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 .

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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 [redacted (b) (4)]:

[redacted (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** [redacted (b) (4)]
3. **Recommend** [redacted (b) (4)] **60 mCi is the recommended maximum and weight-based dosing more accurately captures the lower range.**
4. **Recommend removing statement** [redacted (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)** [redacted] (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 [redacted] (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.** [redacted] (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.

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

/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.

APPENDIX C. HUMAN FACTORS STUDY

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)]. 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.

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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)

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/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

---

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 (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)

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: (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 (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.

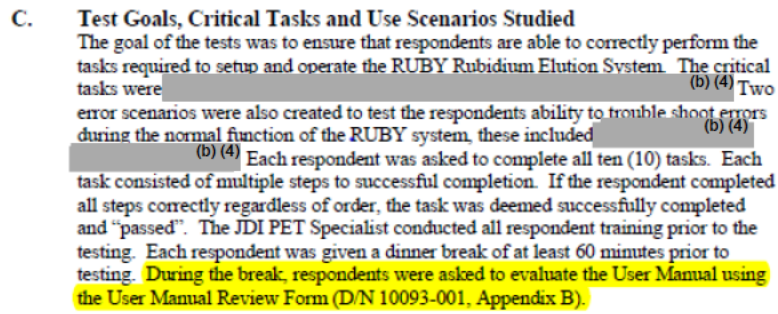
Task 2. (b) (4)			
Task Step	**Description of Step**	**User Completion**	**PASS/FAIL**
1	(b) (4)		
2			
3			
4			
5			
6			

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:

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;
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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

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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) [redacted] 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) [redacted] There are several granular steps that must be successfully completed (b) (4) [redacted] The sub-tasks were structured to initiate a workflow, including (b) (4) [redacted]

   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.

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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.

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[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).*

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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.

APPEARS THIS WAY ON ORIGINAL

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			

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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

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

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.

---

[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)

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/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 (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
- 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.

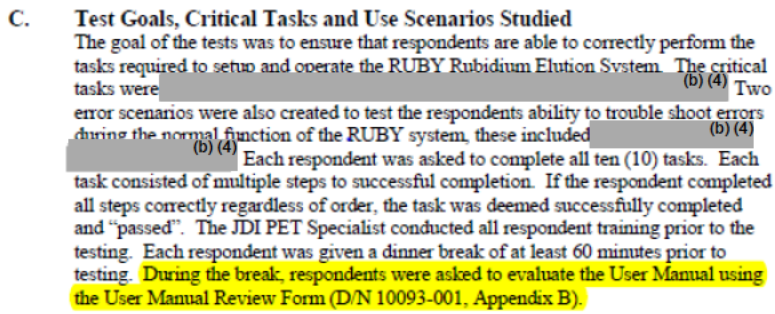
Task 2. (b) (4)			
Task Step	**Description of Step**	**User Completion**	**PASS/FAIL**
1	(b) (4)		
2			
3			
4			
5			
6			

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)

