF that are Histology Positive

**For E = Extra Prostatic Region**

**EL** = # E Region Lesions detected by any Modality and which have Histology (+/-)

**ELP** = # Among the EL that are Histology Positive

**ELF** = # Lesions among the EL that were detected by Fluciclovine

**ELFP** = # Among the ELF that are Histology Positive

**Final Variables:**

The final variables are dedicated to diagnoses for which the entries above are inadequate, under the assumption that each subject is recurrent for cancer:

**DF** = 1 if variables above do not clearly provide at least one diseased region; = 0 otherwise

**DS** = Source of Positive Diagnosis when DF=1 (Follow-Up, Rising PSA, Detection of lesion by modalities other than F-18, but without Histology verification or Histology Positivity, etc.)

**DR** = Region to which the Positivity Default is allocated

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015 (cont.):**

**Rationale for Data Set**

It is difficult to determine a meaningful pair of statistics (such as Sensitivity/Specificity) for the Emory data. The Sponsor settles on a single primary statistic, Positive Predictive Value = PPV, defined at a lesion level (across subjects). The Data set defined above provides access to several alternative pairs of statistics that the reviewer considers relevant to Fluciclovine performance. (It also allows for validation of several of the Sponsor's statistics, including the Sponsor's PPV.) We note here that the concern that the alternative "Within-Subject" or strictly "Subject Level" PPVs suggested below might not be dependent on Prevalence, whatever Prevalence might mean in the context of the Emory Study. What is most important is that reasonable "pairs" of statistics can be considered that address both Overcalling and Undercalling for Fluciclovine. We illustrate with the Prostate/Prostate Bed variables. Definitions for the other regions are identical.

**Here's a first Pair: (F means Fluciclovine; H means Histology):**

**Within Subject Level Positive Predictive Value for the Region:**

**PPV = BLFP/BLF** = Proportion of F detections that are H Positive  
Equivalent to:

**Within Subject Level False Positive Rate:**

**FP = 1 - PPV** = Proportion of F detections that are H Negative

**Paired with:**

**Within Subject level Sensitivity for the Region:**

**SE = BLFP/BLP** = Proportion of H Positives that are F detections  
Equivalent to:

**Within Subject Level False Negative Rate for the Region:**

**FN = 1 - SE** = Proportion of H Positives missed by F

*Thus, we can pair the Overcalling of Fluciclovine with its complementary Undercalling, on a "Within Subject" Region based level.*

**Please note: The data set should be in Excel Format.**

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015 (cont.):**

**Requested Tables**

**Table#1**

**Distribution of Profile of Lesion Detections (Entries are # Subjects)**

The intention here is to gather Subject Level profiles of distributions of lesion detections both or all image types and for Fluciclovine Images in particular, under restrictions on the lesion status with respect to Histology.

“All Lesions” means with or without Histology

“Lesions with Histology” means only lesions that have Histology results

“Lesions with Histology = +” means only lesions with Positive Histology

	All Lesions		Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images	All Images	F Images
<b>B =0, E = 0</b>						
<b>B =0, E = 1</b>						
<b>B =0, E&gt;1</b>						
<b>B =1, E = 0</b>			<b>NHA(1,0)</b>			
<b>B =1, E = 1</b>						
<b>B =1, E&gt;1</b>	<b>NA(1, &gt;1)</b>					<b>NF+(1, &gt;1)</b>
<b>B &gt;1, E = 0</b>						
<b>B &gt;1, E = 1</b>						
<b>B &gt;1, E&gt;1</b>		<b>NF(&gt;1,&gt;1)</b>				

Note: B = Prostate/Prostate Bed; E = All other Regions

**Meaning of Categories and Entries**

**NA (1, >1):** Number of Subjects with exactly one detection in B and more than one detection in E (over all lesions, all Image types)

**NF (>1,>1):** Number of Subjects with at least two detections in B and at least two detections in E (over all lesions, but restricted to Fluciclovine Images)

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015 (cont.):**

**NHA (1, 0):** Number of Subjects with exactly one detection in B and no detections in E (restricted to lesions with histology, but over all Image types)

**NF+ (1, >1):** Number of subjects with exactly one detection in B, but at least two detections in E (restricted to lesions with Positive Histology, and restricted to Fluciclovine Image reads)

**Table#2: Statistical Profile on # Detected Lesions by Location/Image Type/Histology**

	All Lesions		Lesions with Histology		Lesions with Histology = +	
	All Images	F Images	All Images	F Images	All Images	F Images
<b>B</b>						
Mean						
Sigma						
Median						
Max						
Min						
<b>E</b>						
Mean						
Sigma						
Median						
Max						
Min						

Note: B = Prostate/Prostate Bed; E = All other Regions

$$\text{Mean (All, B, F)} = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions in Subject K (among N Subjects)}$$

when the Region is B, the Image Type is Fluciclovine, and the range is over all lesions

$$\text{Mean (His=+, E, All Images)} = (1/N) \sum_1^N S_K \text{ where } S_K = \# \text{ Lesions in Subject K (among N}$$

Subjects) when the Region is E, the Image Type is All, and the range is over all lesions with Positive Histology

**NDA 208054: Axumin [F-18] Fluciclovine**

**FDA Statistical Information Request – December 28, 2015 (cont.):**

**Tables for Lesion Detections Fluciclovine versus Other Images  
(Six Tables) Lesion Level**

**Meaning of Entries: (Holds for all Tables)**

**L(Y,Y) = # Lesions detected by both OTHER and Fluciclovine**

**L(N,Y) = # Lesions not detected by OTHER, but by Fluciclovine**

**L(Y,N) = # Lesions detected by OTHER, but not by Fluciclovine**

**Table (3,1) (All Lesions/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>	<b>L(Y,Y)</b>	<b>L(Y,N)</b>	
<b>OTHER = No</b>	<b>L(N,Y)</b>		

**Table (3,2) (All Lesions/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table (3,3) (Lesions with Histology/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table (3,4) (Lesions with Histology/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table (3,5) (Lesions with Positive Histology/Prostate/Prostatic Bed)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

**Table (3,6) (Lesions with Positive Histology/Extra Prostatic)**

	<b>F = Yes</b>	<b>F = No</b>	
<b>OTHER = Yes</b>			
<b>OTHER = No</b>			

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/s/  
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THUY M NGUYEN  
12/28/2015



NDA 208054

**INFORMATION REQUEST**

Blue Earth Diagnostic Ltd.  
Attention: Michelle Wilson, Ph.D.  
Expert Regulatory Consultant  
118 Palm Springs Drive  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin (Fluciclovine F-18), 335 to 8200 MBq/ml or 9 to 221 mCi/ml, multi-dose vial for injection.

We also refer to your September 28, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by January 10, 2015, in order to continue our evaluation of your NDA.

1. Regarding buildings and facilities where the drug product is manufactured:
  - a. Describe the manufacturing building and facilities and provide legible floor plans showing the location of (b) (4)  
(b) (4)  
control testing, etc. Identify each room in the manufacturing facility by name and/or number and indicate their air cleanliness classification.
  - b. Identify all critical equipment that are used in the manufacture of the drug product, indicate their make/model and provide their location and air cleanliness classification of the location.
2. Regarding the microbiological monitoring of the manufacturing environment, bulk drug solution, (b) (4)
  - a. Describe the monitoring process and provide the alert levels, action levels and frequencies for air, surface and personnel monitoring. Identify the sampling methods used including the sampling/growth media and incubation conditions.

