CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213227Orig1s000

PRODUCT QUALITY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

MEMORANDUM

The applicant submitted the final prescribing information (PI) in the amendment dated 21-Aug-2020 (seq. 023). The final prescribing information is acceptable from a product quality perspective.

In submission dated 10-Aug-2020, the applicant submitted the following revised composition table (section 3.2.P.1).

Table 3.2.P.1-1 Components of copper Cu 64 dotatate injection drug product

Component	Function	Quality Standard	Quantity per one millilitre (1 mL)	Quantity per vial
Copper Cu-64 dotatate	Drug Substance/Active Pharmaceutical Ingredient	GMP	1.00 mCi[a]	4.0 mCi[a]
Ascorbic Acid	(b) (4)	USP	40 mg	160 mg
Dehydrated alcohol (ethanol)		USP	0.05 mL (v/v)	0.2 mL
Sterile Water for Injection		USP	(b) (4)	
Sodium Hydroxide		USP	As needed for pH adjustment (pH range 5.5-7.5)	
Hydrochloric Acid		USP		

[a] At calibration [at 1700CT (b) (4)].
[b] Specification: as (b) (4) related substances.

This table differs from the previously submitted composition table in that the previous table (b) (4)

(b) (4)

This revision is ACCEPTABLE.

Ravindra Kasliwal

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Date: 8/25/2020 01:41:34PM
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/s/

RAVINDRA K KASLIWAL
08/25/2020 02:05:38 PM

Office of Pharmaceutical Quality

NDA 213227

Integrated Quality Assessment

U.S. FOOD & DRUG ADMINISTRATION

Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213227
Assessment 1

Drug Product Name	copper Cu 64 dotatate injection
Dosage Form	Injection
Strength	4.0 mCi (1 mCi/mL) at calibration
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	RadioMedix, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
0004	03-Jan-2020	All
0006	27-Jan-2020	Drug Product
0008	20-Mar-2020	Manufacturing, Drug Product
0009	03-Apr-2020	Biopharmaceutics, Drug Product
0010	09-Apr-2020	Biopharmaceutics
0012	04-May-2020	Biopharmaceutics
0015	03-Jun-2020	Drug Product
0016	08-Jun-2020	Drug Product
0017	10-Jun-2020	Drug Product
0019	29-Jun-2020	Drug Product
0020	22-Jul-2020	Drug Product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Martin Haber	Suong Tran
Drug Product	Ravindra Kasliwal	Danae Christodoulou
Manufacturing	Krishna Ghosh	Vidya Pai
Microbiology	Laura Wasil	Julie Nemecek
Biopharmaceutics	Pranali Chatterjee	Min Li
Regulatory Business Process Manager	Anika Lalmansingh	

Application Technical Lead	Ravindra Kasliwal, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Office of Pharmaceutical Quality recommends an **approval** action for copper Cu 64 dotatate injection, the proposed new drug product in NDA 213227.

Copper Cu 64 Dotatate Injection will be distributed as a single-dose vial containing 4 mCi/vial (1 mCi/mL) of copper Cu-64 dotatate at calibration date and time (at 1700CT (b) (4) (b) (4) The drug product is in a sterile solution of 40 mg/mL ascorbic acid and (b) (4) (v/v) ethanol at a solution pH of 5.5 - 7.5. The drug product is contained in a 10 mL (b) (4) glass vial affixed with a gray (b) (4) rubber stopper (b) (4) and aluminum crimp cap. The sealed vial is contained in (b) (4) The drug product expires 2 hours after the calibration date and time, ensuring that the desired dose is available for patent administration within the expiration dating period.

Basis for recommendation:

- Copper Cu 64 dotatate injection will be manufactured by Curium US LLC at the Curium's Maryland Heights, MO manufacturing facility for RadioMedix. The drug product manufacturing facility has been deemed to be acceptable from CGMP perspective for the manufacture of proposed sterile, non-pyrogenic, injectable radioactive drug product.

- Dotatate (DOTA-D-Phe-c(Cys-Tyr-D-Trp-Lys-Thr-Cys)-Thr), a (b) (4) cyclic 8-amino acid peptide functionalized at the N-terminal end with DOTA via an amide bond is manufactured and supplied as (b) (4) The applicant has referenced DMF (b) (4) The DMF has been reviewed and has been deemed acceptable to support this application. (b) (4) has described procedures for the acceptance of (b) (4) lots at their site and the procedures have been deemed adequate. Additionally, the (b) (4) (b) (4) manufacturing facility has been deemed to be acceptable from CGMP perspective for the manufacture (b) (4) as described in DMF (b) (4)

- (b) (4)

(b) (4) The DMF has been reviewed and has been deemed acceptable to support this application.

