CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	12/11/2014
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	202153
Applicant Name	Jubilant Draximage
Date of Submission	June 18, 2010
PDUFA Goal Date	10/11/2014
Proprietary Name **Established (USAN) Name**	Ruby-Fill Rubidium Rb82 Chloride for Injection
Dosage Form **Strength**	Sterile solution for injection The generator contains (b) (4) Sr82. (b) (4) generator delivers a single dose of NMT 60mCi and (b) (4) a maximum volume of 60mL per infusion (b) (4)
Indications	for assessing regional myocardial perfusion (b) (4)
Regulatory Action	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
Clinical	Ira Krefting MD
CMC	David Place PhD, Milagros Salazar PhD, and Eldon Leutzinger PhD
OGD/Microbiology	Dupeh Palmer PhD
OGD/DLRS	Shimer Martin
DMEPA	Michelle Rutledge PharmD, Yelena Maslov Pharm D
CDRH/GHDB	Ryan McGowan and Alan Stevens
CDRH/DRH	Andrew Kang MD
CDRH	Quynh Nhu Nguyen PhD

OND - Office of New Drugs
ONDQA - Office of New Drug Quality Assessment
CMC - Chemistry Manufacturing and Controls
DMEPA - Division of Medication Error Prevention and Analysis
OGD - Office of Generic Drugs
DLRS - Division of Legal and Regulatory Support

CDRH - Center for Devices and Radiological Health
DRH - Division of Radiological Health
DAGRID - Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices
GHDB - General Hospital Devices Branch

1. Introduction

This review summarizes my assessment of the approvability of this application under section 505(b)(2) of the statute.

Product

Ruby-Fill is a Strontium 82/Rubidium 82 (Sr82/Rb82) generator and drug infusion and delivery system that provides an eluted solution of the drug substance Rubidium Rb82 Chloride in sterile 0.9% saline. The generator contains (b) (4) 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 is regulated as a drug while the drug product delivery system is regulated as a device.

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 Rubidium82 eluate. The drug product is proposed for use for cardiac perfusion imaging using Positron Emission Tomography (PET).

Regulatory History

The manufacturer, Jubilant Draximage, submitted this marketing 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. The reference listed drug was approved in 1989.

The final product is Rubidium Chloride Rb 82 Injection USP solution administered to a patient by infusion. The product (b) (4) contains the active ingredient, rubidium chloride (b) (4) and the inactive ingredient 0.9% sodium chloride.

OGD's Division of Legal and Regulatory Support (Shimer Martin) 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 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 OND CMC reviewer (Dr. Leutzinger) in a December 12, 2012 memorandum underscored the importance of this difference. The potential for medication error exists if the incorrect rate of infusion specified for a Cardiogen-82 generator were used for the Ruby-Fill 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.

2. Chemistry Manufacturing and Controls

The Ruby-Fill elution system is diagrammed below. [redacted]

[redacted]

Product Quality

I concur with the assessment by the CMC reviewer Dr. Place that the level of post–approval testing proposed [redacted] is inadequate. This is a critical deficiency [redacted]

The CMC reviewer determined that product complies with the USP monograph for the Rubidium 82 generator. [redacted] The generator is eluted with additive–free 0.9% sodium chloride for injection (USP). [redacted] $Sr82Cl_2$ is the precursor radionuclide. It is sourced from [redacted] The CMC reviewer Dr. Salazar reviewed the manufacturing processes under DMF [redacted] and found them to be adequate.

Device Components

I concur with the assessment by the GHDB reviewers Drs. McGowan and Stevens (see May 5, 2014 review) that critical deficiencies in the application with regard to the elution system preclude an assessment of the safety and efficacy of the system.

The infusion system consists of [redacted] The elution system's physical layout and system integration are designed for real-time error detection and process monitoring. [redacted]

The elution system is provided with all the components necessary for use, including an onboard dose calibrator and a computer. The unit is on wheels for positioning near the PET camera in close proximity to the patient receiving the infusion of drug.

The consultants' evaluation called attention to the need for requirements and specifications of the infusion system, performance testing and risk analysis and software analysis. Serious deficiencies also included the lack of verification of compliance with sterility, biocompatibility and electrical safety and electromagnetic compatibility standards.

Microbiological Quality

I concur by 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.

