

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202153Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

<b>Clinical Pharmacology Review</b>	
<b>NDA</b>	202-153
<b>Submission Date</b>	December 28, 2015 (SDN 30) May 3, 2016 (SDN 33) July 25, 2016 (SDN 44)
<b>Brand Name</b>	RUBY-FILL (rubidium Rb 82 generator)
<b>Formulation</b>	For intravenous administration
<b>OCP Reviewer</b>	Christy S John, Ph.D.
<b>OCP Team Leader</b>	Gene M. Williams, Ph.D.
<b>OCP Division</b>	Division of Clinical Pharmacology V
<b>OND Division</b>	Division of Medical Imaging Products
<b>Applicant</b>	Jubilant Draximage, Inc.
<b>Submission Type</b>	Resubmission/Class 2
<b>Dosing regimen</b>	(b) (4)
<b>Indication</b>	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

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## 1 EXECUTIVE SUMMARY

The current NDA is a re-submission of a 505(b)(2) NDA that received a complete response (CR) on December 18, 2014. The CR letter was issued due to deficiencies in clinical (human factors study and training materials) and chemistry and manufacturing controls (CMC). The prior NDA was not reviewed by clinical pharmacology because of the similarity of the product and proposed package insert to those of the referenced approved product, Cardiogen. The current submission is being reviewed because labeling negotiations for the current NDA resulted in the applicant suggesting that section **2 Dosage and Administration** of their package insert deviate from that of Cardiogen.

The proposed package insert changes are supported by literature publications and broadly consistent with the guidelines of professional societies. In principle, we find them acceptable.

### 1.1 Recommendations

The re-submission is approvable from a clinical pharmacology perspective.

### Labeling Recommendations

Our recommendations for the package insert appear in Section **3 DETAILED LABELING RECOMMENDATIONS**.

### 1.2 Post-Marketing Requirements and Commitments

We have no recommendations for PMRs or PMCs.

### 1.3 Summary of Clinical Pharmacology Findings

No clinical or clinical pharmacology studies were conducted by the applicant. The reference drug for the current 505 (b) (2) NDA is Cardiogen. The Cardiogen package insert recommends a dose of 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30-60 mCi), and an upper limit of 2220 MBq (60 mCi).

Rather than duplicating the Cardiogen package insert, the applicant proposes weight-based dosing. To support their proposal, the applicant conducted a MEDLINE database search for the period of 1/1/2007 to 6/29/2016. Of the 36 pertinent articles, studies, 12 studies used weight-based dosing (3-10 MBq/kg) with a mid-range of activity 24 mCi and a range 16-32 mCi. There were 16 studies using weight-based dosing which did not provide the dose, the mean activity administered in these studies was 44 mCi, and the lowest administered dose was 20 mCi. Eight studies used fixed dosing with a mid-range activity of 44 mCi and the lowest administered dose was 15 mCi. None of the 36 studies included comparisons between two or more doses.



The applicant's proposal to base recommendations on current clinical use as identified by literature articles and the judgment of professional societies is reasonable. The proposal includes a dose range sufficiently wide to allow institutions with 2D-imaging cameras to dose within the package insert recommendations. At the same time, those with 3D-imaging cameras can choose lower doses that are within the package insert range. As coupling the dose with the imaging technology is currently rejected, we agree with the proposal to give a broad dose range. We also agree with the use of weight-based dosing, as it is supported by the clinical use data and will minimize unnecessary radiation exposure.

## **SIGNATURES**

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Reviewer: Christy S John, Ph.D.  
Division of Clinical Pharmacology V

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Team Leader: Gene Williams, Ph.D.  
Division of Clinical Pharmacology V

Cc: DMIP: PM F. Lutterodt.; MTL I. Krefting; MO M. Fedowitz, I. Krefting  
DCPV: DDD B. Booth; DD A. Rahman

