

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202153Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **202153**

SUPPL #

HFD #

Trade Name **Ruby-Fill**

Generic Name **Rubidium-RB-82 Chloride**

Applicant Name **Jubilant Draximage Inc.**

Approval Date, If Known **September 30, 2016**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒

NO ☐

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

505(b)(2)

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

YES ☐

NO ☒

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

This application relied on published literature, including literature on CardioGen-82 and Labeling and FDA's previous finding of safety and effectiveness (clinical,nonclinical and CMC)

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

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☒

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# 19414

CardioGen-82 (rubidium Rb-82 Chloride) generator

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could

independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

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

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

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2

YES ☐

NO ☐

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

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

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

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

Investigation #1

IND #

YES ☐

!
!
! NO ☐
! Explain:

Investigation #2

IND #

YES ☐

!
!
! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐

NO ☐

If yes, explain:

=====

Name of person completing form: **Frank A. Lutterodt**

Title: **Senior Regulatory Project Manager, Division of Medical Imaging Products**

Date: **September 27, 2016**

Name of Division Director signing form: **Libero Marzella**

Title: **Director, Division of Medical Imaging Products**

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

APPEARS THIS WAY ON ORIGINAL

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

/s/

FRANK A LUTTERODT
09/28/2016

LIBERO L MARZELLA
09/28/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202153	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ruby-Fill Established/Proper Name: Rubidium RB 82 Generator Dosage Form: Injection		Applicant: Jubilant Draximage Inc. Agent for Applicant (if applicable): INC., Research LLC
RPM: Frank Lutterodt		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: September 20, 2016 <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 September 30, 2016		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☐ None CR-12-18-2014
❖ 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

BLAs: Subpart E

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

Subpart H

- ☐ Approval based on animal studies

- !! FORMCHECKBOX ¹ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

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) Approval
9/30/16

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)
- Original applicant-proposed labeling

☒ Included

☒ 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/non-acceptability letter(s) (indicate date(s))
- Review(s) (indicate date(s))

3/16/16 Granted
3/9/16

❖ Labeling reviews (indicate dates of reviews)

RPM: ☒ None
DMEPA: ☐ None 6/7/16
DMPP/PLT (DRISK):
☒ None
OPDP: ☐ None 9/15/16
SEALD: ☒ None
CSS: ☐ None
Product Quality ☒ None
Other: ☐ None ADL-9/14/16

Administrative / Regulatory Documents

❖ RPM Filing Review⁴/Memo of Filing Meeting (indicate date of each review)

10/26/2010

❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee

☐ Not a (b)(2) 12/21/15 and
9/12/16

❖ NDAs/NDA supplements only: Exclusivity Summary (signed by Division Director)

☒ Completed

❖ Application Integrity Policy (AIP) Status and Related Documents
<http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm>

- Applicant is on the AIP

☐ Yes ☒ No

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

- 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 (approvals only) - Date reviewed by PeRC _____ - If PeRC review not necessary, explain: _____	Does not Trigger PREA
❖ 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>	
❖ 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)	
❖ 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 9/19/16
Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	☒ No mtg
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>	
❖ 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 TBD
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	☐ None TBD
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)	N/A
• 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)	6/18/2010
❖ 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
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

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
❖ 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 9/23/16
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	☐ None 9/21/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	☐ None CDRH 9/29/16
❖ 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)	9/21/16
☐ Review & FONSI (indicate date of review)	
☒ Review & Environmental Impact Statement (indicate date of each review)	9/21/16
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	☒ Acceptable- 1/29/2016 Re-evaluation date: ☐ 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): <u>Flush List</u> • Notify the Division of Online Communications, Office of Communications	☐ Done N/A
❖ 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 N/A
❖ 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	☒ Done



NDA 202-153

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Jubilant DraxImage, Inc.
Attention: Aziz R. Nuritdinov
Regulatory Associate, Regulatory
Strategy, Consulting & Submissions
Inc. Research, LLC, US Agent
441 Vine Street, Suite 400
Cincinnati, OH 45202

Dear Mr. Nuritdinov:

Please refer to your New Drug Application (NDA) resubmission dated December 28, 2015, received December 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ruby-Fill® (Rubidium Rb-82 Generator (b) (4) mCi).

On June 15, 2016, we received your June 11, 2016, 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 September 30, 2016.

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 September 16, 2016.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

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

CC: Magali Lurquin
Associate Director, Regulatory Affairs
Jubilant DraxImage Inc.
16751 Trans-Canada Highway
Kirkland, Quebec, Canada, H9H 4J4

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
06/29/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202153

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

INC Research, LLC
US Agent for
Jubilant DraxImage, Inc.
4800 Falls of Neuse Road, Suite 600
Raleigh, NC 27609

ATTENTION: Susan P. Spooner, Ph.D.
Associate Director/INC Research, LLC

Dear Dr. Spooner:

Please refer to your New Drug Application (NDA) Class 2 Resubmission dated December 28, 2015, received December 30, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rubidium Rb-82 Generator Injection.

We also refer to your December 22, 2015, correspondence, received December 23, 2015, requesting review of your proposed proprietary name, Ruby-Fill.

We have completed our review of the proposed proprietary name, Ruby-Fill and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your December 22, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Frank Lutterodt, Regulatory Project Manager in the Office of New Drugs at (301) 796-4251.

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/

LOUIS R FLOWERS

03/16/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES

03/16/2016



NDA 202-153

**ACKNOWLEDGE –
CLASS 2 RESUBMISSION**

INC Research LLC
US Agent for
Jubilant Draximage Inc.
Attention: Susan P. Spooner, Ph.D.
Associate Director, Regulatory Strategy, Consulting and Submissions
4800 Falls of Neuse Road, Suite 600
Raleigh, NC 27609

Dear Dr. Spooner:

We acknowledge receipt on December 30, 2015, of your December 28, 2015, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (b) (4) (Rubidium Rb-82 Generator (b) (4) mCi).

We consider this a complete, class 2 response to our December 18, 2014 action letter. Therefore, the user fee goal date is June 30, 2016.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Senior Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

CC: Magali Lurquin
Associate Director, Regulatory Affairs
Jubilant DraxImage Inc.
16751 Trans-Canada Highway
Kirkland, Quebec, Canada, H9H 4J4

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/s/

FRANK A LUTTERODT
01/08/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202153

MEETING MINUTES

INC Research LLC
Attention: Susan P. Spooner, Ph.D.
U.S. Agent for Jubilant Draximage Inc.
4800 Falls of Neuse Rd., suite 600
Raleigh, NC 27609

Dear Dr. Spooner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We also refer to the telecon between representatives of your firm and the FDA on July 20, 2015. The purpose of the meeting was to discuss your Usability Study protocol, Microbial challenge and cross-contamination protocols and Annual drug safety reports. .

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 Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

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

Norman LaFrance MD, ME, FACP, FACNP
Chief Medical Officer,
Senior Vice President, Medical & Regulatory Affairs
Jubilant Draximage Inc, Jubilant Pharma Ltd
16751 Trans-Canada Highway
Kirkland, Quebec- Canada H9H4J4

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: July 20, 2015, 2:00PM to 3:00PM
Meeting Location: Teleconference

Application Number: NDA 202-153
Product Name: Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).
Indication: Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease

Applicant Name: Jubilant Draximage Inc.

FDA ATTENDEES

Libero Marzella Gorovets, M.D., Director, Division of Medical Imaging Products, (DMIP)
Alex Gorovets, M.D., Deputy Director, DMIP,
Eldon Leutzinger, Ph.D., CMC Lead, DNDPII
Eric Duffy, Ph.D., Director, DNDPII
Ira Krefting, M.D., Deputy Director for Safety, DMIP
Jessica Cole, Ph.D., Division of Microbiology Assessment, Branch 3
CDR Alan Stevens, Reliability and Mechanical Engineering, OMPT/CDRH/ODE/DAGID/GHDB
Lena Maslov, Pharm. D., Team Lead, CDER DMEPA
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

M. Norman LaFrance, MD, Chief Medical Officer, Senior Vice President, Medical and Regulatory Affairs, Jubilant Draximage Inc., Jubilant Pharma Ltd.

(b) (4) Consultant - (b) (4)
(b) (4) Consultant for JDI (b) (4)

Ms. Tamara Mills, Director, Cardiac PET Products
Ms. Guylaine Roy, PhD, Manager Quality and Regulatory Compliance, Medical Devices
Ms. Anita MacDonald, PET Product Specialist

M. Paul Donnelly, Quality Engineer, Medical Device Manager
Ms. Amanda Donovan, Manager Radioactive Products, R&D
M. Franklin Jean, Quality Control Manager
M. Maxime Lamontagne, Subject Matter Expert, Environmental Surveillance Program,
Jubilant HolisterStier Inc.
Ms. Magali Lurquin, Senior Manager, Regulatory Affairs
Ms. Hiba Soulaihi, Senior Project Leader, Regulatory Affairs

1.0 BACKGROUND

Following receipt of a Complete Response (CR) Letter dated December 18, 2014 for NDA 202-153, Jubilant DraxImage Inc. (JDI) met with FDA on March 18, 2015 to discuss the path forward. During the face-to-face meeting on March 18th 2015, it was agreed that JDI will submit proposed responses and testing strategies to address some of the CR letter questions in one or multiple Type C meeting package(s) for review by the FDA and to confirm that JDI responses are on track to address the FDA CRL inquiries. FDA received a correspondence from JDI on May 5, 2015 requesting a meeting to discuss their usability study protocol, microbial challenge and cross-contamination protocols and annual drug safety reports. The meeting was granted as a Type C teleconference to occur on July 20, 2015 and FDA provided preliminary responses to the applicant on July 17, 2015. JDI provided clarification document to FDA via e-mail on July 20, 2015. The following constitutes the discussion the July 20, 2015 teleconference.

2. DISCUSSION

Introduction

Dr. LaFrance thanked the Agency for this meeting, for the Agency's thorough review and comments to the Meeting Package and asked to waive the introduction of JDI attendees for sake of time. They added that JDI attendees will introduce themselves as they speak and the list of all attendees will be provided in JDI draft Meeting Minutes.

The Agency agreed and its attendees presented themselves.

Dr. LaFrance started the discussion and expressed JDI's satisfaction on the Agency's agreement on most of the questions raised by JDI in the Meeting Package. JDI proposed to add details and clarification on the Microbiology/Viral contamination's question of the Meeting Package in order to address the Agency concerns that were raised in the Agency's Preliminary Meeting Comments. Although sterility data has been previously submitted and found acceptable for the generator's eluent over the 60 day use period, JDI clearly understood the Agency's questions on the system's microbiology contamination and patient cross-contamination questions. The agenda of the Type C meeting TCON was as follows:

Meeting Package Question	Discipline	Topic	Related Questions in the Complete Response Letter (CRL)
1	Clinical	Usability and Training Material	1, 2,
2	Quality	User Manual	4, 12
3	Microbiology	Microbial contamination and Cross-contamination	6e, 6.1, 9d, 19
4	Safety	Safety	Safety question of the CRL

Q1 – Usability and Training Material

- In reference to the Agency Preliminary Meeting Comments, JDI confirmed their understanding that the Agency agreed that no additional Human Factors Study is needed following the changes proposed to (b) (4) the RUBY Rubidium Elution System and the Agency also agreed on the minor classification of the changes proposed to the User Manual. The Agency will review the Human Factors Study data during the application review process.
- JDI requested a clarification regarding the Agency's position on the Training Material that was submitted with the Meeting Package on June 17, 2015. JDI provided a roadmap for the Training Material that was submitted in Appendix 7 of the Meeting Package June 17th and re-sent, for clarity, separately on July 17th with the request to add to the July 20th TCON agenda. The agenda item noted that JDI requested the Agency to confirm the acceptability of the Training Program presented in Appendix 7.

Summary of Q1 discussion:

- The Agency confirmed that Appendix 7, representing the initial and on-going Training Program and the Instructions for Use Manual (IFU), was reviewed and found to be very detailed and satisfactory.
- The Agency requested a clarification about JDI's evaluation of the follow-up Training.
- JDI explained that the original training will be done on the clinical site for the first certification and that the users will be re-certified every 2 years on site unless there are updates to the Software or the User Manual that mandate earlier certification.
- In response to the Agency's question, JDI confirmed that the original training and the follow-up trainings will be done by a JDI's instruction specialist. The agency found this acceptable and was in agreement.

