

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208870Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208870 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Drax Exametazime Established/Proper Name: Kit for the Preparation of Tc99m Exametazime (b) (4) Dosage Form: Lyophilized		Applicant: Jubilant DraxImage Inc. Agent for Applicant (if applicable): INC Research LLC
RPM: Alberta Davis-Warren		Division: Division of Medical Imaging Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: August 16, 2017 <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>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>August 20, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☐ Received
❖ Application Characteristics ³		

¹ 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.

² 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).

³ 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 5
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ 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)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters (including approval letter with final labeling)	Action(s) and date(s) 8-17-17
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☒ Included
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format)	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
Most-recent draft labeling	☒ Included
❖ Proprietary Name	Acceptability letter 8-11-17
- Acceptability/non-acceptability letter(s) (indicate date(s)) - Review(s) (indicate date(s))	Reviews: 8-10-17
❖ Labeling reviews (indicate dates of reviews)	RPM: ☒ None 9-15-16 DMEPA: ☒ None 8-15-17, 8-11-17, 7-7-17, 11-22-16 DMPP/PLT (DRISK): ☒ None OPDP: ☒ None 3-22-17 SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Other: ☒ None: ADL – 7-25-17 DMIP Health Physicist – 3-24-17 DPMH – 3-30-17
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	9-15-16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☐ Not a (b)(2) cleared on 7-10-17
❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	

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

Applicant is on the AIP	☐ Yes ☒ No
- This application is on the AIP - If yes, Center Director's Exception for Review memo <i>(indicate date)</i> - If yes, OC clearance for approval <i>(indicate date of clearance communication)</i>	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics <i>(approvals only)</i> Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Does not trigger PREA</u>	
❖ Breakthrough Therapy Designation	☒ N/A
Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) <i>(include only the completed template(s) and not the meeting minutes)</i>	
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> <i>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</i>	
❖ 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>	X
❖ 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)	X
❖ Minutes of Meetings	
If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	☒ N/A or no mtg
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☒ ~~No mtg~~ 10-21-14
EOP2 meeting <i>(indicate date of mtg)</i>	☒ No mtg
Mid-cycle Communication <i>(indicate date of mtg)</i>	☒ N/A
Late-cycle Meeting <i>(indicate date of mtg)</i>	☒ N/A
Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <i>(indicate dates of mtgs)</i>	12-4-15
❖ Advisory Committee Meeting(s)	☒ No AC meeting
Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	☒ None
Division Director Summary Review <i>(indicate date for each review)</i>	☒ None
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☒ ~~None~~ 8-8-17
PMR/PMC Development Templates <i>(indicate total number)</i>	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (indicate date for each review)	☒ No separate review
• Clinical review(s) (indicate date for each review)	3-22-17
• Social scientist review(s) (if OTC drug) (indicate date for each review)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☒ and include a review/memo explaining why not (indicate date of review/memo)	8-1-17
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review) ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (indicate date(s) of submission(s)) - REMS Memo(s) and letter(s) (indicate date(s)) - Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)	☒ None
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☒ No separate review
Statistical Team Leader Review(s) (indicate date for each review)	☒ No separate review
Statistical Review(s) (indicate date for each review)	☒ ~~None~~ 3-31-17 consultative review
Clinical Pharmacology ☒ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☐ No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ No separate review
Clinical Pharmacology review(s) (indicate date for each review)	☐ None
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	☐ None requested

⁵ 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).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ No separate review
• Supervisory Review(s) (indicate date for each review)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☒ ~~None~~ 8-2-17
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (indicate date for each review)	☐ None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☒ ~~None~~ 8-8-17
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☒ ~~None~~ 3-31-17 Statistical consult review
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	7-21-17
☐ Review & FONSI (indicate date of review)	
☐ Review & Environmental Impact Statement (indicate date of each review)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

⁶ 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: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ 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	☒ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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/s/

ALBERTA E DAVIS WARREN
08/23/2017

From: Davis-Warren, Alberta E
To: ["Ousmane Diallo"](#)
Cc: [Hiba Soulaihi](#); [Rana Temsah](#); [Magali Lurquin](#); [Norman LaFrance MD](#); aziz.nuritdinov@incresearch.com
Subject: RE: NDA 208870 Drax Exametazime/ Courtesy copy of response sequence 0029/One additional edit
Date: Wednesday, August 16, 2017 12:14:00 PM
Attachments: [DRAX Exametazime FDA to SPONSOR edit-draft-pi.docx](#)
Importance: High

Hello Ousmane,

We made one additional edit in section 16 (attached). If acceptable, please accept the change and resubmit the label today.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9899 fax
Alberta.Davis-Warren@fda.hhs.gov

From: Ousmane Diallo [<mailto:odiallo@jdi.jubl.com>]
Sent: Wednesday, August 16, 2017 10:42 AM
To: Davis-Warren, Alberta E
Cc: Hiba Soulaihi; Rana Temsah; Magali Lurquin; Norman LaFrance MD; aziz.nuritdinov@incresearch.com
Subject: RE: NDA 208870 Drax Exametazime/ Courtesy copy of response sequence 0029

Dear Alberta,

In response to your request below, pls find attached a courtesy copy of sequence 0029.
The official sequence in eCTD format is about to be submitted today to the FDA through ESG.

Best regards,

Ousmane.

De : Davis-Warren, Alberta E [<mailto:Alberta.Davis-Warren@fda.hhs.gov>]
Envoyé : 15 août 2017 15:39
À : Ousmane Diallo <odiallo@jdi.jubl.com>; aziz.nuritdinov@incresearch.com
Cc : Hiba Soulaihi <HSoulaihi@jdi.jubl.com>; Rana Temsah <rtemsah@jdi.jubl.com>; Magali Lurquin <mlurquin@jdi.jubl.com>
Objet : NDA 208870 Drax Exametazime
Importance : Haute

Dear Ousmane and Aziz,

Attached are FDA's revisions to the NDA 208870 Drax Exametazime label (Edits version and clean version).

Also, please add the conditionally approved proprietary name to the following:

Radiation label

Radiolabeled leukocytes-lead-pot labels

Leukocyte-labeling-schematic

rcp-efficiency-worksheets

Please respond to the information request by tomorrow **Wednesday, August 16, 2017 at 11:00 am ET**. When sending the label officially and via secure email, provide a redline and clean version of the label.

Please contact me if you have any questions and please confirm receipt of email.

Thank you,

Alberta

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

301-796-3908 office

301-796-9899 fax

Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
08/16/2017

From: Davis-Warren, Alberta E
To: "Ousmane Diallo"; ["aziz.nuritdinov@incresearch.com"](mailto:aziz.nuritdinov@incresearch.com)
Cc: [Hiba Soulaihi \(HSoulaihi@jdi.jubl.com\)](mailto:Hiba.Soulaihi@jdi.jubl.com) (HSoulaihi@jdi.jubl.com); [Rana Temsah \(rtemsah@jdi.jubl.com\)](mailto:Rana.Temsah@jdi.jubl.com); ["mlurquin@jdi.jubl.com"](mailto:mlurquin@jdi.jubl.com)
Subject: NDA 208870 Drax Exametazime
Date: Tuesday, August 15, 2017 3:39:00 PM
Attachments: [8-15-17-FDA to SPONSOR annotated-draft-pi.docx](#)
[8-15-17-FDA to SPONSOR clean-draft-pi.docx](#)
Importance: High

Dear Ousmane and Aziz,

Attached are FDA's revisions to the NDA 208870 Drax Exametazime label (Edits version and clean version).