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

One 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 and expiry of generator is defined by level of Sr82 (0.01 microCi/mCi rb82) and Sr 85 (0.1 microCi /mCi Rb 82) breakthrough. The breakthrough limits are the same as those for Ruby-Fill and the RLD and are acceptable. Other expiry criteria for time post calibration date or total eluate volume (respectively 60 days and 30 L for Ruby-Fill).

Human Factors Studies

I concur with the FDA reviewers' findings that these deficiencies of human factors studies prevent the verification of the adequacy of the human factor testing and are grounds for a complete response action.

The FDA human factors specialist Quynh Nhu Nguyen on May 29, 2014 completed a consultative review of the human factor validation study and usability risk analysis report provided by the Applicant. The reviewer determined that the study report was materially incomplete and identified concerns with the methodology used in the studies. The FDA primary clinical reviewer (Dr. Krefting) independently reviewed the study reports and agreed with the consultant on the key deficiencies in the study reports.

Dr. Krefting identified the following specific deficiencies that need to be addressed.

- The protocols for the studies titled: “Ruby Rb-82 Elution System Usability Risk Analysis” (10/17/2013) and “Ruby Rubidium Elution System Summative Usability Validation Report” (1/28/2014) were not provided.
- Data from a testing site (Brigham and Women’s and Cardiac Imaging Associates) were not provided.
- It is not clear if a separate training manual or the general user manual was used for the testing and if mitigation strategies have been adopted and retesting performed.

Break-through testing validation

I concur with the FDA reviewer finding on May 29, 2014 that the generator breakthrough testing procedure is acceptable.

Dr. Andrew Kang performed a consultative review of the validation study to assess the accuracy of the break-through testing of the generator. Break-through testing is a critical product quality control procedure that the user is required to perform daily. The testing is designed to assess the level of Strontium 82 and 85 activity in the Rubidium 82 eluate and is one of the determinants of generator expiry.

8. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

9. Pediatrics

No pediatric plan was needed because of the initial date of the submission and none 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. Dr. Rutledge’s assessment is consistent with previous review conducted by DMEPA on December 16, 2010.

Review of the product labeling has been deferred. We have asked DMEPA to evaluate the potential for medication errors and recommend mitigation strategies that might be needed for the use of CardioGen-82 and Ruby-Fill in the same clinical facility. Both final products consist of radioactive Rubidium for use in cardiac imaging. However, the two rubidium generators differ in the volumes and flow rates of the injected infusion into the patient.

Office of Compliance

The Office of Compliance performed an inspection of the facility for manufacturing, packaging and labeling of commercial batches of Rubidium generator at Jubilant Draximage and issues an "acceptable" decision on January 16, 2014. The OC also inspected the following facilities: (b) (4) Each facility was determined to be acceptable and the overall recommendation by the Office on May 1, 2014 was "acceptable".

Labeling Review

The manufacturer has revised the labeling on OGD's advice. Dr Krefting review describes a number of differences between the use of the Ruby-Fill and the RLD that raise the potential of medication errors. This issue remains under review.

I concur with Dr. Krefting's assessment that the lack of adequate information in the application regarding the training program for the users is a major deficiency. Training requirements and training packages should be finalized prior to marketing.

Complete review of the labeling is deferred until the deficiencies in the application are addressed.

11. Decision/Risk Benefit Assessment

I agree with the assessments by the clinical and human factors specialist reviewers, the CMC reviewers, and the GHDB reviewers that serious deficiencies in the marketing application preclude an assessment of the safety and efficacy of Ruby-Fill.

DMIP communicated to the applicant the outstanding deficiencies in the NDA in teleconferences held on December 12 and 17, 2014. The applicant will need to address the outstanding issues for Ruby-Fill related to human factor studies, training program for the users and a testing program for post-approval (b) (4) Data on the overall system performance and reliability, electrical safety and electromagnetic compatibility, biocompatibility and infection control are needed. Validation of the system software is also necessary.

Given these deficiencies a complete response action will be taken.

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/s/

LIBERO L MARZELLA
12/18/2014

Date: 11/28/14

Division of Medical Imaging Products

Clinical Review

Ruby-Fill

NDA 202-153

Reviewer: Ira Krefting, M.D.