- b. Describe the actions to be taken when levels are exceeded.
  - c. Provide the certificate of analysis for (b) (4)
  - d. Provide a description of the periodic or routine monitoring methods used for yeasts, molds and anaerobes in the manufacturing environment.
3. Provide the certificate of analyses for the other vials and all other reagents and each filter type used in the manufacture of the drug product.
4. Regarding media fill procedure and specifications:
- a. We acknowledged that acceptable media fill data were provided for the PETNET Solutions, Inc.'s (b) (4) facilities. Provide the dates these media fills were performed. If media fill data provided are not within (b) (4) of the submission date, then provide more recent media fill data.
  - b. Describe the actions to be taken whenever there is a media fill failure. Describe all investigations and include any contaminant identification, records review and personnel retraining that are performed.
  - c. Describe all activities that must take place in order to re-qualify the line (b) (4)  
(b) (4)
5. We acknowledged that endotoxins testing is provided using the (b) (4) (b) (4) method. Specify when after EOS testing will be initiated. We also acknowledged that in all the endotoxins tests no inhibition/enhancement occurred at (b) (4) dilution. Provide the dilution at which product will be routinely tested for endotoxins. Describe all the actions to be taken when endotoxins levels are exceeded and describe the procedures to examine the (b) (4) for defects prior to use.
6. (b) (4)
7. (b) (4)



If you have any questions, please contact me, at (240) 402-2690.

Sincerely,

**Thao M.  
Vu -A**

Digitally signed by Thao M. Vu -A  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
cn=Thao M. Vu -A,  
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Date: 2015.12.23 12:35:51 -05'00'

Thao M. Vu, R.Ph  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



NDA 208054

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Blue Earth Diagnostics Ltd  
c/o Michelle Wilson, Ph.D.  
Virtual Regulatory Solutions  
U.S. Agent for Blue Earth Diagnostics  
118 Palm Springs Drive  
Fairfield, OH 45014

ATTENTION: Michelle Wilson, Ph.D.  
Expert Regulatory Strategist

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA), dated and received September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fluciclovine <sup>18</sup>F Injection, 335-8200 MBq/mL (9 – 221 mCi/mL).

We also refer to your correspondence, dated and received September 28, 2015, requesting review of your proposed proprietary name, Axumin.

We have completed our review of the proposed proprietary name, Axumin and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 28, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Thuy Nguyen, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1427.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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IRENE Z CHAN on behalf of TODD D BRIDGES  
12/10/2015



**NDA 208054**

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Michelle Wilson, Ph.D.  
U.S. Agent for Blue Earth Diagnostics  
118 Palm Springs Dr.  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to the New Drug Application (NDA) dated and received on September 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Axumin [F-18] Fluciclovine.

We also refer to your amendments dated October 1, 15, 21, 23 and November 24, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a) this application is considered filed 60 days after the date we received your application.

The review classification for this application is Priority. Therefore, the User Fee Goal Date is May 27, 2016.

This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>).

During our filing review of the application, we identified the following potential review issues and have the following comments and information requests:

**Pharmacology / Toxicology**

1. In FDA Preliminary Meeting Responses dated on June 24, 2014, FDA stated that “FDA agrees that reproductive toxicity studies could be waived with scientific justification for a single dose PET agent with an indication for prostate cancer. Please provide a justification in your NDA submission.” However, FDA could not locate such justification in your NDA submission dated 09/28/15. Provide the justification or provide the location of the justification if you have done so in your NDA submission.

**Chemistry**

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 (b) (4) of (<sup>18</sup>F)-Fluciclovine. Also, provide data that could show (b) (4) of (<sup>18</sup>F)-Fluciclovine.

**Clinical Pharmacology**

1. Provide the bioanalytical method reports, including raw concentration-time data, for the PK data in the submission.
2. Provide the corresponding assay method validation reports.
3. Provide in electronic format (.xpt) patient level dosing data for all the clinical studies including the Emory and Bologna studies. The provided data will be merged with previously submitted datasets, so each patient needs a unique identifier that will allow such merging.

We are providing the above comments to give you preliminary notice of potential review issues.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

**Please provide a formal official response to the FDA by December 4, 2015.**

**PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling of November 24, 2015, we have identified the following labeling issues and have the following **Labeling Comments**:

1. In the Table of Contents (TOC), all section and subsection headings must be indented according to the PLR format.
2. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling. Recommended language for the reference statement: “Advise the patient to read the FDA-approved patient labeling (Patient Information). “

We request that you re-submit the labeling (in Microsoft Word format) that addresses the above issues by December 4, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Additional labeling comments may be forthcoming during the review.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely-manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate along with an electronic copy submission via Gateway, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide and Patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide and Patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see:  
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies dated October 15, 2015, for this application. Once we have reviewed your request, we will notify you of our decision.

**NDA 208054: Axumin [F-18] Fluciclovine**  
**Page 5**

If you have any questions regarding this NDA, please contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) or (301) 796-1427.

Sincerely,

*{See appended electronic signature page}*

Libero Marzella, M.D., Ph.D.  
Division Director  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

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/s/  
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THUY M NGUYEN  
11/25/2015

LIBERO L MARZELLA  
11/25/2015

**From:** Nguyen, Thuy M  
**To:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); "VRS Secure"  
**Cc:** [Jenny.Greenhorn \(J.Greenhorn@blueearthdx.com\)](mailto:Jenny.Greenhorn@blueearthdx.com)  
**Subject:** Dr. Wilson (for Spon - BED): NDA 208054 / Axumin - [F-18] Fluciclovine: FDA Statistical Reviewer's Comments - 10/23/15 / re: Statistical Response, 10/22/15 / re: submission dated 09/28/15  
**Date:** Friday, October 23, 2015 12:31:00 PM  
**Attachments:** [NDA\\_208054\\_Efficacy\\_Stats\\_Diagram.pdf](#)

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Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin / [F-18] Fluciclovine, submission dated September 28, 2015, and your statistical response of October 22, please find below the **FDA Statistical Reviewer's Comments - October 23, 2015:**

**Thank you for the statistical response of October 22, 2015.**

**I will likely have the need for further clarification as I examine the datasets you have specified as relevant to Efficacy.**

**Additionally, once I have a clear conception of these datasets, I might request that you derive one or two datasets from them that could facilitate the analyses.**

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
(301) 796-1427

**From:** VRS Secure [mailto:[vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)]  
**Sent:** Thursday, October 22, 2015 4:05 PM  
**To:** Nguyen, Thuy M  
**Cc:** [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com); [Jenny.Greenhorn \(J.Greenhorn@blueearthdx.com\)](mailto:Jenny.Greenhorn@blueearthdx.com)  
**Subject:** Re: Dr. Wilson (for Spon - BED): NDA 208054 / Axumin - [F-18] Fluciclovine: FDA Statistical Information Request - 10/22/15 / re: submission dated 09/28/15

Hello Thuy,

The BED statistician has replied. The answers to the FDA inquiry follow.