Also, please add the conditionally approved proprietary name to the following:

- Radiation label
- Radiolabeled leukocytes-lead-pot labels
- Leukocyte-labeling-schematic
- rcp-efficiency-worksheets

Please respond to the information request by tomorrow **Wednesday, August 16, 2017 at 11:00 am ET**. When sending the label officially and via secure email, provide a redline and clean version of the label.

Please contact me if you have any questions and please confirm receipt of email.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9899 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
08/15/2017

From: Davis-Warren, Alberta E
To: aziz.nuritdinov@incresearch.com; "Ousmane Diallo"
Cc: [Hiba Soulaihi \(HSoulaihi@jdi.jubl.com\)](mailto:Hiba.Soulaihi@jdi.jubl.com) (HSoulaihi@jdi.jubl.com); [Rana Temsah \(rtemsah@jdi.jubl.com\)](mailto:Rana.Temsah@jdi.jubl.com)
Subject: NDA 208870 label
Date: Friday, August 11, 2017 3:10:00 PM
Attachments: [8 2017 FDA to sponsor edits.docx](#)
[8 2017 FDA to sponsor Clean.docx](#)
[NDA 208870 Carton and container comments label comments 8 11 2017.docx](#)
Importance: High

Dear Aziz and Ousmane,

Attached are FDA's revisions to the NDA 208870 Kit for the Preparation of Technetium Tc99m Exametazime label (Edits version and clean version). Also attached are comments regarding the package insert, carton and container labeling.

Please provide a response to the edits and comments by secure email and through the official channels by this **Monday, August 14, 2017 at 1 pm ET** . When sending the label officially and via secure email, provide a redline and clean version of the label.

Please contact me if you have any questions and please confirm receipt of email.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9899 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
08/11/2017



NDA 208870

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Jubilant DraxImage Inc.
c/o Aziz R. Nuritdinov
INC Research, LLC
4800 Falls of Neuse Rd., Suite 600
Raleigh, NC 27609

ATTENTION: Aziz Nuritdinov
US Agent

Dear Mr. Nuritdinov:

Please refer to your New Drug Application (NDA), dated and received July 20, 2016, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Kit for the Preparation of Tc 99m Exametazime (b) (4) 0.5 mg/vial [equivalent to 0.37 GBq- 2.00 GBq (10 mCi- 54 mCi) at time of reconstitution].

We also refer to your May 29, 2017, correspondence, received May 30, 2017, requesting review of your proposed proprietary name, Drax Exametazime.

We have completed our review of the proposed proprietary name, Drax Exametazime and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your May 29, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Tri Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Alberta Davis-Warren, Regulatory Project Manager, in the Office of New Drugs at (301) 796-3908.

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/

TODD D BRIDGES
08/11/2017

From: Davis-Warren, Alberta E
To: "Rana Temsah"; aziz.nuritdinov@incresearch.com
Cc: [Magali Lurquin](#); [Ousmane Diallo](#); [Hiba Soulaihi](#)
Subject: NDA 208870 Exametazime label
Date: Monday, July 31, 2017 11:53:00 AM
Attachments: [PI Exametazime-clean FDA to Sponsor 7.31.2017.docx](#)
[OPDP DMEPA comments on Carton labeling.docx](#)
Importance: High

Dear Rana and Aziz,

Attached are FDA's revisions to the NDA 208870 Exametazime label. Also attached are comments regarding the carton and container labeling.

Please provide a response to the edits by secure email and through the official channels by this Friday, August 4, 2017. When sending the label officially and via secure email, provide a redline and clean version of the label.

Please confirm receipt of email and please contact me if you have any questions.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9899 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
07/31/2017

From: Davis-Warren, Alberta E
To: aziz.nuritdinov@incresearch.com; [Rana Temsah \(rtemsah@jdi.jubl.com\)](mailto:Rana.Temsah@jdi.jubl.com)
Subject: NDA 208870 label
Date: Wednesday, June 21, 2017 3:08:00 PM
Attachments: [6 2017 NDA 208870 -FDA to Sponsor.docx](#)
[6 2017 Carton and Container Comments to the Sponsor.docx](#)

Dear Aziz and Rana,

Attached are FDA's revisions to the NDA 208870 Kit for the Preparation of Technetium Tc99m Exametazime label. Also attached are comments regarding the carton and container labeling.

Please provide a response to the edits by secure email and through the official channel by next Wednesday, June 28, 2017. When sending the label officially and via secure email, provide a redline and clean version of the label.

Please note if there are several revisions to the label or if you have several questions, please provide the revised labels prior to Wednesday, June 28, 2017. Please contact me if you have any questions and please confirm receipt of email.

Thank you,

Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-796-9899 fax
Alberta.Davis-Warren@fda.hhs.gov

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/s/

ALBERTA E DAVIS WARREN
06/21/2017



NDA 208870

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Jubilant DraxImage Inc.
c/o Aziz R. Nuritdinov
U.S. Agent-Regulatory Associate, Regulatory Strategy, Consulting & Submissions
INC Research, LLC
4800 Falls of Neuse Rd., Suite 600
Raleigh, NC 27609

Dear Mr. Nuritdinov:

Please refer to your New Drug Application (NDA) dated July 15, 2016, received July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4).

On April 7, 2017, we received your April 7, 2017, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 20, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2013 through 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 23, 2017.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-796-3908.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

LIBERO L MARZELLA
04/11/2017

MEMORANDUM OF TELECONFERENCE

Teleconference Date: March 24, 2017

Application Number: NDA 208870

Product Name: Kit for the Preparation of Technetium Tc 99m Exametazime
(b) (4)

Sponsor/Applicant Name: Jubilant DraxImage

Subject: Drug Product , process and drug substance pending issues

FDA Participants:

Libero Marzella, MD, PhD, Director, DMIP
Nushin Todd, MD, PhD, Clinical Team Leader, DMIP
Michele Fedowitz, MD, Associate Director of Labeling, DMIP
Danae Christodoulou, PhD, Branch Chief, DNDPII
Eldon Leutzinger, PhD, CMC Team Leader, DNDPII
Dhanalakshmi Kasi, PhD, CMC Reviewer, DNDPII
Donna Christner, PhD, Branch Chief, DNPAPI
Michael Klapal, Consumer Safety Officer, OPF
Poonam Delvadia, PhD, Biopharm reviewer, ONDP
Alberta Davis-Warren, RPM, DMIP

Sponsor/Applicant Participants:

Norman LaFrance, Chief Medical Officer, Senior VP Medical & Regulatory Affairs
Magali Lurquin, Associate Director, Regulatory Affairs
Rana Temsah, Senior Specialist, Regulatory Affairs
Bill Riddoch, Director, Research & Development
Walter Menabo, Laboratory Manager, Research & Development
Riadh Zriba, Scientific Researcher, Research & Development
Tara Pradhan, Director of Quality Operation
Sebastien Naud, Manager, Quality
Arun Kumar Singh, Manager, BE & Six Sigma
Ram Mullur, PMO Lead
Alexandre Boily, Manager of Technical Services

1.0 BACKGROUND: On July 15, 2016, Jubilant DraxImage submitted NDA 208870 Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) to the Division of Medical Imaging products. During the review cycle for this new drug application, OPQ sent several information requests(IRs) to the applicant. Jubilant DraxImage provided responses to all IRs however a few of their responses do not fully address quality concerns. The purpose of the tcon

is to discuss the pending CMC issues the applicant has not adequately responded to. On March 23, 2017 FDA provided a summary to Jubilant (attached) to assist in the discussion. On March 24, 2017 Jubilant DraxImage provided their response to FDA's summary (attached).

