CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202153Orig1s000

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

September 15, 2016

NDA: 202153

Drug Product Name
Proprietary: Ruby-Fill® (Rubidium Rb-82 Generator)
Non-proprietary: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/28/2015	12/30/2015	N/A	1/7/2016
6/11/2016	6/15/2016	N/A	6/15/2016
8/16/2016	8/17/2015	N/A	8/17/2016

Applicant/Sponsor
Name: Jubilant DraxImage Inc.
Address: 16751 Trans-Canada Highway
Kirkland, Quebec
Canada H9H4J4
Representative: Susan P. Spooner, Ph.D.
Telephone: 919-745-2492
Fax: 513-763-7628

Name of Reviewer: Yeissa Chabrier-Roselló, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION** NDA Resubmission

2. **SUBMISSION PROVIDES FOR:** Response to CMC deficiencies in Agency's Complete Response letter

3. **MANUFACTURING SITE:**
Jubilant DraxImage Inc.
16751 TransCanada Highway
Kirkland, QC
Canada H9H4J4

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Generator for PET parenteral solution ((b) (4) mCi), delivered intravenously

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for 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.

B. **SUPPORTING/RELATED DOCUMENTS:**
N202153typeCmeetingR1.pdf review by J. Cole dated 7/22/2015
202153.doc by D. Palmer dated 1/3/2011
202153a1.doc by D. Palmer dated 2/29/2012

C. **REMARKS:** This is an eCTD submission. This review covers the responses for the complete response letter sent on 12/18/2014. The meeting package memo N202153typeCmeetingR1.pdf (dated 7/22/2015) by J. Cole is referenced in this review. The review also references the teleconference with the firm on 5/5/2016 pertaining to the dye ingress testing to assess patient cross-contamination during the drug product's shelf-life of 60 days. Subsequently, an information request was sent regarding these issues on 5/26/2016, and is referenced in this review; the information request response was received 6/15/2016. A subsequent information request was sent in July 2016 which was followed by a teleconference with the sponsor on 7/13/2016. This review includes the two information requests and corresponding information request responses (6/17/2016 & 8/17/2016). The review of the two information request responses is located at the end of this review.

Filename: 202153-FINAL.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –
The drug product is a rubidium generator for intravenous delivery of the PET parenteral solution ((b) (4) mCi). The drug product/generator is to be used continuously for up to 60 days. (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

D. Contains Potential Precedent Decision(s) - ☒ Yes ☐ No

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist/Yeissa Chabrier-Roselló, Ph.D.
Microbiology Secondary Reviewer/Jessica Cole, Ph.D.

C. CC Block
cc: Field Copy /Panorama

Product Quality Microbiology Assessment

The subject NDA resubmission (submitted December 30, 2015) provides responses to the product quality and the infection control for the subject drug product. For the purpose of this review, only the deficiencies and/or relevant deficiency parts that pertain to the microbiology assessment/sterility assurance of the subject drug product are reviewed below. The deficiencies, which are italicized below, were drafted by the original CDRH reviewer and conveyed to the firm in the Agency's 12/18/2014 complete response letter. Additionally, the information requests sent on 5/26/2016 and July 2016 and the corresponding responses are reviewed at the end of this document.

(b) (4)

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APPEARS THIS WAY ON ORIGINAL

Product Quality Microbiology Review

June 3, 2016

NDA: 202153

Drug Product Name
Proprietary: Ruby-Fill® (Rubidium Rb-82 Generator)
Non-proprietary: N/A

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12/28/2015	12/30/2015	N/A	1/7/2016

Applicant/Sponsor
Name: Jubilant DraxImage Inc.
Address: 16751 Trans-Canada Highway
Kirkland, Quebec
Canada H9H4J4
Representative: Susan P. Spooner, Ph.D.
Telephone: 919-745-2492
Fax: 513-763-7628

Name of Reviewer: Yeissa Chabrier-Roselló, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUBMISSION** NDA Resubmission

2. **SUBMISSION PROVIDES FOR:** Response to CMC deficiencies in Agency's Complete Response letter

3. **MANUFACTURING SITE:**
Jubilant DraxImage Inc.
16751 TransCanada Highway
Kirkland, QC
Canada H9H4J4

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Generator for PET parenteral solution ((b) (4) mCi), delivered intravenously

5. **METHOD(S) OF STERILIZATION:** (b) (4)

6. **PHARMACOLOGICAL CATEGORY:** Indicated for 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.