BED doesn't believe that the (b)(4) ADLES4 datasets are contained within NDA 208054. BED would appreciate further clarification if possible.

The efficacy datasets are listed below. In addition, a diagram that shows the inter-relationship between the study datasets is attached.

The information contained in this email will be formally submitted to the NDA as an information amendment as soon as possible. Please let me know if you have any questions. Enjoy your evening.

Best wishes,

**Michelle**

Michelle Wilson, Ph.D.  
Expert Regulatory Strategist  
Virtual Regulatory Solutions, Inc.  
[vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)  
[www.VirtualRegulatorySolutions.com](http://www.VirtualRegulatorySolutions.com)  
(c) 513-578-5671

**BED001**

- The analysis datasets for effectiveness are ADLES and ADLES2. They contain the necessary information from ADSL (subject-level analysis dataset) also. Further description of these 2 datasets can be found in the Analysis Data Reviewer Guide for BED001, sections 5.2.8 and 5.2.9.
- ADLES contains the comparison of Fluciclovine vs Biopsy, "Histopathology +" and Choline. The conditions to subset to these 3 comparisons are to use `LESCATCD="F18FvBio", "F18vBio2" and "F18FvC11"` respectively. See sections 3.5.1-3.5.3 of the Analysis Data Reviewer Guide for BED001 for more information.
- ADLES2 contains the comparison of Fluciclovine against other imaging techniques. The conditions to subset to the relevant imaging techniques can be found in section 3.5.4 of the Analysis Data Reviewer Guide for BED001.

**BED002**

- The analysis datasets for effectiveness are ADLES and ADLES2. Further description of these 2 datasets can be found in the Analysis Data Reviewer Guide for BED002, sections 5.2.2 and 5.2.3.
- ADLES contains the comparison of blinded read of Fluciclovine (data collected in BED002 CRF) against site assessment of Biopsy, "Histopathology +" and Choline (BED001 data). The conditions to subset to these 3 comparisons are to use `LESCATCD="F18FvBio", "F18vBio2" and "F18FvC11"` respectively. See sections 3.5.1-3.5.3 of the Analysis Data Reviewer Guide for BED001 for more information.

**BED007**

- The analysis dataset for effectiveness is ADLES. Further description of this dataset can be found in the Analysis Data Reviewer Guide for BED007, section 5.2.2.
- ADLES contains the comparison of blinded read of Fluciclovine (data collected in

BED002 CRF) against blinded read of Choline (BED007 data). The condition to subset is to use LESCATCD="F18FvC11".

### **Relationships between BED001, BED002 and BED007 data**

In the BED002 Study Data Reviewer Guide, section 3.1, there is a diagram describing the relationships between the data in BED001, BED002 and BED007. The diagram is attached.

On Thu, Oct 22, 2015 at 1:56 PM, Nguyen, Thuy M <[Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)> wrote:  
Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin / [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – October 22, 2015:**

1. **The FDA Statistical Reviewer has isolated the following 5 data sets as relevant to Efficacy:** (b) (4) **ADLES2/ADLES4/ADSL.**  
**Is this the relevant list, and is it complete? If not, provide the complete list.**

Please provide a response via email to me by 3:00 pm, EST – today, October 22, 2015, and follow up as a formal official response submission to the FDA.

If you have any questions, please contact me.

Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
US FDA CDER - Division of Medical Imaging Products  
[\(301\) 796-1427](tel:3017961427)

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Virtual Regulatory Solutions, Inc.



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/s/  
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THUY M NGUYEN  
10/23/2015

**From:** Nguyen, Thuy M  
**To:** "[Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com)"; "[VRS Secure](#)"; "[Jenny.Greenhorn \(J.Greenhorn@blueearthdx.com\)](mailto:Jenny.Greenhorn@blueearthdx.com)"  
**Subject:** Dr. Wilson (for Spon - BED): NDA 208054 / Axumin - [F-18] Fluciclovine: FDA Statistical Information Request - 10/22/15 / re: submission dated 09/28/15  
**Date:** Thursday, October 22, 2015 1:56:00 PM

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Dear Dr. Wilson (for Sponsor – BED),

Regarding NDA 208054: Axumin / [F-18] Fluciclovine, submission dated September 28, 2015, please find below the **FDA Statistical Information Request – October 22, 2015:**

**1. The FDA Statistical Reviewer has isolated the following 5 data sets as relevant to Efficacy:** (b) (4) /ADLES2/ADLES4/ADSL.

**Is this the relevant list, and is it complete? If not, provide the complete list.**

Please provide a response via email to me by 3:00 pm, EST – today, October 22, 2015.

and follow up as a formal official response submission to the FDA.

If you have any questions, please contact me.

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

US FDA CDER - Division of Medical Imaging Products

(301) 796-1427

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/s/  
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THUY M NGUYEN  
10/22/2015



NDA 208054

**INFORMATION REQUEST**

Blue Earth Diagnostic Ltd.  
Attention: Michelle Wilson, Ph.D.  
Expert Regulatory Consultant  
118 Palm Springs Drive  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin™ (Fluciclovine F-18), 335 to 8200 MBq/ml or 9 to 221mCi/ml, multi-dose vial for injection.

We also refer to your September 28, 2015, submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response by October 27, 2015.

In your Environmental Analysis, you claim a categorical exclusion from an environmental assessment in accordance with 21 CFR 25.31(b). However, a claim for a categorical exclusion must be accompanied by a statement that, to the applicant's knowledge, no extraordinary circumstances exist, in accordance with 21 CFR 25.15(a) and (d). No such statement was provided. Therefore, please resubmit a revised Environmental Analysis that includes a statement regarding extraordinary circumstances.

If you have any questions, please contact me, at (240) 402-2690.

Sincerely,

**Thao M. Vu -A**

Digitally signed by Thao M. Vu -A  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Thao M. Vu -A,  
0.9.2342.19200300.100.1.1=2001699412  
Date: 2015.10.20 08:33:59 -04'00'

Thao M. Vu, Rph  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research

Dear Dr. Wilson (for BED),

Thank you for confirming that BED would like to proceed with today's Type C – Teleconference August 3, 2015 at 12:00 – 1:00 pm, US EST, to discuss the Meeting Questions #2, 8, 10, 11, 12 & 14, and as well as the Sponsor's Additional Information for Question 12:

In regards to the response to Question 12 concerning the pH of the product, we would like to provide the Division with some information in advance of the discussion. The effect of pH on radiochemical purity of the product has been investigated. The data, illustrated in the figure below, indicate that radiochemical purity decreases at higher pH (>6). Thus, in order to preserve the radiochemical purity for the duration of the intended shelf life, the pH is limited to below 6.

**FIG. 1: Relation between pH and decrease of radiochemical purity** (b) (4)



The FDA looks forward to the discussion and will call into the following Sponsor number:

Dial-In #: (b) (4)

Code: (b) (4) #

Thank you for your kind offer to provide additional information that may be helpful during our discussion today prior to the scheduled teleconference. We have provided additional information for Question 12 below.

We have also provided a list of the BED tcon participants and have confirmed that we would like to discuss Questions 2, 8, 10, 11, 12 & 14. Please let me know if you need any further information. We look forward to talking with FDA shortly.