2.0 DISCUSSION:

FDA and Jubilant DraxImage briefly discussed FDA's summary and Jubilant DraxImage response to the summary. Included in Jubilant DraxImage's response were dates they were providing additional information for FDA to review. FDA accepted DraxImage's position on drug product items 1 (specification for unidentified impurities in the lyophilized product) and 5 (radiochemical purity specification). DraxImage accepted FDA's position for drug product item 2 (inclusion of visual appearance for the reconstituted Tc 99m exametazime solution in the PI), item 3 (specification for stannous content in the kit) and process comment 3 (revision of holding time to (b)(4)). Draximage will provide response for drug product comment 4 on March 31, 2017, comment 6 on April 7, 2014, comment 7 on April 14, 2014, process comment 1 on March 29, 2017 and for process comment 3, revised batch record submission date will be provided later. FDA informed the applicant that their responses will need to be reviewed before we can provide additional feedback. The applicant understood and agreed. FDA also mentioned to the applicant that we are towards the end of the current review clock for this application. Once FDA receives the additional information from Jubilant DraxImage, FDA will need to extend the review clock to give adequate time to review the submission.

3.0 ACTION ITEMS:

Jubilant will completely address FDA's 3-23-17 summary by providing additional CMC information on the following dates: March 29, March 31, April 7 and April 14, 2017. FDA will extend the review clock upon receipt of the April 7th submission

4.0 ATTACHMENTS

- 3-23-17 FDA summary of Pending issues related to Drug Product, Process and Drug Substance
- 3-24-17 Jubilant DraxImage response to FDA summary

NDA 208870 Summary for March 24, 2017 Teleconference with Jubilant DraxImage

Pending issues related to Drug Product and Process

Drug product

1. Revise your unspecified impurity level for your lyophilized drug product to (b) (4) % at release and stability based on ICH Q3B R2.
2. We expect that labeling instructions in the PI are supported by quality data for the reconstitution of the drug product. As such, include visual inspection as part of the radiopharmacy release test for the reconstituted Tc 99m exametazime solution to make sure that there is no particulate matter present. Your data supports that Tc 99m exametazime is a clear solution.
3. Revise the stannous chloride content at release to (b) (4) µg/vial based on your available stability data for exhibit batch 4L263. This ensures that stannous chloride will not fall out of specification at the end of shelf life of the lyophilized product.
4. In our information request 3 sent on 03/02/2017, we have requested HPLC traces for assay, impurity analysis for the lyophilized drug product and ITLC traces (b) (4) (b) (4) for the reconstituted solution to support the batch analysis data provided in Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2 in Batch Analyses Section (3.2.P.5.4). You have responded by submission of a 400-500 pages report for each lot consisting of a scanned copy of hand written lab notebook pages which are difficult to read. Please extract from this report and submit only the data HPLC traces for assay, impurity analysis for the lyophilized drug product and ITLC traces (b) (4), plus all the calculations) to support the data provided in Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2.
5. Your radiochemical purity for the three exhibit batches is > (b) (4) %. We recommend that you revise the limit for radiochemical purity of the reconstituted solution from not less than (b) (4) % to not less than (b) (4) % based on the data. This is a current RCP criterion for radiopharmaceuticals widely accepted in the field.

6. In our earlier information request sent on 09/15/16, we recommended that you validate the ITLC method against an HPLC method for the reconstituted solution. Provide raw HPLC and ITLC data, for example original chromatogram traces to show that your ITLC method is equivalent or better than the HPLC method. Draximage committed to provide response in the first week April. What is the current status of the report and planned date of submission?
7. Provide extractables and leachables profile for your container and closures. Draximage committed to provide response in the first week April. What is the current status of the report and planned date of submission?

Process:

1. You have radiolabeled 3 exhibit batches (Lot 4L263, Lot 5B142 and Lot 5F648) in your lab and provided data in the submission (Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2 in Batch Analyses Section (3.2.P.5.4)) but you have not provided any detailed description for the radiolabeling of Exametazime with Tc 99m in Section 3.2.P.3.3 (Description of manufacturing process and process controls) to support labeling instructions in the PI section 2.4 (Preparation and Labeling Instructions). Provide step by step process description for radiolabeling including all calculations involved in the analysis of the impurities and the radiolabeled drug product to support labeling instructions for the reconstitution of Tc 99 exametazime in the PI section 2.4 (Preparation and Labeling Instructions).
2. In your manufacturing process you provided a (b) (4)
(b) (4)
3. Your microbiology and physicochemical data support a holding time of (b) (4) rather than (b) (4). Revise the holding time (b) (4)

Pending issues related to Drug Substance

1. Provide the typical scale and yield for each major step of the API manufacturing.
2. Provide representative chromatograms for all the HPLC analytical methods (b) (4) including peak identification, RRTs and integration. Provide the resolution of close peaks.
3. (b) (4) How is completion of the reaction assured?
4. Due to the extremely simple structure of the API (due to symmetry), attempt to identify unspecified impurities produced by forced degradation (e.g., using MS, NMR). Provide chromatograms with labeled peaks and integration to demonstrate resolution. For conditions which show meaningful changes, plot amounts at each time point (0-24 hours) for each impurity. (b) (4)

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/s/

ALBERTA E DAVIS WARREN
03/30/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: **Aziz R. Nuritdinov**
FAX/EMAIL **aziz.nuritdinov@incresearch.com**
Phone: **513-763-4219**
Pages, including cover sheet **3**
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: March 2, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Microbiology section of your submission, we have the following Information Request:

The provided response and the reference to page 18 of the enclosed guide, **Manuf-process-and-controls-spk5895-e.pdf**, which includes the statement, [REDACTED] (b) (4)

[REDACTED]

[REDACTED] are acknowledged.

If the requested information is contained in a DMF, then please provide a letter of authorization with the specific submission dates and location of the requested information within the DMF.

NDA 208870

Please respond to the information request by **tomorrow Friday, March 3, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **tomorrow Friday, March 3, 2017**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

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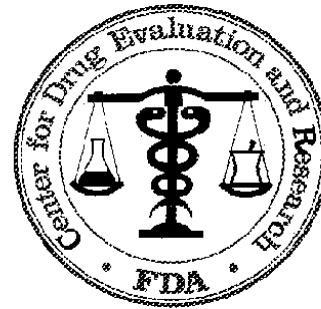
/s/

ALBERTA E DAVIS WARREN
03/02/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet 4
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: March 2, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the CMC section of your submission, we have the following Information Request:

Drug Product

1. Include appearance as part of the release test specification for the reconstituted solution Tc 99m Exametazime and provide test results for the exhibit batches (Lot 4L263, Lot 5B142 and Lot 5F648).
2. Shelf life of the reconstituted drug product is stated in the PI section 2.4 (Preparation and Labeling Instructions) to be 30 min. Provide stability data (appearance, Radiochemical purity and pH) at 30 min time point to support your shelf life.
3. In your package insert (b) (4) you have stated that the labeled autologous WBCs with exametazime should be administered to the patients as soon as possible and preferably within two hours. Provide supporting data to justify shelf life of 2 h.
4. Hydroxylethyl starch is used in the preparation of autologous leukocytes as stated in the PI section 2.4 (Preparation and Labeling Instructions). Provide specification, COA from vendor and the manufacturer for hydroxylethyl starch.

