CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	Sept. 8, 2016
From	Ira Krefting, M.D.
Subject	Cross-Discipline Team Leader Review
NDA Supplement#	202-153
Applicant	Jubilant Draximage
Date of Submission	June 18, 2010
PDUFA Goal Date	Sept. 30, 2016
Proprietary Name / Non-Proprietary Name	Ruby Fill/ Rubidium 82
Dosage form(s) / Strength(s)	Intravenous dosing 10-30 Megabecquerels (Mbq)/kg [0.27-0.81 millicuries (mCi/kg)]
Applicant Proposed Indication(s)/Population(s)	RUBY-FILL is a closed system used to produce rubidium Rb 82 chloride injection for intravenous administration. Rubidium Rb 82 chloride injection is indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease. Population: Adult patients
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as the applicant's proposal

Benefit-Risk Summary and Assessment

The Ruby-Fill generator and infusion system provides an improvement in the imaging modalities currently available to aide in the diagnosis of coronary artery disease. Coronary artery disease is a significant, ubiquitous public health concern and prompt, accurate diagnosis to facilitate early treatment is important. Another Rubidium generator, CardioGen (during the initial submission and review cycle - designated as the Reference Listed Drug – RLD), was approved in 1989, so there is extensive clinical experience with Rubidium 82 cardiac imaging. The major safety concern with Rubidium generators is the inadvertent release of excess radioactive Strontium, the Rubidium 82 parent, into an administered dose of Rubidium 82 (called: "breakthrough" see below). Advances in PET imaging devices and extensive clinical experience, allowed for approval of weight based dosing methodology for Ruby-Fill, whereas the RLD had a general dosing recommendation. Potential microbiologic egress and the inability of the Ruby-Fill to deliver the labeled dosing range through its life cycle were specific review issues which were successfully resolved.

Rubidium 82 with a 75 second half life is intravenously infused into a patient being evaluated for coronary artery disease. Since Rubidium has similar chemical and physical characteristics to Potassium, Rubidium as if were Potassium, will be taken up by viable cardiac cells; obstructed coronary vessels and dead cardiac will not show this uptake. Positrons emitted as Rubidium 82 decays will be imaged by PET, Positron Emission Tomography, outlining vascular regions of obstruction and infarction.
Rubidium 82 PET cardiac images are considered by some clinicians to be clearer than SPECT cardiac images. Ruby-Fill provides Rubidium 82, the identical imaging drug produced by CardioGen. The PET images produced with the Rubidium 82 from Ruby-Fill should be of the same quality as those from CardioGen and for which there is extensive clinical experience. The radiation exposure with Rubidium is lower than the exposure with SPECT agents. (b) (4)

Over the course of the NDA review the major safety concerns and undeliverable dosing issue were evaluated and resolved:

Regarding excess Strontium (breakthrough) in the eluate: All Rubidium generators have a small, allowable amount of Strontium 82 and 85 in the eluate administered to the patient. (b) (4) Ruby-Fill employs a computerized system of daily testing to monitor the level of Strontium in the eluate. Strontium may deposit in bone and with its long half life mayincrease the radiation exposure of patients (b) (4) re-testing for Strontium "breakthrough" is automatically performed after every 4 patients. (b) (4) Generators are also removed from service when 30 liters of saline have passed through them or after 60 days. (b) (4)

(b) (4)

Regarding microbiologic concerns: Microbiologic contamination risk was investigated by a dye study recommended by the microbiology reviewers. The reviewers designed a study with the sponsor (b) (4) Data from this study led the microbiology reviewers to conclude the microbiological safety of Ruby-Fill is acceptable.