## 2 QUESTION-BASED REVIEW

### 2.2 GENERAL CLINICAL PHARMACOLOGY

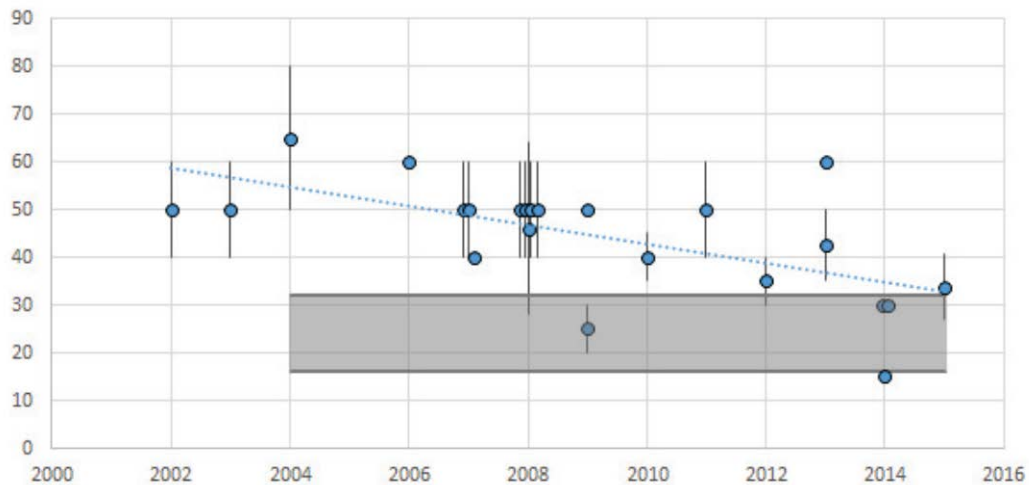
#### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The reference drug for the current 505 (b) (2) NDA is Cardiogen. The Cardiogen package insert recommends a dose of 1480 MBq (40 mCi), with a range of 1110-2220 MBq (30-60 mCi).

No clinical studies were conducted by the applicant.

Rather than duplicating the Cardiogen package insert, the applicant proposes weight-based dosing. To support their proposal, the applicant conducted a MEDLINE search for the period of 1/1/2007 to 6/29/2016. Of the 36 pertinent articles, 12 studies used weight-based dosing (3-10 MBq/kg; 0.081-0.27 mCi/kg) with a mean activity of 24 mCi and a range 16-32 mCi. There were 16 studies using weight-based dosing which did not provide the dose, the mean activity administered in these studies was 44 mCi, and the lowest administered dose was 20 mCi. Eight studies used fixed dosing with a mean activity of 44 mCi, and a lowest administered dose of 15 mCi. None of the 36 studies included comparisons between two or more doses.

The applicant presents data showing that from 2002 to 2016 there was a trend of decreasing administered radioactivity (**Figure 1**).



**Figure 1.** Administered radioactivity (mCi) versus time (calendar year); each data point is a literature study, vertical lines are ranges within the study, points in gray area not included in dotted trend line.

*Reviewer's Comment*

A formal meta-analysis for efficacy was not conducted by the applicant. The applicant's implicit reasoning is that the widespread use of lower dosing is evidence that lower doses provide adequate efficacy.

The decrease in dose across time that the applicant presents coincides with the introduction of 3D PET imaging equipment. 3D acquisition can allow greater resolution, thus allowing equi-effective imaging at lower radioactivity doses.



The applicant's proposal to base recommendations on current clinical use identified from literature articles and the judgment of professional societies is reasonable. The proposal includes a dose range sufficiently wide to allow those with 2D-imaging cameras to dose within the package insert recommendations. At the same time, those with 3D-imaging cameras can choose the lower doses that are within the package insert range. As coupling the dose with the imaging technology is currently rejected, we agree with the proposal to give a broad dose range. We also agree with the use of weight-based dosing, as it is supported by the clinical use data and will minimize unnecessary radiation exposure.

### **3 DETAILED LABELING RECOMMENDATIONS**

The package insert proposed in the July 25, 2016 submission, together with our recommended edits, appears below as **Table 1**.

Table 1. Package Insert	
Applicant's Proposed	Reviewer's Recommended
(b) (4)	<p><b>2.2 Recommended Dose and Administration Instructions</b></p> <ul style="list-style-type: none"> <li>• The recommended weight-based dose of Rb 82 to be administered per rest or stress component of a PET myocardial perfusion imaging (MPI) procedure is between 10-30 Megabecquerels (MBq)/kg [0.27-0.81 millicuries (mCi)/kg].</li> <li>• Do not exceed a single dose of 2220 MBq (60 mCi).</li> <li>• Use the lowest dose necessary to obtain adequate cardiac visualization and individualize the weight-based dose depending on multiple factors, including, patient weight, imaging equipment and acquisition type used to perform the procedure. For example, 3D imaging acquisition may require doses at the lower end of the recommended range compared to 2D imaging.</li> </ul>

Comment [WGM1]: Section number changed (b) (4) to 2.2 due to re-arrangement of other elements of section 2 by Medical Officer

(b) (4)

- Administer the single dose at a rate of 15 - 30 mL/minute through a catheter inserted into a large peripheral vein; do not exceed an infusion volume of 60 mL.
- Instruct patients to void as soon as a study is completed and as often as possible thereafter for at least one hour.
- The maximum available activity (delivery limit) will decrease as the generator ages [*see Dosage and Administration (2.8)*].