JDI Post-Meeting clarification regarding training of new employee at the site:

As described in Appendix 7 of the Meeting Package, RUBY Training & Certification will be provided to all users by JDI at time of installation. 1-2 super-users are identified at each clinical site (typically this would be a team leader, lead PET/CT technologist, an experienced

technologists expected to be at the site for a long period of time) and could train a new employee at the site **IF** they meet the following criteria:

1. They inform JDI of new employee to be certified
2. Super-user on site has been certified by JDI personnel
3. Super-user has current JDI certification (within 2 years of initial training or latest certification)
4. JDI to provide paperwork to site for certification purposes
5. Super-users can only train and certify technologists at their clinical site

Re-training and re-certification will be provided by JDI every 2 years (or more often if major changes have occurred or major changes in software require re-training onsite) as was indicated during the meeting. Any technologist who was trained by a Super-user onsite would be trained and certified by JDI personnel at that time.

Q2 - User Manual

- JDI acknowledged the Agency requests communicated in the Meeting Preliminary Comments and confirmed that testing per the applicable clauses of the IEC 60601-1 were done, and that JDI will identify these clauses and submit the CSA test reports with this information in the response package to the CRL.

Q3 – Microbial Contamination and Cross-Contamination

- JDI explained that all the information that is included in the 'Micro Clarification Document' and which was sent to the Agency on July 20, 2015 in support to this meeting is excerpted from the appendices provided in the Meeting Package application of June 17, 2015.
- JDI indicated that this document serves to address the Agency issues raised in the Preliminary Meeting Comments.

Summary of Q3 discussion:

1. (b) (4)
 - In response to the Agency's comment (b) (4)
JDI explained (b) (4)
 - The Agency clarified their observation (b) (4)
 - (b) (4)

- The Agency reiterated [REDACTED] (b) (4)
- JDI agreed but reviewed on the call [REDACTED] (b) (4)
- The Agency indicated that the current Media Fill testing strategy (Appendix 15 of the Meeting Package) calls to collect data at different testing points. Particularly, the data to be collected [REDACTED] (b) (4) is currently proposed for 'Information Only'. The Agency stated it would need to re-evaluate its 3rd comment of the Microbiology question if JDI is not intending to declare [REDACTED] (b) (4)
- JDI acknowledged the Agency's rationale and agreed to submit the data to be collected [REDACTED] (b) (4); that is to convert from for 'Information Only' to presentation of the data in the response package to the CRL.
- JDI reiterated that the sterility assurance of the patient dose does not rely on [REDACTED] (b) (4)
- Based on the clarification provided by JDI, the Agency acknowledges its new understanding [REDACTED] (b) (4) but requested from JDI to consider providing the Agency with data from the Media Fill study [REDACTED] (b) (4) to support the sterility of the patient dose and to justify the exclusion of the [REDACTED] (b) (4) test.
- JDI agreed to provide the requested information in the response package to the CRL.
- JDI added that it is intending to perform microbial assessment studies during which the Media Fill testing will be performed and questioned if [REDACTED] (b) (4) testing data collected during that study would be of added value.
- The Agency expressed its concern regarding the capability of the system to maintain aseptic condition for the 60 day use period in the clinical setting. The collection of [REDACTED] (b) (4) testing data as proposed above by JDI may be useful but not required. The Agency is re-considering JDI's proposal to collect the data at two (2) collection points during the Media Fill study as for 'Information Only' if the system is capable of maintaining the sterility [REDACTED] (b) (4). JDI further agreed to include the data to be collected [REDACTED] (b) (4) in the response to the CRL.
- The Agency pointed [REDACTED] (b) (4) and requested JDI consider in its studies [REDACTED] (b) (4) that represent sources for microbial ingress to confirm the sterility of the patient doses during the 60 day use period of the system.

- o JDI agreed to provide all the information collected from the microbial assessment studies within the expiry period (up to 60 days) of the system in the response package to the CRL.
- o In response to the Agency's request for clarification on the data collected on day 63, JDI described the methodology proposed in Appendix 15:
 - o JDI will collect samples from the clinical simulation study throughout the 60 days use period of the generator for sterility and bacterial endotoxins testing.
 - o At day 60, the system will be filled with a growth media and samples will be eluted, collected and tested for any microbial growth.
 - o The system will be refilled with growth media and will be incubated for 3 days. The system will be eluted and the samples collected will be tested for any microbial growth for 'Information Only'.
- o The Agency indicated that it will re-evaluate the data as it becomes available. Most important is the sensitivity of the Media Fill test data in comparison with the periodic testing. For example, if results vary, safety would be questionable
- o In summary, JDI acknowledged and agreed to the Agency's recommendation to provide all the data to be collected during the microbial assessment studies for the Agency's review and assessment of the system capability to maintain its sterility. Specifically, JDI agreed to submit in the response package to the CRL all the information and testing data, including those collected for 'Information Only' during the microbial assessment studies.

JDI Post-Meeting comment:

The product has been used in Canada in clinical setting in over than 22,000 patients without issues of sterility or contamination reported to date. This is an indication of the system's capability to maintain aseptic condition for the 60 day use period in the clinical setting when used as prescribed. The above discussed studies will be performed and data will be presented to the Agency in the response package to the CRL to analytically confirm the absence of contamination in the patient dose.

2. *Dye Ingress Test*

- o JDI concurred with the Agency's comment and agreed to include a positive control in the study protocol.
- o With regard to sensitivity of the method, JDI explained that it will be determined based on the Limit Of Detection and that quantification level of the (b) (4) will be based on a calibration curve.
- o The Agency agreed.

3. *'For Information Data' and Bacterial Endotoxins during the Microbial assessment studies – Appendix 15 of the Meeting Package*

- o JDI indicated that the all the sterility data as previously discussed will be submitted to the Agency in the response package to the CRL. JDI explained that all RUBY-FILL generator components (b) (4) are prepared under controlled conditions and are tested for bacterial endotoxins prior to release. In addition, bacterial endotoxin testing is

planned to be performed during the microbial assessment study as presented in Appendix 15 of the Meeting Package and will also be submitted to the Agency.

- The Agency explained that the reason for their comment pertained to their concern that the system may not be capable of maintaining sterility during the use period of 60 days as it was initially understood. However, following the (b) (4) discussions that occurred above, the Agency acknowledged that sterility can be maintained and the bacterial endotoxins testing will be assessed under JDI plans for the microbial assessment study.

4. Risk Assessment – Viral Contamination

- JDI explained that (b) (4) the RUBY Rubidium Elution System are designed with redundant safety measures that complement each other and contribute to mitigate risks of patient's contamination. Failure of these safety measures has to occur simultaneously for viral contamination to happen.
- In response to the Agency's request about the (b) (4) Study that is mentioned in the 'Micro Clarification Document' provided prior to the meeting, JDI agreed to submit the plan of this study with JDI draft Meeting Minutes and the completed report in the response package to the CRL.
- With respect to the proposed dye ingress study, the Agency asked about the dynamic flow component in the study and its implication on the fault of blood refluxing back into the patient IV line.
- JDI acknowledged the importance of the dynamic component in the dye ingress study, to better reflect the actual conditions of use, and agreed to amend the study to include it. JDI confirmed and summarized that the dye ingress study will include four (4) sequences (b) (4)

(b) (4) The four (4) sequences represent an artificial, worst case scenario as it doubles the typical infusions received by a patient undergoing a rest/stress procedure. The set-up of the system during the study will be as follows:

- (b) (4)
- JDI reviewed that the proposed dye ingress study is very conservative from a standard of care and routine use medical standpoint. Considering that the patient dose is administered by intravenous injection into the peripheral venous system [at several millimeters pressure], which significantly decreases the likelihood/reality of back flow from patient into the patient IV Line [which is replaced for each patient]. Back flow if it occurs, is typically only in the angio cath [actual IV access].
- The Agency concurred that all the faults described in the Agency's Type C Meeting Preliminary responses would need to occur simultaneously for a patient contamination to occur. The dye ingress test, alone, is not sufficient to totally eliminate contamination risk. The Agency added that the table provided in the 'Micro Clarification Document' under the viral risk assessment section is acceptable but further clarified its expectation to provide additional descriptions and probability explanations for the risk of patient contamination.

- o JDI concurred and proposed to establish a risk assessment report once all the proposed studies are completed. Based on the data acquired, the contamination risks including those raised by the Agency will be explained in this report. Residual risks will be evaluated against benefits and will be mitigated wherever feasible. This information will be submitted in the response package to the CRL.
- o The Agency requested JDI to identify (b) (4) and to provide information on their performance specifications.
- o JDI agreed.

Q4 – Safety

JDI clarified that their understanding of the Agency's July 17th Preliminary Responses indicated that no additional safety information other than that submitted in the Meeting Package will be provided in the response package to the CRL. The Agency further stated in its Meeting Preliminary Comments that the benefit/ risk ratio of the product is favorable and not altered by the submitted safety reports. JDI agreed and confirmed this information would be provided in the formal response package to the CRL and no additional safety data is required.

The Agency concurred and is satisfied with the information provided.

Summary and Action Items

- o **JDI summarized the meeting discussion and presented the actions items as follows:**
 - o **Q1: Training Material**
 - The Agency agreed on the adequacy of the Training Material submitted in the Meeting Package.
 - o **Q2: User Manual**
 - The IEC testing and reports (CSA) will be submitted in the response package to the CRL.
 - o **Q3: Microbiology and cross-contamination:**
 - The (b) (4) testing might be performed during the clinical simulation study.
 - All Data from the Media Fill study will be submitted to the Agency in the response package to the CRL, including those initially identified as for 'Information Only'.
 - The dye ingress study plan and protocol will be modified to include specific controls and the dynamic flow component.
 - Summary of the (b) (4) Study will be provided with JDI draft Meeting Minutes.
 - (b) (4) performance specifications will be provided in the response package to the CRL.
 - An overall risk assessment report for the viral contamination will be prepared and submitted in the response package to the CRL. If indicated, this would also be provided in a future Type C meeting request.

Conclusion

The Agency expressed its satisfaction of the discussion, JDI responses and the progress made by JDI for this application. JDI appreciated this feedback as it is keen to provide the Agency the information it needs to allow critical patient access to this important technology.

JDI agreed to send the draft Meeting Minutes to the Agency for the week of July 27, 2015.

In response to the Agency's request, JDI confirmed that the product is currently only used in Canada and in Switzerland [one site].

JDI thanked the Agency for the productive and excellent discussion, guidance and collaboration.

ATTACHMENTS AND HANDOUTS

- FDA's July 17, 2015 Preliminary Responses
- JDI's clarification Document

13 Pages have been Withheld in Full as duplicate copy of AdminCorres 7.17.15 Meeting Preliminary Comments immediately following this page; 5 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

ALEXANDER GOROVETS
08/18/2015



NDA202153

MEETING PRELIMINARY COMMENTS

INC Research LLC
Attention: Mrs. Susan P. Spooner
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
4800 Falls of Neuse Rd., suite 600
Raleigh, NC 27609

Dear Mrs Spooner:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We also refer to your May 5, 2015, correspondence, received May 7, 2015, requesting a meeting to discuss your Usability Study protocol, Microbial challenge and cross-contamination protocols and Annual drug safety reports. Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:

Preliminary Meeting Comments

APPEARS THIS WAY ON ORIGINAL



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Guidance

Meeting Date and Time: July 20, 2015, 2:00PM to 3:00PM
Meeting Location: Teleconference

Application Number: NDA 202-153
Product Name: Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

Indication: Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease

Sponsor/Applicant Name: Draximage, a division of Draxis Specialty Pharmaceuticals Inc.

FDA ATTENDEES (tentative)

Libero Marzella Gorovets, M.D., Director, Division of Medical Imaging Products, (DMIP)
Alex Gorovets, M.D., Deputy Director, Division of Medical Imaging Products, Eldon
Leutzing, Ph.D., CMC Lead, Branch Chief, DNDPII
Ramesh Raghavachari, Ph.D., DNDPII
Ira Krefting, M.D., Deputy Director for Safety, DMIP
Jessica Cole, Ph.D., Division of Microbiology Assessment, Branch 3
LCDR QuynhNhu Nguyen, M.S., Biomedical Engineer/Combination Products Human Factors Specialist, CDER DMEPA
CDR Alan Stevens, Reliability and Mechanical Engineering, OMPT/CDRH/ODE/DAGID/GHDB
Ryan McGowan, Biomedical Engineer, OMPT/CDRH/ODE/DAGID/GHDB
Lena Maslov, Pharm. D., Team Lead, CDER DMEPA
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

M. Norman LaFrance, MD, Chief Medical Officer, Senior Vice President, Medical and Regulatory Affairs, Jubilant Draximage Inc., Jubilant Pharma Ltd.

