CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	9/29/2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	202153
Applicant Name	Jubilant DraxImage, Inc.
Dates of Submission	June 18, 2010, resubmitted on 12/30/2015 as Class 2
PDUFA Goal Date	6/30/2016, extended to 9/30/2016 due to a major amendment on 6/11/2016
Proprietary Name **Established (USAN) Name**	Ruby-Fill (Rubidium Rb 82 Generator) Rubidium chloride Rb 82
Dosage Form **Strength**	Sterile solution for intravenous injection. The generator contains between 85 and 115 mCi of Sr82. When eluted at a rate between 15 and 30mL/min, the generator delivers a single dose between 10 and 60mCi of 82RbCl injection at a maximum volume of 60mL per infusion.
Indication	Rubidium Rb 82 chloride injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
<u>Product Quality</u> ONDP/Division II/Branch VI (Drug substance, Drug Product, Process, DMF) OPQ/OPF (Microbiology) OPQ/OPF/DBP/BI (Facilities) OPS/OGD (Microbiology, Regulatory)	 AnneMarie Russell PhD, David Place PhD, Milagros Salazar PhD, and Eldon Leutzinger PhD Yeissa ChabrierRosello PhD and Jessica Cole PhD Michael Klapal Dupeh Palmer PhD, and Martin Shimer
<u>Devices</u> CDRH/GHDB DRH (Radiological Health)	 Robert Myers, Ryan McGowan , Sarah Mollo, Donald Witters, Michael Long, Joseph Jorgens, and Alan Stevens Andrew Kang MD
<u>Clinical</u> DMIP: CDTL Labeling	 Ira Krefting MD Michele Fedowitz MD
DMEPA	Michelle Rutledge PharmD, Yelena Maslov Pharm D, and QuynhNhu Nguyen MS

CDRH: Center for Devices and Radiological Health
CDTL- Cross Discipline Team Leader
CMC - Chemistry Manufacturing and Controls
DMF - Drug Master File
DMEPA - Division of Medication Error Prevention and Analysis
GHDB - General Hospital Devices Branch
OGD - Office of Generic Drugs
ONDP - Office of New Drug Products
OPQ - Office of Pharmaceutical Quality
OPS - Office of Pharmaceutical Science

1. Introduction

This review summarizes my assessment of the approvability of this application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. .

Product

Ruby-Fill is a Strontium 82/Rubidium 82 (Sr82/Rb82) generator and drug infusion and delivery system (Ruby elution system, (b) (4)) that provide an eluted solution of the drug substance Rubidium Rb82 Chloride in sterile additive free 0.9% saline. The generator contains between 85 and 115 mCi of Sr82 at calibration time.

The complete system is composed of a saline bag (b) (4) Rb-82 generator column, (b) (4) and radiation calibrator system. The radionuclide generator contains Sr82 chloride adsorbed onto hydrous (b) (4) stannic oxide packed in a column. The generator eluate containing Rb82 Cl has a stand-alone indication for Positron Emission Tomography (PET) imaging of the myocardium to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease. For these reasons the rubidium Rb82 generator is defined as a PET drug and is regulated under 21 CFR 212. The various components of the drug product delivery system, with the exception of the dose calibrator, are also are also regulated as drugs.

Rb82 decays by positron emission with a half-life of 1.3 minutes to stable krypton gas. Due the short Rb82 half-life the generator with its drug infusion system is designed to deliver promptly an injection of the Rb82Cl eluate.

Regulatory History

The manufacturer, Jubilant Draximage, submitted the original application on June 18, 2010 to the Office of Generic Drugs (OGD) as an abbreviated new drug application (ANDA). The drug product is Ruby-Fill a Sr82/Rb82 generator and drug infusion and delivery system. The Applicant referenced as the listed drug CardioGen-82 a Sr82/Rb82 generator containing 90-150 mCi of Sr 82 and marketed by Bracco Diagnostics under NDA 019414. FDA approved the reference listed drug in 1989.

The final product is rubidium chloride Rb 82 Injection USP solution administered to a patient by infusion. The product [redacted] contains the active ingredient, rubidium Rb82 chloride [redacted] and the inactive ingredient 0.9% sodium chloride.

