CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CHEMISTRY REVIEW(S)

Chemistry, Manufacturing and Controls (CMC) Labeling Memo – User Manual

NDA 202-153

Ruby-Fill® (Rubidium Rb 82 Generator)

Jubilant DraxImage, Inc.

by
Chemistry Reviewer: Anne Marie Russell, Ph.D.
Office of New Drug Products
Division of New Drug Products 2 (Branch VI)
for
Division of Medical Imaging Products (DMIP)

1. NDA 202-153

2. Labeling Memo – "The Ruby Rubidium Elution System User Manual"

3. REVIEW DATE: 20-Sept-2016

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date (Panorama)
Chemistry Review #2 Complete Response (Anne Marie Russell Ph.D., CMC reviewer)	20-SEP-2016

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Receipt Date	DARRTS SDN	Contents
Quality amendment	12-Sep-2016	email	Response to Information Request #3 – volume expiry (30L)
Quality amendment	25-Sep-2016	email	Response to User Manual Information Request

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	16751 Trans-Canada Highway Kirkland, Quebec Canada H9H 4J4
Representative:	Susan P. Spooner, Ph.D. INC Research, LLC, 4800 Falls of Neuse Road Suite 600 Raleigh, NC 27609 phone 919-745-2492
Telephone:	(514) 630–7087

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby-Fill® [1]
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2).

The reference listed drug (RLD) is Cardiogen 82 (N019414)

10. PHARMACOL. CATEGORY: Cardiac Positron Emission Tomography

[1] The Ruby-fill ^{82}Rb generator is operated by the Ruby-Fill® Elution System (RbES) (b) (4)

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY/PACKAGING: Variable strength eluent (mCi/mL) depending on generator release activity level, generator age, elution system operation mode and time between elutions. Column is loaded with (b) (4) ^{82}SrCl at calibration (adsorbed onto SnO_2). Dose is 10 – 60 mCi ^{82}Rb.

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: ^{82}RbCl
Molecular Weight: 117.5 daltons

17. RELATED/SUPPORTING DOCUMENTS:
A. DMFs: none.
B. Other Documents: none.

Chemistry Memo

Ruby Rubidium Elution System User Manual

In CMC Review #2 (Complete Response), two open issues (D1 and D2 below) with the User Manual were still under negotiation with the Applicant at the time of document completion, so this follow-up memo reviews the User Manual and documents the outcome.

(b) (4)

[redacted]

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Evaluation: Acceptable

Overall Evaluation of the User Manual: Acceptable as revised.

E. Label - PI (Prescribing Information)
This CMC reviewer provided input to the following sections of the PI throughout labeling negotiations with the Applicant: Highlights, Section 2.4 Elution System, Section 2.6 (b) (4) Eluate Testing Protocol, 2.8 RUBY-FILL Dose Delivery Limit, Section 3 Dosage Forms and Strengths, Section 11 Description and Section 16 How Supplied and Storage/Handling. Negotiations with the Applicant were ongoing when this memo was finalized - see approval letter for the final version of the PI

Signatures:
Primary Reviewer
Anne Marie Russell, Ph.D. CMC reviewer, ONDP, Division II, Branch VI

Secondary Reviewer:
Danae Christodoulou, Ph.D. Acting Branch Chief, ONDP, Division II, Branch VI

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

/s/

ANNE M RUSSELL
09/28/2016

DANAE D CHRISTODOULOU
09/28/2016

NDA 202153
Resubmission

OPQ N202153 Integrated Quality Assessment

Review Date: 09/23/2016

Drug Name/Dosage Form	Rubyfill[R] Rubidium Rb 82 Generator/Intravenous Infusion
Strength	(b) (4) not to exceed a total of 60 mL
Route of Administration	Intravenous infusion
Rx/OTC Dispensed	Rx
Applicant	Jubilant DraxImage Inc. (JDI), 16751 Trans-Canada Highway, Kirkland, Quebec, Canada H9H 414
US agent, if applicable	Susan P. Spooner, Ph.D., INC Research, LLC (4800 Falls of Neuse Road, Suite 600, Raleigh, NC 27609; phone 919-745-2492)

Quality Review Data Sheet

1. **LEGAL BASIS FOR SUBMISSION: 505(b)(2) – RLD is Cardiogen-82 (NDA 19414)**

2. **RELATED/SUPPORTING DOCUMENTS:**
   A. **DMFs:**

Table 1 Drug Master Files (DMFs)

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS[1]	DATE REVIEW COMPLETED	REVIEWER
(b) (4)	II		(b) (4)	3	01/17/2012 (adequate)	Milagros Salazar, Ph.D.
	II			3	01/18/2012 (adequate)	Milagros Salazar, Ph.D.

[1]The DMF
[2]Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3]Reviewed previously and no revision since last review

   B. **Other Documents:** *IND, RLD, or sister applications*
   N/A

3. **CONSULTS:**

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
CDRH			Robert Meyer, MS

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Drug Product	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Process	Anne Marie Russell, Ph.D.	ONDP/Branch VI/Division II
Microbiology	Yeissa ChabrierRosello, Ph.D.	OPQ/OPF/Microbiology
Facility	Michael Klapal	OPQ/OPF/DBP/BI
Biopharmaceuticals	N/A	N/A
Project Manager (R.Ph.)	Thao Vu, R.Ph.	OMPT/CDE/OPQ/OPRO/DPMI/RBPMBI
Application Technical Lead	Eldon E. Leutzinger, Ph.D.	ONDP/Branch VI/Division II
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental Assessment (EA)	N/A	N/A

Table 2 Documents Reviewed

DOCUMENT	RECEIPT DATE	DESCRIPTION	Section/reviewer
Complete Response (Resubmission-Class 2)	12/30/2015	Submission in response to Complete Response Letter	Anne Marie Russell, Ph.D., ONDP/Branch VII/Division II
Quality amendments	06/01/2016 O6/29/2016 08/30/2016 09/12/2016	Response to IR's	Anne Marie Russell, Ph.D., ONDP/Branch VII/Division II

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202153 for Rubyfill is recommended for approval, from the standpoint of Chemistry, Manufacturing and Controls, pending conclusions by the CDRH review (not yet final as of the date of this Integrated Executive Summary). Both Microbiology and Manufacturing Facilities are recommending approval.

1. Summary of Complete Response issues & Subsequent IR's, Facilities

ISSUE		STATUS
CMC From Complete Clinical Response Letter (12/18/2016)	Deficiency #3 – (1) clinical use simulation and (2) post approval testing protocol (b) (4) Deficiency #4 – clarification of Rubyfill Elution System Instructions	**Resolved** – clinical use simulation found acceptable. Post-approval testing protocol (b) (4) acceptable. Clarifications of Elution System instructions acceptable – response of 06/01/2016
CMC	CMC IR of 5/13/2016 – (b) (4)	**Resolved** – (b) (4) post-

(Continue from Complete Response Issues)	[redacted] (b) (4)	approval stability protocol resolved **Resolved** – [redacted] (b) (4) stability testing – response of 06/01/2016