Regarding an undeliverable labeled dose: Detailed review of the generator output testing by the CMC staff led to the finding that Ruby-Fill in clinical use could not reliably produce the Rubidium doses in the upper range of the proposed labeled dosing (60 mCi) as the generator aged toward expiration. The older the generator, the smaller the maximum dose it can produce. Therefore heavier patients requiring higher Rubidium doses could not be adequately imaged with the Rubidium 82 output from an older generator. This limitation has been added to labeling. The sponsor has also demonstrated that the generator can also produce the low dose of 10 mCi.

In toto, Ruby-Fill provides a safe modality for imaging patients with suspected or clinically diagnosed coronary artery disease. The major safety concern of Strontium breakthrough has been dealt with through a vigorous Strontium monitoring requirement which has proven effective when instituted for CardioGen; computerization in Ruby-Fill has made the monitoring process more efficient. (b) (4) The risk of microbiologic contamination has beencontrolled. Dosing limitations by generator age have been added to the label and instructions for use manual to minimize the risk that patients requiring a high Rubidium dose will be unable to undergo a scheduled imaging study due to the inability of the generator to produce that dose. New dosing recommendations are now weight based.

The review team has determined that the Ruby-Fill pharmaceutical quality is acceptable and the risks of, Strontium breakthrough and microbiologic ingress, haveadequately controlled. The risk benefit ratio is favorable and Ruby-Fill is recommended by the CDTL for approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Coronary artery disease evaluation	**No new clinical data was presented in the NDA. However, the RLD, CardioGen approved in 1989, has been useful in the evaluation of coronary artery disease. Since both generators are systems for the production of Rubidium 82, equal utility is expected from Ruby-Fill**
Current Treatment Options	Myocardial perfusion imaging CardioGen • SPECT scans • Exercise testing	Ruby-Fill is useful for the evaluation of myocardial perfusion in patients with known or suspectedcoronary artery disease.
Benefit	• Less radiation exposure compared to radioactive imaging agents used with SPECT scan • PET scans havegood image quality and acceptable diagnostic performance	Ruby-Fill is a Rubidium 82 generator with a design that limits the potential for radioactive Strontium 82, the parent of Rubidium, to enter the dose administered to a coronary imaging patient
Risk	• Undiagnosed coronary artery disease • Unintended radiation exposure to Strontium in the event of a breakthrough	Undiagnosed can lead to sudden death. Ruby-Fill when used according to the label serves as a diagnostic imaging aid with minimal risk. Otherwise more invasive tests.
Risk Management	• Presence of radioactive Strontium breakthrough into the administered dose. The risk is managed by: • Strontium alert and expiration levels. Improved testing for possible breakthrough	Improved testing for possible Strontium breakthrough compared to the RLD

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1. Background

Product Information

Ruby-Fill is a Rubidium 82 generator that provides the drug product Rubidium 82. Rubidium decays in 75 seconds to inert Krypton gas and is promptly infused into a patient for cardiac perfusion imaging using Positron Emission Tomography. The system consists of generator containing the parent element Strontium 82 (Sr82) and a computerized drug delivery system that delivers a solution of the Rubidium (Rb82) in sterile (Calcium free) 0.9% saline; referred to in this review and label as the eluate. (b) (4) saline from a standard source is passed through the generator to dissolve Rubidium 82 as Strontium 82, the parent, decays; the eluate is then monitored for radioactivity in the infusing sytem and then immediately administered to the imaging patient. The generator contains 85-115 mCi of Sr82 at calibration time prior to the generator's release for clinical use. figure 1 shows a schematic of the generator and elution system