5. Table 3.2.P.5.4-1 and Table 3.2.P.5.4-2 provided in Batch Analyses Section (3.2.P.5.4) contains batch data for lots 4L263, Lot 5B142 and Lot 5F648. To support the data provide HPLC traces for assay, impurity analysis for the lyophilized drug product and ITLC traces (b) (4) for the reconstituted solution. Label all the chromatograms clearly with lot numbers and include all the calculations involved in the analysis.
6. In our earlier information request sent on 09/15/16, we recommended that you validate the ITLC method against an HPLC method for the reconstituted solution. Provide raw HPLC and ITLC data, for example original chromatogram traces to show that your ITLC method is equivalent or better than the HPLC method.

Process

1. You have not provided any detailed description for the radiolabeling of Exametazime with Tc 99m in Section 3.2.P.3.3 (Description of manufacturing process and process control) to support labeling instruction in the PI section 2.4 (Preparation and Labeling Instructions). Provide step by step process description for radiolabeling including all calculations involved in the analysis of the impurities and the radiolabeled drug product to support labeling instruction in the PI section 2.4 (Preparation and Labeling Instructions). Alternatively, provide the master (blank) batch record and completed batch record for the 3 exhibit batches Lot 4L263, Lot 5B142 and Lot 5F648).
2. In your response dated 02/02/2017, you have provided the holding time limits for the manufacturing process at various stages of the lyophilized product based on your development batches. Also provide the exact time you hold the drug product at different stages of the manufacturing process for the 3 exhibit batches Lot 4L263, Lot 5B142 and Lot 5F648 in a table form.
3. You have established hold time limits for (b) (4) based on your development batches as per your response on 02/02/2017. (b) (4)
(b) (4)
(b) (4)
(b) (4)
4. You have identified holding time of (b) (4) (b) (4) it is not supported by data. Provide supporting data.

NDA 208870

Please respond to the information request by **March 8, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **March 8, 2017**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
03/02/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: **Aziz R. Nuritdinov**
FAX/EMAIL **aziz.nuritdinov@incresearch.com**
Phone: **513-763-4219**
Pages, including cover sheet **3**
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: March 1, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Microbiology section of your submission, we have the following Information Request:

The provided Response, [REDACTED] for Agency Comment 1 in the submission dated 2.28.2017 (response to Agency letter dated 2.16.2017) is noted. However, the data provided in the attachment, [REDACTED]

The following statement provided in Response 4a (in submission dated 1.9.2017) to Agency Information Request dated 12.7.2016 (Reference ID 4023959)), (b) (4)

If this information is in a DMF, then please provide a LOA referencing the submission date(s), Volume(s), Section(s) and page(s) number where this specific information can be located.

Please respond to the information request by **close of business tomorrow Thursday, March 2, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **close of business tomorrow Thursday, March 2, 2017**.

Please contact me if you have any questions.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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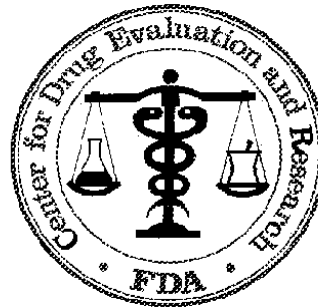
/s/

ALBERTA E DAVIS WARREN
03/01/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet 3
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: February 16, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Microbiological section of your submission, we have the following Information Request:

1.



(b) (4)

(b) (4) If the information is contained within a DMF, then please provide an LOA from the DMF holder indicating the submission dates and location of the relevant information.

2.



(b) (4)

3. Please indicate the dilution that will be used for routine bacterial endotoxins testing of the finished drug product.

Please respond to the information request by **February 27, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **February 27, 2017**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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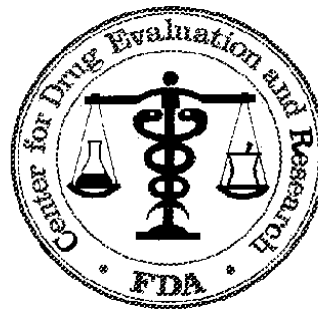
/s/

ALBERTA E DAVIS WARREN
02/16/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet 2
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: February 14, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the CMC section of your submission, we have the following Information Request:

Provide a drug product sample kit for the preparation of Technetium Tc 99m Exametazime (b) (4). Include Vial containing the lyophilized drug product with label, placed in a secondary container with label, label for the radioactive reconstituted solution for pharmacy use, (b) (4) label for the reconstituted solution.

Please deliver the drug product sample kit to the following address:

Alberta Davis-Warren
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5439
10903 New Hampshire Avenue
Silver Spring, Maryland

Use zip code 20903 if shipping via United States Postal Service (USPS).

Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

Please respond to the information request by **February 21, 2017**.

NDA 208870

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
02/14/2017

From: Davis-Warren, Alberta E
To: ["Rana Temsah"; Nuritdinov, Aziz](#)
Cc: [Norman LaFrance MD](#); [Magali Lurquin](#)
Subject: RE: Information request for NDA 208870
Date: Thursday, January 19, 2017 12:53:00 PM
Attachments: [image001.png](#)
[image002.png](#)

Dear Rana,

Please see the following comments:

For Question 5, it is release data. For Question 6, we request that you provide (1) a table of data for assay, impurities (from analysis) and the radiochemical purity. Additionally (for Question 6), we request the HPLC, GC and ITLC chromatograms. Typical chromatograms and tables of raw data that support the method validation package.

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

301-796-3908 office

301-595-7922 fax

Alberta.Davis-Warren@fda.hhs.gov

FDA does not ensure the security of email communications. If you desire to communicate by secure email, please establish a secure email channel by contacting SecureEmail@fda.hhs.gov.

From: Rana Temsah [<mailto:rtemsah@jdi.jubl.com>]
Sent: Tuesday, January 10, 2017 10:00 AM
To: Davis-Warren, Alberta E; Nuritdinov, Aziz
Cc: Norman LaFrance MD; Magali Lurquin
Subject: RE: Information request for NDA 208870
Importance: High

Dear Alberta,

Thank you for the email. We already started working on the questions but the team needed some clarifications on the following items under Drug product (letter attached) to be able to provide the right answers:

Question 5:

Provide raw data (HPLC, GC and ITLC) for the lyophilized drug product and the reconstituted solution from all the exhibit batches 4L263, 5B142 and 5F648.

The team is asking if we are requested to provide release data or stability data to answer this question.

Question 6:

You have not provided any raw data for assay, impurity analysis and radiochemical purity in the analytical procedure and method validation section. Provide HPLC, GC and ITLC traces to support your analytical method validation package.

