Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Amendment.

2. SUBMISSION PROVIDES FOR: Response to Agency's deficiency letter and T-cons held between this reviewer and the applicant.

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride. (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission. The subject amendment provides responses to the microbiology deficiencies conveyed to the applicant in the Agency's March 1, 2011 deficiency letter. A discrepancy between the initial submission and the 5/18/11 amendment regarding the applicant's description of the (b) (4) generator (b) (4) was noted by the reviewer. Clarification was requested in T-cons held on 7/27/11, and 7/29/11 between this reviewer and the applicant. Additional sterility data (b) (4) was also requested, and the applicant was asked to reference and link SOPs for parametric release in the release specification sheet, the CoA and batch release records. The requested information was submitted in the 8/29/11 amendment.

filename: 202153a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –None identified.

C. Assessment of Risk Due to Microbiology Deficiencies – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Lynne Ensor, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

The subject amendment provides a response to the microbiology deficiencies conveyed to the applicant in the Agency's March 1, 2011deficiency letter. The original deficiencies are italicized. Additionally, the amendment contains requested information submitted in the 8/29/11 amendment.

(b) (4)

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/s/

DUPEH G Palmer-Ochieng
09/16/2011

ELIZABETH T MCNEAL
09/16/2011
Checked file and submission links. All correct. Thos application in not in RFS.

NEAL J SWEENEY
02/28/2012

LYNNE A ENSOR
02/29/2012

Product Quality Microbiology Review

November 1, 2010

ANDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Chloride Rb 82 Generator

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
06/18/2010	06/30/2010	N/A	10/29/2010

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Draximage
Address: 16751 Trans Canada Highway,
Kirkland, Quebec, Canada H9H 4J4

U.S. Agent: Kendle International Inc.
7361 Calhoun Place Suite 500
Rockville, MD 20855-2765

Representative: Hari Nagaradona, Director Regulatory Affairs
Telephone: (301) 838-3120

Name of Reviewer: Dupeh Palmer Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of a sterile drug product/PET drug product application.

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride. (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission.

filename: 202153.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies – Questions regarding the (b) (4) [redacted] validation studies.

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with the microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**

The proposed product consists of a (b) (4) generator that produces Rb-82 by the decay of Strontium-82 (Sr), and an accessory elution system for eluting ^{82}RbCl Injection containing ^{82}RbCl in 0.9% sodium chloride.

Proposed maximum commercial batch size: A maximum of (b) (4) generators are manufactured per batch.

- **Drug product composition –** (Folder m3, 32-body-data, 32-drug-prod, 32p1-desc-comp, p. 2 of 3).

All components used in the manufacturing of ^{82}RbCl injection are presented in the following table.

Table P.1 – 1: List of components of the dosage form, their function, reference to quality standard, and amount on per-unit basis

Ingredients	Ingredient function	Quality Standard	Quantity per generator
^{82}SrCl$_2$	Starting Material	House	(b) (4)
(b) (4) Stannic Acid	Adsorbent	House	
Sodium Chloride	(b) (4)	USP / Ph. Eur.	
			(b) (4)

* At calibration time

- **Description of container closure system –** (Folder m3, 32-body-data, 32-drug-prod, 32p7-cont-closure, p. 4 of 85).

A diagram of the Ruby-Fill™ (Rubidium Rb 82) generator column was provided. Components of the column are shown in the table below and include (b) (4)

(b) (4)

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

A. PACKAGE INSERT

Storage temperature: (b) (4) °C; Route of administration: IV; Container: Single dose administered with additive free 0.9% Sodium Chloride Injection. Due to the short half-life of Rb-82, most of the radioactivity in the eluate decays within (b) (4) minutes from the end of elution.

Acceptable

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 202153 APPLICANT: Draximage

DRUG PRODUCT: Rubidium Chloride Rb 82 Generator

Microbiology Deficiencies:

1. Regarding validation studies conducted [redacted (b) (4)]

(a) Please provide data summaries from [redacted (b) (4)] studies with performance dates.

(b) Please state the manufacturer, genus/species of the endotoxin used in challenge studies, and provide endotoxin recovery results including results for positive controls.

(c) Please provide all acceptance criteria associated with successful [redacted (b) (4)] validation runs.

2. The endotoxin dose, at the proposed endotoxin specification of NMT [redacted (b) (4)] EU/mL and the maximum adult dose of [redacted (b) (4)] MBq indicated in the package labeling, exceeds the Agency's limit of 175 EU/dose for injected radiopharmaceuticals. Please revise the endotoxin specification for the drug product to conform to the Agency's 175 EU/dose limit and provide the appropriate documentation to reflect the change (e.g. finished product specification and stability protocol, endotoxin test validation data summary, and any supporting exhibit batch endotoxin test data).

3. Data to support parametric release of the drug product are not provided. Please provide data to support parametric release of the drug product. Alternatively, the sterility release specification could be revised to comply with 21 CFR 211.165 (a) which states:

Sec 211.165 Testing and release for distribution.
(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfaction conformance to final specifications for the drug product, including identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted in specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

DUPEH G Palmer-Ochieng
12/22/2010

ELIZABETH T MCNEAL
12/22/2010
Checked file and submission link. Both correct.

LYNNE A ENSOR
01/03/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	202-153
Submission Date	December 28, 2015 (SDN 30) May 3, 2016 (SDN 33) July 25, 2016 (SDN 44)
Brand Name	RUBY-FILL (rubidium Rb 82 generator)
Formulation	For intravenous administration
OCP Reviewer	Christy S John, Ph.D.
OCP Team Leader	Gene M. Williams, Ph.D.
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Medical Imaging Products
Applicant	Jubilant Draximage, Inc.
Submission Type	Resubmission/Class 2
Dosing regimen	(b) (4)
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

Table of Contents

1 EXECUTIVE SUMMARY

The current NDA is a re-submission of a 505(b)(2) NDA that received a complete response (CR) on December 18, 2014. The CR letter was issued due to deficiencies in clinical (human factors study and training materials) and chemistry and manufacturing controls (CMC). The prior NDA was not reviewed by clinical pharmacology because of the similarity of the product and proposed package insert to those of the referenced approved product, Cardiogen. The current submission is being reviewed because labeling negotiations for the current NDA resulted in the applicant suggesting that section **2 Dosage and Administration** of their package insert deviate from that of Cardiogen.

The proposed package insert changes are supported by literature publications and broadly consistent with the guidelines of professional societies. In principle, we find them acceptable.

1.1 Recommendations

The re-submission is approvable from a clinical pharmacology perspective.

Labeling Recommendations

Our recommendations for the package insert appear in Section **3 DETAILED LABELING RECOMMENDATIONS.**

1.2 Post-Marketing Requirements and Commitments

We have no recommendations for PMRs or PMCs.

1.3 Summary of Clinical Pharmacology Findings

No clinical or clinical pharmacology studies were conducted by the applicant. The reference drug for the current 505 (b) (2) NDA is Cardiogen. The Cardiogen package insert recommends a dose of 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30-60 mCi), and an upper limit of 2220 MBq (60 mCi).

Rather than duplicating the Cardiogen package insert, the applicant proposes weight-based dosing. To support their proposal, the applicant conducted a MEDLINE database search for the period of 1/1/2007 to 6/29/2016. Of the 36 pertinent articles, studies, 12 studies used weight-based dosing (3-10 MBq/kg) with a mid-range of activity 24 mCi and a range 16-32 mCi. There were 16 studies using weight-based dosing which did not provide the dose, the mean activity administered in these studies was 44 mCi, and the lowest administered dose was 20 mCi. Eight studies used fixed dosing with a mid-range activity of 44 mCi and the lowest administered dose was 15 mCi. None of the 36 studies included comparisons between two or more doses.

The applicant's proposal to base recommendations on current clinical use as identified by literature articles and the judgment of professional societies is reasonable. The proposal includes a dose range sufficiently wide to allow institutions with 2D-imaging cameras to dose within the package insert recommendations. At the same time, those with 3D-imaging cameras can choose lower doses that are within the package insert range. As coupling the dose with the imaging technology is currently rejected, we agree with the proposal to give a broad dose range. We also agree with the use of weight-based dosing, as it is supported by the clinical use data and will minimize unnecessary radiation exposure.

SIGNATURES

Reviewer: Christy S John, Ph.D. Division of Clinical Pharmacology V	Team Leader: Gene Williams, Ph.D. Division of Clinical Pharmacology V

Cc: DMIP: PM F. Lutterodt.; MTL I. Krefting; MO M. Fedowitz, I. Krefting
DCPV: DDD B. Booth; DD A. Rahman

2 QUESTION-BASED REVIEW

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The reference drug for the current 505 (b) (2) NDA is Cardiogen. The Cardiogen package insert recommends a dose of 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30-60 mCi).

No clinical studies were conducted by the applicant.

Rather than duplicating the Cardiogen package insert, the applicant proposes weight-based dosing. To support their proposal, the applicant conducted a MEDLINE search for the period of 1/1/2007 to 6/29/2016. Of the 36 pertinent articles, 12 studies used weight-based dosing (3-10 MBq/kg; 0.081-0.27 mCi/kg) with a mean activity of 24 mCi and a range 16-32 mCi. There were 16 studies using weight-based dosing which did not provide the dose, the mean activity administered in these studies was 44 mCi, and the lowest administered dose was 20 mCi. Eight studies used fixed dosing with a mean activity of 44 mCi, and a lowest administered dose of 15 mCi. None of the 36 studies included comparisons between two or more doses.

The applicant presents data showing that from 2002 to 2016 there was a trend of decreasing administered radioactivity (**Figure 1**).

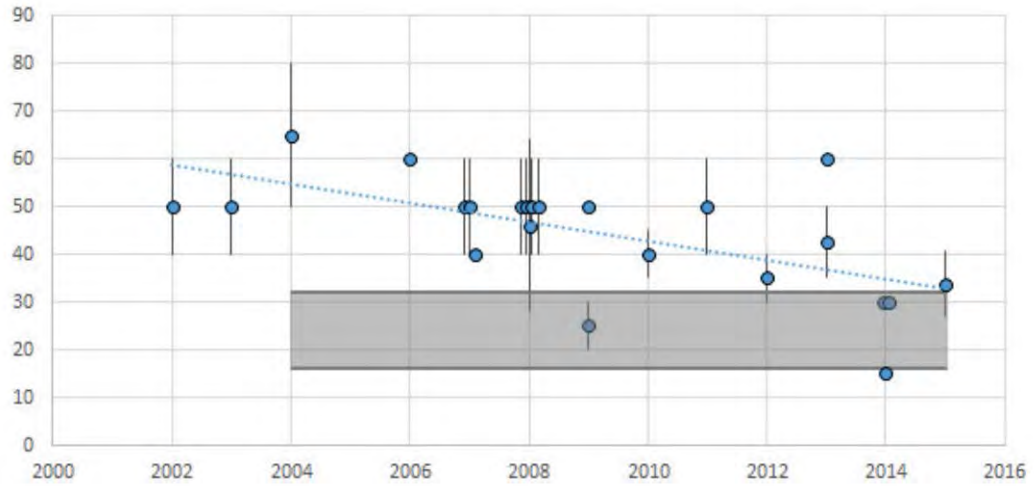

Figure 1. Administered radioactivity (mCi) versus time (calendar year); each data point is a literature study, vertical lines are ranges within the study, points in gray area not included in dotted trend line.

Reviewer's Comment
A formal meta-analysis for efficacy was not conducted by the applicant. The applicant's implicit reasoning is that the widespread use of lower dosing is evidence that lower doses provide adequate efficacy.

The decrease in dose across time that the applicant presents coincides with the introduction of 3D PET imaging equipment. 3D acquisition can allow greater resolution, thus allowing equi-effective imaging at lower radioactivity doses.

The applicant's proposal to base recommendations on current clinical use identified from literature articles and the judgment of professional societies is reasonable. The proposal includes a dose range sufficiently wide to allow those with 2D-imaging cameras to dose within the package insert recommendations. At the same time, those with 3D-imaging cameras can choose the lower doses that are within the package insert range. As coupling the dose with the imaging technology is currently rejected, we agree with the proposal to give a broad dose range. We also agree with the use of weight-based dosing, as it is supported by the clinical use data and will minimize unnecessary radiation exposure.

3 DETAILED LABELING RECOMMENDATIONS

The package insert proposed in the July 25, 2016 submission, together with our recommended edits, appears below as **Table 1**.

Table 1. Package Insert	
Applicant's Proposed	**Reviewer's Recommended**
(b) (4)	**2.2 Recommended Dose and Administration Instructions** • The recommended weight-based dose of Rb 82 to be administered per rest or stress component of a PET myocardial perfusion imaging (MPI) procedure is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg]. • Do not exceed a single dose of 2220 MBq (60 mCi). • Use the lowest dose necessary to obtain adequate cardiac visualization and individualize the weight-based dose depending on multiple factors, including, patient weight, imaging equipment and acquisition type used to perform the procedure. For example, 3D imaging acquisition may require doses at the lower end of the recommended range compared to 2D imaging.

Comment [WGM1]: Section number changed (b) (4) to 2 2 due to re-arrangement of other elements of section 2 by Medical Officer

(b) (4)

- Administer the single dose at a rate of 15 - 30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 mL.
- Instruct patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.
- The maximum available activity (delivery limit) will decrease as the generator ages *[see Dosage and Administration (2.8)]*.

2.3 Image Acquisition Guidelines

For Rest Imaging:

- Administer a single ("rest") rubidium Rb 82 chloride dose;
- Start imaging 60-90 seconds after completion of the infusion of the rest dose and acquire images for 3-7 minutes.

(b) (4)	For Stress Imaging: • Begin the study 10 minutes after completion of the resting dose infusion, to allow for sufficient Rb 82 decay; • Administer a pharmacologic stress agent in accordance with its prescribing information; • After administration of the pharmacologic stress agent, administer the second dose of Rb 82 at the time interval according to the prescribing information of the pharmacological stress agent; • Start imaging 60-90 seconds after completion of the stress rubidium Rb 82 chloride dose infusion and acquire images for 3-7 minutes. For Both Rest and Stress Imaging: • If a longer circulation time is anticipated (e.g., in a patient with severe left ventricular dysfunction), start imaging 120 seconds after the rest dose. • Acquisition may be started immediately post-injection if dynamic imaging is needed.

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/s/

CHRISTY S JOHN
09/30/2016

GENE M WILLIAMS
09/30/2016
I concur with the recommendations

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	202153*
Drug Product Name	Rubidium Chloride Rb-82 Generator (Ruby-Fill®)
Strength(s)	N/A** (Generator of (b) (4) mCi of Strontium 82 (Sr 82))
Applicant Name	Jubilant DraxImage Inc.
Address	16751 TransCanada Highway Kirkland, Quebec, Canada H9H 4J4
Applicant's Point of Contact	Hari Nagaradona INC Research, LLC *** 7361 Calhoun Place, Suite 500 Rockville, MD 20855-2765
Contact's Telephone Number	301-296-1370
Contact's Fax Number	301-838-3182
Original Submission Date(s)	6/18/2010
Submission Date(s) of Amendment(s) Under Review	N/A
Reviewer	Rong Wang, Pharm.D., Ph.D.
Study Number (s)	NA
Study Type (s)	(b) (4)
Strength (s)	Generator of (b) (4) mCi Sr 82
Clinical Site	NA
Clinical Site Address	NA
Analytical Site	NA
Analytical Site Address	NA
OUTCOME DECISION	**ADEQUATE**

* As advised by the Agency, the current submission was converted from an Abbreviated New Drug Application (ANDA) under section 505 (j) to a New Drug Application (NDA) under Section 505 (b) (2) of the statute. The OGD retains limited authority to approve 505(b)(2) applications and NDA 202153 was determined to be one of those applications[1,2]. Therefore, NDA 202153 is being reviewed by the Office of Generic Drugs (OGD).

** In the Orange Book, the strength is listed as N/A for the RLD product.

*** According to the Form-356h submitted on 1/17/2013.

[1] Note: Details please also see the internal email communications within OGD in section 4 Appendix in the current review.

[2] DARRTS: ANDA 202153; EDR submission on 1/17/2013; Cover Letter.

1 EXECUTIVE SUMMARY

This application which was initially submitted as an Abbreviated New Drug Application (ANDA), (b) (4) for the test product, Rubidium Chloride Rb 82 Generator, (b) (4) mCi of Sr-82 at calibration time. The reference listed drug (RLD) product is Cardiogen-82® (rubidium chloride Rb 82 Generator), 90-150 mCi of Sr-82 at calibration time, manufactured by Bracco Diagnostic, Inc. (NDA 019414, approved on 12/29/1989).

According to the internal meeting minutes dated 11/16/2012[3], the generic applicant for ANDA 202153 proposed different 'condition of use' in the label for the test product (Infusion Rate and Maximum Volume to be administered) compared to the RLD product. Due to differences in the drug products' labeling, the Office of Generic Drugs (OGD) considered that the test product is NOT eligible for approval under section 505 (j) of the statute. Additionally, on December 12, 2012, the Office of New Drug Quality Assessment (ONDQA) completed its initial quality assessment on the test product, in response to the consult request from the OGD's Division of Chemistry. The ONDQA reviewer (b) (4) raised safety concerns for the different infusion rate proposed for the test product (Ruby-Fill®) from the RLD product (Cardiogen-82®). As advised by the Agency, the firm then resubmitted the application to the OGD as a New Drug Application (NDA) under section 505 (b) (2)[1] (for details please also see section 4 Appendix). According to the email sent by Thomas Hinchliffe from OGD, NDA 202153 will still be reviewed by OGD.

Rubidium Chloride Rb 82 Generator (Ruby-Fill) contains Sr 82 chloride adsorbed onto hydrous (b) (4) stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces the final product, Rubidium Chloride Rb 82 Injection USP. (b) (4) The Division of Bioequivalence I (DBI) has reviewed the component and composition of the final product. The final product, Rubidium Chloride Rb 82 Injection USP solution administered to a patient by infusio (b) (4) contains the active ingredient, rubidium chloride (b) (4) and the inactive ingredient (0.9% sodium chloride). (b) (4)

(b) (4)

[3] DARRTS: ANDA 202153; DOAN, DAT T 11/16/2012 N/A 11/16/2012 FRM-MINUTES-01(Internal Meeting Minutes) Original-1 (Unknown) Archive

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information[4]

Test Product	Rubidium Chloride Rb 82 Generator, (b) (4) mCi of Sr 82 (Ruby-Fill®)
Reference Product	Cardiogen-82® (rubidium chloride Rb-82 Generator) , 90-150 mCi of Sr 82
RLD Manufacturer	Bracco Diagnostics Inc.
NDA No.	019414
RLD Approval Date	December 29, 1989
Indication[5]	CardioGen-82® is a closed system used to produce rubidium chloride Rb 82 for intravenous injection use. Rubidium chloride Rb 82 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.

3.2 PK/PD Information[5]

Bioavailability	Intravenous, therefore 100%.
Food Effect	Not applicable for I.V. injection
Tmax	Not indicated in the drug label
Metabolism	Not indicated in the drug label
Excretion	With a physical half-life of 75 seconds, Rb-82 is very rapidly converted by radioactive decay into trace amount of stable Kr-82 gas, which is passively expired by the lungs. Renal and hepatic excretion is not anticipated to play an essential role in Rb-82 elimination, although some of the Rb-82 dose may be excreted in the urine prior to radioactive decay.
Half-life	The physical half-life of Rb-82 is 75 seconds.
Drug Specific Issues (if any)	**Black Box Warning** **WARNING: UNINTENDED STRONTIUM-82 (Sr-82) AND STRONTIUM-85 (Sr-85) RADIATION EXPOSURE** Unintended radiation exposure occurs when the levels of Sr-82 or Sr-85 in the rubidium Rb 82 chloride injection exceed specified limits Perform generator eluate tests: (b) (4)

[4] Orange Book, Search Term: rubidium, last accessed on 1/22/2013.
[5] Drugs@ FDA, Search term: rubidium; Label information, last access 1/22/2013

	(b) (4)

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	N/A-Waiver Request

Analytes to measure (in plasma/serum/blood):	NA
	(b) (4)
Source of most recent recommendations:	None available from OGD. However, FDA's draft Guidance- FDA Oversight of PET Drug Products – Questions and Answers, issued February 2012 is available @ http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf

Summary of OGD or DBE History (for details, see Appendix 4.2):	As of 1/22/2013, the OGD has received only one control correspondence related to Rubidium Rb 82 generator, which was submitted by Draximage on 6/12/2008. The control correspondence was requesting a type C meeting with the Agency to discuss issues related to filing requirement, chemistry, manufacturing and control (CMC) and clinical/pre-clinical data. This control correspondence still remains open in the database. As of 1/22/2013, no protocols were listed for Rubidium Chloride Rb 82 generator in the OGD protocol database. As of 1/22/2013, there is no other ANDA application submitted to the OGD for Rubidium Chloride Rb 82 Generator besides the current ANDA. According to DARRTs, Draximage submitted an ANDA (ANDA 202134) to the Office of Generic Drugs on June 21, 2010 to seek approval of generic Rubidium Chloride Rb 82 injection. Draximage also submitted another ANDA (ANDA 202153) seeking approval of Rubidium Chloride Rb 82 generator on 6/30/2010. According to the memo dated on 1/6/2011 (DARRTS, **Shimer, Martin H, 1/06/2011, FRM-ADMIN-29 (Cancel Application), General Information-1**), ANDA 202134 was canceled due to the following reason: *Since both the information submitted for the Rubidium Chloride 82 Generator, in the context of ANDA 202153, and the drug product information submitted in the context of ANDA 202134 are reviewed and regulated by CDER it is unnecessary to maintain two ANDAs for these products. For that reason the information originally submitted in ANDA 202134 was converted into an amendment to ANDA 202153. All information related to the Draximage Rubidium Chloride Generator and Injection Drug Product will now be reviewed in the context of ANDA 202153.*

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	Yes	1
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	No	-

3.5 Formulation

Location in appendix	Section 3.7, Page 7
If a tablet, is the RLD scored?	NA
If a tablet, is the test product biobatch scored	NA
Is the formulation acceptable?	Yes
If not acceptable, why?	Not Applicable

3.6 Waiver Request(s)

Strengths for which waivers are requested	(b) (4) mCi of Sr-82 at calibration time
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	Yes. However, the final determination is pending the acceptance by the Division of Chemistry (b) (4)
If not then why?	Please see comment below

3.7 Formulation

Table 1. Comparative Formulation of the Final Product (Rubidium Chloride Injection Solution) for the Test and RLD Products

Ingredients	Rubidium Chloride Rb 82 Generator Test Product Draximage Inc.	Cardiogen-82® Generator RLD product Bracco Diagnostics Inc.[6]	Function
Rubidium Chloride	Variable (mCi/mL)	Variable (mCi/mL)	Active Ingredient
Sodium Chloride	0.9%*	0.9%**	Inactive Ingredient

*Module 3, Section 3.2.P.1 page 1 of 3 of the original submission indicates that additive free 0.9% Sodium Chloride Injection USP is used for elution of the product. Rubidium Chloride Injection is a solution of RbCl in 0.9% sodium chloride.

** The RLD product labeling states additive-free Sodium Chloride Injection USP is used to elute the generator but does not specify a concentration of sodium chloride used in the elution. However, per Study Protocol # 20484-1 in NDA 019414 (Volume A1.1), normal saline was used to elute the generator in the clinical study.

Is there an overage of the active pharmaceutical ingredient (API)?	No.
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	See below

Reviewer's Comments:

1) Rubidium Chloride Rb 82 Generator (Ruby-Fill) contains Sr 82 chloride adsorbed onto hydrous (b) (4) stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces the final (finished) product, Rubidium Chloride Rb 82 Injection USP. (b) (4) So the final product, Rubidium Chloride Rb Injection is a sterile, non-pyrogenic aqueous solution of RbCl in 0.9% sodium chloride, which is a parenteral solution intended solely for administration by injection. Due to the extremely short physical half-life (75 seconds) of the finished drug product, it needs to be manufactured at the facility where it is to be administered.

2) For PET drugs, the radioactive concentration (e.g., mCi/mL) at the calibration time is generally considered to be the strength. For the multi-dose generator this is generally at the end of synthesis (EOS) i.e. the end of manufacturing of the finished drug product.

The test product (Rubidium Chloride Rb Injection) contains (b) (4) the same inactive ingredient (0.9% sodium chloride) as the RLD product. However, the radioactivity of Rb 82 per mL of eluate (i.e. the concentration of active ingredient in the final

[6] NDA019414, volume 1.1(hardcopy), Clinical Report #20484-1.

product) could vary depending on the elution rate and the potency of the Rb 82 generator (the radioactivity of Sr 82) decay corrected to the day of administration. It should also be noted that although the radioactivity of Rb 82 per mL of eluate could vary in both test and RLD products, the dose (i.e. radioactivity of Rb 82) administered to a patient is precisely controlled by a specifically designed infusion system for both test and RLD products, respectively. (b) (4)

3) The information (b) (4) has been consulted to CDRH for review. But, there has not been a formal review by CDRH (b) (4)

4) The Office of New Drug Quality Assessment (ONDQA) has completed its initial quality assessment on ANDA 202153 in response to a consult request from the Division of Chemistry. The reviewer of ONDQA listed the following table in the review, comparing the dosing between the test product (Ruby-fill) and the reference product (Cardiogen-82)[7]:

	Max Activity (single dose)	Range of Dose (single dose)	Max Volume (single dose)	Rate of Infusion
Ruby-Fill	60 mCi (Rec: (b) (4) mCi)	(b) (4) – 60 mCi	60 mL	(b) (4) mL/min
Cardiogen-82	60 mCi (Rec: 40 mCi)	30 – 60 mCi	100 mL	50 mL/min

The reviewer of ONDQA provided the following comments with regard to the infusion rates:

The infusion rates are different. The rate for Cardiogen-82 is 50 mL/min, compared to (b) (4) *mL/min for Ruby-Fill. That for Cardiogen-82 is* (b) (4) *greater than for Ruby-Fill. Hence, the maximum volume for Cardiogen is* (b) (4) *100 mL. The maximum volume for Ruby-Fill is* (b) (4) *60 mL.*

(b) (4)

[7] DARRTS: ANDA 202153; LEUTZINGER, ELDON E 12/12/2012 N/A 12/12/2012 FRM-ADMIN-01(Memorandum to File) Original-1 (Unknown) Archive

[redacted] (b) (4)

5) In response to the meeting request submitted by the applicant (Draximage) on 10/25/2012, an internal meeting was held to discuss the questions related to ANDA 202153. According to the meeting minutes dated on 11/16/2012[3], Shimer Martin from OGD provided the following comment with regard to the approval eligibility of the test product as ANDA:

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.***

6) As advised by the Agency, on 1/17/2013, the firm submitted the request for conversion of ANDA 202153 to NDA 202153 under 505 (b) (2) regulations[2]. As per the email communication sent by Thomas Hinchliffe on January 15, 2013, the resubmitted NDA 202153 will be reviewed by OGD (please see section 4 Appendix for details)

7) Based on the information above, the determination [redacted] (b) (4) of radioactive Rubidium Chloride as the finished product is deferred to the Division of Chemistry (DC). The DB will incorporate the DC's recommendations with regards to the strength of the finished product manufactured on-site, in to the final BE determination.

3.8 Deficiency Comments

None

3.9 Recommendation

1. [redacted] (b) (4)

[redacted] (b) (4)

2. The application is adequate from the bioequivalence standpoint.

3.10 Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	The final product, Rubidium Chloride Injection is produced on-site where it is to be administered to the patient by eluting the column of the generator containing strontium Sr 82. The radioactivity (dose) of Rubidium Chloride is controlled by the specifically designed infusion system. Therefore, the determination (b) (4) of radioactive Rubidium Chloride as the finished product is deferred to the Division of Chemistry (DC).

4 APPENDIX

From: Nguyen, Hoainhon T
To: Tampal, Nilufer; Wang, Rong
Cc: Nguyen, Hoainhon T
Subject: FW: Bioequivalence Question for NDA 202153 - Resubmission required
Date: Tuesday, January 15, 2013 10:30:42 AM

FYI. We will defer the difference in Conditions of Use and any issues related to the generator to the Division of Chemistry. We will limit our review to the final injection product.
Thanks,
Hoai

From: Shimer, Martin
Sent: Tuesday, January 15, 2013 10:28 AM
To: Nguyen, Hoainhon T
Subject: RE: Bioequivalence Question for NDA 202153 - Resubmission required

Hoai,

(b) (4)

This application will not be awarded an AP rating when it is approved due to the differences in the labeling of this product when compared to the RLD.
Thanks,
Marty

From: Nguyen, Hoainhon T
Sent: Tuesday, January 15, 2013 10:22 AM
To: Shimer, Martin
Cc: Nguyen, Hoainhon T
Subject: Bioequivalence Question for NDA 202153 - Resubmission required

Hi Marty,
Is DBI supposed to review this NDA application? Does the firm request an AB rating for its 505(b)(2) route?
Thanks,
Hoai

From: Chang, Sherry
Sent: Tuesday, January 15, 2013 9:31 AM
To: Tampal, Nilufer
Cc: Wang, Rong; Nguyen, Hoainhon T; Ramson, Teresa
Subject: FW: NDA 202153 - Resubmission required

Hello Nilufer,
I am forwarding Tom's email to you.
Please be noted that the application ANDA 202153 (Rubidium chloride injection) Rong is currently reviewing now becomes NDA 202153.
Thanks,
Sherry

From: Hinchliffe, Thomas
Sent: Tuesday, January 15, 2013 8:17 AM
To: Cuthbert, Gerrard D; Doan, Dat; Kalinina, Marina
Cc: Middleton, Saundra T; Shimer, Martin; West, Robert L; Wang, Rong; Chang, Sherry; Kiester, Craig; Ensor, Lynne A; Conner, Dale P; Shin, Melaine M; D'Costa, Rosario; Mueller, Albert J; Gonitzke, Mark; Doan, Dat; Ames, Timothy W
Subject: RE: NDA 202153 - Resubmission required

Thanks Gerrard, Saundra,
Since this is supposed to be an NDA reviewed by OGD then DARRTS should reflect this as an NDA not an ANDA.. Gerrard what do we need to do to correct. The responsible Organization is still OGD of course so nothing should change there.. In addition, Any letters OGD issues should

be using the OND templates, not the ANDA 505 (j) templates.
I see this has been under review for a while and we have been issuing ANDA style letters my error.. From this point forward lets ensure only NDA style letters go out, including the TA or AP letter. Here is the address to the eroom for CDER Standard Templates http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee which houses all NDA templates. Any questions about the templates you Michael Folkendt is the NDA expert...
I am cc'ing the review team in DARRTS so they are aware and can make the adjustment.
Tom
Thomas Hinchliffe, PharmD
CDR, U.S. Public Health Service
Special Assistant to the Director for GDUFA
Office of Generic Drugs
Food and Drug Administration
HFD-600 Rm 3016, MPN4
240-276-9314 (tel)
240-743-8298 (mobile)
240-276-9327 (fax)
"UNLESS someone like you cares a whole awful lot, nothing is going to get better. It's not." - Dr. Seuss
From: Middleton, Saundra T
Sent: Tuesday, January 15, 2013 8:05 AM
To: Hinchliffe, Thomas
Subject: FW: NDA 202153 - Resubmission required
fyi...
From: Shimer, Martin
Sent: Tuesday, January 15, 2013 6:19 AM
To: Cuthbert, Gerrard D; Kalinina, Marina
Cc: CDER ESUB; Middleton, Saundra T; Doan, Dat
Subject: RE: NDA 202153 - Resubmission required
Once the recent submission from Draximage is reviewed, a memo is drafted, and the sponsor pays the PDUFA user fee, this application will become a 505(b)(2) application-an NDA. OGD retains limited authority to approve 505(b)(2) applications and this will be one of those applications. Moving forward this application will be paying an NDA user fee and will be considered an NDA for approval purposes. This application should be coded as a NDA.
Thanks,
Marty
From: Cuthbert, Gerrard D
Sent: Monday, January 14, 2013 3:49 PM
To: Cuthbert, Gerrard D; Kalinina, Marina
Cc: CDER ESUB; Middleton, Saundra T; Shimer, Martin; Doan, Dat
Subject: RE: NDA 202153 - Resubmission required
resending to include attachments.
Gerrard D. Cuthbert
Management Analyst
CDER/OBI/DDMSS/DRMT
Tele: (301) 796-3981
Gerrard.Cuthbert@fda.hhs.gov
From: Cuthbert, Gerrard D
Sent: Monday, January 14, 2013 3:46 PM
To: Kalinina, Marina
Cc: CDER ESUB; Middleton, Saundra T; Shimer, Martin; Doan, Dat
Subject: RE: NDA 202153 - Resubmission required
Hello Marina:
Per our conversation with Saundra, this application should retain the application type

"ANDA". However, we do realize that it is being reviewed under 505(b)(2) regulations.
The applicant should change the US-regional.xml to reflect it is an ANDA.
Marty/Dat:
Please confirm.
Thanks.

Gerrard D. Cuthbert
Management Analyst
CDER/OBI/DDMSS/DRMT
Tele: (301) 796-3981
Gerrard.Cuthbert@fda.hhs.gov

From: Kalinina, Marina
Sent: Monday, January 14, 2013 9:10 AM
To: Cuthbert, Gerrard D
Cc: CDER ESUB
Subject: FW: NDA 202153 - Resubmission required

Good morning Gerrard
Do you know anything about OGD/sponsor communications about this ANDA to be submitted as NDA?
They submitted Fillable Form and Cover letter as for ANDA, but US-regional.xml has it as NDA.
We rejected it once as a mismatch but they got back to us and saying that this is intentionally sent this way.
We are not sure what is the deal here.
On Friday I left message on RPM voicemail, but got no response yet.
Any information on this matter would be appreciated.
THANK YOU!