B. **SUPPORTING/RELATED DOCUMENTS:**
N202153typeCmeetingR1.pdf review by J. Cole dated 7/22/2015
202153.doc by D. Palmer dated 1/3/2011
202153a1.doc by D. Palmer dated 2/29/2012

C. **REMARKS:** This is an eCTD submission. This review covers the responses for the complete response letter sent on 12/18/2014. The meeting package memo N202153typeCmeetingR1.pdf (dated 7/22/2015) by J. Cole is referenced in this review. The review also references the teleconference with the firm on 5/5/2016 pertaining to the dye ingress testing to assess patient cross-contamination during the drug product's shelf-life of 60 days. Subsequently, an information request was sent regarding these issues on 5/26/2016, and is referenced in this review.

Filename: 202153.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -
The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a rubidium generator for intravenous delivery of the PET parenteral solution ((b) (4) mCi). The drug product/generator is to be used continuously for up to 60 days. (b) (4)

B. Brief Description of Microbiology Deficiencies –
Please see letter of deficiency in Section 3 of this review.

C. Assessment of Risk Due to Microbiology Deficiencies – High

D. Contains Potential Precedent Decision(s) - ☒ **Yes** ☐ **No**

III. Administrative

A. Reviewer's Signature _____

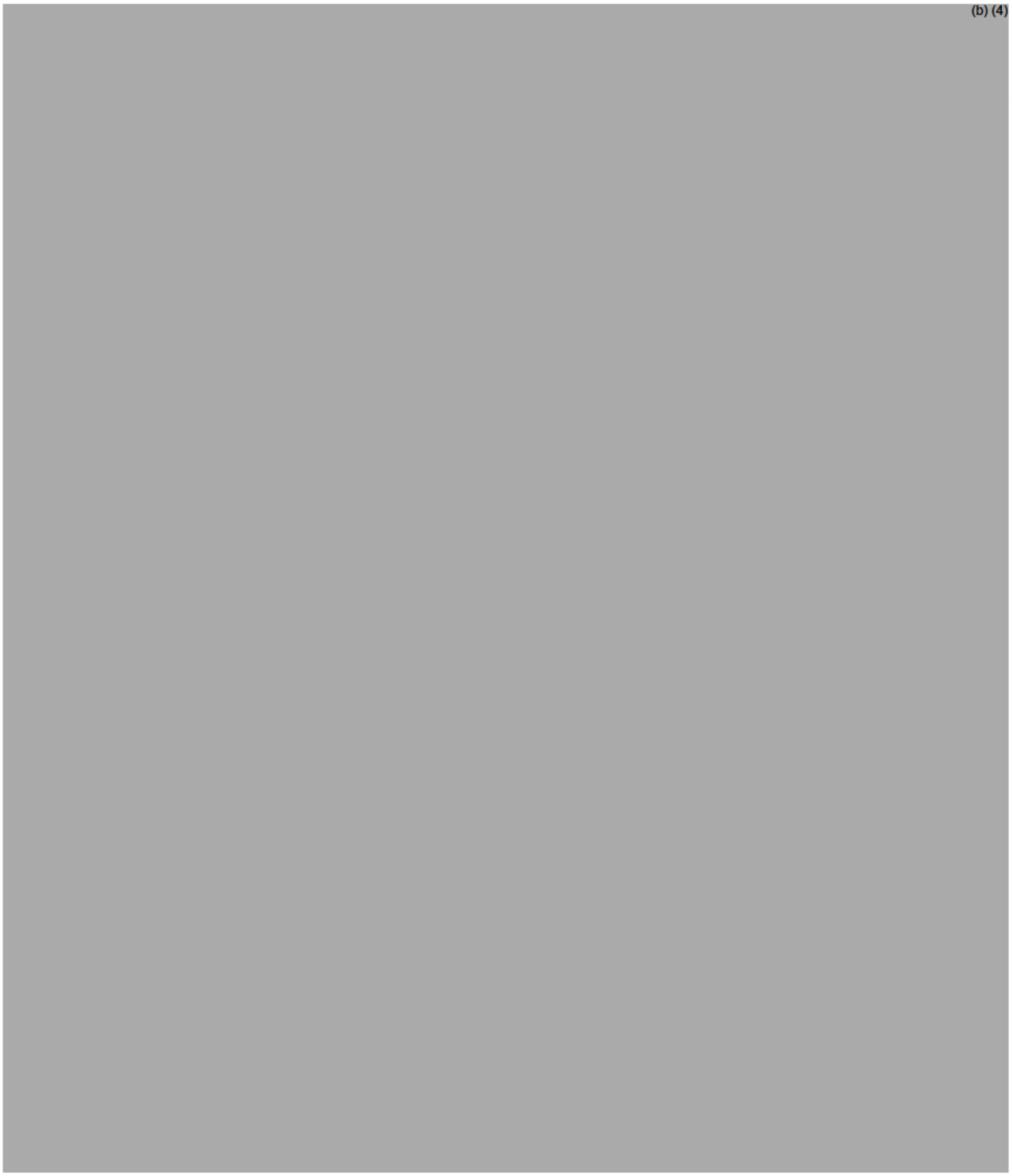
B. Endorsement Block
Microbiologist/Yeissa Chabrier-Roselló, Ph.D.
Microbiology Secondary Reviewer/Jessica Cole, Ph.D.