ISSUE		STATUS
CMC (uncertainty in 10 – 60 mCi dose)	CMC IR of 05/16/2016 – (1) assessment of uncertainty in the dose (10 – 60 mCi) at the maximum and (2) minimum range of the system operation (flow rates, ^{82}Rb concentration, elution volume).	**Resolved** - issues (1) and (2) – response of 06/01/2016
CMC (new low dose limit of 10 mCi)	CMC IR of 5/16/2016 – (1) capability of dose calibrator to detect new alert limits (0.004 µCi ^{82}Sr/mCi ^{82}Rb, 0.04 µCi ^{85}Sr/mCi ^{82}Rb) in the new dose of 10 mCi, (2) DL for strontium and assessment of uncertainty of measurement at lowest level (~ 0.01 µCi), (3) calculations to determine the reported capability, (4) study reports (data, analysis) referenced in document "RUBY-FILLRubidum Rb 82 Generators.	**Resolved** – issues (1), (2), (3) and (4) – response of 06/01/2016
CMC (System Performance; Capability of Delivering Patient Dose)	CMC IR of 5/16/2016 – (1) assessment of delivered dose volume, strength and rate of delivery over lifetime of generator (release, mid-life, expiry) for minimum (10 mCi) and maximum (60 mCi). (2) assessment of uncertainty of values in (1) basis of assessment. (3) Rationale for [redacted] (b) (4) delivery rate proposed in label	**Resolved** - issues (1) and (2) – response of 06/01/2016. **Resolved** – issue (3) - response of 09/12/2016
Microbiology	Lack of dye ingress validation (1) testing [redacted] (b) (4) and (2) the limitations of the dye ingress test to simulate possible microbial ingress into the system	**Resolved** – issues (1) and (2) – responses of 8/17/2016

ISSUE		STATUS
Biopharm	N/A	N/A
Facilities	**^{82}Sr** – manufacture (b) (4) & established manufacturer of ^{82}Sr. **Drug Product** (*Jubilant Draximage* – drug manufacturer, *Jubilant Hollisterstier* – release & stability tester, (b) (4) – release & stability tester. (b) (4) – release & stability tester	**Resolved** (b) (4) – Corrections involving validation of test methods for ^{82}Sr completed (b) (4) acceptable by profile **Facilities in manufacture of drug product found acceptable on basis of profile and inspectional history**
CDRH	Review of the Dose Delivery System involves several aspects, ranging from software to the physical system (b) (4) From the standpoint of those issues involving the physical system, the only mechanical issue that remained after review in CDRH (b) (4)	**Conclusions on this issue, software and any other issues are pending as of the date of this integrated executive summary**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
None

II. Summary of Quality Assessments

INTRODUCTION:

The product from Rubyfill (Rubidium Rb 82 Generator) is ^{82}RbCl in saline, without excipients. It is produced in a "radionuclide generator" with the long/short-lived radionuclide pair (^{82}Sr/^{82}Rb). Due to the short physical half-life of ^{82}Rb (75 seconds), ^{82}RbCl is administered directly to a patient through an infusion delivery system connected to the generator. Based on the governing principles of a radionuclide generator, $^{82}Sr^{2+}$ is expected to remain stationary on a short chromatography column of hydrous stannic oxide, allowing for $^{82}Rb^{+}$ to elute from the column, thus effecting separation of $^{82}Rb^{+}$ from $^{82}Sr^{2+}$ (parent radionuclide). Hydrous stannic oxide is the stationary phase ("matrix"), whereas 0.9% Sodium Chloride (USP) is the mobile phase.

A. Drug Substance [USAN Name] Quality Summary

Chemically, the drug substance is **^{82}RbCl** and the USAN is Rubidium Chloride Rb 82. Rubidium (Rb) is Element 37 belonging to Group 1 of the Periodic Table, commonly referred to as the alkali metals, with electronic configuration of [Kr]$5s^1$. By virtue of the very large size of the 2nd ionization potential, Rb ion exists solely in the +1 oxidation state, and the chemistry of Rb and all

its isotopes is that of Rb^+. Rubidium possesses 32 isotopes, of which only 2 are naturally occurring (^{85}Rb, 72.2% natural abundance; ^{87}Rb, 27.8% natural abundance and radioactive with long physical half-life of 4.9×10^{10} years). The remaining isotopes, including ^{82}Rb, are radioactive and are not found in nature. The product of the decay of ^{82}Rb is stable Kr [$^{82(37+45)}_{37}Rb \rightarrow {}^{82(36+46)}_{36}Kr + \beta^+ + \nu$], in which a proton is converted to a neutron [$p^+ \rightarrow n + \beta^+ + \nu$ (neutrino)], resulting in a change in Z from 37 to 36. In this process, two particles (β^+ and ν) carry away the energy of the nuclear transition, and the energy spectrum of the positrons is a continuous distribution, as opposed to a emission of a discrete energy peak. Once β^+ particles are formed, they have a finite, but very short lifetime. On collision with electrons, the β^+ particles annihilate forming two 511 KeV γ-rays at approximately 180^0 apart, the basis of PET imaging with ^{82}Rb.

^{82}Rb is obtained from ^{82}Sr, and the overall process characterizing the nuclear transformations is as follows: $^{82(38+44)}_{38}Sr \rightarrow {}^{82(37+45)}_{37}Rb \rightarrow {}^{82(36+46)}_{36}Kr + \beta^+ + \nu$. ^{82}Sr (absorbed as $^{82}Sr^{2+}$ to the column matrix) decays by orbital electron capture (EC) in which the **nucleus absorbs one of the atom's orbital electrons, reacting with a proton, neutralizing it with formation of a neutron and a neutrino** [$e^- + p^+ \rightarrow n + \nu$ (neutrino)]. Overall, there is a change in Z from 38 to 36. This is seen in the Periodic Table, with ^{82}Sr going from Group 2 to ^{82}Rb in Group 1, then wrapping around (left-wise) in the Periodic Table to stable ^{82}Kr of the Inert Gasses (Group 18).

The conversion of ^{82}Sr to ^{82}Rb occurs on the generator column [$^{82}Sr \rightarrow {}^{82}Rb + \nu$], since the ^{82}Sr (as $^{82}Sr^{2+}$) stays put (in principle), although some relatively small amounts of $^{82}Sr^{2+}$ leaks out, by virtue of the imperfect chemistry of absorption to stannic oxide matrix.

QUALITY SUMMARY **– the radionuclidic identity of the drug substance (due to ^{82}Rb) is defined by well-established physics ($^{82}Sr \rightarrow {}^{82}Rb + \nu$), and radiochemical identity ($^{82}RbCl$) by the exchange process that occurs on the generator column matrix** (b) (4) **releasing $^{82}Rb^+$ (with Cl^-) with elution by saline. There are no radionuclide impurities arising from the nuclear transformation itself. The only issue pertinent to the quality of the $^{82}RbCl$ is that of** (b) (4)

B. Drug Product [Established Name] Quality Summary

Rubyfill [Rubidum Rb 82 Generator]. The generator eluate (containing $^{82}RbCl$) is administered directly to patients, and has a stand-alone indication (*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*). Hence, **by 21 CFR 310.3(n), Rubyfill (Rubidium Rb 82 Generator) is considered a drug, and furthermore defined as a PET drug and regulated under 21 CFR 212**. All of the CMC information pertaining to the generator, its manufacture and controls is in the NDA.

Rubyfill (Rubidium Rb 82 Generator) is a radionuclide generator that contains (b) (4) $^{82}SrCl_2$ adsorbed onto hydrous (b) (4) stannic oxide in a column (b) (4) The System front view and Schematic owing the internal network of functional parts is reproduced from the NDA, as follows:

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(b) (4)

Dose of ^{82}RbCl to Patient

(b) (4)

(b) (4) JDI is proposing to extend the dose range to 10 – 60 mCi, introducing a **new low dose limit of 10 mCi**.

- **New Low Dose (10 mCi)**

Several issues arose regarding this new dose limit, namely (IR, 5/13/2016) affecting risk to the patient, namely (a) uncertainty of the dose delivered, and (b) uncertainty in the detectability of strontium breakthrough.

ISSUE – **New Low Dose #1 (5/13/2016)** – IR #1 - **assessment of uncertainty in the in dose range (10 – 60 mCi)** – **RESOLVED**. (b) (4)

(b) (4)

ISSUE – **New Low Dose #2** (5/13/2016) – IR #1 - **limit of detection** – **RESOLVED**. The limit of detection of the dose calibrator is determined (b) (4)

(b) (4)

Summaries of Rubyfill elution system performance testing is provided.