(b) (4) Consultant - (b) (4)

Ms. Tamara Mills, Director, Cardiac PET Products
Ms. Guylaine Roy, PhD, Manager Quality and Regulatory Compliance, Medical Devices
Ms. Anita MacDonald, PET Product Specialist

M. Paul Donnelly, Quality Engineer, Medical Device Manager
Ms. Amanda Donovan, Manager Radioactive Products, R&D M.
Franklin Jean, Quality Control Manager
M. Maxime Lamontagne, Subject Matter Expert, Environmental Surveillance Program,
Jubilant HolisterStier Inc.
Ms. Lise Bourgon, Pharmacovigilance Leader, Medical and Regulatory Affairs
Ms. Magali Lurquin, Senior Manager, Regulatory Affairs
Ms. Hiba Soulaihi, Senior Project Leader, Regulatory Affairs

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for Monday, July 20,, 2015, 2:00 PM to 3:00 PM, between Draximage and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Following receipt of a Complete Response (CR) Letter dated December 18, 2014 for NDA 202-153, Jubilant DraxImage Inc. (JDI) met with FDA on March 18, 2015 to discuss the path forward. During the face-to-face meeting on March 18th 2015, it was agreed that JDI will submit proposed responses and testing strategies to address some of the CR letter questions in one or multiple Type C meeting package(s) for review by the FDA and to confirm that JDI responses are on track to address the FDA CRL inquiries.

The following constitutes FDA's preliminary responses to questions in the June 17, 2015 meeting package.

2.0 DISCUSSION

2.1 Category/Discipline A

9.1 Clinical

9.1.1 Background Information:

In Question 1 of the FDA Complete Response Letter, the FDA stated that:

‘The reports of the human factor studies titled: “Ruby Rubidium Elution System Summative Usability Validation Report” and “Ruby Rb-82 Elution System Usability Risk Analysis” are materially incomplete and requested the following:

- a. Study protocols;*
- b. Data (in the same format as the Hartford site) from subjects at the Brigham and Women’s and Cardiac Imaging Associates sites participating in the study;*
- c. Training or user manual that was the basis of training for the validation report;*
- d. Mitigation strategies (such as responses to computer input errors) that have been instituted and the report of any additional study performed to confirm the effect of these strategies.’*

In Question 2 of FDA Complete Response Letter, the FDA requested:

‘A training/re-training program and training packages need to be finalized prior to marketing and specifically requested:

- a. an initial and on-going training program and a methodology to evaluate its effectiveness;*
- b. a final version of an Instructions for Use (IFU) document which is structured with a table of contents, index, page numbering and a section on responding to serious patient emergencies involving Ruby-Fill administration. Clarify whether this IFU is intended to also serve as a training manual or if a separate training manual will be provided.’*

To adequately respond to Questions 1 and 2, JDI is providing in this meeting package the original Human Factor Usability Study Protocol utilized for the usability testing, the report, the complete data, the usability FMEA (uFMEA) as well as User Manual that were the basis for user training at the time of usability testing was conducted.

This set of information was collected

(b) (4)

(b) (4)

In the previous meeting package of the Type A meeting that occurred with the FDA on March 18, 2015, JDI explained that this change (b) (4) has no impact on the original Human Factor Usability Study but still proposed a bridging study (b) (4). The FDA concurred with JDI's justification on the minor characterization of the (b) (4) change and determined that a bridging/ additional study is not required to test the (b) (4) change provided that the User Manual contains only minor changes related mostly to the (b) (4) and provided the Agency finds the original Human Factors study results as acceptable upon submission of the full report (Please refer to the FDA comment in the meeting minutes on page 10 of [Appendix 1](#)).

Accordingly, JDI is providing in this meeting package an updated version of the User Manual that includes changes:

- To address the FDA questions raised in the CRL (Questions 2.b, 4 and 12)
 - Other changes proposed by JDI, which are associated with the incorporation of electrical safety and electromagnetic compatibility requirements as per CSA request, a restructuring of content (in a more chronological order), changes to instructions to correspond with revised (b) (4) the addition of images and a change of paragraph structure for the content to a step by step structure (b) (4) for ease of readability for the user. A table of contents, an index as well as page numbers were also added.

All the changes are related to formatting and document structure and are proposed mostly for clarification purposes. The changes did not trigger any significant text content that would affect the usability testing.

FDA Response to 9.1.1

We agree

9.1.2 Question:

JDI is seeking the FDA's review and approval of the original Human Factor Usability Protocol, Reports and Data as well as the FDA's acceptance of the changes proposed to the User Manual.

JDI is requesting this review of Data to ensure that JDI responses are in alignment with the FDA expectations and to confirm that the changes proposed to the User Manual whether requested by the FDA in the CRL or proposed by JDI are acceptable and no additional Human Factor Usability Study (partial or complete) is needed.

Does the Agency concur?

FDA Response to 9.1.2

At this time, we agree that no additional human factors study is needed. However, final determination of the acceptability of your human factor studies will be done during application review process. Additionally, labeling changes to the user manual will be evaluated during NDA review as well.

9.2 Quality

9.2.1 Background Information:

The FDA in its Complete Response Letter to the above mentioned NDA requested details to be added to the User Manual. Specifically, the FDA stated in its request under Question 4:

‘Regarding the Ruby Elution System Instructions for Use (IFU) document:

- a. Clarify the description and sources of the listed supplies, and whether they are supplied by Jubilant DraxImage with the Elution System;*
- b. Specify the recommended (b) (4) (see page 10, supplies);*
- c. Describe and label (b) (4) as they are essential to the operation of the Elution System (page A|1– system consumables).’*

In addition, the FDA had requested, in Question 12 of the CRL, the documentation to support (b) (4) that was stated in the User Manual (version 5) submitted by JDI on March 18, 2014 (Please refer to [Appendix 20](#), page 45) and reviewed by the FDA at that time:

‘The manual states that the system is (b) (4) Please provide documentation to support this claim.’

As part of its response to Questions 1 and 2 of the CRL (discussed above), JDI has revised the User Manual to include the information requested by the FDA in Question 4 and has also removed the reference in the User Manual (b) (4)

(b) (4)

9.2.2 Question:

JDI is submitting herein the updated User Manual and is seeking the FDA's review, acceptability and completeness of the updates to the User Manual that relate specifically to the FDA's request for details described in Questions 4 and 12.

Does the Agency concur?

FDA Response to 9.2.2

The proposal to remove (b) (4) is acceptable. When you resubmit the NDA, please identify the applicable sections (b) (4) and provide the test reports supporting conformance.

9.3 Microbiology**9.3.1 Background Information:**

In the Complete Response Letter (CRL) dated of December 18, 2014 (See [Appendix 2](#)), the FDA communicated queries in Questions 6e, 6.1, 9d and 19 regarding the microbial contamination and cross-contamination for our NDA 202-153.

It was agreed with the FDA during the Type A face-to-face meeting that was held on March 18, 2015 that Microbial challenge and cross-contamination protocols will be submitted in a Type C Meeting Package for FDA review.

Below is the text excerpted from the FDA CRL related to that topic:

□ Question 6.e of the CRL:

'We have identified some of the system hazards that need to be addressed, which include:

e. Biological safety (biocompatibility, sterility, infectious agent cross-contamination between patients). It is noted that the final specifications for the delivery system (b) (4) and accessory components have not been submitted and there is no information in the submission to demonstrate that biocompatibility, sterility, shelf life of disposables, and infectious agent cross-contaminations of patients have been adequately addressed.'

□ Question 6.1 of the CRL:

'Your own analyses may have identified additional system hazards. Please provide a system level hazard analysis (e.g. fault tree analysis) identifying the causes of the system hazards we have identified from our review and any additional system hazards you may have identified. For each identified cause, provide the following:

- a) *Describe the control method for each identified cause.*
- b) *For each cause, provide an explanation justifying the adequacy of the control to mitigate the respective system hazard.*
- c) *Provide evidence verifying the control method adequately addresses the respective cause / hazard.'*

☐ *' Question 9-d of the CRL:*

The submission does not provide information regarding possible degradation of system components over the 60 day use period. Possible causes of safety and effectiveness degradation include the following:

- d. *Microbiological growth.'*

☐ *Question 19 of the CRL:*

' We are concerned about the risk of disease transmission occurring from cross-contamination in devices (b) (4) such as yours. The information in your submission does not provide adequate assurance that the risk of cross-contamination has been adequately mitigated by the design of your system and that the risk outweighed by the benefit (b) (4) Provide the following information:

- a. *Demonstrate that the risk of cross-contamination has been adequately mitigated, which should include suitable challenge testing to support your conclusions.*
- b. *Provide information supporting the conclusion that cross-contamination risks are outweighed by the benefit (b) (4)*

9.3.2 Question:

A risk analysis and evaluation including a Fault-Tree Analysis (FTA) was performed in order to establish the testing strategies to address the microbial contamination and the cross- contamination risks. Testing plans were then prepared to describe the proposed testing strategy.

JDI is presenting the risk assessment document as well as the proposed testing plans in this meeting package for review and approval by the FDA as well as the FDA feedback and recommendation if these submitted plans do not meet the FDA expectations and requirements. With the FDA's concurrence on the proposed testing strategies, detailed protocols will be established and executed. The reports and the data will be submitted in JDI's response to the CRL.

FDA Response to 9.3.2

Does the Agency concur with the proposed testing strategies?

We agree with the overall microbiology testing strategy but have the following comments.

1. We note that (b) (4) is not tested for integrity. The proposed system QC includes (b) (4). Please consider (b) (4) that would be required prior to patient administration. If this is not feasible, the NDA should contain an explanation (b) (4) and a description of how the infection risk to patients (b) (4) is mitigated.
2. The methylene blue dye ingress test described in Appendix 16 3000067-P v01 should include a positive control that demonstrates the test systems are capable of detecting dye ingress, should it occur. The sensitivity of the assays, at a specified methylene blue concentration, should be defined when possible.
3. Results from studies described in Appendix 15 3000069-D v01, including those collected for information only, should be submitted to the Agency for review. As no endotoxin release test is proposed, the results from these studies should be used to understand and address (if applicable) the potential for endotoxin contamination of the final patient dose.
4. The risk assessment in Appendix 14 identifies basic faults that must occur for a viral contamination to happen. These include:

(b) (4)

The dye ingress study provided in Appendix 16 appears to be addressing only the check valve fault and does not address the potential for the other faults to occur. Further, we have the following review issues with the proposed dye ingress study:

- The testing is conducted (b) (4).
The design and performance (b) (4) has not been evaluated.

The response to the CR letter should address the issues with the dye ingress study and should present evidence that the other identified viral contamination faults have been adequately mitigated or verified with evidence.

9.4 Safety

9.4.1 Background Information:

Safety Update Information was requested in the FDA's Complete Response Letter. the FDA stated:

'When you respond to the above deficiencies, include a safety update as described at 21 CFR314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level

1. *Describe in detail any significant changes or findings in the safety profile*
2. *When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:*
 - *Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.*
 - *Present tabulations of the new safety data combined with the original NDA data*
 - *Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above*
 - *For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials*
3. *Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified*
4. *Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events*
5. *Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data*
6. *Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time)*
7. *Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries*
8. *Provide English translations of current approved foreign labeling not previously submitted'*

In the Type A meeting package that was submitted to the FDA on February 13 2015, JDI clarified to the FDA that at time of submission of RUBY-FILL™ (which was initially submitted as a generic product under 505j (2) with the reference listed drug Cardiogen-82), the initial application did not contain clinical data. Following the review of the application and the recommendation given by the FDA, the application under 505j (2) was converted to a 505(b) (2) application. In the process of conversion, it was confirmed by the FDA that the submission did not require clinical data.

Although JDI is not sponsoring any clinical studies using RUBY-FILL® or the RUBY Rubidium Elution System, RUBY-FILL® generators have been distributed to the Canadian ARMI trial (Rubidium-82 - An Alternative Radiopharmaceutical for Myocardial Imaging), and to some hospitals conducting their own small single-site clinical study. Therefore, JDI proposed in that meeting package of the Type A meeting that was held on March 18, 2015 to use the Canadian Annual Drug Safety Reports. JDI explained that this data will include safety reports of adverse events from post-market surveillance and from the literature.

The FDA has agreed to review the available Canadian Annual Drug Safety Reports to be submitted in a formal type C meeting package to confirm the acceptability of these reports or to provide feedback if needed.

9.4.2 Question:

A Safety Update Report has been prepared and is included in this meeting package. The safety report discusses the Safety Data gathered from all the Canadian Annual Drug Safety Reports since September 2011 (date of RUBY-FILL® approval in Canada) as well as the Safety Data captured from September 2014 to March 2015 (a closing date to generate up-to-date information).