Marina Kalinina
Regulatory Information Specialist
OBI/DDMSS/ESUB
Phone: (301) 796-7591
Marina.Kalinina@fda.hhs.gov

From: Marie-Josée Audet [mailto:mjaudet@jdi.jubl.com]
Sent: Friday, January 11, 2013 3:43 PM
To: CDER ESUB
Cc: Magali Lurquin; Genevieve Paradis; Marie Pierre Ekoka
Subject: NDA 202153 - Resubmission required

Good Day,
We have received a rejection notice, please refer to the attached documents.
Our application number is NDA 202153 and it is for a new drug application 505(b)(2)
The document attached refers to the Application number ANDA 202153 and USRegional. XML file as an NDA.
The attached document refers to 2 deficiencies
1. The Application Type (ANDA) is identified in the Cover letter
2. The Application Type (ANDA) is identified in the Fillable 356H
Since our current situation is not simple, please take into consideration into your review of this dossier that we are converting a previously submitted ANDA to an NDA. This was previously agreed with the office of Generic Drug and they also confirmed to keep the same number that was assign to the previous ANDA.
We kindly request your assistance in this matter, if any changes are required in the attached and referenced document, please let us know. If this submission could be

received as is, we would appreciate, let us know if we need to resend through the gateway.

Best regards,

Marie-Josée Audet
Documentalist, Regulatory Affairs & Jr. Project Manager
Jubilant DraxImage Inc.
A Jubilant Life Sciences Company
Tel.: (514) 694-8220 #4442 | Fax.: (514) 694-9295
www.draximage.com

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202153

APPLICANT: Jubilant DraxImage Inc.

DRUG PRODUCT: Rubidium Chloride Rb 82 Generator (Ruby-Fill®), (b) (4) mCi of Sr 82

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

5 OUTCOME PAGE

COMPLETED ASSIGNMENT FOR 202153 ID: 15909

Reviewer: Wang, Rong **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Rubidium Chloride Rb 82 Generator (Ruby-Fill®), (b) (4) mCi of Sr 82
Jubilant DraxImage Inc

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15909	6/18/2010	Other	(b) (4)	1	1
				Bean Total:	1

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/s/

RONG WANG
01/30/2013

NILUFER M TAMPAL
01/30/2013

HOAINHON N CARAMENICO
02/01/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER
02/01/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Memorandum

Date:	March 8, 2016
Reviewer:	Michelle Rutledge, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Ruby-Fill (Rubidium Rb-82 Generator) Injection
Application Type/Number:	NDA 202153
Applicant/sponsor:	Jubilant Draximage, Inc
OSE RCM #:	2015-2442718

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CONTENTS

1 INTRODUCTION

This memorandum is to re-assess the proposed proprietary name, Ruby-Fill, under NDA 202153, which was found acceptable in previous OSE Reviews# 2014-17160[1] and 2010-1489 and 2010-1495[2]. The Applicant did not submit an external name study for this proposed proprietary name, however the applicant did submit a list of drugs reviewed containing the term 'rubi' in their tradename (See Appendix A).

2 METHODS AND DISCUSSION

To re-assess the proposed proprietary name, the Division of Medication Error Prevention and Analysis (DMEPA), conducted a gap analysis and searched the POCA database to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name reviews #2014-17160 and #2010-1489 and 2010-1495. Additionally, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. Our evaluation has not altered our previous conclusion regarding the acceptability of the proposed proprietary name. Additionally, the Applicant submitted seven names that contained the letter string 'rubi' in the names. None of those names represent a potential source of confusion (See Appendix A). Furthermore, our POCA search identified a new proposed proprietary name (b) (4)*** that does not represent a potential source of drug name confusion (see Appendix B). As a result, we maintain that the name is acceptable.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The March 7, 2016 search of USAN stems did not find any USAN stems in the proposed proprietary name.

3 CONCLUSIONS

The proposed proprietary name is acceptable from both a promotional and safety perspective.

If you have further questions or need clarifications, please contact Janet Anderson, OSE Project Manager, at 301-796-0675.

3.1 COMMENTS TO THE APPLICANT

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

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[1] Rutledge M. Proprietary Name Review Memorandum for Ruby-Fill (NDA 202153). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Apr 1. 4 p. OSE RCM 2014-17160

[2] Merchant L. Proprietary Name, Label and Labeling Review for Ruby-Fill (ANDA 202153). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 Dec 16. 25 p. OSE RCM 2010-1489 and 2010-1495.

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4 REFERENCES

1. Rutledge M. Proprietary Name Review Memorandum for Ruby-Fill (NDA 202153). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Apr 1. 4 p. OSE RCM 2014-17160
2. Merchant L. Proprietary Name, Label and Labeling Review for Ruby-Fill (ANDA 202153). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 Dec 16. 25 p. OSE RCM 2010-1489 and 2010-1495.
3. USAN Stems **(http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united states-adopted-names-council/naming-guidelines/approved-stems.page?)**

   USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A: Low Similarity Names (e.g., combined POCA score is ≤49%)

No.	Name	POCA Score (%)
1.	Berubigen	36
2.	Cerubidine	34
3.	Daunorubicin hydrochloride	15
4.	Doxorubicin	32
5.	Epirubicin hydrochloride	17
6.	Idarubicin hydrochloride	17
7.	Varubi	37

Appendix B: Names not likely to be confused or not used in usual practice settings for the reasons described**.**

No.	Name	POCA Score (%)	Failure preventions
1.	(b) (4)*** (Phonetic Score: 83)	68	This name was identified in the Name Entered by Safety Evaluator database. However, the proposed proprietary name was withdrawn by the Applicant after being found acceptable in OSE Review#2011-4562. IND 079726 is pending.

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/s/

MICHELLE K RUTLEDGE
03/08/2016

YELENA L MASLOV
03/09/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Proprietary Name Memorandum

Date:	April 1, 2014
Reviewer:	Michelle Rutledge, PharmD Division of Medication Error Prevention and Analysis
Team Leader	Yelena Maslov, PharmD Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Ruby-Fill (Rubidium Rb-82 Generator) Injection
Application Type/Number:	NDA 202153
Applicant/sponsor:	Jubilant Draximage, Inc
OSE RCM #:	2014-17160

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CONTENTS

1 INTRODUCTION

This memorandum is to re-assess the proposed proprietary name, Ruby-Fill, under NDA 202153, in response to a request from the Division of Medical Imaging Products (DMIP). DMEPA previously found the name acceptable in OSE Review# 2010-1489 and 2010-1495 dated December 16, 2010.

2 METHODS AND DISCUSSION

For re-assessments of the proposed proprietary name, DMEPA conducted a gap analysis and searched the POCA database (see section 4) to identify names with orthographic and phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review #2010-1489 and 2010-1495. Additionally, we evaluated the previously identified names of concern considering any lessons learned from recent post-marketing experience, which may have altered our previous conclusion regarding the acceptability of the proposed proprietary name. Our evaluation has not altered our previous conclusion regarding the acceptability of the proposed proprietary name. Additionally, our POCA search did not identify any new names that represent a potential source of drug name confusion. As a result, we maintain that the name is acceptable.

Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. The April 1, 2014 search of USAN stems did not find any USAN stems in the proposed proprietary name.

3 CONCLUSIONS

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

If you have further questions or need clarifications, please contact Vasantha Ayalasomayajula, OSE Project Manager, at 240-402-5035.

4 REFERENCES

1. ANDA 202153 Propriety name, label and labeling review dated December 17, 2010 (*OSE Review 2010-1489* & OSE Review 2010-1495)

2. ***USAN Stems*** *(http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page?)*

USAN Stems List contains all the recognized USAN stems.

3. ***Phonetic and Orthographic Computer Analysis (POCA)***
POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

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/s/

MICHELLE K RUTLEDGE
04/02/2014

YELENA L MASLOV
04/02/2014

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 16, 2010
Application Type/Number:	ANDA 202153
To:	Peter Rickman, Director Division of Labeling Review Branch Office of Generic Drugs
Through:	Melina Griffis RPh, Team Leader Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Lubna Merchant MS, Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name, Label and Labeling Review
Drug Name(s):	Ruby-Fill (Rubidium Rb-82 Generator) Injection
Applicant:	Draximage
OSE RCM #:	2010-1489 and 2010-1495

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CONTENTS

EXECUTIVE SUMMARY

This review summarizes DMEPA's evaluation of the proposed proprietary name, labels, and labeling for Ruby-Fill (Rubidium Rb-82 Generator) Injection. Our evaluation of the proposed proprietary name Ruby-Fill did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Ruby-Fill conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the ANDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

Our label and labeling risk assessment indicates the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. We provide label and labeling recommendations in section 5 of this review.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from Draximage. dated June 21, 2010, for an assessment of the proposed proprietary name, Ruby-Fill, regarding potential name confusion with other proprietary or established drug names in the usual practice settings. Additionally, the Applicant submitted container label for review as part of the ANDA submission, which we evaluated to identify vulnerabilities that may cause confusion leading to medication error.

1.2 PRODUCT INFORMATION

Ruby-Fill (Rubidium Rb-82 Generator Injection) is a PET radiopharmaceutical for cardiac perfusion imaging. It will be prescribed by a cardiologist to outpatient, or in a hospital setting for cardiac perfusion tests. Ruby-Fill is administered by injection using a product specific (b) (4) system, capable of accurately measuring and delivering the desired activity of Rubidium Rb-82 Chloride Injection. (b) (4) Ruby-Fill is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of (b) (4) mCi and is enclosed in a lead shield. Cardiogen-82 is the reference-listed drug for Ruby-Fill.

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Ruby-Fill. Section 2.3 identifies specific information associated with the methodology for assessment of the proposed labels and labeling.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter 'R' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[1,2]

To identify drug names that may look similar to Ruby-Fill, the DMEPA safety evaluators also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (four, capital letter 'R' and 'F', and lower case 'b', and 'l'), down strokes (one, lower case 'y'), cross strokes (one, lower case 'f'), and dotted letters (one, lower case 'i'). Additionally, several letters in Ruby-Fill may be vulnerable to ambiguity when scripted (See Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Ruby-Fill.

When searching to identify potential names that may sound similar to Ruby-Fill, the DMEPA safety evaluators search for names with similar number of syllables (three), stresses (Ru-by and fill), and placement of vowel and consonant sounds. (See Appendix B). The Sponsor's intended pronunciation (Ru-bi-fil) was also taken into consideration, as it was included in the Proprietary Name Review Request. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

2.2 PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescription was communicated during the FDA prescription studies. (See Appendix C for samples and results).

2.3 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication

---

[1] Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at http://www.ismp.org/Tools/confuseddrugnames.pdf

[2] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[3]

2.3.1 Adverse Event Reporting System (AERS) Database

The reference listed drug, Cardiogen-82, for the proposed product is currently marketed; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors related to the labels, labeling or packaging of Cardiogen-82 that may also occur with Ruby-Fill. An AERS search was conducted on October 6, 2010 using the trade name "Cardiogen" established name 'Rubidium"and verbatim term "Cardioge%' and 'Rubidiu%" The reactions used were the HLGT term, "Medication Errors," and the PT term, "Product Quality Issue."

The reports were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the reports to determine if the error could also occur with Ruby-Fill. Those reports that did not describe a medication error or did not describe an error applicable to this review (e.g. errors involving concomitant drugs) were excluded from further analysis. Duplicate reports were combined into cases. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

2.3.2 Label and Labeling Risk Assessment

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) to evaluate the label and labeling submitted as part of the February 26, 2010, submission (Appendices H).

3 RESULTS

3.1 DATA BASE AND INFORMATION SOURCES

The searches yielded a total of 10 names as having some similarity to the name Ruby-Fill.

Five of the names were thought to look like Ruby-Fill. These include: Nulytely, Rapaflo, Rebif, Redisol and Rubesol. The remaining five names were thought to look and sound similar to Ruby-Fill: Rebetol, Robathol, Rubella Virus Vaccine, Robinul, and Rubivite.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of October 6, 2010.

3.2 EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Ruby-Fill.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.3 PRESCRIPTION ANALYSIS STUDIES

A total of 33 practitioners responded to the prescription analyses studies with ten of the participants interpreting the scripted name sample correctly as "Ruby-Fill," with correct interpretation occurring in both of the written studies. However, for practitioners interpreting the written prescription for Ruby-Fill incorrectly, none of the responses overlapped with any existing drug product name. In the verbal studies, two participants understood the spoken proposed name sample correctly as "Ruby-Fill". See Appendix C for the complete listing of interpretations from the verbal and written prescription studies

3.4 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in five additional names which were thought to look or sound similar to Ruby-Fill and represent a potential source of drug name confusion. These names included: Ruby-Fill, Nivigil, Rubywood, Pulzium, and Poly-ICLC.

One name "Ruby-Fill" was not evaluated further since it was identified on the U.S. Patent and Trademark Office website registered for this product. Thus, we evaluated fourteen names: four identified by the primary safety evaluator and 10 identified in Section 3.1 above.

3.5 COMMENTS FROM THE DIVISION OF MEDICAL IMAGING PRODUCTS (DMIP) AND OFFICE OF GENERIC DRUGS (OGD)

3.5.1 Initial Phase of Review

In response to the OSE, July 20, 2010 e-mail, DMIP did not forward any concerns on the proposed name at the initial phase of the name review.

In response to the OSE, July 20, 2010 e-mail, the Office of Generic Drugs (OGD), did not respond with any concerns on the name Ruby-Fill.

3.5.2 Midpoint of Review

DMEPA notified OGD via e-mail that we had no concerns with the proposed proprietary name, Ruby-Fill, on December 01, 2010. Per e-mail correspondence from OGD on December 01, 2010, they indicated the Division had no other issues with the proposed proprietary name, Ruby-Fill.

3.6 LABEL AND LABELING RISK ASSESSMENT

The Division of Medication Error Prevention and Analysis (DMEPA) evaluated the identified medication errors involving the Reference Listed Drug, Cardiogen-82. In addition, our assessment of the container label submitted by the Applicant has identified vulnerabilities that could lead to medication errors.

3.6.1 Adverse Event Reporting System (AERS) Database

The AERS search conducted on October 6, 2010, did not retrieve any cases.

3.6.2 Label and Labeling

Our label and labeling risk assessment identified needed improvement in the following areas:

- Deleting the graphic next to the proprietary name presentation.
- Using a different font color to increase the prominence of the warning and relocating the warning statement to the principal display panel (PDP).

4 DISCUSSION

Ruby-Fill is the proposed proprietary name for Rubidium Rb 82 Generator Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. The Applicant proposes to use the term 'Fill' in their proprietary names for a range of radiopharmaceutical products and aides intended to be used in nuclear medicine. During a teleconference with the Applicant dated December 1, 2010, we discussed our concern with the Applicant's proposal to use the term 'Fill' in future proposed proprietary names for pharmaceutical products. DMEPA informed the Applicant that use of the term 'Fill' may affect the acceptability of future proposed proprietary names and needs to be limited to a single product to avoid confusion within the product line.

4.1 PROMOTIONAL ASSESSMENT

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA, DMIP and OGD concurred with the findings of DDMAC's promotional assessment of the proposed name.

4.2 SAFETY ASSESSMENT

DMEPA evaluated 14 names for their potential similarity to the proposed name, Ruby-Fill. No other aspects of the name were considered to pose potential confusion with the name.

Five of the fourteen names did not undergo failure mode and effect analysis (FMEA) because they were either vitamin supplements not dispensed pursuant to a prescription, discontinued proprietary names for products available under the established name or other proprietary names, or names with limited information (see Appendices D-F).

Failure mode and effects analysis (FMEA) was applied to determine if the proposed proprietary name could potentially be confused with the remaining nine names and lead to medication errors. This analysis determined that the name similarity between Ruby-Fill and all of the identified names was unlikely to result in medication error for the reasons presented in Appendices G.

4.3 LABEL AND LABELING RISK ASSESSMENT

The label and labeling risk assessment indicates the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. We identified needed improvement in the following areas: Use of distracting graphic next to the proprietary name presentation and lack of prominence of the warning statement. We provide label and labeling recommendations in section 5 below.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Ruby-Fill, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Ruby-Fill, for this product at this time. The Applicant will be notified via letter.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

The proposed labels and labeling risk assessment noted areas of needed improvement in order to minimize the potential for medication errors. We request the recommendations for the container label and carton labeling in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Sandra Griffith, project manager, at 301-796-2445.

5.1 COMMENTS TO THE APPLICANT

5.1.1 Proprietary Name Risk Assessment

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

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 this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

5.2 COMMENTS TO OFFICE OF GENERIC DRUGS

5.2.1 Label and Labeling Risk Assessment

A. **Container Label**

1. (b) (4) The

proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.

2. Relocate the total activity statement such that it appears below the established name, and above the statement 'Diagnostic agent....use'

3. We recommend that a different color font (such as red) or bolding of letters be utilized for the warning statement that appears on the side panel to increase its prominence and highlight this information.

4. Add the statement 'Generator column must not be removed from lead shield' to the warning.

6 REFERENCES

1. Micromedex Integrated Index (http://csi.micromedex.com)

Micromedex contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion.

3. Drug Facts and Comparisons, online version, St. Louis, MO (http://factsandcomparisons.com)

Drug Facts and Comparisons is a compendium organized by therapeutic course; it contains monographs on prescription and OTC drugs, with charts comparing similar products.

4. FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. Drugs@FDA (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and "Chemical Type 6" approvals.

7. Electronic online version of the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm)

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

8. U.S. Patent and Trademark Office (http://www.uspto.gov)

USPTO provides information regarding patent and trademarks.

9. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

10. Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at (www.thomson-thomson.com)

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Natural Medicines contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

12. Stat!Ref (www.statref.com)

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

13. USAN Stems (http://www.ama-assn.org/ama/pub/about-ama/our-people/coalitions-consortiums/united-states-adopted-names-council/naming-guidelines/approved-stems.shtml)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

Red Book contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

15. Lexi-Comp (www.lexi.com)

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [4]

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [5] DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and

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[4] National Coordinating Council for Medication Error Reporting and Prevention. http://www nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[5] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

monitoring the impact of the medication.[6] DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly in spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly and even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g.,"T" may look like "F," lower case 'a' looks like a lower case 'u,' etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name.

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication

[6] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Lastly, the DMEPA staff also considers the potential for the proposed proprietary name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare

professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to DMEPA.

4. Comments from the OND review Division or Generic drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[7] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to orthographically or phonetically similar drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

[7] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, Expert Panel Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

> ***"Is the proposed proprietary name convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?"***

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

> ***"Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?"***

The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

a. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].

b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].

c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.

d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.

e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, the proprietary name may be misleading or, inadvertently, introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that

could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

The threshold set for objection to the proposed proprietary name may seem low to the Sponsor. However, the safety concerns set forth in criteria a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), the Joint Commission, and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Sponsor can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Sponsors have undertaken higher-leverage strategies, such as drug name changes, in the past but at great financial cost to the Sponsor and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for approving the error-prone proprietary name. Moreover, even after Sponsors' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval. . (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Ruby-Fill	Scripted may appear as	Spoken may be interpreted as
Upper case 'R'	B, Pr, n, s	wr
Lower case 'u'	Any vowel	Any vowel
Lower case 'b'	L, k, h	D, P
lower case 'y'	P, f	E, I, u
Upper case 'f'	t	
lower case 'i'	Any vowel	Any vowel
lower case 'l'	b, h, d, s	el

Appendix C: FDA Prescription Study for Ruby-Fill

Figure 1. Ruby-Fill Study Samples (conducted on July 15, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
Medication Order-1 Ruby-Fill for cardiac perfusion test	Ruby-Fill for cardiac perfusion test
Outpatient Rx Ruby-Fill for cardiac perfusion test	

Table 1: Responses to Prescription Study

Inpatient Medication Order-1	Inpatient Medication Order-2	Voice Prescription
Rubybill	Ruby-Fill	Rubyfill
Orubyfill	Ruby-fill	Rubifil
Onubybill	Ruby-Fill	Rubifill
Prubyfill	Rulry- fill	Rubifil
Orulbyfill?	Ruby - Fill	Rubifell
Prubyfill	Ruby-Fill	Rubifill
Orabyfill	Ruby0Fill	Rubifill
Orubyfill	Ruby-Fill	Rubyfill
Onulybli	Ruby - fill	Rubyfil
Orubyfill	Rutry Fill	Rubifill
	Tuby-Fill	
	Ruby-fill	
	Ruhy Fill	

Appendix D: OTC, nutritional supplement or product not identified as drug and not dispensed pursuant to a prescription.

Proprietary Name	Similarity to Ruby-Fill	Reason
Rubywood	Look	Herbal product (Red sandalwood)
Robathol	Look and sound	Bath oil

Appendix E: Discontinued proprietary names for products available under the established name or other proprietary names.

Proprietary Name	Similarity to Ruby-Fill	Status
Rubivite	Look and sound	Name discontinued, marketed under established name. Preliminary usage data indicates that the product in not prescribed under the name Rubivite.

Appendix F: Names with limited information

Proprietary Name	Similarity to Ruby-Fill	Status
Redisol	Look	Name found in Micromedex. No other information could be obtained from any other pharmaceutical databases.
Rubesol	Look	Name found in Micromedex. No other information could be obtained from any other pharmaceutical databases.

Appendix G : Products with orthographic, phonetic and/or multiple differentiating product characteristics minimize the risk for medication errors.

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Nulytely (Polyethylene Glycol-sodium bicarbonate sodium chloride and potassium chloride) Oral Solution	Look alike	Single strength 420 g-5.72 g-11.2 g- 1.48 g per 4000 mL	240 mL (8 oz) every 10 minutes, until 4 L are consumed	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has an additional upstroke 'l' at the end of the name while Nulytely has a additional downstroke 'y' at the end of the name.* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Route of Administration: *Intravenous infusion using a specific infusion system vs. oral* Dosage Form: *Stannic oxide column encased in lead shield vs. oral solution* Frequency: *One time vs. every 10 minutes, until 4 L are consumed*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Rapaflo (Silodosin) Capsules	Look alike	4 mg 8 mg	1 capsule once daily	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has an additional downstroke 'y' and a additional upstroke 'l' at the end of the name which is absent in Rapaflo* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Route of Administration: *Intravenous infusion using a specific infusion system vs. oral* Dose: (b) (4) *mCi vs. one capsule or 4mg, and 8mg* Dosage Form: *Stannic oxide column encased in lead shield vs. capsules* Frequency: *One time vs. once daily*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Rebif (Interferon beta-1a) Injection Solution	Look alike	8.8 mcg/0.2 mL 22 mcg/0.5 mL 44 mcg/0.5 mL	4.4 mcg to 44 mcg subcutaneously given one to three times weekly.	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has a downstroke 'y' and additional upstrokes 'l' at the end of the name which is absent in Rebif* *Ruby-Fill (8 letters) appears longer than Rebif (5 letters) when scripted* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies* *Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Dosage form: *Stannic oxide column encased in lead shield vs. injection solution* Frequency: *One time vs. one to three times daily* Strength: (b) (4) *millicuries vs. 8.8 mcg/0.2 mL, 22 mcg/0.5 mL and 44 mcg/0.5 mL*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Rebetol (Ribavirin) Capsules and Oral Solution	Look and sound alike	Capsule: 200 mg Oral Solution: 40 mg/mL	Adults: 400 mg to 600 mg twice daily. Pediatrics: 15 mg/kg/day in 2 divided doses or 200 to 400 mg	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has an additional downstroke 'y' and a additional upstroke 'l' at the end of the name which is absent in Rebetol* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Route of Administration: *Intravenous infusion using a specific infusion system vs. oral* Dosage Form: *Stannic oxide column encased in lead shield vs. capsules or oral solution* Frequency: *One time vs. twice daily*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Rubella Virus Vaccine powder for Injection	Look and sound alike	Single strength 1000 units/vial	Inject 0.5 mL subcutaneously once	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has an additional downstroke 'y' which is absent in Rubella virus vaccine* *Rubella virus vaccine (3 words) appears longer than Ruby-Fill when scripted.* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies* *Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Dosage form *Stannic oxide column encased in lead shield vs. injection solution* Dose: (b) (4) *mCi vs. 0.5 mL*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Robinul (Glycopyrrolate) Tablets and Injection Solution	Look and sound alike	Single strength Tablets: 1 mg Injection Solution: 0.2 mg/mL	Adults: Oral: 1 mg to 2 mg 2-3 times/day Intramuscular or Intravenous: 0.1 mg -0.2 mg 3-4 times/day. Pediatrics: Oral: 40 -100 mcg/kg/dose 3-4 times/day Intramuscular or Intravenous: 4-10 mcg/kg/dose every 3-4 hours	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has an additional downstroke 'y' and a additional upstroke 'f' and 'l' in the name which is absent in Robinul.* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Frequency: *One time vs. 2 to 4 times daily* Dosage form *Stannic oxide column encased in lead shield vs. injection solution*
Nuvigil (Armodafinil) Tablets	Sound alike	50 mg 150 mg 250 mg	150 mg -250 mg once daily	Differences in product characteristics minimize the likelihood of medication error in the usual practice setting. Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Route of Administration: *Intravenous infusion using a specific infusion system vs. oral* Dosage Form: *Stannic oxide column encased in lead shield vs. tablets* Frequency: *One time vs. once daily*

Product name with potential for confusion	Similarity to Ruby-Fill	Strength	Usual Dosage and Administration	Name confusion is prevented by the combination of stated product characteristics, orthographic, and/or phonetic differences as described.
Ruby-Fill (Rubidium Rb 82 Generator) Injection Solution	**N/A**	(b) (4) **millicuries of strontium SR-82**	(b) (4)	**N/A**
Pulzium (Tedisamil) Injection Solution	Look alike	Single strength 20 mg/10 mL	0.48 mg/kg for males and 0.32 mg/kg for females through intravenous injection once	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has additional upstrokes 'f' and 'l' at the end of the name which is absent in Pulzium* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Dosage Form: *Stannic oxide column encased in lead shield vs. injection solution*
Poly-ICLC Injection Solution	Look alike	Single strength 2 mg/mL	10 to 30 mcg/kg given subcutaneously one to three times weekly	Orthographic differences in the names, in conjunction with differences in product characteristics, minimize the likelihood of medication error in the usual practice setting. Orthographic: *Ruby-Fill has a upstroke 'f' which introduces a downstroke in that position and is absent in Poly-ICLC* Setting of use: *Nuclear pharmacy vs. inpatient or outpatient pharmacies Nuclear medications are ordered, procured, and dispensed pursuant to the regulations by U.S. Nuclear Regulatory Commission.* Dosage Form: *Stannic oxide column encased in lead shield vs. injection solution* Frequency: *One time vs. one to three times weekly*

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/s/

LUBNA A MERCHANT
12/16/2010

MELINA N GRIFFIS
12/16/2010

DENISE P TOYER
12/17/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Inter-center Consult Memorandum

Design Review: CDER NDA 202153 - CDRH ICC1600048

Date: September 29, 2016

To: Frank A Lutterodt OMPT/CDER/OND/ODEIV/DMIP

From: Robert Meyer, Mechanical Engineering Reviewer
General Hospital Devices Branch (GHDB),
Division of Anesthesiology, General Hospital, Respiratory,
Infection Control, & Dental Devices (DAGRID),
Office of Device Evaluation (ODE),
Center for Devices and Radiological Health (CDRH)

Subject: Device Constituent Part Design Review: ICC 1600048 / NDA 202153

Drug: Rb-82

Equipment: RUBY-FILL®- Rubidium Rb 82 Generator

Sponsor: Jubilant Draximage Inc.,

Recommendation: The equipment is approvable.

I. Purpose

To evaluate the documents provided which are intended to justify the safety and effectiveness of the Ruby-fill elution system .

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

XVI. Additional Comments:

N/A

XVII. Recommendation

After review of the provided documents it is evident the drug, otherwise identified as system, is able to deliver Rb 82 chloride as specified. From a device perspective this system is approvable.

XVIII. Concurrence Table

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Branch Sign-Off	

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/s/

FRANK A LUTTERODT
09/30/2016

Division of Medical Imaging Products
ADL Labeling Review

Product	Ruby-fill
NDA	202153
Supporting Documents	30, 33, 44
Date	September 29, 2016

Background

Change to Dosing Information

- The sponsor presented their proposed label on December 28, 2015 (SD 30).
- They were asked to update to comply with PLLR and submitted a revised label on May 5, 2016 (SD 33).
- The sponsor complied with PLLR, and included a change in dosing based upon SNMMI/ASNC/SCCT Guidelines.
- We cannot accept society guidelines alone as the basis for dose changes. As such, on June 29, 2016 an Information Request was sent to the sponsor to perform a comprehensive assessment of the publications from the medical literature that support this expanded dosing range; with copies of the cited publications.
- The sponsor responded July 25, 2016 (SD 44). The sponsor further modified their request to change to weight-based dosing.

The sponsor proposed the following weight-based dosing (b) (4):

(b) (4)

Labeling Recommendations:

1. **Recommend using weight based dosing; providing a range inclusive of 2D and 3D dosing; specifically, 10-30 MBq/kg.**
2. **Recommend removing detailed information** (b) (4)
3. **Recommend** (b) (4) **60 mCi is the recommended maximum and weight-based dosing more accurately captures the lower range.**
4. **Recommend removing statement** (b) (4)

Agreed upon label:

- **The recommended weight-based dose of rubidium Rb 82 is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg].**

- **Do not exceed a single dose of 2220 MBq (60 mCi)** (b) (4)

Review of Material Submitted

The sponsor presents a literature review to assess the specific values or ranges of the administered activities reported in peer reviewed studies using Rb-82 Chloride injection for MPI.

Search Strategy

The sponsor performed a MEDLINE database search on PubMEd from 1/1/2007-6/29/2016 for "Rubidium-82 myocardial perfusion" in humans.
62 articles were returned

Excluded:
17 were excluded (9 review articles of Rb-82, 2 meta-analyses, 2 case reports, 2 F18 flurpiridaz, one F-18 tracers, one chart reviews)
9 further excluded because they did not report the administered activity.

36 Eligible articles were identified.

Of the 36 studies returned, 12 studies used weight based dosing (3-10 MBq / kg) with a mid-range of activity 24 mCi and a range 16-32 mCi.

Reviewer comments: These studies provide strong evidence of weight based dosing and support of lower activities.

Additionally, there were 16 studies using weight-based dosing (MBq / kg not given) which resulted in a mean activity of 44.4 mCi with a lower bound to the range of 20 mCi. Eight studies used fixed dosing with a mid-range activity of ~44 mCi and a lower bound to the range of 15 mCi.

Not returned in their meta-analysis, they also cite the ARMI study[1]. The authors used weight based dosing (10 MBq/kg) in approximately 1500 patients with known or suspected CAD using the Ruby-Fill Elution system. Forty patients with a low likelihood (LLK) of CAD were used to a develop normal database to be used for quantification of myocardial perfusion and diagnosis of CAD using low-dose Rb 82 and 3D EPT CT imaging. In addition, 70 patients who had angiography and PET CT were used to evaluate the accuracy of the database using automated analysis (SSS). The ARMI study used doses of 10 MBq / kg with a mid-range activity of ~25 mCi and a range of 9.7 – 56 mCi. Sensitivity and specificity were evaluated in a group of 70 CAD patients using stenosis ≥ 50% by coronary angiography (ICA) as the gold-standard for presence of disease. Sensitivity, specificity and overall accuracy were 100%, 71% and 89% respectively in CAD patients without previous revascularization or LV dysfunction.

Reviewer's comments: This study is the strongest evidence of weight-based dosing showing 10 MBq / kg in ~ 1500 patients. This study shows acceptable validation of the efficacy of the lower doses used in 3 D PET MPI

Additionally, the sponsor presented a breakdown of dose used over time which shows doses lowering over time. Table 1 is excerpted from the submission to display the difference in dosing from earlier studies (2007-2008) to later studies (2009-2016).

Table 1: Administered Activity by Period

Period	Fixed Activity	Minimum	Maximum	Mid-point
2007-2008	50	41.5	62.4	50.9
2009-2016	37	33.8	44.3	37.4

Reviewer's Comments: The table shows lower minimum and midpoint activities. Likely representing the lower doses permitted with new technology.

Conclusions:

It is this reviewer's opinion that the totality of the evidence supports the efficacy of weight-based dosing, and results in a favorable risk-benefit profile for the drug.

Weight based dosing is used commonly in clinical practice. There is ample evidence for the use of weight based dosing and lower doses presented in the submission. In the analysis of the publications with weight-based dosing, the mean dose was 24-44.4 mCi and the lower bound of the dose range is 9.7-20 mCi. In the analysis of the publications over time, the mid-point and minimum doses are also lower; ~34 mCi and 37 mCi, respectively (table 1).

Weight based dosing would ensure that larger patients would still receive larger doses for an adequate study. For example, with dosing 10-15 MBq / kg, a 136 kg patient would receive 36.8 – 55 mCi. The weight based dosing conforms to currently recommended doses (30-60 mCi) for a larger patient. Therefore, efficacy in larger patients is not an issue because they are the very patients still receiving the higher doses (see Table 1). In fact, the continued use of higher doses may be explained by the fact that larger patients, in general, undergo PET Rb-82 because of the better imaging qualities of PET in larger patients relative to Tc-99m SPECT imaging.

Smaller patients will be receiving the lower doses with weight-based dosing. It is this reviewer's opinion that the technology advances support continued efficacy with lower doses. There have been upgrades in PET technology (3 D scanning, iterative reconstruction software) which permit lower doses. Furthermore, the ARMI trial[1], showed evidence of efficacy for weight based dosing. The risk of any possible decreased efficacy is outweighed by the enhanced safety afforded from lower radiation absorbed dose.

Finally, the technology and equipment available at each institution is varied. Weight-based dosing allows for optimization of technology improvements at different institutions, without committing to *absolute* lower doses, especially for larger patients. Additionally, there are nuances to this technology and choosing a dose. Lower doses may in fact produce better images on certain equipment. Weight-based dosing allows for the nuances of the equipment and dose to be handled by the clinician.