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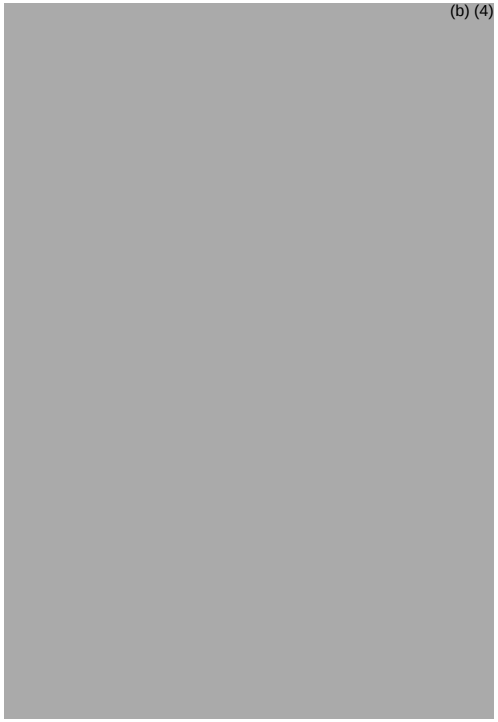

Figure 1: Ruby-Fill Schematic

Therapeutic context

Ruby-Fill is intended to aide in the diagnosis of coronary artery disease. The PET images produced following its administration show areas of possible coronary artery disease which potentially could be treated with a variety of modalities. The intended population is adults, primarily out patients, with clinical risk factors and/or symptoms of coronary artery disease.

Regulatory History

Ruby-Fill, NDA 202-153, received a complete response to its first cycle review on December, 18, 2014. The Complete Response letter outlined multiple deficiencies identified in the CMC, microbiologic, and electronic aspects of the NDA;

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these deficiencies were summarized in 22 major questions/comments to the sponsor. This CDTL document encapsulates the second review cycle during which the sponsor provided specific responses to the 22 questions/comments and developed remedies such as additional studies to rectify the deficiencies identified in the Complete Response letter.

This is the second review cycle. N202-153 was filed as an ANDA with Office of Generic Drugs (OGD) on June 18, 2010 and transferred to DMIP as a 505(b)(2) NDA on September 17, 2014. During the review in OGD, CDRH was consulted for various design and electronic issues. Due to the novelty of the generator and its computerized controls, the reviews took an extensive time period. Concerns were raised about its comparability to CardioGen (N019-414), the reference listed drug (RLD). Following an internal review, OGD determined that critical differences in design and conditions of use were present compared to CardioGen and the application was transferred to DMIP.

DMIP led the subsequent review which concluded with the identification of multiple deficiencies primarily related to CMC, microbiologic and electronic issues. A CR letter issued on December 18, 2014 which catalogued the deficiencies and provided recommendations for remedies. The sponsor submitted a revision on December 30, 2015 for this review with an action date of June 30, 2016. The review was extended 90 days to September 30, 2016 due to a major amendment for further microbiological engress testing.
Foreign Use: The Ruby-Fill generator with a different infusion system has been in limted use as part of clinical trials in Canada and Switzerland.

2. Product Quality

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(b) (4)

(b) (4)

Figure 2:

I concur with the conclusions of Dr. Russell that the sponsor provide adequate data to support approval.
Following their resubmission, the sponsor engaged in a dialogue with the CMC staff via IR letters and TCONs to address the deficiencies identified in the CR letter of December 18, 2014.
Below is summary of the resolution of these deficiencies (numbering from the CR letter):

Deficiency #3: Post approval (b) (4) testing
Resolution: (b) (4)

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(b) (4)

Deficiency # 4: Ruby elution system instructions for use (IFU) document (b) (4)
Resolution: Recommended edits made to the IFU document. (b) (4)

Deficiency #18b: Particulate Matter. Review of this issue is contained in Appendix 1 of Dr. Russell's review. The particulate matter meets specifications of USP <788>.

CMC issues identified during the review

Ability of the generator to produce the entire labeled dose range:
The sponsor proposed extending the dose range of 30-60 mCi from the RLD to 10-60 mCi.