- **System Performance**

The clinical team (DMIP) had requested an explanation of the slower maximum infusion rate (30 mL/min). That for Cardiogen-82 is 50 mL/min.

ISSUE – **System Performance** (5/13/2016) – IR #2 – absence of demonstrated **capability of the Rubyfill system to deliver minimum and maximum dose (10 mCi and 60 mCi) at the beginning of generator life to its expiration, test method and controls - RESOLVED**. In a tcon with JDI (7/13/2016), additional data was requested. Data was provided by Draximage (b) (4)

(b) (4)

ISSUE – **System Performance** (9/06/2016) – IR #3 – absence of **data use to support proposed Rubyfill labeled elution volume of 30 L at expiry – RESOLVED**. Data provided (9/12/2016) are not primary stability data, because of differences between test conditions and commercial operation, and between development and commercial generators. As a consequence, these data are of a secondary nature. Yet, it is pertinent that at the 30 L expiry point, the release acceptance criteria were not exceeded. Some data from Canadian generators (b) (4) were provided. These generators were operated to simulate clinical use, although not using the commercial elution system. The impact of differences do not adversely affect the breakthrough performance (shown by JDI). The data from the Canadian generators is primary and supportive of the 30 L expiry. The sum total of all the data assures that breakthrough performance of the commercial generators will be met at 30 L expiry. **In light of these considerations, it is to be noted that the stability data provided does not include data from 3 commercial generators operated with the commercial elution system and with commercial** (b) (4) **Hence, the post-approval stability program will be very important in confirming the expected performance of the commercial product**.

Microbiology

After the initial review (06/03/2016) and responses to address multiple deficiencies, the issues that remained were (1) lack if dye ingress validation testing (b) (4) and (2) the limitations of the dye ingress test to simulate possible microbial ingress into the system. Based on the information to address the issues in (1), their results demonstrate that the risk of cross-contamination (b) (4) is well controlled by the safeguards put in place (b) (4) Regards (2), the firm's response is twofold. (b) (4)

These assessments and rationale were deemed to be acceptable by the microbiologist

reviewer (Yeissa ChabrierRossello, Ph.D.) for a final determination that all microbiology deficiencies identified in the application are resolved.

Dose Delivery System

Review of the Dose Delivery System involves several aspects, ranging from software to the physical system (b) (4) From the standpoint of those issues involving the physical system, the only mechanical issue that remained after review in CDRH (Robert Meyer, M.S.), (b) (4)
The final review conclusion on this issue, including an assessment by DMIP, and of the software and any other issues is pending as of the date of this integrated executive summary.

Rubyfill User Manual

(b) (4)

(b) (4)

These issues relating to improvements in the User Manual are currently under negotiation with JDI.

Labeling

Some final labeling changes (Michele Fedowitz, M.D., DMIP; Anne Marie Russell, Ph.D., ONDP) are proposed to the Outer Label (main label, assay label) and will be communicated to JDI. There are no other outstanding labeling issues, other than the continuing negotiations with JDI on the User Manual.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Rubyfill
Non Proprietary Name of the Drug Product	Rubidium Rb 82 Generator
Non Proprietary Name of the Drug Substance	Rubidium Chloride Rb 82 (USAN)
Proposed Indication(s) including Intended Patient Population	Imaging of the myocardium under rest or pharmacologic stress in patients with suspected or existing coronary artery disease
Duration of Treatment	N/A
Maximum Daily Dose	60 mCi
Alternative Methods of Administration	N/A

D. Biopharmaceutics Considerations
N/A

E. Novel Approaches
N/A

F. Any Special Product Quality Labeling Recommendations
None

G. Process/Facility Quality Summary (see Attachment A)
See I.A. Recommendations and Conclusion on Approvability (Summary of Complete Response Issues & Subsequent IT's, Facilities)

H. Life Cycle Knowledge Information (see Attachment B)
N/A

Risk Assessment - Drug Product (Rubidium Rb 82 Generator)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking***	**Risk Mitigation Approach**	**Final Risk Evaluation[6]**	**Lifecycle Considerations/ Comments****
Radionuclidic Identity/purity	(b) (4)		N/A	(b) (4)	N/A
Radiochemical identity			N/A		N/A
Radiochemical purity			N/A		N/A
Chemical Purity			N/A		N/A
Strength (mCi/mL)			Data provided to address		N/A
pH			N/A		N/A
Stability			N/A		N/A

Microbiology		(b) (4)	Information to resolve deficiencies	(b) (4)	N/A

1. Radionuclidic Identity/Purity – sources of ^{82}Sr (b) (4) previously reviewed under DMF's, and determined to be acceptable for use in the rubidium generator.
2. Radiochemical Identity/Purity – established in (b) (4) DMF's.
3. Chemical Purity – Trace Metals – established in (b) (4) DMF's.
4. Microbiology – see Microbiology Review (Yeissa ChabrierRosello, Ph.D.); RPN (after modification when applicable) x S x D.
5. Overall Risk Assessment, (b) (4) (low, based on resolution of all issues for CMC & Microbiology).

Application Technical Lead: Eldon E. Leutzinger, Ph.D., CMC Lead

Chemistry, Manufacturing and Controls (CMC)
Review of Complete Response
Drug Product

NDA 202-153

Ruby-Fill® (Rubidium Rb 82 Generator)

Jubilant DraxImage, Inc.

by
Chemistry Reviewer: Anne Marie Russell, Ph.D.
Office of New Drug Products
Division of New Drug Products 2 (Branch VI)
for
Division of Medical Imaging Products (DMIP)

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-153

2. REVIEW #2 (Complete Response)

3. REVIEW DATE: 11-MAY-2016

4. REVIEWER: Anne Marie Russell, Ph.D.

5. PREVIOUS DOCUMENTS:

Document	Document Date (DARRTS)
Chemistry Review #1 (David Place Ph.D., CMC reviewer)	19-SEP-2014
CMC memo #1 (David Place Ph.D., CMC reviewer)	11-Dec-2014
CMC memo #2 (David Place Ph.D., CMC reviewer)	11-Dec-2014
FDA action letter (Complete Response (CR))	18-Dec-2014

History of the application: This is the second review cycle. N202-153 was originally filed in 2006 as an ANDA and was converted to NDA (505b2) due to clinical differences from the Reference Listed Drug (Cardiogen N019414). The original NDA 505b2 application was not approved. See CR letter, issued 18-Dec-2014.

Review Clock: The original PDUFA date for this Complete Response was 30-Jun-2016. On 29-Jun-2016, the review clock was extended to 30-Sep-2016 due to receipt of a major amendment (CDRH).

6. SUBMISSION(S) BEING REVIEWED:

Document	Document Receipt Date	DARRTS SDN	Contents
Complete Response (Resubmission Class 2)	30-Dec-2015	30	Complete response to CR letter.
Quality Amendment	01-Jun-2016	36	Response to Information Request #1
Quality Amendment	29-Jun-2016	43	Response to Information Request #2
Quality Amendment	30-Aug-2016	47	Response to Information Request #2 – clinical simulation test
Quality amendment	12-Sep-2016	email	Response to Information Request #3 – volume expiry (30L)

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	16751 Trans-Canada Highway Kirkland, Quebec Canada H9H 4J4
Representative:	Susan P. Spooner, Ph.D. INC Research, LLC, 4800 Falls of Neuse Road Suite 600 Raleigh, NC 27609 phone 919-745-2492
Telephone:	(514) 630–7087

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby-Fill® [1]
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2).