- Copper Cu 64 dotatate injection used in the pivotal phase 3 clinical studies (IND# 131797) was manufactured by RadioMedix Inc (9701 Richmond Ave, Suite: 222, Houston, TX 77042, USA). Commercial copper Cu 64 dotatate Injection will be manufactured by Curium US LLC at their Maryland Heights, MO facility. Copper Cu 64 dotatate injection manufactured at commercial scale (registration batches) was deemed to be comparable to that of the clinical trial material (Biopharmaceutics Review).

- Copper Cu 64 dotatate injection manufacturing and controls are adequately defined. The drug product manufacturing process and procedures are adequate for the manufacture of proposed sterile, nonpyrogenic drug product that is suitable for intravenous injection.

- The quality of the components used in the drug product have been adequately justified, controlled, and has been qualified through successful manufacture and stability.

- The drug product specifications and the analytical procedures are adequate to control the identity, strength, purity and quality of the drug product. The control strategy for impurities (organic, residual solvents, elemental impurities, radiochemical and radionuclidic) is adequate.

- The container and closure system (clear glass vial with aluminum crimp sealed stopper) is adequate to maintain the quality, stability and sterility of the drug product throughout the shelf-life of the product.

- The copper Cu 64 dotatate injection drug product has a proposed expiration dating period of 48 hours. The submitted long-term stability data supports a 48-hour **expiration dating period for when stored at controlled room temperature 20 to 25° C (68 to 77°F)**. Expiration will be defined in product labeling (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

RadioMedix has developed copper Cu 64 dotatate injection as a radioactive diagnostic agent for use with positron emission tomography (PET) of somatostatin receptor (SSTR) positive neuroendocrine tumors (NETs) in adults. New drug application (NDA) 213227 is a 505(b)(2) application. Copper Cu 64 dotatate is an NME and has not been marketed in the U.S.

Copper Cu 64 dotatate was submitted under IND 131797 by RadioMedix, Inc.. On May 18, 2016, orphan drug designation was granted to Cu-64 dotatate as a diagnostic for the management of NETs. Under IND 131797, Fast Track designation was granted for this product on December 19,

2018. The application was granted rolling review status on June 27, 2019. Module 4 (Nonclinical Study Reports), Module 5 (Clinical Study Reports) and Module 2 summaries (except Quality Overall Summary) were included in the initial submission on July 8,2019. The remainder of the NDA was submitted on January 3, 2020 with product quality data.

The copper Cu64 dotatate molecule has three regions, namely the somatostatin analog octreotate, the chemical linker tetraxetan (DOTA) and the positron emitter Cu-64. The somatostatin analog octreotate binds to SSTRs and is similar to octreotide, except the C-terminal threoninol is replaced with threonine. DOTA-Tyr3-octreotate is a (b) (4) cyclic 8 amino acid peptide covalently conjugated to DOTA, forming DOTA-octreotate (dotatate). Upon radiolabeling, Cu-64 binds to the DOTA portion of the molecule forming Cu-64 dotatate.

The current NDA is the first to be submitted for an imaging drug labeled with a copper Cu 64 radionuclide. Cu-64 emits positrons with an emission yield that allows for PET imaging. It has a half-life of 12.7 hours, which enables manufacturing of the drug product centrally and distribution to other parts of the U.S. The relatively long half-life of Cu-64 also facilitates delayed imaging after drug administration. The lower mean positron range, or distance a positron travels from emission until annihilation, is shorter for Cu-64 (1 mm) compared to Ga-68 (4 mm). A shorter range theoretically results in increased spatial resolution.

Currently, In-111 pentetreotide (compatible with planar and single-photon emission tomography (SPECT)), Gallium Ga 68 dotatate and Gallium Ga 68 dotatoc (compatible with PET imaging) are available in the US. In general PET imaging provides superior imaging outcomes than SPECT imaging. While Ga-68 dotatate and Ga-68 dotatoc PET have provided important new imaging options, they have been associated with limited availability to patients (limited availability of Ga-68 and Ga-68 generator shortages). Cu-64 is PET-compatible, (b) (4) and has a relatively long half-life of 12.7 hours. As such, Cu-64 dotatate has the potential to allow nationwide distribution of an SSTR PET agent from a central manufacturing source without dependence on Ga-68 generators.

Copper Cu 64 dotatate injection will be supplied as a single-dose vial containing 4 mCi/vial (1 mCi/mL) at calibration date and time. The drug product is in a sterile solution of 40 mg/mL ascorbic acid and (b) (4) (v/v) ethanol at a solution pH of 5.5 to 7.5. The drug product is presented in a 10 mL (b) (4) glass vial affixed with a gray (b) (4) rubber stopper (b) (4) and aluminum crimp cap. The sealed vial is contained in (b) (4) The drug product expires 2 hours after the calibration date and time, ensuring that the desired dose is available for patient administration within the expiration dating period.

Cu 64 dotatate binds to somatostatin receptors with highest affinity for subtype 2 receptors (SSTR2). It binds to cells that express somatostatin receptors including malignant neuroendocrine cells, which overexpress SSTR2 receptors. Cu 64 is a positron (β^+) emitting radionuclide with an emission yield that allows positron emission tomography (PET) imaging. The clinical evaluation has found a favorable overall benefit relative to the risk.