OGD's Division of Legal and Regulatory Support (Martin Shimer) determined on November 16, 2012 that the application was not eligible for submission under 505(j) because the proposed conditions of use of Ruby-Fill are not the same as those of the proposed RLD due to differences in the rates of infusion ([redacted] ml/min vs. 50 ml/min) and total volumes (maximum of 60 ml vs.100 ml) of the drug product. The ONDP CMC reviewer (Dr. Leutzinger) in a December 12, 2012 memorandum underscored the importance of this difference. The potential for medication error existed if the incorrect rate of infusion specified for a Cardiogen-82 generator were used for the RubyFill generator.

As a result of this finding, the applicant submitted on January 17, 2013 a request for conversion of ANDA 202153 to NDA 202153 under the 505(b)(2) regulations. On January 15, 2013 OGD confirmed that the Office would continue to review the application using its authority to approve 505(b)(2) applications. Finally on September 17, 2014 OGD informed the applicant that DMIP would take the lead in the review of the NDA.

On December 18, 2014 FDA issued a Complete Response letter. The letter included a complete listing of the deficiencies in the application and recommendations to the applicant for addressing them. The major deficiencies involved: human factor study reports and adequacy of user training program; protocols for stability testing of the generator; elution system description and specifications, hazard analysis and safety requirements, performance and reliability, software verification and validation. Sterility assurance was another critical deficiency because of lack of demonstration of control of the risk of cross contamination [redacted]

On December 15, 2015 FDA received a Class 2 resubmission. On June 30, 2016 FDA received a major amendment to the application and extended the review goal date to September 30, 2016.

2. Chemistry Manufacturing and Controls

Product Quality

I concur with the recommendation by the FDA CMC reviewer Dr. Russell that the application be approved from the standpoint of Chemistry, Manufacturing and Controls.

I concur with the assessment by the FDA Microbiology reviewers Dr. Chabrier-Rosello and Dr. Cole that the Applicant has addressed the Microbiology quality deficiencies. I concur that on the basis of acceptable sterility assurance, the application can be approved.

I note that the deficiencies identified by the FDA Chemistry Manufacturing and Controls reviewer Dr. Place regarding the level of post–approval testing proposed (b) (4) have been adequately addressed in the present submission

I reference my earlier concurrence with the findings by the FDA CMC reviewer Dr. Salazar who evaluated the manufacturing processes under DMF (b) (4) and found them to be adequate.

I reference my concurrence with the assessment on May 27, 2011 by the FDA Microbiology reviewer Dr. Palmer that the applicant has demonstrated an adequate level of sterility assurance for the manufacturing process of the generator.

Ruby-Fill Critical Quality Attributes: CMC

Ruby-Fill and its RLD Cardiogen-82 use hydrous stannic oxide as column matrix, and the separation is of the same chemical system (82Sr2+ / 82Rb+). Ruby-Fill differs from the RLD (b) (4)

The specifications for the radionuclide purity of the generator eluate are critical quality attributes for the safety and efficacy of Ruby-Fill. The labeling defines the expiry limits for safe and effective use of the generator. (b) (4)

The CMC reviewer verified the system's performance over the life-time of the generator for the recommended doses, the capability of the dose calibrator to detect strontium at alert levels for the low (10 mCi) dose, and the generator elution volume expiry of 30L. The reviewer requested incorporation of a new flow rate limit (15 mL) in the Ruby-Fill elution system and clear display of current maximum deliverable Rb82Cl dose. The latter provision was considered important for use in patient scheduling and weight based dosing.

Ruby-Fill Critical Quality Attributes: Microbiological

The figure below shows the Ruby-Fill elution system (as diagrammed by the applicant) with emphasis on the fluid path for the administration of Rb82 Cl injection. The potential for a breach in in sterility assurance of the drug product during installation and use including the potential for cross-contamination was an important concern evaluated by the FDA Microbiology reviewers.

The FDA reviewers considered the microbial contamination risks and the following mitigation steps: (b) (4) These steps were considered adequate.