Provision of a low dose of Rubidium 82
Recent clinical publications suggested that doses below those in the RLD label might be adequate and spare low weight patients unnecessary radiation exposure. During the review cycle the sponsor requested that doses below the RLD recommendations be added to the Ruby-Fill label; the lowest dose being 10 mCi. This request for low dosing was extensively investigated by Ann Marie Russell, the CMC reviewer, and I agree with her conclusions. The labeling implications for this dosing was reviewed by Dr. Fedowitz (section 11).
The review investigation centered around the ability of the generator to accurately provide doses in the 10 mCi range particularly the concern that a "fully [Strontium 82] loaded" generator early in its life cycle could produce a low dose at a volume that could be administered to the patient. CMC also questioned Strontium breakthrough detectability in these low doses.
Resolution: The sponsor provided clinical simulation testing that demonstrates that the generator performs within the sponsor's 10% acceptance criteria for dose error for the for total administered doses of (b) (4) mCi of Rubidium 82. This span of Rubidium 82 radioactive content would generally be sufficient for the final proposed labeled dosing range for likely patients (0.27-0.81 mCi/kg).

(b) (4)

See Figure 2 above.

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Summary Statement from Ann Marie Russell, the CMC reviewer (Executive Summary, page 21):

"The average dose error in [redacted] (b) (4) ranged from 2-3%, in [redacted] (b) (4) they ranged from 2-4% and in [redacted] (b) (4) they ranged from 2-3%. Additionally, all of the individual measured dose errors met the Ruby RbES system requirement specifications (± 10%) and were well within the U.S. Nuclear Regulatory Commission (*i.e. NRC)* limits for Dose Accuracy of Diagnostic Radiopharmaceuticals (± 20%)".

Provision of a 60 mCi Rubidium 82 dose

The CMC reviewers noted that based on the additional data provided by the sponsor, the generator could not provide the upper limit dose of 60 mCi as the generator advanced in age towards expiration.

Resolution: The inability to provide a large dose has significant clinical implications since a patient requiring such a dose might be schedule for a scan only to arrive at the imaging and told it could not be performed. If performed with a lower dose in a heavy patient, the resultant images might be unintereptable. The sponsor provided the graph in figure 3 which demonstrates the maximum dose that can be delivered as a function of generator age. In view of this finding, labeling has been revised to inform the clinician of the maximum dose available over the generator's lifecycle. Additionally, the installed software will reject a dosing order if the generator cannot provide that dose on a given day in its life cycle. The instructions for use manual has been significantly revised to inform the operator of the availability of a selected weight based dose.

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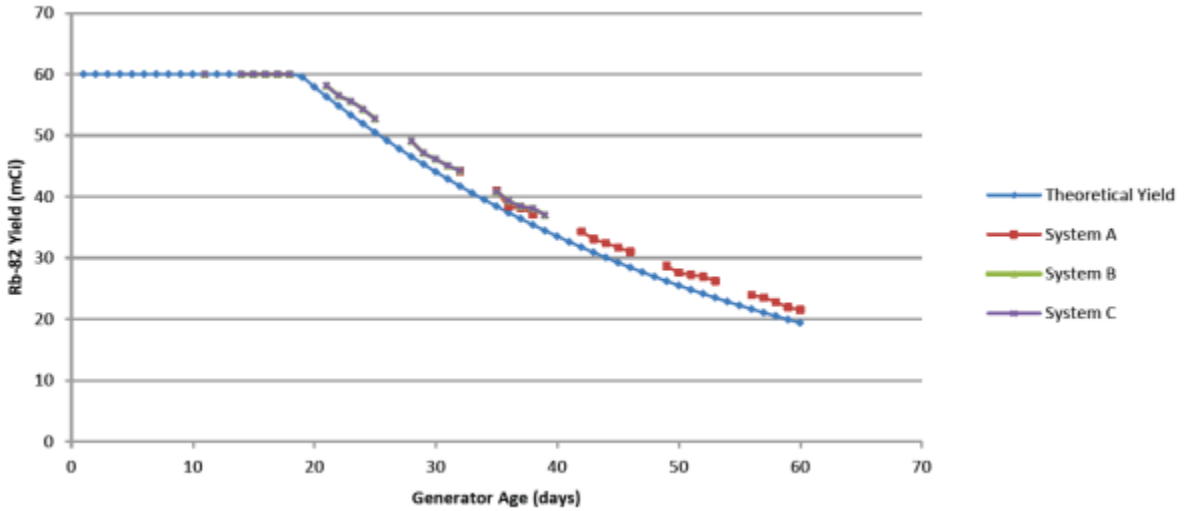