The reference listed drug (RLD) is Cardiogen 82 (N019414)

10. PHARMACOL. CATEGORY: Cardiac Positron Emission Tomography

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY/PACKAGING: Variable strength eluent (mCi/mL) depending on generator release activity level, generator age, elution system operation mode and time between elutions. Column is loaded with (b) (4) ^{82}SrCl at calibration (adsorbed onto SnO_2). Dose is 10 – 60 mCi ^{82}Rb.

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed ___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: ^{82}RbCl
Molecular Weight: 117.5 daltons

[1] The Ruby-fill ^{82}Rb generator is operated by the Ruby-Fill® Elution System (RbES) (b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: N/A. DMFs have been reviewed in previous review cycles. No new DMFs in this submission.

B. **Other Documents:** none.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Facility Inspection	NA		
Pharm/Tox	NA		
Biopharm	NA		
Labeling Nomenclature Committee	NA		
Methods Validation	NA		
DMEPA			
Environmental Assessment	NA		
Microbiology	acceptable	15-Sept-2016	Yeissa Chabrier-Roselló, Ph.D.
CDRH	pending		Robert Meyer. M.S.

Chemistry Review for NDA 202-153 Complete Response

I. Recommendations

A. Recommendation and Conclusion on Approvability:
From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is recommended for approval, pending acceptable findings by the CDRH review, which is not yet final as of this writing. The proposed volume expiry (30L) and time expiry (60 days) for the generator is granted, when operated using the commercial elution system (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None

II. Review of Applicant's Response to CMC Deficiencies:

Two CMC deficiencies were identified in the 18-Dec-2014 Complete Response letter to the Applicant under the heading PRODUCT QUALITY items #3 and #4.

The format of this review is as follows: the deficiency from the Complete Response letter is in normal font, *the Applicant's response provided in this submission is in italics* and **the reviewer's evaluation is in bold font**.

Deficiency #3

(b) (4)

Applicant's response (received 30-Dec-2015):
In this Complete Response submission, the Applicant provided a revised post-approval stability protocol (b) (4)

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III. Additional issues which arose during review:

Background: This reviewer compiled Table A which compares Cardiogen generator (RLD) with the Ruby-fill proposed commercial generator:

Table A Rubidium-82 generator: Comparison to RLD		
Characteristic	Cardiogen generator (RLD)	Ruby-Fill generator
Dose	30 – 60 mCi Rb 82	10 – 60 mCi Rb 82
Flow rate	50 mL/min	15 – 30 mL/min
Elution volume per dose	< 100 mL	< 60 mL
Elution time per dose	Not specified	(b) (4)
Radioactivity delivered by generator*		
• at calibration (Day 0/ 1.00)	90 – 150 mCi Rb 82	85 – 115 mCi Rb 82
• at first clinical use (Day 11/ 0.737)	(b) (4) mCi Rb 82	(b) (4) mCi Rb 82
• at end of expiry^	(b) (4) mCi Rb 82 (^Day 42/ 0.312)	(b) (4) mCi Rb 82 (^Day 60/ 0.189)
How dose is delivered	User manually operates Cardiogen system control panel	User input to Ruby-fill system software interface, software controls infusion.
Operation modes	(b) (4)	
Expiry - time	42 days	60 days
Expiry - volume	17L of eluent	30 L of eluent
Calibration dose	N/A	35mL at 20 mL/min

*Calculated from fraction remaining in Table 6 Cardiogen 82 and Ruby-fill labels

A. New low dose (10mCi):

During the review cycle, Jubilant DraxImage (JDI) proposed to extend the dose range (b) (4) to 10 – 60 mCi, which introduced a new low dose limit (10mCi). The review issues from a CMC standpoint for the new low dose are two fold – the risk to the patient regarding uncertainty in the dose administered and the detectability of strontium breakthrough.

Dose uncertainty: Any measurement has an inherent uncertainty due to the limitation of the equipment and the measuring method. (b) (4) The Complete Response submission and the original NDA submission did not provide an assessment of the uncertainty of these radioactivity measurements – see comment below.

Strontium breakthrough detectability: The levels of strontium (^{82}Sr and ^{85}Sr) in the patient dose are monitored daily in the calibration dose eluted during the Daily Quality Control (Section 7 in the User Manual). The eluent is allowed to decay out the ^{82}Rb and the residual radioactivity is measured by the dose calibrator. The system then calculates the levels of strontium using the measured residual radioactivity, equations and limits specified in the Ruby-fill label. It is unknown if the strontium breakthrough alert limit (^{82}Sr 0.004 per µCi/mCi of ^{82}Rb,

^{85}Sr 0.04 per µCi/mCi of ^{82}Rb) in the new low dose (10 mCi) is below the detectability limit of the system. An evaluation of the Limit of Detection (LOD) of strontium breakthrough in the system is needed - see comment below.

The following three comments were sent to the Applicant on 13-May-2016 in CMC Information Request #1, response received 1-Jun-2016:

1. **Provide an assessment of the uncertainty in the dose (10 – 60 mCi) administered to the patient at the maximum and minimum range of the system operation (e.g. flow rates, ^{82}Rb concentration, elution volume/time). Explain the basis for each assessment. Tabulate the data where possible.**

Response: Applicant provided dose error data from Clinical Simulation Test 4 (Protocol ##3000069-P/ Appendix 8-2 Clinical Simulation Study Report).

(b) (4)

(b) (4)

Dose Range	Flow-Rate	Average Dose Error
(b) (4)		

Table 6

(b) (4)

Review:

(b) (4)

(b) (4)

Table B
Dose Accuracy in Clinical Simulation Test 4

Dose (mCi)	Flow rate (mL/min)	Dose Error (%)		
		avg	min	max

(b) (4)

(b) (4)

(b) (4)

As per Michele Fedowitz, M.D., clinical reviewer, (via email on 8-June-2016) the dose error is not clinically significant and is acceptable.

Evaluation: Acceptable

2. **Limit of detection for strontium in new low dose (10 mCi):**
   a. **Discuss the capability of the dose calibrator to detect strontium at alert levels (^{82}Sr 0.004 per µCi/mCi, ^{85}Sr 0.04 per µCi/mCi) in the new low dose of 10mCi. Include an assessment of the limit of detection (LOD) for strontium using the supplied dose calibrator unit and the uncertainty in that dose calibrator measurement** (b) (4) **Provide calculations used to determine the reported capability.**

   Response: The Applicant explained that breakthrough levels are reported as the amount of strontium per the amount rubidium (e.g. ^{82}Sr 0.004 µCi/mCi ^{82}Rb and ^{85}Sr 0.04 µCi/mCi ^{82}Rb) and are assessed during the daily calibration of the system. (b) (4)

   Per the recently submitted report (RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing), the Limit of Detection (LOD) of the dose calibrator is experimentally determined (b) (4)

(b) (4)

[redacted]

Evaluation: Acceptable. (b) (4) [redacted] The alert limit is essentially at or below the limit of detection of the dose calibrator when the generator is at expiry, but not earlier. This is acceptable because of the extensive margin built into the alert limits to assure patient safety.

b. Provide the study reports (data, analysis) referenced in the document "RUBY-FILL® Rubidium Rb 82 Generators - Evaluation of Strontium Isotope Breakthrough" (Appendix 3-1) which summarized test results for:

- **i. RES.RBY.SDY.034 Volume Limits and Strontium Breakthrough**
- **ii. RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing**
- **iii. RES.RBY.SDY.042 Interim Report: Summary of RbES (b) (4) Performance Testing**
- **iv. RES.RBY.SDY.054 REPORT: Summary of Ruby-Fill Elution System Performance Testing**

v. **RES.RBY.SDY.070 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Low Usage**
vi. **RES.RBY.SDY.072 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Extreme Usage**

Response: Reports provided.
Evaluation: Acceptable. See Maximum volume at expiry (30L) in Section C below.