Background

Ruby Fill is a "bed-side" drug production system to produce rubidium 82 (Rb 82), a radioactive drug administered during nuclear cardiac testing to aid in the identification of coronary artery disease by outlining regions of decrease myocardial perfusion. Ruby Fill consists of a Rb 82 generator column containing radioactive strontium (Sr 82), the parent of Rb 82, and an administration cart with computerized functions for direct administration of Rb 82 to the cardiac imaging patient. Rb 82 mimics Potassium which is metabolically active in cardiac muscle and extracted by the myocardium proportionally to blood flow; therefore Rubidium 82's radioactive emissions provide images of functioning/ nonfunctioning cardiac muscle and coronary blood flow. Ruby Fill is similar to CardioGen, a rubidium generator that has been on the market for over 20 years, but differs from CardioGen in generator design and Rb 82 dose administration parameters.

The main safety concern inherent to Rubidium generators is leaching of radioactive Strontium isotopes from the generator column into the elution which is then injected into a patient. Rubidium 82 has a half-life of 75 seconds, the Strontium isotopes have longer half-lives and expose the patient to unnecessary additional radiation. Rubidium generators should be designed and labeling instructions provided, to insure that the radioactive isotopes of Strontium in the patient infusion is below the USP standards: The activity level of Sr 82 should not be more than 0.02 microCi per mCi of Rb 82 and Sr 85 is not more than 0.2 microCi per mCi of Rb 82 (USP Monographs: Rubidium Chloride Rb 82 Injection). For example, the Strontium level expiration limits for CardioGen were set at: 0.01 microCi/ mCi of Rb 82 for Sr 82 and 0.1 microCi/ mCi Rb 82 for Sr 85 (both half of the USP limits).

Regulatory History

The application was received on June 18, 2010 and was initially managed by OGD since Ruby-Fill was considered a generic product with CardioGen being the reference listed drug (RLD). Upon further review, differences in design and administration rates were identified and led to the application being reclassified as a 505(b)(2). In view of this designation and DMIP's familiarity with CardioGen, the application was transferred to DMIP for further review and regulatory action.

Clinical Data

No clinical data was provided in the application and none is needed. The supportive clinical studies cited in the Clinical Studies section (section 14) of the proposed Ruby Fill label are the same studies cited in the existing CardioGen label. The literature citations provided in the original Ruby Fill application date from the early 1990's and relate to the general development of a rubidium generator.

CMC Review

Dr. David Place reviewed the design of the Ruby-Fill generator column that contains Strontium 82. A pure saline solution (no Calcium should be present) is passed through the column to capture Rb 82 which is the daughter of the radioactive decay of Strontium 82. Rubidium 82 undergoes further decay to Krypton, an inert gas, which is expelled from the lungs. Dr. Place found no deficiencies with the column design. (b) (4) Elution of the Ruby-Fill generator in a manner consistent with clinical usage (item G, Dr. Place's review) did not reveal any Strontium in the elution until day (b) (4) of generator elution and then the Strontium was at a minimal level below concerns for Strontium "breakthrough" (Strontium in the elution beyond the USP or product defined limit).

Dr. Place did identify a critical concern: The post-approval testing is inadequate. The sponsor plans to (b) (4) Dr. Place recommends that (b) (4) (item H, Dr. Place's review).

Human Factors

The human factors study should demonstrate that representative operators can use the manual – Instructions for Use (IFU) effectively. To evaluate the adequacy of the human factors study, DMIP reviewed the following sponsor provided reports:

Ruby Rb-82 Elution System Usability Risk Analysis (10/17/2013)
Ruby Rubidium Elution System Summative Usability Validation Report (1/28/2014)

Rb-82 Elution System Hazard Analysis (4/28/2011)

In general the sponsor followed the guidance titled: “Applying Human Factors and Usability Engineering to Optimize Medical Device Design“ for performing a human factors study and presenting the results. As recommended in the guidance likely users, in this case nuclear technologists, performed the testing procedures on a standard Ruby-Fill production line generator in simulation mode. This scenario adequately reproduced the clinical experience and allowed for the identification of any safety issues in the operation of Ruby-Fill. The performance of the technologists was observed; coaching was only done when failure to perform a specific task would impede the rest of the testing procedure (such as difficulty with use of the “on” switch). The participants also rated the quality of the instruction manual. The sponsor did not provide all the detailed testing results from the participants, precluding FDA’s ability to adequately review the study. From the limited information available for review, no major safety issues were identified.