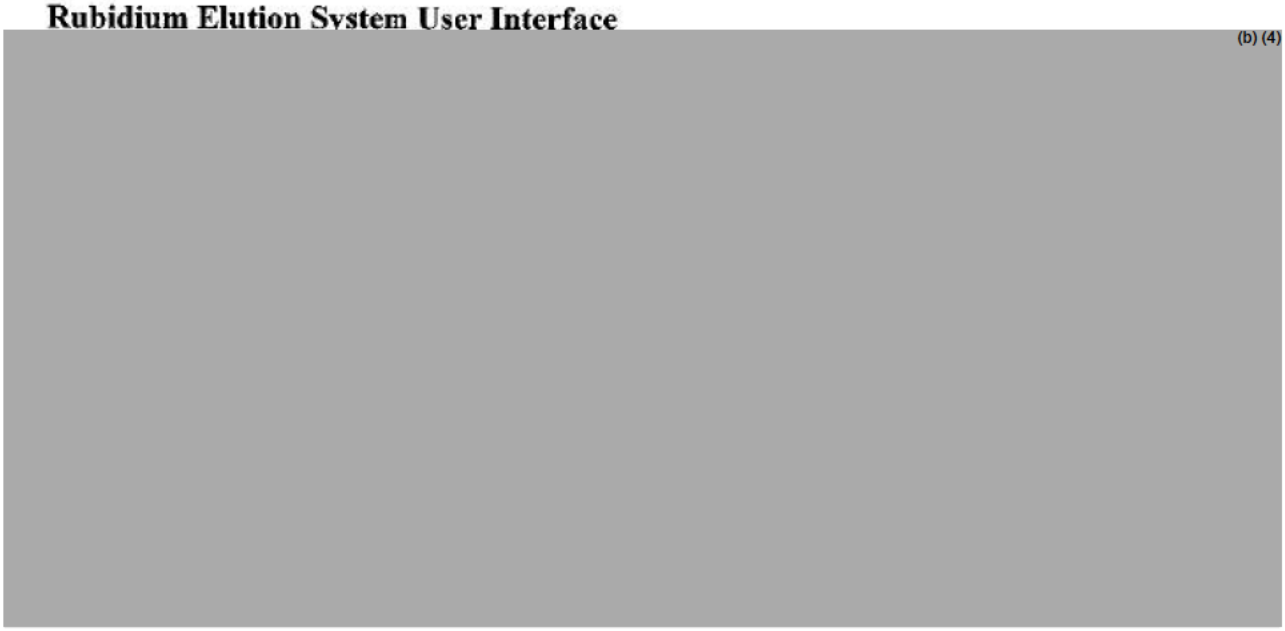
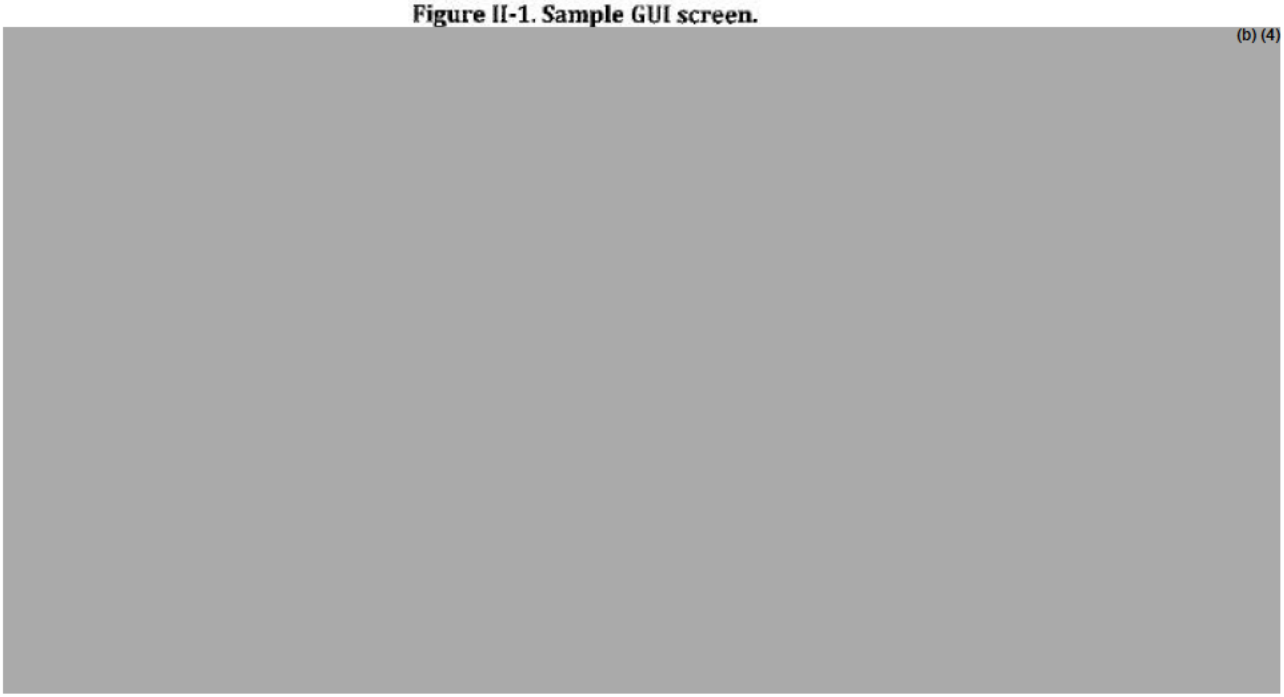


Figure II-1. Sample GUI screen.