However the results of initial testing did not fully support the adequacy of the mitigation steps. In particular the FDA reviewers requested that the applicant provide additional data on the functionality of the components (b) (4) to prevent patient to patient contamination. The applicant conducted additional validation studies (b) (4) using a dye ingress methodology, positive controls, and simulated worst case conditions. I agree with the Microbiology reviewers that the validation study results show the risk of cross-contamination (b) (4) is well controlled (b) (4)

Device Components

I concur with the assessment by the Mechanical Engineering reviewer Robert Meyer of the General Hospital Devices Branch that the device constituents of Ruby-Fill (Ruby Rubidium Elution System (b) (4)) are acceptable.

I concur with the assessment by the FDA Biocompatibility reviewer Sarah Mollo that the testing of the Ruby-Fill fluid path assembly is adequate and the results are acceptable.

I concur with the conclusions by the FDA reviewers Donald Witters and Michael Long that the electrical and EMC safety of the device are acceptable.

I concur with the assessment by the FDA software reviewer Joseph Jorgens that the software is verified adequately and is acceptable.

I reference my concurrence with Dr. Andrew Kang's May 29, 2014 review of the validation study to assess the accuracy of the break-through testing. The FDA reviewer found the generator breakthrough testing procedure to be acceptable.

The Ruby Elution System is a mobile cart that houses all the components required for the measurement and intravenous infusion of rubidium 82 chloride injection. The system includes a computer (b) (4) generator well, shielding, eluate radioactivity counter, dose calibrator (b) (4)

(b) (4)

In the previous review cycle, the FDA reviewers identified several critical device deficiencies regarding requirements and specifications of the infusion system, performance testing and risk analyses, software analyses, compliance with sterility, biocompatibility and electrical safety, and electromagnetic compatibility standards.

I reference Robert Myer's primary review for the detailed assessment of the applicant's response to each of these deficiencies. I agree with the reviewer's assessment that the deficiencies have been adequately addressed.

The applicant has provided specifications for the Elution System hardware and software performance, usability, and safety. The FDA reviewers examined all the technical specifications, the protocols for testing, the summary of test results and the traceability matrix relating requirements to verification reports for each specific system component. The reviewer determined that the testing methods used and the results are generally acceptable.

In particular, the FDA reviewers examined the quality control testing of Rb82Cl injection conducted to demonstrate the functionality of the generator and elution system under simulated clinical conditions. This testing included the satisfactory verification of the specified accuracy for Rb82Cl dose, volume administered, flow-rate, and elution time. Of critical importance was the verification of the accuracy of the Elution System to detect strontium breakthrough within the specified limits. The FDA reviewers also determined that the testing and results (b) (4) was acceptable. The applicant's risk analysis was also considered adequate.

3. Nonclinical Pharmacology and Toxicology

The applicant did not include nonclinical studies and this submission does not require additional nonclinical data.

4. Clinical Pharmacology and Biopharmaceutics

There is no new clinical pharmacology information in this NDA and none is needed.

5. Clinical Microbiology

This section is not applicable to this NDA.

6. Clinical/Statistical Efficacy

The submission does not include any new efficacy data and none are needed because the Rb82 Cl drug products are identical.

7. Safety

The critical safety issue with Sr82/Rb82 generators is the potential for breakthrough of Sr82 and Sr85. For this reason daily testing of the generator eluate is needed; more intensive testing is needed after small amounts of Sr are detected (alert level) in the eluate. Expiry of the generator is defined by specified level of Sr82 and Sr 85 breakthrough.

The following are the essential labeling specifications for the safe use of the generator.

- Do not exceed a single dose of 2220 MBq (60 mCi)
- Stop use of a generator at an Expiration Limit of:
  - 30 L for the generator's cumulative eluate volume, or
  - 60 days post generator calibration date, or
  - An eluate Sr-82 level of 0.01 µCi /mCi Rb-82, or
  - An eluate Sr-85 level of 0.1 µCi /mCi Rb-82
- Do not exceed a total infusion volume of 60 mL

Rubidium Rb 82 chloride is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration. The use of the radiopharmaceutical contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Labeling mitigates these risks by the following measures: stressing the need for safe handling to minimize radiation exposure to the patient and health care providers; encouraging patients to void as soon as a study is completed; providing organ dosimetry data to estimate radiation absorbed doses; recommending weight-based dosing, and recommending a new lower dose limit.

Myocardial perfusion imaging using Rb82Cl requires the pharmacologic induction of cardiac stress. The stress testing is associated with serious adverse reactions in patients with coronary artery disease. Availability of resuscitation equipment and staff are recommended in labeling to mitigate risk.