The team is asking if providing typical chromatograms would be sufficient to answer this question or we are to provide raw data.

Thank you in advance!

Best regards,

Rana

Spécialiste Sénior, Affaires Règlementaires, JDI
Senior Specialist, Regulatory Affairs, JDI
Ext.: 2079

From: Davis-Warren, Alberta E [mailto:Alberta.Davis-Warren@fda.hhs.gov]
Sent: January-09-17 4:21 PM
To: Nuritdinov, Aziz <Aziz.Nuritdinov@INCResearch.com>
Cc: Rana Temsah <rtemsah@jdi.jubl.com>
Subject: RE: Information request for NDA 208870

Thank you Aziz.
Alberta

From: Nuritdinov, Aziz [mailto:Aziz.Nuritdinov@INCResearch.com]
Sent: Monday, January 09, 2017 3:45 PM
To: Davis-Warren, Alberta E
Cc: Rana Temsah (rtemsah@jdi.jubl.com)
Subject: RE: Information request for NDA 208870

Dear Alberta,

Thank you for the email. I confirm receipt of this correspondence.

Regards,

Aziz R. Nuritdinov | Regulatory Associate | Regulatory Strategy, Consulting & Submissions
INC Research | 4800 Falls of Neuse Rd. | Suite 600 | Raleigh, NC 27609, USA
Office (513) 763-4219 | Fax (513) 763-7628
aziz.nuritdinov@incresearch.com | www.incresearch.com | **INC Research®**



From: Davis-Warren, Alberta E [<mailto:Alberta.Davis-Warren@fda.hhs.gov>]
Sent: Monday, January 09, 2017 11:11 AM
To: Nuritdinov, Aziz
Cc: Rana Temsah (rtemsah@jdi.jubl.com); SM_GRC_Email
Subject: Information request for NDA 208870

Dear Aziz,

Please see the attached information request regarding NDA 208870.

Please contact me if you have any questions and please confirm receipt of email.

Thank you,
Alberta

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-595-7922 fax
Alberta.Davis-Warren@fda.hhs.gov

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Notice:

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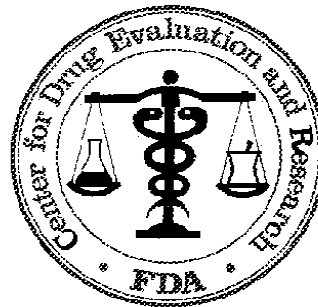
/s/

ALBERTA E DAVIS WARREN
01/19/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet 2
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: January 13, 2017

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Biopharmaceutics section of your submission, we have the following Information Request:

The submission of % cell efflux radioactivity (%CER) in the requested format is acknowledged. However, it is noted that the %CER data in Table 2 of the response to information request document [0008(8); 12/19/2016; Module 1.11.4] do not match with the data in .xpt file titled 'cer – Cell Efflux Radioactivity' [0008(8); 12/19/2016; Module 3.2.P.2]. Specifically, the C_{max} and AUC values in Table 2 do not represent the %CER reported for a specific subject. For example, C_{max} and AUC values for Typenex Desc. WSF9826, WTT9680, and WPN4676 (First 12 rows of Table 2), appear to be switched. Such as, C_{max} and AUC values of WSF9826 presented in Table 2 (first 4 rows of Table 2) are actually the values for WPN4676 (Rows # 9-12 of Table 2). This error is also noted in several places of Table 2 (e.g., including but not limited to WSF9881 and WPN5311). Correct these errors and resubmit Table 2.

Please respond to the information request by **12 pm ET, January 23, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **12 pm ET, January 23, 2017**.

Please contact me if you have any questions.

Thank you.
Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products

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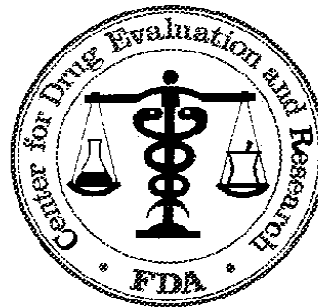
/s/

ALBERTA E DAVIS WARREN
01/13/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To:	<u>Aziz R. Nuritdinov</u>	From:	<u>Alberta Davis-Warren</u>
FAX/EMAIL	<u>aziz.nuritdinov@incresearch.com</u>	FAX:	<u>301-595-7922</u>
Phone:	<u>513-763-4219</u>	Phone:	<u>301-796-3908</u>
Pages, including cover sheet	<u>3</u>	Date:	<u>January 9, 2017</u>
RE: <u>Information Request for NDA 208870</u>			

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the CMC section of your submission, we have the following Information Request:

Drug Product

1. You have provided the drug product composition table for the lyophilized material in your original submission. In our earlier information request dated 09/15/16, we have asked you to provide the drug product composition table for the reconstituted solution. Your reconstituted drug product composition table 3.2.P.1-1 provided in Section 3.2.P.1 does not contain any radioactivity (Tc 99m) information; instead it is provided in the note section. Provide a separate drug product composition table for the final reconstituted solution including radioactivity information in the table.
2. In our earlier information request sent on 09/15/16, we recommended that you validate the ITLC method against an HPLC method for the reconstituted solution. Provide raw HPLC and ITLC data, for example original chromatogram traces to show that your ITLC method is equivalent or better than the HPLC method.
3. Your release specification limit for the Sn content is (b) (4) µg/vial. Stannous chloride content for one of your exhibit batches (4L263) is (b) (4) µg and it is decreased to (b) (4) µg/vial (upright/inverted) at long term storage condition after storing at 12 months. Based on this observation the drug product with (b) (4) µg stannous chloride content at release may fail upon storage. We recommend that you either revise your stannous chloride content at release or provide data for your drug product with (b) (4) µg stannous chloride content to establish shelf life.

4. Your radiochemical purity for the three exhibit batches is > (b) (4) %. We recommend you to revise the limit for radiochemical purity of the reconstituted solution from (b) (4) % to (b) (4) % based on the data.
5. Provide raw data (HPLC, GC and ITLC) for the lyophilized drug product and the reconstituted solution from all the exhibit batches 4L263, 5B142 and 5F648.
6. You have not provided any raw data for assay, impurity analysis and radiochemical purity in the analytical procedure and method validation section. Provide HPLC, GC and ITLC traces to support your analytical method validation package.
7. In order to show that your analytical method is stability indicating, provide raw HPLC data to support your forced degradation study results for the drug product.
8. Provide extractables and leachables profile for your container and closures.

Process

1. You have provided the extractables and leachables profile for the equipment used in the manufacturing of the lyophilized product in section 3.2.P.3.5.2.2 and mentioned that there is no detectable amounts of leachables in the sample. Provide the summary of extractables and leachables and the amount found in a tabular form under all testing conditions.
2. (b) (4)
Also justify how this information from your exhibit batch will be used to control your commercial batches.
3. (b) (4)
Clarify how the risk is mitigated.
4. Provide the hold time study results for your exhibit batches.
5. We acknowledge that you have provided a yield report for the exhibit batches. Provide a table for actual, reconciliation and rejection yields for preparation of (b) (4) for all the 3 exhibit batches and propose yield limits for your commercial batches for all the stages.