Proposed Indication(s) including Intended Patient Population	Copper Cu 64 Dotatate is indicated for use with positron emission tomography (PET) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) in adult patients.

Duration of Treatment	One time use prior to imaging.
Maximum Daily Dose	148 (b) (4) MBq (4 (b) (4) mCi) administered as an intravenous bolus injection
Alternative Methods of Administration	Intravenous only

B. Quality Assessment Overview

Drug Substance: Adequate

Dotatate (DOTA-D-Phe-c(Cys-Tyr-D-Trp-Lys-Thr-Cys)-Thr), a (b) (4) cyclic 8-amino acid peptide functionalized at the N-terminal end with DOTA via an amide bond. It is manufactured and supplied (b) (4)

The manufacturing and controls information is provided in DMF (b) (4). DMF # (b) (4) was reviewed by Martin Haber on 5/6/2020 and found adequate.

Drug Product: Adequate

Copper Cu64 dotatate manufacture is performed (b) (4)

(b) (4)

(b) (4) The DMF has been reviewed by Ravindra K. Kasliwal and has been deemed acceptable to support this application.

The quality of copper Cu 64 dotatate is tested during the release testing of copper Cu dotatate injection. Based on the outcome of the stability studies, a 48-hour shelf life for copper Cu 64 dotatate injection drug product is supported when stored at stored at controlled room temperature 20° to 25°C (68° to 77°F). Expiration will be defined in product labeling as (b) (4)

Labeling: Adequate

The PI and the labels were reviewed, and the comments sent to the applicant. Revised CAN and VIAL labels were received in amendment dated 07/2020 and are adequate.

Manufacturing: Adequate

Pre-approval inspections (PAI) were requested for (Curium US LLC.) who is the manufacturer of the (b) (4) final drug product (copper Cu 64 dotatate injection). PAI was also requested (b) (4) (b) (4)

A desk review under 706/704(a) process was completed for Curium (b) (4) due to COVID 19 travel restrictions. On that basis the facilities were found to be acceptable.

The manufacturing process was deemed to be adequate.

Biopharmaceutics: Adequate

The Copper Cu 64 Dotatate Injection used in the pivotal phase 3 clinical studies (IND# 131797) was manufactured by RadioMedix Inc (9701 Richmond Ave, Suite: 222, Houston, TX 77042, USA). Commercial Copper Cu 64 Dotatate Injection will be manufactured by Curium US LLC at their Maryland Heights, MO facility. Copper Cu 64 Dotatate Injection manufactured at commercial scale (registration batches) was deemed to be comparable to that of the clinical trial material (refer to Biopharm Review).

Microbiology : Adequate

All information related to sterility assurance and product manufacturing is covered under DMF (b) (4) reviewed by Laura Wasil (review date 19-Jun-2020) and deemed adequate.

C. Risk Assessment

From Initial Risk Identification	Assessment

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Appearance	Appearance is clear and colorless which becomes yellowish later on. Ascorbic acid solutions are known to turn yellow with exposure to heat and in the presence of oxygen.	Low	(b) (4)	Acceptable	No impact to Radiochemical Purity or any other test was observed as a result of this color change. No significant change in the Ascorbic Acid content was observed from the initial value even at elevated (55°C)temperature. Therefore, the color change has no impact on the quality of the product.
Radioactive concentration (RAC)	Adsorption losses during manufacturing; adsorption in drug product container/ closure; Malfunctioning dose calibrator.	Low		Acceptable	(b) (4)
Content uniformity and total vial radioactivity	(b) (4) – drug product manufacturing.	Low		Acceptable	Since each patient dose is required to be assayed for the correct radioactivity amount at the site of use, this attribute does not have a direct effect patient dose and safety.

			(b) (4)		
Apparent specific activity	The (b) (4) can affect apparent specific activity.	Medium		Acceptable	(b) (4)
Radionuclidic purity	(b) (4)	High		Acceptable	A thorough assessment (b) (4) was performed. (b) (4) The method was adequately validated and was suitable.
Radio chemical purity	Quality of components (excipients), elemental impurities, container closure interactions,	High		Acceptable	Radiochemical purity issues can show up as complaints related to poor image quality.

	radioactive concentration during manufacture and radiolysis during storage can affect radiochemical purity.		(b) (4)		
(b) (4) related substances	(b) (4)	High		Acceptable	Level (b) (4) is not a safety concern.
Impurities	Impurities can come from (b) (4)	High		Acceptable.	The mass amounts of impurities are low and generally not a safety concern.