### **2.3 Image Acquisition Guidelines**

#### For Rest Imaging:

- Administer a single (“rest”) rubidium Rb 82 chloride dose;
- Start imaging 60-90 seconds after completion of the infusion of the rest dose and acquire images for 3-7 minutes.



(b) (4)

For Stress Imaging:

- Begin the study 10 minutes after completion of the resting dose infusion, to allow for sufficient Rb 82 decay;
- Administer a pharmacologic stress agent in accordance with its prescribing information;
- After administration of the pharmacologic stress agent, administer the second dose of Rb 82 at the time interval according to the prescribing information of the pharmacological stress agent;
- Start imaging 60-90 seconds after completion of the stress rubidium Rb 82 chloride dose infusion and acquire images for 3-7 minutes.

For Both Rest and Stress Imaging:

- If a longer circulation time is anticipated (e.g., in a patient with severe left ventricular dysfunction), start imaging 120 seconds after the rest dose.
- Acquisition may be started immediately post-injection if dynamic imaging is needed.

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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.**  
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/s/  
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CHRISTY S JOHN  
09/30/2016

GENE M WILLIAMS  
09/30/2016  
I concur with the recommendations

## DIVISION OF BIOEQUIVALENCE REVIEW

<b>ANDA No.</b>	202153*
<b>Drug Product Name</b>	Rubidium Chloride Rb-82 Generator (Ruby-Fill®)
<b>Strength(s)</b>	N/A** (Generator of (b) (4) mCi of Strontium 82 (Sr 82))
<b>Applicant Name</b>	Jubilant DraxImage Inc.
<b>Address</b>	16751 TransCanada Highway Kirkland, Quebec, Canada H9H 4J4
<b>Applicant's Point of Contact</b>	Hari Nagaradona INC Research, LLC *** 7361 Calhoun Place, Suite 500 Rockville, MD 20855-2765
<b>Contact's Telephone Number</b>	301-296-1370
<b>Contact's Fax Number</b>	301-838-3182
<b>Original Submission Date(s)</b>	6/18/2010
<b>Submission Date(s) of Amendment(s) Under Review</b>	N/A
<b>Reviewer</b>	Rong Wang, Pharm.D., Ph.D.
<b>Study Number (s)</b>	NA
<b>Study Type (s)</b>	(b) (4)
<b>Strength (s)</b>	Generator of (b) (4) mCi Sr 82
<b>Clinical Site</b>	NA
<b>Clinical Site Address</b>	NA
<b>Analytical Site</b>	NA
<b>Analytical Site Address</b>	NA
<b>OUTCOME DECISION</b>	<b>ADEQUATE</b>

\* As advised by the Agency, the current submission was converted from an Abbreviated New Drug Application (ANDA) under section 505 (j) to a New Drug Application (NDA) under Section 505 (b) (2) of the statute. The OGD retains limited authority to approve 505(b)(2) applications and NDA 202153 was determined to be one of those applications<sup>1,2</sup>. Therefore, NDA 202153 is being reviewed by the Office of Generic Drugs (OGD).

\*\* In the Orange Book, the strength is listed as N/A for the RLD product.

\*\*\* According to the Form-356h submitted on 1/17/2013.

<sup>1</sup> Note: Details please also see the internal email communications within OGD in section 4 Appendix in the current review.

<sup>2</sup> DARRTS: ANDA 202153; EDR submission on 1/17/2013; Cover Letter.

## 1 EXECUTIVE SUMMARY

This application which was initially submitted as an Abbreviated New Drug Application (ANDA), [REDACTED] (b) (4)

[REDACTED] for the test product, Rubidium Chloride Rb 82 Generator, (u) (4) mCi of Sr-82 at calibration time. The reference listed drug (RLD) product is Cardiogen-82<sup>®</sup> (rubidium chloride Rb 82 Generator), 90-150 mCi of Sr-82 at calibration time, manufactured by Bracco Diagnostic, Inc. (NDA 019414, approved on 12/29/1989).

According to the internal meeting minutes dated 11/16/2012<sup>3</sup>, the generic applicant for ANDA 202153 proposed different 'condition of use' in the label for the test product (Infusion Rate and Maximum Volume to be administered) compared to the RLD product. Due to differences in the drug products' labeling, the Office of Generic Drugs (OGD) considered that the test product is NOT eligible for approval under section 505 (j) of the statute. Additionally, on December 12, 2012, the Office of New Drug Quality Assessment (ONDQA) completed its initial quality assessment on the test product, in response to the consult request from the OGD's Division of Chemistry. The ONDQA reviewer [REDACTED] (b) (4)

[REDACTED] raised safety concerns for the different infusion rate proposed for the test product (Ruby-Fill<sup>®</sup>) from the RLD product (Cardiogen-82<sup>®</sup>). As advised by the Agency, the firm then resubmitted the application to the OGD as a New Drug Application (NDA) under section 505 (b) (2)<sup>1</sup> (for details please also see section 4 Appendix). According to the email sent by Thomas Hinchliffe from OGD, NDA 202153 will still be reviewed by OGD.