B. **System performance/ Flow rate of eluent:**

During label review, the clinical team requested an explanation of the slower maximum infusion rate recommended for Ruby-fill (30 mL/min) compared to the reference listed drug Cardiogen (50 mL/min). Additional data regarding infusion times and full system performance are needed to evaluate the clinical impact.

The following comment was sent on 13-May-2016 in CMC Information Request #1, response received 1-Jun-2016.

3. **For the maximum (60mCi) and minimum (10mCi) dose range, provide an assessment of the delivered volume, concentration (mCi/mL) and rate of delivery (mL/min) for the lifetime of the generator (release, mid-life and expiry). Include an assessment of the uncertainty in the values and explain the basis for each assessment. Describe the rationale for the 30 mL/min maximum rate proposed in the draft label. Tabulate the information, where possible.**

Response: Data provided for minimum, intermediate and maximum dose at generator release, mid-point and expiry, in Tables 11, 12 and 13 below.

Time Point	Dose (mCi)	Volume (mL)	Flow-Rate (mL/min)	Elution Time (sec)
(b) (4)				

(b) (4)

The maximum flow of the Ruby-Fill system is 30 mL/min (b) (4)

Initial Evaluation: Not Acceptable. (b) (4) Data were not provided for a minimum dose (10 mCi) delivered from a generator at release and for a maximum dose (60mCi) delivered from a generator at mid-point and expiry. These conditions represent the limits of the system. (b) (4)

(b) (4)

(b) (4)

The following deficiency was sent to the Applicant on 20-Jun-2016 in CMC Information Request #3:

CMC Deficiency: (b) (4)

Information needed to resolve the deficiency:

1. **Provide data to demonstrate that the commercial system is capable of delivering the maximum and minimum dose (10mCi and 60mCi) at the beginning and end of generator lifetime within the proposed operating range of the system** (b) (4) **Include raw data, averages, n value, uncertainty and range of values (minimum and maximum).**

   First Response: received 29-Jun-2016 (SDN #43):
   No new clinical simulation test data provided. (b) (4)

(b) (4)

Initial evaluation: Not acceptable. In this response, JDI summarized previously submitted clinical simulation data, which had already been reviewed and found to be inadequate because data at system limits were missing. In the 13-Jul-2016 tcon, FDA advised that additional data were needed and JDI agreed to conduct additional testing and submit.

(b) (4)

Second Response: received 30-Aug-2016 (SDN #47) Clinical Simulation Study Report – Dosing Evaluation. The submitted Executive Summary is copied below:

(b) (4)

[redacted]

Final Evaluation: Acceptable. Data were provided to demonstrate that the minimum dose (10 mCi) is delivered throughout the generators' lifetime (60 days) at the minimum and maximum operating conditions (flow, time, elution volume) in all three elution modes. (b) (4)

[redacted]

(b) (4)

(b) (4)

These clinical performance results were provided to the clinical review team to assess the suitability of the clinical simulation test, who found them acceptable.

2. **Provide the test method used to produce the data and summarized descriptions of how the reported data (volumes, flow and times) are determined. Include data for dose, flow, time (infusion, elution), system mode and volume (infusion, elution, total). Briefly describe the fluid path of the system as it delivers the entire infusion to the patient, including the radioactive dose and any non-radioactive saline – for each mode of operation, if different.**

Response: received 29-Jun-2016 (SDN #43): The submission described the test method, including how reported data are determined (see summary below, Table C, compiled by this reviewer) and the method used to determine accuracy of that reported data in the dose error calculations. The fluid paths were also described in diagrams, see Appendix.

Evaluation: Acceptable. The test method and calculation of dose error are acceptable. Dose, volume and flow rate accuracy were determined against the "true" value and precision was determined from repeat (n=2) measurements.

Table C. Summary of how submitted data are determined in clinical simulation tests		
Data	System component	"True" value
(b) (4)		

*This true value is a best estimate based on use of a calibrated dose calibrator (b) (4)

3. **Describe the controls in place which prevent the system from operating when an undeliverable dose is requested by the user. This may include for example - software lockout controls, user manual instructions and labeling language.**

Response received 29-Jun-2016 (SDN #43): JDI described the software controls in place and the constraints on the deliverable dose for all parameters (Table 6 below):

Parameter	Minimal value	Maximal value
(b) (4)		

Table 6- generator activity level constraints

Evaluation: Acceptable. (b) (4)

(b) (4)

C. **Maximum volume at expiry (30L):**

The Ruby-fill label (Section 2.7), in keeping with the RLD Cardiogen label, specifies three attributes for expiry: volume (30L), time (60 days) and strontium breakthrough level (Sr 82 and Sr 85) as follows:

> 2.7 RUBY-FILL® Expiration
> Stop use of the RUBY-FILL® Rubidium Rb 82 Generator once any one of the following Expiration Limits is reached:
>
> - A total elution volume of 30 L has passed through the generator column, or
> - Expiration date of the generator (60 days post-manufacturing), or
> - An eluate Sr 82 level of 0.01 µCi/mCi (kBq/MBq) Rb 82, or
> - An eluate Sr 85 level of 0.1 µCi/mCi (kBq/MBq) Rb 82

The acceptance criteria for two of these attributes, time and breakthrough level, have been found acceptable in the previous review cycle. Acceptable stability data were provided in the original submission to support the 60 day expiry (see CMC review#1 David Place, Ph.D. 19-SEP-2014). The strontium breakthrough levels are based on the (b) (4)

The third attribute, volume (30L), was not discussed in CMC review #1. In this review cycle, the report "Investigation of Volume Limits and Strontium Breakthrough" RES.RBY.SDY.034 dated April 2014 to support the expiry volume was submitted on 01-Jun-2016 in Quality Amendment (DARRTS SDN#36). Figure 2 in the report (below) provides Sr-82 breakthrough values to show that generator (b) (4) delivered 30L of doses with strontium levels below the breakthrough acceptance criteria (b) (4)

(b) (4)

Initial Evaluation: Not Acceptable. The submission provides a summary report (b) (4)

(b) (4)

The following comment was sent to the Applicant in Information Request #3 on 6-Sept-2016:

1. **Provide data to support the proposed Ruby-fill generator labeled elution volume expiry of 30L. Describe the test procedure used to collect the data and differences from the proposed commercial product (e.g. generator, elution system, operating conditions).**

Response: Received (via email) 12-Sep-2016.

The Applicant provided four pieces of information to support their proposed 30L expiry data:

1. Developmental and validation generators – stability data in original NDA (30-Jun-2010):

(b) (4)

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Response: At the time of completing this review, this User Manual issue is still under negotiation with the Applicant. See subsequent CMC labeling memo.

Final Overall Evaluation of the Application:

Pending acceptable findings by CDRH review, which is not yet final as of this writing, the NDA is recommended for approval from a CMC standpoint, with the proposed volume expiry (30L) and time expiry (60 days) when operated using the commercial elution system (b) (4)

Pertinent communications with the Applicant during the Review Cycle:

Communication type	Date sent to Applicant	CMC comments & deficiencies
tcon	11-May-2016	See minutes in DARRTS. CMC discussed dose and calibration.
CMC Information Request #1	13-May-2016	1. Post-approval stability protocol: (b) (4) [redacted] 2. Provide an assessment of the uncertainty in the dose (10 – 60 mCi) administered to the patient at the maximum and minimum range of the system operation (e.g. flow rates, ^{82}Rb concentration, elution volume/time) . Explain the basis for each assessment. Tabulate the data where possible.