JDI is seeking the FDA's review of this Safety Update Report to confirm the Agency's acceptance of the Safety Update information and to confirm that no additional safety information is required for the response to the CRL.

Does the Agency concur?

FDA Response to 9.4.2

We concur that the submitted safety information does not alter the risk benefit ratio.

Additional Comments

We note the progress you have made to date in addressing the issues identified in our CR letter. We will comment on your labeling during the NDA review.

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
07/17/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-153

MEETING MINUTES

INC Research LLC
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Attention: Greg Hockel
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

Dear Mr. Hockel:

Please refer to your New Drug Application (NDA) dated June 18, 2010, received June 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We also refer to the meeting between representatives of your firm and the FDA on March 18, 2015. The purpose of the meeting was to obtain clarifications on some of the questions in the December 18, 2014 Complete Response letter and to discuss the best process to provide the information to FDA.

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

If you have any questions, call Frank Lutterodt, Regulatory Project Manager at (301) 796-4251.

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Stalled Development
Meeting Date and Time: Wednesday, March 18, 2015, 9:30 AM to 11:00 AM
Meeting Location: White Oak Building 22, Conference Room: 1311
Application Number: NDA 202-153
Product Name: Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).
Indication: Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease
Sponsor/Applicant Name: Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Meeting Chair: Libero Marzella
Meeting Recorder: Frank Lutterodt

FDA ATTENDEES

Libero Marzella Gorovets, M.D., Director, Division of Medical Imaging Products, (DMIP)
Alex Gorovets, M.D., Deputy Director, Division of Medical Imaging Products, Eldon
Leutzinger, Ph.D., CMC Lead, Branch Chief, DNDPII
Ramesh Raghavachari, Ph.D., DNDPII
Ira Krefting, M.D., Deputy Director for Safety, DMIP
CDR Alan Stevens, Reliability and Mechanical Engineering, OMPT/CDRH/ODE/DAGID/GHDB
Jessica Cole, Ph.D., Division of Microbiology Assessment, Branch 3
LCDR QuynhNhu Nguyen, M.S., Biomedical Engineer/Combination Products Human Factors Specialist, CDER DMEPA (by phone)
Lena Maslov, Pharm. D., Team Lead, CDER DMEPA
Frank Lutterodt, Senior Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

M. Norman LaFrance, MD, Chief Medical Officer, Senior Vice President, Medical and Regulatory Affairs, Jubilant Draximage Inc., Jubilant Pharma Ltd.
Ms. Tamara Mills, Director, Cardiac PET Products
Ms. Magali Lurquin, Senior Manager, Regulatory Affairs
Ms. Guylaine Roy, Ph.D., Regulatory Affairs Specialist
M. Paul Donnelly, Quality Engineer, Medical Device Manager

Ms. Anita MacDonald, PET Product Specialist

M. Bill Riddoch, Ph.D., Director of R&D

Ms. Amanda Donovan, Manager Radioactive Products, R&D (by phone)

M. Abmel Xiques Castillo, Research Scientist, R&D

M. Étienne Lefort, Project Manager, Medical Device Development (by phone)

Ms. Lise Bourgon, Pharmacovigilance Leader, Medical and Regulatory Affairs (by phone)

(b) (4) Consultant, (b) (4)

1.0 BACKGROUND

Following receipt of a Complete Response (CR) Letter dated December 18, 2014 for NDA 202-153, Jubilant DraxImage Inc. (JDI) requested the opportunity to obtain clarifications on some of the CR questions and to discuss the best process to provide the information to FDA. Consequently, JDI submitted a formal meeting request on January 30, 2015 and FDA granted a Type A face-to-face meeting for March 18, 2015 as per FDA letter dated February 09, 2015. The following constitutes items in FDA's preliminary comments discussed at the March 18, 2015 face-to-face meeting.

FDA sent Preliminary Comments to JDI on March 16, 2015 (see attachment on page 10).

2. DISCUSSION

Following introductions among FDA and JDI participants, the meeting began with FDA and the JDI participants expressing mutual appreciation for the collaboration and communication during the NDA process. The agenda for the meeting was as follows:

- Question1 and Question 2: Usability and Training program
- Question 6: Hazard analysis and safety requirements
- Question6e, Question 9d and Question 19a: Microbiology and cross-contamination
- Question 9: System Performance and Reliability
- Question 15: Off-the-shelf software
- Question17 and Question 18: Shelf-life and biocompatibility
- Safety Update
- Conclusion

I. Q1 – Usability and Q2 – Training Program

Q1a: Number of users and user group

JDI clarified that there is only one key user group, i.e. Nuclear Medicine Technologists and agreed to enroll 15 users as part of the proposed bridging usability study.

Q1b: Canadian vs. US users

JDI explained the rationale behind why Canadian users had been proposed and provided background on the equivalence and clinical training of Canadian and US Nuclear Medicine Technologists, i.e. both professional training are recognized by the US based American Registry of Radiological Technologists (ARRT).

FDA described why they normally request US users: the medication system use and the way a product is used and ordered and administered normally differ from country to country based on the practice of medicine. In order to establish practice and usability in the US, FDA wants to be sure that the use environment is exactly the same in US. JDI understands this Agency concern and provided clarity that, unlike some therapeutic (b) (4) applications, the utilization of Rb82Cl, and hence this product, will not differ between the US and Canada---this is Nuclear Cardiology standard of care/use which is constant between US and Canada (and other countries). For example, there is common Nuclear Cardiology acquisition and analysis approved instrumentation and software worldwide.

JDI further explained that JDI user training will be identical for US and Canadian users and those users will perform the same tasks on the elution system. Furthermore, the elution system will have identical performance in both the US and Canada. For these reasons, JDI would thus like to have the opportunity to have user representatives from both US and Canadian users to reach the total of 15 users for the bridging study.

FDA is open to review JDI justification for use of Canadian users, provided that JDI can demonstrate that users and use environment are the same. Based on the rationale provided by JDI in the bridging usability protocol, FDA will determine whether Canadian users can be acceptable or not. JDI appreciates the Agency's preference for US User selection and will make every effort to select 15 US Users or provide the rationale above to FDA if Canadian sites are needed. In addition, FDA requested that testing records be in English if Canadian users are used and French will not be acceptable. JDI understands and agreed with this requirement.

Q1c:

JDI clarified that the previous usability study was performed as per FDA guidance on human factors and that all subjects successfully passed this study.

- JDI further clarified that in order to facilitate FDA's review of the previous usability data and results, a roadmap annotating the data location to FDA will be provided. JDI committed to also provide subjective usability data that were not provided in the original meeting package.
- JDI explained that based on the initial results, an additional usability testing is planned and will focus (b) (4)
- Using the supportive PowerPoint slide #2 (provided on March 17, 2015), JDI described the original and current (b) (4) components, and highlighted the very minor changes (b) (4)

- (b) (4)
- FDA questioned the rationale (b) (4)
The issue was also confirmed during testing.
 - JDI further emphasized that there were no changes to the elution system (b) (4)
 - FDA agreed that focusing the new usability testing (b) (4) will be adequate. However, FDA also recommended that JDI provide the proposed usability testing protocol for review. FDA also request with this protocol the user manual and training material which will be used for this study to allow the Agency an opportunity to comment prior to execution. —see FDA addendum on page 10.
- Q1 – Usability Study and Q2 – Training
 - JDI requested FDA’s preferred process/mechanism to provide the FDA with study protocol, training program and user manual for comments prior to execution.
 - FDA requested that all this information be submitted as Type C Meeting request (to ensure its inclusion into the NDA file).

II. Q6 – Hazard analysis and safety requirements

JDI committed to provide the FDA with fault-tree analyses (hazard analyses) for the risks listed in question 6 of the RubyFill Complete Response Letter [CRL] and for other major risks that were identified as part of the various FMEA documents.

Q6a: Unintended radiation exposure

JDI requested clarification from FDA on whether the question was targeted to breakthrough or to (b) (4) FDA responded that the question was addressing both aspects.

JDI explained (b) (4)

- (b) (4)
- JDI explained that the system performs an automated daily QC procedure to detect breakthrough. (b) (4)
- JDI also described that preliminary measurements were done (b) (4)
- FDA had the following questions on the elution system: 1) Where is the activity counter and dose calibrator? 2) What does the (b) (4) activity counter measure? 3a) How does the user know that the activity counter is calibrated and 3b) Does the system detect it if the activity counter is not working? 4) Is the daily QC compulsory? 5) Is the (b) (4) calibrated? And, 6) How are expired/used generators handled and is there any recycling or parts re-used? Using the supportive PowerPoint slide #3, JDI answered all these questions as follows:

(b) (4)

- FDA asked for clarification on the method used to measure Sr-85/Sr-82 breakthrough. (b) (4)

III. Q6e, 9d, 19a – Microbiology and cross-contamination

Using the supportive PowerPoint slide #3, JDI described the various components of the system that are in contact with the injected solution:

There is a generator, RUBY-FILL®

Then, JDI described that sterility assurance was addressed by a 3-pronged approach:

Sterilization of all components:

Labeling and Training:

User training emphasizes on the need for use of aseptic techniques (b) (4). Such techniques are also inherent to the professional training of Nuclear Medicine Technologists.

Both, User Manual and labeling, indicate to users that use of aseptic techniques is critical through warnings.

- FDA expressed needing information for microbiology and cross-contamination (b) (4)
(b) (4)
- FDA also mentioned that (b) (4) it cannot be considered as risk mitigation for patient to patient cross contamination.
- FDA requests supportive data demonstrating that microbiological growth and cross-contamination between patients will not occur and suggests JDI to assume that all junctions can be contaminated and that pathogens might grow on them.
 - JDI asked FDA if an alternative to microbial challenge methods, such as (b) (4) would be acceptable. This methodology would be more sensitive and provide the most conservative testing for small molecules such as viruses.
- FDA agreed and is open to the (b) (4) if adequately justified and scientifically supported. JDI offered a protocol review, prior to study execution, and FDA agreed that these protocols could be submitted in a meeting package for FDA review.
- FDA also suggested (at the end of the meeting concluding statements) JDI consider testing/eluting expired/returned generators for microbial contamination as this would be provide data on the expected bioburden in the generators during routine use . If found sterile, that will provide good supportive information that microbial growth is not an issue, although it was stated that alone, this would not be sufficient.
- JDI will evaluate the feasibility to perform this testing.

IV. Q9 – System Performance and Reliability

Q9a: Exposure to radiological activity (b) (4) over 60 days)

JDI described (b) (4)
(b) (4) In addition, JDI is currently doing activity measurement.

Overall, JDI explained [REDACTED] (b) (4)

Q9 b and c: [REDACTED] (b) (4) (wear and tear)

JDI requested clarification [REDACTED] (b) (4)

FDA requested that the rationale of the [REDACTED] (b) (4) and the usage model be properly defined to ensure acceptability of the data that will be generated. Also, they requested definition of tolerable degradation levels.

V. Q15 – Off-the-shelf (OTS) software

JDI stated that the Risk Assessment of the off-the-shelf [OTS] software components [SW] determined that all risks were negligible or tolerable after mitigations. Also, that the OTS SW components were validated as part of the elution system SW, that none of the components was custom made or developed solely for the RUBY Elution system and that the SW components were not accessible to users. Thus, JDI believes that Basic Documentation provides the required validation and, therefore, that audits of OTS suppliers are not required.

FDA stated that, if on review of OTS and software validation documentation they were satisfied, then Basic Documentation could suffice. However, FDA confirmed that this was a review question. JDI will provide SW supportive documentation in one the subsequent formal Meeting request.

VI. Q17 – [REDACTED] (b) (4) Shelf-Life and Q18 – Biocompatibility

JDI asked if accelerated shelf-life data and biocompatibility data (if required as per ISO 10993 risk assessments) could be submitted separately from the rest of the answers to the CRL, but during the review process.

FDA mentioned that these data are critical for approval and have to be reviewed prior to approval. FDA queried why JDI wants to submit these data separately. JDI explained that it will be the last sets of data to come in and the bulk of other data could be submitted earlier.

VII. Safety Update

JDI described that Canadian Annual Drug Safety Reports are available since the approval of the generator in Canada (in 2011). These reports describe adverse events from post-marketing surveillance. JDI indicates that there have never been safety issues reported with the use of the generator since approval in Canada, and that most of the information on safety is available in scientific publications. JDI proposed to submit these reports as safety update.

FDA asked if the criteria for reporting in Canada were similar to the ones in US. JDI confirmed it was the same.

FDA agreed to review the available Canadian Annual Drug Safety Reports [via a formal Type A Meeting request] from JDI and FDA will confirm the acceptability of these reports – or provide feedback if needed.