C. CC Block
cc: Field Copy /Panorama

Product Quality Microbiology Assessment

The subject NDA resubmission (submitted December 30, 2015) provides responses to the product quality and the infection control for the subject drug product. For the purpose of this review, only the deficiencies and/or relevant deficiency parts that pertain to the microbiology assessment/sterility assurance of the subject drug product are reviewed below. The deficiencies, which are italicized below, were drafted by the original CDRH reviewer and conveyed to the firm in the Agency's 12/18/2014 complete response letter.

(b) (4)



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3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

NDA: 202153 APPLICANT: Jubilant DraxImage Inc.

DRUG PRODUCT: Ruby-Fill® (Rubidium Rb-82 Generator)

Microbiology Deficiencies:

The studies and results provided for the dye ingress test of the Ruby-Fill system's components, as currently designed, (b) (4) demonstrates that the patient cross-contamination risk has not been fully mitigated by the system's current safety features. We acknowledge the Hazard analysis and justification in the submission for why these results do not pose a risk to patients; however, we disagree with the conclusions and assessments. The studies provided did not perform in a predictable way. (b) (4) A scientific explanation regarding the referenced studies and results was not provided in the validation report or during the teleconference on 5/5/2016. As discussed in said teleconference, the Agency has serious concerns with the dye ingress system/methodology used. The results, data analysis and interpretations for the dye ingress test results provided in document "Appendix 9-3 Dye Ingress Testing Report.pdf" are of concern to the Agency. Therefore, we request that the following points be addressed in subsequent studies to better assess the risk of patient cross-contamination with the current design for the Ruby Fill system. The studies should show (b) (4)

i. Provide dye ingress test studies (b) (4) .

ii. Clearly state the in-use parameters proposed for patient administration to include (b) (4) conditions. If the conditions used for the dye ingress test are different (e.g. worst case) to the in-use parameters, provide a rationale.