Figure 3: RUBY RbES (Effusion System) Performance (i.e. available dose) According to Generator Age – Three systems tested

Strontium breakthrough measurement at low Rubidium 82 dose:
Resolution: The sponsor explained that the breakthrough is determined by the daily calibration which uses a standard dose of 35 ml and depends on the amount of Rubidium 82 delivered by the generator in the calibration dose – not a specific patient dose.

CDRH Review
I concur with the CDRH recommendation for approval in the review by Robert Meyer. CDRH provided an analysis of the following deficiencies:

Deficiency #6: Hazard analysis and safety requirments
Resolution: The sponsor provided acceptable Fault Tree Analyses (FTA) and Design Failure Mode and Effect Analyses.

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Deficiency #7: System performance and reliability – software issues
Resolution: The sponsor identified the delivery mode specifications which are acceptable and verified adequately.

Deficiency #8: Performance, reliability and safety of mechanical components of the system
Resolution: The sponsor provided an acceptable Traceability Matrix.

Deficiency #9: (CDRH aspect) [redacted]
Resolution: [redacted] there is no evidence of degradation by radiation. The sponsor also provided adequate information regarding functionality and biocompatibility.

Deficiency #10: Waste management
Resolution: The daily waste is far less than the waste container 1 Liter volume. It would take several days of operator error for an overflow.

Deficiency #11: Risk assessment of residual drug in the administration lines
Resolution: [redacted]
The minimum time between patient procedures is 10 minutes and Rubidium 82 has a half life of 75 seconds. Due to this short half life, CDRH considered the risk of residual drug exposure as acceptable.

Deficiency #12: Documentation [redacted]
Resolution: [redacted] Ruby-Fill passed all of the [redacted] tests.

Deficiency #13: Risk assessment of air within the infusion system
Resolution: [redacted]
CDRH noted [redacted] but this is no clinical concern since Rubidium 82 is administered intravenously and air would be trapped in the lung. Air bubbles are safely introduced intravenously for some echocardiogram studies.

Deficiency #14: Verified and validated software
Resolution: Software consultant, Joseph Jorgens III, reviewed the software and deemed it acceptable.

Deficiency #15: Review of off-the-shelf (OTS) software

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Resolution: Software consultant, Joseph Jorgens III, reviewed the software and deemed it acceptable.

Deficiency #16: Electrical safety and electromagnetic compatibility
Resolution: Ruby-Fill was tested for compliance with appropriate electrical standards and deemed approval.

Deficiency #18: (CDRH aspect) Risk assessment of the device-related residuals
Resolution: See Deficiency 9 and 11.

3. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology data was provided with this submission and none is necessary since the drug Rubidium 82 has already been in clinical use for over 20 years.

4. Clinical Pharmacology

Clinical pharmacology supplied a review supporting the weight-based dosing recommendation.

5. Clinical Microbiology

The microbiology reviewed focused on the potential for organisms to migrate from the patient [redacted] (b) (4) and such egress could potentially infect subsequent patients. I agree with the conclusions reached by Drs. Jessica Cole and Yeissa Chabrier Rosello that the sponsor has provided adequate information and studies to demonstrate that the Microbiological safety of the elution system is acceptable.

Deficiency #5: Mitigation of contamination [redacted] (b) (4)
Resolution: The sponsor provided details [redacted] (b) (4)

Deficiency #9: Data demonstrating that 60 days will degrade microbiologic safety.
Resolution: Clinical simulation testing: "The results show that through the duration of the system's shelf-life, the drug product remains sterile and meets the acceptance criterion for endotoxin limit."