N202-153 CHEMISTRY REVIEW#2

Communication type	Date sent to Applicant	CMC comments & deficiencies
		3. Limit of detection for strontium in new low dose (10 mCi): a. Discuss the capability of the dose calibrator to detect strontium at alert levels (^{82}Sr 0.004 per µCi/mCi, ^{85}Sr 0.04 per µCi/mCi) in the new low dose of 10mCi. Include an assessment of the limit of detection (LOD) for strontium using the supplied dose calibrator unit and the uncertainty in the dose calibrator measurement [redacted] (b) (4) Provide calculations used to determine the reported capability. b. Provide the study reports (data, analysis) referenced in the document "RUBY-FILL® Rubidium Rb 82 Generators - Evaluation of Strontium Isotope Breakthrough" (Appendix 3-1) which summarized test results for: i. RES.RBY.SDY.034 Volume Limits and Strontium Breakthrough ii. RES.RBY.SDY.033 Ruby-Fill Elution System (RbES) Breakthrough Testing iii. RES.RBY.SDY.042 Interim Report: Summary of RbES [redacted] (b) (4) Performance Testing iv. RES.RBY.SDY.054 REPORT: Summary of Ruby-Fill Elution System Performance Testing v. RES.RBY.SDY.070 REPORT: Summary of Ruby-Fill Elution System Performance Testing-Low Usage vi. RES.RBY.SDY.072 REPORT: Summary of Ruby-Fill Elution System 4. For the maximum (60mCi) and minimum (10mCi) dose range, provide an assessment of the delivered volume, concentration (mCi/mL) and rate of delivery (mL/min) for the lifetime of the generator (release, mid-life and expiry). Include an assessment of the uncertainty in the values and explain the basis for each assessment. Describe the rationale for the 30 mL/min maximum rate proposed in the draft label. Tabulate the information, where possible.

Communication type	Date sent to Applicant	CMC comments & deficiencies
CMC Information Request #2	20-Jun-2016	**CMC Deficiency #1: Undeliverable dose.** System performance has not been demonstrated over the lifetime of the generator for the full range of doses (10mCi to 60mCi) within the operating range of the system, consequently some doses may not be deliverable. The data provided from Clinical Simulation Test 4 did not provide test results for 10mCi at generator release or for 60mCi at generator expiry – conditions which represent the limits of the system as labeled. Information needed to resolve the deficiency: 1. Provide data to demonstrate that the commercial system is capable of delivering the maximum and minimum dose (10mCi and 60mCi) at the beginning and end of generator lifetime within the proposed operating range of the system (b) (4) (b) (4) (b) (4) Include raw data, averages, n value, uncertainty and range of values (minimum and maximum). 2. Provide the test method used to produce the data and summarized descriptions of how the reported data (volumes, flow and times) are determined. Include data for dose, flow, time (infusion, elution), system mode and volume (infusion, elution, total). Briefly describe the fluid path of the system as it delivers the entire infusion to the patient, including the radioactive dose and any non-radioactive saline – for each mode of operation, if different. 3. Describe the controls in place which prevent the system from operating when an undeliverable dose is requested by the user. This may include for example - software lockout controls, user manual instructions and labeling language. **CMC Comment #1:** Your proposal (b) (4) in your stability protocol is not acceptable. Revise the post-approval stability protocol (b) (4) (b) (4)
tcon	23-Jun-2016	See minutes in DARRTS. CMC discussed data to support deliverable doses.
Clock Extension	29-Jun-2016	No CMC information was sent. The clinical division informed the Applicant "On June 15, 2016, we received your June 11, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee

Communication type	Date sent to Applicant	CMC comments & deficiencies
		goal date is September 30, 2016."
Tcon	13-Jul-2016	See minutes in DARRTS. CMC discussed data to support deliverable doses.
Information Request #3	6-Sept-2016	Provide data to support the proposed Ruby-fill generator labeled elution volume expiry of 30L. Describe the test procedure used to collect the data and differences from the proposed commercial product (e.g. generator, elution system, operating conditions)."
Information Request #4 (joint with clinical)	15-Sept-2016	We are concerned that your user manual does not clearly explain (b) (4) [redacted] (b) (4) [redacted]

IV. Labeling:

Labeling is ongoing by the review team at this time. See CMC labeling memo.

V. Overall recommendation: The application, as amended, is recommended for approval pending acceptable review by CDRH.

VI. Signatures:

CMC primary reviewer: Anne Marie Russell, Ph.D. I recommend approval (pending acceptable CDRH review).

CMC secondary reviewer: Danae Christodoulou, Ph.D. Branch Chief. I concur.

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Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 9/22/2016 02:58:25PM
GUID: 5050dd27000012a4c69bfc70b47660b7

Anne Russell

Digitally signed by Anne Russell
Date: 9/22/2016 02:56:53PM
GUID: 508da7210002a03c7e3cba5e276a8027

Facility -1

ASSESSMENT OF THE FACILITIES

(b) (4)

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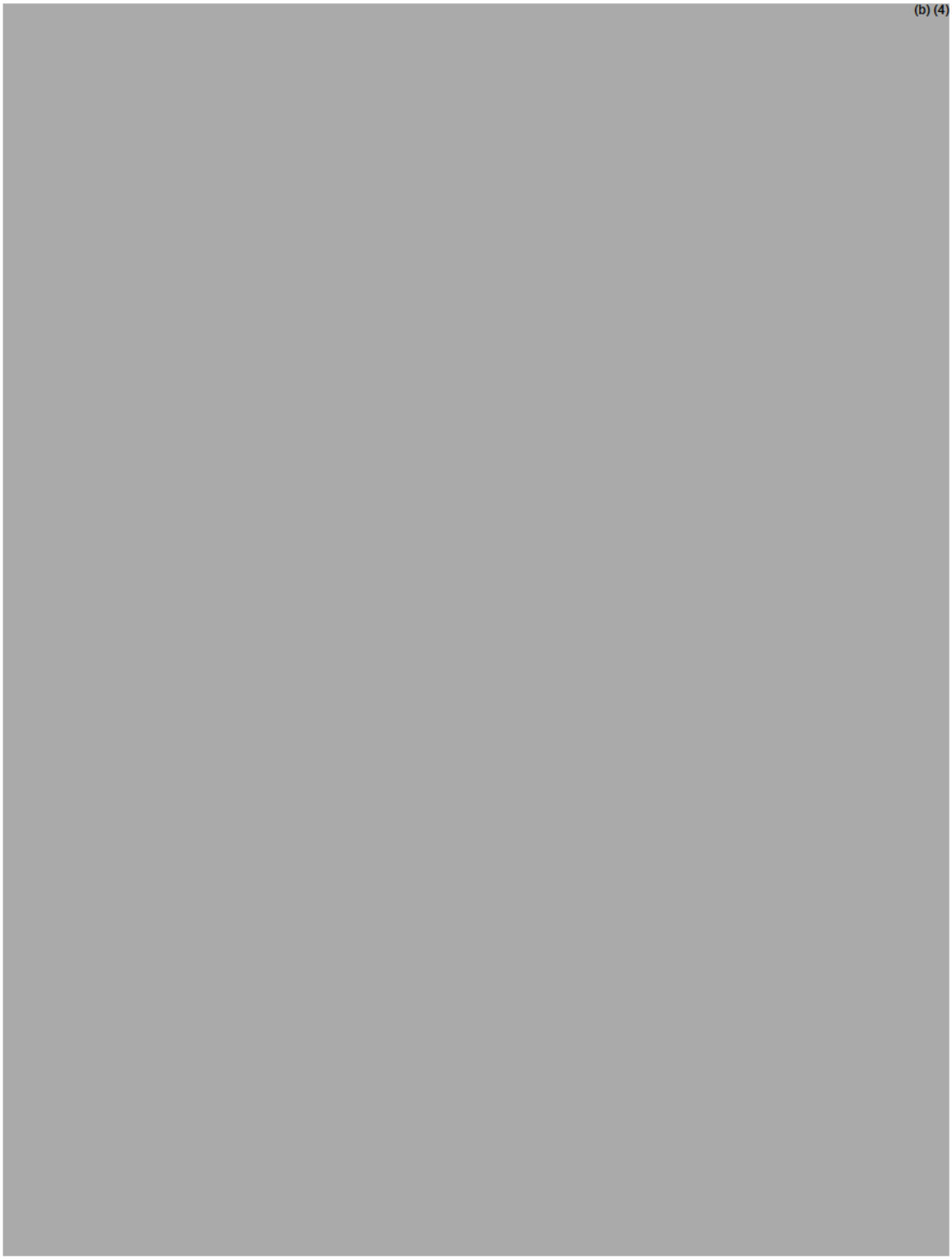
Facility -9



OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

There appears to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facility's inspection results, inspectional history, and relevant experience. The facilities are determined acceptable to support approval of NDA202153

Michael Klapal
4/18/16

Secondary Review Comments and Concurrence:

I concur with Mr. Klapal's recommendations.