	(b) (4)		(b) (4)		
Ethanol content	Ethanol is an excipient and its content can be affected (b) (4)	Medium		Acceptable	The amount of ethanol in the drug product is low and is not a safety concern.
pH	(b) (4)	Low		Acceptable	(b) (4)
(b) (4) content	(b) (4)	Low		Acceptable	(b) (4) determined as part of the drug product release by a validated method.
Bacterial Endotoxins	Contaminated materials, inadequate control over the manufacturing process.	Medium		Acceptable	None.
Sterility	Poor environmental controls during manufacturing; Poor aseptic techniques during manufacturing; Deficient control of the	High		Acceptable	Deficient environmental controls, personal aseptic practices, or deviation from a validated process may lead to product contamination and sterility failures. It is

	manufacturing operation (b) (4) breach of container closure integrity.		(b) (4)		noted that it is a PET drug and the drug product is released prior to completion of the sterility test.
Particulate matter	Particulates can come from the manufacturing process	Medium		Acceptable	The radioactive materials are generally assessed by visual observation.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

Application Technical Lead Name and Date:

Ravindra K. Kasliwal, Ph.D. ***24-Aug-2020***
Office of New Drug Products
Office of Pharmaceutical Quality

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	5/6/2020	Reviewed by Martin Haber, Ph.D.
	II			Adequate	7/9/2020	Reviewed by Ravindra Kasliwal, Ph.D.
	II			Adequate	7-13-2020	Reviewed by Drug product, microbiology and manufacturing reviewers

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	131797	RadioMedix Inc, 9701 Richmond Ave, Suite: 222, Houston, TX 77042, USA

2. CONSULTS: None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Under Review by OSE
Established name(s)	(copper Cu 64 dotatate injection)	Acceptable as it is all in lower case and in parentheses. The applicant has proposed established name for the drug product.
Route(s) of administration	Intravenous	Adequate – consistent with the mode of administration.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: (b) (4) (3)	This is a single dose vial that contains 4 mCi (1 mCi/ml) at calibration time. The strength is what is safe and effective for a single dose (4 mCi) which is what is packaged in the single dose vial. The statement should be revised to: • **Injection: 148 MBq (4 mCi) (37 MBq (1 mCi) per 1 mL) of copper Cu 64 dotatate in a single-dose vial (3)**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Not stated	Single-dose vial

1.2 FULL PRESCRIBING INFORMATION

The section 2.2 (Administration) supplied by applicant should be changed to:

2,2 Recommended Dosage and Administration Instructions

Administration

- Use copper Cu 64 dotatate injection within 2 hours after calibration time.
- Use aseptic technique and radiation shielding when withdrawing and administering copper Cu 64 dotatate injection.
- Inspect copper Cu 64 dotatate injection visually for particulate matter and discoloration before administration. Do not use the drug if the solution contains particulate matter or is discolored.
- Calculate the necessary volume to administer based on measured activity, volume, calibration time, and date.
- Use a dose calibrator to measure the patient dose immediately prior to administration of (b) (4).
- After injection of copper Cu 64 dotatate injection, administer an intravenous flush of 0.9% sodium chloride injection, USP.
- Dispose of any unused drug in a safe manner in compliance with applicable regulations.

Section 3 (DOSAGE FORMS AND STRENGTHS)

Recommend revising the dosage form and strength (3) section to:

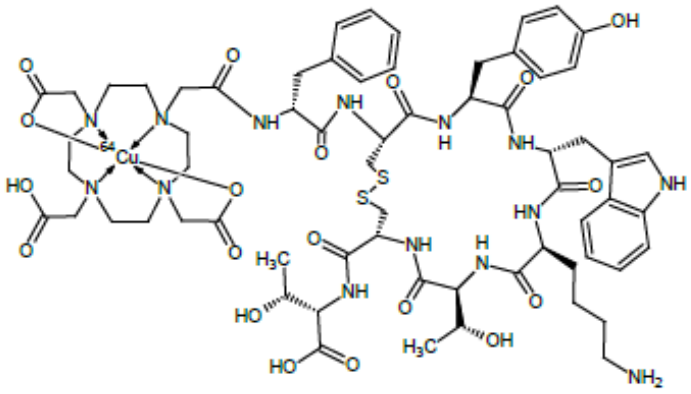
Injection; sterile, clear, colorless to yellow solution in a 10 mL single-dose vial containing 148 MBq (4 mCi) (37 MBq (1 mCi) per 1 mL) of copper Cu 64 dotatate at calibration date and time.

2.3.1 Section 11 (DESCRIPTION)

Recommend revising the description section (11) to:

(b) (4) **Chemical Characteristics**

(b) (4) contains copper Cu 64 dotatate, which is a radioactive diagnostic drug for use with PET imaging. Chemically, copper Cu 64 dotatate is described as copper (Cu 64)-N-[(4,7,10-Tricarboxymethyl-1,4,7,10- tetraazacyclododec-1-yl) acetyl]-Dphenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophanyl-L-lysyl-L-threoninyl-L-cysteinyl-L-threonine-cyclic (2-7) disulfide. The molecular weight is 1497.2 Daltons and the following is the structural formula:



(b) (4) is a sterile, clear, colorless to yellow solution for intravenous use. Each 10 mL single-dose vial contains 4 mCi (148 MBq) of copper Cu 64 dotatate at calibration date and time in 4 mL solution volume. Additionally, each mL of the solution contains 40 mg ascorbic acid, 0.05 ml of dehydrated alcohol, USP (ethanol) in sterile water for injection, USP . The pH is adjusted with sodium hydroxide, hydrochloric acid and is between 5.5 to 7.5.