Deficiency #17: Sterility for the disposable components of the Ruby Elution System.
Resolution: The firm provided package labeling detailing the sterilization process (b) (4)

Deficiency #19: Concern about the risk of disease transmission occurring from cross contamination (b) (4)

Resolution:
The sponsor agreed to perform another dye ingress study simulating conditions of use as specified by the microbiology reviewers.

From the microbiology review page 19:

(b) (4)

See Figure 4.

Figure 4: Simulation testing for dye egress. (b) (4)

Overall Microbiology Conclusion

The microbiology reviews found the test results acceptable and recommended approval.

6. Clinical/Statistical- Efficacy

The submission does not include any new efficacy data and none are needed because the performance characteristics of Rubidium 82 PET are well known.

7. Safety

The major safety issue based on previous experience with CardioGen is the potential for excess Strontium 82 and Strontium 85 to enter the administered eluate . Strontium 82 with a half-life of 25 days is the parent of Rubidium and Strontium 85 (half-life 65 days) is also contained in the generator. As noted previously in this review, the main theoretical concern is bone marrow toxicity from these bone seeking, long lived radioactive Strontium isotopes. Ruby-Fill has a computerized system to perform daily tests for Strontium in the eluate. Once an "Alert" level is reached indicating an increased, but still acceptable level of Strontium in the eluate, repeat Strontium testing is then performed after every 4 patients. If the Strontium level on this repetitive testing reaches (b) (4) the generator has reached expiration and removed from clinical service. Additionally, expiration can also be reached after 30 liters of flows through the generator or after 60 days of use. Exceeding these volume and time parameters may in themselves lead to Strontium "breakthrough". The Ruby-Fill computerized system will not allow dosing to occur if these parameters are exceded.

Safety Update
The sponsor provided updated safety information. Ruby-Fill has not been in routine clinical use outside of the United States. There have been some clinical trial use in Switzerland and Canada. In Canada, Ruby-Fill has been used in the ARMI (Alternative Radiopharmaceutical for Myocardial Imaging) and other smaller clinical studies. The sponsor reports one case in 2011 of Strontium "breakthrough" in which the patient did receive unintended radiation exposure. Investigation of the case reveal that the Ruby-Fill generator had undetected manufacturing deficiencies which were not a systemic issues.

Other CR questions related to Safety

I concur with the DMEPA reviewers that the sponsor provided an adequate Human Factors study and training program.

Deficiency #1 Inadequate data reporting in the Human Factors Study
Resolution: The sponsor provided additional data from study participants at all the sites where the study was performed. With this additional data. DMEPA concluded the Human Factors Study was acceptable and demonstrated that Ruby-Fill could be used properly by trained nuclear medicine technicians

Deficiency#2 Provision of a training program
Resolution: The sponsor provided detailed plans for a training/re-training program; DMEPA concluded that the plans were adequate.

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8. Advisory Committee Meeting

No advisory committee is needed since Rubidium 82 is not a new molecular entity.

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

There are no outstanding relevant regulatory issues.

11. Labeling

Updated labeling
I concur with the review and recommendations by Dr. Fedowitz.

Prescribing Information

Dosing and Administration

The labeling review centered on determining an optimal dosing regimen based on the data provided by the sponsor concerning the minimum and maximal doses the generator could provide over its life cycle. Additionally the sponsor provided publications which indicated that advances in PET imaging equipment allowed for the administration of lower doses than originally recommended by the sponsor and in the CardioGen label.