iii. Include a description of the negative and positive controls for the studies. It is expected that the test will demonstrate 100% efficacy (b) (4)

[redacted] (b) (4)

iv. Provide the limit of detection for the dye ingress assay.

v. Describe the function and design of the [redacted] (b) (4) system component, which reduce the risk of patient cross-contamination. Give operational characteristics [redacted] (b) (4) and any other relevant characteristics [redacted] (b) (4). Indicate the location for each of these components during the proposed in-use time with a diagram.

vi. Describe the limitations of the dye ingress test in terms of fluid properties that may influence dye transport compared to viral and bacterial transport.

Yeissa Chabrier Rosello -S

Digitally signed by Yeissa Chabrier Rosello -S
Date: 2016.06.03 14:28:19 -04'00'

Jessica Cole -S

Digitally signed by Jessica Cole -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jessica Cole -S, 0.9.2342.19200300.100.1.1=2000397920
Date: 2016.06.03 14:31:20 -04'00'

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 21 July 2015

TO: Frank Lutterodt
Regulatory Business Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(301) 796-5148

THROUGH: Stephen Langille, PhD
Microbiology Branch Chief
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: NDA: 202-153
Submission Date: 17 June 2015 (received 19 June 2015)
Drug Product: Ruby-Fill (Rubidium Rb 82 Generator)
Applicant: Jubilant Draximage, Inc.

A product quality microbiology review of the meeting package for NDA 202-153 is complete. This meeting package is a follow up to the Type A meeting package received on 18 February 2015 and the associated microbiology review dated 17 April 2015. The Type A meeting request was submitted after issuance of the 18 December 2014 complete response letter.

The applicant has submitted a summary of studies to address microbial contamination and patient-to-patient cross contamination issues raised in the complete response letter. Appendices 14-16 contain the proposed testing strategies.

Appendix 13- 3000061-D v01 Device Description
This document describes the design of the elution system. (b) (4)

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/s/

JESSICA COLE
07/22/2015

STEPHEN E LANGILLE
07/22/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 31 March 2015

TO: Frank Lutterodt
Regulatory Health Project Manager
CDER/OND/DMIP

FROM: Jessica G. Cole, PhD
Review Microbiologist
CDER/OPQ/OPF/Division of Microbiology Assessment
(301) 796-5148

THROUGH: Stephen E. Langille, PhD
Acting Branch Chief
CDER/OPQ/OPF/Division of Microbiology Assessment

SUBJECT: NDA: 202-153
Submission Date: 13 February 2015
Drug Product: RUBY-FILL (Rubidium Rb-82 Generator)
Applicant: Jubilant Draximage Inc.

A product quality microbiology review of the Type A meeting package for NDA 202-153 is complete. This NDA described a PET drug product (generator) intended for intravenous administration. This NDA was originally submitted as ANDA 202-153 and was recommended for approval on the basis of sterility assurance by a microbiology reviewer from the Office of Generic Drugs. That review found the sterility assurance information acceptable (b) (4) The microbiology review did not assess the risk for use according to the proposed product insert (b) (4)

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/s/

JESSICA COLE
04/16/2015

STEPHEN E LANGILLE
04/17/2015

Product Quality Microbiology Review

December 15, 2014

NDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Rb 82 Chloride for Injection

Review Number: #3

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
9/23/13	9/24/13	N/A	4/11/14

Submission History (for ANDA amendments only): N/A

Submit Date	Microbiology Review #	Review Date(s)
6/18/10	1	11/1/2010
5/18/11	2	5/27/11
8/29/11		

Applicant/Sponsor
Name: Jubilant Draximage Inc.
Address: 16751 TransCanada Highway, Kirkland, Quebec, Canada H9H 4J4

U.S. Agent
Name: Greg Hockel and Dr. Norma LaFrance
Address: 7361 Calhoun Place Suite 500, Rockville, MD 20855-2765
Telephone: (301) 926-6148/(514) 235-8754; Fax: (30) 838-3182/(514) 694-9295

Name of Reviewer: Dupeh Palmer, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Gratuitous Amendment.