The attendees at the t-con will be:

Dr Jonathan Allis	Chief Executive Officer, Blue Earth Diagnostics Ltd (BED)
Dr David Gauden	Head of Marketing, BED
Mr Albert Chau	Head of Statistics, BED
Ms Jenny Greenhorn	VP Regulatory Affairs, BED
Dr Matthew Miller	Head of Imaging, BED
Dr Katharine Nagle	Head of CMC & QA, BED
Dr Michael Nazerias	Director Regulatory Affairs and Quality Systems; PETNET
Dr Penny Ward	Chief Medical Officer, BED
Dr Michelle Wilson	Expert Regulatory Strategist, VRS

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

U.S. FDA CDER – Division of Medical Imaging Products

Office: (301) 796-1427

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THUY M NGUYEN  
08/07/2015

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**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING  
PRODUCTS (DMIP)**

**TYPE C GUIDANCE MEETING MINUTES**

**IND: 107707**

**DRUG NAME: [F-18] Fluciclovine**

**SPONSOR: Blue Earth Diagnostics Ltd (BED)**

**DATE: Monday, August 3, 2015**

**SPONSOR PARTICIPANTS:**

Jonathan Allis, Ph.D., Chief Executive Officer, Blue Earth Diagnostics Ltd (BED)  
Albert Chau, Ph.D., Head of Statistics, BED  
David Gauden, Ph.D., Head of Development, BED  
Jenny Greenhorn, Vice-President, Regulatory Affairs, BED  
Matthew Miller, M.D., Head of Imaging, BED  
Katharine Nagle, Ph.D., Head of CMC & QA, BED  
Michael Nazerias, Director, RA & Quality Systems, PETNET  
Penny Ward, Ph.D., Chief Medical Officer, BED  
Michelle Wilson, Ph.D., Expert Regulatory Strategist, Virtual Regulatory Solutions (VRS)

**FDA PARTICIPANTS:**

Charles Ganley, M.D., Office Director  
Alex Gorovets, M.D., Deputy Division Director  
Ravi Kasliwal, Ph.D., Chemistry Reviewer  
Bayo Lanionu, Ph.D., Pharm/Tox Team Leader  
Eldon Leutzinger, Ph.D., Chemistry Reviewer  
Libero Marzella, M.D., Ph.D., Division Director  
Tony Mucci, Ph.D., Statistical Reviewer  
Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager  
Yanli Ouyang, Ph.D., Pharm/Tox Reviewer  
Jesse Wells, Ph.D., Microbiology Team Leader  
Gene Williams, Ph.D., Clinical Pharmacology Team Leader  
Jyoti Zalkikar, Ph.D., Statistical Team Leader

**AGENDA: Regarding the Sponsor Meeting Package dated July 2, 2015, the FDA Preliminary Meeting Responses of July 31, 2015 (Attachment #1), and the Sponsor Chemistry Comment (Attachment #2), the Sponsor would like to discuss Meeting Question #2, 8, 10, 11, 12 & 14.**

**Regarding Meeting Question #2 - Clinical**

The Sponsor explained that [F-18] Fluciclovine appears useful for patients with high PSA values undergoing scanning for the detection of metastatic disease after prostate cancer biopsy confirmation before treatment. The Sponsor stated the use of [F-18] Fluciclovine for (b) (4) there is no means to distinguish benign prostate hypertrophy from prostate cancer. The FDA stated this will be a review issue during the review of the NDA submission since it will depend on the patient population and data.

**Regarding the Meeting Question # 8 – Clinical Pharmacology**

The Sponsor stated they will address all of the FDA clinical pharmacology comments outlined in the FDA Meeting Responses dated June 24, 2014.

**Regarding the Meeting Question #10 - Statistical**

The Sponsor stated they will implement the FDA Statistical Items A and B.

The FDA clarified that Item C is in regards to the readers and that there may be a within-patient dependency on how likely it might be that a reader may identify other lesions after identifying the first lesion. The FDA will provide additional statistical comments in the FDA meeting minutes regarding the within-patient dependency (See Attachment A).

**Regarding the Meeting Question #11 – Chemistry**

Regarding Item #1, the Sponsor stated that they will include the information for [F-18] Fluoride manufacture in the 3.2S Module for [F-18] Fluciclovine drug substance to which the FDA agreed would be acceptable.

Regarding Item #3, the FDA stated the process validation sections should contain a summary of the validation studies and results obtained for both the drug product and precursor with the full results available for inspection at the manufacturing site.

**Regarding the Meeting Question #12 – Chemistry**

With regards to the Sponsor's Chemistry Comment dated 08/03/15 (Attachment #2), the FDA requested and the Sponsor agreed to provide in the NDA submission a justification for the target pH range and why the pH range is tolerable. The Sponsor stated that there have been no reports of irritation. The FDA asked what volume of product will be administered (up to 5 mL) and the Sponsor will provide the data in the NDA regarding in-use stability if the product is diluted with saline.

**Regarding the Meeting Question #12 – Chemistry (cont.)**

The FDA stated that the specific activity (s.a.) of the drug will need to be justified based on the data for clinical batches. The FDA would like to see the individual batch data as well as a range to see if the s.a. is variable. The Sponsor stated that there are no historical data for the early individual batches because the s.a. was estimated after decay. The Sponsor explained that the acceptance criteria would be based on the range and on safety testing and that the mechanism of uptake does not suggest that specific activity is a critical factor (sponsor indicated that the amino acids do not seem to affect the uptake). The Sponsor will provide justification in the NDA submission.

**Regarding the Meeting Question #14 – Chemistry (cont.)**

The Sponsor will (b) (4) manufacturing sites (b) (4) and have been inspected by the FDA.

**Additional Discussion**

The FDA asked about the possibility of a food effect. The Sponsor stated that patients had been fasting 4 hours prior to a [F-18] Fluciclovine scan. The Sponsor will perform a literature review regarding the possible food effect for [F-18] Fluciclovine.

The Sponsor anticipates submitting an NDA by the end of September 2015.

Regarding the pediatric waiver request, the FDA will inform the Sponsor of the regulatory status when it becomes available, however, the FDA's decision would not delay the filing of the NDA.

**Meeting Minutes Recorded By: T.Nguyen, DMIP**

**ATTACHMENT - A:**

**FDA Additional Statistical Comments regarding Meeting Question #10 (Post-TCON)**

We will focus on Sensitivity statistics for the Region Level. Sensitivity statistics on the Lesion Level will be similar, and Specificity considerations will be analogous.