Rubidium Chloride Rb 82 Generator (Ruby-Fill) contains Sr 82 chloride adsorbed onto hydrous (b) (4) stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces the final product, Rubidium Chloride Rb 82 Injection USP. [REDACTED] (b) (4)

[REDACTED] The Division of Bioequivalence I (DBI) has reviewed the component and composition of the final product. The final product, Rubidium Chloride Rb 82 Injection USP solution administered to a patient by infusio (b) (4) (4)

[REDACTED] contains the active ingredient, rubidium chloride (b) (4) and the inactive ingredient (0.9% sodium chloride). [REDACTED] (b) (4)

[REDACTED] (b) (4)

<sup>3</sup> DARRTS: ANDA 202153; DOAN, DAT T 11/16/2012 N/A 11/16/2012 FRM-MINUTES-01 (Internal Meeting Minutes) Original-1 (Unknown) Archive

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### 3 SUBMISSION SUMMARY

#### 3.1 Drug Product Information<sup>4</sup>

<b>Test Product</b>	Rubidium Chloride Rb 82 Generator, (b) (4) mCi of Sr 82 (Ruby-Fill®)
<b>Reference Product</b>	Cardiogen-82® (rubidium chloride Rb-82 Generator) , 90-150 mCi of Sr 82
<b>RLD Manufacturer</b>	Bracco Diagnostics Inc.
<b>NDA No.</b>	019414
<b>RLD Approval Date</b>	December 29, 1989
<b>Indication<sup>5</sup></b>	CardioGen-82® is a closed system used to produce rubidium chloride Rb 82 for intravenous injection use. Rubidium chloride Rb 82 injection is a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.

#### 3.2 PK/PD Information<sup>5</sup>

<b>Bioavailability</b>	Intravenous, therefore 100%.
<b>Food Effect</b>	Not applicable for I.V. injection
<b>Tmax</b>	Not indicated in the drug label
<b>Metabolism</b>	Not indicated in the drug label
<b>Excretion</b>	With a physical half-life of 75 seconds, Rb-82 is very rapidly converted by radioactive decay into trace amount of stable Kr-82 gas, which is passively expired by the lungs. Renal and hepatic excretion is not anticipated to play an essential role in Rb-82 elimination, although some of the Rb-82 dose may be excreted in the urine prior to radioactive decay.
<b>Half-life</b>	The physical half-life of Rb-82 is 75 seconds.
<b>Drug Specific Issues (if any)</b>	<p><b><u>Black Box Warning</u></b></p> <p><b>WARNING: UNINTENDED STRONTIUM-82 (Sr-82) AND STRONTIUM-85 (Sr-85) RADIATION EXPOSURE</b></p> <p>Unintended radiation exposure occurs when the levels of Sr-82 or Sr-85 in the rubidium Rb 82 chloride injection exceed specified limits</p> <p>Perform generator eluate tests:</p> <p>(b) (4)</p>

<sup>4</sup> Orange Book, Search Term: rubidium, last accessed on 1/22/2013.

<sup>5</sup> Drugs@ FDA, Search term: rubidium; Label information, last access 1/22/2013

		(b) (4)
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### 3.3 OGD Recommendations for Drug Product

<b>Number of studies recommended:</b>	N/A-Waiver Request
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<b>Analytes to measure (in plasma/serum/blood):</b>	NA	(b) (4)
<b>Source of most recent recommendations:</b>	None available from OGD. However, FDA's draft Guidance- FDA Oversight of PET Drug Products – Questions and Answers, issued February 2012 is available @ <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM290024.pdf</a>	

**Summary of OGD or DBE History (for details, see Appendix 4.2):**

As of 1/22/2013, the OGD has received only one control correspondence related to Rubidium Rb 82 generator, which was submitted by Draximage on 6/12/2008. The control correspondence was requesting a type C meeting with the Agency to discuss issues related to filing requirement, chemistry, manufacturing and control (CMC) and clinical/pre-clinical data. This control correspondence still remains open in the database.

As of 1/22/2013, no protocols were listed for Rubidium Chloride Rb 82 generator in the OGD protocol database.

As of 1/22/2013, there is no other ANDA application submitted to the OGD for Rubidium Chloride Rb 82 Generator besides the current ANDA.