CDRH also performed a review of the human factors studied and identified several methodological deficiencies such as concerns about the background training of the technologists and coaching. These concerns were reconciled in a dialogue between DMIP and CDRH; For example; DMIP deemed it acceptable for participating technologist not to have experience with CardioGen; the testing could be done in small cohorts of 2 technologists at a time; and limited coaching was acceptable as noted above.

DMIP identified the following critical concerns upon reviewing the human factor study reports submitted by the sponsor:

1. The protocols for the listed studies were not provided to FDA.
2. The detailed results were not provided to FDA from subjects at the Brigham and Women’s and Cardiac Imaging Associates sites participating in the study reported in the “Ruby Rubidium Elution System Summative Usability Validation Report”.
3. From the provided data, DMIP cannot discern whether a separate training manual or the user manual provided to FDA was the basis of operational learning for the subjects who participated in the studies.
4. Regarding the “Ruby Rb-82 Elution System Usability Risk Analysis”: DMIP cannot discern which mitigation strategies (such as responses to computer inputing errors) have been instituted and whether additional testing has been performed to confirm their efficacy.

Label Review

The supplied label generally parallels the CardioGen label and has been updated through subsequent submissions as modifications have taken place to the CardioGen label. This labeling review section highlights the differences between Ruby-Fill and CardioGen; this section should not be construed as a complete labeling review. Comparisons with CardioGen are solely for illustrative purposes.

The Ruby Fill label states that the infusion system automatically checks the dose for the level of Rb 82 and contaminants of Sr 82 and Sr 85; for CardioGen these functions require dose manipulations and hand calculations by the user. Below is a comparison of the Ruby-Fill labeled submitted on 9/23/2013 (CTD Module I -1.14.1.3 Package Insert) to the CardioGen label approved on 2/08/2012.

- Boxed Warning:

  a. The Ruby Fill alert levels (when additional Sr testing should be done) for Sr 82 and Sr 85 are double those of CardioGen. *Reviewer's Note: The CardioGen Alert Limit was set by the sponsor* (b) (4) *for the presence Sr 82 and Sr 85 in the administered dose (see Background section. Subsequent "stress" testing of CardioGen generators demonstrated that these Alert Limits were appropriate to ensure product quality.*

  b. When the alert levels are reached for Ruby Fill, repeat breakthrough testing is performed after every 4 patients instead of 750 ml for CardioGen. *Reviewer's Note: For Ruby Fill, after the alert limit was reached, repetitive testing would take place* (b) (4) *--see section 2.2 b below. "After every 4 patients" is vague and does not account for the potential of small dose volumes. Final labeling should contain a repetitive testing interval determined by a specific elution volume metric in mL).*

  c. The volume expiration limit is 30 L compared to 17 L for CardioGen.

  d. The time expiration limit is 60 days compared to 42 for CardioGen.

  e. The expiration levels of Sr 82 and Sr 85 are identical for Ruby Fill and CardioGen.

Section 2 Dosage and Administration

- **2.2 Rubidium Rb 82 Chloride Injection Dosage:**

  a. Ruby-fill is to be eluted at a rate of (b) (4) mL/minute; for CardioGen the rate is 50 ml/min.

  b. For Ruby Fill the maximum administered volume is 60 ml and a cumulative volume (rest/stress) of 120 ml; for CardioGen the maximum administered volume is 100 mL and a cumulative volume (rest/stress) of 200 mL. *(Reviewer's Note: With both Ruby Fill and CardioGen the same amount of Rb 82 is delivered over the same time period. Only the volume of the infusion varies.)*

- **2.4 Directions for Eluting Rubidium Rb 82 Chloride Injection**

  a. Discard the first 75 mL each day; for CardioGen discard 50 mL

- **2.5 Eluate Testing Protocol**

  a. The Ruby Fill label states: (b) (4) *Reviewer's Note:* (b) (4) *The user manual provides details on the actual operation of the Ruby Fill generator (see below).*

  b. For Ruby Fill 75 mL of Sodium Chloride Injection is to be flushed automatically; the CardioGen label states 50 mL.

  c. For Ruby Fill the generator recharge is "approximately 15.2 minutes"; for CardioGen it is 10 minutes.

  d. After step 7, the label states: " (b) (4) Table 1 to calculate the decay factor for Rb-82; step 4 (above). *Reviewer's Note: The label probably is referring to "R" which is described in step 3 & 5. The calculations seem to be made automatically anyway.*

- **3 Dosage Forms and Strengths**

  a. Ruby Fill has (b) (4) millicuries of Sr-82 at calibration time; CardioGen has 90-150.