Vidya Pai
4/26/2016

Tertiary Review Comments and Concurrence:

I concur with the above recommendations.
Krishna Ghosh
5/16/2016

MEMORANDUM to FILE

To: NDA **202–153**

From: David A. Place, PhD Reviewing Chemist

Through: Eldon Leutzinger, PhD, Chemistry Lead

Through: Eric Duffy, PhD Director, ONDQA Division III

Subject: CMC Comparison of Labeling (Package Insert) and User Manual Documents for RubyFill

Date: December 29, 2014

Background – Jubilant DraxImage has submitted two key Amendments to NDA 202–153 that relate to the preparation and use of the Drug Product – both an updated Package Insert as well as a User Manual.

The titles, filenames, DARRTS submissions, and filing dates of these documents are as follows:

- Package Insert 1 14 1 3 Package Insert (clean) (2).doc SDN # 16 9/23/2013
- User Manual user–manual 18MAR2014.pdf SDN # 19 3/25/2014

The Table of Contents of both documents are reproduced on the following pages.

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

/s/

DAVID A PLACE
12/11/2014

ELDON E LEUTZINGER
12/11/2014

RAMESH RAGHAVACHARI
12/11/2014
for Eric Duffy

MEMORANDUM to FILE

To:	NDA **202–153**	
From:	David A. Place, PhD	Reviewing Chemist
Through:	Eldon Leutzinger, PhD,	Chemistry Lead
Through:	Eric Duffy, PhD	Director, ONDQA Division III
Subject:	Review Update	
Date:	December 10, 2014	

Background – The following document contains several updates based on the 9/17/2014 Primary CMC review.

Note that the review cover page lists identifies the submission as an **ANDA**. After receipt, the submission was reclassified as an **NDA**. The review was done for the Division of Medical Imaging, not the Office of Generic Drugs.

H. Post–Approval Stability Protocol and Commitment – Post-approval, the sponsor proposes to carry out (b) (4) the proposed protocol below.

(b) (4)

The deletion of this sentence will improve consistency with the actions CMC will recommend to the sponsor.

Deficiencies to Communicate – ***(Suggested additions are in bold italic type)***.

The post–approval testing protocol needs to be more rigorous. (b) (4) [redacted]

(b) (4) [redacted]

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

/s/

DAVID A PLACE
12/11/2014

ELDON E LEUTZINGER
12/11/2014

RAMESH RAGHAVACHARI
12/11/2014
for Eric Duffy

Review of Chemistry, Manufacturing, and Controls

NDA 202–153

Ruby–Fill®

Jubilant DraxImage, Inc.

by

Chemistry Reviewer: David A. Place, PhD

Division of New Drug Quality Assessment III Branch IX

for

Clinical Review Division: HFD–160

Division of Medical Imaging
and
Office of Generic Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA 202–153

2. REVIEW # 1

3. REVIEW DATE: 17–SEP–2014

4. REVIEWER: David A. Place, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	18–JUN–2010
Amendment	19–MAY–2011
Labeling Amendment (Container)	20–DEC–2011
Labeling Amendment (Package Insert)	25–OCT–2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Jubilant DraxImage
Address:	PO Box 1000, Montville, NJ 07045–1000
Representative:	Philip Johnson, Deputy Director, Global Regulatory Affairs
Telephone:	(973) 487–2181

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ruby–Fill®
b) Non-Proprietary Name: Rubidium Rb–82 Chloride for Injection
c) Code Name/# (ONDQA only): NA
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: NA
- Submission Priority: NA

9. LEGAL BASIS FOR SUBMISSION: Not Applicable to NDAs

10. PHARMACOLOLGICAL CATEGORY/INDICATION: Cardiac Positron Emission Tomography

11. DOSAGE FORM: Sterile solution for injection.

12. STRENGTH/POTENCY:

13. ROUTE OF ADMINISTRATION: IV

14. Rx /OTC DISPENSED: _X_ Rx ____ OTC

15a. SPOTS (Special Products On–Line Tracking System)

_____SPOTS product – Form Completed __X__Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCTS: Not Applicable

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): Rubidium Rb–82 Chloride for Injection
IUPAC name: Rubidium Rb–82 Chloride for Injection
CAS Registry No. [132486-03-4]
Molecular Formula: $^{82}RbCl$
Molecular Weight: 117.5 daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: NA

DMF #	Type	Holder	Item Referenced	Code[a]	Status[b]	Date Review Completed	Comments
(b) (4)	II		(b) (4)	3	Adequate	1/18/2012	Updated 4/17/2012
	II			3	Adequate	1/18/2012	Updated 8/31/2012

a Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

b Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

Patent: NA

Exclusivity: NA.

18. STATUS:

ONDC:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/16/2014	OC
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	Acceptable per this CMC review	9/17/2014	D. Place
DMEPA	Acceptable	4/2/2014	M. Rutledge
EA	Categorical Exclusion – Acceptable	9/17/2014	D. Place
Microbiology	Acceptable	2/29/2012	D. Palmer–Ochieng
DMIP/safety	Deficiencies Identified	6/27/2014	I. Krefting

OGD:

CONSULTS/ CMC Related Reviews	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	N/A		
Methods Validation	N/A		
Labeling	N/A		
Bioequivalence	N/A		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW (OGD Only): ***Not Applicable***

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Chemistry Review for NDA 202–153

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 202–153 is not recommended for approval from a CMC standpoint until a complete response on identified CMC deficiencies is received from the sponsor.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None identified.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The Ruby-Fill® 82Sr/82Rb generator provides an eluted solution of the drug substance, Rubidium Rb82 Chloride Injection in sterile normal saline. ^{82}Rb is produced on the generator by the radioactive decay of ^{82}Sr. ^{82}Sr remains bound to the column while ^{82}Rb is eluted from the column as RbCl with 0.9% sodium chloride.

^{82}Rb decays by positron emission with a half-life of 1.273 minutes (76.38 sec) to stable ^{82}Kr gas. Due to this very short half–life, the Ruby–Fill elution system will be located in very close proximity to directly dose the patient being imaged to allow prompt injection of the Rubidium–82 eluate. Also, due the short half–life (as with other PET radioisotopes), proactive sterility controls must be in place.

B. Description of How the Drug Product is Intended to be Used

It is indicated as an agent for positron emission tomography (PET) imaging, specifically for the assessment of myocardial perfusion to aid in the diagnosis of coronary artery disease, as the Rubidium ions mimic the cardiac biological function of Potassium ions. As this product involves a radionuclide generator and a product delivery device (b) (4) there are two important issues: (1) how the (b) (4) works with the generator and (2) the nature of the various factors underlying user interaction with the system to assure operation of the system to produce a safe product. Accordingly, consults are requested for CDRH Device Engineering and CDRH Human Factors Assessment.