VIII. Conclusion

FDA mentioned that a Type C (Teleconference or Written Request only) Meeting requests is the process to be used to provide FDA required information for their review – e.g, study protocols prior to execution, safety data, clarifying questions on data required as part of the CRL answers, etc. JDI and FDA agree that these subsequent Type C Meeting requests may only require a written response or clarification by FDA; if a TCON is deemed required/desirable, these will be scheduled on an as needed basis.

JDI thanked the FDA for these options, excellent discussion, guidance and collaboration. JDI committed to the process to utilize subsequent Type C Meeting request[s] and information meeting package[s] in order to provide the required detail[s] to obtain FDA comments on the usability study, training program, as well as on microbial challenge study prior to execution.

JDI also committed to send the March 18, 2015 Type A Draft Meeting Minutes to FDA by March 27th.

FDA thanked JDI and agreed to provide comments and feedback to JDI to ensure conduct of acceptable studies and requested an estimate of the timelines for submissions when possible.

FDA ADDENDUM TO MEETING MINUTES

In the meeting minutes above you described the changes (b) (4) as very minor and explained that the additional human factor study would focus (b) (4). Subsequent to internal post-meeting discussions we offer the following guidance.

We agree with your characterization of the changes as minor and have determined that an additional Human Factor study (b) (4) and associated instructions is not necessary provided that the Users' Instruction Manual contains only minor changes related mostly to the (b) (4) and provided the Agency finds your original Human Factors study results as acceptable upon submission of the full report.

Please provide in your NDA resubmission the information on the HF study requested in our preliminary meeting comments. We encourage you to provide in the resubmission the justification for the use of Canadian technologists who may have participated in the usability study supporting your application.

ATTACHMENTS AND HANDOUTS

FDA's March 16, 2015 Preliminary Responses.

JDI's March 18, 2015 PowerPoint slides.

22 Pages have been Withheld in Full as Duplicate Copy of AdminCorres
3.16.15 Meeting Preliminary Comments immediately following this page

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this
page

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
04/09/2015



NDA 202-153

MEETING PRELIMINARY COMMENTS

INC Research LLC
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Attention: Greg Hockel
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

Dear Mr. Hockel:

Please refer to your New Drug Application (NDA) dated June 18, 2010, received June 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).

We also refer to your January 30, 2015, correspondence requesting a meeting to obtain clarification on comments within the FDA's December 18, 2014 Complete Response letter.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

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

ENCLOSURE:
Preliminary Meeting Comment



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type A
Meeting Category: Stalled Development
Meeting Date and Time: Wednesday, March 18, 2015, 9:30 AM to 11:00 AM
Meeting Location: White Oak Building 22, Conference Room: 1421
Application Number: NDA 202-153
Product Name: Ruby-Fill (Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi).
Indication: Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease
Applicant Name: Draximage, a division of Draxis Specialty Pharmaceuticals Inc.

FDA ATTENDEES (tentative)

Libero Marzella Gorovets, M.D., Director, Division of Medical Imaging Products, (DMIP)
Alex Gorovets, M.D., Deputy Director, Division of Medical Imaging Products, (DMIP)
Eric Duffy, Ph.D., Director, Division of New Drug Quality Assessment III, (DNQIII)
Eldon Leutzinger, Ph.D., CMC Lead, DNQIII
Ira Krefting, M.D., Deputy Director for Safety, DMIP
CDR Alan Stevens, Reliability and Mechanical Engineering, OMPT/CDRH/ODE/DAGID/GHDB
Ryan McGowan, Biomedical Engineer, OMPT/CDRH/ODE/DAGID/GHDB
Lynne Ensor, Ph. D., Acting Division Director, Division of Microbiology Assessment, OPQ/OPF
Steven Langille, Ph.D., Branch Chief, Division of Microbiology Assessment, Branch 3
LCDR QuynhNhu Nguyen, M.S., Biomedical Engineer/Combination Products Human Factors Specialist, CDER DMEPA
Lena Maslov, Pharm. D., Team Lead, CDER DMPEA
Frank Lutterodt, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

M. Norman LaFrance, MD, Chief Medical Officer, Senior Vice President, Medical and Regulatory Affairs, Jubilant Draximage Inc., Jubilant Pharma Ltd.
Ms. Tamara Mills, Director, Cardiac PET Products
Ms. Magali Lurquin, Senior Manager, Regulatory Affairs
Ms. Guylaine Roy, PhD, Regulatory Affairs Specialist
M. Paul Donnelly, Quality Engineer, Medical Device Manager

Ms. Anita MacDonald, PET Product Specialist

M. Bill Riddoch, PhD, Director of R&D

Ms. Amanda Donovan, Manager Radioactive Products, R&D

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Ms. Lise Bourgon, Pharmacovigilance Leader, Medical and Regulatory Affairs

(b) (4) Consultant, (b) (4)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Wednesday, March 18, 2015, 9:30 AM to 11:00 AM, White Oak Building 22, Conference Room: 1421 between Draximage and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Following receipt of a Complete Response (CR) Letter dated December 18, 2014 for NDA 202-153, Jubilant DraxImage Inc. (JDI) requested the opportunity to obtain clarifications on some of the CR questions and to discuss the best process to provide the information to FDA in a collaborative manner as directed in two pre-CR teleconference calls (TCNs) with the Medical Imaging Review Division in December 2014. . Consequently, JDI submitted a formal meeting request on January 30, 2015 and FDA granted a Type A face-to-face meeting for March 18, 2015 as per FDA letter dated Feb. 09, 2015. The following constitutes FDA's preliminary responses to questions in the February 13, 2015 meeting package.

2.0 DISCUSSION

2.1. Clinical

Question 1:

FDA original questions from the CRL dated December 18, 2014 are in italic below.

CLINICAL

- 1) *The reports of the human factor studies titled: “Ruby Rubidium Elution System Summative Usability Validation Report” and “Ruby Rb-82 Elution System Usability Risk Analysis” are materially incomplete. We request that you provide the following:*
 - a. *Study protocols;*
 - b. *Data (in the same format as the Hartford site) from subjects at the Brigham and Women’s and Cardiac Imaging Associates sites participating in the study;*
 - c. *Training or user manual that was the basis of training for the validation report;*
 - d. *Mitigation strategies (such as responses to computer input errors) that have been instituted and the report of any additional study performed to confirm the effect of these strategies.*

In the meeting request, JDI communicated that usability protocol and data we be provided in the CRL answer. However, in preparation for the meeting, JDI realized that for the FDA to be able to provide input on the usability testing questions listed below, the original summative testing protocol and data are needed. Consequently, the approved usability study protocol utilized for the original summative usability testing, the complete data set as requested, as well as the user manual that was the basis for user training at the time of usability testing was conducted, are provided as part of supportive data in section 10 to facilitate discussion. In addition, the protocol synopsis for the bridging study described below is also provided in section 10.

JDI will be performing an additional usability study testing with the new (b) (4) to confirm our earlier evaluations that usability has not been impacted with the new design. This usability testing will be performed with 5 health care professionals, all of whom will be certified nuclear medicine technologists, representative of the intended user population of the RUBY Rubidium Elution System. Training will include an updated version of the User Manual, an oral presentation, live demonstration and hands on, supervised real time training on the Rubidium Elution System for the tasks described in the protocol, and as were performed for the original usability testing. Because the original (b) (4) usability testing remains largely applicable, the additional usability testing will focus on repeating the testing of Task 2 only: (b) (4) of the original usability testing; all other tasks in the original usability testing are not impacted by the new (b) (4) design, remain applicable and, hence, will not be repeated.

A. *Is this proposed additional usability study sufficient to bridge the old and a new*
(b) (4)

design in regards to usability?

FDA Response to Question 1A:

No, we do not believe that the testing with only 5 healthcare professionals is adequate to validate the new (b) (4) (and the revised training program). For a human factors validation study, we recommend that you include at least 15 representative users.

- B. Participants, for the additional usability testing, will target 5 technologists at the Ottawa Heart Institute [UOHI], Canada, who have been previously involved with the ARMI Trial study. Canadian Nuclear Medicine credentialing is essentially identical to US technologists. Because the RUBY-FILL® generator is approved in Canada, the UOHI has the greatest RUBY-FILL® product experience. *Would it be acceptable to use Canadian registered nuclear medicine technologists for this round of usability testing?*

FDA Response to Question 1B:

You can include Canadian users for your purpose, however, we request that you conduct the testing with 15 representative users that reside in the US. Ensure that your study report clearly differentiate the results from Canadian users to US users.

- C. *Does the FDA agree that the Summative Usability Testing will not require a full repeat?*

Following input from the DMIP, the Training program will be modified as needed. For information, (b) (4)

(b) (4) will require modifications to the validated training program and User Manual. Consequently, JDI is planning a partial testing to validate (b) (4) to complete this gap.

FDA Response to Question 1C:

We do not have sufficient information at this time to answer your question. Please address the following:

1. You submitted the usability data for 11 of the 15 participants at part of the validation report in Annex within this meeting package. Please note that this will be a review issue when the NDA is resubmitted and we reserve providing our review comments as appropriate. At this time, we ask that you ensure that your study report includes both performance and subjective data and a detailed analysis of any task failures/use errors that might have occurred during this study. The analysis should determine the nature of failures, the causes of failures (by aspects of the

design of the device, its labeling, the content or proximity of training), and the clinical impact. Your analysis should also discuss whether modifications are required, and whether additional human factors testing are needed, and if so, ensure that you employ best practice for evaluating human factors and provide test results that demonstrate the effectiveness of the modifications.

2. We also recommend that you perform an additional human factors validation study with at least 15 representative users to validate the modified product user interface which includes the new (b) (4) design and the revised training program. However, your study synopsis did not include sufficient information for our review. In addition, we do not believe the use of questionnaire to assess ease of use will provide us the necessary subjective data that we need for our review. Please submit a full human factors validation study protocol. Please see comment # 4 for what to include in your study protocol.
3. We recommend that you submit the previous usability study results and the additional human factors validation study protocol before proceeding with the additional study as we may have additional comments on the protocol based on your previous usability study results.
4. Please ensure that your additional human factors validation study protocol include the following:

- a. Description of Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials. Also, include all screen shots of the graphical user interface (GUI).

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

In the Human Factors/usability validation study, the participants should use the instructions as they desire while interacting with the device. For essential knowledge, users can be asked questions directly. Afterward, you should ask specifically about any errors, problems or hesitations that were observed. The participants should provide subjective feedback regarding any wording in the instructions that they found confusing, misleading or incomplete.

- b. Description of User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive

assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels,) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

For devices sold in the United States, FDA has consistently requested that the participants in a validation test to be representative of the U.S. population and to reside in the U.S.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the conclusion that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Performance Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Subjective Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Guidance on human factors procedures to follow can be found in Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management, available online at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. There is a more recent draft guidance document that includes the current thinking on human factors at CDRH and recommended approaches to human factors evaluation and testing: Applying Human Factors and Usability Engineering to Optimize Medical Device Design: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm>

Question 2:

A training/re-training program and training packages need to be finalized prior to marketing. We request that you provide:

- a. An initial and on-going training program and a methodology to evaluate its effectiveness;*

b. A final version of an Instructions for Use (IFU) document which is structured with a table of contents, index, page numbering and a section on responding to serious patient emergencies involving Ruby-Fill administration. Clarify whether this IFU is intended to also serve as a training manual or if a separate training manual will be provided.

A training program has been developed by JDI for new users of Ruby-Fill® and as mentioned in the meeting request, this program is now part of the present package and can be found in section 10 for FDA's review, input and suggested improvements, if any, as early as possible. This program includes an on-site, 4-day segment, which provides oral presentations, hands-on demonstration and application of all functions of the Rubidium Elution System.

- A. As the FDA has indicated that the training program will require special attention, and close collaboration with the DMIP, JDI is providing the training program elements in its current state, to facilitate early discussions with FDA as soon as possible. ***Will the DMIP begin pre-review of the training program in order to provide JDI with timely comments, training program modifications and/or appropriate testing, if required?***

FDA Response to Question 2A:

DMIP will review the training program as part of the overall review of the application. However, specific modifications will be provided following review of the HF study request outlined in the FDA response to question 1. These modifications and /or remediations will reflect a further understanding of user performance and task failure identified in the requested HF study.