(b) (4)



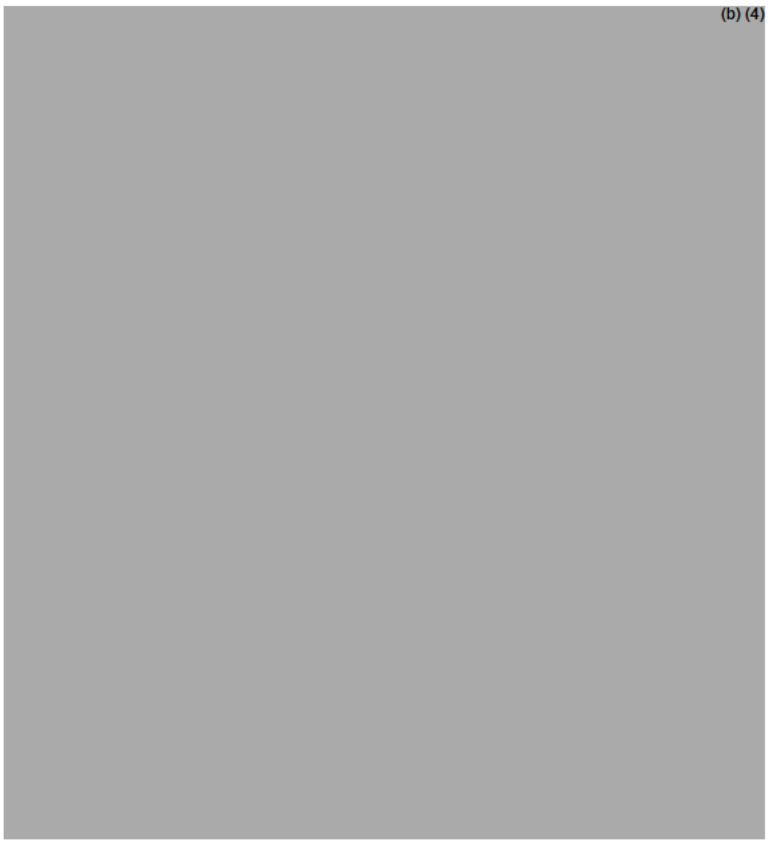


Figure II-2. RbES User Interface Overview.

(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 (b) (4)

Generator 2:

Test sample solution (sln 2A) was prepared (b) (4) . Test sample solution, (sln 2B) was prepared (b) (4)

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 (b) (4) 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 (b) (4) minute window was used after (b) (4) 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 (b) (4) 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:

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]% 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.

Deficiency in sponsor response 1 and 2:

[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

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

/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}

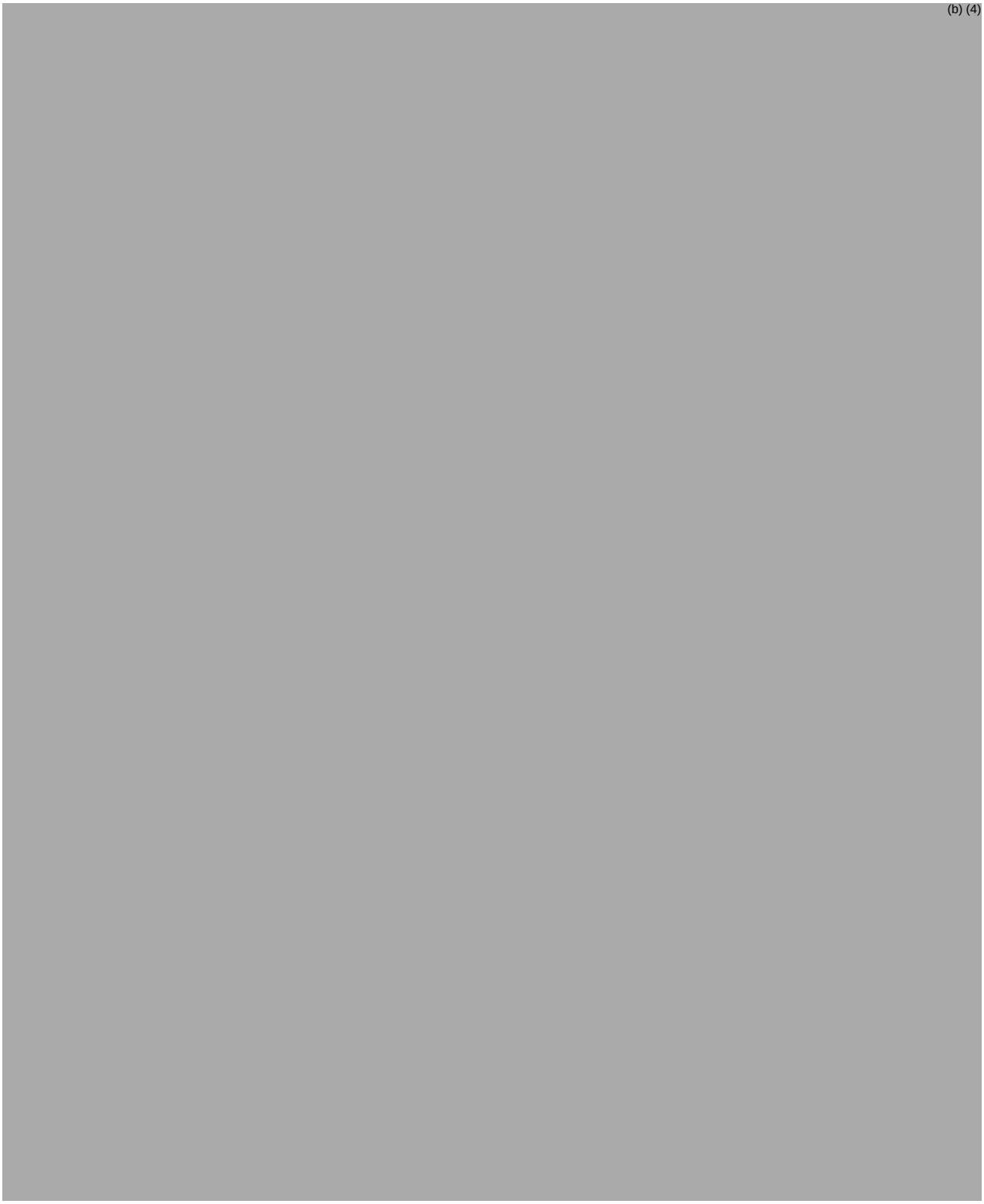
Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