According to DARRTs, Draximage submitted an ANDA (ANDA 202134) to the Office of Generic Drugs on June 21, 2010 to seek approval of generic Rubidium Chloride Rb 82 injection. Draximage also submitted another ANDA (ANDA 202153) seeking approval of Rubidium Chloride Rb 82 generator on 6/30/2010. According to the memo dated on 1/6/2011 (DARRTS, **Shimer, Martin H, 1/06/2011, FRM-ADMIN-29 (Cancel Application), General Information-1**), ANDA 202134 was canceled due to the following reason:

*Since both the information submitted for the Rubidium Chloride 82 Generator, in the context of ANDA 202153, and the drug product information submitted in the context of ANDA 202134 are reviewed and regulated by CDER it is unnecessary to maintain two ANDAs for these products. For that reason the information originally submitted in ANDA 202134 was converted into an amendment to ANDA 202153. All information related to the Draximage Rubidium Chloride Generator and Injection Drug Product will now be reviewed in the context of ANDA 202153.*



### 3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	-
Single-dose fed	No	-
Steady-state	No	-
In vitro dissolution	No	-
Waiver requests	Yes	1
BCS Waivers	No	-
Clinical Endpoints	No	-
Failed Studies	No	-
Amendments	No	-

### 3.5 Formulation

Location in appendix	Section 3.7, Page 7
If a tablet, is the RLD scored?	NA
If a tablet, is the test product biobatch scored	NA
Is the formulation acceptable?	Yes
If not acceptable, why?	Not Applicable

### 3.6 Waiver Request(s)

Strengths for which waivers are requested	(b) (4) mCi of Sr-82 at calibration time
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	Yes. However, the final determination is pending the acceptance by the Division of Chemistry (b) (4)
If not then why?	Please see comment below

### 3.7 Formulation

**Table 1. Comparative Formulation of the Final Product (Rubidium Chloride Injection Solution) for the Test and RLD Products**

Ingredients	Rubidium Chloride Rb 82 Generator Test Product Draximage Inc.	Cardiogen-82® Generator RLD product Bracco Diagnostics Inc. <sup>6</sup>	Function
Rubidium Chloride	Variable (mCi/mL)	Variable (mCi/mL)	Active Ingredient
Sodium Chloride	0.9%*	0.9%**	Inactive Ingredient

\*Module 3, Section 3.2.P.1 page 1 of 3 of the original submission indicates that additive free 0.9% Sodium Chloride Injection USP is used for elution of the product. Rubidium Chloride Injection is a solution of RbCl in 0.9% sodium chloride.

\*\* The RLD product labeling states additive-free Sodium Chloride Injection USP is used to elute the generator but does not specify a concentration of sodium chloride used in the elution. However, per Study Protocol # 20484-1 in NDA 019414 (Volume A1.1), normal saline was used to elute the generator in the clinical study.

Is there an overage of the active pharmaceutical ingredient (API)?	No.
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	See below

**Reviewer’s Comments:**

1) Rubidium Chloride Rb 82 Generator (Ruby-Fill) contains Sr 82 chloride adsorbed onto hydrous <sup>(b) (4)</sup>stannic oxide in a column. Elution of the generator column with 0.9% Sodium Chloride Injection USP produces the final (finished) product, Rubidium Chloride Rb 82 Injection USP. <sup>(b) (4)</sup>

<sup>(b) (4)</sup> So the final product, Rubidium Chloride Rb Injection is a sterile, non-pyrogenic aqueous solution of RbCl in 0.9% sodium chloride, which is a parenteral solution intended solely for administration by injection. Due to the extremely short physical half-life (75 seconds) of the finished drug product, it needs to be manufactured at the facility where it is to be administered.

2) For PET drugs, the radioactive concentration (e.g., mCi/mL) at the calibration time is generally considered to be the strength. For the multi-dose generator this is generally at the end of synthesis (EOS) i.e. the end of manufacturing of the finished drug product.

The test product (Rubidium Chloride Rb Injection) contains <sup>(b) (4)</sup> the same inactive ingredient (0.9% sodium chloride) as the RLD product. However, the radioactivity of Rb 82 per mL of eluate (i.e. the concentration of active ingredient in the final

<sup>6</sup> NDA019414, volume 1.1(hardcopy), Clinical Report #20484-1.

product) could vary depending on the elution rate and the potency of the Rb 82 generator (the radioactivity of Sr 82) decay corrected to the day of administration. It should also be noted that although the radioactivity of Rb 82 per mL of eluate could vary in both test and RLD products, the dose (i.e. radioactivity of Rb 82) administered to a patient is precisely controlled by a specifically designed infusion system for both test and RLD products, respectively. (b) (4)

[Redacted]

3) The information (b) (4) has been consulted to CDRH for review. But, there has not been a formal review by CDRH (b) (4)