Let  $T(k)$  = Number of regions in Patient  $k$  that are Positive by the Truth Standard

Let  $D(k)$  = Number among the  $T(k)$  that are detected by Fluciclovine

Here are two possible statistics: (  $N$  = Number of patients)

$$(1): D(\text{Within-Patient}) = (1/N) \sum_1^N D(k)/T(k)$$

$$(2): D(\text{Across Regions}) = \sum_1^N D(k) / \sum_1^N T(k)$$

$D(\text{Within Patient})$  is an average of independent observations ( within-patient ratios), so the dependencies take care of themselves – simply normalize with respect to the Sample Variance of the ratios  $D(k)/T(k)$

$D(\text{Across Regions})$  is statistically more complicated, but its variance can be approximated by the Delta Method, or preferably by Bootstrap methods if  $N$  is not large enough. The Delta Method yields:

$$\text{Variance (Across Regions)} = (1/N) (D/T)^2 ( V(D)/D^2 + V(T)/T^2 - 2C(T,D)/T*D )$$

Where:

$D$  = Mean of  $D(k)$  ;  $T$  = Mean of  $T(k)$

$V(D)$  = Variance of the  $D(k)$  ;  $V(T)$  the variance of the  $T(k)$

$C(T,D)$  = Covariance of  $T(k)$  ,  $D(k)$

**ATTACHMENT #1: FDA Preliminary Meeting Responses – July 31, 2015**

APPEARS THIS WAY ON ORIGINAL

**\*CONFIDENTIAL**

**U.S. FDA CDER - DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)**

**July 31, 2015**

**Dear Dr. Michelle Wilson, Ph.D. ,  
Virtual Regulatory Solutions (VRS)  
Office: (513) 578-5671 / Email: [Michelle.Wilson@vrsmail.com](mailto:Michelle.Wilson@vrsmail.com) / [vrs\\_secure@vrsmail.com](mailto:vrs_secure@vrsmail.com)  
For Sponsor: Blue Earth Diagnostic, Ltd (BED)  
BED: Ms. Jenny Greenhorn / Email: [J.Greenhorn@blueearthdx.com](mailto:J.Greenhorn@blueearthdx.com)**

**Regarding IND 107707: [F-18] Fluciclovine, Meeting Package dated July 2, 2015, please find attached the FDA Preliminary Meeting Responses, July 31, 2015.**

**Please review and let me know (via email) by 8:00 a.m., EST, August 3, 2015, if BED would like to**  
**1) proceed with the teleconference on August 3, 2015 at 12:00 – 1:00 p.m., EST, or**  
**2) cancel the teleconference.**

**If BED still wishes to proceed with the teleconference, please specify which Meeting Questions / Responses / Comments BED would like to discuss.**

**Also, by 8:00 a.m., EST, August 3, 2015 (via email to my attention), BED may provide preliminary clarification comments to the FDA meeting responses / comments which BED feels may better facilitate the teleconference discussion and follow-up the clarification comments as a formal official submission to the FDA.**

**If you have any questions, please contact me.**

**Sincerely,  
Thuy M. Nguyen  
Senior Regulatory Health Project Manager  
U.S. FDA CDER – Division of Medical Imaging Products  
Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)  
Office: (301) 796-1427**

**\*CONFIDENTIAL**

**U.S. FDA – CDER: DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP)**

**IND 107707: [F-18] Fluciclovine**

**Sponsor: Blue Earth Diagnostics, Ltd (BED)**

**Type C Teleconference: August 3, 2015**

Regarding the Meeting Package dated July 2, 2015, below are the FDA preliminary meeting responses / comments, July 31, 2015, in preparation for the teleconference on August 3, 2015.

These have not been fully vetted internally and should not be considered as an official position of the FDA. It is shared with the Sponsor solely to promote a collaborative and successful discussion during the teleconference. The FDA meeting minutes will reflect agreements and discussion and might not be consistent with these preliminary meeting responses / comments.

**SPONSOR MEETING QUESTION #1 – Proposed indication in recurrent prostate cancer**

*In the June 26, 2014 Type C meeting minutes, FDA commented on BED's proposed indication for F18-fluciclovine:*

*Proposed Indication: F18-fluciclovine is a radioactive diagnostic agent indicated (b) (4) for positron emission tomography (PET) imaging (b) (4) with suspected prostate cancer recurrence (b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4).*

(b) (4)

*FDA Comment: “We consider the indication statement to be data driven and although we have no current objections to the proposed indication statement, we encourage you to explore the use of F18-fluciclovine in other populations of patients with prostate cancer including patients undergoing initial evaluation.”*

**SPONSOR MEETING QUESTION #1 – Clinical (cont.)**

*In FDA's written response to the February 4, 2015 Type C meeting, FDA further comments on the proposed indication:*

*FDA Comment: "Reduce the gap between patients targeted by your indication statement and studied in your Phase 3 trials. In particular, our understanding is that (b) (4) have not been pre-specified in the eligibility criteria of any Phase 3 trial. Thus we recommend omitting this language."*

*On the basis of FDA's feedback as well as emerging information from the clinical database, the proposed indication has been amended to:*

*F18-fluciclovine is a radioactive diagnostic agent for positron emission tomography (PET) imaging (b) (4) men with suspected prostate cancer recurrence (b) (4) based (b) (4) on elevated blood prostate specific antigen (PSA) levels following (b) (4)*

*Does the Division agree that this is the appropriate indication?*

**FDA RESPONSE #1 - Clinical**

Based on our clinical understanding of the pivotal BED-002 study, we agree that the proposed indication statement is an appropriate starting point for future NDA review.

**SPONSOR MEETING QUESTION #2 – Use in other prostate cancer populations**

*Further to the Agency's comments in the June 26, 2014 meeting minutes concerning use of F18-fluciclovine in other populations of patients with prostate cancer, BED has collected information on subjects who have received F18-fluciclovine as part of the diagnostic evaluation of primary prostate cancer. The BED-001 database currently includes 95 subjects with primary prostate cancer who have been scanned with F18-fluciclovine either at Emory University or as part of the Special Access Scheme operated in Norway. In addition, a further 21 patients with confirmed localized primary disease were scanned in Study GE-148-002 (Turkbey et. al., 2014). There have also been 2 studies in primary prostate cancer conducted in Japan; a phase IIA study in 10 patients and a phase IIB study in 72 patients at intermediate and high risk of lymph node (LN) involvement and patients with advanced primary disease and known metastases.*

*A total experience in primary disease in approximately 198 patients will therefore be provided in the NDA. Further details of the type of patients scanned, the purpose of the scan and the available results will be provided in the briefing document.*

*It is proposed that the data on primary prostate cancer will be presented and discussed in Module (b) (4). Although limited, BED believes that these data should be reflected in the prescribing information to inform physicians of the most appropriate use of the product.*

**SPONSOR MEETING QUESTION #2 – Clinical (cont.)**

*Does the Division agree that the data in primary prostate cancer should be included in the prescribing information?*

**FDA RESPONSE #2**

We agree that all available information for studies of F18-fluciclovine in the setting of primary prostate cancer, including the 198 patients outlined in your question, should be included in your NDA submission. Our preliminary understanding is that F18-fluciclovine may be effective for the localization of recurrent but not primary prostate cancer. An important goal of our NDA review will be to evaluate this preliminary understanding and its rationale and to ensure that (b) (4) are clearly communicated in the eventual prescribing information.