(See Attachments)

NOTE TO THE CHEMIST:

FOR THE RECORD:

(b) (4)



(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)

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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)

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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	CODE NAME *(If any)*
Rubidium Rb 82 Generator	Ruby-Fill	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT 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
OGD

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 (a)(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
	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:

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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. (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.

MODULE 2
SUMMARIES ACCEPTABLE

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) (b) (4) *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.* *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

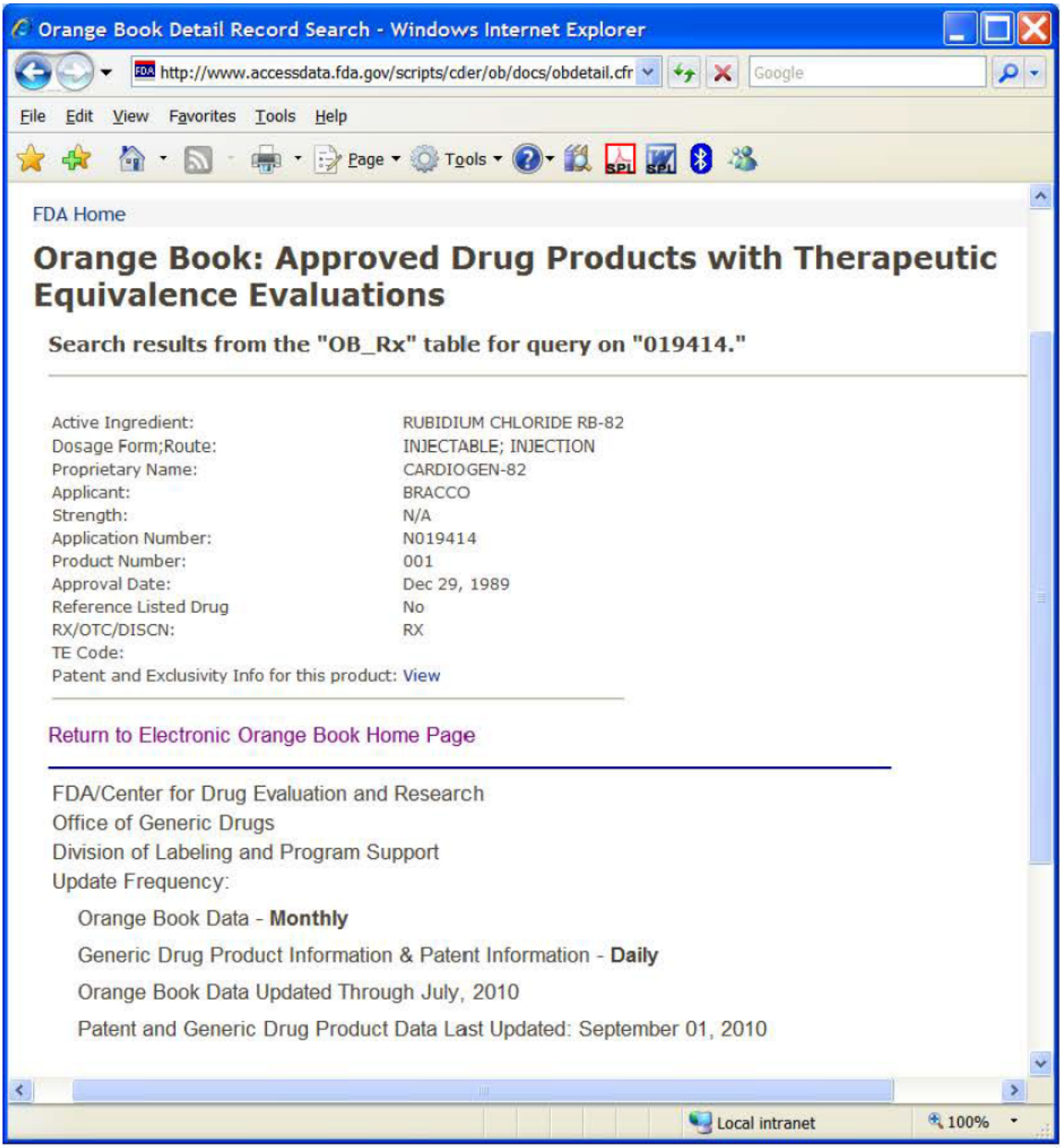
CLINICAL STUDY REPORTS

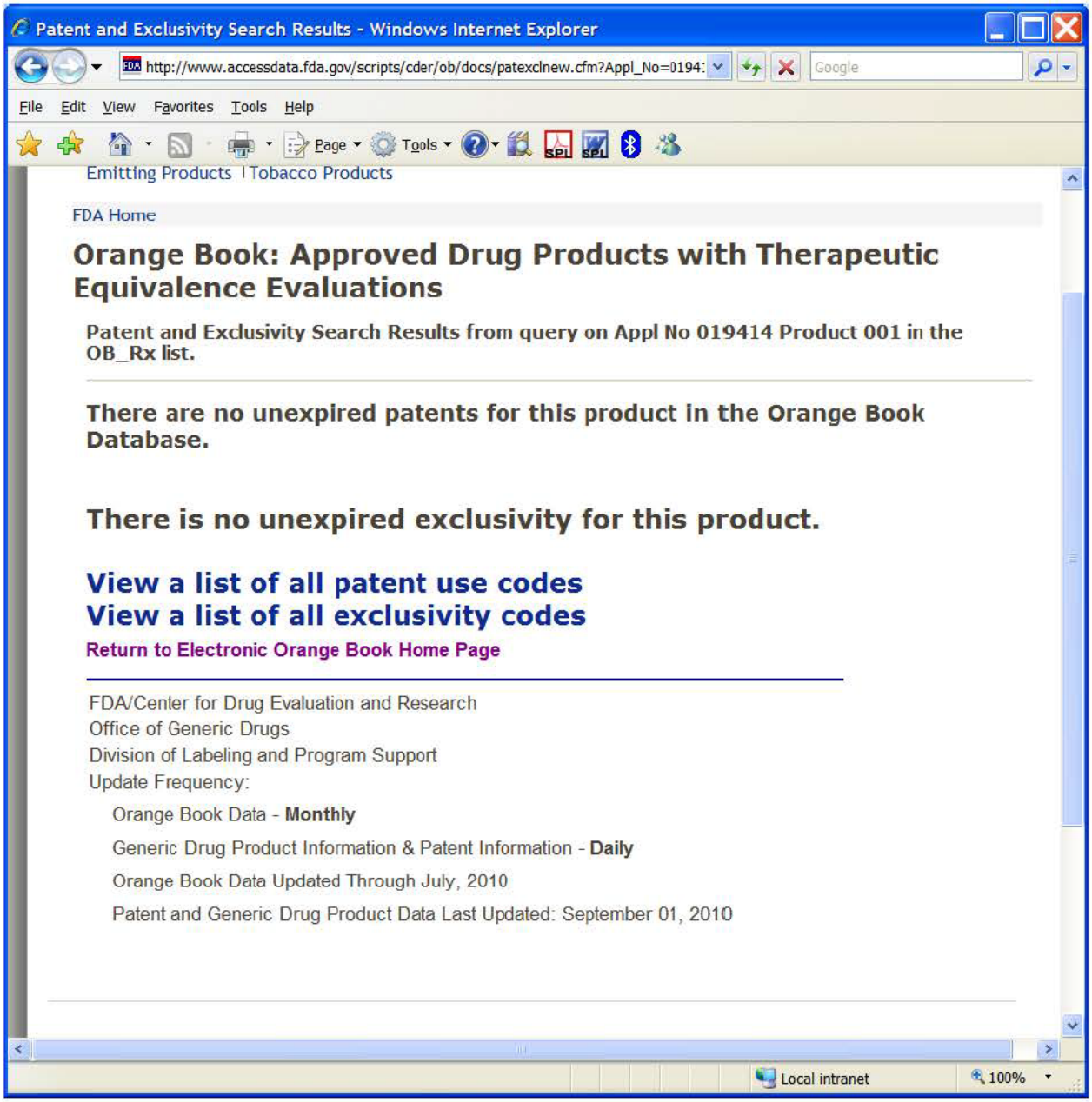
ACCEPTABLE

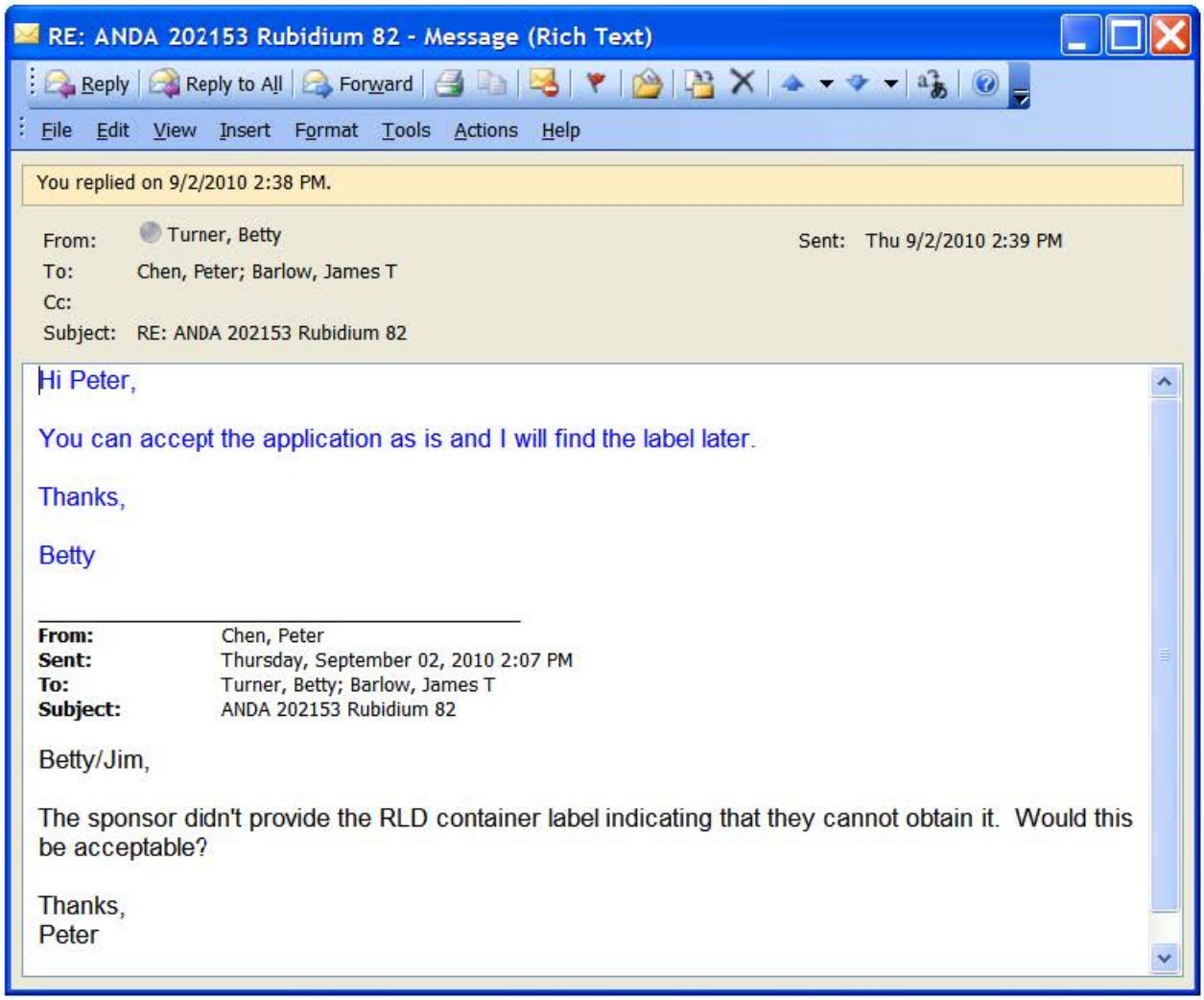
5.2	**Tabular Listing of Clinical Studies**	☐

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	☐


Orange Book Detail Record Search - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfr
Google
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
100%


Patent and Exclusivity Search Results - Windows Internet Explorer
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=0194:
Google
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
Local intranet
100%


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

x x x COMMUNICATION RESULT REPORT (SEP. 22. 2010 2:03PM) x x x

FAX HEADER: CDER/OGD/DLPS

TRANSMITTED/STORED : SEP. 22. 2010 2:02PM FILE MODE OPTION	ADDRESS	RESULT	PAGE
033 MEMORY TX	913018383182	OK	2/2

REASON FOR ERROR
E-1) HANG UP OR LINE FAIL
E-2) BUSY
E-3) NO ANSWER
E-4) 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) You should explain this disconnect.