Recommend following section 11.1 for physical properties for this radiopharmaceutical product:

(b) (4) **Physical Characteristics**

Table 2 and Table 3 display the principal radiation emission data and physical decay of Cu 64.

Copper Cu 64 decays with a half-life $t_{1/2}$=12.7 hours:

- 17.6% by positron emission to Ni 64 followed by emission of two 511 keV annihilation photons,
- 38.5% by beta decay to Zn 64,
- 43.8% by electron capture to Ni 64, and
- 0.475% by gamma radiation/internal conversion.

Table 3. Principal Radiation Emission Data (>1%)

Radiation/Emission	% Disintegration	Mean Energy (keV)
Positron (β^+)	17.6	278
Beta (β^-)	38.5	190.7
Gamma (γ)	35.7 0.48	511 1346

Table 4. Physical Decay Chart of Cu 64

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1.00	18	0.374
1	0.947	24 (1 day)	0.270

3	0.849	36 (1.5 days)	0.140
6	0.721	48 (2 days)	0.073
9	0.612	72 (3 days)	0.020
12	0.520	96 (4 days)	0.005

(b) (4) **External Radiation**

Gamma constant: 3.6 X 10^{-5} mSv/hr per MBq at 1 meter (0.133 mrem/hr. per mCi at 1meter)

Table 4 displays the radiation attenuation by lead shielding of Cu 64.

Table 5. Radiation Attenuation of Cu 64 by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.51	0.5
1.60	0.1
3.45	0.01
6.83	0.001

2.3.2 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Recommend following for this section:

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

(b) (4) (NDC 69945-064-01) is supplied as a sterile, clear, colorless to yellow solution in a 10 mL single-dose vial containing 148 MBq (4 mCi) (37 MBq (1 mCi) per mL) of copper Cu 64 dotatate at calibration date and time.

The sealed vial is contained in a shielded (lead) container for radiation protection. The product is shipped in a Type A package.

(b) (4)

Storage and Handling

Store (b) (4) in an upright position within the lead shielding to protect handlers from exposure to radiation.

Store (b) (4) at controlled room temperature 20˚C to 25˚C (68˚F to 77˚F). Do not use and discard (b) (4) 2 hours after the calibration date and time.

This radiopharmaceutical is for distribution and use by persons under license by the U.S. Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State. Store and dispose of (b) (4) in compliance with the appropriate regulations of the government agency

authorized to license the use of this radionuclide.

2.3.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured, Packaged and distributed for: Curium US LLC 2703 Wagner Place Maryland Heights, MO 63043	Adequate

2.0 PATIENT LABELING

There is no patient labeling for this radiopharmaceutical product prepared and administered by licensed health care practitioner.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (Version submitted on 29-Jun-2020)

(b) (4)

Assessment: *Currently Inadequate*

The following comments should be sent to the company.

1. Revise the established name for the drug product to "(copper Cu 64 dotatate injection)".

2. Include statement "Sterile" on the label. We recommend upper right of the (b) (4) trademark.
3. Revise the storage statement to, Store upright at controlled room temperature 20˚C to 25˚C (68˚F to 77˚F) in a shielded container.

The above comments were sent to the applicant on 08-Jul-2020. In the e-mail response (10-Jul-2020) to the comments, the company submitted the following revised container label. The revised container label is acceptable.

(b) (4)

Can Labeling (Version submitted on 29-Jun-2020)

(b) (4)

Assessment: *Currently Inadequate*
The following comments should be sent to the applicant.

1 Revise the established name for the drug product to "(Copper Cu 64 Dotatate Injection)".

2 Revise the (b) (4) statement to "Recommended adult dosage: 148 MBq (4 mCi) - See Prescribing Information" and relocate the statement under "Rx Only".

3 Revise the composition statement to: "Each mL Contains 37 MBq (1 mCi) of copper Cu 64 dotatate at calibration date and time, 40 mg ascorbic acid, 0.05 ml of dehydrated alcohol (ethanol) in sterile water for injection. Sodium hydroxide and / or hydrochloric acid is added for pH adjustment.

4 Delete the entire (b) (4) statement.

5 Revised the storage statement to: Store upright at controlled room temperature 20° to 25°C (68° to 77°F) in a shielded container.

The above comments were sent to the applicant on 08-Jul-2020. In the e-mail response (10-Jul-2020) to the comments, the company submitted the following revised can label. The revised can label is acceptable.

(b) (4)

Overall Assessment and Recommendation:

The revised labeling is Adequate.