Please respond to the information request by **February 1, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **February 1, 2017**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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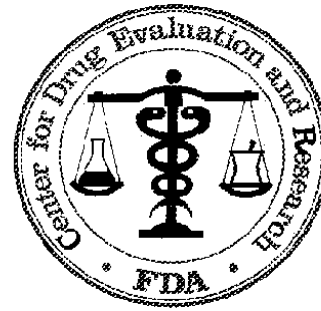
/s/

ALBERTA E DAVIS WARREN
01/09/2017

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet: 4
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: December 7, 2016

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of the Microbiology section of your submission, we have the following Information Request:

1. In regard to building and facilities, please provide information regarding pressure differentials and personnel flow within the controlled and uncontrolled areas in the manufacturing and filling area indicated for routine production of the subject drug product.

2. With regard to manufacturing of the drug product:

a)

b)

c)

(b) (4)

3.

4.

5.

6.

7.

(b) (4)

8.

Please respond to the information request by **January 7, 2017**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **January 7, 2017**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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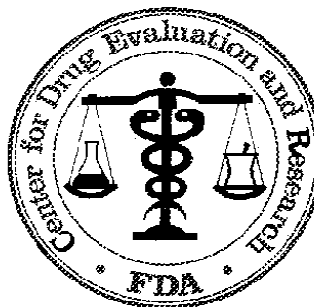
/s/

ALBERTA E DAVIS WARREN
12/07/2016

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov

FAX/EMAIL aziz.nuritdinov@incresearch.com

Phone: 513-763-4219

Pages, including cover sheet:5

RE: Information Request for NDA 208870

From: Alberta Davis-Warren

FAX: 301-595-7922

Phone: 301-796-3908

Date: December 5, 2016

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Request:

BIOPHARMACEUTICS INFORMATION REQUEST

The submission of responses to 74 day letter biopharmaceutics comments is acknowledged. However, in order to continue reviewing your submission, providing the following additional information/data:

1. The submitted % labeling efficiency and % cell efflux radioactivity data are not in an appropriate format for review purposes. Provide these datasets as SAS transport files (.xpt files) in the following format (Table 1 and 2). If relevant, provide definition files for the dataset requested in the above file format.

Table 1. % Labeling Efficiency (Reference and Test Product)

<i>Date</i>	<i>Subject/blood sample</i>	<i>Gender</i>	<i>Age</i>	<i>Fast/Fed state</i>	<i>Typenex Desc.</i>	<i>Product</i>	<i>Vial Lot Number</i>	<i>Radioactivity associated with WBC (A) (units)</i>	<i>Radioactivity associated with LPP Wash (B) (units)</i>	<i>% Labelling Efficiency [(A/(A+B))×100]</i>
	1			Fast	WSF9826	Reference	13055380			
	1			Fast	WTT9680	Test	5B142			
	1			Fast	WPN4676	Reference	13055380			
	1			Fast	WTW0315	Test	5F648			
	2									
	2									
	2									
	2									

Table 2. % Cell Efflux Radioactivity (Reference and Test Product)

Date	Subject/blood sample	Gender	Age	Fast/Fed state	Typenex Desc.	Product	Vial Lot Number	Time (min)	Radioactivity in cells (mCi) (E)	Radioactivity in supernatant (mCi) (F)	% Cell efflux radioactivity $[(F \times 100)/(E + F)]$	C _{max}	AUC _{0-t}
	1			Fast	WSF9826	Reference	13055380	15					
	1			Fast	WSF9826	Reference	13055380	90					
	1			Fast	WSF9826	Reference	13055380	180					
	1			Fast	WSF9826	Reference	13055380	240					
	1			Fast	WTT9680	Test	5B142	15					
	1			Fast	WTT9680	Test	5B142	90					
	1			Fast	WTT9680	Test	5B142	180					
	1			Fast	WTT9680	Test	5B142	240					
	1			Fast	WPN4676	Reference	13055380	15					
	1			Fast	WPN4676	Reference	13055380	90					
	1			Fast	WPN4676	Reference	13055380	180					
	1			Fast	WPN4676	Reference	13055380	240					
	1			Fast	WTW0315	Test	5F648	15					
	1			Fast	WTW0315	Test	5F648	90					
	1			Fast	WTW0315	Test	5F648	180					
	1			Fast	WTW0315	Test	5F648	240					
	2												
	2												
	2												
	2												

2. Submit radiochemical purity, WBC count, and cell viability data in the above similar format.
3. Provide the radioactivity measurement units of the labeling data [WBC (A) and LPP (B)] provided in Table 3A(1) and 3A(2) of submitted Appendices [0007(7) dated 10/31/2016, 3.2.P.2].
4. It is noted that, though %labeling efficiency data were analyzed using two one-sided t-test, the absolute differences between test and reference were used instead of the test and reference ratio for in vitro BE analysis. Therefore, provide the two one-sided t-test statistical analyses for % labeling

NDA 208870

efficiency and apply 90% confidence interval approach. The acceptance criteria for the ratio of the product averages to conclude bioequivalence should be between 80-125%. Conduct the statistical analysis comparing each test lot to each RLD lot by the above recommended approach.

Please respond to the information request by **COB, December 19, 2016**. Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **COB, December 19, 2016**.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
12/05/2016



NDA 208870

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Jubilant DraxImage Inc.
c/o Aziz R. Nuritdinov
U.S. Agent-Regulatory Associate, Regulatory Strategy, Consulting & Submissions
INC Research, LLC
441 Vine Street, Suite 400
Cincinnati, OH 45202

Dear Mr. Nuritdinov:

Please refer to your New Drug Application (NDA) dated July 15, 2016, received July 20, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4)

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 **Standard**. Therefore, the user fee goal date is May 20, 2017.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 22, 2017.

During our filing review of your application, we identified the following potential review issues:

Biopharmaceutics:

We acknowledge that a formal biowaiver request for the proposed Kit for Preparation of Technetium Tc 99m Exametazime (b) (4) has been submitted referencing 21 CFR 320.22 (b)(1)(i) and (ii) and is further supported by quality comparability and in vitro equivalence study comparing the test and reference drug product (Ceretek™). We have identified the lack of some

relevant information. In order to continue reviewing your submission, please provide the following information/data.

- a. Reference is made in the In Vitro Equivalence Study report [0001(1), Module 3.2.P.2] to the following:
 - i. Appendix C (Raw Data in Appendix M, pg 16) for WBC counts,
 - ii. Appendix D (Raw Data in Appendix L, pg 17), for radiochemical purity for each vial,
 - iii. Appendix E (Raw Data in Appendix N, pg 18) for labeling efficiency,
 - iv. Appendix F (Raw Data in Appendix O, Pg 23) for cell viability, and
 - v. Appendix G (Raw Data in Appendix P, Pg 23) for cell efflux.

However, these Appendices are not presented in the report. Submit the referenced Appendices and related individual sample data for the above attributes.