2. SUBMISSION PROVIDES FOR: Gratuitous labeling information with sterility assurance relevance

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission. The applicant's 9/23/13 gratuitous amendment was consulted to be reviewed by Dat Doan from OGD/DLPS because a BlackBox warning was added to the package insert. No other labeling changes from that provided in the initial submission are indicated in the 9/23/13 amendment. The original submission was an ANDA that was converted to a NDA on 4/9/13. The original microbiology review (202153a1.doc dated 5/27/11 by D. Palmer) was recommended for approval based on sterility assurance of the drug product. The US agent(s) shown above on page 1 of this review was obtained from the most recent 5/12/14 submission that does not contain microbiology information.

Filename: 202153a2.doc
Template version: OGD modified_AP_2013v3.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

B. Brief Description of Microbiology Deficiencies –None identified.

C. Assessment of Risk Due to Microbiology Deficiencies – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

D. Contains Potential Precedent Decision(s) - ☐ **Yes** ☒ **No**

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Marla Stevens-Riley, Ph.D.
Microbiology Division Director (Acting)/Lynne Ensor, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

The applicant's 9/23/13 gratuitous amendment was consulted to be reviewed by Dat Doan from OGD/DLPS because a BlackBox warning was added to the package insert. No other labeling changes from that provided in the initial submission are indicated in the 9/23/13 amendment. The original submission was an ANDA that was converted to a NDA on 4/9/13. The original microbiology review (202153a1.doc dated 5/27/11 by D. Palmer) was recommended for approval based on sterility assurance of the drug product.

The drug product (Rubidium Rb 82 chloride injection) consists of a (b) (4) Ruby-Fill™ generator column that produces Rb-82 by the decay of Strontium-82 (Sr-82), and an accessory elution system (b) (4) A black box label has been added to the package insert in the October 25, 2012 submission; however, the September 23, 2013 submission contains a reformatted version of the labeling. The BlackBox warning in the updated package insert contains user information to prevent unintended radiation exposure during elution and delivery of the eluate to the patient, and specifies that the generator must be discarded when the following conditions (named "expiration limits" by the applicant) are exceeded: 30 L of cumulative generator eluate volume, 60 days post generator calibrator date, Sr-82 and Sr-85 levels of 0.01µCi/mCI Rb-82 and 0.1µCi/mCI Rb-82 respectively in the generator eluate.

Note to Reviewer: User information in the labeling Blackbox warning including expiration limits for the generator, are provided to prevent unintended radiation exposure during elution from the generator and delivery of the drug product to the patient, and should not adversely affect the sterility assurance of the drug product.

Acceptable

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/s/

DUPEH G Palmer-Ochieng
12/15/2014

EILEEN T MONAGHAN
12/17/2014

MARLA K STEVENS RILEY
12/17/2014

LYNNE A ENSOR
12/17/2014

Product Quality Microbiology Review

May 27, 2011

ANDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Chloride Rb 82 Generator

Review Number: #2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
5/18/2011	5/19/2011	N/A	5/23/2011
8/29/11	9/1/11	N/A	9/2/11

Submission History (for amendments only): N/A

Submit Date	Microbiology Review #	Review Date(s)
06/18/2010	1	11/1/2010

Applicant/Sponsor
Name: Draximage
Address: 16751 Trans Canada Highway,
Kirkland, Quebec, Canada H9H 4J4

U.S. Agent: Kendle International Inc.
7361 Calhoun Place Suite 500
Rockville, MD 20855-2765

Representative: Hari Nagaradona, Director Regulatory Affairs
Telephone: (301) 296 1370

Name of Reviewer: Dupeh Palmer Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Amendment.

2. SUBMISSION PROVIDES FOR: Response to Agency's deficiency letter and T-cons held between this reviewer and the applicant.