[1] Kaster, et.al J Nucl Cardiol. 2012 Dec;19 (6):1135-45

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/s/

MICHELE B FEDOWITZ
09/29/2016

505(b)(2) ASSESSMENT

Application Information		
NDA # **202153**	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Ruby-Fill Established/Proper Name: Rubidium-RB-82 Chloride Dosage Form: injection Strengths: (b) (4) mCi of Sr-82 at calibration time		
Applicant: Jubilant Draximage		
Date of Receipt: **6/30/2010**		
PDUFA Goal Date: **9/30/2016**	Action Goal Date (if different):	
RPM: **Frank Lutterodt**		
Proposed Indication(s): **Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography 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.**		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature, including literature on CardioGen-82 and Labeling	**Prescribing Information and Training Manuals**
CardioGen-82	**FDA's previous finding of safety and effectiveness (clinical, Nonclinical, CMC)**

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Clinical Study is not required. There was comparative physical chemical characterization.

In addition, the clin pharm review notes the following: The test product (Rubidium Chloride Rb Injection) contains (b) (4) **the same inactive ingredient (0.9% sodium chloride) as the RLD product. However, the radioactivity of Rb 82 per mL of eluate (i.e. the concentration of active ingredient in the final product) could vary depending on the elution rate and the potency of the Rb 82 generator (the radioactivity of Sr 82) decay corrected to the day of administration. It should also be noted that although the radioactivity of Rb 82 per mL of eluate could vary in both test and RLD products, the dose (i.e. radioactivity of Rb 82) administered to a patient is precisely controlled by a specifically designed infusion system for both test and RLD products, respectively.** (b) (4)

The relied upon literature describes the use of CardioGen-82, the applicant's Ruby-Fill Generator product approved in Canada, and Rb82 generally for PET imaging. The bridge to CardioGen82 is described above. For the published literature on PET imaging with Rb82 without naming a specified product, the information from the literature are directly relevant to this drug product as the findings are based on the dose and exposure to the Rb82 radioactive isotope and are independent of the drug product formulation. As noted in the above paragraph, the dose of the Rb82 active ingredient administered to patients using the Ruby-Fill system is precisely controlled using an infusion system.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

CardioGen-82

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on

		the product? (Y/N)
CardioGen-82	**NDA 19414**	**Y**

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*

*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The Ruby Fill apparatus is a new drug delivery and infusion system to produce Rubidium (Rb-82) for use in nuclear cardiac testing. CardioGen (the relied upon listed drug) has an older Rb-82 generator system. In addition, Ruby Fill differs from Cardio-Gen with respects to the rate of infusion and the maximum volume of solution to be administered.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): **NDA 19414 Cardiogen-82**

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☐ NO ☒
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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/s/

FRANK A LUTTERODT
09/23/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 15, 2016

To: Frank Lutterodt, Project Management Staff
Division of Medical Imaging Products (DMIP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: RUBY-FILL® (Rubidium Rb 82 Generator)
To produce rubidium Rb 82 chloride injection, for intravenous use
NDA 202153

On March 7, 2016, DMIP consulted OPDP to review the draft Package Insert (PI) for RUBY-FILL® (Rubidium Rb 82 Generator), a closed system used to produce rubidium Rb 82 chloride injection for intravenous use in adult patients with suspected or existing coronary artery disease.

OPDP reviewed the proposed substantially complete version of the PI provided by Frank Lutterodt via e-mail on September 8, 2016 titled "NDA202153 Ruby-Fill WORKING LABEL AMR(2) ". OPDP's comments are provided in the attached version of the substantially complete labeling.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

18 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

MEENA RAMACHANDRA
09/15/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	Hari Cheryl Sachs, MD, Team Leader
NDA Number:	202,153
Sponsor:	Jubilant Draximage Inc.
Drug:	Ruby-fill (rubidium Rb-82 chloride)
Dosage Form and Route of Administration:	Solution for intravenous (IV) injection
Indication (Adults only):	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.
Proposed Pediatric Regimen:	None
Date of internal meeting:	May 5, 11, and 12, 2016
Division Consult Request:	The Division of Medical Imaging Products (DMIP) requests DPMH participation for labeling for this 505(b)(2) application for a newly marketed product.

Background

Ruby-fill (rubidium Rb-82 chloride) is submitted as a 505(b)(2) NDA application which intends to rely on data from another rubidium agent (Cardiogen-82, NDA 19,414). The sponsor is seeking an indication 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 (the same indication as Cardiogen-82).

Cardiogen-82 is labeled for use in adults only and Ruby-fill is likewise under premarket review for use in adults only. In 2010, the Pediatric and Maternal Health Staff (PMHS, now DPMH) performed a labeling review for Cardiogen-82 to assist in bringing labeling into Physician Labeling Rule (PLR) format (NDA 19,414; Best J; March 23, 2010). The PMHS review noted that pediatric patients with congenital heart disease or acquired coronary artery abnormalities who may require an evaluation of cardiac perfusion might be available for clinical study.[1] However, the July 29, 2010 Approval Letter for Cardiogen-82 states that pediatric studies under the Pediatric Research Equity Act (PREA) were waived because studies are impossible or highly impracticable due to the rarity of the condition(s) in children. A search performed for this review identified no PPSR or pediatric Written Request for Cardiogen-82. A review of the clinicaltrials.gov website failed to identify other likely pediatric indications for study. Per email communications with the DMIP project manager [(Lutterodt, F., June 20, 2016) and clinical review team (Krefting I., MD; email May 20, 2016)], the Division determined that studies under PREA are not applicable for because the NDA is a 505(b)(2) application for which the studies were deemed impracticable for the reference listed drug (RLD, Cardiogen-82), and for which the current application does not represent a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration compared to the RLD

The current consult request states that DMIP requests assistance in "reviewing section 8 and other sections to Peds and Maternal health of the prescribing information." The entire labeling including the Highlights section has been reviewed. DPMH participated in the labeling meeting of May 11, 2016. No pediatric-specific safety issues were identified on review of labeling or at the labeling meeting of May 11, 2016. Since the drug will not be indicated for use in children, this review focus on 8.4 (Pediatric Use). The review will also show the Boxed Warning, and Section 1 (Indications and Usage) which are identical to current Cardiogen-82 labeling and acceptable from a DPMH perspective; however further review of these and other sections of labeling are deferred to DMIP and other consultants including the Maternal Health team. The Maternal Health Review will be performed separately.

For each section of labeling, the proposed labeling is presented first, followed by DPMH recommendations (if any) in ***bold italics***.

[1] Chhatriwalla A, Prieto L, Brunken R Cerqueira M, Younoszai A, Jaber W. Preliminary data on the diagnostic accuracy of rubidium 82 cardiac PET perfusion imaging for the evaluation of ischemia in a pediatric population. Pediatr Cardiol (2008) 29:732–738

Boxed Warning

WARNING: UNINTENDED STRONTIUM-82 (Sr-82) AND STRONTIUM-85 (Sr-85) RADIATION EXPOSURE

Please see full prescribing information for complete boxed warning

- **Unintended radiation exposure occurs when the levels of Sr-82 or Sr-85 in the rubidium Rb 82 chloride injection exceed limits. (5.1)**
- **Perform generator eluate tests:** (b) (4)

2) Determine Rb-82, Sr-82, Sr-85 levels in the eluate:

- **Once daily, prior to any drug administration, and**
- **With additional daily tests after detection of an Alert Limit.** (b) (4)

3) Stop use of the generator at its Expiration Limit. (b) (4)

Reviewer comment: The Boxed Warning (b) (4) *is acceptable.*

1 Indications and Usage

RUBY-FILL® Rubidium Rb 82 Generator is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is 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.

Reviewer comment: The indication is identical to the current indication in RLD labeling, clearly indicates that the drug is indicated for adults only, and is acceptable from a DPMH perspective.

5 Warnings and Precautions

Reviewer comment: (b) (4) *The safety issues discussed would be relevant to patients of any age and would not be uniquely relevant to pediatric patients.*

5.1 Unintended Sr-82 and Sr-85 Radiation Exposure

Unintended radiation exposure occurs when the Sr-82 and Sr-85 levels in rubidium Rb 82 chloride injections exceed the specified generator eluate limits. (b) (4)

To minimize the risk of unintended radiation exposure, strict adherence to a daily eluate testing protocol is required. Stop using the rubidium generator when the expiration limits are reached [see Dosage and Administration (b) (4) and (b) (4)].

5.2 Risks Associated with Pharmacologic Stress

Pharmacologic induction of cardiovascular stress may be associated with serious adverse reactions such as myocardial infarction, arrhythmia, hypotension, bronchoconstriction, and cerebrovascular events. Perform pharmacologic stress testing in accordance with the pharmacologic stress agent's prescribing information and only in the setting where cardiac resuscitation equipment and trained staff are readily available.

(b) (4)

8 Use in Special Populations

8.4 Pediatric Use

(b) (4)

Reviewer comment: The following revision is recommended by DPMH to enhance readability. There is no plan to include any juvenile toxicity data in labeling.

***The safety and effectiveness of** Rubidium Rb 82 chloride injection in pediatric patients have not been established.*

Conclusion and Recommendations

The above comments were presented to DMIP and were discussed at the internal labeling meeting of May 11, 2016. The reader is directed to final negotiated labeling (pending) which may contain additional changes not described in this review.

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/s/

ETHAN D HAUSMAN
06/21/2016

HARI C SACHS
06/21/2016
I agree with these labeling recommendations.

LABEL AND LABELING AND HUMAN FACTORS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 7, 2016
Requesting Office or Division:	Division of Medical Imaging Products (DMIP)
Application Type and Number:	NDA 202153
Product Name and Strength:	Ruby-Fill (Rubidium Rb-82 Generator) Injection (b) (4) mCi
Product Type:	Combination
Rx or OTC:	Rx
Applicant/Sponsor Name:	Jubliant Draximage, Inc
Submission Date:	December 30, 2015
OSE RCM #:	2016-216
DMEPA Primary Reviewer:	Michelle Rutledge, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD
DMEPA Acting Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) requested DMEPA to review human factors Study Results, Instructions for Use, container label, carton labeling and prescribing information for Ruby-Fill (Rubidium Rb-82 Generator) Injection. This NDA was resubmitted to the FDA on December 30, 2015 as a response to a Complete Response.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
Training Program	D
Labels and Labeling	E

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEW

3.1 PRODUCT OVERVIEW

This proposed combination product consists of multiple components such as generator, elution system, (b) (4) which produces and delivers rubidium 82 chloride (82RbCl) for injection (See Appendix A for the information regarding Ruby-Fill (b) (4)). Specialized training will occur for each person using Ruby-fill and will be identical to the training that occurred on the Validation human factors Study. Training will follow a specific course outline containing all steps of the product use, hands-on demonstrations, followed by successful completion of a quiz and test. Upon completion of the training, the intended user will receive a certificate. Please refer to Appendix E for detailed information regarding the proposed training program. The training appears adequate and effective according to the human factors Validation study.

3.2 HUMAN FACTORS STUDY

Methodology

We found the Applicants' proposed methodology of the human factors (HF) Study in terms of objectives training provided, use environment, tasks tested to be acceptable. We also note that although 15 representative participants were included in the Validation human factors study, they were collected from three different study sites (See Table 1 below). Please see Appendix C for regarding additional information about the human factor study.

Table 1: Validation human factors Study Sites

Clinic/Hospital	Location	Number of Respondents
Hartford Hospital	Hartford, CT	4
Brigham and Women's Hospital	Boston, MA	6
Cardiac Imaging Associates	Los Angeles, CA	5
	Total:	15

Results

The study demonstrated with training, users are able to use the product safely and effectively. Although some errors have occurred, we attributed these errors to be study artifacts, more specifically, the study participants did not perform specific tasks because they knew they are in a simulated use testing environment. We also note that errors occurred only in the first one of the three testing sites (i.e., Hartford Hospital). The Applicant indicated that after the first study site, they revised the moderator's script to further clarify the tasks and that resulted in no errors seen in the other two sites (Brigham and Women's Hospital and Cardiac Imaging Associates). Please see Appendix C for the details of the errors seen at the Hartford site. Given that the errors were attributed as study artifacts, we found the study results acceptable.

3.3 LABELS AND LABELING REVIEW

Based on the proposed HF study, we do not recommend additional revisions for the Instructions for Use, training, or training manual/course outline.

Additionally, we reviewed the proposed label and labeling and identified the following areas of vulnerability to errors.

- Readability of the container label

4 CONCLUSION & RECOMMENDATIONS

We found the HF study results to be acceptable. We have no additional recommendations for the instructions for use, training, training manual/course outcome, and prescriber information labeling. Our review of the container label has identified several areas that can be modified improve the readability of the information on the label.

4.1 RECOMMENDATIONS FOR JUBILANT DRAXIMAGE, INC

We recommend the following be implemented prior to approval of this NDA:

A. CONTAINER LABEL

1. [redacted] (b) (4) The proprietary name, established name, and strength should be the most prominent information communicated on the principal display panel.
2. Increase font size of strength to help increase prominence of this important product information.

B. PATIENT ACTIVITY RECORD

1. See A1. above and implement accordingly.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ruby-Fill that Jubliant Draximage, Inc submitted on April 26, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for RUBY-FILL and the Listed Drug, CARDIOGEN-82		
Product Name	**Ruby-Fill**	**Cardiogen-82**
Initial Approval Date	N/A	December 29, 1989
Active Ingredient	rubidium Rb 82 Generator	rubidium Rb 82 generator
Indication	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	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
Route of Administration	Intravenous	Intravenous
Dosage Form	A closed system used to produce rubidium Rb 82 chloride injection	A closed system used to produce rubidium Rb 82 chloride injection
Strength	(b) (4) mCi Sr-82 at calibration time	**90-150** millicuries Sr-82 at calibration time
Dose and Frequency	(b) (4) Do not exceed a single dose of 2220 MBq (60 mCi).	The recommended adult (70 kg) dose of rubidium Rb 82 chloride injection is 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30- 60 mCi) infused intravenously at a rate of **50 mL/minute**, not to exceed a total volume of **100 mL**. Do not exceed a single dose of 2220 MBq (60 mCi)

How Supplied	**RUBY-FILL®** Rubidium Rb 82 Generator consists of Sr-82 adsorbed on a hydrous stannic oxide column with an activity of (b) (4) **mCi Sr-82** at calibration time. **A lead shield encases the generator.** The container label provides complete assay data for each generator. (b) (4) Use **RUBY-FILL®** only with an appropriate, properly calibrated **Elution** System labeled for use with the generator. Receipt, transfer, handling, possession or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission (NRC), Agreement States or Licensing States as appropriate.	**CardioGen-82** (rubidium Rb 82 generator) consists of Sr-82 adsorbed on a hydrous stannic oxide column with an activity of **90-150 millicuries** Sr-82 at calibration time. **A lead shield surrounded by a labeled plastic container encases the generator.** The container label provides complete assay data for each generator. Directions for determining the activity of Rb-82 eluted from the generator are described above [see Dosage and Administration (2.5)]. Use **CardioGen-82 (rubidium Rb 82 Generator)** only with an appropriate, properly calibrated **infusion** system labeled for use with the generator. Receipt, transfer, handling, possession or use of this product is subject to the radioactive material regulations and licensing requirements of the U.S. Nuclear Regulatory Commission, Agreement States or Licensing States as appropriate.
Storage	Store the generator at 20-25 ºC (68-77 ºF).	Store the generator at 20-25°C (68-77°F) [See USP].

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APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 25, 2016, we searched the L:drive using the terms, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 4 previous reviews, and we confirmed that our previous label and labeling recommendations were implemented or considered.

Information to include in the citation for previous reviews:

Label and Label Review and Proprietary Name Review

Merchant, Lubna. Label and Labeling Review for Ruby-Fill. ANDA 202153. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 Dec 16. RCM No.: 2010-1489 and 2010-1495.

Proprietary Name Review

Rutledge, Michelle. Proprietary Name Review for Ruby-Fill. NDA 202153. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Mar 08. RCM No: 2015-2442718.

Rutledge, Michelle. Proprietary Name Review for Ruby-Fill. NDA 202153. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 Apr 01. RCM No: 2014-17160.

Medication Error Consult Review

Vora, Neil. Medication Error Consult Review for Ruby-fill. NDA 202153. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Feb 02. RCM No: 2-14-2387.

Intended Device Users, Uses, Use Environments and Training

The intended users of the RUBY Rubidium Elution System (RES) are certified/registered Nuclear Medicine Technologists with certification and registration in the United States. The technologists perform 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. The technologists perform imaging in hospitals and clinics with PET or PET/CT cameras. Nuclear Medicine Technologists are trained to work with radiopharmaceuticals and minimize their exposure to radioactive materials. For this Summative Usability Validation Test, 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. .

IV. User Task Selection, characterization and prioritization

The tasks that were selected for Summative Validation Testing are the User tasks required to setup the elution system, perform Daily QC, perform patient infusions and manage elution system data. Users were also asked to evaluate the User Manual.

Table IV-1 shows the relative risk levels for each task as identified by the usability Failure Modes and Effects Analysis (uFMEA, D/N 3000030).

Table IV-1. Task Risk Level.

Task Number	Task Name	Risk Level
1	(b) (4)	Negligible
2		Undesirable
3		Tolerable
4		Undesirable
5		Tolerable
6		Undesirable
7		Tolerable
8		Undesirable
9		Undesirable
10		Negligible

The (b) (4) (Task 2) and (b) (4) (Tasks 6, 8 and 9) were the only tasks determined to have undesirable risk in the uFMEA.

Validation Testing

A. Test type

The Summative Usability Test took place in the clinical use environment of the Cardiac PET lab at Hartford Hospital and Brigham and Women's Hospital. In Los Angeles, testing took place in a conference room at the Cardiac Imaging Associates. The RbES was tested in simulation mode without actual live generators. The

Simulation mode is able to mimic all tasks that the user is required to perform including patient infusions and system setup functions. There were no patients present during the testing as the tests occurred after normal clinic hours. The RbES used in testing was a production level device (Serial Number [redacted], manufactured by [redacted]).

B. Test Participants

A total of fifteen (15) participants were tested in the Summative Usability Validation Test. The number of participants at each location is shown in table VI-1. The participants were all certified Nuclear Medicine Technologists, U.S. residents currently practicing in U.S. Cardiac PET labs, representative of the actual RbES user population.

Table VI-1. Number of Participants by location.

Clinic/Hospital	Location	Number of Respondents
Hartford Hospital	Hartford, CT	4
Brigham and Women's Hospital	Boston, MA	6
Cardiac Imaging Associates	Los Angeles, CA	5
	Total:	15

C. Test Goals, Critical Tasks and Use Scenarios Studied

The goal of the tests was to ensure that respondents are able to correctly perform the tasks required to setup and operate the RUBY Rubidium Elution System. The critical tasks were [redacted] (b) (4) Two error scenarios were also created to test the respondents 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. If the respondent completed all steps correctly regardless of order, the task was deemed successfully completed and "passed". The JDI PET Specialist conducted all respondent training prior to the testing. Each respondent was given a dinner break of at least 60 minutes prior to testing. During the break, respondents were asked to evaluate the User Manual using the User Manual Review Form (D/N 10093-001, Appendix B).

D. Technique for Capturing unanticipated use errors

The technique used for capturing unanticipated use errors was to interview each respondent following each task, specifically asking about points of delay or confusion where the user made a mistake or failed to complete a step. All respondents were videotaped as well for further review later at the time of analysis.

E. Definition of Performance Failures

A respondent failed a task if the task steps were not completed successfully or in a manner that would prevent the test from continue. Respondents were specifically asked to elaborate on failed steps whether or not the entire task had been failed or not. Also, respondents were asked about near misses or moments of hesitation or apparent confusion during the duration of the tests.

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APPENDIX D. TRAINING PROGRAM

1.11.4.2 Response to CRL Q2
From Response to Complete Response Letter (CRL), dated December 18, 2014

CLINICAL

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.

JDI Response to CRL Question 2:
a. Training program:
The training program was presented in the June 2015 meeting package and discussed in July during the Type C meeting. FDA found it to be detailed and satisfactory (please refer to the FDA comments in the August 18, 2015 meeting minutes on page 3 of **Appendix 1-1**).

The training materials are the same materials that were included in the meeting package. The training package is enclosed in **Appendix 2-1**, being comprised of:
- Training Roadmap
- Overview of Training Program
- Working Instructions 2067INS01 and the related Forms

It should be emphasized and reiterated that the original user training will be performed by a JDI specialist at the clinical customer site for the first certification. Additionally, these certified users will be re-certified every two years on site or when updates to the Software or the User Manual become available whichever is earlier. That is, Software or User Manual updates mandate earlier certification. The Training & Certification will be provided to all users by JDI at the time of installation. One to two, more highly trained 'super-users' will be identified at each clinical site (typically this would be a team leader, lead PET/CT technologist, or a senior technologist with significant experience and nuclear cardiology technologist certification expected to be at the site for a long period of time to maintain site competency and who can train a new site employee[s] providing these new employees meet all of the following criteria:
- Site will inform JDI of the new employee to be certified
- Super-user on site has been certified by JDI personnel
- Super-user has current JDI certification (within two years of initial training or latest certification)

JDI will provide appropriate verification to the site for certification of newly trained users when evidence of successful training is provided. Super-users can only train and certify technologists, locally, at their own clinical site.

A re-training Form (2067FRM07) is associated with the 2067INS01 and it was added post July Type C meeting, to complete the training program and to comply with the FDA expectations. The working instructions 2067INS01 were also updated accordingly to add this new form.

b. Instructions for Use:
The User Manual, structured as FDA requested and presented in **Appendix 2-2** serves also as a training manual. A description of the changes incorporated after execution of the Usability study is also provided. None of these changes were deemed to impact the applicability of the Usability study that was performed.

The User Manual that was used as the basis of the Usability Study (refer to **Appendix 1-4**) was updated to include the following changes:
- To address the FDA questions raised in the Complete Response Letter (CRL Questions 2.b, 4 and 12)

These changes were related to formatting and document structure and were proposed largely for clarification purposes. The changes did not trigger any significant text content that would affect the conducted usability testing, presented with CRL Question 1.

Since the June 2015 Type C Meeting, additional changes were included in the version of User Manual presented in **Appendix 2-2,** as follows:

- Addition of a Table of Contents, Index, page numbers, and a clearer section on warnings and precautions (answering FDA CRL Question 2b)
- Clarification of supplied accessories, (b) (4) and elimination of (b) (4) which were in previous versions by inadvertence (answering FDA CRL Question 4)
- Clarification that the RUBY RbES is (b) (4) (answering FDA CRL Question 12).
- Other changes proposed by JDI, which are associated with the incorporation of electrical safety and electromagnetic compatibility requirements as per CSA requirements, a re-structuring 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 for the (b) (4) installation part for ease of readability for the user

- Additional changes related to formatting and document structure and are proposed for clarification purposes. These changes did not trigger any text content that would affect the usability testing
- Update of software screenshots to reflect change from Software version (b) (4) to Software version (b) (4)
- Update of several figures, including updated (b) (4) and labeling of first two figures showing system components, to reflect change of (b) (4) and introduction of (b) (4) designed by (b) (4) and manufactured by (b) (4)
- Troubleshooting section has been completely revised including full description of the error messages displayed by the software and additional steps for troubleshooting
- Addition of warnings, including (b) (4)
- Movement (b) (4) to correspond with Software version (b) (4)
- Addition of (b) (4) (if required)
- Small edits and formatting, including font size, use of capital letters on various words.

(b) (4)

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

APPENDIX E. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Ruby-Fill labels and labeling submitted by Jubliant Draximage, Inc on December 20, 2015.

- Container label
- Carton labeling
- Instructions for Use/User Manuel (not listed)
- Prescribing Information (not listed)

G.2 Label and Labeling Images

(b) (4)

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

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

/s/

MICHELLE K RUTLEDGE
06/07/2016

YELENA L MASLOV
06/07/2016

QUYNHNHU T NGUYEN
06/07/2016

Human Factors (HF) Review

Consult Number:	ICC1600201 AND SPONSOR RESPONSES
Document Number:	NDA 202153
Applicant:	Draximage
Trade Name:	Ruby-Fill
Consult Type:	Human Factors
Requestor:	Michelle K. Rutledge
Requestor Home:	CDER\ OSE\ DMEPA
Requested Consultant:	Shannon Hoste
Consultant Home:	CDRH\ ODE\ DAGRID\ HFPMET
Date Requested:	RESPONSE VIA EMAIL ON 5/4/16, SECOND RESPONSE VIA EMAIL ON 6/3/16
Due Date:	RESPONSE REVIEW DUE 5/20/16, SECOND RESPONSE REVIEW DUE 6/6/16
Instructions:	*In a Complete Response letter dated December 18, 2014, the Applicant provided the following questions:*

Question 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 thereport of any additional study performed to confirm the effect of these strategies.

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.

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).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

Intended use: RUBY-FILL® is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. 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.

Key considerations for conducting a HF review: ICC – review HF data per consult questions

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Date consult sent: June 6, 2016

HF Recommendation: The sponsor has provided adequate information to support that the Usability validation study was representative of expected use and that the data supports approval of this submission.

HF Review

The review team has indicated in a 6/2/16 conference call that the labeling testing during the training decay period is not of concern due to the brevity of the testing. Additionally it was determined that by not performing the certification testing with the participants, the simulated use testing represented a more conservative perspective of device use. Therefore deficiency items 2 and 3 below were closed. The remaining deficiency which requested further information to establish the representativeness of the simulated use study was addressed by the sponsor in their 6/3/16 email. They have established that their testing was presented in a representative manner of use and this deficiency is also closed.

Communication History

FDA Interactive Question posed on 6/2/16:
You outline the task and the task steps in tables 1 through 10 (pages 8 -26) within your human factor study protocol. We are unclear whether the study moderator used this table to capture use performance from each participant in the study, or whether the moderator read out loud and instruct the study participants to perform each task as part of the usability assessment of the device. Please provide a clarification to facilitate our review of the data that you presented in the study report.

JDI Response 6/3/16:

The study moderator used the tables [Tasks] 1-10 (pages 8-26 within the human factor protocol) to capture use performance from each of the 15 participants in the usability study. The moderator did not read out loud and instruct the study participants to perform each task as part of the assessment of the elution system. For example, for Task 2 (page 9-11), the moderator asked each participant to independently perform (b) (4) The moderator used the task table (page 9-11) to ensure the participant performed all steps outlined (numbered 1-41 in the table for Task 2) to complete the task (b) (4) .

Deficiency from CDRH HF Consult 5/20/16: You have provided responses to deficiency/AI questions with regards to the representativeness of your simulated use study (Summative Usability Test Validation). However, with regards to task breakdown, facilitator interaction and evaluation of the user manual, your responses do not contain adequate information to confirm that the study was conducted in a manner that simulated expected/representative use. Below are specific details with regards to your responses on Human Factors items 1, 2 & 3.

1) In the expected use of the subject device the users of the system will not be provided a facilitator to walk them step-by-step through the tasks of use. Therefore presenting and evaluating the sub-tasks in isolation, while it may indicate how the system supports that individual sub-task (such as (b) (4)), will not provide evidence that a representative user can navigate through the full use scenario resulting in safe and effective use of the system. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.
2) In the expected use of the subject device the users of the system will not be provided a facilitator to instruct them to review the user manual and to "search and find" critical information prior to use. Therefore asking this of participants in a simulated use study is not representative. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.
3) You indicated that "all training was provided by the same trainer in the same format; it was based on demonstrations to ensure that each participant was able to independently perform the following tasks on the system: (b) (4) The onsite user training includes a proficiency testing (2067FRM03) that must be completed with a perfect grade of (100%) for each user to become certified on the RUBY-FILL® system." Please confirm that the proficiency testing was completed in the simulated use study as it is a component of the expected use scenario.

Sponsor response from May 4, 2016 email: (**black** FDA text, blue sponsor response)

1. **You have provided further study details in Appendix 1-2 Summative Usability Test Validation Protocol. Within this protocol you indicated tasks within which you have identified more granular tasks steps. It is not clear how the tasks were presented to the participants in the study. In order to evaluate representative use the tasks should be structured/directed in a way that initiates a work flow and should not direct the participant through that workflow. Please provide further detail on the facilitator to participant interaction, indicating how the tasks and task step breakdown was utilized in the study.**

   Within Appendix 1-2 Summative Usability Test Validation Protocol, there are 10 tasks listed that were examined in the study (Table V-1). Each of the 10 tasks were further broken down into more granular task steps (Tables on pages 8-26 of 28 or 217-235 as numbered for the CRL response submission). The granular, or sub-tasks were steps that were necessary to be sequentially completed by the study participants in order to successfully complete the tasks. The sub-steps were structured in a way that initiated a workflow for the user and were presented to the study

participants by the way of hands-on demonstration on the elution system by the JDI Specialist (trainer). For a participant to successfully complete each of the 10 tasks, the Human Factors Specialist (evaluator) evaluated the completion of the granular or sub-tasks. For example, one task was [redacted] (b) (4) There are several granular steps that must be successfully completed [redacted] (b) (4). The sub-tasks were structured to initiate a workflow, including [redacted] (b) (4)

5/20/16 CDRH HF review - Response is not adequate. In the expected use of the subject device the users of the system will not be provided a facilitator to walk them step by step through the tasks of use. Therefore looking only at use errors on isolated sub-task by sub-task basis does not provide evidence that a representative user can safely and effectively use the system. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.

2. **Within Appendix 1-3 Summative Usability Test Validation Report you have indicated that during the 1 hour training decay the participants were directed to complete the User Manual Review Form. As demonstrated in your Appendix 1-8 this is a very detailed assessment of the user manual and as such would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training routine and is adding rigor to the study, prior to collection of objective/performance data, it is not representative of actual use. Please provide Summative Usability Testing which represents the expected use.**

The training decay period was allowed for each participant and exceeded one hour for most of the participants. We confirm that the User Manual assessment (Appendix 1-8) was not part of the usability training for the participants. The assessment of the User Manual (UM) was a high-level and very brief "search and find" assessment. It was thought and considered to be a minor effort for each of the participants and, in fact, was confirmed because it did take about 10-15 minutes to complete. This assessment was not for training purposes or for evaluating training performed by the JDI Specialist. Its purpose was to make sure users could find information quickly within the manuscript.

As it was stated in the Summative Usability Test Validation Protocol (Appendix 1-2,) there was a minimum of 1 hour between the training and evaluation for every participant. Most participants had a much longer period between training and evaluation (>1 hour) because each participant was evaluated independently and therefore each had to wait the training decay period (about an hour) plus the amount of time for the participants ahead of them to have their testing completed. The evaluation time for each participant was a minimum of 30 minutes.

The Summative Usability Testing was performed by the applicant under the oversight of an independent Human Factors expert. All 15 participants successfully passed, as per the expert's evaluation (see Summative Usability Test Validation report, Appendix 1-3).We confirm and are confident that the Summative Usability Testing provided represents expected use because the study has placed the onus solely on training. The training was provided in the same exact format as it will be provided for real clinical users.
The UM will be introduced to the users at each clinical site but will not be used specifically for training purposes. It will be left on site as an adjacent resource for users to obtain information if and when needed.

5/20/16 CDRH HF review – Response is not adequate. In the expected use of the subject device the users of the system will not be provided a facilitator to instruct them to review the user manual and to "search and find" critical information prior to use. Therefore asking this of participants in a simulated use study is not representative. Please provide Summative Usability Testing which

represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.

3. **Within Appendix 1-3 Summative Usability Test Validation Report you indicated that the training did not emphasize that [redacted] (b) (4) would impact the product. You indicate that subsequent users were explicitly trained [redacted] (b) (4) Simulated usability testing is structured to provide the expected final use training and you have indicated that this training was updated during the study. Please clarify and provide further information on the representativeness of the study training and if the final training materials were updated accordingly after testing.**

Consequent on Hartford Site training experience, the training included a verbal statement to all further trainees to act during testing with the human factors specialist as if they were in a real clinical environment (i.e. as working with a radioactive generator versus the mock generator used for training and evaluation). This included [redacted] (b) (4)

There were no modifications made to the training program after the Hartford Hospital site other than emphasizing on the necessity to act as the generator is radioactive. All training material for the safe and accurate use of the system has remained the same. It is henceforth expected that during proficiency testing of the system (RUBY Certification Quiz and Usability Proficiency Checklist, 2067FRM03) that each user will be using the system as if they were working with a radioactive generator. It has to be explicitly stated that JDI will remain on site after the initial radioactive generator installation to ensure correct and safe use of the system and, to make the user comfortable with the use of Ruby Rubidium Elution System and Ruby-Fill® Rubidium 82 generator.
The training has followed all points mentioned in the checklist 2067FRM02. There was no training script used for the Human Factors study. All training was provided by the same trainer in the same format; it was based on demonstrations to ensure that each participant was able to independently perform the following tasks on the system: [redacted] (b) (4) The onsite user training includes a proficiency testing (2067FRM03) that must be completed with a perfect grade of (100%) for each user to become certified on the RUBY-FILL® system. The [redacted] (b) (4) is covered under #7 of the Proficiency Checklist – *Correctly perform generator installation (with aseptic technique).*

5/20/16 CDRH HF review – Response is adequate. Question though, did they include the certification testing in the simulated use testing?

Deficiency from May 1, 2016 consult:

1. You have provided further study details in Appendix 1-2 Summative Usability Test Validation Protocol. Within this protocol you indicated tasks within which you have identified more granular tasks steps. It is not clear how the tasks were presented to the participants in the study. In order to evaluate representative use the tasks should be structured/directed in a way that initiates a work flow and should not direct the participant through that workflow. Please provide further detail on the facilitator to participant interaction, indicating how the tasks and task step breakdown was utilized in the study.