- b. We note that RLD lot # 12966581 (expiry date – (b) (4)) was tested in the in vitro equivalence study past its expiry (testing dates – (b) (4) for blood samples # 22 to 27). Provide justification on the use of the expired RLD lot in the in vitro equivalence study.
- c. Provide rationale for not using both RLD lots for blood samples from all subjects for in vitro equivalence study. For example, RLD lot # 12966581 is used for blood sample # 22 to 25; whereas, for blood sample # 1 to 21, RLD lot # 13053380 is used. Two blood samples (# 26 and 27) used both RLD lots for the in vitro equivalence study.
- d. Provide in vitro equivalence data analysis by batch (i.e., comparing each test lot to each RLD lot). Alternatively, provide in vitro equivalence data analysis considering the comparison of each test lot with RLD lot # 13053380.
- e. We note that blood samples were collected from two groups of healthy adult donors that – (1) were in well hydrated fasted state; and (2) were on a standardized meal. Provide a rationale for using blood samples from both groups of subjects for in vitro equivalence study. Identify the blood samples from fasted or fed state subject(s) in Table 2 of in vitro equivalence study report [0001(1), Module 3.2.P.2, Pg 18 of the report]. Consider including fasted and fed state as a covariate for in vitro equivalence data analysis or provide justification for pooling data from both groups for equivalence analysis.

CMC:

1. In Table 3.2.P.1-1, you provided the quantitative composition of the kit. In addition, please also provide a quantitative composition table for the reconstituted Tc 99m Exametazime (b) (4) drug product.
2. Your release specification for the reconstituted drug product includes only the attributes of pH, and radiochemical purity by TLC. Include radionuclidic identity, purity and radiochemical purity as part of your release specification. We recommend that you validate your TLC method for radiochemical purity against an HPLC method.
3. Provide information about the Tc99m generator(s) used to radiolabel the kit from your exhibit batches along with batch record and batch analysis data for the reconstituted solution.
4. Submit three drug product samples from each lot of your exhibit batches (Lot 4L263, Lot 5B142 and Lot 5F648).

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. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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, we have identified the following labeling issues and have the following labeling comments:

1. The preferred presentation for cross-references in the Full Prescribing Information, (FPI) is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”
2. Please remove the cross-reference in the Contraindications section of the FPI. If no contraindications are known, this section must state, “None”.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 7, 2016. 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.

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, 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). 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) 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call Alberta Davis-Warren, Regulatory Project Manager, at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

LIBERO L MARZELLA
09/15/2016

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet: 2
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: September 12, 2016

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Request:

We request you submit all labels and worksheets listed on carton labeling.

These include:

- **Radiation labels**
- **Labeling Efficiency/Radiochemical Purity Testing worksheets**
- **Leukocyte labeling schematic**

Please submit by COB, September 20, 2016.

Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **COB, September 20, 2016.**

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
09/12/2016

From: [Davis-Warren, Alberta E](#)
To: ["Marie Pierre Ekoka"](#)
Cc: ["Magali Lurquin"](#); ["Norman LaFrance MD"](#); ["Nuritdinov, Aziz"](#)
Subject: RE: NDA 208870 / eCTD sequence 0005 - Response to the FDA Information Request (Ref. ID 3982962) - Revised label- additional clarification
Date: Friday, September 09, 2016 3:01:52 PM

Dear Marie-Pierre,

As per our conversation, here is the revised information request:

Please submit a current annotated draft label in which every change (added words or deleted words) compared to the RLD (Ceretec NDA 19829) label are shown in color.

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren

Regulatory Health Project Manager

Division of Medical Imaging Products

Office of Drug Evaluation IV

301-796-3908 office

301-595-7922 fax

Alberta.Davis-Warren@fda.hhs.gov

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From: Davis-Warren, Alberta E
Sent: Friday, September 09, 2016 2:11 PM
To: 'Marie Pierre Ekoka'
Cc: Magali Lurquin; Norman LaFrance MD; 'Nuritdinov, Aziz'
Subject: RE: NDA 208870 / eCTD sequence 0005 - Response to the FDA Information Request (Ref. ID 3982962) -Revised label

Dear Marie-Pierre,

In regards to submitting the revised label to the FDA gateway, submit a current annotated draft label in which your changes (additions or deletions) from the relied upon product (Ceretec NDA 19829) are clearly marked. We prefer these changes in red or "tracked changes" mode.

Please submit the revised label by noon ET, Tuesday September 13, 2016.

Please contact me if you have any questions.

Thank you,
Alberta

Alberta E. Davis-Warren

Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
301-796-3908 office
301-595-7922 fax

Alberta.Davis-Warren@fda.hhs.gov

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From: Marie Pierre Ekoka [\[mailto:mpekoka@jdi.jubl.com\]](mailto:mpekoka@jdi.jubl.com)

Sent: Friday, September 09, 2016 12:03 PM

To: Davis-Warren, Alberta E

Cc: Magali Lurquin; Norman LaFrance MD; 'Nuritdinov, Aziz'

Subject: TR: NDA 208870 / eCTD sequence 0005 - Response to the FDA Information Request (Ref. ID 3982962)

Importance: High

Dear Alberta,

I noticed a bug in the file "annotated-draft-labeling-text.pdf" that I sent in the previous e-mail. The comments' panel did not appear. So, I'm re-sending with the correct file.

Kind regards,
Marie-Pierre

Marie-Pierre Ekoka, M.Sc.

Senior Project Leader, Regulatory Affairs

Jubilant DraxImage Inc.

16751, Trans-Canada Highway

Kirkland, QC, Canada H9H 4J4

Tel: (514) 630-7045 | Fax: (514) 694-9295

www.draximage.com

 Thank you for considering our environment before printing this document.

De : Marie Pierre Ekoka

Envoyé : 9 septembre 2016 11:45

À : 'Davis-Warren, Alberta E'

Cc : Magali Lurquin; Norman LaFrance MD; 'Nuritdinov, Aziz'

Objet : NDA 208870 / eCTD sequence 0005 - Response to the FDA Information Request (Ref. ID 3982962)

Importance : Haute

Dear Alberta,

This is to inform you that an amendment to our NDA 208870 for Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4) will be submitted early next week through the FDA gateway (ESG) as the eCTD sequence 0005 of this application. We are targeting Monday or Tuesday

at the latest for the official submission of this eCTD sequence through ESG. However, you will be informed on any change, in the event we experience some issues or delay in the execution.

As kindly offered in your letter (Reference ID 3982962), in order to expedite the review process, please find attached a courtesy copy of this submission. The conversion of the revised labeling to XML is ongoing and the resulting SPL files will be submitted in the official eCTD submission.

Should you need additional information regarding this, please do not hesitate to communicate with me.

Kindest regards,
Marie-Pierre

Marie-Pierre Ekoka, M.Sc.

Senior Project Leader, Regulatory Affairs

Jubilant DraxImage Inc.

16751, Trans-Canada Highway

Kirkland, QC, Canada H9H 4J4

Tel: (514) 630-7045 | Fax: (514) 694-9295

www.draximage.com

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/s/

ALBERTA E DAVIS WARREN
09/09/2016

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To: Aziz R. Nuritdinov
FAX/EMAIL aziz.nuritdinov@incresearch.com
Phone: 513-763-4219
Pages, including cover sheet: 3
RE: Information Request for NDA 208870

From: Alberta Davis-Warren
FAX: 301-595-7922
Phone: 301-796-3908
Date: September 7, 2016

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the address above by mail. Thank you.

Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Request:

We note your proposed indication statement is importantly different from the current approved USPI for Ceretec (NDA 19829). Your proposed indication for Exametazime (b) (4)

[Redacted content]

Please respond to this request by no later than **Friday noon ET, September 9, 2016.**

Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by **Friday noon ET, September 9, 2016.**

NDA 208870

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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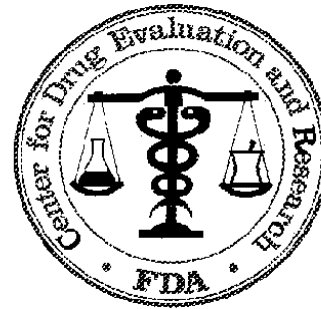
/s/

ALBERTA E DAVIS WARREN
09/07/2016

FAX

**FOOD AND DRUG ADMINISTRATION
DIVISION OF MEDICAL IMAGING PRODUCTS**

5901-B Ammendale Road
Beltsville, Maryland 20705



To:	<u>Aziz R. Nuritdinov</u>	From:	<u>Alberta Davis-Warren</u>
FAX/EMAIL	<u>aziz.nuritdinov@incresearch.com</u>	FAX:	<u>301-595-7922</u>
Phone:	<u>513-763-4219</u>	Phone:	<u>301-796-3908</u>
Pages, including cover sheet:	<u>3</u>	Date:	<u>August 10, 2016</u>
RE: <u>Information Request for NDA 208870</u>			

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Dear Mr. Nuritdinov:

We make reference to your New Drug Application (NDA) for Kit for the Preparation of Technetium Tc99m Exametazime (b) (4) dated July 15, 2016, received on July 20, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act. During our review of your submission, we have the following Information Request:

On December 4, 2014, the Food and Drug Administration published the "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015.

During our preliminary review of your submitted labeling, we found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information by 8/30/16

- a review and summary of all available published literature regarding Technetium TC-99 Exametazime [also known as hexamethylpropylene amine oxime (HM-PAO)] use in pregnant and lactating women,
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format

NDA 208870

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please submit an amendment to your application with your response to the request using the official channels. To expedite the review process, please send me a courtesy copy through e-mail (Alberta.Davis-Warren@fda.hhs.gov) by August 30, 2016.

Please contact me if you have any questions.

Thank you.

Alberta E. Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
CDER, FDA

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/s/

ALBERTA E DAVIS WARREN
08/10/2016



NDA 208870

NDA ACKNOWLEDGMENT

Jubilant DraxImage Inc.
c/o Aziz R. Nuritdinov
U.S. Agent-Regulatory Associate, Regulatory Strategy, Consulting & Submissions
INC Research, LLC
441 Vine Street, Suite 400
Cincinnati, OH 45202

Dear Mr. Nuritdinov:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Kit for the Preparation of Technetium Tc 99m Exametazime (b) (4)

Date of Application: July 15, 2016

Date of Receipt: July 20, 2016

Our Reference Number: NDA 208870

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 18, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

ALBERTA E DAVIS WARREN
07/28/2016



PIND 123604

**MEETING REQUEST-
WRITTEN RESPONSES**

INC Research, LLC
Attention: Susan P. Spooner, Ph.D.
US Agent for Jubilant DraxImage Inc.
4800 Falls of Neuse Road
Suite 600
Raleigh, NC 27609

Dear Dr. Spooner:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Kit for the Preparation of Tc-99m Exametazime (b) (4)

We also refer to your submission dated September 28, 2015, containing a Type C meeting request. The purpose of the requested meeting was to obtain feedback on the proposed *in vitro* White Blood Cell (WBC) labeling study protocol.

Further reference is made to our Meeting Granted letter dated October 8, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your September 28, 2015 background package.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure: Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: PIND 123604
Product Name: Kit for the Preparation of Tc-99m Exametazime (b) (4)
Indication: Indicated for the leukocyte label scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease
Sponsor/Applicant Name: Jubilant DraxImage Inc.
Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

On September 24, 2014, Jubilant DraxImage Inc. had a Type B Pre-IND meeting with the Division of Medical Imaging Products. The purpose of the meeting was to discuss the regulatory strategy and development data needed to support a 505(b)(2) NDA for the Kit for the Preparation of Technetium Tc-99m Exametazime (b) (4). The reference listed drug (RLD) for this product is NDA 19829, Ceretec. The difference between this NDA and the RLD is the sponsor will be seeking approval for only one of the two approved indications: leukocyte labeled scintigraphy as an adjunct in the localization of intra-abdominal infection and inflammatory bowel disease. (b) (4). For the September 24th meeting, FDA provided feedback to the sponsor regarding their request for a biowaiver based on 21 CFR 320.22. FDA stated that the request for a biowaiver appears reasonable; however, granting the biowaiver is a review issue and will be evaluated during the NDA review period. FDA also requested that the sponsor include *in vitro* equivalence study results for the White blood Cell (WBC) radiolabeling efficiency in the NDA submission to support the biowaiver request. In addition, FDA recommended the sponsor provide a formal study protocol draft for the Agency to review and provide feedback. The purpose for this written responses only meeting is to obtain feedback on the proposed *in vitro* WBC labeling study protocol.

2.0 QUESTIONS AND RESPONSES

We have reviewed the Meeting Package submitted on September 28, 2015, and provide the following response to your question in bold font.

Does the FDA find the design of the proposed *in vitro* bioequivalence study protocol acceptable for ensuring the equivalency of Jubilant DraxImage (JDI)'s product with the reference drug, Ceretec, for the White Blood Cell (WBC) radiolabeling efficiency?

FDA Response:

1. We agree with the use of labeling efficiency and efflux radioactivity as the metrics for assessment of bioequivalence.
2. Regarding efflux radioactivity: the area under the curve (AUC) of the efflux versus time curve should be the endpoint used for statistics. This requires that the protocol be modified to increase sampling so that an AUC can be determined. Please justify your choice of the duration over which you will sample and the timepoints of sampling.
3.  (b) (4)
4. We recommend that you provide power calculations (80% to 90%) and relevant sample sizes based on varied estimates of the variability in labeling efficiency and efflux radioactivity. For a broad range of drugs, a confidence interval limit of log-transformed 20% (i.e., 80% to 125%) for the ratio of the product averages (geometric mean) has been adopted for use as the criterion for concluding BE. Please justify an appropriate CI limit based on the range of acceptable performance for labeling efficiency and efflux radioactivity.
5. Please clarify what is meant by a drug performance test in the table shown on page 10.

3.0 ADDITIONAL COMMENTS **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [*PLR Requirements for Prescribing Information*](#) and [*PLLR Requirements for Prescribing Information*](#) websites including:

- 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 related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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/s/

ALBERTA E DAVIS WARREN
12/04/2015



PIND123604

MEETING MINUTES

INC Research, LLC
Attention: Gregory M. Hockel, Ph.D.
US agent for Jubilant DraxImage Inc.
7361 Calhoun Place, Suite 500
Rockville, MD 20855

Dear Dr. Hockel:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Kit for the Preparation of TechnetiumTc-99m Exametazime (b) (4)

We also refer to the telecon between representatives of your firm and the FDA on September 24, 2014. The purpose of the meeting was to discuss the regulatory strategy and development data needed to support a 505(b)(2)NDA for the proposed product.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

10 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

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10/21/2014