- **16 How Supplied/Storage and Handling**

a. The Ruby-Fill generator is encased in a lead shield; CardioGen is encased in a lead shield surrounded by a labeled plastic container.

b. The Ruby-Fill generator should be stored at [redacted] C ([redacted] F); CardioGen is to be stored at 20-25° C (68-77° F)

Conclusions of the Labeling Review

The Ruby Fill label generally follows both the format and details of the CardioGen label; the Rb 82 dose administered to the patient is the same with either generator. [redacted] Ruby-Fill is [redacted] contained in a smaller volume (60 mL –Ruby-Fill versus 100 mL CardioGen). The Ruby-Fill label is generally clear and indicates that most preparatory steps will be performed automatically by the onboard computer.

User Manual

User Manual version 4.5 was reviewed.

The manual is aimed at the technologist and provides basic information about the system and details about operating the system and quality controls. [redacted]

[redacted]

For illustration, graphical user interfaces (GUI) taken from the provided manual are shown below.

Figure 1: Display before starting a patient

Figure 1: Patient set up with infusion options

Conclusions of the Manual Review

The instructions appear succinct and easy to follow. (*See the Human Factors section for further details on the expectations for a manual – Instructions for Use- IFU document.)* The recommendations for the user manual reflect general observations:

- The table of contents should have a page number adjoining each listed item for quick reference. An index would also be helpful.
- A section on responding to critical, serious emergencies would be helpful.
- The manual contains several typographical errors, lacks clear page numbering and text overrunning images – a final edition will require further editing.
- It is unclear whether this particular version of the manual has been validated for use by representative, potential operators.

Training

This reviewer was unable to identify a "Training Manual" in the submissions from the sponsor. This review is based on the information quoted from the User Manual version 4.5:

(b) (4)

The draft guidance containing training recommendations for training with devices (cited above) has the following advice that is relevant to Ruby-Fill:

"Training requirements and training packages should be finalized prior to clinical use of the device, whether that use occurs with the IDE submission or following FDA clearance".

Conclusion of the Review of the Training Provision

- No information is presented to judge the adequacy of this program, its effectiveness, and need for retraining. The sponsor has not fulfilled the recommendations of the draft guidance.
- The training program could parallel the voluntary program instituted by the CardioGen sponsor.

- The sponsor should develop a program to monitor the use of the generators and confirm the safe use by the clinical sites. Unless adverse reactions or irregularities are identified in generator use, reporting can be on a routine basis consistent with NDA safety reporting requirements.

Regulatory Action

Rub-Fill is Rb 82 generator undergoing review through the 505 (b)(2) pathway. This review has identified deficiencies that need to be addressed. For this reason I recommend a CR action. A complete review of the package insert will be deferred until all the CMC, manual and training issues are addressed.

Below are the specific deficiencies to be addressed by the sponsor:

1. CMC- The post-approval testing is inadequate. As recommended by Dr. Place, the sponsor should provide an adequate post-approval (b) (4) program.

2. Regarding the incomplete information in the Human Factors Studies. The following requests are made:

    a. Provide the protocols for the human factor studies.

    b. Detailed results from subjects participating in the Ruby Rb-82 Elution System Usability Risk Analysis at the Brigham and Women's and the Cardiac Imaging Associates sites are missing. Provide the details results in the same format as the results from the Hartford site.

    c. For the deficiencies (such as computer input errors) identified in the "Ruby Rb-82 Elution System Usability Risk Analysis" provide the mitigation strategies and the results of testing that supports the utility of the proposed mitigation stategies

3. Regarding the Training Program- Provide specific proposals for a training program and a methodology to document its effectiveness. Training requirements and training packages should be finalized prior to clinical use.

4. Regarding the User Manual- Provide 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.

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/s/

IRA P KREFTING
12/09/2014

LIBERO L MARZELLA
12/11/2014
I concur with Dr. Krefting's assessment and recommended regulatory action