C. Basis for Approvability or Not-Approval Recommendation

A critical CMC issue has been identified in the Chemistry sections of the submission. The level of post–approval testing proposed is inadequate. (b) (4)

III. Administrative

A. Reviewer's Signature

Chemist	David A. Place, PhD	_____	Date: 17-SEP-2014

B. Endorsement Block

Chemistry Lead	Eldon Leutzinger, PhD	_____	Date:
Division Director	Eric P. Duffy, PhD	_____	Date:

cc: Orig. NDA 202–153
HFD–160

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	ANDA202153/000	**Sponsor:**	DRAXIMAGE
Org. Code:	600		7361 CALHOUN PL STE 500
Priority:			ROCKVILLE, MD 20855
Stamp Date:	30-JUN-2010	**Brand Name:**	
PDUFA Date:	30-APR-2011	**Estab. Name:**	RUBIDIUM CHLORIDE RB 82
Action Goal:		**Generic Name:**	
District Goal:	01-MAR-2011	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; GENERATOR; RUBIDIUM CHLORIDE RB-82; (b) (4) mCi	

FDA Contacts:	R. D COSTA	Prod Qual Reviewer	(HFD-623)	2402768407
	M. GONITZKE	Product Quality PM	(HFD-600)	2402768422
	D. DOAN	Regulatory Project Mgr	(HFD-617)	2402769336
	ID = 109049	Team Leader		

Overall Recommendation:	ACCEPTABLE	on 16-JAN-2014	by T. WILSON	()	2404024226
	PENDING	on 02-OCT-2013	by EES_PROD		

Establishment:	**CFN:**	**FEI:**	3009003838
	JUBILANT DRAXIMAGE INC 16751 RTE TRANS CANADA KIRKLAND, , CANADA H9h 4j4		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	POSITRON EMISSION TOMOGRAPHY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-JAN-2014		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	27-DEC-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** (b) (4) **FEI:** (b) (4) (b) (4)		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE OTHER TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-MAR-2013		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

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(b) (4)

Batch Records – Executed, bilingual batch records have been submitted, fully reflecting the manufacturing process and controls.

Satisfactory.

Labeling – The PACKAGE INSERT contains the following black box warning:

(b) (4)

Satisfactory. The Package Insert is equivalent to the reference listed drug.

Container Labels – Since Ruby–Fill is radioactive, there are no internal labels.

Outer Main Label – This label is applied to the lead "pig". It is general in nature.

Satisfactory. Note: None of the labeling (b) (4)

(b) (4)

Deficiencies to Communicate –

The post–approval testing protocol needs to be more rigorous. (b) (4)

(b) (4)

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/s/

DAVID A PLACE
09/17/2014

ELDON E LEUTZINGER
09/17/2014

ERIC P DUFFY
09/19/2014

Initial Quality Assessment (IQA)
For
Division of New Drug Quality Assessment III, Branch VII
Office of New Drug Quality Assessment

OND Division: OGD
ANDA: 202-153
Applicant: Draximage
16751 Autoroute Transcanadienne / Trans-Canada Highway
Kirkland(Quebec) Canada H9H 4J4
Stamp Date: 06/30/2010
Trademark: Ruby-Fill
USAN: None
INN: None
Company Code: None
Established: Rubidium Rb 82 Generator
Dosage Form: Sterile solution
Route of Administration: IV
Indication: assessment of regional myocardial perfusion [redacted] (b) (4)

CMC Lead: Eldon E. Leutzinger, Ph.D., Branch VII

ONDQA Fileability (N/A) YES NO
(OGD function)

Comments for 74-Day Letter: N/A

Summary and Critical Issues:

A. Summary

The **Drug Product** (Ruby-Fill) is a radionuclide generator (Rubidium Chloride Rb 82 Generator) that contains at calibration [redacted] (b) (4) $^{82}SrCl_2$ adsorbed onto hydrous [redacted] (b) (4) stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces Rubidium Chloride Rb 82 Injection USP. It contains [redacted] (b) (4) $^{82}RbCl$ activity delivered depends on the elution rate and the amount of volume eluted, based on the intended dose, as well as (of course) the amount of $^{82}SrCl_2$ adsorbed onto the column. [redacted] (b) (4)
the set up is shown as follows. See the next review page.

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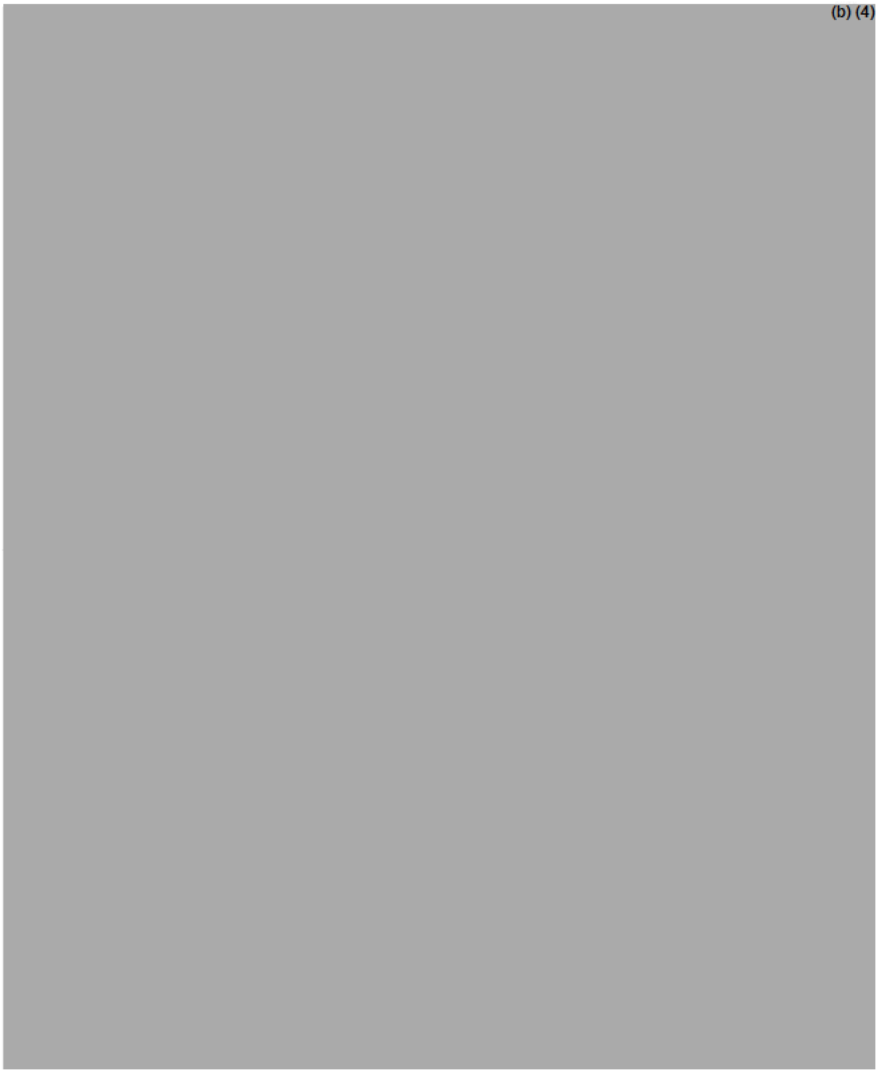
In this IQA, I have not tried to capture all of the considerations and issues that might be involved in this ANDA, but have tried to identify those issues I think are most important and in particular in relation to ^{82}Sr breakthrough, since it relates most severely to generator column performance.

Manufacturing Facilities:



CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 11/27/2012
Division of New Drug Quality Assessment III, Branch VII

Division Director: Eric Duffy, Ph.D.
Division of New Drug Quality Assessment III

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/s/

ELDON E LEUTZINGER
11/28/2012

ERIC P DUFFY
12/12/2012