- B. During the FDA-JDI TCONs before the CRL was issued, the premise (b) (4) was mentioned as a potential option. Because this was not further addressed in the FDA CRL and JDI does not have access or information (b) (4) JDI proposes to provide this as a post-approval commitment in cooperation with FDA input. ***Is deferring (b) (4) to a post approval commitment, to allow JDI to assess with customer and FDA input a best training and design, acceptable?***

FDA Response to Question 2B:

DMIP agrees that (b) (4) can be deferred to a post approval commitment (b) (4)

2.2. Product Quality

Hazard analysis and safety requirements

- 6) *We have completed our review of the documentation submitted in support of the Ruby Elution System. During our review we evaluated the documentation to determine if hazards associated with the use of this device are adequately addressed. A document titled “Draximage Rb-82 Version 3 Hazard Analysis”, dated May 2011, was provided for review. This document does not provide the detailed analysis of hazards, hazard causes, and safety requirements implemented to assure the safety the Ruby Elution System. To assure the safety of the delivery system, we need to review documentation demonstrating that potential hazards to the patient and user have been reasonably mitigated. We have identified some of the system hazards that need to be addressed, which include:*
- Unintended radiation exposure (patient and healthcare provider)*
 - Rubidium delivery error (overdose or underdose)*
 - Volume overload*
 - Embolus (air or particulate)*
 - Biological safety (biocompatibility, sterility, infectious agent cross-contamination between patients). It is noted that the final specifications for the delivery system (b) (4) and accessory components have not been submitted and there is no information in the submission to demonstrate that biocompatibility, sterility, shelf life of disposables, and infectious agent cross-contaminations of patients have been adequately addressed.*

JDI acknowledges that not all the information/data noted in the CRL question was submitted (b) (4) and that not all hazard analyses, FMEA documents, and applicable supportive documents to address various hazards were submitted. JDI will provide the following up-to-date hazard analyses and FMEAs which address the hazards listed in question 6 of the CRL to ensure the safety of the system:

- System Risk Management Plan
- System Hazard Analysis
- (System) Usability Risk Analysis
- System Design FMEA
- System Process FMEA
- (System and Software) Usability FMEA
- Software Risk Management Plan
- Software Level of Concern
- Software FMEA
- Off-the-shelf Software FMEA
- (b) (4) Risk Management Plan
- (b) (4) Design FMEAs

- (b) (4) Process FMEAs
- (b) (4) clinical use FMEAs
- Risk Management Report

Are the above listed documents sufficient in terms of risk management documents? Note: Other supportive documents, such as design verification and/or validation reports, will also be provided to address risks mentioned in other CRL questions.

FDA Response to Question 6:

- a. We have concern, (b) (4) for potential radioactive cross contamination of long half-life isotopes; Sr-82 and Sr-85 between patients. Please confirm that the documents you provide will cover verification procedures, and ensure that there is no cross contamination from patient to the next patient.

b.c.d. Item #6 from the CRL requested three items:

- A fault tree analysis identifying the causes of the enumerated system hazards;
- A document describing the mitigations implemented to control the hazard causal factors identified in the fault tree analysis and explanation supporting the adequacy of the mitigation; and,
- Evidence demonstrating that the mitigation is effective.

The documentation identified in your briefing package, such as failure modes effects analysis (FMEA), risk management report, risk management plan, system hazard analysis, etc., are all important documents that we expect would be useful in the hazard causal factor identification process. For example, the fault tree could include component-level malfunctions as basic event, which were identified through FMEA processes.

Therefore, we agree the documents you have identified in your briefing package are important. However, these documents alone do not appear to be sufficient to address CRL issue #6.

- e. We are unable to assess the sterility assurance and associated microbiology for the proposed system/drug product, with regard to deficiency 6.e., until the documents associated with this deficiency are provided to the Agency for comment/review. The overall risk assessment should include a comprehensive evaluation of the potential for microbial contamination (b) (4)

. A discussion (b) (4)

(b) (4) should be included in the risk assessment. These, as well as other microbiological concerns, should be addressed in a microbiology risk assessment that provides a comprehensive assessment for microbial contamination of the sterile drug product line. This risk assessment should include the risk for environmental contamination as well as patient-to-patient contamination. (b) (4)

The application should include a justification (b) (4)

System performance and reliability

9) (b) (4)
The submission does not provide information regarding possible degradation of system components over the 60 day use period. Possible causes of safety and effectiveness degradation include the following:

a. Exposure to radiological activity.

b. (b) (4)

c. (b) (4)

d. Microbiological growth.

Provide data demonstrating that 60 day use of the components will not degrade the safety and effectiveness of the system to an unacceptable level.

A description (b) (4) are at the beginning of section 9. Our approach to addressing the issues raised by the FDA is described below:

- Exposure to radiological activity: With our CRL answer, we will provide mathematical calculations as Design Verification to demonstrate that accumulated radiation dose acquired over 60 days does not degrade (b) (4) performance.

- (b) (4)
The bench tests evaluate the following:

(b) (4)

- Microbiological growth: JDI's approach to preventing microbiological growth is predominantly based on inherent safety by design. (b) (4)
[REDACTED]
Design
verification bench test data will demonstrate (b) (4)
[REDACTED]
- Note – The data which demonstrates (b) (4)
[REDACTED]
the FDA agree with
JDI's

FDA Response to Question 9:

We do not have sufficient information on the proposed microbiological testing of the eluate to be able to answer this question. You should demonstrate that the microbial control of the system is adequate for the proposed maximum usage duration (b) (4)

[REDACTED]
It is expected that microorganisms will be introduced into the test system during routine clinical use and the eluate test should provide information to define the microbiological risks and not merely rely (b) (4)
Without additional data, (U) (4) For additional information see our comments above for Question 6.

Your submission should include validation of the modeling used to support an analytical verification that a 60 day exposure to radiological substances does not degrade (b) (4)

Regarding the (b) (4)

In principle, we agree with the approach you have outlined. We have the following comments for your consideration during design test development, which should be covered in the verification testing protocol:

- a) We agree with testing above the expected usage rates. We recommend that you identify the expected boundary conditions [REDACTED] (b) (4)
- b) The test protocol should identify explicit acceptability criteria.
- c) It is recommended that the same design verification performance tests be conducted [REDACTED] (b) (4)
- d) If accelerated testing employed, you should identify the acceleration factor and rationale for how the acceleration factor isn't expected to impact testing results. Where accelerated testing is employed, it is recommended that you include multiple test groups utilizing different acceleration factors so that final results can be analytically evaluated.

Regarding microbiological growth: It is uncertain that compliance [REDACTED] (b) (4)

Software

15) *If the system includes off-the-shelf (OTS) software, you should provide the following information:*

- f. *Evidence that the product development methodologies used by the OTS Software developer are appropriate and sufficient for the intended use of the OTS Software within the Ruby Elution System. This should include an audit of the OTS Software developer's design and development methodologies used in the construction of the OTS Software. This audit should thoroughly assess the development and qualification documentation generated for the OTS Software*

OTS FMEA has been performed and determined that risk associated with OTS software is negligible or tolerable after mitigation (no undesirable and intolerable risks). We believe that this corresponds to a moderate level of concern, as defined in the OTS Software Guidance document. This guidance also specifies that providing OTS special documentation package (described in section 2.5 of the guidance) is expected only for OTS representing a major level of concern after mitigation. We performed software validation on a complete software solution, including the OTS software in order to ensure that OTS functionalities perform as expected.

Does FDA agree that this satisfies FDA's OTS software information requirements?

FDA Response to Question 15:

The note on OTS Software Guidance, section 2.5.1 applies only when an audit cannot be conducted and the level of concern cannot be mitigated. The resubmission should address both points. If the audit cannot be conducted, you should provide the documentation supporting mitigation to below a major level of concern software. If the submission documents demonstration adequate control and mitigation of hazards related to OTS software, then we would agree that Section 2.5.1 of OTS Guidance document is satisfied along with explanation for why the software development audit cannot be conducted.

Biocompatibility and infection control

- 17) *All drug path devices are required to be sterile. The submission does not contain any data demonstrating assurance and maintenance of sterility for the disposable components of the Ruby Elution System. Provide the following information:*

- i. *Provide documentation supporting the shelf life of the disposable components*

With the CRL answer, complete design verification data at time zero will be available. *Will it be acceptable to provide stability dat* (b) (4)

during the review period of other CRL answers (i.e. to submit these data separately from the main CRL answers package)? In addition, is it acceptable to submit real-time stability data to support (b) (4)
 as a post-approval commitment?

FDA Response to Question 17:

We will agree to review (b) (4) However, the resubmission should include a real-time protocol with defined acceptability criteria.

- 18) *Identify the finished products that comprise the drug pathway and provide data demonstrating the biocompatibility of these products. Included in this, you should provide a chemical and particulate characterization on the final, finished, fluid contacting drug pathway components demonstrating that risk of harm from device-related residues is reasonably low. All testing should be conducted on finished, sterile product. For the assessment, we recommend the following:*
- c. *Device-related residual characterization alone may not provide appropriate information for risk of harm from device-related residues. The Agency recommends a comprehensive risk assessment of the device-related residuals based on route of*

exposure, toxicokinetics and toxicodynamics, and allowable limits in the intended population proposed for the new device

All components (b) (4) as per the supplier specifications. All materials are also used in other medical devices. Additionally, the new (b) (4) will be tested for leachables and extractables as well as chemical requirements as per ISO (b) (4). Following this chemical characterization of materials, an ISO 10993-1 Risk Assessment Report will be prepared by an experienced toxicologist to determine if biocompatibility testing in animals is warranted or may be waived based on a solid scientific rationale and data. Complete details on the components and materials of the new (b) (4) as well as the ISO 10993-1 Risk Assessment Report will be provided as part of the CRL answer. Based on current data, JDI does not expect that the new (b) (4) will raise toxicological concerns and this expectation has been confirmed by our consultant toxicologist. As noted above, the results of leachables and extractables will determine whether animal testing is required.

If the risk assessment determines that biocompatibility testing on the new (b) (4) is required to satisfy requirements of ISO 10993-1 and the April 2013 FDA draft guidance on the use of ISO 10993 (for blood path indirect contact device), would it be acceptable to provide such biocompatibility testing data as a post-approval commitment? This data would be submitted prior to commercial launch.

FDA Response to Question 18:

Review of the risk assessment approach will be a review issue and if it is determined that specific biocompatibility tests are needed, it is expected that these will be included as part of the premarket submission.

- 19) *We are concerned about the risk of disease transmission occurring from cross-contamination in devices (b) (4) such as yours. The information in your submission (b) (4) assures that the risk of cross-contamination has been adequately mitigated by the design of your system and that the risk outweighed by the benefit (b) (4). Provide the following information:*

- a. Demonstrate that the risk of cross-contamination has been adequately mitigated, which should include suitable challenge testing to support your conclusions.*

JDI approach to prevent risk of cross-contamination is also based on inherent safety by design. (b) (4)

The Design Verification tests described under question 9 – microbiological

growth above will demonstrate the performance (b) (4)

Does the Agency agree that such an approach is acceptable?

FDA Response to Question 19:

No. Based upon the information provided, we do not agree that the risk of cross-contamination between patients has been adequately controlled through system design.

Additional information is requested (b) (4)

(b) (4)

PRESCRIBING INFORMATION – PROPRIETARY NAME

21) *Please refer to correspondence dated, DATE which addresses the proposed proprietary name, PROPRIETARY NAME. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.*

The trade-names of the (b) (4) accessories are:

RUBY Rubidium Elution
SystemTM

(b) (4)

Regarding the RUBY-FILL[®] generator, it is our understanding that the trade-name assessment provided in June 2010 is still accurate, and therefore, will be resubmitted as is, but with a copy of the most recent draft Prescribing Information.

a. ***Does the FDA agree that the trade-names for (b) (4) the accessories do not require a trade-name review, as any myocardial perfusion imaging (MPI) procedure is***

always ordered by the type of procedure, the PET agent or rarely, the trade-name of the PET agent, but never by the name of the devices used to administer the product?

b. Does FDA agree with re-submission of past, still accurate, trade name?

FDA Response to Question 21:

21 (a)

No proprietary names for (b) (4) accessories need to be submitted.

21(b)

Yes, please resubmit the proposed proprietary name, Ruby-Fill, for FDA's review.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level

- 1. Describe in detail any significant changes or findings in the safety profile*
- 2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:*
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.*
 - Present tabulations of the new safety data combined with the original NDA data*
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above*
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials*
- 3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified*
- 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events*
- 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data*
- 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time)*

7. *Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries*
8. *Provide English translations of current approved foreign labeling not previously submitted*

RUBY-FILL®, Rubidium Rb 82 Generator was initially submitted as a generic product under 505j (2) with the reference listed drug Cardiogen-82. The initial application did not contain clinical data. Following the review of the application and the recommendation given by the FDA, the application under 505j (2) was converted to a 505(b) (2) application. In the process of conversion, it was confirmed by the FDA that the submission did not require clinical data.