2. Within Appendix 1-3 Summative Usability Test Validation Report you have indicated that during the 1 hour training decay the participants were directed to complete the User Manual Review Form. As demonstrated in your Appendix 1-8 this is a very detailed assessment of the user manual and as such would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study, prior to collection of objective/performance data, it is not representative of actual use. Please provide Summative Usability Testing which represents the expected use.
3. Within Appendix 1-3 Summative Usability Test Validation Report you indicated that the training did not emphasize that (b) (4) would impact the product. You indicate that subsequent users were explicitly trained (b) (4) Simulated usability testing is structured to provide the expected final use training and you have indicated that this training was updated during the study. Please clarify and provide further information on the representativeness of the study training and if the final training materials were updated accordingly after testing.

Reviewers Notes

Request

Question 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 thereport of any additional study performed to confirm the effect of these strategies.*

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.*

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).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

HF Activities

1.11.4.1 Response to CRL Q1.pdf

They provide a summary of where to find the requested data (in the appendices reviewed below.)

1.11.4.2 Response to CRL Q2.pdf

It should be emphasized and reiterated that the original user training will be performed by a JDI specialist at the clinical customer site for the first certification. Additionally, these certified users will be re-certified every two years on site or when updates to the Software or the User Manual become available whichever is earlier. That is, Software or User Manual updates mandate earlier certification. The Training & Certification will be provided to all users by JDI at the time of installation. One to two, more highly trained 'super-users' will be identified at each clinical site (typically this would be a team leader, lead PET/CT technologist, or a senior technologist with significant experience and nuclear cardiology technologist certification expected to be at the site for a long period of time to maintain site

competency and who can train a new site employee[s] providing these new employees meet all of the following criteria: ...

b. Instructions for Use:

The User Manual, structured as FDA requested and presented in Appendix 2-2 serves also as a training manual. A description of the changes incorporated after execution of the Usability study is also provided. None of these changes were deemed to impact the applicability of the Usability study that was performed.

The User Manual that was used as the basis of the Usability Study (refer to Appendix 1-4) was updated to include the following changes:

- To address the FDA questions raised in the Complete Response Letter (CRL Questions 2.b, 4 and 12)

These changes were related to formatting and document structure and were proposed largely for clarification purposes. The changes did not trigger any significant text content that would affect the conducted usability testing, presented with CRL Question 1.

Since the June 2015 Type C Meeting, additional changes were included in the version of User Manual presented in Appendix 2-2, as follows:

- Addition of a Table of Contents, Index, page numbers, and a clearer section on warnings and precautions (answering FDA CRL Question 2b)
- Clarification of supplied accessories (b) (4) which were in previous versions by inadvertence (answering FDA CRL Question 4)
- Clarification that the RUBY RbES is (b) (4) (answering FDA CRL Question 12).
- Other changes proposed by JDI, which are associated with the incorporation of electrical safety and electromagnetic compatibility requirements as per CSA requirements, a re-structuring 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 for the (b) (4) installation part for ease of readability for the user
- Additional changes related to formatting and document structure and are proposed for clarification purposes. These changes did not trigger any text content that would affect the usability testing
- Update of software screenshots to reflect change from Software version (b) (4) to Software version (b) (4)
- Update of several figures, including updated (b) (4) and labeling of first two figures showing system components, to reflect change of (b) (4) and introduction of (b) (4) designed by (b) (4) and manufactured by (b) (4)
- Troubleshooting section has been completely revised including full description of the error messages displayed by the software and additional steps for troubleshooting
- Addition of warnings, including (b) (4) (b) (4) (b) (4)
- Movement of (b) (4) section to correspond with Software version (b) (4)
- Addition of (b) (4) (if required)
- Small edits and formatting, including font size, use of capital letters on various words.

1.11.4.4 Response to CRL Q4.pdf

*As part of its response to Questions 1 and 2 of the CRL, JDI has revised the User Manual **(Appendix 2-2)** that includes the information requested by this question. At page 9, the User Manual identifies the supplies provided by JDI and the supplies the user must provide and also specifies the recommended (b) (4) that should be used.*

The User Manual removes the reference to [redacted] (b) (4) *as they are not required for installation of the generator.*

For usability protocol review - Do any of these changes require HF validation? This would be answered by their response to question 2.

Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf

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.

Appendix 1-2 Summative Usability Test Validation Protocol.pdf

- Intended user identified (*certified/registered Nuclear Medicine Technologist with certification/registration in the country of use*), targeting 15 users in the US.
- Simulated use environment and mock generator.
- They indicate the highest risk level; however it is not clear if this is based on potential severity of harm (rather than a risk index) associated with a use error for each task. Based on Appendix 1-5 these do appear to be risk index terms (severity x occurrence) They did not use these to eliminate tasks from evaluation.
- User manual is included in the evaluation.
- One hour training decay.

- While this indicates that they are collecting objective and subjective data, do they use both sets of data in their analysis? Yes they do evaluate both.

User Tasks

The following task tables will be used in the usability tests as test data sheets for recording test results. Each task table contains multiple steps and will prescribe the order of task completion for each user. Following each task, a series of questions will be asked of the user to assess their assessment of the difficulty of comprehension and ease of safe execution for each task. Additional questions may be asked for marketing purposes and will not be evaluated on a pass/fail basis.

Acceptance Criteria

The task steps will be evaluated as pass or fail for each participant. If a user fails to complete a task correctly, it will be recorded as a failure. The task interview will attempt to identify if the user was aware of the task failure and evaluate the potential root cause of the failure. The facilitator may correct the failure if necessary to complete the subsequent task. The final report will analyze the total number of failures by participants and the risk that the failure poses in respect to patient or user safety.

- They have very granular task steps, example below. Were these just for facilitator tracking or did the participant get directed to do each of these task steps? See deficiency 1.

Task 2. (b) (4)			
Task Step	**Description of Step**	**User Completion**	**PASS/FAIL**
1	(b) (4)		
2			
3			
4			
5			
6			

APPEARS THIS WAY ON ORIGINAL

Appendix 1-3 Summative Usability Test Validation Report.pdf

- How detailed is this User Manual Review Form? This could likely negate the intent of the training decay time. An example of this form is seen starting on page 20/321 of appendix 1-8. This is a very detailed assessment and would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study prior to use it is not

representative of actual use. See deficiency 2.

C. **Test Goals, Critical Tasks and Use Scenarios Studied**

The goal of the tests was to ensure that respondents are able to correctly perform the tasks required to setup and operate the RUBY Rubidium Elution System. The critical tasks were (b) (4) Two error scenarios were also created to test the respondents ability to trouble shoot errors during the normal function of the RUBY system, these included (b) (4) (b) (4) Each respondent was asked to complete all ten (10) tasks. Each task consisted of multiple steps to successful completion. If the respondent completed all steps correctly regardless of order, the task was deemed successfully completed and "passed". The JDI PET Specialist conducted all respondent training prior to the testing. Each respondent was given a dinner break of at least 60 minutes prior to testing. During the break, respondents were asked to evaluate the User Manual using the User Manual Review Form (D/N 10093-001, Appendix B).

- Did they update the training materials accordingly?

(b) (4)

Appendix 1-4 User Manual-previous version-Basis for Training.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-5 Usability FMEA-Basis for Training.pdf
They did use risk index rather than severity alone when indicating criticality of tasks.

Appendix 1-6 Graphic User Interface-Screen Shots.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-7 Summative Usability Objective Testing Data.pdf
This was summarized in appendix 1-3 as well.

Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
The user manual evaluation (example starting on 20/321) was quite detailed. This is concerning since they conducted this prior to task performance evaluation and during the "training decay" time period.

Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
Subjective data and sponsor response. It could be recommended to ask more open ended questions as part of subjective data collection in the future.

Appendix 2-1 Training Package.pdf
There is a certification program. This contains an example of the evaluation criteria.

Appendix 2-2 RUBY User Manual-newly proposed.pdf
This is as they indicated in their response.

Appendix 6-13 Usability FMEA.pdf
While they do utilize a risk index the high severity items are found in the evaluated tasks.

Materials Reviewed

- 1.11.4.1 Response to CRL Q1.pdf
- 1.11.4.2 Response to CRL Q2.pdf
- 1.11.4.4 Response to CRL Q4.pdf/
- Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf
- Appendix 1-2 Summative Usability Test Validation Protocol.pdf
- Appendix 1-3 Summative Usability Test Validation Report.pdf
- Appendix 1-4 User Manual-previous version-Basis for Training.pdf
- Appendix 1-5 Usability FMEA-Basis for Training.pdf
- Appendix 1-6 Graphic User Interface-Screen Shots.pdf
- Appendix 1-7 Summative Usability Objective Testing Data.pdf
- Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
- Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
- Appendix 2-1 Training Package.pdf
- Appendix 2-2 RUBY User Manual-newly proposed.pdf
- Appendix 6-13 Usability FMEA.pdf

End of Review

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

/s/

TRI M BUI NGUYEN
06/07/2016

Human Factors (HF) Review

Consult Number:	ICC1600201 AND SPONSOR RESPONSE
Document Number:	NDA 202153
Applicant:	Draximage
Trade Name:	Ruby-Fill
Consult Type:	Human Factors
Requestor:	Michelle K. Rutledge
Requestor Home:	CDER\ OSE\ DMEPA
Requested Consultant:	Shannon Hoste
Consultant Home:	CDRH\ ODE\ DAGRID\ HFPMET
Date Requested:	RESPONSE VIA EMAIL ON 5/4/16
Due Date:	RESPONSE REVIEW DUE 5/20/16
Instructions:	*In a Complete Response letter dated December 18, 2014, the Applicant provided the following questions:*

Question 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:

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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 thereport of any additional study performed to confirm the effect of these strategies.

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a. an initial and on-going training program and a methodology to evaluate its effectiveness;
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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 [redacted] (b) (4) *(see page 10, supplies);*
c. describe and label [redacted] (b) (4) *as they are essential to the operation of the Elution System (page A|1– system consumables).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

Intended use: RUBY-FILL® is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. 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.

Key considerations for conducting a HF review: ICC – review HF data per consult questions

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Date consult sent: May 20, 2016

HF Recommendation: The sponsor has not provided adequate information to indicate that the Usability validation study was representative of actual use. Please see comment under HF Review below.

HF Review

You have provided responses to deficiency/AI questions with regards to the representativeness of your simulated use study (Summative Usability Test Validation). However, with regards to task breakdown, facilitator interaction and evaluation of the user manual, your responses do not contain adequate information to confirm that the study was conducted in a manner that simulated expected/representative use. Below are specific details with regards to your responses on Human Factors items 1, 2 & 3.

1) In the expected use of the subject device the users of the system will not be provided a facilitator to walk them step-by-step through the tasks of use. Therefore presenting and evaluating the sub-tasks in isolation, while it may indicate how the system supports that individual sub-task (such as [redacted] (b) (4), will not provide evidence that a representative user can navigate through the full use scenario resulting in safe and effective use of the system. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.
2) In the expected use of the subject device the users of the system will not be provided a facilitator to instruct them to review the user manual and to "search and find" critical information prior to use. Therefore asking this of participants in a

simulated use study is not representative. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.

3) You indicated that "all training was provided by the same trainer in the same format; it was based on demonstrations to ensure that each participant was able to independently perform the following tasks on the system: (b) (4) The onsite user training includes a proficiency testing (2067FRM03) that must be completed with a perfect grade of (100%) for each user to become certified on the RUBY-FILL® system." Please confirm that the proficiency testing was completed in the simulated use study as it is a component of the expected use scenario.

Communication History

Sponsor response from May 4, 2016 email: (**black** FDA text, blue sponsor response)

1. **You have provided further study details in Appendix 1-2 Summative Usability Test Validation Protocol. Within this protocol you indicated tasks within which you have identified more granular tasks steps. It is not clear how the tasks were presented to the participants in the study. In order to evaluate representative use the tasks should be structured/directed in a way that initiates a work flow and should not direct the participant through that workflow. Please provide further detail on the facilitator to participant interaction, indicating how the tasks and task step breakdown was utilized in the study.**

   Within Appendix 1-2 Summative Usability Test Validation Protocol, there are 10 tasks listed that were examined in the study (Table V-1). Each of the 10 tasks were further broken down into more granular task steps (Tables on pages 8-26 of 28 or 217-235 as numbered for the CRL response submission). The granular, or sub-tasks were steps that were necessary to be sequentially completed by the study participants in order to successfully complete the tasks. The sub-steps were structured in a way that initiated a workflow for the user and were presented to the study participants by the way of hands-on demonstration on the elution system by the JDI Specialist (trainer). For a participant to successfully complete each of the 10 tasks, the Human Factors Specialist (evaluator) evaluated the completion of the granular or sub-tasks. For example, one task was (b) (4) There are several granular steps that must be successfully completed (b) (4) The sub-tasks were structured to initiate a workflow, including (b) (4)

   5/20/16 CDRH HF review - Response is not adequate. In the expected use of the subject device the users of the system will not be provided a facilitator to walk them step by step through the tasks of use. Therefore looking only at use errors on isolated sub-task by sub-task basis does not provide evidence that a representative user can safely and effectively use the system. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.

2. **Within Appendix 1-3 Summative Usability Test Validation Report you have indicated that during the 1 hour training decay the participants were directed to complete the User Manual Review Form. As demonstrated in your Appendix 1-8 this is a very detailed assessment of**

the user manual and as such would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training routine and is adding rigor to the study, prior to collection of objective/performance data, it is not representative of actual use. Please provide Summative Usability Testing which represents the expected use.

The training decay period was allowed for each participant and exceeded one hour for most of the participants. We confirm that the User Manual assessment (Appendix 1-8) was not part of the usability training for the participants. The assessment of the User Manual (UM) was a high-level and very brief "search and find" assessment. It was thought and considered to be a minor effort for each of the participants and, in fact, was confirmed because it did take about 10-15 minutes to complete. This assessment was not for training purposes or for evaluating training performed by the JDI Specialist. Its purpose was to make sure users could find information quickly within the manuscript.

As it was stated in the Summative Usability Test Validation Protocol (Appendix 1-2,) there was a minimum of 1 hour between the training and evaluation for every participant. Most participants had a much longer period between training and evaluation (>1 hour) because each participant was evaluated independently and therefore each had to wait the training decay period (about an hour) plus the amount of time for the participants ahead of them to have their testing completed. The evaluation time for each participant was a minimum of 30 minutes.

The Summative Usability Testing was performed by the applicant under the oversight of an independent Human Factors expert. All 15 participants successfully passed, as per the expert's evaluation (see Summative Usability Test Validation report, Appendix 1-3).We confirm and are confident that the Summative Usability Testing provided represents expected use because the study has placed the onus solely on training. The training was provided in the same exact format as it will be provided for real clinical users.
The UM will be introduced to the users at each clinical site but will not be used specifically for training purposes. It will be left on site as an adjacent resource for users to obtain information if and when needed.

5/20/16 CDRH HF review – Response is not adequate. In the expected use of the subject device the users of the system will not be provided a facilitator to instruct them to review the user manual and to "search and find" critical information prior to use. Therefore asking this of participants in a simulated use study is not representative. Please provide Summative Usability Testing which represents expected use scenarios. It is recommended that you submit your detailed protocol for review to the Agency prior to testing.

3. **Within Appendix 1-3 Summative Usability Test Validation Report you indicated that the training did not emphasize that** (b) (4) **would impact the product. You indicate that subsequent users were explicitly trained** (b) (4) **Simulated usability testing is structured to provide the expected final use training and you have indicated that this training was updated during the study. Please clarify and provide further information on the representativeness of the study training and if the final training materials were updated accordingly after testing.**

Consequent on Hartford Site training experience, the training included a verbal statement to all further trainees to act during testing with the human factors specialist as if they were in a real clinical environment (i.e. as working with a radioactive generator versus the mock generator used for training and evaluation). This included (b) (4)

[redacted] (b) (4)

There were no modifications made to the training program after the Hartford Hospital site other than emphasizing on the necessity to act as the generator is radioactive. All training material for the safe and accurate use of the system has remained the same. It is henceforth expected that during proficiency testing of the system (RUBY Certification Quiz and Usability Proficiency Checklist, 2067FRM03) that each user will be using the system as if they were working with a radioactive generator. It has to be explicitly stated that JDI will remain on site after the initial radioactive generator installation to ensure correct and safe use of the system and, to make the user comfortable with the use of Ruby Rubidium Elution System and Ruby-Fill® Rubidium 82 generator.
The training has followed all points mentioned in the checklist 2067FRM02. There was no training script used for the Human Factors study. All training was provided by the same trainer in the same format; it was based on demonstrations to ensure that each participant was able to independently perform the following tasks on the system: [redacted] (b) (4) The onsite user training includes a proficiency testing (2067FRM03) that must be completed with a perfect grade of (100%) for each user to become certified on the RUBY-FILL® system. The [redacted] (b) (4) is covered under #7 of the Proficiency Checklist – *Correctly perform generator installation (with aseptic technique).*

5/20/16 CDRH HF review – Response is adequate. Question though, did they include the certification testing in the simulated use testing?

Deficiency from May 1, 2016 consult:

1. You have provided further study details in Appendix 1-2 Summative Usability Test Validation Protocol. Within this protocol you indicated tasks within which you have identified more granular tasks steps. It is not clear how the tasks were presented to the participants in the study. In order to evaluate representative use the tasks should be structured/directed in a way that initiates a work flow and should not direct the participant through that workflow. Please provide further detail on the facilitator to participant interaction, indicating how the tasks and task step breakdown was utilized in the study.
2. Within Appendix 1-3 Summative Usability Test Validation Report you have indicated that during the 1 hour training decay the participants were directed to complete the User Manual Review Form. As demonstrated in your Appendix 1-8 this is a very detailed assessment of the user manual and as such would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study, prior to collection of objective/performance data, it is not representative of actual use. Please provide Summative Usability Testing which represents the expected use.
3. Within Appendix 1-3 Summative Usability Test Validation Report you indicated that the training did not emphasize that [redacted] (b) (4) would impact the product. You indicate that subsequent users were explicitly trained [redacted] (b) (4) Simulated usability testing is structured to provide the expected final use training and you have indicated that this training was updated during the study. Please clarify and provide further information on the representativeness of the study training and if the final training materials were updated accordingly after testing.

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Reviewers Notes

Request

Question 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 thereport of any additional study performed to confirm the effect of these strategies.*

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.*

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* [redacted] (b) (4) *. (see page 10, supplies);*
> *c. describe and label* [redacted] (b) (4) *as they are essential to the operation of the Elution System (page A|1– system consumables).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

HF Activities

1.11.4.1 Response to CRL Q1.pdf

They provide a summary of where to find the requested data (in the appendices reviewed below.)

1.11.4.2 Response to CRL Q2.pdf

It should be emphasized and reiterated that the original user training will be performed by a JDI specialist at the clinical customer site for the first certification. Additionally, these certified users will be re-certified every two years on site or when updates to the Software or the User Manual become available whichever is earlier. That is, Software or User Manual updates mandate earlier certification. The Training & Certification will be provided to all users by JDI at the time of installation. One to two, more highly trained 'super-users' will be identified at each clinical site (typically this would be a team leader, lead PET/CT technologist, or a senior technologist with significant experience and nuclear cardiology technologist certification expected to be at the site for a long period of time to maintain site

competency and who can train a new site employee[s] providing these new employees meet all of the following criteria: ...

b. Instructions for Use:

The User Manual, structured as FDA requested and presented in Appendix 2-2 serves also as a training manual. A description of the changes incorporated after execution of the Usability study is also provided. None of these changes were deemed to impact the applicability of the Usability study that was performed.

The User Manual that was used as the basis of the Usability Study (refer to Appendix 1-4) was updated to include the following changes:

- To address the FDA questions raised in the Complete Response Letter (CRL Questions 2.b, 4 and 12)

These changes were related to formatting and document structure and were proposed largely for clarification purposes. The changes did not trigger any significant text content that would affect the conducted usability testing, presented with CRL Question 1.

Since the June 2015 Type C Meeting, additional changes were included in the version of User Manual presented in Appendix 2-2, as follows:

- Addition of a Table of Contents, Index, page numbers, and a clearer section on warnings and precautions (answering FDA CRL Question 2b)
- Clarification of supplied accessories (b) (4) which were in previous versions by inadvertence (answering FDA CRL Question 4)
- Clarification that the RUBY RbES is (b) (4) (answering FDA CRL Question 12).
- Other changes proposed by JDI, which are associated with the incorporation of electrical safety and electromagnetic compatibility requirements as per CSA requirements, a re-structuring 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 for the (b) (4) installation part for ease of readability for the user
- Additional changes related to formatting and document structure and are proposed for clarification purposes. These changes did not trigger any text content that would affect the usability testing
- Update of software screenshots to reflect change from Software version (b) (4) to Software version (b) (4)
- Update of several figures, including updated (b) (4) and labeling of first two figures showing system components, to reflect change of (b) (4) and introduction of (b) (4) designed by (b) (4) and manufactured by (b) (4)
- Troubleshooting section has been completely revised including full description of the error messages displayed by the software and additional steps for troubleshooting
- Addition of warnings, including (b) (4) (b) (4) (b) (4)
- Movement of (b) (4) section to correspond with Software version
- Addition of (b) (4) (if required)
- Small edits and formatting, including font size, use of capital letters on various words.

1.11.4.4 Response to CRL Q4.pdf

*As part of its response to Questions 1 and 2 of the CRL, JDI has revised the User Manual **(Appendix 2-2)** that includes the information requested by this question. At page 9, the User Manual identifies the supplies provided by JDI and the supplies the user must provide and also specifies the recommended (b) (4) that should be used.*

The User Manual removes the reference [redacted] (b) (4) *as they are not required for installation of the generator.*

For usability protocol review - Do any of these changes require HF validation? This would be answered by their response to question 2.

Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf

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.

Appendix 1-2 Summative Usability Test Validation Protocol.pdf

- Intended user identified (*certified/registered Nuclear Medicine Technologist with certification/registration in the country of use*), targeting 15 users in the US.
- Simulated use environment and mock generator.
- They indicate the highest risk level; however it is not clear if this is based on potential severity of harm (rather than a risk index) associated with a use error for each task. Based on Appendix 1-5 these do appear to be risk index terms (severity x occurrence) They did not use these to eliminate tasks from evaluation.
- User manual is included in the evaluation.
- One hour training decay.

- While this indicates that they are collecting objective and subjective data, do they use both sets of data in their analysis? Yes they do evaluate both.

User Tasks

The following task tables will be used in the usability tests as test data sheets for recording test results. Each task table contains multiple steps and will prescribe the order of task completion for each user. Following each task, a series of questions will be asked of the user to assess their assessment of the difficulty of comprehension and ease of safe execution for each task. Additional questions may be asked for marketing purposes and will not be evaluated on a pass/fail basis.

Acceptance Criteria

The task steps will be evaluated as pass or fail for each participant. If a user fails to complete a task correctly, it will be recorded as a failure. The task interview will attempt to identify if the user was aware of the task failure and evaluate the potential root cause of the failure. The facilitator may correct the failure if necessary to complete the subsequent task. The final report will analyze the total number of failures by participants and the risk that the failure poses in respect to patient or user safety.

- They have very granular task steps, example below. Were these just for facilitator tracking or did the participant get directed to do each of these task steps? See deficiency 1.

Task 2. (b) (4)			
Task Step	**Description of Step**	**User Completion**	**PASS/FAIL**
1	(b) (4)		
2			
3			
4			
5			
6			

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Appendix 1-3 Summative Usability Test Validation Report.pdf

- How detailed is this User Manual Review Form? This could likely negate the intent of the training decay time. An example of this form is seen starting on page 20/321 of appendix 1-8. This is a very detailed assessment and would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study prior to use it is not

representative of actual use. See deficiency 2.

C. **Test Goals, Critical Tasks and Use Scenarios Studied**

The goal of the tests was to ensure that respondents are able to correctly perform the tasks required to setup and operate the RUBY Rubidium Elution System. The critical tasks were (b) (4) Two error scenarios were also created to test the respondents ability to trouble shoot errors during the normal function of the RUBY system. these included (b) (4) (b) (4) Each respondent was asked to complete all ten (10) tasks. Each task consisted of multiple steps to successful completion. If the respondent completed all steps correctly regardless of order, the task was deemed successfully completed and "passed". The JDI PET Specialist conducted all respondent training prior to the testing. Each respondent was given a dinner break of at least 60 minutes prior to testing. During the break, respondents were asked to evaluate the User Manual using the User Manual Review Form (D/N 10093-001, Appendix B).

- Did they update the training materials accordingly?

The two users from the first test day failed to close the generator well cover. The training did not emphasize that closing the cover would impact the testing. There was no live generator used and the cover did not provide any shielding from radioactive material. The subsequent users were explicitly trained to close the generator well cover. One user failed to read the volume collected in the graduated cylinder to proceed in the setup validation sequence. He repeated the Pump validation and entered a correct value to complete the task.

Appendix 1-4 User Manual-previous version-Basis for Training.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-5 Usability FMEA-Basis for Training.pdf
They did use risk index rather than severity alone when indicating criticality of tasks.

Appendix 1-6 Graphic User Interface-Screen Shots.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-7 Summative Usability Objective Testing Data.pdf
This was summarized in appendix 1-3 as well.

Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
The user manual evaluation (example starting on 20/321) was quite detailed. This is concerning since they conducted this prior to task performance evaluation and during the "training decay" time period.

Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
Subjective data and sponsor response. It could be recommended to ask more open ended questions as part of subjective data collection in the future.

Appendix 2-1 Training Package.pdf
There is a certification program. This contains an example of the evaluation criteria.

Appendix 2-2 RUBY User Manual-newly proposed.pdf
This is as they indicated in their response.

Appendix 6-13 Usability FMEA.pdf
While they do utilize a risk index the high severity items are found in the evaluated tasks.

Materials Reviewed

- 1.11.4.1 Response to CRL Q1.pdf
- 1.11.4.2 Response to CRL Q2.pdf
- 1.11.4.4 Response to CRL Q4.pdf/
- Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf
- Appendix 1-2 Summative Usability Test Validation Protocol.pdf
- Appendix 1-3 Summative Usability Test Validation Report.pdf
- Appendix 1-4 User Manual-previous version-Basis for Training.pdf
- Appendix 1-5 Usability FMEA-Basis for Training.pdf
- Appendix 1-6 Graphic User Interface-Screen Shots.pdf
- Appendix 1-7 Summative Usability Objective Testing Data.pdf
- Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
- Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
- Appendix 2-1 Training Package.pdf
- Appendix 2-2 RUBY User Manual-newly proposed.pdf
- Appendix 6-13 Usability FMEA.pdf

End of Review

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

/s/

TRI M BUI NGUYEN
06/06/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Memorandum

Date: May 26, 2016 **Date Consulted:** March 7, 2016

From: Jane Liedtka MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Ira Krefting, MD, Medical Officer
Division of Medical Imaging Products (DMIP)

Drug: Ruby-Fill (Rubidium, RB 82)

Indication: Ruby-Fill is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. 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

NDA: NDA 202153

Applicant: Jubilant Draximage Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- Applicant's submitted background package for NDA.
- Draft Ruby-Fill labeling in PLLR received on May 5, 2016.

- DPMH review of Eovist (gadoxetate disodium), NDA 022090/S-011. Erica Radden, M.D. Medical Officer. March 20, 2015. DARRTS Reference ID 3718182.
- Labeling for CardioGen 82, NDA 19414

Consult Question:

"This is a resubmission after complete response and since we never got to review the labeling as it was submitted to OGD initially, we will be doing so during this cycle. This is a 505 (b) (2) NDA, referring to clinical information in NDA 19414, CardioGen 82. The applicant has basically copied the PI for CardioGen 82. DMIP requests assistance in reviewing section 8 and other sections relevant to Peds and Maternal health of the prescribing information."

INTRODUCTION AND REGULATORY BACKGROUND

On March 7, 2016, Division of Medical Imaging Products (DMIP) requested a consultation from the Division of Pediatric and Maternal Health (DPMH) to provide assistance to DMIP in reviewing the labeling for Ruby-Fill (Rubidium, RB 82), NDA 202153. Ruby-Fill is a closed system used to produce rubidium RB 82 chloride injection for intravenous use. RB 82 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.

NDA 202153 was originally submitted via the 505(b) (2) pathway with CardioGen 82 as the reference listed drug (RLD) and was received on June 30, 2010. The RLD for Ruby-Fill, CardioGen 82 was approved in 1990. Multiple amendments to NDA 202153 were submitted throughout 2012, 2013, and 2014. On December 18, 2014, the applicant received a complete Response (CR) due to multiple clinical and product quality issues. On December 28, 2015, the NDA was resubmitted. An updated label in PLLR format was requested by the division and was received on May 5, 2016. A review of the published literature regarding Ruby-Fill use in pregnant and lactating women and a review and summary of relevant cases reported in the applicants' pharmacovigilance database to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling was not included.

Rb 82 and Drug Characteristics

Rubidium is a chemical element with symbol Rb and atomic number 37[1]. Rubidium is not known to be necessary for any living organisms. However, rubidium ions are handled by living organisms in a manner similar to potassium ions, being actively taken up by plants and by animal cells due to their identical charge. Rubidium 82, one of the element's non-natural isotopes, is produced by electron-capture decay of strontium 82 with a half-life of 25.36 days. The subsequent decay of rubidium 82 with a half-life of 76 seconds to stable krypton 82 happens by positron emission.

[1] Wikipedia, Accessed on May 6, 2016.

Rubidium 82 is used for positron emission tomography (PET). Rubidium is very similar to potassium and, therefore, tissue with high potassium content will also accumulate the radioactive rubidium. One of the main uses is in myocardial perfusion imaging. The very short half-life of 76 seconds makes it necessary to produce the rubidium 82 from decay of strontium 82 close to the patient[2].

Ruby-Fill® Rubidium Rb 82 Generator is supplied in the form of Strontium Sr 82 adsorbed on a lead-shielded hydrous stannic oxide (b) (4) column with an activity of 85-115 mCi Sr 82 at calibration time.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[3] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[4] format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

RB 82 and Nonclinical Considerations

No studies have been performed to evaluate carcinogenic potential, mutagenicity potential, teratogenic potential, or to determine whether rubidium Rb 82 chloride injection may affect fertility in males or females.

RB 82 and Pregnancy

DPMH conducted a search of published literature in PubMed and Embase using the search terms "rubidium 82 and pregnancy", "rubidium 82 and pregnant women", "rubidium 82 and pregnancy and birth defects", "rubidium 82 and pregnancy and congenital malformations", "rubidium 82 and pregnancy and stillbirth", "rubidium 82 and spontaneous abortion" and "rubidium 82 and pregnancy and miscarriage". No reports of adequate and well-controlled studies of rubidium 82 use in pregnant women were found. No reports of pregnancies occurring during or following rubidium 82 exposure were found. There was no information regarding rubidium 82 in Reprotox or TERIS.

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[2] Jadvar, H.; Anthony Parker, J. (2005). "Rubidium-82". Clinical PET and PET/CT. p. 59.
[3] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[4] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

RB 82 and Lactation

DPMH conducted a search of published literature in PubMed and Embase using the search terms "rubidium 82 and lactation" and "rubidium 82 and breastfeeding" and no relevant data was found. In addition, the Lactation Database (LactMed)[5] and Thomas Hale's book Medications and Mothers' Milk 2014 was searched regarding the use of rubidium 82 during breastfeeding and there was no information.

It is not known whether rubidium 82 is present in human breast milk.

In Micromedex under "Pregnancy and Lactation" the statement "Infant risk cannot be ruled out" was provided[6]. LactMed states the following:

> Information in this record refers to the use of rubidium chloride Rb 82 as a diagnostic agent. No information is available on the use of rubidium chloride Rb 82 during breastfeeding. The manufacturer recommends withholding breastfeeding for 1 hour after a diagnostic dose of rubidium chloride Rb 82.This length of time is greater than 10 half-lives of the radioisotope, so the nursing infant should not be exposed to radiation if this guideline is followed. The mother can nurse just before administration of the radiopharmaceutical. If the mother has expressed and saved milk prior to the examination, she can feed it to the infant during the period of nursing interruption.[1][2][3]

The Applicant's proposed Ruby-Fill lactation labeling states that

> **8.2 Lactation**
> Risk Summary
> (b) (4)
> [redacted]
>
> Clinical considerations
> *Minimizing Exposure*

[5] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[6] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 3/15/16.

(b) (4)

Reviewer Comment

DPMH recommends amending the proposed labeling to update the language with current labeling practices. In specific, replacing the word (b) (4) *with* (b) (4) *in the first paragraph, removing the word* (b) (4) *and replacing* (b) (4) *with RB 82 in the second paragraph, and rewording the clinical considerations statements to "Exposure to RB 82 chloride through breast milk can be minimized if breast-feeding is discontinued when RB 82 chloride injection is administered. Do not resume breast-feeding until at least one hour after completion of Ruby-Fill infusion". The one hour time period is taken from the recommendation for Cardiogen which was approved in 1990 and is the RLD for this 505 (b) (2) NDA.*

(b) (4)

CONCLUSIONS

Based on the literature review and review of the pharmacovigilance database, DPMH has the following recommendations for Ruby-Fill (rubidium 82) labeling:

- Highlights of Prescribing Information (HPI):
  - Removal (b) (4) from the Use in Specific Populations section of the HPI
  - Rewording of the lactation statement in the Use in Specific Populations section of the HPI
- Pregnancy, Section 8.1: Rewording of the Risk Summary section
- Pregnancy, Section 8.2: DPMH recommends amending the proposed labeling to replace the word (b) (4) with (b) (4) in the first paragraph,to remove the word (b) (4) and replace (b) (4) with RB 82 in the second paragraph and to reword the clinical considerations, minimizing exposure to "Exposure to RB 82chloride through breast milk can be minimized if breast-feeding is discontinued when RB 82 chloride injection is administered. Do not resume breast-feeding until at least one hour after completion of RUBY-FILL infusion"
- (b) (4)
- Patient Counseling, Section 17: Rewording of both the pregnancy and the lactation statements in Section 17

RECOMMENDATIONS

DPMH revised the HPI and sections 8.1, 8.2, 8.3 and 17 of Ruby-Fill (rubidium 82) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Ruby-Fill (rubidium 82) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Do not resume breastfeeding until at least one hour after completion of RUBY-FILL infusion. (8.2)

FULL PRESCRIBING INFORMATION

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are no data available on the use of rubidium Rb 82 in pregnant women. Animal reproduction studies with rubidium Rb 82 chloride have not been conducted. However, all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering rubidium Rb 82 chloride injection administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from RB 82 and the gestational timing of exposure.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of RB 82 chloride (b) (4) in human milk, the effects on the breastfed infant or the effects on milk production. Due to the short half-life of RB 82 chloride (75 seconds), exposure of a breast fed infant through breast milk can be minimized by temporary discontinuation of breastfeeding *[see Clinical Considerations]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RB 82, any potential adverse effects on the breastfed child from RB 82 or from the underlying maternal condition.