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride. (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission. The subject amendment provides responses to the microbiology deficiencies conveyed to the applicant in the Agency's March 1, 2011 deficiency letter. A discrepancy between the initial submission and the 5/18/11 amendment regarding the applicant's description of the (b) (4) generator (b) (4) was noted by the reviewer. Clarification was requested in T-cons held on 7/27/11, and 7/29/11 between this reviewer and the applicant. Additional sterility data (b) (4) was also requested, and the applicant was asked to reference and link SOPs for parametric release in the release specification sheet, the CoA and batch release records. The requested information was submitted in the 8/29/11 amendment.

filename: 202153a1.doc

Executive Summary

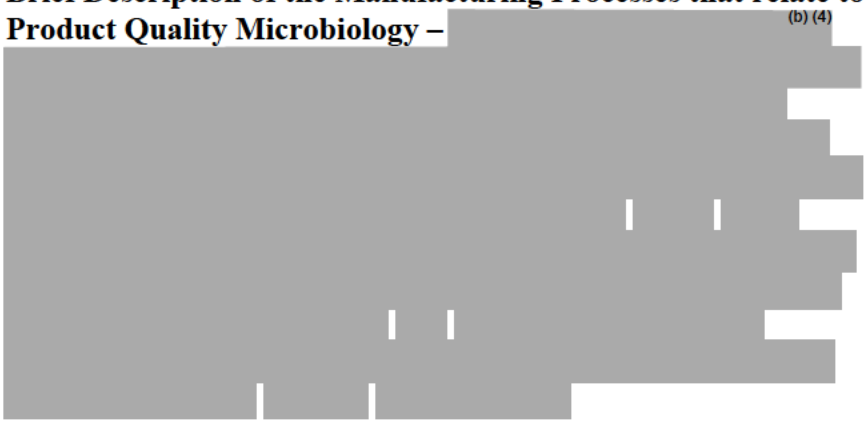
I. Recommendations

A. Recommendation on Approvability –
The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)



B. Brief Description of Microbiology Deficiencies –None identified.

C. Assessment of Risk Due to Microbiology Deficiencies – No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Lynne Ensor, Ph.D.

C. CC Block
cc: Field Copy

Product Quality Microbiology Assessment

The subject amendment provides a response to the microbiology deficiencies conveyed to the applicant in the Agency's March 1, 2011deficiency letter. The original deficiencies are italicized. Additionally, the amendment contains requested information submitted in the 8/29/11 amendment.

(b) (4)

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/s/

DUPEH G Palmer-Ochieng
09/16/2011

ELIZABETH T MCNEAL
09/16/2011
Checked file and submission links. All correct. Thos application in not in RFS.

NEAL J SWEENEY
02/28/2012

LYNNE A ENSOR
02/29/2012

Product Quality Microbiology Review

November 1, 2010

ANDA: 202153

Drug Product Name
Proprietary: N/A
Non-proprietary: Rubidium Chloride Rb 82 Generator

Review Number: #1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
06/18/2010	06/30/2010	N/A	10/29/2010

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Draximage
Address: 16751 Trans Canada Highway,
Kirkland, Quebec, Canada H9H 4J4

U.S. Agent: Kendle International Inc.
7361 Calhoun Place Suite 500
Rockville, MD 20855-2765

Representative: Hari Nagaradona, Director Regulatory Affairs
Telephone: (301) 838-3120

Name of Reviewer: Dupeh Palmer Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of a sterile drug product/PET drug product application.