**SPONSOR MEETING QUESTION #3 – Pivotal Efficacy Studies**

*The studies that will be presented in the NDA to support the efficacy of the product in the proposed indication are outlined in Table 1. Refer to Section 10.1 for more detailed information.*

*As discussed at the Type C meeting held June 26, 2014 and subsequently in follow up advice received February 4 and 26, 2015, the pivotal efficacy data package will consist of*

- *a study establishing diagnostic performance vs histology-based Standard of Truth based on original site read (Emory R01);*
- *a study establishing the detection rate of F18-fluciclovine vs the approved agent C11-choline based on site read (Bologna);*
- *and a confirmatory central blinded read of the Emory R01 and Bologna data by three independent readers trained in the proposed routine clinical read methodology (BED-002);*
- *a study establishing the detection rate of F18-fluciclovine vs the approved agent C11-choline based on independent central image evaluation by an expert reader proficient in C11- choline PET-CT evaluation data (BED-007).*

*These data will be supported by an overall analysis of the diagnostic performance of the product from all sources using the original site reads (BED-001). Evaluation of the total efficacy population in BED-001 by various key sub-groups will also be presented to demonstrate the applicability of the efficacy across the biochemically recurrent prostate cancer population.*

*Refer to IND 107707 SN0030 Training Manual for the read methodology and reader training plan supporting the commercial clinical use of the product in the intended indication. Table 1 summarizes the key results available from analysis of the BED001 data collection. Data from BED002 is not available at this time. Refer to Sections 10.1.2 to 10.1.6 for short summaries of the studies discussed in Table 1.*

**SPONSOR MEETING QUESTION #3 – Clinical & Statistical (cont.)**

*Does the Agency agree that this package will form an adequate basis for an NDA submission?*

**FDA RESPONSE #3 – Clinical & Statistical**

Please refer to FDA item #1 in our Type C written response of February 4, 2015. We agree that the proposed package appears adequate to test the two pivotal efficacy hypotheses for BED-002 recommended and proposed in your statistical analysis plan dated May 11, 2015. Please also see the FDA Responses #2 and #10, herein.

**SPONSOR MEETING QUESTION #4 – Safety Database**

*As discussed with the Division previously, a retrospective collection of data on F18-fluciclovine has been conducted in order to provide as comprehensive a safety database as possible (BED-001). Based on the current database, it is estimated that information on 713 subjects exposed to F18-fluciclovine will be included in the analysis of safety presented in the NDA. This includes more than 500 men with recurrent prostate cancer. A more detailed summary of exposure is in Section 10.1.4.5.*

*Does the Agency agree that this package will form an adequate basis for the NDA submission?*

**FDA RESPONSE #4 – Clinical**

Please refer to FDA item #7 in our Type C written response of June 24. Again, we agree that the proposed number for the F18-fluciclovine database appears reasonable, assuming that the safety population is adequately characterized in your NDA submission and that potential safety signals are not confounded by other investigational drugs.

**SPONSOR MEETING QUESTION #5 – Presentation of literature review**

*In the minutes of the June 26, 2014 Type C meeting, the division requested a literature review of published studies on F18-fluciclovine which included histological evaluation for presence/absence of cancer. It is proposed to include a discussion of key clinical literature which meet these criteria in Module 2.7.3 Summary of Clinical Efficacy and the full list of all articles in 5.4. Literature References. BED will use a publication cut-off date of June 30, 2015.*

*Does the Division agree with this proposal?*

**FDA RESPONSE #5**

We agree, assuming your NDA submission is not unreasonably delayed beyond the proposed June 30 cutoff.

**SPONSOR MEETING QUESTION #6 – ISS / ISE**

*A comprehensive summary of the efficacy of F18-fluciclovine will be provided in Module 2.7.3 Summary of Clinical Efficacy and a comprehensive summary of safety will be provided in Module 2.7.4 Summary of Clinical Safety. As the development program for F18-fluciclovine is relatively small, BED anticipates that the Module 2 Summaries will be within the ICH recommended page limitation of a total of 400 pages. As such, BED does not intend to submit an Integrated Summary of Efficacy or Integrated Summary of Safety in Module 5.3.5.3: Reports of Analyses of Data from More than One Study.*

*Does the Division agree with this approach?*

**FDA RESPONSE #6**

Yes. Please note that you will need to submit the ISS and ISE sections in Module 5 in accordance with the regulations for NDA submissions 21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi). In each section you will need to explain where in the submission the integrated analyses of the relevant safety and efficacy data are located.

**SPONSOR MEETING QUESTION #7 – Study Data Sets**

*BED intends to submit CDISC-compliant SDTM and ADaM datasets for BED001 which will include data from all the sites. In addition, relevant SDTM/ADaM datasets on imaging findings from BED002 and BED007 will be provided. All associated documentation (eg, define files) will also be submitted per FDA requirements. BED does not intend to include SAS programs in the NDA, but they will be available upon FDA request.*

*Does the Division agree with this approach?*

**FDA RESPONSE #7**

Yes. For additional information, please see:

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.

**SPONSOR MEETING QUESTION #8 – Clinical Pharmacology**

*Does the Division agree that the information outlined in this response addresses the points raised on the clinical pharmacology of fluciclovine [F-18]?*

**FDA RESPONSE #8**

The Division does not agree that you have addressed all of the points. Your description of fluciclovine's in vitro activity at OATP1B1, the receptor pharmacology of fluciclovine, and pharmacokinetics in rats and monkey, do not address items 1 – 4 conveyed prior to the meeting of June 26, 2014. Thus, the ability of what's present in the literature to support an NDA is unclear. The NDA should address each of the four items, and the sub-items (A. – D.) under the fourth item. Your search strategy for addressing the items should be provided in the NDA. If literature searches reveal that information is not available, provide a narrative justifying that the lack of information will not significantly impact safety and efficacy. The adequacy of what is provided and your justification if items cannot be provided will be a review issue at the time of NDA filing.

**SPONSOR MEETING QUESTION #9 – Safety Update**

*BED is not currently sponsoring any clinical trials with active recruitment of new patients.*

(b) (4)

(b) (4)

*Based on this limited additional safety information, BED do not propose to submit a 120 day safety update to the NDA.*

*Does the Agency agree that submission of a 120-day update is not required?*

**FDA RESPONSE #9**

We do not agree. Per 21 CFR 314.50 (d)(5)(vi)(b), a 120-day safety update to the NDA is required.

**SPONSOR MEETING QUESTION #10 – Other Aspects to Consider- Clinical Program**

*Are there any other aspects of the clinical development plan or clinical sections of the NDA that the Agency would like to comment on, or that BED should take into consideration?*

**FDA RESPONSE #10 - Statistical**

Comments on several statistical issues are presented below:

It is our understanding that three readers will perform new reads of F18-fluciclovine images on both the Emory and the Bologna data, and that an additional reader will be trained to read the C11-choline images.

(A): Regarding F18-fluciclovine versus C11-choline comparisons:

You state that the C11-choline read will be compared to the majority F18-fluciclovine read at a lesion/region/patient level using the Kappa statistic. We again recommend that each F18-fluciclovine reader be compared to the C11-choline reader, and that the objective should be:

At least 2 of the 3 C18-fluciclovine readers achieve a Kappa of at least 50% with respect to the C11-choline reader.

**FDA RESPONSE #10 – Statistical (cont.)**

(B): Regarding the hypotheses covering minimal success for F18-fluciclovine with respect to Truth:

These hypotheses have been stated as follows:

H0: Sens = .50 versus H1: Sens  $\geq$  .50

H0: Spec = .50 versus H1: Spec  $\geq$  .50

These statements are neither exact, nor complete. Our recommendation is:

A particular reader will be tested through:

(\*): H0: Either Sens or Spec  $\leq$  .50 versus H1: Both Sens and Spec  $>$  .50

And:

Overall success requires that at least 2 of the 3 readers achieve H1 in (\*).