Clinical Considerations

Minimizing Exposure

Exposure to RB 82 chloride through breast milk can be minimized if breastfeeding is discontinued when RB 82 chloride injection is administered. Do not resume breastfeeding until at least one hour after completion of RUBY-FILL infusion.

17 Patient Counseling Information

Pregnancy

Advise a pregnant woman of the potential risk to a fetus.

Lactation

Advise lactating women that exposure to RB 82 chloride through breast milk can be minimized if breastfeeding is discontinued when RB 82 chloride injection is administered. Advise lactating women not to resume breastfeeding for at least one hour after completion of [redacted] infusion.

(b) (4)

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

/s/

JANE E LIEDTKA
05/26/2016

TAMARA N JOHNSON
05/27/2016

LYNNE P YAO
05/27/2016

Human Factors (HF) Review

Consult Number:	ICC1600201
Document Number:	NDA 202153
Applicant:	Draximage
Trade Name:	Ruby-Fill
Consult Type:	Human Factors
Requestor:	Michelle K. Rutledge
Requestor Home:	CDER\ OSE\ DMEPA
Requested Consultant:	Shannon Hoste
Consultant Home:	CDRH\ ODE\ DAGRID\ HFPMET
Date Requested:	3/17/16
Due Date:	4/14/16
Instructions:	*In a Complete Response letter dated December 18, 2014, the Applicant provided the following questions:*

Question 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 thereport of any additional study performed to confirm the effect of these strategies.

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.

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 [redacted] (b) (4) *(see page 10, supplies);*
c. describe and label [redacted] (b) (4) *as they are essential to the operation of the Elution System (page A|1– system consumables).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

Intended use: RUBY-FILL® is a closed system used to produce rubidium Rb 82 chloride injection for intravenous use. 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.

Key considerations for conducting a HF review: ICC – review HF data per consult questions

---

Date consult sent: May 1, 2016

HF Recommendation: There are a few items in there Usability validation study that are unclear, potentially compromising the representativeness of the study.

HF Review

Deficiency:

1. You have provided further study details in Appendix 1-2 Summative Usability Test Validation Protocol. Within this protocol you indicated tasks within which you have identified more granular tasks steps. It is not clear how the tasks were presented to the participants in the study. In order to evaluate representative use the tasks should be structured/directed in a way that initiates a work flow and should not direct the participant through that workflow. Please provide further detail on the facilitator to participant interaction, indicating how the tasks and task step breakdown was utilized in the study.
2. Within Appendix 1-3 Summative Usability Test Validation Report you have indicated that during the 1 hour training decay the participants were directed to complete the User Manual Review Form. As demonstrated in your Appendix 1-8 this is a very detailed assessment of the user manual and as such would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study, prior to collection of objective/performance data, it is not representative of actual use. Please provide Summative Usability Testing which represents the expected use.
3. Within Appendix 1-3 Summative Usability Test Validation Report you indicated that the training did not emphasize that [redacted] (b) (4) would impact the

product. You indicate that subsequent users were explicitly trained [redacted] (b) (4) [redacted]. Simulated usability testing is structured to provide the expected final use training and you have indicated that this training was updated during the study. Please clarify and provide further information on the representativeness of the study training and if the final training materials were updated accordingly after testing.

Reviewers Notes

Request

Question 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 thereport of any additional study performed to confirm the effect of these strategies.*

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.*

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).*

Therefore, we would like the Human Factors team to review the attached Summative Usability Study. Please see the following Appendices in DARRTS submitted on December 28, 2015 in m1, 1.11 Information amendment, Appendixes to M1, Appendices 1.1 – 2.2. If you cannot access these files, please let us know.

HF Activities

1.11.4.1 Response to CRL Q1.pdf

They provide a summary of where to find the requested data (in the appendices reviewed below.)

1.11.4.2 Response to CRL Q2.pdf

It should be emphasized and reiterated that the original user training will be performed by a JDI specialist at the clinical customer site for the first certification. Additionally, these certified users will be re-certified every two years on site or when updates to the Software or the User Manual become available whichever is earlier. That is, Software or User Manual updates mandate earlier certification. The Training & Certification will be provided to all users by JDI at the time of installation. One to two, more highly trained 'super-users' will be identified at each clinical site (typically this would be a team leader, lead PET/CT technologist, or a senior technologist with significant experience and nuclear cardiology technologist certification expected to be at the site for a long period of time to maintain site

competency and who can train a new site employee[s] providing these new employees meet all of the following criteria: ...

b. Instructions for Use:

The User Manual, structured as FDA requested and presented in Appendix 2-2 serves also as a training manual. A description of the changes incorporated after execution of the Usability study is also provided. None of these changes were deemed to impact the applicability of the Usability study that was performed.

The User Manual that was used as the basis of the Usability Study (refer to Appendix 1-4) was updated to include the following changes:

- To address the FDA questions raised in the Complete Response Letter (CRL Questions 2.b, 4 and 12)

These changes were related to formatting and document structure and were proposed largely for clarification purposes. The changes did not trigger any significant text content that would affect the conducted usability testing, presented with CRL Question 1.

Since the June 2015 Type C Meeting, additional changes were included in the version of User Manual presented in Appendix 2-2, as follows:

- Addition of a Table of Contents, Index, page numbers, and a clearer section on warnings and precautions (answering FDA CRL Question 2b)
- Clarification of supplied accessories (b) (4) which were in previous versions by inadvertence (answering FDA CRL Question 4)
- Clarification that the RUBY RbES is (b) (4) (answering FDA CRL Question 12).
- Other changes proposed by JDI, which are associated with the incorporation of electrical safety and electromagnetic compatibility requirements as per CSA requirements, a re-structuring 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 for the (b) (4) installation part for ease of readability for the user
- Additional changes related to formatting and document structure and are proposed for clarification purposes. These changes did not trigger any text content that would affect the usability testing
- Update of software screenshots to reflect change from Software version (b) (4) to Software version (b) (4)
- Update of several figures, including updated (b) (4) and labeling of first two figures showing system components, to reflect change of (b) (4) and introduction of (b) (4) designed by (b) (4) and manufactured by (b) (4)
- Troubleshooting section has been completely revised including full description of the error messages displayed by the software and additional steps for troubleshooting
- Addition of warnings, including (b) (4) (b) (4) (b) (4)
- Movement of (b) (4) section to correspond with Software version
- Addition of (b) (4) (if required)
- Small edits and formatting, including font size, use of capital letters on various words.

1.11.4.4 Response to CRL Q4.pdf

*As part of its response to Questions 1 and 2 of the CRL, JDI has revised the User Manual **(Appendix 2-2)** that includes the information requested by this question. At page 9, the User Manual identifies the supplies provided by JDI and the supplies the user must provide and also specifies the recommended (b) (4) that should be used.*

The User Manual removes the reference [redacted] (b) (4) *as they are not required for installation of the generator.*

For usability protocol review - Do any of these changes require HF validation? This would be answered by their response to question 2.

Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf

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.

Appendix 1-2 Summative Usability Test Validation Protocol.pdf

- Intended user identified (*certified/registered Nuclear Medicine Technologist with certification/registration in the country of use*), targeting 15 users in the US.
- Simulated use environment and mock generator.
- They indicate the highest risk level; however it is not clear if this is based on potential severity of harm (rather than a risk index) associated with a use error for each task. Based on Appendix 1-5 these do appear to be risk index terms (severity x occurrence) They did not use these to eliminate tasks from evaluation.
- User manual is included in the evaluation.
- One hour training decay.

- While this indicates that they are collecting objective and subjective data, do they use both sets of data in their analysis? Yes they do evaluate both.

User Tasks

The following task tables will be used in the usability tests as test data sheets for recording test results. Each task table contains multiple steps and will prescribe the order of task completion for each user. Following each task, a series of questions will be asked of the user to assess their assessment of the difficulty of comprehension and ease of safe execution for each task. Additional questions may be asked for marketing purposes and will not be evaluated on a pass/fail basis.

Acceptance Criteria

The task steps will be evaluated as pass or fail for each participant. If a user fails to complete a task correctly, it will be recorded as a failure. The task interview will attempt to identify if the user was aware of the task failure and evaluate the potential root cause of the failure. The facilitator may correct the failure if necessary to complete the subsequent task. The final report will analyze the total number of failures by participants and the risk that the failure poses in respect to patient or user safety.

- They have very granular task steps, example below. Were these just for facilitator tracking or did the participant get directed to do each of these task steps? See deficiency 1.

Task 2. (b) (4)			
Task Step	**Description of Step**	**User Completion**	**PASS/FAIL**
1	(b) (4)		
2			
3			
4			
5			
6			

APPEARS THIS WAY ON ORIGINAL

Appendix 1-3 Summative Usability Test Validation Report.pdf

- How detailed is this User Manual Review Form? This could likely negate the intent of the training decay time. An example of this form is seen starting on page 20/321 of appendix 1-8. This is a very detailed assessment and would negate the intent of a training decay period. Additionally as such an assessment is not part of the standard training rotuine and is adding rigour to the study prior to use it is not

representative of actual use. See deficiency 2.

C. **Test Goals, Critical Tasks and Use Scenarios Studied**

The goal of the tests was to ensure that respondents are able to correctly perform the tasks required to setup and operate the RUBY Rubidium Elution System. The critical tasks were (b) (4) Two error scenarios were also created to test the respondents ability to trouble shoot errors during the normal function of the RUBY system. these included (b) (4) (b) (4) Each respondent was asked to complete all ten (10) tasks. Each task consisted of multiple steps to successful completion. If the respondent completed all steps correctly regardless of order, the task was deemed successfully completed and "passed". The JDI PET Specialist conducted all respondent training prior to the testing. Each respondent was given a dinner break of at least 60 minutes prior to testing. During the break, respondents were asked to evaluate the User Manual using the User Manual Review Form (D/N 10093-001, Appendix B).

- Did they update the training materials accordingly?

The two users from the first test day failed to close the generator well cover. The training did not emphasize that closing the cover would impact the testing. There was no live generator used and the cover did not provide any shielding from radioactive material. The subsequent users were explicitly trained to close the generator well cover. One user failed to read the volume collected in the graduated cylinder to proceed in the setup validation sequence. He repeated the Pump validation and entered a correct value to complete the task.

Appendix 1-4 User Manual-previous version-Basis for Training.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-5 Usability FMEA-Basis for Training.pdf
They did use risk index rather than severity alone when indicating criticality of tasks.

Appendix 1-6 Graphic User Interface-Screen Shots.pdf
Not reviewed in detail as part of the summative report review.

Appendix 1-7 Summative Usability Objective Testing Data.pdf
This was summarized in appendix 1-3 as well.

Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
The user manual evaluation (example starting on 20/321) was quite detailed. This is concerning since they conducted this prior to task performance evaluation and during the "training decay" time period.

Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
Subjective data and sponsor response. It could be recommended to ask more open ended questions as part of subjective data collection in the future.

Appendix 2-1 Training Package.pdf
There is a certification program. This contains an example of the evaluation criteria.

Appendix 2-2 RUBY User Manual-newly proposed.pdf
This is as they indicated in their response.

Appendix 6-13 Usability FMEA.pdf
While they do utilize a risk index the high severity items are found in the evaluated tasks.

Materials Reviewed

- 1.11.4.1 Response to CRL Q1.pdf
- 1.11.4.2 Response to CRL Q2.pdf
- 1.11.4.4 Response to CRL Q4.pdf/
- Appendix 1-1 FDA Official Meeting Minutes August 18 2015.pdf
- Appendix 1-2 Summative Usability Test Validation Protocol.pdf
- Appendix 1-3 Summative Usability Test Validation Report.pdf
- Appendix 1-4 User Manual-previous version-Basis for Training.pdf
- Appendix 1-5 Usability FMEA-Basis for Training.pdf
- Appendix 1-6 Graphic User Interface-Screen Shots.pdf
- Appendix 1-7 Summative Usability Objective Testing Data.pdf
- Appendix 1-8 Raw Summative Subjective Usability Testing Data.pdf
- Appendix 1-9 Summary of Summative Subjective Usability Testing Data.pdf
- Appendix 2-1 Training Package.pdf
- Appendix 2-2 RUBY User Manual-newly proposed.pdf
- Appendix 6-13 Usability FMEA.pdf

End of Review

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/s/

TRI M BUI NGUYEN
05/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

*** This document contains proprietary information that cannot be released to the public***

DATE: May 27, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Eldon Leutzinger, Chemist, CDER/OPS/ONDQA/DNDQAIII

SUBJECT: **NDA 202153**
Applicant: Jubilant Draximage, Inc
Drug Constituent: Rubidium Rb-82 Chloride
Device Constituent: Ruby Elution System
(positron emission tomography products, PET)
Intended Use: assessing regional myocardial perfusion
CDRH CTS Tracking No.: 1400268

QuynhNhu Nguyen, Combination Products Human Factors Specialist

APPEARS THIS WAY ON ORIGINAL

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: NDA 202153
Applicant: Jubilant Draximage, Inc
Drug Constituent: Rubidium Rb-82 Chloride
Device Constituent: Ruby Elution System
(positron emission tomography products PET)
Intended Use: assessing regional myocardial perfusion

CDRH Human Factors Involvement History

- 4/16/2014: CDRH HFMET was contacted by Alan Stevens (CDRH) to discuss whether an HF study was needed.
- 4/28/2014: CDRH HFMET was forwarded a list of FDA questions and Sponsor's responses pertaining to CDRH engineering review. Part of the list referenced usability test report and system hazard analysis. This consultant requested the Project Manager (PM) to request that information from the Sponsor. The PM provided the Sponsor's response, which included usability risk analysis, and system validation (summative) study report.
- 4/29/2014: CDRH HFMET participated in an internal meeting with the review team to discuss the need for human factors assessment.
- 5/29/2014: CDRH HFMET provided review recommendations to CDER.

Overview and Recommendations

The Office of Pharmaceutical Science, Center for Drugs Evaluation and Research, requested a consultative review from Human Factors Premarket Evaluation Team for the Human Factors validation study report contained in the NDA # 202153 submitted by Jubilant Draximage Inc for the rubidium elution system.

Note that on July 15, 2011, FDA notified the public and medical imaging community about the potential for inadvertent, increased radiation exposure in patients who underwent or will be undergoing cardiac positron emission tomography (PET) scans with Rubidium (Rb-82) Chloride injection from CardioGen-82 manufactured by Bracco Diagnostics, Inc. The manufacturer, Bracco Diagnostics, Inc. has decided to voluntarily recall CardioGen-82. On 1/12/2012, FDA updated healthcare professionals and the public about preliminary findings from ongoing investigations following the voluntary recall of CardioGen-82 by the manufacturer. FDA is working with the manufacturer to revise the CardioGen-82 labeling to better describe how to use the generator. See link for more details:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm263157.htm#.U1l0Mn3Af7k.email

The usability risk analysis and human factors study report were found to be incomplete. This consultant would like to convey the following deficiencies to CDER and the Sponsor:

The usability risk analysis and human factors study report were found to be incomplete. Furthermore, we identified some concerns associated with the human factors methodology and approach that was employed in the study.

Please address the following:

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).
2. Your reported that there is a specific known risk associated with inadvertent, increased radiation exposure in patients who underwent or will be undergoing cardiac positron emission tomography (PET) scans with Rubidium (Rb-82) Chloride injection from CardioGen-82. You indicated that the RUBY Rubidium System calculates generator breakthrough at each daily QC measurement, and in situations where the levels are found to be (b) (4) the software will prompt the user to complete additional calibration and breakthrough measurements after the equivalent volume of 4 patients has eluted through the generator. Please provide the rationale for how you set the level limits and equivalent volume of 4 patients to be the safety limit. In addition, explain how your human factors study was designed to focus on demonstrating the effectiveness of the mitigations that you implemented for this specific risk.
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.
    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.

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.
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.
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.
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.

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.
5. Please provide all screen shots of the GUI.

Appendix 1: Summary of Human Factors Validation (Summative) Study Report

Two rounds of formative evaluations were conducted. The Sponsor made modifications to the device user interface to address use-related issues that were seen in those studies.

Fifteen certified nuclear medicine technologists (currently working in PET/CT labs) were enrolled in the validation study. The following table provides high-level tasks that each participant performed during the study. These tasks were evaluated in in a usability Failure Mode and Effects Analysis (uFMEA, D/N3000030). Each task contains multiple steps to successfully complete the task.

Task Number	Task Name	Risk Level
1	(b) (4)	Negligible
2		Undesirable
3		Tolerable
4		Undesirable
5		Tolerable
6		Undesirable
7		Tolerable
8		Undesirable
9		Undesirable
10		Negligible

The study report only showed results from four participants from the Hartford site. These results showed that:

(b) (4)

Subjective data were collected from study participants on the failed tasks. However, analysis of these data were not included in the study report to determine the root cause from the perspective of the users, and whether additional mitigations are needed.

Appendix 2: Device Description

The RUBY Rubidium Elution System is medical device that produces Rubidium Chloride by eluting sodium chloride through the Strontium filled generator.

Rubidium Elution System User Interface

(b) (4)

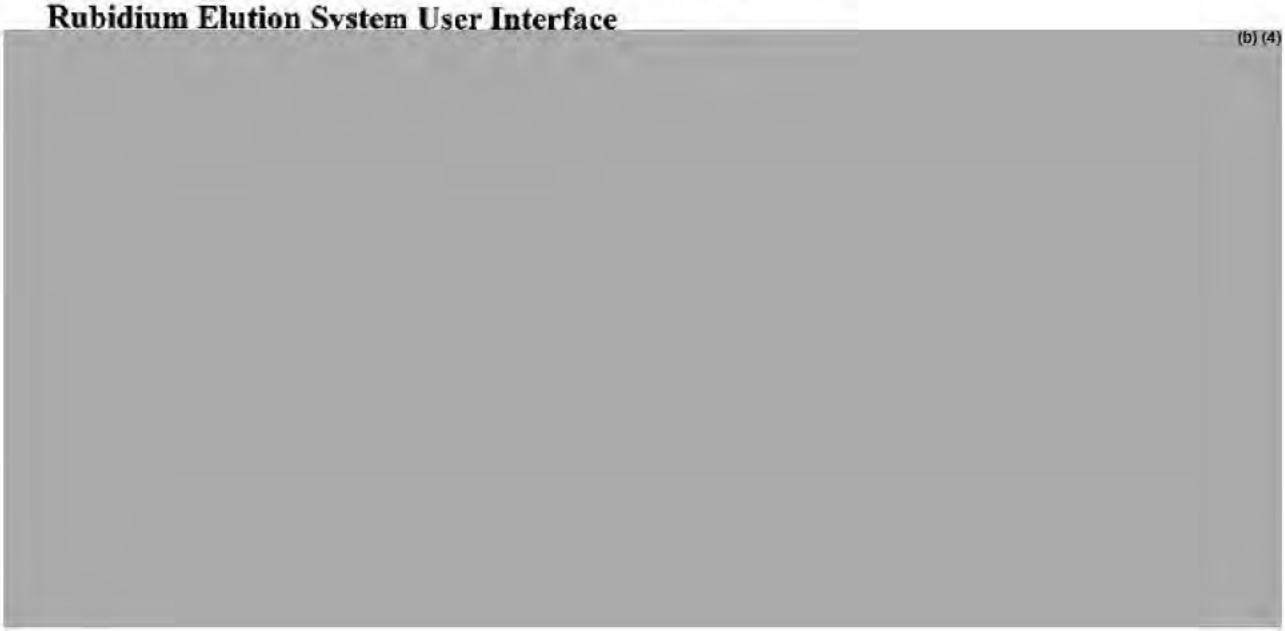


Figure II-1. Sample GUI screen.

(b) (4)

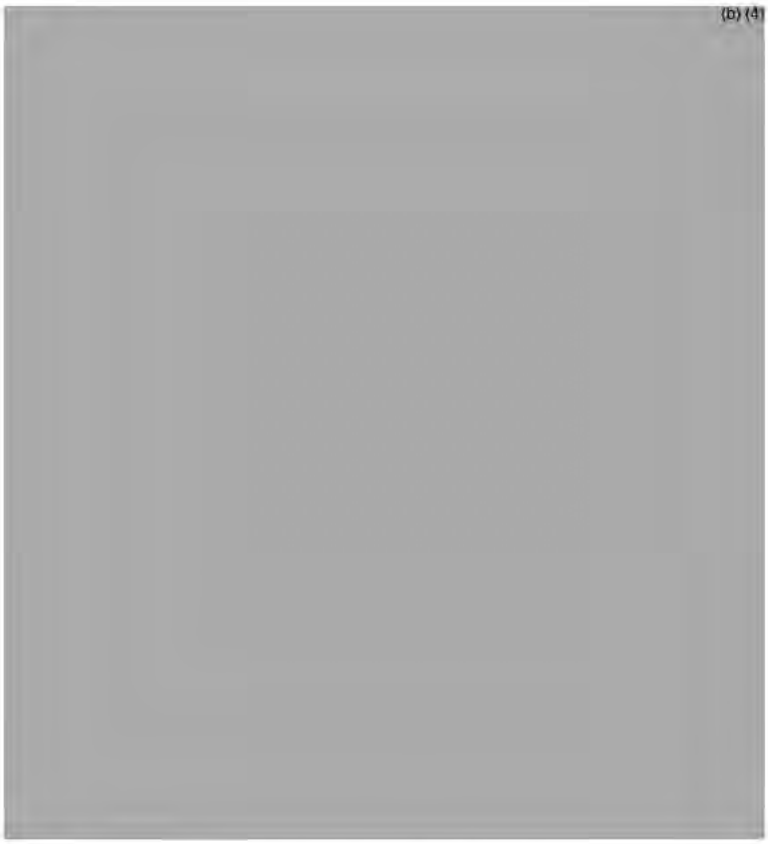
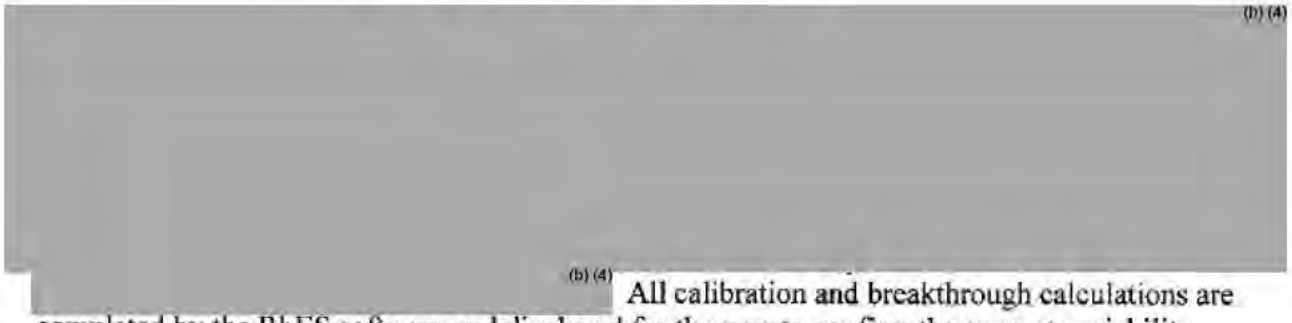


Figure II-2. RbES User Interface Overview.



(b) (4) All calibration and breakthrough calculations are completed by the RbES software and displayed for the user to confirm the generator viability.

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/s/

DAT T DOAN
09/08/2014

This is a review that was completed by Dr. Andrew Kang from CDRH being checked into DARRTS by Dat Doan from OGD. Checked in as "Summary Review/Administrative Review" because CDRH Review is not a choice in DARRTS.

Review
Ruby-Fill Elution System (RbES)
Break-through test
NDA202153

May 29, 2014

To: Dat Doan
Regulatory Project Manager
CDER/OGD

From: Andrew Kang, MD
CDRH/OIR/DRH/NMRTB

Doc. No.: #NDA202153, Ruby-Fill ES

Subject: Break-through test review

Review:
Sponsor has prepared 2 Rb-82 generators, [redacted] (b) (4)
and tested both on dose calibrator, [redacted] (b) (4) model.

Generator 1:

Test sample solution 1 (sln 1A) has been prepared [redacted]

Generator 2:

Test sample solution (sln 2A) was prepared [redacted]. Test sample solution, (sln 2B) was prepared [redacted]

Break-through Study:

Daily QC test was performed on the RbES and repeated for calibration and breakthrough test and Rb-82 activity is collected in a [redacted] mL vial in the integrated dose calibrator. A breakthrough sample is collected in the chamber of dose calibrator and compared to the activity of Sr-82/Sr-85 sample to calculate the actual breakthrough value. Accuracy measurements were performed by comparison to theoretical value and the Sr-82/Sr-85 activity was used to estimate the detection capabilities of the dose calibrator.

Breakthrough measurement:

A [redacted] minute window was used after [redacted] seconds Rb-82 measurement to measure the breakthrough activity. All activities were converted to decay- corrected value. The test was performed on generator 1 and 2 for two time points; at the new generator and at the expiry time point. The generator 2 has been tested twice in low background room.

Test Results:

Statistically, data collected by one time measurement or one repeated measurement may not be verifiable for the accuracy, however, above measurements for all variable concentrations showed that the breakthrough doses above [redacted] uCi are generally within less than 10% accuracy from the actual

known Sr-82 value. However, the breakthrough doses less than (b) (4) uCi of Sr-82 showed variable accuracy more than 10 to 20% difference from the actual known value. (b) (4) Breakthrough doses less than (b) (4) uCi may have over 10 to 20% variability of the accuracy, however, these low level of breakthrough activities may be clinically insignificant.

Conclusion:

The additional data submitted for Sr-82 breakthrough tests are acceptable, showing evidence of detectability of the dose calibrator to detect the critical levels of breakthrough doses

Andrew Kang, MD
CDRH/OIR/DRH/NMRTB

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/s/

DAT T DOAN
09/08/2014

DMIP Review of: CDRH Human Factors Consult

and

The Safe Use Submissions

Ruby-Fill NDA 202,153

FDA Document Reviewed

CDRH Human Factors Consult

Sponsor's Source Documents Reviewed

Ruby Rubidium Elution System Summative Usability Validation Report

Ruby Rb-82 Elution System Usability Risk Analysis

Draximage Rb-82 Version 3 Hazard Analysis

Checklist-Summary of data and documentation supporting the Ruby-Fill (b) (4) accessories

DMIP Comments

Overview

The CDRH report encompasses the sponsor's source documents; CDRH highlights multiple deficiencies in both the risk analysis and methodology of the HF study provided by the Ruby Fill sponsor. DMIP agrees with these findings. As detailed below, DMIP finds the outline of the Ruby-Fill radiation monitoring plan acceptable.

The source documents from the sponsor also identify several deficiencies with suggested remedies which were not addressed by CDRH. The salient deficiencies are enumerated below. The available documents do not indicated whether the suggested remedies have been incorporated into revised operating instructions and their efficacy subsequently tested.

Comments on the Specific Deficiencies noted in the CDRH Review of the HF Study

DMIP will not repeat the explicit deficiencies enumerated by CDRH, but highlight specific issues which we feel are important for safe use of Ruby-Fill. The CDRH consult provides a comprehensive information request to the sponsor to resolve the identified deficiencies.

1. Deficiencies of the risk analysis: CDRH has enumerated important deficiencies that should be addressed in a more comprehensive use-related risk analysis. Most striking is that there is no performance information on the critical task of responding to alarms, warnings and precautions.

   Based on the limited information in the provided report and aside from the alarm response issues, DMIP does note that the sponsor did choose other appropriate mechanical tasks to evaluate the ability of a clinical staff to operate the Ruby Fill instrument. Most users appeared able to use Ruby-Fill following instruction. The participant testing was done soon after the instruction. The sponsor says the same instruction would be given to actual clinical users.

2. Methodological Deficiencies: DMIP is also perplexed by the study report containing detailed test results from only 4 participants at one of the three testing sites. (Discussed below)

3. Inadvertent, increased radiation exposure. CRDH questions the rationale for monitoring the radiation in the eluate for patient administration. The criteria provided by the Ruby-Fill manufacturer should be viewed within the context of the previous CardioGen safety investigations and changes to the CardioGen label. This extensive history may not have been available to the CDRH reviewer.

   The criteria for daily quality control measurements of the eluate for Strontium$^{82\&85}$ "breakthrough" stem from the 2012 revision of the CardioGen label. Though the Ruby-Fill criteria may not be identical to CardioGen they appear reasonable and acceptable [redacted] (b) (4)

DMIP review of the documents provided by the sponsor

Deficiencies noted in the Ruby Rubidium Elution System Summative Usability Validation Report

This document provided a list of failure modes and their effect; CDRH has extensively reviewed this document. A total of 15 participants at 3 sites were tested in the final Summative Usability Validation Test. Following instructions, participants were tested on the multiple procedures that make up the following critical tasks:

(b) (4)

As noted by CDRH, curiously, detailed test results for these tasks are only presented for the four participants at the Hartford site. Generally the participants were able to learn to carry out these tasks. The reader is referred to an absent? Appendix B for more test results. The provided report only has comments from the other 9 participants about the user manual.

The reported testing results are encouraging in that some nuclear technologists could learn to operate Ruby-Fill. However, for a proper review test results are needed from the other participants.

Deficiencies noted in the Ruby Rb-82 Elution System Usability Risk Analysis

This document outlined a Failure Mode and Effects Analysis (FMEA). DMIP is most concerned about actions involving a failure mode with a Risk Rating of U – Undesirable and the recommended remedies. Most troubling examples:

Item 24: Enter (wrong) (b) (4) – Remedy: "A warning statement should be added in the User Manual. In addition we should ask legal to craft a statement that JDI/KDI will not be responsible…… Could be part of training during initial setup".

Item 112: Entering inaccurate (b) (4) – Remedy: "Include a message in the user manual stressing the importance of entering this information correctly."

These failures are so significant that warnings beyond additional text are warranted. Perhaps the internal computer software can be enhanced to warn or shut down the system if unusual information is entered.

DMIP Review of the Draximage Rb-82 Version 3 Hazard Analysis

This document is more of a general outline of the use and safety features of Ruby-Fill. DMIP did not identify any deficiencies.

Checklist-Summary of data and documentation supporting Ruby-Fill [redacted] (b) (4) accessories

DMIP is interested in the additional data possibly held by the sponsor on Strontium breakthrough studies and data that supports expiration after 30 L have run through the generator. Though not mentioned in the report, DMIP would also be interested in the data supporting the number of days of service until the generator reaches expiration (independent of the 30 L expiration criterion).

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/s/

IRA P KREFTING
06/27/2014

Inter-Center Consult Review
Review of Sponsor Response to FDA Questions (Device)
ANDA 202153 (Received 5/21/13)

Ruby-Fill®, Rubidium Rb-82 Generator

By Jubilant DraxImage

To: Dat Doan,
Regulatory Project Manager,
OGD

From: Andrew Kang, MD
Medical Officer
CDRH/OIR/DRH/NMRTB

Doc. No: ANDA #202153

Name: Ruby-Fill®, Rubidium Rb-82 Generator

Description of the system:
Ruby-Fill® is Rubidium Rb-82 Generator, which elutes positron emitting Rb-82 radionuclide for PET cardiac perfusion imaging. Ruby-Fill® contains parent isotope, Sr-82, which is produced by (b) (4)

The daughter isotope, Rb-82, is eluted by injection of sterile saline solution into the system, and the final product is infused into the patient by IV line.

Radioisotope property:

Strontium-82 (Sr-82), parent isotope:
Physical T1/2 life is 25.5 days. Each batch is produced as > (b) (4) ml of Sr^{82} Cl_2 at calibration date, specific activity of > (b) (4) mCi/mg of Sr at calibration date. It contains contaminants of (b) (4) and negligible amounts of (b) (4) Gamma ray major photopeak is (b) (4) keV, minor peak at (b) (4) keV, and it may includes (b) (4) keV (b) (4)

Rubidium-82 (Rb-82), daughter isotope:
Physical T1/2 life is 75 seconds and it decays to stable Kr-82. Rb-82 produces 511 keV positron emissions, which is useful for PET cardiac perfusion imaging.

Infusion System:
The system consists of [redacted]

Dose calibrator:
[redacted]

Sr-82 and Sr-85 breakthrough test:
Daily procedures start with a saline flush of the system, followed by a calibration run, and breakthrough test. The Sr-82/Sr-85 breakthrough limits have been set for daily QC test as follows.

0.02 uCi of Sr-82/mCi of Rb-82
0.2 uCi of Sr-85/mCi of Rb-82 and, if reaches these level, replace the generator.

An alert level has been set at each infusion at [redacted] (0.004 uCi of Sr-82) breakthrough ---- Repeat QC breakthrough test during the day

Safety limit is set at [redacted] (0.01 uCi of Sr-82) ---- stop using the generator, call tech. service.

Device related issues:
The device related issues can be summarized in 3 issues.