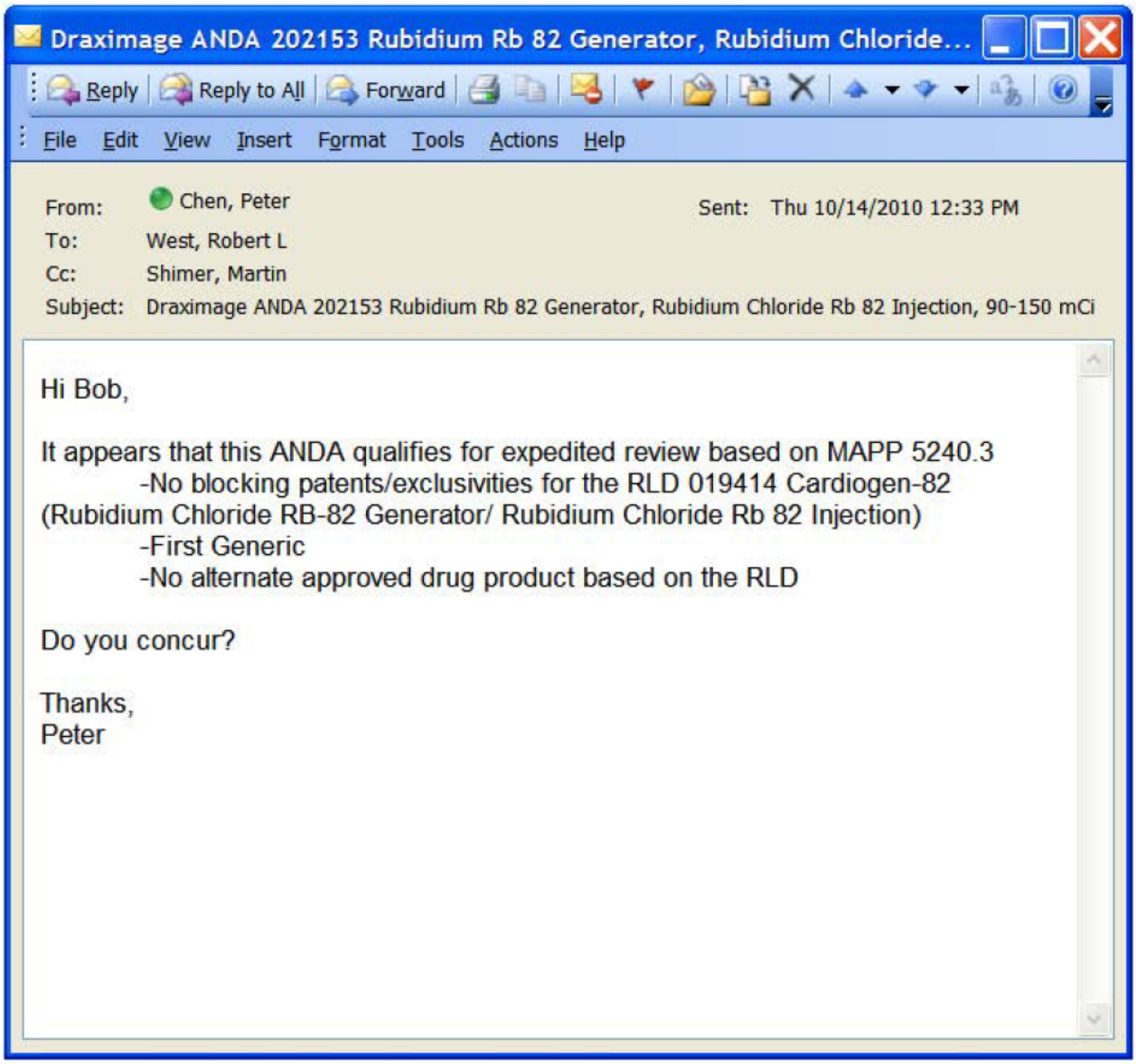
For the Environmental Impact Analysis Statement, please certify whether you have adhered to all Federal, State and Local environmental laws.