[Redacted]

4) The Office of New Drug Quality Assessment (ONDQA) has completed its initial quality assessment on ANDA 202153 in response to a consult request from the Division of Chemistry. The reviewer of ONDQA listed the following table in the review, comparing the dosing between the test product (Ruby-fill) and the reference product (Cardiogen-82)<sup>7</sup>:

	Max Activity (single dose)	Range of Dose (single dose)	Max Volume (single dose)	Rate of Infusion
Ruby-Fill	60 mCi (Rec: (b) (4) mCi)	(b) (4) – 60 mCi	60 mL	(b) (4) mL/min
Cardiogen-82	60 mCi (Rec: 40 mCi)	30 – 60 mCi	100 mL	50 mL/min

The reviewer of ONDQA provided the following comments with regard to the infusion rates:

*The infusion rates are different. The rate for Cardiogen-82 is 50 mL/min, compared to (b) (4) mL/min for Ruby-Fill. That for Cardiogen-82 is (b) (4) greater than for Ruby-Fill. Hence, the maximum volume for Cardiogen is (b) (4) 100 mL. The maximum volume for Ruby-Fill is (b) (4) 60 mL.*

[Redacted]

<sup>7</sup> DARRTS: ANDA 202153; LEUTZINGER, ELDON E 12/12/2012 N/A 12/12/2012 FRM-ADMIN-01(Memorandum to File) Original-1 (Unknown) Archive

5) In response to the meeting request submitted by the applicant (Draximage) on 10/25/2012, an internal meeting was held to discuss the questions related to ANDA 202153. According to the meeting minutes dated on 11/16/2012<sup>3</sup>, Shimer Martin from OGD provided the following comment with regard to the approval eligibility of the test product as ANDA:

*Both the Statute at 505(j)(2)(A)(v) and the regulations at 21 CFR 314.94(a)(8)(iv) allow for differences in labeling that are due to differences in manufacturer/manufacturing or in the labeling of a drug product submitted pursuant to an approved Suitability Petition(21 CFR 314.93). Furthermore, the CFR at 314.92 describes drug products for which an ANDA may be submitted. Among the criteria for submission as an ANDA under 314.92, is the requirement that an applicant's proposed drug product has the same conditions of use as the drug product cited as your Basis of Submission. The Dosage and Administration section of your proposed drug product incorporates differences related to the rate of infusion and the maximum volume of solution to be administered. The Office of Generic Drugs does NOT consider these changes to be permissible differences due to a difference in manufacturer/manufacturing. Rather, these changes are differences in Conditions of Use. An ANDA applicant may NOT seek approval of a drug product that differs in Conditions of Use from the NDA product which it cites as its Basis of Submission. For this reason, **the Office of Generic Drugs believes that your current drug product is NOT eligible for submission under section 505(j) of the statute.***

6) As advised by the Agency, on 1/17/2013, the firm submitted the request for conversion of ANDA 202153 to NDA 202153 under 505 (b) (2) regulations<sup>2</sup>. As per the email communication sent by Thomas Hinchliffe on January 15, 2013, the resubmitted NDA 202153 will be reviewed by OGD (please see section 4 Appendix for details)

7) Based on the information above, the determination (b) (4)  
[redacted] of radioactive Rubidium Chloride as the finished product is deferred to the Division of Chemistry (DC). The DB will incorporate the DC's recommendations with regards to the strength of the finished product manufactured on-site, in to the final BE determination.

### 3.8 Deficiency Comments

None

### 3.9 Recommendation

1. [redacted] (b) (4)

(b) (4)

2. The application is adequate from the bioequivalence standpoint.

### 3.10 Comments for Other OGD Disciplines

Discipline	Comment
<b>Chemistry</b>	The final product, Rubidium Chloride Injection is produced on-site where it is to be administered to the patient by eluting the column of the generator containing strontium Sr 82. The radioactivity (dose) of Rubidium Chloride is controlled by the specifically designed infusion system. Therefore, the determination [REDACTED] (b) (4) [REDACTED] of radioactive Rubidium Chloride as the finished product is deferred to the Division of Chemistry (DC).

## 4 APPENDIX

**From:** Nguyen, Hoainhon T  
**To:** Tampal, Nilufer; Wang, Rong  
**Cc:** Nguyen, Hoainhon T  
**Subject:** FW: Bioequivalence Question for NDA 202153 - Resubmission required  
**Date:** Tuesday, January 15, 2013 10:30:42 AM

FYI. We will defer the difference in Conditions of Use and any issues related to the generator to the Division of Chemistry. We will limit our review to the final injection product.