(C): At lesion and region level, and for both the Kappa calculation and the Sensitivity and Specificity calculations, there could be within-patient dependencies in detections. Therefore, the statistics should incorporate provisions for such dependencies.

**SPONSOR MEETING QUESTION #11 – M3 TOC**

*Does the Division agree with this structure?*

**FDA RESPONSE #11 - Chemistry**

In addition to the proposed content and organization of eCTD module 3, we also recommend the following:

- Include 3.2S Module for F-18 fluoride manufacture.
- If a section of eCTD is not applicable, indicate “not applicable” along with the reason instead of omitting the section.
- The process validation sections should at least contain a summary of the validation studies performed and results obtained.

**SPONSOR MEETING QUESTION #12 – Drug Product Specifications**

*Does the Division agree that the proposed drug product specification is appropriate?*

**FDA RESPONSE #12 – Chemistry & Microbiology****FDA Chemistry Response:**

While proposed test attributes appear reasonable, the acceptability of acceptance criteria and test methods will be evaluated at the time of NDA review. Additionally, we recommend the following:

- Based on the proposed pH range of (b) (4) -6.0 for the product, the injection solution would appear to be outside (b) (4) of the generally desirable pH of between 4.5 and 8.0, with 7.4 being optimal. We recommend that the solution be formulated to have a pH that is suitable for intravenous injections.
- Provide a rationale for having alternate ID tests. Data must be provided to show that the tests are equivalent. Also, you must designate one of the test methods as the regulatory method.
- The level of each impurity should be justified for safety based on total daily exposure of each impurity (based on the maximum volume that may be injected).
- The specific activity of the drug will need to be justified based on the data for clinical batches.

**FDA Microbiology Response**

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. Typically, an IND would include the testing method for the product (initiated after product manufacture), acceptance criteria and the actions to be taken in case product fails to meet specifications.

Sterility testing must be initiated (b) (4) the product and any failures must be investigated and reported to the receiving facility with recommendations.

**SPONSOR MEETING QUESTION #13 – Comparison of manufacturing platforms**

*Does the agency agree that the two manufacturing platforms can be supported in the NDA?*

**FDA RESPONSE #13 - Chemistry**

If the manufacturing platforms utilize similar chemistry, provide product of similar purity and composition the approach may be submitted in the NDA. Detailed information regarding each of the manufacturing unit should be provided in the NDA.

**SPONSOR MEETING QUESTION #14 – Comparability Protocol**

*It is anticipated that two sites using the (b) (4) system will be included in the initial NDA submission.* (b) (4)

*Does the agency agree (b) (4) ?*

**FDA RESPONSE #14**

**FDA Chemistry Response:**

(b) (4)

**FDA Microbiology Response:**

The Sponsor intends to include two sites in the initial NDA submission. (b) (4)

(b) (4)

**SPONSOR MEETING QUESTION #15 – Formulation Comparison**

*Does the Division agree that the data provided supports the comparability of the Emory material with product manufactured via the (b) (4) process?*

**FDA RESPONSE #15 - Chemistry**

Your approach to comparing the product (b) (4) is reasonable. In the NDA, you should also discuss the effect of formulation difference on safety or efficacy of the product, effect of additional or higher level of impurities on safety of the product. In addition, you should also discuss any differences in the specific activity of the products obtained by the (b) (4) processes.

**SPONSOR MEETING QUESTION #16 – Other aspects to consider**

*Are there any other aspects of the CMC NDA program that the Agency would like to comment on, or that BED should take into consideration?*

**FDA RESPONSE #16 - Microbiology**

The Meeting Package dated 07/02/15, provided some description of the production process for the drug product. Typically, PET drug products are sterilized (b) (4) and an IND application would contain a description of the overall manufacturing process and sterilization process used. An IND would include the release specification for (b) (4) integrity (not provided), sterility, and endotoxins limits and provide a general description of the test methods for performing the test. More detailed test method description and method validation data should be included in the NDA submission.

There are several FDA Guidances available for PET drug products. One of those guidances is provided as a courtesy in the following link: “*Guidance PET Drugs — Current Good Manufacturing Practice (CGMP)*” - <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm266640.pdf>

**SPONSOR MEETING QUESTION #17 – NDA TOC**

*The NDA TOC is in Appendix 2. Does the Agency have any further comments regarding the NDA table of contents?*

**FDA RESPONSE #17**

FDA Chemistry Response: While the TOC appears reasonable, we refer you to the FDA Response #11 (above) for module 3 TOC.

**SPONSOR MEETING QUESTION #18 – NDA Filing Basis**

*BED proposes to file a full NDA in accordance with section 505(b)(1) of the FD&C Act. The NDA will include full reports and source data.*

*Does the Division agree that this is the correct basis for the application?*

**FDA RESPONSE #18 - Clinical**

Assuming you own rights to all data sufficient to demonstrate safety and efficacy within your NDA, we agree.

**SPONSOR MEETING QUESTION #19 – Data Exclusivity**

*Based on patents 5808146, 5817776 and WO2013/093025 and the data generated in support of the NDA, BED believes that the product will benefit from (b) (4).*

*Does the agency concur with this assessment?*

**FDA RESPONSE #19 - Clinical**

Exclusivity determinations are made after NDA review.

**SPONSOR MEETING QUESTION #20 – Priority Review**

*BED believes that the NDA for the proposed fluciclovine (18F) indication warrants priority review as recurrent prostate cancer is a serious condition with a high rate of mortality. There is evidence that F18-fluciclovine will provide significant benefit to patients in terms of its diagnostic performance. In addition F-18 has a wider commercial availability compared to agents based on the very short half-life isotope C-11. Evidence that F18-fluciclovine provides significant benefit in the diagnosis of recurrent prostate cancer will be further discussed in the briefing document.*

*Does the Division agree that there is a strong possibility that the NDA would receive priority review?*

**FDA RESPONSE #20 - Clinical**

Please see FDA: “Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics,” Appendix C, for details on the process for requesting priority NDA review. Priority determinations are made after NDA filing. However, we agree that recurrent prostate cancer is a serious condition and that F18 compares favorably to C11 in terms of its potential for wider patient access to this imaging modality.

**SPONSOR MEETING QUESTION #21 – Pediatric Waiver**

*The Initial Proposed Pediatric Study Plan was submitted to the IND on May 12, 2014 (SN 0022). This included a request for a waiver from conducting pediatric studies in prostate cancer based on this condition not occurring in children. No feedback on this submission has been received.*

*Can the Division confirm that this waiver request has been accepted?*

**FDA RESPONSE #21 - Clinical**

We appreciate your reference to the submission of May 12, 2014, and will respond with additional information as an addendum to the meeting minutes.

**SPONSOR MEETING QUESTION #22 – Brand Name**

*Does the Division agree with the sponsor’s plan to submit the Brand Name package at the time the NDA is submitted (sequence number 0001)?*

**FDA RESPONSE #22 - Clinical**

Yes.