3. MANUFACTURING SITE:
DRAXIMAGE, a division of DRAXIS Specialty Pharmaceuticals Inc.
16751 TransCanada Highway
Kirkland, Quebec, Canada, H9H 4J4

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: A Ruby-Fill™ (Rubidium Rb 82) generator for IV administration of sterile, pyrogen-free Rubidium Chloride Rb 82 (^{82}RbCl) in 0.9% sodium chloride. (b) (4) the generator delivers a single dose of NMT 60mCi and (b) (4) (b) (4) a maximum volume of 60mL per infusion (b) (4)

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: A positron emission tomography (PET) product indicated for assessing regional myocardial perfusion (b) (4)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: This is an electronic submission.

filename: 202153.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4)

[redacted]

B. Brief Description of Microbiology Deficiencies – Questions regarding the (b) (4) [redacted] validation studies.

C. Assessment of Risk Due to Microbiology Deficiencies – The safety risk associated with the microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / Dupeh Palmer, Ph.D.
Microbiology Team Leader/Lynne Ensor, Ph.D.

C. CC Block

cc: Field Copy

Product Quality Microbiology Assessment

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**

The proposed product consists of a (b) (4) generator that produces Rb-82 by the decay of Strontium-82 (Sr), and an accessory elution system for eluting ^{82}RbCl Injection containing ^{82}RbCl in 0.9% sodium chloride.

Proposed maximum commercial batch size: A maximum of (b) (4) generators are manufactured per batch.

- **Drug product composition –** (Folder m3, 32-body-data, 32-drug-prod, 32p1-desc-comp, p. 2 of 3).

All components used in the manufacturing of ^{82}RbCl injection are presented in the following table.

Table P.1 – 1: List of components of the dosage form, their function, reference to quality standard, and amount on per-unit basis

Ingredients	Ingredient function	Quality Standard	Quantity per generator
^{82}SrCl$_2$	Starting Material	House	(b) (4)
(b) (4) Stannic Acid	Adsorbent	House	
Sodium Chloride	(b) (4)	USP / Ph. Eur.	
			(b) (4)

* At calibration time

- **Description of container closure system –** (Folder m3, 32-body-data, 32-drug-prod, 32p7-cont-closure, p. 4 of 85).

A diagram of the Ruby-Fill™ (Rubidium Rb 82) generator column was provided. Components of the column are shown in the table below and include (b) (4)

(b) (4)

13 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT

Storage temperature: (b) (4) °C; Route of administration: IV; Container: Single dose administered with additive free 0.9% Sodium Chloride Injection. Due to the short half-life of Rb-82, most of the radioactivity in the eluate decays within (b) (4) minutes from the end of elution.

Acceptable

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 202153 APPLICANT: Draximage

DRUG PRODUCT: Rubidium Chloride Rb 82 Generator

Microbiology Deficiencies:

1. Regarding validation studies conducted [redacted (b) (4)]

(a) Please provide data summaries from [redacted (b) (4)] studies with performance dates.

(b) Please state the manufacturer, genus/species of the endotoxin used in challenge studies, and provide endotoxin recovery results including results for positive controls.

(c) Please provide all acceptance criteria associated with successful [redacted (b) (4)] validation runs.

2. The endotoxin dose, at the proposed endotoxin specification of NMT [redacted (b) (4)] EU/mL and the maximum adult dose of [redacted (b) (4)] MBq indicated in the package labeling, exceeds the Agency's limit of 175 EU/dose for injected radiopharmaceuticals. Please revise the endotoxin specification for the drug product to conform to the Agency's 175 EU/dose limit and provide the appropriate documentation to reflect the change (e.g. finished product specification and stability protocol, endotoxin test validation data summary, and any supporting exhibit batch endotoxin test data).

3. Data to support parametric release of the drug product are not provided. Please provide data to support parametric release of the drug product. Alternatively, the sterility release specification could be revised to comply with 21 CFR 211.165 (a) which states:

Sec 211.165 Testing and release for distribution.
(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfaction conformance to final specifications for the drug product, including identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted in specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Lynne A. Ensor, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

DUPEH G Palmer-Ochieng
12/22/2010

ELIZABETH T MCNEAL
12/22/2010
Checked file and submission link. Both correct.

LYNNE A ENSOR
01/03/2011