Although JDI is not sponsoring any clinical studies using Rubidium Rb-82 or the Ruby Rubidium Elution System, JDI has partially funded the Canadian ARMI trial (Rubidium-82 - An Alternative Radiopharmaceutical for Myocardial Imaging), which is an investigator-initiated study by the University of Ottawa Heart Institute (Dr. Rob Beanlands and Rob DeKemp) which used an earlier prototype version of JDI's elution system. JDI's Rubidium Rb-82 generators have been distributed to clinical sites participating in the ARMI study since April 2010.

In addition, generators have been distributed to some hospitals conducting their own small single- site clinical study. Therefore, JDI proposes to cover the period since April 2010 for purposes of the Safety Update. Data will include safety reports of adverse events from those sites and from the literature. ***Does FDA agree that the proposed period of coverage is acceptable?***

In addition, JDI would like confirmation that the submission of the safety update in the Complete Response will not result in an additional or new PDUFA fee, since the initial application did not contain clinical data, or a Module 5. Does the FDA agree that submission of a safety update will not result in an additional PDUFA fee?

FDA Response to Question :

The safety update in the complete response will not result in an additional or PDUFA fee

Administrative questions (not part of CRL)

JDI would also like to take the meeting opportunity to ask the administrative questions below.

- A. The (b) (4) device accessories shall bear a NDC number and are not subject to the Unique Identifier requirement or the DSCSA (the (b) (4) will bear a serial number). ***Does FDA agree?***

FDA Response to Question :

The opinion of the UDI team is the device constituents of your system will require UDIs. Under 21 CFR 801.30(b)(3), NDC numbers are sufficient only if the combination device comes under 21 CFR 3.2(e)(1). This particular system more properly comes under 21 CFR 3.2(e)(2) or 3.2(e)(3). [REDACTED] (b) (4)

[REDACTED] UDI may be required to be permanently marked on the actual constituents as well included on the device labels.

- B. For information, JDI will be declared as manufacturer [REDACTED] (b) (4)
[REDACTED] (different than what previously submitted in previous amendments and Forms 365h). JDI intends to perform the final release and to distribute all components to the market [REDACTED] (b) (4) *What is FDA guidance on registering subcontractors, with respect to manufacturing site designation and PDUFA?*

FDA Response to Question :

Any subcontractor who performs any of the manufacturing/testing/packing/labeling steps involving the drug product itself (not the manufacturing of the packaging, labels, or delivery devices) is required to register under 21 CFR 207, and list the product(s) under their own labeler code and NDC. Note that the listing should be one of the unfinished drug marketing categories, such as DRUG FOR FURTHER PROCESSING.

- C. Since JDI will be declared the manufacturer [with subcontractors] and will perform final release and distribution, *does the FDA agree that PDUFA fees will be assessed only upon JDI?*

FDA Response to Question :

For PDUFA – only the applicant is eligible for application/product and establishment fees. We don't assess their subcontractors, packagers, distributors are not assessed for the fees.

- D. JDI would like confirmation that the submission of the safety update in the Complete Response will not trigger a new PDUFA fee, since the initial application did not contain clinical data, or a Module 5. *Can the FDA confirm that no new PDUFA fee will be applied?*

See response to Safety Update question on previous page

FDA Response to Question :

- E. JDI has investigated how post-approval quality changes should be addressed in the future, and is requesting that the FDA provide some advice on a general approach, since the guidelines for post-approval changes to combination products doesn't quite correspond to this type of product. ***Does the FDA agree that using a risk-based approach for the assessment of post-approval changes (minor risk, medium risk, major risk) as described in the 2004 guidance entitled 'Changes to and Approved NDA or ANDA' will be acceptable and applicable to changes relating to the device components of the product?***

FDA Response to Question :

It is pre-mature to discuss post –approval changes.

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/s/

LIBERO L MARZELLA
03/16/2015

Division of Medical Imaging Products (DMIP)
Briefing Document for the DMIP –CDRH Meeting

**Questions and Comments Regarding the Review by CDRH of the Human Factors
Studies Provided by the Sponsor – The DMIP Perspective**

Since the Ruby Fill apparatus is a completely new drug delivery and infusion system to produce Rubidium (Rb-82) for use in nuclear cardiac testing, FDA questioned whether a Human Factors study is needed to confirm its safe operation by nuclear technologists in a clinical facility. FDA is particularly concerned because CardioGen (an older Rb-82 generator system) and Ruby Fill have different operating instructions and potentially could be present in the same clinical facility. The sponsor provided two reports perhaps in an effort to demonstrate that sufficient Human Factor type studies had already been performed to confirm the safe use of Ruby Fill.

CDRH reviewed these reports and provided some comments. DMIP has a different perspective and interpretation of some of the information in the reports. A meeting has been scheduled so DMIP can share its clinical perspective with CDRH.

The goals of the meeting are to reconcile the views and conclusions of DMIP and CDRH and to decide whether the current sponsor reports satisfy the potential requirement for a new Human Factors study.

Sponsor (JDI) Documents Reviewed:

Ruby Rb-82 Elution System Usability Risk Analysis (10/17/2013)

Ruby Rubidium Elution System Summative Usability Validation Report (1/28/2014)

The following questions and comments were extracted from the CDRH review; each is followed by the DMIP perspective. The CDRH text is in blue.

CDRH

1. The risk analysis identified 131 steps with negligible risk rating, 84 with tolerable rating, and 21 with undesirable rating. However, the analysis did not include a rationale for how the risks were rated. In addition, the analysis did not include a discussion of the potential negative clinical consequences of use errors and task failures, and of mitigation strategies employed to reduce all use related risks. Please provide a comprehensive use-related risk analysis for your proposed product. This analysis should include a comprehensive evaluation of all the steps

involved in using your device (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies you employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies. We need this information to ensure that all potential risks involved in using your device have been considered and adequately mitigated and the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the device).

DMIP

The Ruby Rb-82 Elution System Usability Risk Analysis says the steps were identified from the scientific literature, experience (including complaints) and from similar versions and similar products. Potential use failure modes were also identified in ISO 14971 Annexes C and E, and IEC 60601-1 (I am not familiar with these source documents.)

I have been unable to locate Appendix A which shows the results of the Failure Modes and Effects Analysis (FMEA) and the Ruby Rb82 Elution System Risk Management Plan (KDI 11-001). Section 11 of The Ruby Rb-82 Elution System Usability Risk Analysis appears to have a summary of Appendix A. Section 12 summarizes steps with an “Undesirable” rating with consequences resulting from an error and mitigation suggestions. Lacking is the methodology to validate the risk-mitigation strategies.

The Ruby Rubidium Elution System Summative Usability Validation Report (1/28/2014) states that the study was conducted according to Ruby Rubidium Elution System Summative Usability Test Protocol (10090-001). I have been unable to locate this document.

Therefore the risk analysis strategies requested by CDRH may be present in sponsor documents which were not provided to FDA.

From the available documents, the assignment of failure mode rating such as Negligible, Tolerable, Undesirable, etc. to various tasks appear appropriate. For example, tasks (b) (4) have a Tolerable risk. The tasks with an Undesirable risk are listed in Appendix 1.0 of this document.

CDRH

2. This question pertains to strontium breakthrough testing.

DMIP

The sponsor designed a strontium testing plan which is very similar to CardioGen; DMIP has safety experience with this testing plan and finds it acceptable.

CDRH

3. We are concerned that the methodology employed in the HF study does not represent best practice for evaluating human factors. Specifically,

- a. The study report specified that the intended users of the systems are certified/registered Nuclear Medicine Technologists, and 15 of these users were included in the study. However, we are unclear whether the study participants include representative users, that may have experience with the CardioGen system, and those that are naïve to using this and similar systems.

DMIP

The study report says the Nuclear Medicine Technologists had experience in US nuclear cardiac PET imaging. Unless they were working at a few university centers, the predominant other PET nuclear cardiac agent is CardioGen. DMIP does not see the necessity for nuclear technologists to have clinical usage experience with CardioGen. Therefore DMIP concludes that the selection of respondents is acceptable.

- b. The report indicated that the technologists were trained to setup and to perform infusions using the RUBY System. However, in the discussion of the study results, you clarified that training was not provided to users on performing certain tasks in the first tests, and in subsequent tests, they were trained. We are unclear of the content of the training, and it was administered in the study. We are also unclear of how the training provided to study participants is reflective of training that actual users will receive. Also, we are unclear the meaning of “first tests” and “subsequent tests” that were referenced in the report.

DMIP

According to the study report: “...the technologists were trained to setup and perform infusions using the Ruby Rubidium Elution System, as a Jubilant DraxImage PET Specialist with the aid of the User Manual would train them in the initial field installation of the system”. The nuclear technologist testing appears to have been done in cohorts of 2 technologists. For example, the initial two users failed (b) (4)

“Subsequent” users were explicitly trained (b) (4)

Other errors included not leaving the room when the study was being done and radioactive Rubidium 82 would have been administered (no patient was present during the testing). DMIP concludes that it is appropriate to adjust the training based on errors made by the first cohort.

- c. We are unclear on how the tasks were selected for the study. The study tasks should be derived from a comprehensive use-related risk analysis. Please provide a rationale for the tasks selected for the study, and describe how these tasks are linked to the risk analysis. In addition, the study tasks are defined at a high level, and that there are multiple steps in each task. We ask that you define your priority tasks at a

level where we can understand which sub-task or step is considered critical i.e. task failures or use errors can lead to harm.

DMIP

The task selection was derived from the FMEA cited above and seems to generally reflect common sense problems encountered with a rubidium generator. How can you further sub-divide tasks (b) (4)?

- d. The report showed that the participants were coached i.e. receiving assistance from test moderator, while performing study tasks. Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Please explain how the assistance provided represented realistic use. Also, please clarify if actual users are expected to receive assistance, and how that assistance will be provided to actual use.

DMIP

Coaching seems to have been limited to the first cohort of 2 respondents. If coaching was not provided on such basic tasks as turning on Ruby Fill (hold the power button in) (b) (4) the rest of the study could not proceed. The failures from the first cohort influenced the teaching provided to the next groups of respondents, such as emphasis on how to turn on Ruby Fill (see DMIP comment 3b). Compared to realistic use, the respondents had to be reminded to walk out of the room if an actual patient was present and receiving rubidium 82. The Ruby Fill instrument was a production level model run in simulation mode which mimics all tasks that the user is required to perform including patient infusions and system setup functions.

- e. The report did not describe the use environments and conditions tested in the study. Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

DMIP

Two sites for the testing were the clinical use environment of the Cardiac PET lab at Hartford Hospital and Brigham and Women's Hospital. The third site was a conference room at the Cardiac Imaging Associates facility in Los Angeles. Therefore two sites were a clinical use environment.

- f. The study report did not include an evaluation of use performance on alarms, warnings, and caution statements included in the Instructions for Use. Interpreting and abiding by alarms and warnings is considered to represent critical tasks for users and therefore should be tested since inability to understand or take note of the warnings could lead to patient harm. Please submit study results and analysis for use performance on alarms, warnings, and caution statements.

DMIP

From the study report: “The critical tasks were [REDACTED] (b) (4) [REDACTED] Two error scenarios were also created to test the respondent’s ability to trouble shoot errors during the normal function of the RUBY system, these included [REDACTED] (b) (4) [REDACTED] Each respondent was asked to complete all ten (10) tasks. Each task consisted of multiple steps to successful completion”. This testing for these two error scenarios appears appropriate and consistent with clinical practice.

CDRH

4. The study report is incomplete because it provided data only from four participants from the Hartford site. There were no data submitted for the remaining 11 participants from the other two sites. In addition, the report provided subjective data from several study participants on task failures/use errors. Furthermore, there was no analysis provided to identify the root cause of the task failures/use errors, and to determine whether additional mitigations are needed. Please modify the study report include:
 - a. Performance data for all 15 study participants
 - b. Subjective data for all 15 study participants.
 - c. Analysis of performance and subjective data. This analysis should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures (by aspects of the design of the device, its labeling, the content or proximity of training), and the clinical impact. Your analysis should also discuss whether modifications are required, and whether additional human factors testing are needed, and if so, ensure that you employ best practice for evaluating human factors and provide test results that demonstrate the effectiveness of the modifications.

DMIP

Clearly information on the other respondents is lacking (which may be contained in Appendix A or B which I cannot find). If all of the respondents passed the tasks, what failure analysis is needed?

CDRH

5. Please provide all screen shots of the GUI. (Graphical User Interface)

DMIP

Agreed.

DMIP

General Comment: I am unclear what modifications have been made to Ruby Fill to mitigate potential problems identified in the FMEA report.