Thanks,  
Hoai

**From:** Shimer, Martin  
**Sent:** Tuesday, January 15, 2013 10:28 AM  
**To:** Nguyen, Hoainhon T  
**Subject:** RE: Bioequivalence Question for NDA 202153 - Resubmission required  
Hoai,

(b) (4)  
This application will not be awarded an AP rating when it is approved due to the differences in the labeling of this product when compared to the RLD.

Thanks,  
Marty

**From:** Nguyen, Hoainhon T  
**Sent:** Tuesday, January 15, 2013 10:22 AM  
**To:** Shimer, Martin  
**Cc:** Nguyen, Hoainhon T  
**Subject:** Bioequivalence Question for NDA 202153 - Resubmission required

Hi Marty,  
Is DBI supposed to review this NDA application? Does the firm request an AB rating for its 505(b)(2) route?

Thanks,  
Hoai

**From:** Chang, Sherry  
**Sent:** Tuesday, January 15, 2013 9:31 AM  
**To:** Tampal, Nilufer  
**Cc:** Wang, Rong; Nguyen, Hoainhon T; Ramson, Teresa  
**Subject:** FW: NDA 202153 - Resubmission required

Hello Nilufer,

I am forwarding Tom's email to you.

Please be noted that the application ANDA 202153 (Rubidium chloride injection) Rong is currently reviewing now becomes NDA 202153.

Thanks,  
Sherry

**From:** Hinchliffe, Thomas  
**Sent:** Tuesday, January 15, 2013 8:17 AM  
**To:** Cuthbert, Gerrard D; Doan, Dat; Kalinina, Marina  
**Cc:** Middleton, Sandra T; Shimer, Martin; West, Robert L; Wang, Rong; Chang, Sherry; Kiester, Craig; Ensor, Lynne A; Conner, Dale P; Shin, Melaine M; D'Costa, Rosario; Mueller, Albert J; Gonitzke, Mark; Doan, Dat; Ames, Timothy W  
**Subject:** RE: NDA 202153 - Resubmission required

Thanks Gerrard, Sandra,

Since this is supposed to be an NDA reviewed by OGD then DARRTS should reflect this as an NDA not an ANDA.. Gerrard what do we need to do to correct. The responsible Organization is still OGD of course so nothing should change there.. In addition, Any letters OGD issues should

be using the OND templates, not the ANDA 505 (j) templates.  
I see this has been under review for a while and we have been issuing ANDA style letters my error.. From this point forward lets ensure only NDA style letters go out, including the TA or AP letter. Here is the address to the eroom for CDER Standard Templates <http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee> which houses all NDA templates. Any questions about the templates you Michael Folkendt is the NDA expert... I am cc'ing the review team in DARRTS so they are aware and can make the adjustment.

Tom

Thomas Hinchliffe, PharmD  
CDR, U.S. Public Health Service  
Special Assistant to the Director for GDUFA  
Office of Generic Drugs  
Food and Drug Administration  
HFD-600 Rm 3016, MPN4  
240-276-9314 (tel)  
240-743-8298 (mobile)  
240-276-9327 (fax)

***"UNLESS someone like you cares a whole awful lot,  
nothing is going to get better. It's not." - Dr. Seuss***

**From:** Middleton, Sandra T  
**Sent:** Tuesday, January 15, 2013 8:05 AM  
**To:** Hinchliffe, Thomas  
**Subject:** FW: NDA 202153 - Resubmission required  
[fyi...](#)

**From:** Shimer, Martin  
**Sent:** Tuesday, January 15, 2013 6:19 AM  
**To:** Cuthbert, Gerrard D; Kalinina, Marina  
**Cc:** CDER ESUB; Middleton, Sandra T; Doan, Dat  
**Subject:** RE: NDA 202153 - Resubmission required

Once the recent submission from Draximage is reviewed, a memo is drafted, and the sponsor pays the PDUFA user fee, this application will become a 505(b)(2) application-an NDA. OGD retains limited authority to approve 505(b)(2) applications and this will be one of those applications. Moving forward this application will be paying an NDA user fee and will be considered an NDA for approval purposes. This application should be coded as a NDA.

Thanks,

Marty

**From:** Cuthbert, Gerrard D  
**Sent:** Monday, January 14, 2013 3:49 PM  
**To:** Cuthbert, Gerrard D; Kalinina, Marina  
**Cc:** CDER ESUB; Middleton, Sandra T; Shimer, Martin; Doan, Dat  
**Subject:** RE: NDA 202153 - Resubmission required  
[resending to include attachments.](#)

Gerrard D. Cuthbert

Management Analyst

CDER/OBI/DDMSS/DRMT

Tele: (301) 796-3981

[Gerrard.Cuthbert@fda.hhs.gov](mailto:Gerrard.Cuthbert@fda.hhs.gov)

**From:** Cuthbert, Gerrard D  
**Sent:** Monday, January 14, 2013 3:46 PM  
**To:** Kalinina, Marina  
**Cc:** CDER ESUB; Middleton, Sandra T; Shimer, Martin; Doan, Dat  
**Subject:** RE: NDA 202153 - Resubmission required

[Hello Marina:](#)

[Per our conversation with Sandra, this application should retain the application type](#)



"ANDA". However, we do realize that it is being reviewed under 505(b)(2) regulations. The applicant should change the US-regional.xml to reflect it is an ANDA.