1. The infusion related components, [redacted] should be reviewed by CDRH/ODE/DAGID/GHDB.

2. Software --- the software controls [redacted] The software validation should be reviewed by both CDRH/ODE/DAGID/GHDB and CDRH/OIR/DRH. The software validation procedure has been described in 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. Radioactive dose calibrator --- Sponsor stated that the [redacted] brand dose calibrator has been cleared by CDRH. However, the dose calibrator has been cleared [redacted] The sponsor should consult with the manufacturer of the dose calibrator to ensure the accurate measurement of Rb-82 and Sr-82 / Sr-85 breakthrough measurements. (Larger than [redacted] uCi level)

Sponsor Response to FDA Questions (device), received on May 21, 2013

Response 1and 2:
(The response 1 and 2 have been reviewed by Ryan McGowan, Biomedical Engineer, CDRH/ODE/DAGRID/GHDB. Please refer to attached separate review note.)

Response 3:
Dose Calibrator:
The dose calibrator used in [redacted] Rb-82 generator, is [redacted]

The specification for the [redacted] is following.
Detector Linearity: Within [redacted]% or [redacted] µCi (whichever is greater)
Electrometer Accuracy: Within [redacted]% or [redacted] µCi (whichever is greater)
Overall accuracy: [redacted]% or [redacted] µCi, whichever is greater
Repeatability: [redacted]% above [redacted] mCi short term (24h)

The minimum dose measurable on this dose calibrator is [redacted] uCi, and the lowest measurable dose with accuracy and reproducibility is [redacted] uCi, which is designated as **operational lower limit of the dose calibrator.**

Appendix 1 cotained validation test data for low level activity measurement, provided by [redacted] Medical Nuclear Physicist. The test data includes the following.

Constancy Test: Constancy test is the reproducibility of long time data stability. [redacted]% SD of the variability is acceptable limitation. The test was conducted using [redacted] for 4 weeks duration. The results showed the data from [redacted] to [redacted]% variation, which is within [redacted]% SD, the acceptable limitation.

Accuracy/Precision Test: Accuracy tests have been performed in a various dose range, [redacted] [redacted]% SD is acceptable limit. The the dose accuracy data showed [redacted] showing less than [redacted]% SD variation, which is acceptable.

Activity/Linearity Test: Linearity check for dose calibrator using [redacted] mCi of [redacted] showed measured dose ranging [redacted], average [redacted], which is within the acceptable level of minimum [redacted]

Geometric Test: Geometric variation test is if there is variation of measurement between the dose in a vial vs. a syringe. [redacted]% will be acceptable. Both containers showed acceptable level of consistency.

Reviewer's review note:
[redacted] Rb-82 generator break-through limitations have been set in the original submission as;

0.02 uCi of Sr-82/mCi of Rb-82, and 0.2 uCi of Sr-85/mCi of Rb-82,

An alert level has been set at each infusion at [redacted] (0.004 uCi of Sr-82), and the safety limit is set at [redacted] (0.01 uCi of Sr-82).

[redacted]

When compared the above 4 break-through limitation doses with the **Operational Low Dose Limitation (OLDL) of [redacted] uCi** (referred to page 3), all above minimum required measurable amounts are above the OLDL level and are acceptable.

Appendix 1: Verification Tests data for Dose Calibrator have showed acceptable results in all 4 test categories.

Conclusion:
The above dose calibrator verification tests and specification has provided the ability of accurate measurement of break-through of Sr-82 and Sr-85.

Radiation Counter:
The radiation counter is composed of [redacted] The accuracy of the measurement in activity counter has been tested by comparison with the measurement in dose calibrator. Variable activities from [redacted] MBq to [redacted] MBq have been compared between the dose calibrator and activity counter. The variation ranged between [redacted] to [redacted]%, which is within acceptable level.

CONCLUSION for RESPONSE 3:
The sponsor response 3 has provided acceptable support data for accurate measurement of Sr-82 and Sr-85 break-through data. It also has provided satisfactory test data for the accuracy of dose activity counter. Therefore, the sponsor response 3 has been accepted.

OVERALL CONCLUSION:
The sponsor response 3 has been accepted. However, the response 1 and 2 require more data for validation of the [redacted] assembly and the associated software. The following additional information is required for further review.

<u>Deficiency in sponsor response 1 and 2:</u>

[redacted]

Your submission does not appear to contain or provide enough detail regarding the following device characteristics related to the infusion system:

1. A comprehensive description of the infusion system [redacted] (b) (4)

2. Documentation which provides requirements and specifications of the infusion system

3. A summary of results from performance testing along with copies of test reports referenced for the infusion system including traceability information which traces back to stated requirements and specifications

4. Documentation of risk analysis activates undertaken to address identified system hazards as well as results of the analyses.

5. Information related to software used within the subject system. Please refer to the following Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, and provide copies of relevant information and analysis found within the document. Please note, CDRH often considers [redacted] (b) (4) a "Major" level of concern for the purposes of software review. For a discussion of the software documentation that you should provide in the 510(k) submission, please refer to the following hyperlink:

   http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/uc
   m089543.htm,.

6. Biocompatibility information for patient and fluid contacting portions of the infusions system

7. Sterility information for patient and fluid contacting portions of the infusions system

8. Information demonstrating compliance with relevant electrical safety and electromagnetic compatibility requirements of IEC 60601-1 (1988): Medical electrical equipment – Part 1: General requirements for safety, including Amendment 1 (1991) and Amendment 2 (1995) for Type B equipment and IEC 60601-1 Collateral Standard: Safety requirements for medical electrical systems and IEC 60601-1-2 (2001): Medical Electrical Equipment, Part 1: General Requirements for Safety, 2. Collateral Standard: Electromagnetic Compatibility - Requirements and Tests

---

If you have any questions, please contact me by e-mail or by phone at 301-796-6544.

Andrew Kang, MD
Lead Reviewer (for device)
CDRH/OIR/DRH

Attachment: Copy of review note from Mr. Ryan McGowan, Biomedical Engineer, CDRH/ODE/DAGRID/DHDB

APPEARS THIS WAY ON ORIGINAL

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/s/

DAT T DOAN
07/16/2013

ROBERT L ISER
07/16/2013
Director, DC IV

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202153

Date of Submission: May 20, 2011

Applicant's Name: DRAXIMAGE (a Division of DRAXIS Specialty Pharmaceuticals Inc.)

Product Name: Rubidium Rb 82 Generator

Proprietary Name: RUBY-FILL™

LABELING COMMENTS:

1. **CONTAINER:**

   a. GENERAL COMMENT

   i. [redacted] (b) (4) Please submit separate labels to be the same as the RLD.

   ii. The data on your DECAY CHART goes up to 60 days, while the RLD goes up to 30 days. Please comment or delete to be the same as the reference listed drug.

[redacted] (b) (4)

2. **INSERT:**

a. GENERAL COMMENTS

i. Please refer to the reference listed drug for guidance on formatting of the HIGHLIGHTS section.

ii. Replace the hyphen with "to" when expressing a dosage range.

iii. We note that you made reference to [redacted] (b) (4) However, the reference listed drug does not list this [redacted] (b) (4) in their labeling. Please comment or delete to be the same as the reference listed drug.

b. HIGHLIGTS OF PRESCRIBING INFORMATION

i. Revise [redacted] (b) (4) to read "Initial U.S. Approval: 1989"

ii. Update your version number and revision date.

c. FULL PRESCRIBING INFORMATION

i. Drug Handling-
We note that in your labeling you specify that only additive-free 0.9% Sodium chloride Injection USP is used to elute the generator. However, the reference listed drug does not specify a particular strength. Please comment or delete to be the same as the reference listed drug.

ii. Directions for Eluting Rubidium Rb 82 Chloride Injection-
Under the instructions entitled "When eluting the Ruby-fill™ generator:" revise the fifth bullet to read as follows.

[redacted] (b) (4)

iii. Revise Tables 2 and 5 to be the same as the reference listed drug.

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-Content of Labeling". Please provide the labeling in the Structured Product Labeling (SPL) format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the

CDER web site at the following address -
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{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/

KOUNG U LEE
11/29/2011
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	202153
Date of Submission:	June 18, 2010 (Original submission)
Applicant's Name:	DRAXIMAGE (a Division of DRAXIS Specialty Pharmaceuticals Inc.)
Product Name:	Rubidium Rb 82 Generator
Proprietary Name:	RUBY-FILL™

LABELING COMMENTS:

1. **CONTAINER:**

   a. Please review the attached reference listed drug (RLD) labeling and revise your labeling accordingly.

   b. Revise your storage temperature statement to read [redacted] (b) (4)

2. **INSERT:**

   Please update your insert labeling to be in line with the RLD labeling approved July 28, 2010 (NDA 019414/S-012). The RLD labeling is available on the Drugs@FDA website.

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-Content of Labeling". Please provide the labeling in the Structured Product Labeling (SPL) format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{See appended electronic signature page}

_____

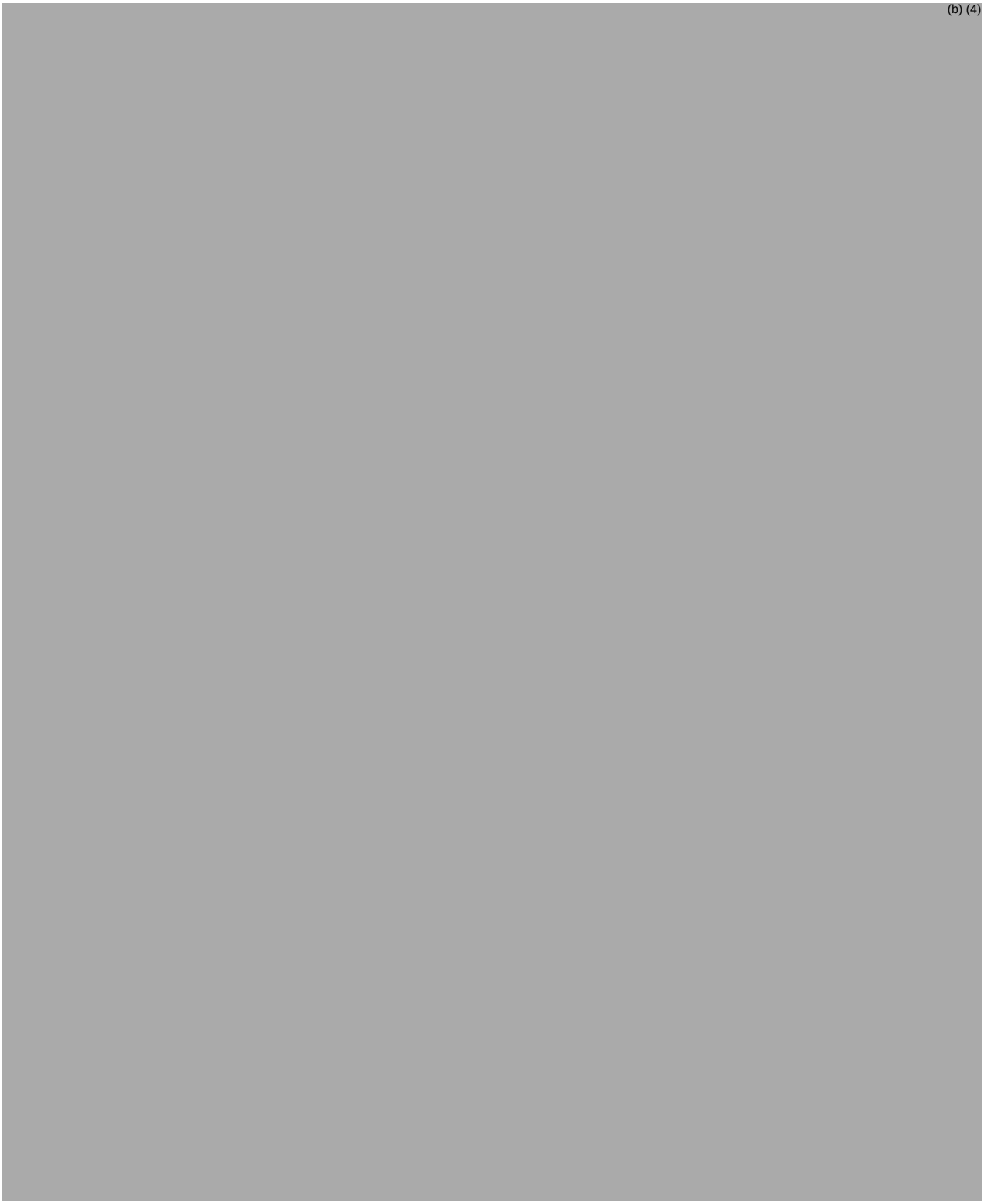
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(See Attachments)

NOTE TO THE CHEMIST:

FOR THE RECORD:

(b) (4)



2. **MEDWATCH:** No reports since labeling approved (Checked 12/13/2010).

3. **PATENT AND EXCLUSIVITY**: (None) Checked 12/13/2010
There are no unexpired patents currently exist for Rubidium Chloride Rb-82. The Orange Book Database reports no unexpired patents and exclusivity held by Bracco Diagnostics Inc. for CardioGen-82® (NDA #N019414), the reference listed drug for this ANDA.

4. **MANUFACTURING FACILITY OF FINISHED DOSAGE FORM**
DRAXIMAGE, (a division of DRAXIS Specialty Pharmaceuticals Inc.)
16751 TransCanada Highway
Kirkland, Quebec
Canada H9H 4J4

5. **USP**: This product is subject to USP 33 monograph (Checked on 12/14/10).

6. **PHARMACOPEIAL FORUM**: Not applicable (Checked on 12/14/10).

7. **INGREDIENTS:**

Table P.1 – 1: List of components of the dosage form, their function, reference to quality standard, and amount on per-unit basis

Ingredients	Ingredient function	Quality Standard	Quantity per generator
$^{82}SrCl_2$	Starting Material	House	(b) (4)
(b) (4) Stannic Acid	Adsorbent	House	
Sodium Chloride	(b) (4)	USP / Ph. Eur.	
			(b) (4)

* At calibration time

8. **PACKAGING CONFIGURATIONS/PRODUCT LINE**:

RLD: CardioGen-82® (Rubidium Rb 82 Generator) consists of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time. A lead shield surrounded by a labeled plastic container encases the generator.

ANDA: Ruby-Fill™ (Rubidium Rb 82 Generator) is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.

9. **DISPENSING/STORAGE TEMPERATURE STATEMENT COMPARISON**

USP: **Packaging, storage, and labeling—** Requirements for packaging, storage, and labeling do not apply; Rubidium Chloride Rb 82 Injection is obtained by elution from the generator and is administered by direct infusion.

RLD: Store the generator at 20-25°C (68-77°F) [See USP].

ANDA: *Insert:* (b) (4)

Container: (b) (4)

Ask the firm to revise their storage temperature statement to read (b) (4)

10. **PROPRIETARY NAME:**

Ruby-Fill™ (Rubidium Rb 82 Generator) Approved 12/22/2010

From: Merchant, Lubna
Sent: Wednesday, December 01, 2010 10:37 AM
To: Griffis, Melina; Griffith, Sandra J; Holquist, Carol A; Turner, Betty
Subject: Proprietary Name Review-Ruby-Fill ANDA 202153

Good Morning,

This email is to notify you that the Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name, Ruby-Fill(Rubidium Rb-82 Generator), is acceptable from a look-alike and sound-alike perspective. In addition, our evaluation did not identify any other factors that render the name unacceptable at this time. Our decision is based upon the information submitted by the Applicant, DDMAC's promotional evaluation, DMIP's initial comments, and DMEPA's safety evaluation.

Please share this information with the Ruby-Fill review team. If the review team believes the name is unacceptable based upon other factors (e.g. clinical, chemistry), please forward the concern and provide rationale.

We ask that you respond to the request within 14 days of the receipt of this communication so that we can finalize our review. We are willing to meet with the division to discuss, if needed.

Thank you
Lubna Merchant

Lubna Merchant, M.S., Pharm.D.
Drug Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Office 301.796.5162
lubna.merchant@fda.hhs.gov

Approval Letter
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

11. **CONTAINER CLOSURE:**

(b) (4)

1 page has been Withheld in Full as B4 (CCI/TS) immediately following this page

Due to the radioactive property of Strontium 82Sr and 82Rb, a primary lead shield (b) (4) surrounds the column to reduce the radiation emitted. The shield consists of (b) (4)

12. **FINISHED PRODUCT DESCRIPTION:**

Ruby-Fill™ (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of (b) (4) millicuries Sr-82 at calibration time. The generator is encased in a lead shield. Complete assay data for each generator are provided on the container label.
Ruby-Fill™ (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of (b) (4) millicuries Sr-82 at calibration time. The generator is encased in a lead shield. Complete assay data for each generator are provided on the container label.

Date of Review: January 7, 2011 Date of Submission: June 18, 2010

Primary Reviewer: Betty Turner Team Leader: Koung Lee

ANDA 202153
NA1

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/s/

BETTY B TURNER
01/20/2011

KOUNG U LEE
01/20/2011
For Wm. Peter Rickman

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 202153

Date of Submission: June 18, 2010 (Original submission)

Applicant's Name: DRAXIMAGE (a Division of DRAXIS Specialty Pharmaceuticals Inc.)

Product Name: Rubidium Rb 82 Generator

Proprietary Name: RUBY-FILL™

LABELING COMMENTS:

1. **CONTAINER:**

   a. Please review the attached reference listed drug (RLD) labeling and revise your labeling accordingly.

   b. Revise your storage temperature statement to read [redacted] (b) (4)

2. **INSERT:**

   Please update your insert labeling to be in line with the RLD labeling approved July 28, 2010 (NDA 019414/S-012). The RLD labeling is available on the Drugs@FDA website.

Revise your labeling, as instructed above, and submit final printed labeling electronically. In addition, please review the guidance for industry titled "Providing Regulatory Submissions in Electronic Format-Content of Labeling". Please provide the labeling in the Structured Product Labeling (SPL) format.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained.

{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

(See Attachments)

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

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/s/

KOUNG U LEE
01/20/2011
For Wm. Peter Rickman

Appendix H

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
** **For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
*** **A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ ***

ANDA #: 202153 **FIRM NAME**: DRAXIMAGE

PIV: NO **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES PER MARTY SEE EMAIL IN 202153 VOL. A1.1

DATED 6/30/2010

DRUG NAME: RUBIDIUM RB -82
DOSAGE FORM: INJECTION (GENERATOR) OF (b) (4) **mCi**

Review Team: (Bolded/Italicized & Checked indicate Assignment or DARRTS designation)

Quality Team: DC4 Team 41 ☒***Activity***	***Bio Team 2: Yih-Chain Huang*** ☒***Activity***
ANDA/Quality RPM: Dat Doan ☒ ***FYI***	Bio PM: Alpita Popat ☐ ***FYI***
Quality Team Leader: Mueller, Albert No assignment needed in DARRTS	***Clinical Endpoint Team Assignment: (No)*** ☐***Activity***
Labeling Reviewer: Betty Turner ☒***Activity***	***Micro Review Random Micro Team 1*** ☒***Activity***

*****Document Room Note: for New Strength amendments and supplements, if specific reviewer(s) have already been assigned for the original, please assign to those reviewer(s) instead of the default random team(s). *****

Letter Date: JUNE 18, 2010 **Received Date**: JUNE 30, 2010

Comments: **EC- 1 YE S** **On Cards:** YES
Therapeutic Code: 5020900 MISCELLANEOUS RADIOPHARMA

Archival copy: CTD FORMAT PAPER **Sections** I
Review copy: YES E-Media Disposition: YES SENT TO EDR
Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product
(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Peter Chen **Date 10/14/2010**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**

Supervisory Concurrence/Date: _____ **Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA:

1. The proposed product is a Rubidium 82 (Rb-82) generator which is composed of Strontium Chloride (Sr-82) bound to (b) (4) stannic acid matrix. Rubidium chloride is eluted with solution of Normal Saline through the generator. According to the sponsor the ^{82}RbCl activity delivered in a given elution depends on the volume, the elution rate, and the Strontium (82Sr) activity adsorbed on the column, based on the intended dose. The elution rate (b) (4) is (b) (4) mL/minute for the ANDA compared to 50 mL/minute for the RLD. However per MHS this is not a concern as this is considered the "manufacturing" rate for the generator (b) (4)
2. Consult request checked into DARRTS on 10/14/2010.
3. Email sent to R.West for concurrance of expedited review status.

The following comments faxed to sponsor on 9/22/2010:
1. For the Environmental Impact Analysis Statement, please certify whether you have adhered to all Federal, State and Local environmental laws.
Adequate for filing per 10/6/2010 correspondence.
2. Please provide the exact addresses, contact names, telephone and fax numbers for the 2 API suppliers (b) (4)
Adequate for filing per 10/6/2010 correspondence.
~~*3. Please revise your samples statement of availability for the API SR-82 to include the lot numbers of those lots used in the manufacture of the finished product.*~~
4. In section 3.2.S.5 please provide information on the reference standards for the API material SR-82
Adequate for filing per 10/6/2010 correspondence
5. Please provide the contact name, telephone and fax number for the drug product manufacturing and for all testing facilities cited in module 3.2.P.3
Adequate for filing per 10/6/2010 correspondence
6. Please provide a reprocessing statement citing 21 CFR 211.115 should you intend to reprocess any batches that does not conform to specifications.
Adequate for filing per 10/6/2010 correspondence
7. You have provided API COAs from (b) (4) and from (b) (4) However according to your executed batch records for finished product Batches (b) (4) the following API batches were used: API batch (b) (4) These batch numbers found in the EBR compared to your submitted API COA batch numbers are different. Please reconcile this discrepancy. Alternatively you may submit release and receipt COAs for the APIs used in the demonstration batches.
Adequate for filing per 10/6/2010 correspondence. COAs provided.
8. You have failed to submit a receipt COA for the API batch (b) (4)
Adequate for filing per 10/6/2010 correspondence. Receipt COA provided.
9. You have submitted drug product COAs and stability data for (b) (4) ; however, you have only submitted EBR for (b) (4) . You should explain this disconnect.
Adequate for filing per 10/6/2010 correspondence. Additional EBRs provided.

1. Edit Application Property Type in DARRTS where applicable for
   a. First Generic Received
      ☒ Yes ☐ No
   b. Market Availability
      ☒ Rx ☐ OTC
   c. Pepfar
      ☐ Yes ☒ No
   d. Product Type
      ☐ Small Molecule Drug (usually for most ANDAs except protein drug products)
   e. USP Drug Product (at time of filing review)
      ☐ Yes ☒ No
2. Edit Submission Patent Records
   ☒ Yes
3. Edit Contacts Database with Bioequivalence Recordation where applicable
   ☐ Yes
4. Requested EER
   ☒ Yes (pending addition of API suppliers into EES)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.	06/18/2010
TELEPHONE NO. *(Include Area Code)* 514-630-7081	**FACSIMILE (FAX) Number** *(Include Area Code)* 514-694-9295

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*

16751 TransCanada Highway
Kirkland, Québec, Canada
H9H 4J4

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*

Hari Nagaradona, Kendle International Inc.

7361 Calhoun Place, Suite 500, Rockville, MD-20855-2765
Tel. 301-296-1370 / Fax: 301-838-3182

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)*:

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Rubidium Rb 82 Generator	Ruby-Fill

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Rubidium Chloride Rb-82	

DOSAGE FORM	STRENGTHS	ROUTE OF ADMINISTRATION
Generator delivering parenteral solution	Generator of (b) (4) mCi	Intravenous

(PROPOSED) INDICATION(S) FOR USE: Rubidium chloride Rb-82 Injection eluted from RubyFill is indicated for assessing regional myocardial perfusion

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)*
- ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50)
- ☑ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
- ☐ BIOLOGICS LICENSE APPLICATION (BLA 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE: ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION:
Name of Drug: Cardiogen-82 Holder of Approved Application: Bracco Diagnostics Inc.

TYPE OF SUBMISSION *(check one)*
- ☑ ORIGINAL APPLICATION
- ☐ AMENDMENT TO APENDING APPLICATION
- ☐ RESUBMISSION
- ☐ PRESUBMISSION
- ☐ ANNUAL REPORT
- ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT
- ☐ EFFICACY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
- ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY
- ☐ CBE
- ☐ CBE-30
- ☐ Prior Approval (PA)

REASON FOR SUBMISSION:

PROPOSED MARKETING STATUS *(check one)*
- ☑ PRESCRIPTION PRODUCT (Rx)
- ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED: 4 THIS APPLICATION IS
- ☐ PAPER
- ☑ PAPER AND ELECTRONIC
- ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Please refer to the Appendix attached to the form for the complete list of facilities applying to this section.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

(b) (4) Type II DMF (b) (4)
Type II DMF

RECEIVED
JUN 30 2010
CDD

FORM FDA 356h (10/05)

This application contains the following items: *(Check all that apply)*	
☑	1. Index
☑	2. Labeling *(check one)* ☑ Draft Labeling ☐ Final Printed Labeling
☑	3. Summary (21 CFR 314.50 (c))
☑	4. Chemistry section
☑	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☑	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☑	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☑	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☑	16. Debarment certification (FD&C Act 306 (k)(1))
☑	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☑	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Charles Vachon, Dir. Reg. Aff. / Hari Nagaradona, US Agent	06/18/2010

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
16751 TransCanada Hwy, Kirkland Qc, Canada H9H 4J4 / 7361 Calhoun Place, Rockville MD-20855	514-630-7081/301-296-1370

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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

FORM FDA 356h (10/05) PAGE 2 OF 4

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2 Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: JUNE 18, 2010	☒

1.2.1	**Form FDA 3674 (PDF) YES 9.a.**	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) YES	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) NO Disclosure Statement (Form FDA 3455, submit copy to Regulatory Branch Chief) NO	☒
1.3.5	**1.3.5.1 Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 1. Patent number(s) "No relevant patents" 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☒ PII ☐ PIII ☐ PIV ☐ (Statement of Notification) ☐ 3. Expiration of Patent(s): NA a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒
1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient submitted Type II DMF No. [redacted] (b) (4) for Strontium-82 b. Type III DMF authorization letter(s) for container closure 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) submitted	☒
1.12.11	**Basis for Submission** NDA# : 19-414 Ref Listed Drug: CARDIOGEN- 82 Firm: BRACCO DIGNOSTICS INC. ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD (Strontium 82 eluted to Rubidium Chloride 82) 3. Inactive ingredients Same as RLD (Normal Saline for elution) 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength (b) (4)	☒
1.12.14	**Environmental Impact Analysis Statement** YES *1. For the Environmental Impact Analysis Statement, please certify whether you have adhered to all Federal, State and Local environmental laws.* *Adequate for filing per 10/6/2010 correspondence*	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): YES	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** 4 copies of draft (each strength and container) submitted **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained Sponsor indicated the RLD container label because of the nature of the product, cannot be obtained - OK per labeling reviewer **1.14.1.3** 1 package insert (content of labeling) submitted electronically submitted ***Was a proprietary name request submitted? Yes (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted **1.14.3.3** 1 RLD label and 1 RLD container label RLD container label not available - ok per labeling reviewer	☒

HOW SUPPLIED

Ruby-Fill™ (Rubidium Rb 82 Generator) is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of (b) (4) millicuries Sr-82 at calibration time. The generator is encased in a lead shield. Complete assay data for each generator are provided on the container label. Directions for determining the activity of rubidium Rb 82 eluted from the generator are provided in this monograph. Ruby-Fill™ (Rubidium Rb 82 Generator) is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.

2.3	**Quality Overall Summary (QOS)** **E-Submission: PDF** submitted **Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage http://www fda.gov/cder/ogd/ **Question based Review (QbR)** **2.3.S** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1 General Information** **2.3.S.2 Manufacture** **2.3.S.3 Characterization** **2.3.S.4 Control of Drug Substance** **2.3.S.5 Reference Standards or Materials** **2.3.S.6 Container Closure System** **2.3.S.7 Stability** **2.3.P** **Drug Product** **2.3.P.1 Description and Composition of the Drug Product** **2.3.P.2 Pharmaceutical Development** **2.3.P.2.1 Components of the Drug Product** **2.3.P.2.1.1 Drug Substance** **2.3.P.2.1.2 Excipients** **2.3.P.2.2 Drug Product** **2.3.P.2.3 Manufacturing Process Development** **2.3.P.2.4 Container Closure System** **2.3.P.3 Manufacture** **2.3.P.4 Control of Excipients** **2.3.P.5 Control of Drug Product** **2.3.P.6 Reference Standards or Materials** **2.3.P.7 Container Closure System** **2.3.P.8 Stability**	☒
2.7	**Clinical Summary (Bioequivalence)** **Model Bioequivalence Data Summary Tables** **E-Submission: PDF** **Word Processed e.g., MS Word** **2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1 Background and Overview** Table 1. Submission Summary Table 4. Bioanalytical Method Validation Table 6. Formulation Data **2.7.1.2 Summary of Results of Individual Studies** Table 5. Summary of In Vitro Dissolution **2.7.1.3 Comparison and Analyses of Results Across Studies** Table 2. Summary of Bioavailability (BA) Studies Table 3. Statistical Summary of the Comparative BA Data **2.7.1.4 Appendix** **2.7.4.1.3 Demographic and Other Characteristics of Study Population** Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study **2.7.4.2.1.1 Common Adverse Events** Table 8. Incidence of Adverse Events in Individual Studies	☐

MODULE 3

3.2.S DRUG SUBSTANCE ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1 Nomenclature** **3.2.S.1.2 Structure** **3.2.S.1.3 General Properties**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Name and Full Address(es)of the Facility(ies) *2. Please provide the exact addresses, contact names, telephone and fax numbers for the 2 API suppliers* [redacted] (b) (4) *Adequate for filing per 10/6/2010 correspondence* 2. Function or Responsibility 3. Type II DMF number for API 4. CFN or FEI numbers	☒
3.2.S.3	**Characterization Reference to DMF**	☒
3.2.S.4	**Control of Drug Substance (Active Pharmaceutical Ingredient)** **3.2.S.4.1 Specification** submitted **3.2.S.4.2 Analytical Procedures** Reference to DMF **3.2.S.4.3 Validation of Analytical Procedures** Reference to DMF 1. Spectra and chromatograms for reference standards and test samples 2. Samples-Statement of Availability and Identification of: a. Drug Substance submitted b. Same lot number(s) **3.2.S.4.4 Batch Analysis** 1. COA(s) specifications and test results from drug substance mfgr(s) (note expiration date is one month on the supplier COA) [redacted] (b) (4) Batches Sr82-031610, Sr82-0040510, and Sr82-052110 [redacted] (b) (4) Batch 09-12-1-39-Sr82 COAs submitted for the API does not match the lot numbers listed in the EBR. 2. Applicant certificate of analysis submitted Reception Numbers R13670(Sr82-031610), R13735(Sr82-0040510), R13781(Sr82-052110) No receipt COA submitted for the [redacted] (b) (4) API **3.2.S.4.5 Justification of Specification** Reference to DMF	☒
3.2.S.5	**Reference Standards or Materials** *4. In section 3.2.S.5 please provide information on the reference standards for the API material SR-82* *Adequate for filing per 10/6/2010 correspondence*	☒
3.2.S.6	**Container Closure Systems Reference to DMF**	☒
3.2.S.7	**Stability Reference to DMF**	☒

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1 Description and Composition of the Drug Product ☒

1. Unit composition

Sponsor provided list of components used in the manufacture of the generator. The end product eluted from the generator is ^{82}Rubidium Chloride Injection in 0.9% sodium chloride solution.

2. Inactive ingredients and amounts are appropriate per IIG

Not applicable as there are no "generator" product types in IIG

Table P.1 – 1: List of components of the dosage form, their function, reference to quality standard, and amount on per-unit basis

Ingredients	Ingredient function	Quality Standard	Quantity per generator
$^{82}SrCl_2$	Starting Material	House	(b) (4)
(b) (4) Stannic Acid	Adsorbent	House	
Sodium Chloride	(b) (4)	USP / Ph. Eur.	
			(b) (4)

* At calibration time

3.2.P.2 Pharmaceutical Development ☒

Pharmaceutical Development Report submitted

3.2.P.3 Manufacture ☒

3.2.P.3.1 Manufacture(s) (Finished Dosage Manufacturer and Outside Contract Testing Laboratories)

1. Name and Full Address(es)of the Facility(ies) submitted
2. CGMP Certification: YES
3. Function or Responsibility submitted
4. CFN or FEI numbers

5. Please provide the contact name, telephone and fax number for the drug product manufacturing and for all testing facilities cited in module 3.2.P.3

Adequate for filing per 10/6/2010 correspondence

3.2.P.3.2 Batch Formula

Maximum batch size: (b) (4) generators

3.2.P.3.3 Description of Manufacturing Process and Process Controls

1. Description of the Manufacturing Process submitted
2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified submitted
3. If sterile product: Aseptic fill / Terminal sterilization
4. Reprocessing Statement

6. Please provide a reprocessing statement citing 21 CFR 211.115 should you intend to reprocess any batches that does not conform to specifications.