Human Factors Studies

I concur with the FDA reviewers' assessment that the deficiencies that prevented the verification of the adequacy of the human factor testing and user training have been addressed in the present submission.

The FDA reviewers determined that the Applicants' methodology of the human factors study in terms of objectives, training provided, use environment, tasks tested are acceptable. The study demonstrated that users who receive training are able to use the product safely and effectively. Ruby-Fill contains multiple components including generator, elution system, (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 include all the necessary steps for safe and effective product use. Hands-on demonstrations will be used in the training and successful completion of a test will be required. Upon completion of the training, the intended user will receive a certificate.

8. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

9. Pediatrics

No pediatric plan was needed for this application because of the initial date of the submission and no plan was provided. The application does not trigger PREA and no pediatric study is planned.

10. Other Relevant Regulatory Issues

Division of Medication Error Prevention and Analysis

I concur with the assessment by the DMEPA reviewer (Dr. Rutledge) on April 1, 2014 that the proposed proprietary name Ruby-Fill is acceptable. Labeling recommendations by the reviewers were accepted by the applicant.

Office of Compliance

I concur with the assessment by Michael Klapal of the Office of Compliance that all the facilities are acceptable to support approval of the application.

There are no significant or outstanding risks to the manufacturing process or final product based on the evaluation of the listed facilities' inspection results, inspectional history, and relevant experience. The Office of Compliance performed the most recent inspection of the facility for manufacturing, release, packaging, labeling, and stability testing of commercial batches of rubidium generator at Jubilant Draximage Inc. (JDI) on 12/17/2015. This facility is considered acceptable for use in the present NDA.

Jubilant Hollister Stier General Partnership (JHS), Canada conducts testing of raw materials, and sterility and endotoxin testing for JDI's finished products. Based on review of previous inspectional findings the facility is considered acceptable.

The Office of Compliance also reviewed the history of inspectional findings for the following control testing laboratories facilities: (b) (4) Each facility was determined to be acceptable.

Labeling Review

I concur with the assessment by Dr. Michele Fedowitz (Associate Director for Labeling) that the Prescribing Information (PI) in its present form is acceptable.

Dr. Fedowitz notes that the major revisions to the PI included changing the format to be consistent with the Pregnancy and Lactation Labeling Rule, and changing the dosage and administration section to provide for weight-adjusted dosing with a lower dosage limit. The recommended dosage is between 10 and 30 Megabecquerels per kg (0.27 to 0.81 millicuries per kg). The review team verified that the comprehensive review of the scientific literature provided by the applicant contained sufficient support for changing the recommended dosing to weight-based

dosing and that Ruby-Fill could deliver the recommended range of doses including a dose as low as 10 mCi. Advances in PET image acquisition technology have made possible the use of lower doses for cardiac visualization and lower doses are consistent with the aim of reducing exposure to radiation to as low as reasonably achievable.

I concur with the assessment by the CMC reviewer Dr. Russell that as revised the User Manual is acceptable. The revisions to the user manual included flow-rate lower limits (15 mL/min), Rb82 delivery activity lower limit (10 mCi) and display of current maximum deliverable dose. The description and sourcing of supplies in the manual were clarified.

Postmarketing Commitments, Other Risk Management Steps
I concur with the FDA reviewer's assessment that none are needed.

11. Decision/Risk Benefit Assessment

I concur with the unanimous recommendation by the FDA reviewers that Ruby-Fill be approved.

In the present application the manufacturer has addressed the deficiencies identified in FDA's complete response letter dated December 18, 2014. The deficiencies included requirements and specifications of the infusion system, performance testing and risk analyses, software analyses, compliance with sterility, biocompatibility and electrical safety and electromagnetic compatibility standards, human factor studies, training program for the users and a testing program for post-approval (b) (4)

I concur with the assessment by the CDTL reviewer, Dr. Krefting, that Rb82Cl remains a valuable diagnostic radiopharmaceutical for use in PET myocardial perfusion imaging at rest and stress in patients with suspected or existing coronary disease. The risk/benefit of the radiopharmaceutical remains unchanged.

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

/s/

LIBERO L MARZELLA
09/30/2016