Marty/Dat:

Please confirm.

Thanks.

Gerrard D. Cuthbert

Management Analyst

CDER/OBI/DDMSS/DRMT

Tele: (301) 796-3981

[Gerrard.Cuthbert@fda.hhs.gov](mailto:Gerrard.Cuthbert@fda.hhs.gov)

**From:** Kalinina, Marina

**Sent:** Monday, January 14, 2013 9:10 AM

**To:** Cuthbert, Gerrard D

**Cc:** CDER ESUB

**Subject:** FW: NDA 202153 - Resubmission required

Good morning Gerrard

Do you know anything about OGD/sponsor communications about this ANDA to be submitted as NDA?

They submitted Fillable Form and Cover letter as for ANDA, but US-regional.xml has it as NDA.

We rejected it once as a mismatch but they got back to us and saying that this is intentionally sent this way.

We are not sure what is the deal here.

On Friday I left message on RPM voicemail, but got no response yet.

Any information on this matter would be appreciated.

THANK YOU!

## **Marina Kalinina**

Regulatory Information Specialist

OBI/DDMSS/ESUB

Phone: (301) 796-7591

[Marina.Kalinina@fda.hhs.gov](mailto:Marina.Kalinina@fda.hhs.gov)

**From:** Marie-Josée Audet [<mailto:mjaudet@jdi.jubl.com>]

**Sent:** Friday, January 11, 2013 3:43 PM

**To:** CDER ESUB

**Cc:** Magali Lurquin; Genevieve Paradis; Marie Pierre Ekoka

**Subject:** NDA 202153 - Resubmission required

Good Day,

We have received a rejection notice, please refer to the attached documents.

Our application number is NDA 202153 and it is for a new drug application 505(b)(2)

The document attached refers to the Application number ANDA 202153 and USRegional.XML file as an NDA.

The attached document refers to 2 deficiencies

1. The Application Type (ANDA) is identified in the Cover letter

2. The Application Type (ANDA) is identified in the Fillable 356H

Since our current situation is not simple, please take into consideration into your review of this dossier that we are converting a previously submitted ANDA to an NDA. This was previously agreed with the office of Generic Drug and they also confirmed to keep the same number that was assign to the previous ANDA.

We kindly request your assistance in this matter, if any changes are required in the attached and referenced document, please let us know. If this submission could be

received as is, we would appreciate, let us know if we need to resend through the gateway.

Best regards,

*Marie-Josée Audet*

Documentalist, Regulatory Affairs & Jr. Project Manager

**Jubilant DraxImage Inc.**

A Jubilant Life Sciences Company

Tel.: (514) 694-8220 #4442 | Fax.: (514) 694-9295

[www.draximage.com](http://www.draximage.com)

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 202153

APPLICANT: Jubilant DraxImage Inc.

DRUG PRODUCT: Rubidium Chloride Rb 82 Generator (Ruby-Fill®), (b) (4) mCi of Sr 82

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.  
Director, Division of Bioequivalence I  
Office of Generic Drugs  
Center for Drug Evaluation and Research

**5 OUTCOME PAGE**

**COMPLETED ASSIGNMENT FOR 202153 ID: 15909**

**Reviewer:** Wang, Rong

**Date Completed:**

**Verifier:** ,

**Date Verified:**

**Division:** Division of Bioequivalence

Rubidium Chloride Rb 82 Generator (Ruby-Fill®), (b) (4)

**Description:** (b) (4) mCi of Sr 82  
Jubilant DraxImage Inc

*Productivity:*

<i>ID</i>	<i>Letter Date</i>	<i>Productivity Category</i>	<i>Sub Category</i>	<i>Productivity</i>	<i>Subtotal</i>
15909	6/18/2010	Other	(b) (4)	1	1
				<b>Bean Total:</b>	<b>1</b>

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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.**  
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/s/  
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RONG WANG  
01/30/2013

NILUFER M TAMPAL  
01/30/2013

HOAINHON N CARAMENICO  
02/01/2013

HOAINHON N CARAMENICO on behalf of DALE P CONNER  
02/01/2013