Plan

1. Request from the sponsor:
 - a. The protocol for the study discussed above
 - b. Detailed test results from the other respondents
 - c. Confirmation that the manual used in the training is the same version to be used in clinical practice
 - d. Confirmation that the Ruby Fill instrument used in the training is the same version to be used commercially
 - e. Screen shots of the Graphical User Interface on the commercially available model
2. Query the sponsor about which mitigations strategies have been put into place and whether testing has been performed to confirmed their efficacy.
3. DMIP, CMC, and CDRH need to discuss if more error scenarios need to be tested.
4. At this junction, a decision cannot be made about the necessity of another HF study.

Addendum:

This briefing document was presented to CDRH in preparation for a meeting with them on 9/18/2014 to discuss their review of HF studies provided by the sponsor.

The response from CDRH via email on 9/18/2014:

Hi all,

In reviewing the briefing document, we are okay if DMIP proceeds with the action plan described on the last page. If so, we do not believe that there is a need to have today's meeting.

Thank you.

-QuynhNhu

Appendix 1.0 Tasks with an Undesirable Risk (Table 12 from Ruby Rb-82 Elution System Usability Risk Analysis)

12. Risk Mitigation and Justification of Steps with an Undesirable “U” Risk Rating:

Step #	Steps/ Failure Mode	Comments	Further Mitigations
1, 2	(b) (4)		
19			
20			
24			
35			

Step #	Steps/ Failure Mode	Comments	Further Mitigations
51	(b) (4)		
53			
57			
67			
68			
70			

Step #	Steps/ Failure Mode	Comments	Further Mitigations
112	(b) (4)		
114			
117, 158			
191			
193			
196			
198			
205			

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/s/

IRA P KREFTING

09/19/2014

Addendum added- documents CDRH concurrence with our plan

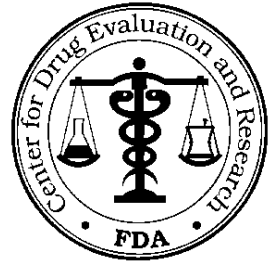
LIBERO L MARZELLA

09/19/2014

QUALITY DEFICIENCY - MINOR

ANDA 202153

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855



TO: INC Research, U.S. Agent for Jubilant Draximage Inc. TEL: 301-296-1370

ATTN: Hari Nagaradona FAX: 301-838-3182

FROM: Dat Doan FDA CONTACT PHONE: (240) 276-9336

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated June 18, 2010, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rubidium Chloride Rb-82 Generator (Ruby-Fill®).

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached ____ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a **QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

*Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855*

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): <http://www.fda.gov/cder/ogd> or Federal Register: <http://www.gpoaccess.gov/fr/>

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If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

Questions to sponsor for ANDA 202153:

1. The ^{(b) (4)} parts of Ruby-Fill®, Rb-82 generator, contains several parts, including ^{(b) (4)} the radionuclide activity counter, ^{(b) (4)} and a dose calibrator. Please describe basic composition materials, and the functional description of each component, and if any component has been approved or cleared by FDA previously, please provide the FDA document number(s) for the component(s).
2. The device, Ruby-Fill®, also uses software. Software should be tested for validation and assessed for risk analysis using FMEA (Failure Mode Effectiveness Analysis) method. Please review the FDA guidance, 'Guidance for premarket submission for software contained in medical device', dated 5/11/05

Go to:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089543.htm>

3. Please provide accuracy assessment data for radionuclide activity counter and dose calibrator for measurement of Rb-82 elution, and Sr-82 and Sr-85 breakthrough measurements. You may discuss with device manufacturers to produce these data.

Sincerely yours,

{See appended electronic signature page}

Robert Iser
Director
Division of Chemistry IV
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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/s/

ROBERT L ISER
04/12/2013
Director, DC IV, OGD

Questions for meeting with Office of Generic Drugs
ANDA 202153 – Rubidium Rb-82 Generator
Jubilant Draximage Inc.

Meeting date: November 19, 2012

Jubilant DraxImage participants: Norman LaFrance, MD; Magali Lurquin; Tamara Mills; others
to be identified depending on pre-call with Dr Doan Nov 9, 2012

Center for Drug Evaluation & Research participants:

- 1) Does the Agency agree that differences in labeling that are due to differences in manufacturer/manufacturing are permissible as per 505(j)(2)(A)(v)? These manufacturing differences, (b) (4)

[REDACTED] consists of the following:

[REDACTED] (b) (4)

Other differences linked to the fact that the product is made by a different manufacturer are more straight-forward and include differences in the brand name and in the total labeled activity of the generator.

Shimer response. Both the Statute at 505(j)(2)(A)(v) and the regulations at 21 CFR 314.94(a)(8)(iv) allow for differences in labeling that are due to differences in manufacturer/manufacturing or in the labeling of a drug product submitted pursuant to an approved Suitability Petition(21 CFR 314.93). Furthermore, the CFR at 314.92 describes drug products for which an ANDA may be submitted. Among the criteria for submission as an ANDA under 314.92, is the requirement that an applicant's proposed drug product has the same conditions of use as the drug product cited as your Basis of Submission. The Dosage and Administration section of your proposed drug product incorporates differences related to the rate of infusion and the maximum volume of solution to be administered. The Office of Generic Drugs does NOT consider these changes to be permissible differences due to a difference in manufacturer/manufacturing. Rather, these changes are differences in Conditions of Use. An ANDA applicant may NOT seek approval of a drug product that differs in Conditions of Use from the NDA product which it cites as its Basis

of Submission. For this reason, the Office of Generic Drugs believes that your current drug product is NOT eligible for submission under section 505(j) of the statute.

- 2) ANDA 202153 has been in review at the agency since June 18, 2010 with significant consultation from the Division of Medical Imaging Products and Office of Combination Products as requested by the OGD. Based on this complex multi-division scheme, we would appreciate the current review status from the CDRH (device components) and Office of New Drug Quality Assessment (CMC aspects).
- 3) In July of 2011, Patricia Love, MD from the Office of Combination Products communicated to the applicant that the Infusion System would be reviewed under the ANDA and Dr. Love provided the following instructions:

"Regarding format, CDER recommends the following:

3.2.P.3, with the software as part of the manufacturing controls (3.2.P.3.3).

2.P.2.6. for any information provided with respect to compatibility of the product with the infusion system or external diluent, tubing, etc."

In addition to Dr. Love stating that the software would be the focus of CDRH review, the applicant is seeking clarification in regards to the scope of the CDRH consult requested by the OGD. These brief communications with the Office of Combination Products seem to indicate that the review of the system is not a typical device review. Dr. Love provided the reference that the status of our system falls under the PET drug classification as per Section SEC. 201. [21 U.S.C. 321] of the Federal Food, Drug, and Cosmetic Act (FD&C Act): (ii), which states:

"The term 'compounded positron emission tomography drug'...

(2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug. "

High level descriptive product information was submitted to the ANDA in December 2011 with the expectation that some parameters would have to be revised pending the conclusion of the RLD [reference listed drug] recall and subsequent investigation and FDA recommendations to the RLD sponsors. Secondary to these new FDA recall recommendations, the applicant has, since the approval of the new RLD labeling, updated the software to allow for alert and expiry parameters. These were transposed into the recent labeling update submitted October 25, 2012; however, CDER has not provided a list of comments or questions identifying the specifics of a data package for the device components of the system. Please provide advice as to how better update our ANDA in this regard.

- 4) Is there any Agency discussion concerning a 505(b)(2) approval route versus 505(j)? Are there any other addressable items around the prolonged generic review? If the generic review process is acceptable, but is expected to require additional prolonged intra-FDA consultation and review time, is a transfer of the submission package to a 505(b)(2) an option to accelerate approval?

- 5) If the Agency determines that the 505(j) ANDA approval route is not appropriate, or determines that it will be delayed, would any GDUFA fee payment be applied to a 505(b)(2) review fee?;
PET Drugs are only exempt from GDUFA fees which only apply to generics so if filing as 505(b)(2), then yes, new drug fees would be applied.
- 6) The final drug product from our ANDA is Rubidium Rb-82 Chloride Injection and is identical to the RLD. Assuming a 505(j) approval, can life-cycle management changes be performed under a 505(b)(2)? Examples of these would be product component improvements, recognition of lower dose requirements for newer imaging equipment (e.g. 3D PET), additional indication claims, etc.
- 7) It has been made clear from OCP communications that this is not a formal drug-device combination and would therefore not be reviewed under their responsibility but rather under OGD responsibility. Since no guidelines currently address post-approval changes to ANDA PET drugs or combination products, does the Agency agree that product changes may use the risk-based classification approach from the FDA Guideline entitled "Changes to and Approved NDA or ANDA" for well-defined product advances that might occur during the life-cycle of this product? For example, can a product improvement such as a user interface, without change in functionality, be approved in the ANDA as a CBE-0 amendment? For another example, could a procedure print out in decimal format versus scientific notation be an annual report?
- 8) Assuming our understanding of the OCP determination in regards to our system is correct (see question 7), the applicant is requesting clarifications in regards to compliance and reporting obligations.

For example, the manufacturer of the Elution system is listed as a manufacturer in section 32P31. Because both the Elution System and Generator are defined as a Drug Product, will our contract manufacture's site be treated as a Drug Product manufacturer and be subject to establishment registration?

- *Because "The term 'compounded positron emission tomography drug'... (2) includes any nonradioactive reagent, reagent kit, ingredient, nuclide generator, accelerator, target material, electronic synthesizer, or other apparatus or computer program to be used in the preparation of such a drug."*

How should adverse events that are due to the Elution System be reported? Should the rules and guidelines for medical device reporting be followed, or should those events be treated under drug Pharmacovigilance systems?

- *Adverse events due to elution system should be reported to FARS (field alert reports).*

What other periodic reporting should be considered? Should data on the manufacture of the Elution Systems be covered in the ANDA annual report?

- *Yes, new data or changes to the manufacture of the elution system should be reported to FDA, and depending on the changes, annual report (minor) and PAS, CBE (major).*

Tcon Attendees:

- *Becky McKnight*
- *Al Mueller*

- Dat Doan
- Bob Iser
- Patricia Love
- Eric Duffy
- Eldon Leutzinger
- Lillie Golson
- Melaine Shin
- Lynne Ensor
- Martin Shimer

Topicsdiscussed:

- Does not qualify as a generic b/c of reasons discussed in answer to question #1 by Marty Shimer. Also, cumulative volume is different & dosing administration parameters are different.

Firm is offering:

- User certification required
- Data reporting requirement for all users.

Postpone meeting with firm:

- Call them to postpone meeting and that we need to look deeper into this issue of 505(j) conversion into 505(b)(2). Firm contact 11/16/12 and told that meeting is postponed because we need to discuss the 505(b)(2) vs. 505(j) issue further.
- Kim Dettelbach will be consulted
- Discussing possibility that if conversion to 505(b)(2) is done, review cycle will not start over?

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/s/

DAT T DOAN
11/16/2012



ANDA 202153

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

DRAXIMAGE, a division of Draxis Specialty Pharmaceuticals
c/o Kendle International Inc.
7361 Calhoun Place, Suite 500
Rockville, Maryland 20855-2765

ATTENTION: Hari Nagaradona, Ph.D.
US Agent

Dear Dr. Nagaradona:

Please refer to your Abbreviated New Drug Application (ANDA) dated June 18, 2010, received June 30, 2010, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act for Rubidium Rb-82 Injection, (b) (4) mCi.

We also refer to your June 21, 2010, correspondence, received June 30, 2010, requesting review of your proposed proprietary name, Ruby-Fill. We have completed our review of the proposed proprietary name, Ruby-Fill and have concluded that it is acceptable.

The proposed proprietary name, Ruby-Fill, will be re-reviewed 90 days prior to the approval of the ANDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your June 21, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of Generic Drugs (OGD) Labeling Reviewer Betty Turner at (240) 276-8728.

Sincerely,

{See appended electronic signature page}

Denise P. Toyer, PharmD.
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DENISE P TOYER
12/22/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 202153

Kendle International Inc.
U.S. Agent for
Draximage, a division of Draxis Specialty Pharmaceuticals Inc.
Attention: Hari Nagaradona, Ph.D.
7361 Calhoun Place, Suite 500
Rockville, MD 20855-2765

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our facsimile dated September 22, 2010 and your correspondence dated October 6, 2010.

NAME OF DRUG: Rubidium Rb 82 Generator,
Rubidium Chloride Rb 82 Injection, (b) (4) mCi

DATE OF APPLICATION: June 18, 2010

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 30, 2010

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Dat Doan
Project Manager
240-276-9336

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

MARTIN H Shimer

10/26/2010

Signing for Wm Peter Rickman