The sponsor provided dosing recommendations based on the guidelines from various academic organizations. FDA responded by requested supporting data to justify their recommendation . The sponsor replied in SD 44 by providing 36 peer reviewed publications in which various doses of Rubidium 82 were utilized. The submission was extensively

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reviewed by Dr. Fedowitz, the DMIP Associate Director for Labeling. Twelve studies used weight based dosing (3-10 MBq/kg) with a mid-range of activity of 24 mCi and a range of 16-32 mCi. There were 16 additional studies using weight-based dosing where the MBq/kg was not provided. In these studies the mean activity was 44.4 mCi with a lower bound in the range of 20 mCi. Eight studies used fixed dosing with a mid-range activity of ~44 mCi and a lower bound in the range of 15 mCi. The most relevant publication cited by the sponsor was the ARMI study (Kaster, et. al. J Nucl Cariol. 2012 Dec 19(6): 1135-45) in which a small subgroup of patients underwent cardiac catheterization:
From Dr. Fedowitz's review.
"The authors used weight based dosing (10 MBq/kg) in approximately 1500 patients to a develop normal database (77 patient studies) to be used for quantification of myocardial perfusion and diagnosis of CAD using low-dose Rb 82 and 3D EPT CT imaging. In addition, 45 patients who had angiography and PET CT were used to evaluate the accuracy of the database using automated analysis (SSS)." Table 1 provides dosing infomation from the study

Dosing Regimen	Mid-range Activity	Range
10 MBq/kg	~25 mCi	9.7-56 mCi

Table 1: Dosing information from the ARMI study

The sponsor provided updated dosing recommendations (b) (4)

(b) (4)

FDA Dosing Recommendations
The review team concluded that the data provided demonstrated that weight based dosing was already in extensive clinical use with doses below the RLD recommendation and the ARMI study in conjunction with the other studies provided adequate supportive data for the sponsor's dosing recommendation.
Since imaging technology rapidly changes and varies with imaging center, (b) (4) the clinician is provided with an extensive dosing range. Differing from the RLD, the label has a weight based dosing recommendation – MBq/kg or mCi/kg – where the lowest dose the generator can produce supported by

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sponsor CMC data is 10 mCi. Except for very low weight patients, most patients would receive doses in the 20 to 30 mCi range which is in the range found in more recent publications provided by the sponsor.

From the draft label with FDA edits accepted by the sponsor:

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

Accuracy of Dosing

The label also notes that the measurement of the radiation dose is accurate within ±10%, a standard set by the sponsor. Using the computerized system, the clinician may put in the patient's weight; with a previously selected MBq/kg (or mCi/kg) from the label, the computer will calculate the dose for the patient.
To alert clinicians to dosing limitations with an aging generator, the label contains a table showing the maximum dose the generator can deliver over its life span.

Boxed Warning, Warnings & Precautions

The Boxed Warning was maintained as with CardioGen because Strontium breakthrough is a fundamental concern with Rubidium 82 generators. Ruby-Fill has safeguards to avoid excess Strontium in the eluate so the "Alert" level parameters which were arbitrarily chosen for CardioGen are less stringent than for Ruby-Fill. Ruby-Fill can accommodate a large volume of saline throughput in the generator and has a longer half-life.

Parameter	CardioGen (RLD)	Ruby-Fill
Alert Limits		
Sr 82 microCi/mCi Rb 82	0.002	0.004
Sr 85 microCi/mCi Rb 82	0.02	0.04
Volume (Liters)	14	20

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Expiration Limits		
Sr 82 microCi/mCi Rb 82	0.01	0.01
Sr 85 microCi/mCi Rb 82	0.1	0.1
Volume (Liters)	17	30
Days	42	60

Table 2: Comparison of Alert and Expiration Parameters for CardioGen and Ruby-Fill

The Instruction for Use document was similarily revised to reflect the changes noted in the labeling.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There are no REMS for Ruby-Fill

Postmarketing Requirements (PMRs) and Commitments (PMCs)

None are needed.

13. Recommended Comments to the Applicant

The CDTL recommends approval.

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/s/

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09/29/2016

LIBERO L MARZELLA
09/29/2016