Primary Labeling Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *16-Jul-2020*

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Danae D. Christodoulou, Ph.D. *16-Jul-2020*

Ravindra Kasliwal

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Danae Christodoulou

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BIOPHARMACEUTICS

NDA: 213227-ORIG-1
Drug Product Name / Strength: (b) (4) (^{64}Cu-DOTATATE Injection), 4.0 mCi
Route of Administration: Intravenous Injection
Applicant Name: RadioMedix, Inc
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Min Li, Ph.D.

EXECUTIVE SUMMARY:

Background: RadioMedix, Inc. is seeking approval of (b) (4) (^{64}Cu-DOTATATE Injection) for the (b) (4) localization of somatostain receptor (SSTR)-expressing neuroendocrine tumors (NETs) *via* the 505 (b)(2) regulatory pathway. The proposed drug product received a Fast Track designation on 12/19/2018 for detection and localization of NETs and an Orphan Drug Designation on 05/18/2016 as a diagnostic agent to be used with positron emission tomography (PET) for management of NET. The proposed product is a single-dose, sterile solution containing 1 mCi/mL or 4 mCi/vial of Copper (Cu)-64 DOTATATE, 40 mg/mL ascorbic acid, and (b) (4) ethanol in 10 mL glass vial for intravenous (IV) administration. The pH of the drug product is maintained between 5.5-7.5.

The NDA is supported by a pivotal Phase 3 clinical study, RMX-18-22 for detection of somatostatin receptor expressing NETs. The NDA is also relying on three safety and efficacy studies conducted with ^{64}Cu-DOTATATE Injection: (i) a comparative diagnostic performance study of the proposed product with the FDA approved NETSPOT™ [a gallium (Ga)-68 radiolabeled DOTATOC imaging product which is available for the management of NET] published in the literature by Johnbeck, 2017, (ii) a Phase 1 clinical study in 14 subjects with a history of NETs published in the literature by Pfiefer *et al*., 2012, and (iii) a retrospective analysis of 112 patients with confirmed NETs published in the literature by Pfiefer *et al*., 2015.

The proposed commercial product, the products used in the pivotal Phase 3 clinical study, RMX-18-22 and formulations used in the referenced literature differ (b) (4) (b) (4) The formulation difference is not expected to alter the pharmacokinetics (PK) of ^{64}Cu-DOTATATE. Therefore, the proposed commercial product is bridged to the products administered in the pivotal Phase 3 clincial study, RMX-18-22 and referenced in the literature per 21 CFR 320.24(b)(6).

OVERALL REVIEW RECOMMENDATION:

From Biopharmaceutics perspective, the NDA 213227 for (b) (4) (^{64}Cu-DOTATATE Injection), 4 mCi/vial is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

➢ LIST OF SUBMISSIONS BEING REVIEWED:

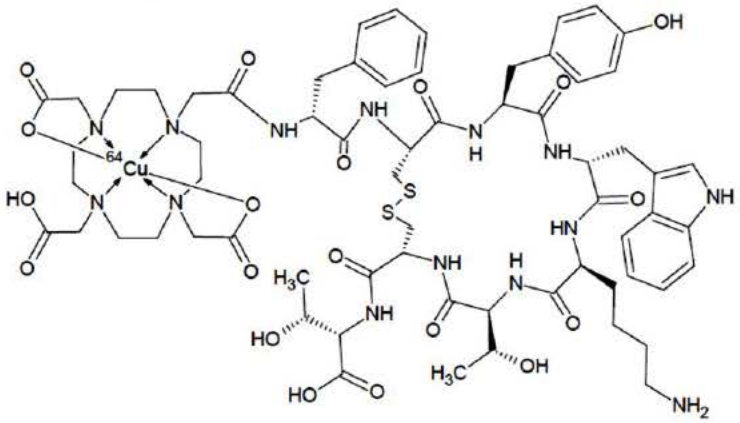
Submissions Reviewed	Reference ID
Original NDA 213227 Submission	Dated 01/03/2020, SDN 4 (\\cdsesub1\evsprod\nda213227\0004\m2\23-qos\introduction.pdf)
Response to Information Request #1	Dated 04/09/2020, SDN 10 (\\CDSESUB1\evsprod\nda213227\0010\m1\us\111-info-amend\response-fda-filing-issues-dated-01mar2020.pdf)
Response to Information Request #2	Dated 05/04/2020, SDN 12 (\\CDSESUB1\evsprod\nda213227\0012\m1\us\12-cover-letter\cover-letter.pdf)

➢ *DRUG SUBSTANCE*:

^{64}Cu-DOTATATE (molecular weight=1497.5 grams/mol; molecular formula=$C_{65}H_{88}N_{14}CuO_{19}S_2$) is composed of three components; the positron-emitting ^{64}Cu, the chemical linker DOTA (tetraxetan), and the somatostatin analog, Octreotate. The proposed drug substance (b) (4) (b) (4) (b) (4) (see **Figure 1**). The molecular structure of ^{64}Cu-DOTATATE is similar to somatostatin as it binds to somatostain receptor subtype 2 with high affinity and specificity. The radiochemical half-life of ^{64}Cu is a short 12.5 hours.