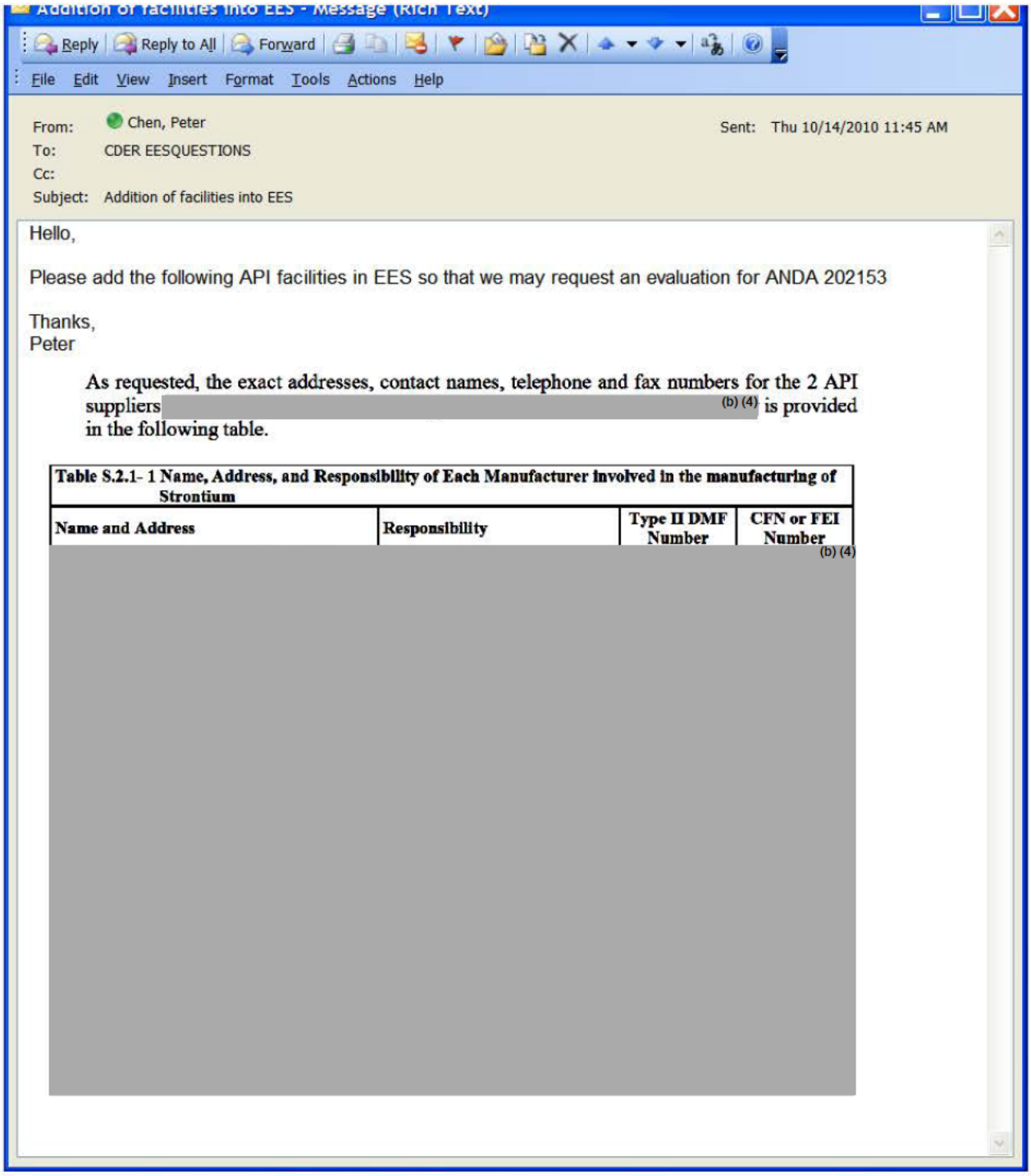
You should provide the exact addresses, contact names, telephone and fax numbers for the 2 API suppliers (b) (4)

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
✆ 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

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

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- ✆ ADVERSE REACTION REPORT
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- ✆ MEETING PLANNED BY _____
- ✆ PRE NDA MEETING
- ✆ END OF PHASE II MEETING
- ✆ RESUBMISSION
- ✆ SAFETY/EFFICACY
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- ✆ CONTROL SUPPLEMENT
- ✆ RESPONSE TO DEFICPENCY LETTER
- ✆ FINAL PRINTED LABELING
- ✆ LABELING REVISION
- ✆ ORIGINAL NEW CORRESPONDENCE
- ✆ FORMULATIVE REVIEW
- X *OTHER ('specify below)*

II.BIOMETRICS

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III.BIOPHARMACEUTICS

- DISSOLUTION
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- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL	PRECLINICAL

COMMENTS

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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