Adequate for filing per 10/6/2010 correspondence

3.2.P.3.4 Controls of Critical Steps and Intermediates submitted

3.2.P.3.5 Process Validation and/or Evaluation

1. Microbiological sterilization validation submitted
2. Filter validation (if aseptic fill)

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified submitted The components of the generator are not considered inactive ingredients. Per 21 CFR 201.10 the term ingredient applies to any substance in the drug. Since the components of the generator are not present in the drug, they are not considered ingredients and by extension, inactive ingredients. Nevertheless the sponsor has submitted release and receipt COAs for the generator components. **3.2.P.4.1 Specifications** 1. Testing specifications (including identification and characterization) 2. Suppliers' COA (specifications and test results) submitted **3.2.P.4.2 Analytical Procedures** **3.2.P.4.3 Validation of Analytical Procedures** **3.2.P.4.4 Justification of Specifications** Applicant COA submitted	☒

MODULE 3
3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1 Specification(s)** submitted for the eluate **3.2.P.5.2 Analytical Procedures** submitted **3.2.P.5.3 Validation of Analytical Procedures** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form submitted 2. Same lot numbers **3.2.P.5.4 Batch Analysis** Certificate of Analysis for Finished Dosage Form submitted (b) (4) **3.2.P.5.5 Characterization of Impurities submitted** **3.2.P.5.6 Justification of Specifications submitted**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted 3. Packaging Configuration and Sizes 4. Container/Closure Testing submitted 5. Source of supply and suppliers address submitted	☒
3.2.P.8	**3.2.P.8.1 Stability (Finished Dosage Form)** 1. Stability Protocol submitted submitted 2. Expiration Dating Period 60 days from first date of manufacture for the generator **3.2.P.8.2 Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments submitted **3.2.P.8.3 Stability Data** 1. 3 month accelerated stability data no - done under storage conditions for 60 days 2. Batch numbers on stability records the same as the test batch **yes**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S Executed Batch Records for drug substance (if available)** **3.2.R.2.S Comparability Protocols** **3.2.R.3.S Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) Batch Reconciliation and Label Reconciliation submitted Theoretical Yield (b) (4) generators Actual Yield (b) (4) generators Packaged Yield (b) (4) *7. You have provided API COAs from and from (b) (4) However according to your executed batch records for finished product Batches (b) (4) the following API batches were used: API batch (b) (4) These batch numbers found in the EBR compared to your submitted API COA batch numbers are different. Please reconcile this discrepancy.* *Adequate for filing per 10/6/2010 correspondence* *8. You have failed to submit a receipt COA for the API batch (b) (4)* *Adequate for filing per 10/6/2010 correspondence* *9. You have submitted drug product COAs and stability data for (b) (4) ; however, you have only submitted EBR for (b) (4) You should explain this disconnect.* *Adequate for filing per 10/6/2010 correspondence* **3.2.R.1.P.2 Information on Components** **3.2.R.2.P Comparability Protocols** **3.2.R.3.P Methods Validation Package** Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5

CLINICAL STUDY REPORTS

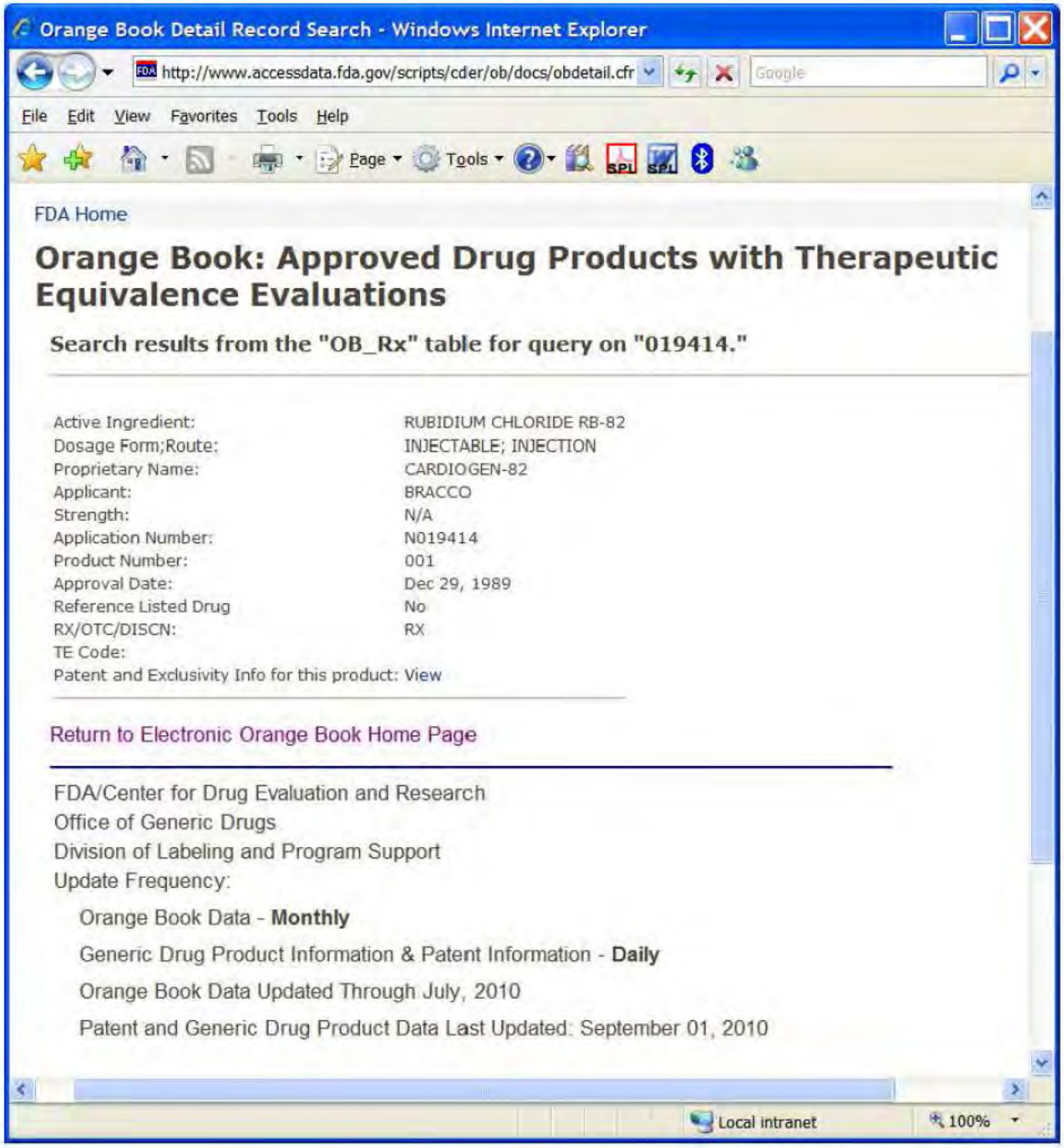
ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐

5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)	☐
	5.3.1.2 Comparative BA/BE Study Reports 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. Summary Bioequivalence tables: Table 10. Study Information Table 12. Dropout Information Table 13. Protocol Deviations **5.3.1.3** **In Vitro-In-Vivo Correlation Study Reports** 1. Summary Bioequivalence tables: Table 11. Product Information Table 16. Composition of Meal Used in Fed Bioequivalence Study **5.3.1.4** **Reports of Bioanalytical and Analytical Methods for Human Studies** 1. Summary Bioequivalence table: Table 9. Reanalysis of Study Samples Table 14. Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples **5.3.7** **Case Report Forms and Individual Patient Listing**	☐
5.4	**Literature References**	☐
	Possible Study Types:	
Study Type	**IN-VIVO BE STUDY(IES) with PK ENDPOINTS** (i.e., fasting/fed/sprinkle) NA 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution: NA	☐
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐

Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% of 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming)	☐
Study Type	**IN-VIVO BE STUDY(IES) with PD ENDPOINTS** (e.g., topical corticosteroid vasoconstrictor studies) 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/19/2009


Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfr
File Edit View Favorites Tools Help
Page Tools
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Search results from the "OB_Rx" table for query on "019414."
Active Ingredient: RUBIDIUM CHLORIDE RB-82
Dosage Form;Route: INJECTABLE; INJECTION
Proprietary Name: CARDIOGEN-82
Applicant: BRACCO
Strength: N/A
Application Number: N019414
Product Number: 001
Approval Date: Dec 29, 1989
Reference Listed Drug No
RX/OTC/DISCN: RX
TE Code:
Patent and Exclusivity Info for this product: View
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through July, 2010
Patent and Generic Drug Product Data Last Updated: September 01, 2010
Local intranet
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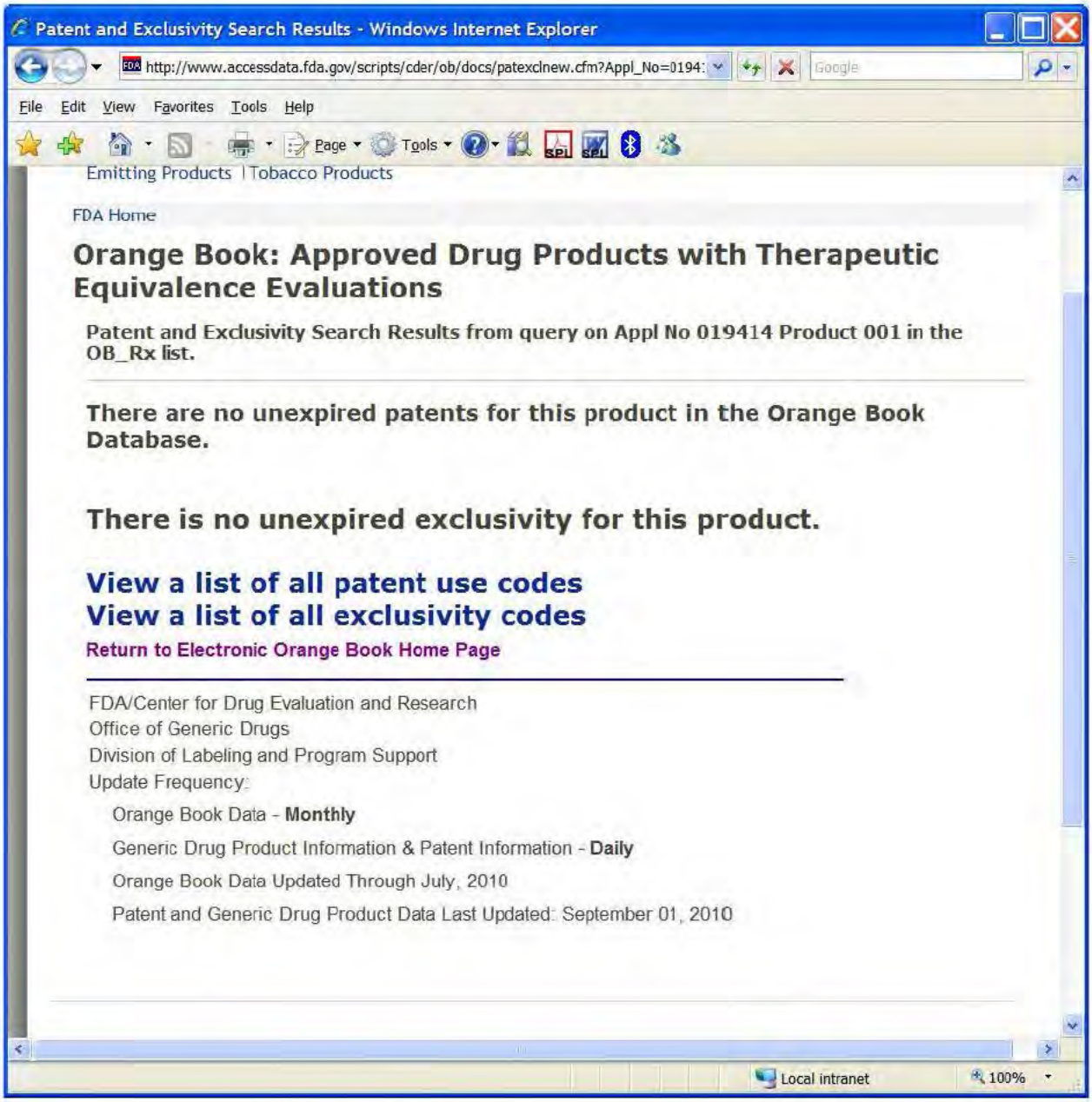
Patent and Exclusivity Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=0194:
File Edit View Favorites Tools Help
Page Tools
Emitting Products | Tobacco Products
FDA Home
Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations
Patent and Exclusivity Search Results from query on Appl No 019414 Product 001 in the OB_Rx list.
There are no unexpired patents for this product in the Orange Book Database.
There is no unexpired exclusivity for this product.
View a list of all patent use codes
View a list of all exclusivity codes
Return to Electronic Orange Book Home Page
FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - Monthly
Generic Drug Product Information & Patent Information - Daily
Orange Book Data Updated Through July, 2010
Patent and Generic Drug Product Data Last Updated: September 01, 2010
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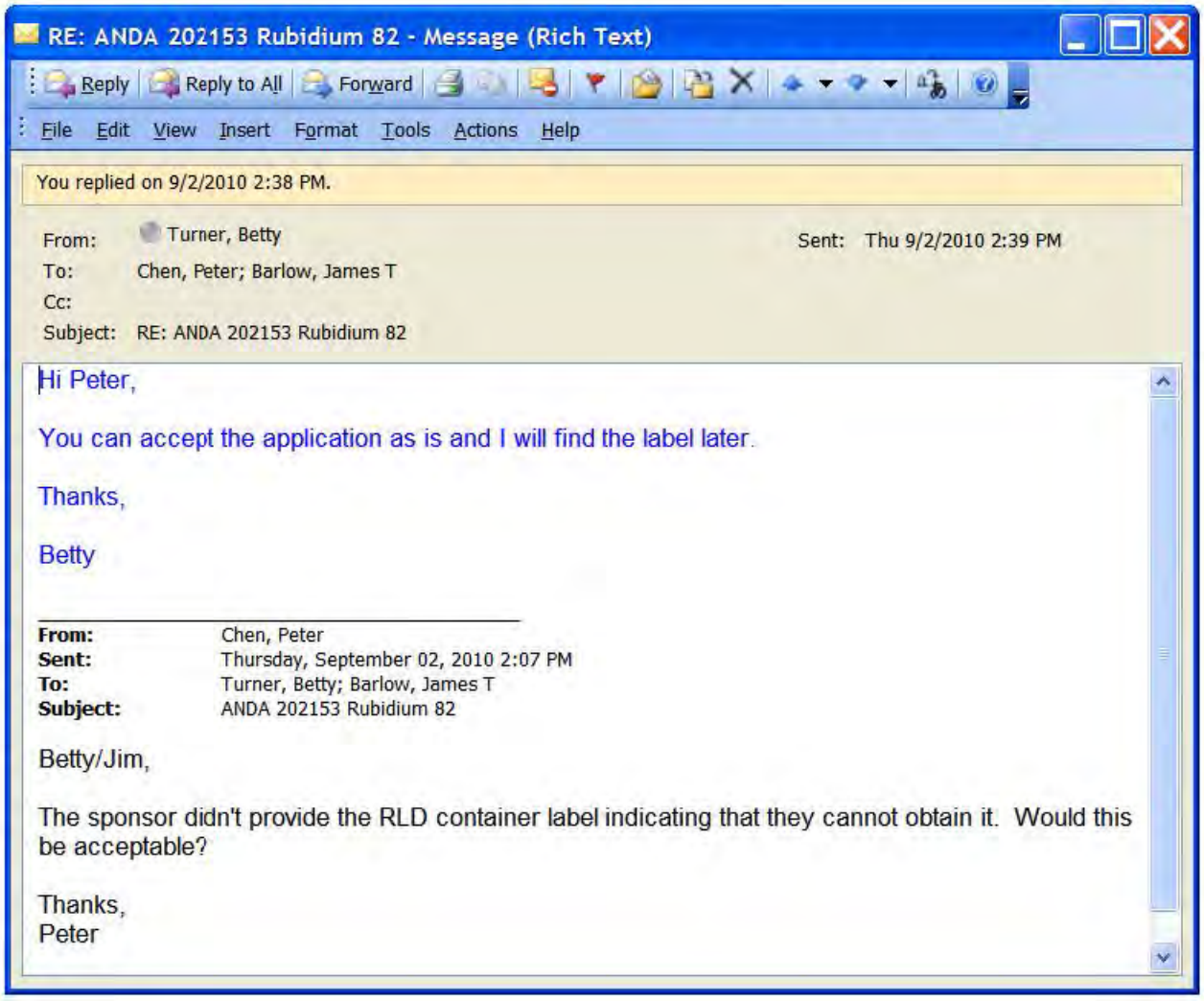


RE: ANDA 202153 Rubidium 82 - Message (Rich Text)

Reply | Reply to All | Forward

File Edit View Insert Format Tools Actions Help

You replied on 9/2/2010 2:38 PM.

From: Turner, Betty
Sent: Thu 9/2/2010 2:39 PM
To: Chen, Peter; Barlow, James T
Cc:
Subject: RE: ANDA 202153 Rubidium 82

Hi Peter,

You can accept the application as is and I will find the label later.

Thanks,

Betty

From: Chen, Peter
Sent: Thursday, September 02, 2010 2:07 PM
To: Turner, Betty; Barlow, James T
Subject: ANDA 202153 Rubidium 82

Betty/Jim,

The sponsor didn't provide the RLD container label indicating that they cannot obtain it. Would this be acceptable?

Thanks,
Peter

* * * COMMUNICATION RESULT REPORT (SEP 22 2010 2:03PM) * * *

FAX HEADER: CDER/OGD/DLPS

TRANSMITTED/STORED FILE MODE	SEP. 22. 2010 2:02PM OPTION	ADDRESS	RESULT	PAGE
099 MEMORY TX		913018383182	OK	2/2

REASON FOR ERROR
E-1) NO ANSWER E-2) BUSY E-3) NO FACSIMILE CONNECTION

FDA FAX

ANDA 202153

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855 (240-276-9327)

TO: Kendle Regulatory Affairs
U.S. Agent for Draximage
ATTN: Hari Nagaradona, Ph.D.

TEL: 301-296-1370
FAX: 301-838-3182

FROM: Peter Chen

TEL: 240-276-8977

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 Rb 82 Generator, Rubidium Chloride Rb 82 Injection, (b) (4) mCi.

Total Pages (2)

SPECIAL INSTRUCTIONS: Please respond to the items identified below within 10 business days. If response is not received within 10 days, the comments will be sent via letter. You can fax (240) 276-8974 or email (peter.chen@fda.hhs.gov) the initial response followed by an official copy to the ANDA. Your cover letter should clearly indicate Quality - Response to Information Request.

You have provided API COAs from (b) (4) and from (b) (4) However according to your executed batch records for finished product Batches (b) (4) the following API batches were used: API batch (b) (4) These batch numbers found in the EBR compared to your submitted API COA batch numbers are different. Please reconcile this discrepancy. Alternatively you may submit release and receipt COAs for the APIs used in the demonstration batches.

You have failed to submit a receipt COA for the API batch (b) (4)

You have submitted drug product COAs and stability data for (b) (4) however, you have only submitted EBR for (b) (4) (b) (4) You should explain this disconnect.

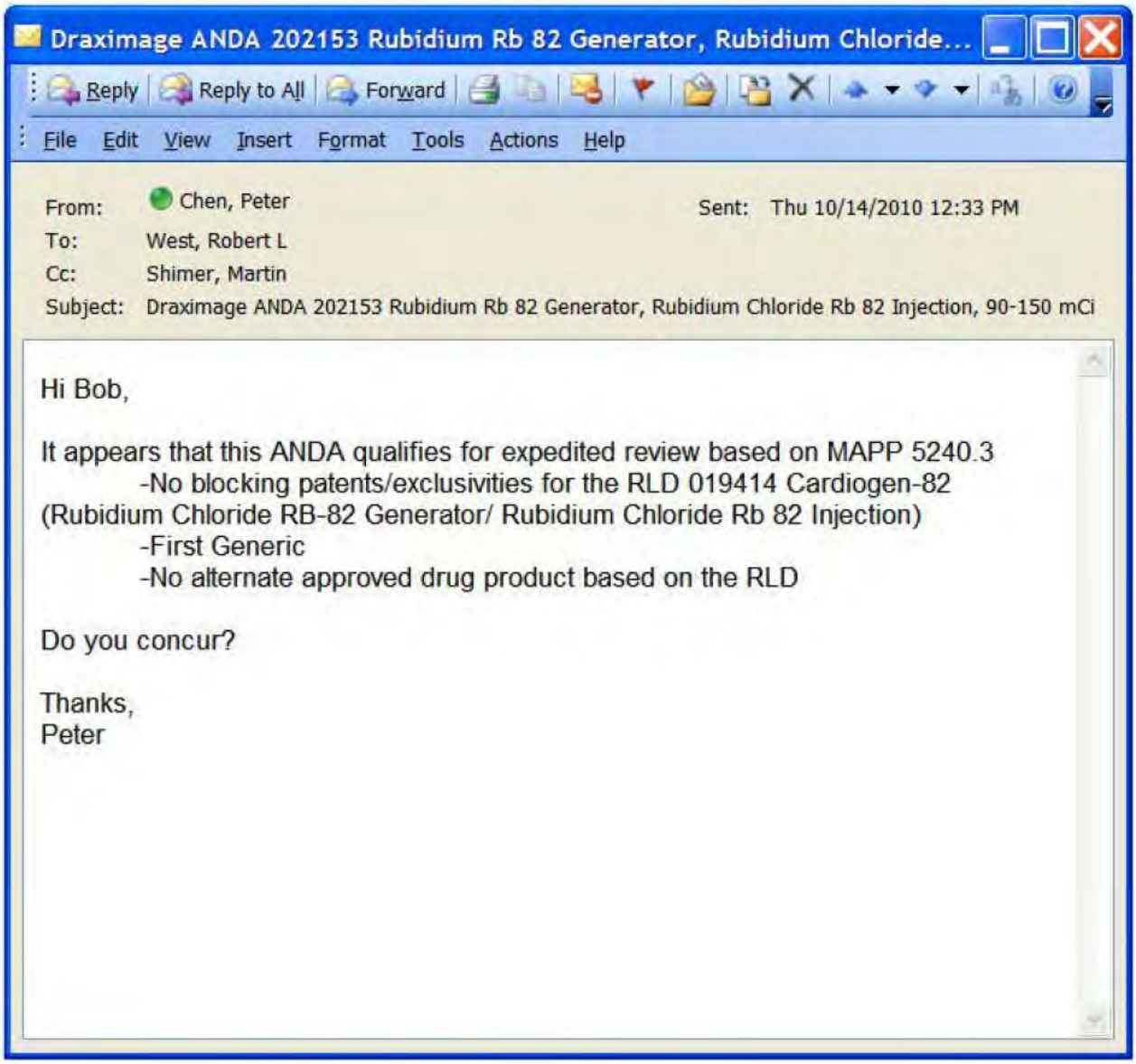
For the Environmental Impact Analysis Statement, please certify whether you have adhered to all Federal, State and Local environmental laws.

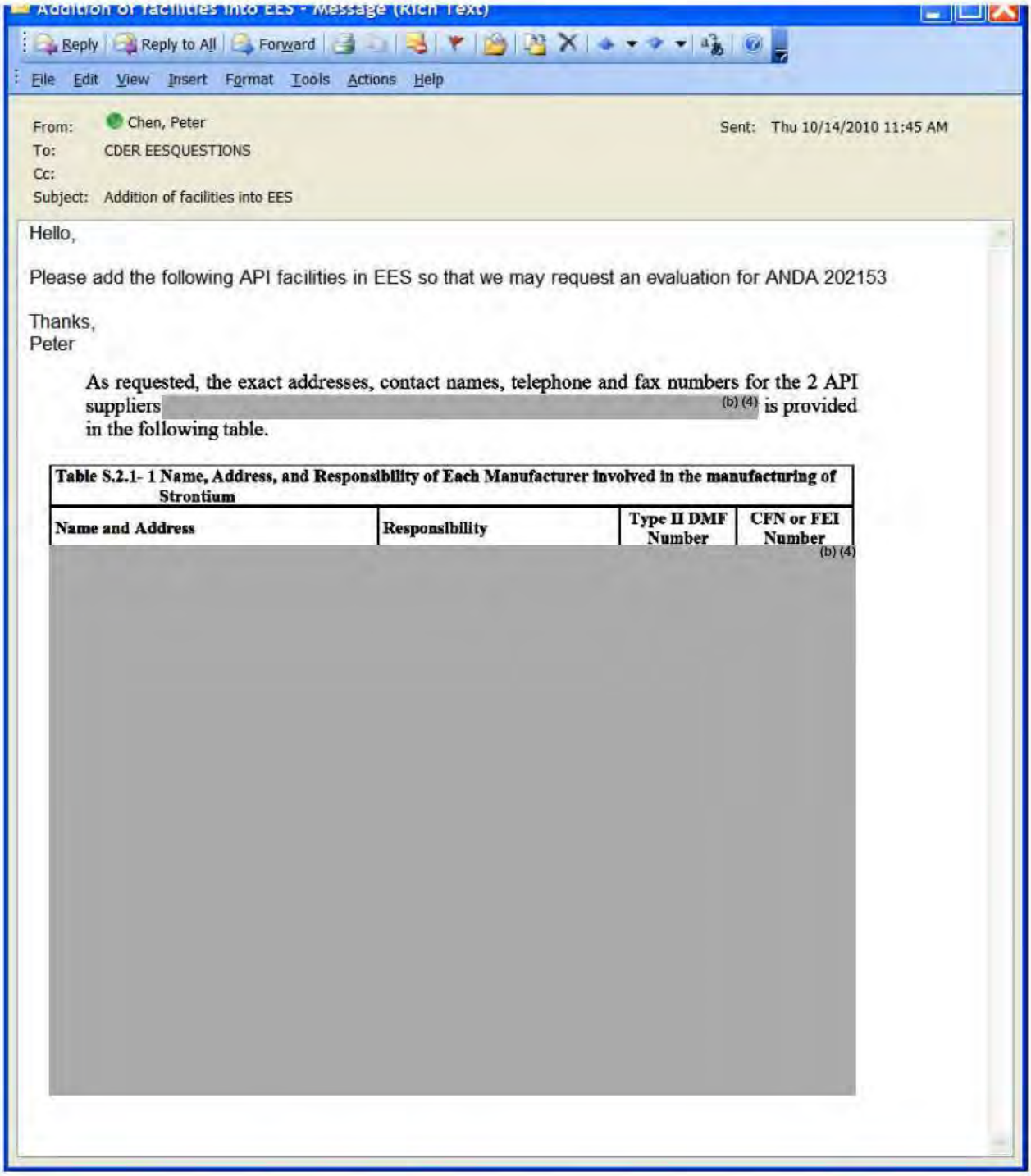
You should provide the exact addresses, contact names, telephone and fax numbers for the 2 API suppliers (b) (4)

In section 3.2.S.5 you should provide information on the reference standards for the API material SR-82 or justify why this section only refers to the DMF.

You should provide the contact name, telephone and fax number for the drug product manufacturing and for all testing facilities identified in module 3.2 P.3.

You should provide a reprocessing statement citing 21 CFR 211.115 should you intend to reprocess any batches that does not conform to specifications.


Draximage ANDA 202153 Rubidium Rb 82 Generator, Rubidium Chloride...
Reply
Reply to All
Forward
File Edit View Insert Format Tools Actions Help
From: Chen, Peter
Sent: Thu 10/14/2010 12:33 PM
To: West, Robert L
Cc: Shimer, Martin
Subject: Draximage ANDA 202153 Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection, 90-150 mCi
Hi Bob,
It appears that this ANDA qualifies for expedited review based on MAPP 5240.3
-No blocking patents/exclusivities for the RLD 019414 Cardiogen-82
(Rubidium Chloride RB-82 Generator/ Rubidium Chloride Rb 82 Injection)
-First Generic
-No alternate approved drug product based on the RLD
Do you concur?
Thanks,
Peter



Addition of facilities into EES - Message (Rich Text)

Reply | Reply to All | Forward

File Edit View Insert Format Tools Actions Help

From: Chen, Peter
Sent: Thu 10/14/2010 11:45 AM
To: CDER EESQUESTIONS
Cc:
Subject: Addition of facilities into EES

Hello,

Please add the following API facilities in EES so that we may request an evaluation for ANDA 202153

Thanks,
Peter

As requested, the exact addresses, contact names, telephone and fax numbers for the 2 API suppliers (b) (4) is provided in the following table.

Table S.2.1- 1 Name, Address, and Responsibility of Each Manufacturer involved in the manufacturing of Strontium

Name and Address	Responsibility	Type II DMF Number	CFN or FEI Number
(b) (4)			

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2010-0456**	
TO *(Division/Office)* DMIHP - HFD-160 Thru: Kim Miller, OODP HFD-106			FROM: Peter Chen OGD/DLPS	
DATE: 10/14/2010	IND NO.	ANDA NO. 202153	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 6/18/2010,
NAME OF DRUG Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Radiopharmaceutical	DESIRED COMPLETION DATE 12/13/2010
NAME OF FIRM Draximage				

REASON FOR REQUEST

I. GENERAL

✆ NEW PROTOCOL	✆ PRE NDA MEETING	✆ RESPONSE TO DEFICPENCY LETTER
✆ PROGRESS REPORT	✆ END OF PHASE II MEETING	✆ FINAL PRINTED LABELING
✆ NEW CORRESPONDENCE	✆ RESUBMISSION	✆ LABELING REVISION
✆ DRUG ADVERTISING	✆ SAFETY/EFFICACY	✆ ORIGINAL NEW CORRESPONDENCE
✆ ADVERSE REACTION REPORT	✆ PAPER NDA	✆ FORMULATIVE REVIEW
✆ MANUFACTURING CHANGE/ADDITION	✆ CONTROL SUPPLEMENT	X *OTHER ('specify below)*
✆ MEETING PLANNED BY _____		

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

DISSOLUTION	DEFICIENCY LETTER RESPONSE
PROTOCOL-- BIOPHARMACEUTICS	BIOAVAILABILITY STUDIES
IN--VIVO WAIVER REQUEST	PHASE IV STUDIES

IV.DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	_SUMMARY OF ADVERSE EXPERIENCE
CASE REPORTS OF SPECIFIC *REACTIONS(List below)*	POISON RISK ANALYSIS
COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

PETER CHEN
10/22/2010

MARTIN H Shimer
10/26/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION** **Consult No: 2010-0456**	
TO *(Division/Office)* DMIHP - HFD-160 Thru: Kim Miller, OODP HFD-106			FROM: Peter Chen OGD/DLPS	
DATE: 10/14/2010	IND NO.	ANDA NO. 202153	TYPE OF DOCUMENT Original	DATE OF DOCUMENT 6/18/2010,
NAME OF DRUG Rubidium Rb 82 Generator, Rubidium Chloride Rb 82 Injection		PRIORITY CONSIDERATION 60 days	CLASSIFICATION OF DRUG Radiopharmaceutical	DESIRED COMPLETION DATE 12/13/2010
NAME OF FIRM Draximage				

REASON FOR REQUEST

I. GENERAL

- ✆ NEW PROTOCOL
- ✆ PROGRESS REPORT
- ✆ NEW CORRESPONDENCE
- ✆ DRUG ADVERTISING
- ✆ ADVERSE REACTION REPORT
- ✆ MANUFACTURING CHANGE/ADDITION
- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
- ✆ PAPER NDA
- ✆ CONTROL SUPPLEMENT
- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
✆ TYPE A OR B NDA REVIEW ✆ END QF PHASE II MEETING ✆ CONTROLLED STUDI ES ✆ PROTOCOL REVIEW ✆ OTHER	✆ CHEMISTRY ✆ PHARMACOLOGY ✆ BIOPHARMACEUTICS ✆ OTHER

III.BIOPHARMACEUTICS

- DISSOLUTION
- PROTOCOL-- BIOPHARMACEUTICS
- IN--VIVO WAIVER REQUEST
- DEFICIENCY LETTER RESPONSE
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV.DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC *REACTIONS(List below)*
- COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- _SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

Please cc Trang Tran, HFD-617 (Trang.Tran@fda.hhs.gov) on the review when it is being checked into DARRTS. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DE LIVERY *(Check one)* MAIL HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

FORM FDA 3291 (7/83)

cc: ANDA
Drug File Folder

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

/s/

PETER CHEN
10/14/2010

TRANG Q TRAN
10/14/2010

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#

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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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: *(an action package is not required for SE8 or SE9 supplements)*
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)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ **No changes**
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: **September 20, 2016**

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.

Actions	
• Proposed action • User Fee Goal Date is **September 30, 2016**	☒ **AP** ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ 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
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(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 ⊥ 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)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ **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)*	☒ **Included**
• Original applicant-proposed labeling	☒ **Included**
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ **Included**
• Original applicant-proposed labeling	☒ **Included**
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ **Included**
❖ Proprietary Name • Acceptability/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 Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	**10/26/2010** ☐ 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 *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ 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) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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.) *(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)*	
❖ 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 *(indicate date of mtg)*	☐ N/A or no mtg **9/19/16**
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ **No mtg**
• EOP2 meeting *(indicate date of mtg)*	☒ **No mtg**
• Mid-cycle Communication *(indicate date of mtg)*	☒ **N/A**
• Late-cycle Meeting *(indicate date of mtg)*	☒ **N/A**
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None **TBD**
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None **TBD**
PMR/PMC Development Templates *(indicate total number)*	☒ 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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done **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 *Application Product Names* 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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
Kirlkland, 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

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

/s/

LOUIS R FLOWERS
03/16/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES
03/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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
Kirlkland, 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]
- JDI agreed but reviewed on the call [redacted]
- 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] 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]
- JDI acknowledged the Agency's rationale and agreed to submit the data to be collected [redacted]; 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]
- Based on the clarification provided by JDI, the Agency acknowledges its new understanding [redacted] but requested from JDI to consider providing the Agency with data from the Media Fill study [redacted] to support the sterility of the patient dose and to justify the exclusion of the [redacted] 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] 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] 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] JDI further agreed to include the data to be collected [redacted] in the response to the CRL.
- The Agency pointed [redacted] and requested JDI consider in its studies [redacted] that represent sources for microbial ingress to confirm the sterility of the patient doses during the 60 day use period of the system.

- 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.
- In response to the Agency's request for clarification on the data collected on day 63, JDI described the methodology proposed in Appendix 15:
  - JDI will collect samples from the clinical simulation study throughout the 60 days use period of the generator for sterility and bacterial endotoxins testing.
  - At day 60, the system will be filled with a growth media and samples will be eluted, collected and tested for any microbial growth.
  - 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'.
- 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
- 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

- JDI concurred with the Agency's comment and agreed to include a positive control in the study protocol.
- 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.
- The Agency agreed.