According to the Applicant, the chemical properties of ^{64}Cu-DOTATATE are similar to that of ^{68}Ga-DOTATATE and Lutetium (Lu) 177-DOTATATE.

Figure 1. Chemical structure of ^{64}Cu-DOTATATE



- ***Pharmacokinetics:*** The pharmacokinetics of ^{64}Cu-DOTATATE was evaluated in the Phase 3 clinical study, RMX-18-22 in which 6 subjects were administered an intravenous bolus dose of ~4 mCi (~148 mBq) proposed product. ^{64}Cu-DOTATATE was rapidly cleared from the plasma with <10% of the total administered radioactive dose in the blood 3 hours post-injection. Approximately, half the total administered radioactive dose was recovered in the urine (16-40%) 6 hours post-administration of ^{64}Cu-DOTATATE Injection, suggesting renal clearance to be the major elimination pathway for ^{64}Cu-DOTATATE.

  Other literature studies indicate uptake of ^{64}Cu-DOTATATE in the kidneys, liver, and spleen.

- ***Manufacturing Sites for ^{64}Cu-DOTATATE Drug Substance:***

(b) (4)

- ***DRUG PRODUCT*:**

The composition of the proposed to-be-marketed (TBM) diagnostic agent, ^{64}Cu-DOTATATE is provided in **Table 2**.

Table 2. Composition of the proposed to-be-marketed ^{64}Cu-DOTATATE diagnostic agent

Component	Function	Quality Standard	Quantity per one millilitre (1 mL)	Quantity per vial
Copper Cu-64 dotatate	Drug Substance/Active Pharmaceutical Ingredient	GMP	1.00 mCi[a]	4.0 mCi[a]
				(b) (4)
Ascorbic Acid	(b) (4)	USP	40 mg	160 mg
Dehydrated alcohol (ethanol)		USP	0.05 mL (v/v)	0.2 mL
Sterile Water for Injection		USP		(b) (4)
Sodium Hydroxide		USP	As needed for pH adjustment (pH range 5.5-7.5)	
Hydrochloric Acid		USP		

[a] At calibration [at 1700CT (b) (4)].
[b] Specification: as (b) (4) related substances.

The proposed product is a radiolabeled diagnostic imaging product to be used as an intravenous bolus injection with positron positron tomography (PET) for the (b) (4) localization of somatostain receptor (SSTR)-expressing neuroendocrine tumors (NETs).

The proposed diagnostic product contains 4 mCi ^{64}Cu-DOTATATE, ascorbic acid, and dehydrated ethyl alcohol in 10 mL glass vial for intravenous (IV) administration. The pH of the drug product is maintained between 5.5-7.5.

It should be noted that the 4 mCi, ^{64}Cu-DOTATATE Injection was provided as a sterile, bulk solution for the Phase 3 clinical study. On the other hand, the commercial product will be provided in a single-use vial containing ^{64}Cu-DOTATATE Injection, 4 mCi/vial (1 mCi/mL).

- ***Manufacturing Sites for ^{64}Cu-DOTATATE Injection Product:***

The Applicant identified Curium US, LLC (Maryland Heights, MD) as the commercial manufacturing site for the proposed ^{64}Cu-DOTATATE Injection product.

The ^{64}Cu-DOTATATE Injection product administered in the pivotal Phase 3 clinical study, RMX-18-22 was manufactured at RadioMedix Inc. (Houston, TX). In order to bridge the two manufacturing sites, the Applicant provided physico-chemical characterization of the clinical batch and the registration batches manufactured at the two sites. The comparability data for the clinical batch and the registration batches will be assessed by the Drug Product Reviewer.

Bridging of the Drug Products used in Various Clinical Studies:

The Applicant is seeking approval for the proposed diagnostic product *via* the 505 (b)(2) regulatory pathway. However, the submission does not reference any LD as there are currently no approved ^{64}Cu-DOTATATE product. On the other hand, there are many DOTATATE containing diagnostic products that have received marketing authorization.

The current submission is supported by a pivotal Phase 3 clinical study, RMX-18-22 in which ^{64}Cu-DOTATATE Injection was administered for imaging with PET-CT scan for detection of somatostatin receptors expressing NETs. Additionally, the Applicant is relying upon the comparative diagnostic performance of ^{64}Cu-DOTATATE Injection to the FDA approved DOTATOC product NETSPOT™ [a gallium (Ga)-68 radiolabeled DOTATOC imaging product that is available for the management of NET in adults and in pediatric patients] for the approval of the proposed product. The current NDA is also supported by safety and efficacy studies conducted with ^{64}Cu-DOTATATE Injection and published in the literature by Pfiefer et al., 2012, 2015, and Johnbeck, 2017.