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/s/  
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THUY M NGUYEN  
07/31/2015

**ATTACHMENT #2: Sponsor Chemistry Comment – August 3, 2015**

APPEARS THIS WAY ON ORIGINAL

Dear Dr. Wilson (for BED),

Thank you for confirming that BED would like to proceed with today's Type C – Teleconference

August 3, 2015 at 12:00 – 1:00 pm, US EST, to discuss the Meeting Questions #2, 8, 10, 11, 12 & 14,

and as well as the **Sponsor's Additional Information for Question 12:**

**In regards to the response to Question 12 concerning the pH of the product, we would like to provide the Division with some information in advance of the discussion. The effect of pH on radiochemical purity of the product has been investigated. The data, illustrated in the figure below, indicate that radiochemical purity decreases at higher pH (>6). Thus, in order to preserve the radiochemical purity for the duration of the intended shelf life, the pH is limited to below 6.**

**FIG. 1: Relation between pH and decrease of radiochemical purity** (b) (4)



The FDA looks forward to the discussion and will call into the following Sponsor number:

**Dial-In #:** (b) (4)

**Code:** (b) (4) #

Thank you for your kind offer to provide additional information that may be helpful during our discussion today prior to the scheduled teleconference. We have provided additional information for Question 12 below.

We have also provided a list of the BED tcon participants and have confirmed that we would like to discuss Questions 2, 8, 10, 11, 12 & 14. Please let me know if you need any further information. We look forward to talking with FDA shortly.

The attendees at the t-con will be:

Dr Jonathan Allis	Chief Executive Officer, Blue Earth Diagnostics Ltd (BED)
Dr David Gauden	Head of Marketing, BED
Mr Albert Chau	Head of Statistics, BED
Ms Jenny Greenhorn	VP Regulatory Affairs, BED
Dr Matthew Miller	Head of Imaging, BED
Dr Katharine Nagle	Head of CMC & QA, BED
Dr Michael Nazerias	Director Regulatory Affairs and Quality Systems; PETNET
Dr Penny Ward	Chief Medical Officer, BED
Dr Michelle Wilson	Expert Regulatory Strategist, VRS

Sincerely,

Thuy M. Nguyen

Senior Regulatory Health Project Manager

U.S. FDA CDER – Division of Medical Imaging Products

Office: [\(301\) 796-1427](tel:3017961427)

Email: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov)

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/s/  
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THUY M NGUYEN  
08/07/2015

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



**NDA 208054**

**LATE-CYCLE MEETING MINUTES**

Michelle Wilson, Ph.D.  
U.S. Agent for Blue Earth Diagnostics  
118 Palm Springs Dr.  
Fairfield, OH 45014

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Axumin ([F-18] Fluciclovine).

We also refer to the Late-Cycle Meeting (LCM) teleconference between representatives of your firm and the FDA on March 22, 2016.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions regarding this NDA, please contact Ms. Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager at: [Thuy.Nguyen@fda.hhs.gov](mailto:Thuy.Nguyen@fda.hhs.gov) or (301) 796-1427.

Sincerely,

*{See appended electronic signature page}*

Nushin Todd, M.D., Ph.D.  
Cross-Discipline Team Leader  
Division of Medical Imaging Products  
Office of Drug Evaluation IV  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration

**Enclosure:**  
Late Cycle Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** March 22, 2016 at 12:30 – 1:00 pm, US EST  
**Meeting Location:** Teleconference

**Application Number:** NDA 208054  
**Product Name:** Axumin ([F-18] Fluciclovine)  
**Sponsor Name:** Blue Earth Diagnostics (BED)

**Meeting Chair:** Nushin Todd, M.D., Ph.D., Cross-Discipline Team Leader (CDTL)  
**Meeting Recorder:** Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager

**FDA ATTENDEES**

Phillip Davis, M.D., Clinical Reviewer  
Eric Duffy, Ph.D., Chemistry Branch Chief  
Charles Ganley, M.D., Office Director  
Alex Gorovets, M.D., Deputy Division Director  
Jagjit Grewal, Office Associate Director of Regulatory Affairs  
Ravi Kasliwal, Ph.D., Chemistry Reviewer  
Bayo Laniyonu, Ph.D., Pharm/Tox Team Leader  
Eldon Leutzinger, Ph.D., Chemistry Team Leader  
Darrell Lyons, OSE – Project Manager  
Lou Marzella, M.D., Ph.D., Division Director  
Carolyn McCloskey, OSE – DEPI Reviewer  
Tony Mucci, Ph.D., Statistical Reviewer  
Thuy M. Nguyen, M.P.H., Senior Regulatory Health Project Manager  
Yanli Ouyang, Ph.D., Pharm/Tox Reviewer  
Stanley Stern, Health Physicist  
Nushin Todd, M.D., Clinical Team Leader / Cross-Discipline Team Leader (CDTL)  
Thao Vu, R.Ph., CMC Project Manager

**EASTERN RESEARCH GROUP ATTENDEES**

(b) (4)

**NDA 208054: Axumin ([F-18] Fluciclovine)  
Late-Cycle Meeting Minutes**

**APPLICANT ATTENDEES**

Jonathan Allis, Ph.D., Chief Executive Officer, BED  
David Gauden, Ph.D., Head of Development, BED  
Caroline Hardwicke, Head of Clinical Operations, BED  
Mike Heslop, President, BED  
Lisa Jenkins, Ph.D., Vice President, Regulatory Strategy and Content Development, VRS  
Matthew Miller, Ph.D. Head of Imaging, BED

(b) (4)

Katharine Nagle, Ph.D., Head of CMC & QA, BED  
Penny Ward, MBBS, FFPM, Chief Medical Officer, BED  
Michelle Wilson, Ph.D., Expert Regulatory Strategist, VRS

**1.0 BACKGROUND**

NDA 208054 was submitted on September 28, 2015, for Axumin ([F-18] Fluciclovine).

**Proposed Indication:** For positron emission tomography (PET) imaging (b) (4) men with suspected prostate cancer recurrence

**PDUFA Goal Date:** May 27, 2016

FDA issued a Late-Cycle Meeting (LCM) Background Package in preparation for this teleconference on March 4, 2016.

**2.0 DISCUSSION**

The purpose of a Late-Cycle Meeting (LCM) / teleconference is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review cycle. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the teleconference will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the teleconference.

**1. Introductory Comments**

The FDA stated there are no major issues and on track for the Goal Date of May 27, 2016.

**NDA 208054: Axumin ([F-18] Fluciclovine)  
Late-Cycle Meeting Minutes**

**2. Labeling / Review Plans**

The FDA will forward to the Sponsor the labeling revisions by April 5, 2016.

The Sponsor asked the types of labeling revisions to expect, to which the FDA stated that they are mostly formatting changes and language suggestions. The FDA also added that more substantive edits will have comments at the margins of the labeling. A response from the Sponsor would be expected in 24 hours to a few days of receipt of the FDA labeling revisions.

Besides the forthcoming FDA labeling comments, the Sponsor asked if there are other review information requests. The FDA responded that no additional information requests are expected.

**3. Wrap-up and Action Items**

This application has not yet been fully reviewed by the signatory authority, division director, and CDTL and, therefore, this teleconference did not address the final regulatory decision for the application.

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/s/  
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THUY M NGUYEN  
03/23/2016

NUSHIN F TODD  
03/23/2016