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

- 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) The four (4) sequences represent an artificial, worst case scenario as it is 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.

- 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.
- The Agency requested JDI to identify (b) (4) and to provide information on their performance specifications.
- 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

- **JDI summarized the meeting discussion and presented the actions items as follows:**
  - **Q1: Training Material**
    - The Agency agreed on the adequacy of the Training Material submitted in the Meeting Package.
  - **Q2: User Manual**
    - The IEC testing and reports (CSA) will be submitted in the response package to the CRL.
  - **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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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEXANDER GOROVETS
08/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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)

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Ramesh Raghavachari, Ph.D., DNDPII
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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
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(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 [redacted] (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 re-structuring 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* [redacted] (b) (4) *(see page 10, supplies);*
c. *Describe and label* [redacted] (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 [redacted] (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 [redacted] (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 [redacted] (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 [redacted] (b) (4) is acceptable. When you resubmit the NDA, please identify the applicable sections [redacted] (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 [redacted] (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:*

(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:

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** [redacted] **is not tested for integrity. The proposed system QC includes** [redacted] **Please consider** [redacted] **that would be required prior to patient administration. If this is not feasible, the NDA should contain an explanation** [redacted] **and a description of how the infection risk to patients** [redacted] **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:**

[redacted]

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** [redacted] **The design and performance** [redacted] **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)

[redacted] (b) (4)

- FDA questioned the rationale [redacted] (b) (4) The issue was also confirmed during testing.
- JDI further emphasized that there were no changes to the elution system [redacted] (b) (4)
- FDA agreed that focusing the new usability testing [redacted] (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 [redacted] (b) (4) FDA responded that the question was addressing both aspects.

JDI explained [redacted] (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) [redacted]

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®

(b) (4) [redacted]

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

Sterilization of all components:

(b) (4) [redacted]

Labeling and Training:

User training emphasizes on the need for use of aseptic techniques [redacted] (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 [redacted] (b) (4)
- FDA also mentioned that [redacted] (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 [redacted] (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 [redacted] (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 ([redacted] (b) (4) over 60 days)

JDI described [redacted] (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

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/s/

LIBERO L MARZELLA
04/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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
M. Abmel Xiques Castillo, Research Scientist, R&D
M. Étienne Lefort, Project Manager, Medical Device Development (by phone, if needed)
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 (TCONs) 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) 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. **<u>Description of Devices and Labeling Used and Training</u>**
   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. **<u>Description of User Tasks and Use-Related Risks Analysis</u>**
   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) (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:*

   a. *Unintended radiation exposure (patient and healthcare provider)*
   b. *Rubidium delivery error (overdose or underdose)*
   c. *Volume overload*
   d. *Embolus (air or particulate)*
   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.*

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

- [redacted] (b) (4) Process FMEAs
- [redacted] (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 [redacted] (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 [redacted] (b) (4) . A discussion [redacted] (b) (4)**

[redacted] 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. [redacted] The application should include a justification [redacted]

System performance and reliability

9) [redacted] *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. [redacted]

c. [redacted]

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 [redacted] 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 [redacted] performance.
- [redacted] The bench tests evaluate the following:

[redacted]

- Microbiological growth: JDI's approach to preventing microbiological growth is predominantly based on inherent safety by design. (b) (4) Design verification bench test data will demonstrate (b) (4)
- Note – The data which demonstrates (b) (4) ***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) **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,** (b) (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*** [redacted] (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*** [redacted] (b) (4) ***as a post-approval commitment?***

FDA Response to Question 17:

We will agree to review [redacted] (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 [redacted] as per the supplier specifications. All materials are also used in other medical devices. Additionally, the new [redacted] will be tested for leachables and extractables as well as chemical requirements as per ISO [redacted]. 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 [redacted] 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 [redacted] 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 [redacted] 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 [redacted] such as yours. The information in your subm surance that the risk of cross-contamination has been adequately mitigated by the design of your system and that the risk outweighed by the benefit [redacted] 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. [redacted]

The Design Verification tests described under question 9 – microbiological

growth above will demonstrate the performance [redacted] (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 [redacted] (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 [redacted] (b) (4) accessories are:

RUBY Rubidium Elution System™

[redacted] (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*** [redacted] (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). (b) (4) 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 (b) (4) (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 (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.

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
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 [redacted] (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) (b) (4) "Subsequent" users were explicitly trained 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 [redacted](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) [redacted](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) 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) 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
			(b) (4)
51			
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/

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) consists of the following:

(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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

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

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

EXHIBIT 21

RUBY RUBIDIUM ELUTION SYSTEM

USER MANUAL

RUBY RUBIDIUM ELUTION SYSTEM

TABLE OF CONTENTS

Manufacturer

Jubilant DraxImage Inc.
16751 Trans-Canada Highway
Kirkland, Québec
Canada H9H 4J4
(514) 630-7080

Jubilant DraxImage Customer Service

If needed, you may contact Jubilant DraxImage Customer Service at 1-888-633-5343.
16751 Trans-Canada Highway
Kirkland, Québec
Canada H9H 4J4

Pharmacovigilance

To report an adverse event, incident or serious patient emergency involving an administration of Rubidium Chloride Rb 82 Injection from the RUBY-FILL® Rubidium Rb 82 generator or the use of the RUBY Rubidium Elution System and its accessories, please refer to the contact information below:

Phone: 1-888-633-5343 or 514-630-7080 – choose option #1
Fax: 1-866-431-4288 or 514-694-3865
Email: Pharmacovigilance@jdi.jubl.com

1. SPECIFICATIONS AND UPS INFORMATION

Specifications

120 V Model Specifications

- Model Number: 500824
- Electrical Specifications: 120V
- Weight: 720 lbs (327.3 kg)
- Length: 27 Inches (68.6 cm)
- Width: 20 Inches (50.8 cm)
- Height: 65 Inches (165.1 cm)

230 V Model Specifications

- Model Number: 500831
- Electrical Specifications: 230V
- Weight: 720 lbs (327.3 kg)
- Length: 27 Inches (68.6 cm)
- Width: 20 Inches (50.8 cm)

- Height: 65 Inches (165.1 cm)

UPS Information

- Tripp Lite: Model #: HCRK

Environmental Conditions for Operation, Transport & Storage

Conditions for Operation:

- Temperature: 15 to 30°C
- Relative Humidity: 30 to 75%rH
- Atmospheric pressure: 70 to 106 kPa

Conditions for Transportation & Storage:

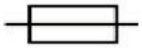
- Temperature: -20 to +65°C
- Relative Humidity: 10 to 90%rH
- Atmospheric pressure: 50 to 106 kPa

System Accuracy and Precision

Parameter	Range	Accuracy	Precision
Rb-82 Delivery Activity	370 – 2220 MBq (10mCi – 60mCi)	≤ 10%	≤ 10%
Delivery Volume	≤ 60 mL	≤ 6ml	≤ 10%
Infusion Time	10-120 seconds	≤ 30%	≤ 10%
Flow Rate	15-30 mL/min	≤ 10%	≤ 10%

1.1 SYMBOLS

MANUAL SYMBOLS	DESCRIPTION
	Warning
	Take Note

SYSTEM SYMBOLS	DESCRIPTION
	Radioactive Hazard Symbol
	Fuse
	Alternating Current
	Dangerous Voltage
	Serial Number
	Type BF Applied Part
	Non-ionizing Radiation
	Follow Instructions for Use
	Catalog (Model) Number
	Manufacturer
	Date of manufacture

	Use-by date
	Batch Code
	Sterilized Using Irradiation
	Do not resterilize
	Do not use if package is damaged
	Non-pyrogenic
	Do not re-use
	Latex Free
	DEHP Free

2. THE RUBY RUBIDIUM ELUTION SYSTEM

2.1 INDICATIONS AND CLINICAL USE

Intended Use:
The RUBY Rubidium Elution System is specifically designed for use with the RUBY-FILL® Rubidium Rb 82 Generator. The RUBY Rubidium Elution System is intended to accurately measure and automatically deliver doses of the radiodiagnostic agent ^{82}RbCl (Rubidium Chloride Rb 82 Injection) for use in cardiac positron emission tomography (PET) imaging.

The RUBY Rubidium Elution System should only be used by physicians and technologists with adequate training and experience in the safe use and handling of radionuclides, and with appropriate certifications from regional or national agencies.

Indications for Use:
The RUBY Rubidium Elution System is designed to be used only with RUBY-FILL® Rubidium Rb 82 Generator for the cardiac PET imaging of adults. Please refer to RUBY-FILL® Rubidium Rb 82 Generator labeling for further information on the indications and dosage recommendations.

2.2 SYSTEM DESCRIPTION

The RUBY Rubidium Elution System is a mobile cart that houses all of the components required for the infusion of Rubidium Chloride Rb 82 for Cardiac PET imaging. It is computer-controlled and allows for real-time monitoring of patient elutions.

The RUBY-FILL® Rubidium Rb 82 Generator provides an elution of Rubidium Chloride Rb 82 Injection which is indicated as an accessory to positron emission tomography (PET) imaging, for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease. Rubidium Chloride Rb 82 Injection can be used when the patient is at rest and/or under pharmacologic stress conditions.

The RUBY Rubidium Elution System uses an intuitive and informative touch screen. The computer controlled, integrated system architecture allows for real-time monitoring of patient infusions. In the event of hardware failure or significant discrepancy of measurements from expected values, the software automatically terminates the elution and display the appropriate error message.

During normal use, the RUBY Rubidium Elution System is positioned in close proximity to the PET camera and the patient is connected to the system via the RUBY IV LINE. The technologist is instructed to leave the room during an infusion and to monitor the patient during the scan.

Do not sit on the RUBY Rubidium Elution System or use the system to transport objects of any kind.

2.3 MAIN SYSTEM COMPONENTS

The main components of the RUBY Rubidium Elution System are (see Fig. 1, RUBY Rubidium Elution System, see Fig. 2, System Components):

1. Dose Calibrator
2. Waste Bottle
3. Pressure Transducer Holder and Connector
4. Pinch valves (four)
5. Photo Multiplier Tube (PMT)
6. Generator Well
7. Peristaltic Pump
8. Touch Screen Computer User Interface (not shown)
9. Removable Storage Compartment (not shown)

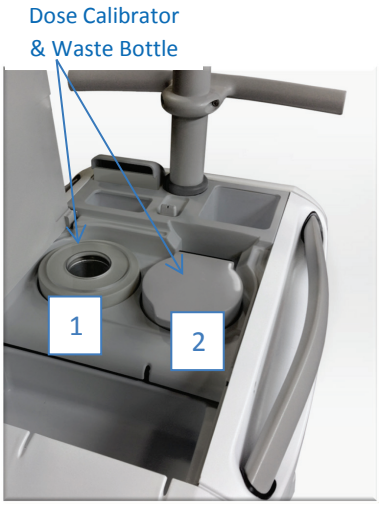


Figure 1, RUBY Rubidium Elution System

The following supplies are required for use with the RUBY Rubidium Elution System. These consumables are supplied by JDI:

1. RUBY SET
2. RUBY SALINE LINE
3. RUBY IV LINE
4. RUBY CONNECTORS
5. 50ml glass vials (with rubber stopper)
6. Sterile luer caps (male and female)
7. Printer Labels

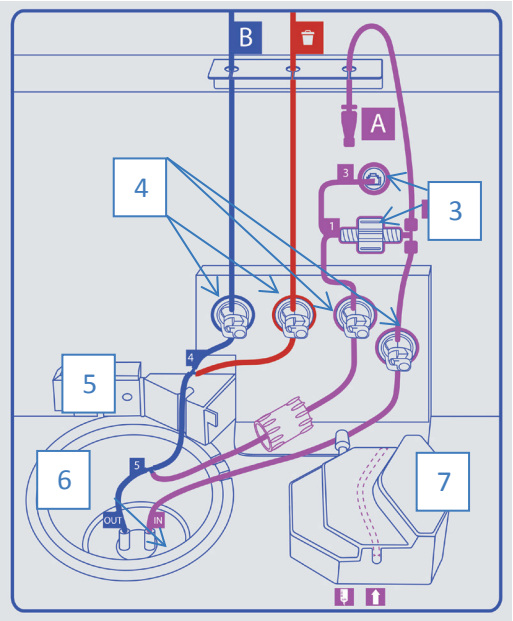


Figure 2, System Components (#3-#7)

The following supplies are also required for use with the RUBY Rubidium Elution System. They are not supplied by JDI and must be purchased separately:

- Sterile needles (20G, 1 inch)
- Sterile 70% isopropyl alcohol wipes
- 0.9% sodium chloride (additive free) injection, USP (bags 500mL or 1000ml)
- Clean gloves
- Disinfectant wipes or equivalent for general cleaning

RUBY SETS, RUBY SALINE LINES, RUBY IV LINES and RUBY CONNECTORS are customized to be used specifically with the RUBY Rubidium Elution System and must be purchased directly from JDI: 1-888-633-5343

3. SYSTEM CONSUMABLES

3.1 RUBY-FILL® RUBIDIUM RB 82 GENERATOR

The Generator always remains inside 1-inch-thick lead shielding. The handle must be removed before the lead cover can be removed. When the cover of the lead container is removed, only the fittings are exposed (see Fig. 3, Generator, Generator Handle & Lead Cover), which allows connection to the RUBY SET via the RUBY CONNECTORS. The Generator is a closed system and has Quick-Connect fittings which are plugged with metal caps for shipping (see Fig. 4, Generator Metal Caps). The inlet to the Generator is the male Quick-Connect and the outlet to the generator is the female Quick-Connect (see RUBY SET Installation, section 6.5). Once the Generator is expired there is no need to recap the Quick Connect fittings on the Generator with the metal caps.

Figure 3, Generator, Generator Handle & Lead Cover

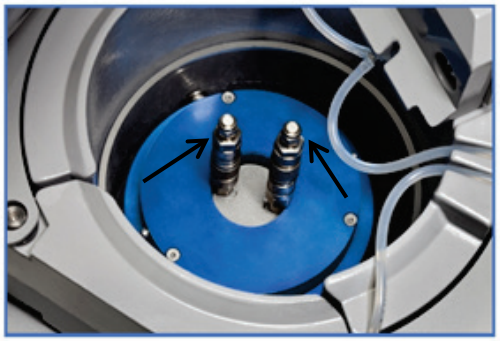


Figure 4, Generator Metal Caps

3.2 RUBY CONNECTORS

The RUBY CONNECTORS (See Fig. 5, RUBY CONNECTORS) link the RUBY SET to the RUBY FILL® Rubidium Rb 82 Generator. The RUBY CONNECTORS are provided sterile with each RUBY FILL® Rubidium Rb 82 Generator. These components mate exclusively with analogous fittings attached to the generator.

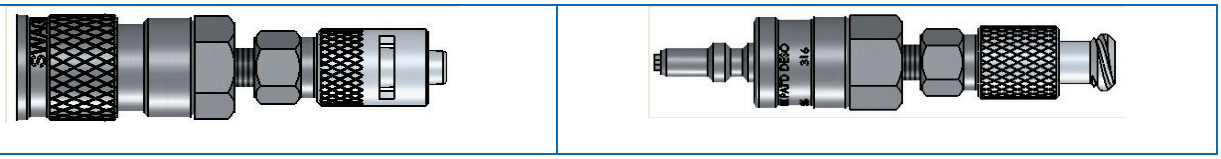


Figure 5, Female RUBY CONNECTOR, Male RUBY CONNECTOR

The RUBY Elution System contains a lithium iron magnesium phosphate battery for safe shut down of the System in a loss of power situation.

3.3 RUBY TUBING SETS

The RUBY SET is a custom-designed tubing set that is installed by the user into the RUBY Rubidium Elution System with each new Generator. The RUBY SET has two important features: an integrated pressure transducer and a flow regulator (RUBY SET Installation, section 6.5)

The pressure transducer monitors the pressure inside the RUBY SET to stop the elution in case of a restriction or poor connection (indicated by a High or Low Pressure Error).

The flow regulator provides a restriction to flow that mimics the restriction that the Generator presents to flow. This allows certain setup activities to be completed without eluting the Generator. The Flow Regulator is set to 250 mL/hr and must sit outside of the Generator Well (RUBY SET Installation, section 6.5).

3.4 SALINE BAGS, RUBY SALINE LINES, RUBY IV LINES

A bag of sterile 0.9% sodium chloride (additive free) injection, USP bag is installed by the user on the elution system to elute the generator. The saline bag hangs from a specially designed hook behind the computer screen (see Fig. 6, Saline Hook).

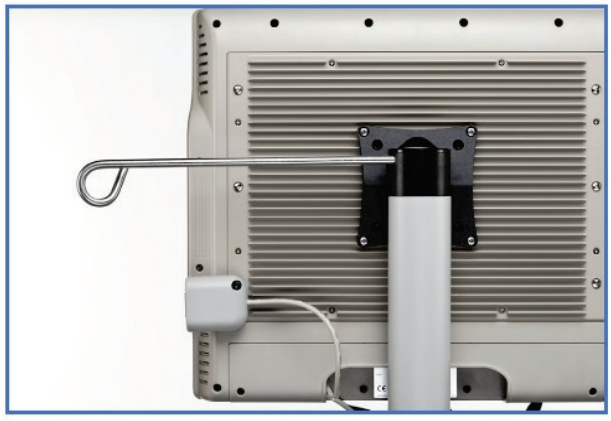


Figure 6, Saline Hook

The RUBY SALINE LINE connects the saline bag to the RUBY SET. The RUBY SALINE LINE is installed by the user through the pump in the elution system and is aseptically connected to the ‘’A’’ end of the RUBY SET via a luer-lock connection (RUBY SALINE LINE Installation, section 6.7).

The RUBY SET terminates with a Luer-Lock fitting, ‘’B’’ where the RUBY IV LINE is connected. An important feature of the RUBY IV LINE is an integrated 0.22 micron vented filter for increased patient safety (RUBY IV LINE Installation, section 6.8)

3.5 REMOVAL OF USED CONSUMABLES AND LIQUID WASTE

The RUBY SET may only be used up to its expiry (limit) date and must be discarded with the generator. The RUBY SALINE LINE must be changed daily with use of the elution system, and with each new saline supply. The RUBY IV LINE must be changed for every patient. All consumables must be removed and discarded with the removal of an expired generator. Since rubidium-82 has a very short half-life (76 seconds), the consumable items should not be radioactive, but it is important to survey each component according to local regulations before discarding since they may have become contaminated with strontium (Sr-82 or Sr-85).

Figure 7, Waste Bottle in Waste Well

Every quality control procedure and patient infusion creates liquid waste (located in either the shielded Waste Container and/or in the calibration vial). This radioactive solution must be discarded according to local regulations. Failure to empty the waste daily could cause the Waste Bottle to overflow into the Waste Well (see Fig. 7, Waste Bottle in Waste Well). If this occurs, remove the Waste Well liner and clean the Waste Well per site-specific procedures. Please consult your site's radiation safety officer (RSO).

4. PRECAUTIONS AND WARNINGS

4.1 USE ONLY WITH APPROVED RADIOPHARMACEUTICALS

The RUBY Rubidium Elution System is designed to operate solely with the RUBY-FILL® Rb 82 Generator, the custom RUBY tubing sets (RUBY SET, RUBY SALINE LINE & RUBY IV LINE) and RUBY CONNECTORS. Do not use any other type of radiopharmaceuticals or accessories. Only licensed and trained personnel should operate the RUBY Rubidium Elution System. Jubilant DraxImage Inc. provides training to all users upon installation.

4.2 AIR EMBOLISM

Air embolism may lead to a serious patient adverse event, including death. Although the system is designed to prevent delivery of air to a patient, the user must be diligent to avoid the introduction of air to the patient during infusion and causing an air embolism. The RUBY IV LINE must be primed prior to patient connection and the line must be visually inspected by the user for the presence of air bubbles prior to patient infusion.

4.3 ASEPTIC TECHNIQUES

Rubidium Chloride Rb 82 Injection is intended to be delivered to patients intravenously and therefore meticulous aseptic technique is required to minimize risks of patient infection or sepsis. The user must be digilent to adhere to strict aseptic technique to ensure patient safety. When making any new connections while installing new RUBY SET and other tubing sets, the user must ensure to not touch any non-sterile surface after the plastic caps have been removed. Particular care shall be made for connecting needleless injection ports (NIP). The following steps must be adhered to at all times while handling and installing the RUBY SET and other tubing sets and consumables.

1. Perform hand hygiene with an anti-microbial soap.
2. Put on clean gloves. Ensure gloves are in good condition (no tears or holes). Disinfect gloves by dispensing a small amount of sterile 70% isopropyl alcohol in gloved hands and rub gloved hands together until dry.
3. Tear the top portion of a sterile, 70% isopropyl alcohol wipe packaging to expose the edge of the wipe and pull the wipe out of the package.
4. Grasp the needleless injection port in your non-dominant hand.
5. With your dominant hand, use the wipe to vigorously scrub the threads and septum of the needleless injection port, being sure to touch only one side of the wipe with your gloved hand.
6. Twist the wipe over the needleless injection port threads in a clockwise-counterclockwise direction several times. Scrub the septum with friction on the top of the needleless injection port, making sure to clean in all crevices.
7. Alternate between twisting the wipe on the threads and scrubbing the septum for at least 15 seconds, covering each area several seconds at a time.
8. Keep the needleless injection port in your non-dominant hand and let it air-dry (~30s) before accessing it with its sterile mate.
9. Avoid touching any critical parts of the connections once they have been disinfected.
10. Each and every time you access a needleless injection port, perform a new 15-second scrub following the same steps.

Use alcohol wipes immediately after the package is opened

Discard alcohol wipes after use. Do not reuse wipes.

Use a new alcohol wipe for each needleless injection port (NIP)

4.4 MOVING AND POSITIONING THE RUBY ELUTION SYSTEM

To transport the RUBY Rubidium Elution System, the user should close all covers and doors and rotate the PC monitor so that it does not impede line of sight. The RUBY Rubidium Elution System is equipped with three handles (2 side handles and one back handle) to maneuver the system as required. The RUBY Rubidium Elution System should not be lifted.

The user must take care in moving the RUBY Rubidium Elution System, as it is heavy. The system must be moved by 2 persons. When moving the elution system, ensure that no body parts, for example, feet or fingers, will be crushed or trapped by the castors.

If the system is moved from one location to another, wait several minutes after re-plugging the elution system into a power outlet for dose calibrator stabilization prior to use.

4.5 HANDLING OF RADIOACTIVE MATERIALS

The RUBY-FILL® Rubidium Rb 82 Generator is loaded with an activity of 3145 – 4255 MBq (85 – 115 mCi) of strontium-82, (Sr-82) which is always accompanied by some amounts of the by-product, Sr-85. The strontium-82 decays and generates rubidium (Rb-82). It is important that all personnel be familiar with the isotopes involved and the decontamination procedures of radioactive materials. Please refer to the Material Safety Data Sheet (MSDS) for the RUBY-FILL® Rubidium Rb 82 Generator for complete information. All interactions with the RUBY Rubidium Elution System should be conducted using As Low As Reasonably Achievable (ALARA) principles.

4.6 EMERGENCY TERMINATION OF PROCEDURE

The RUBY Rubidium Elution System has an emergency **Stop** button on the computer monitor screen that is available at any time during any function (see Fig. 8, Emergency Stop Button). If sudden termination of a procedure is necessary, press **Stop** and the pump will halt and all pinch valves will close. The patient can then be disconnected safely from the elution system until the situation is resolved.

No modification of this equipment is allowed. The system including the RUBY-FILL® Rubidium Rb 82 Generator should only be used by authorized trained personnel and in accordance with its intended use.

Clicking on the RUBY logo takes the user to a tool that recalibrates the PC Monitor. Refer to the **Troubleshooting** section for additional information about this tool.

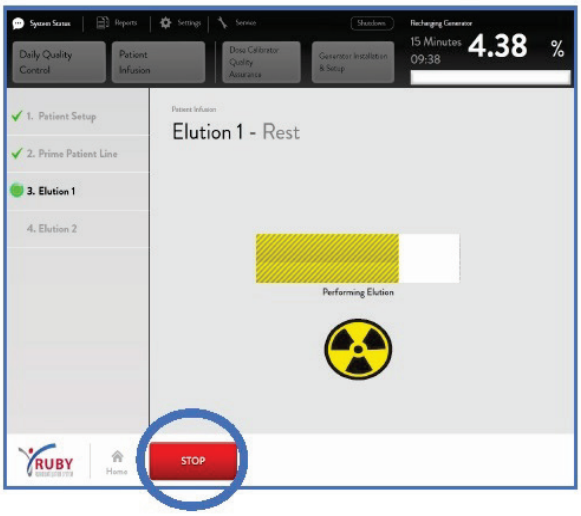


Figure 8, Emergency Stop Button

Decommissioning and disposal of the RUBY Rubidium Elution System should be completed in accordance with appropriate regulations and may require special handling or training. The system contains significant amount of lead in the shielding, which requires disposal as per local regulations. The battery may also require special handling for disposal as per local regulations.

5. SYSTEM BASICS

5.1 POWERING THE SYSTEM

After making sure the cord is connected securely into the RUBY Rubidium Elution System, plug the power cord into a wall outlet. Ensure the wall outlet has appropriate voltage for the RUBY Rubidium Elution System.

Perform these steps in sequence to boot up the computer:

1. Press the **Main On/Off Switch** at the back of the unit to the ON position. ON position is I and OFF position is O (see Fig. 9, Main On/Off Switch).

2.. Open the printer access door (see Fig. 10, Printer Access Door). Hold the **On/Off switch** (top button, Figure 11) until a beep sounds on the UPS control panel, which is located on the frame of the printer access door.

3. Check the lights on the UPS Control Panel inside the printer access door (see Fig. 11, UPS Control Panel). Four green lights indicate the system's battery is fully charged. The uppermost green light indicates that the UPS is powered on. Red lights indicate the battery needs charging before using the system.

4. Press and release the **Computer Power Switch** located at the base of the computer until you hear a small beep, which indicates it is powered on (see Fig. 12, Computer Power Switch).

Figure 9, Main On/Off Switch

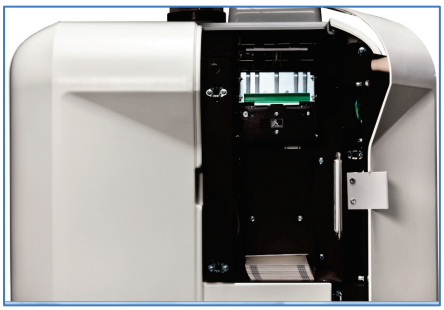


Figure 10, Printer Access Door

Figure 11, UPS Control Panel, On/Off Button circled

Figure 12, Computer Power Switch

The RUBY Rubidium Elution System should be positioned so that it is easy for the user to disconnect the device from the power supply if needed.

The computer monitor will not boot-up and run unless the battery is fully charged, and connected to a power outlet.

To avoid the risk of electric shock, this equipment must only be connected to a supply mains with protective earth. Do not connect into a power bar.

At this point the computer begins booting up, the RUBY Rubidium Elution System software automatically loads and the Initialization Screen appears, automatically followed by the Home Screen (see Fig. 13, Initialization Screen and Fig. 14, Home Screen).

The Home Screen displays information about the current Generator based on results from the Daily QC (Table 1, Information Available on the Homescreen). Most of this information is also available in the System Status Menu at any time. The System Status icon is located in the top left hand corner of the touchscreen monitor.

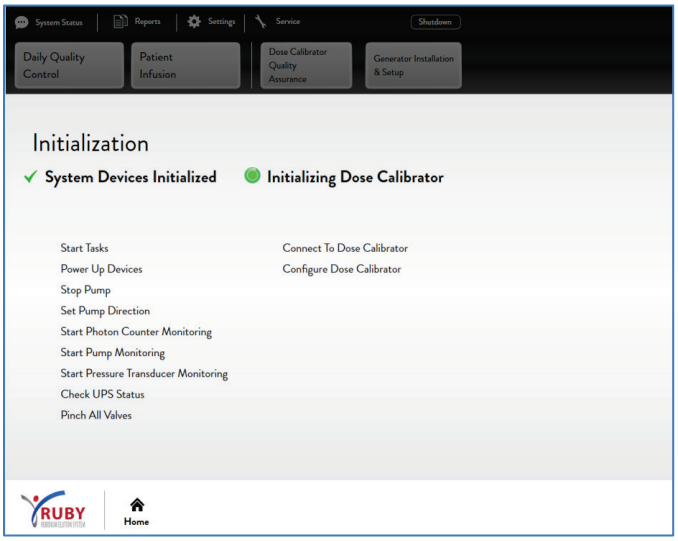


Figure 13, Initialization Screen

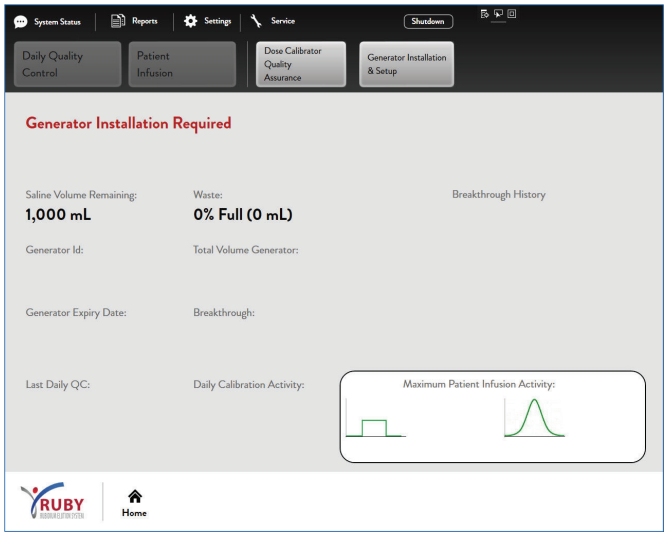


Figure 14, Home Screen

BATTERY - Only qualified service personnel should replace the battery

System Status	This field displays the elution system status. If the status is red, the patient infusion button is disabled. If it is green, the patient infusion button is enabled.
Saline Volume Remaining	Displays the calculated volume of saline in the bag. The System requires at least a 50mL buffer. If less than 50 mL, plus required volume for either daily QC or patient infusions remains, the System requests that the user change the saline bag before performing Daily QC or patient infusions.
Generator ID	Displays the current Generator ID. If no Generator is installed, this field is blank.
Generator Expiry Date	Shows the expiration date of the Generator.
Daily Calibration Activity	Displays Rb-82 activity measured during the last Daily QC.
Waste	Displays calculated volume of fluid in the waste container (maximum 1 L).
Total Volume Generator	Displays total volume eluted through the current Generator (maximum value is 30 L).
Breakthrough	Displays last breakthrough amount calculated in the last daily QC. This reflects the highest measured Sr-82 or Sr-85 value. Refer to the Daily QC section for additional information regarding the USP limits.
Last Daily QC	Shows the date and time of the last successful Daily QC. Daily QC must be repeated at least every 24 hours.
Breakthrough History	A line graph that shows the breakthrough trend and the USP limits for the current generator.
Maximum Patient Infusion Activity	Displays the maximum activity available for patient infusions. Indicates the value for Set Point activity deliveries (Constant Activity mode) or bolus deliveries (Constant Flow and Constant Time modes).

Table 1, Information available on the Homescreen

Information pertaining to the status of the RUBY Rubidium Elution System is available by selecting System Status on the touchscreen monitor at any time

5.2 SOFTWARE ICONS AND COLOR INDICATORS

The RUBY Rubidium Elution System is not equipped with a keyboard or mouse. All operations are

initiated using the Touch Screen. The task bar at the top of the Home Screen has nine buttons, described below, and the Shutdown Button (see Fig. 15, Task Bar and Operation Mode Buttons).

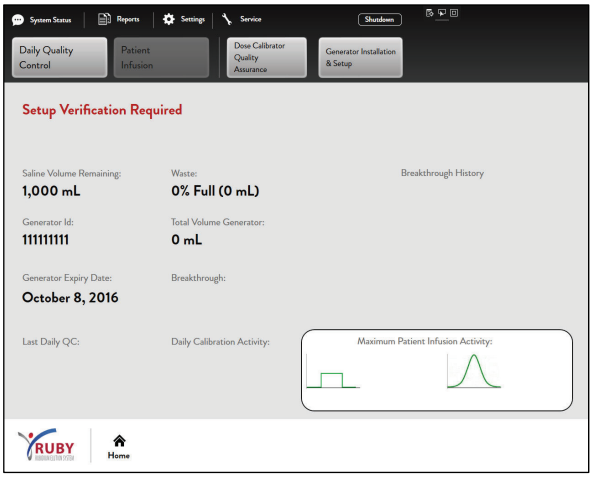


Figure 15, Task Bar and Operation Mode Buttons

The Top Row of the task bar has four access keys. They are:

1. **System Status (text bubble icon):** Displays the status of the system.
2. **Reports** (documents icon): Displays the reports page, allowing the user to consult each report or transfer files to the report application.
3. **Settings** (sprocket icon): Displays all the configurable parameters of the system.
4. **Service** (wrench icon): Accesses the service mode. This function is available only for Jubilant DraxImage Inc. personnel.

The second row of the task bar has four operation modes buttons that are used at different points in the generator life cycle:

1. **Daily Quality Control**: Used every day to perform mandatory checks on the generator and elution system. Refer to section Daily Quality Control, section 7.
2. **Patient Infusion**: Used every day to perform patient procedures. Refer to section Patient Infusions, section 8.
3. **Dose Calibrator Quality Assurance**: Used to perform quality control on the onboard dose calibrator. Refer to section Dose Calibrator Quality Assurance, section 6.1.
4. **Generator Installation & Setup**: Used when a new generator is installed and during Daily Quality Control. Refer to section Operating the System, section 6.3-6.8.