As the proposed product and the products referenced in the literature are different (b) (4) (b) (4) the Applicant was recommended to provide detailed information regarding the diagnostic products used in the literature studies to bridge the proposed products per 21 CFR 320.24(b)(6).

In a response (dated 04/09/2020), the Applicant provided comparative composition of the drug products administered in the literature studies, the pivotal Phase 3 clinical study, RMX-18-22, and the commercial drug product as shown in **Table 3**.

Table 3. Comparative composition of the drug products administered in the literature studies and the pivotal Phase 3 clinical study, RMX-18-22, to provide a bridge to the commercial drug product (b) (4) (^{64}Cu-DOTATATE Injection), 4 mCi/vial

Component	*Pfeifer, 2012*	*Pfeifer, 2015*	*Johnbeck, 2017*	Phase 3	Commercial[1]	Function in Commercial formulation
Copper cu-64 DOTATATE Radioactivity (mCi) – Patient Dose	5.2 – 6.3 mCi (mean: 5.6 mCi)	4.9-6.3 mCi (mean: 5.5 mCi)	4.8-5.9 mCi (mean: 5.4 mCi)	4 mCi (3.6 – 4.4)	4 mCi	Drug Substance
Injection Volume (mL)	Not available			(b) (4)		
(b) (4)						
Ascorbic Acid (mg)						
Ethanol (mg)						

[1] Four mCi vial (4 mL fill volume). Values based on specification limits for (b) (4) ascorbic acid (40 mg/mL), and ethanol ((b) (4)% v/v), sterile water for injection ((b) (4)% v/v). (b) (4)

(b) (4)

The Applicant attributed higher ^{64}Cu-DOTATATE dose (mean 5.4-5.6 mCi) administered in the literature studies by Pfeifer (2012 and 2015) and Johnbeck (2017) to prior experiences of the authors with another PET imaging agent, such as ^{68}Ga-DOTATATE. However, the ^{64}Cu-DOTATATE dose administered in the Phase 3 clinical study and proposed for the commercial product is lower (4 mCi). The ^{64}Cu-DOTATATE dose administered in the Phase 3 clinical study (3.6-4.4 mCi) was based on a dose range-finding study, RMX-17-22 that was conducted to select the lowest radioactive dose that would yield quality images for diagnosic purposes. As 4 mCi-5 mCi yielded good quality images, the Applicant proposed 4 mCi which is the lowest radioactive dose based on ALARA principles for the Phase 3 clinical study and the commercial product. Therefore, the ^{64}Cu-DOTATATE dose in the commercial product is bridged to the formulation evaluated in the Phase 3 study.

(b) (4)

The Phase 3 formulation and the commercial product include additional excipients such as ascorbic acid and ethanol (b) (4) (b) (4) The Applicant noted that the pH of the commercial formulation is between 5.5 to 7.5. (b) (4) (b) (4) (b) (4) The Applicant was recommended to provide the osmolality

data for the Phase 3 formulation and the proposed commercial product in an Information Request dated 04/21/2020.

In a response (dated 05/04/2020), the Applicant refered to the DMF (b) (4) for the osmolality data for three lots (b) (4) and proposed commercial product containing (b) (4) Cu-64 dotatate, (b) (4) ethanol, (b) (4) and water for injection (see **Table 6**). As the radiochemical half-life of ^{64}Cu is 12.5 hours, the Applicant provided osmolality data for the (b) (4) commercial product.

The osmolality data for three lots (b) (4) (b) (4) are between (b) (4) mmol/Kg and the commercial product containing (b) (4) Cu-64 dotatate, (b) (4) ethanol, (b) (4) and water for injection is between (b) (4) mmol/Kg.

The osmolality of blood is between 280-310 mOsmol/Kg, whereas the osmolality data for (b) (4) solutions and the commercial product is slightly high. According to the Applicant, the slightly higher osmolality data will not pose a safety concern.

As the proposed product is a single-use infusion product, the higher osmolality data may not be of concern. The Pharmacology Reviewer and the Drug Product Reviewer confirmed that higher osmolality data would not be a safety concern.

Table 6. Osmolality data for three lots (b) (4) (b) (4)

Sample	Osmolality (mmol/kg)	Composition (b) (4)

Based on the totality of the information provided, the proposed commercial product and the products administered in the pivotal Phase 3 clinical study, RMX-18-22 and referenced in the literature that differ (b) (4) appears to not alter the safety, efficacy, or disposition of ^{64}Cu-DOTATATE. The proposed commercial product is bridged to the products administered in the pivotal Phase 3 clincial study, RMX-18-22 and referenced in the literature per 21 CFR 320.24(b)(6).

- ***POST-APPROVAL COMMITMENTS:*** **None**

- ***LIST OF DEFICIENCIES:*** **None**

- ***OVERALL REVIEW RECOMMENDATION:***

From Biopharmaceutics perspective, the NDA 213227 for (b) (4) (^{64}Cu-DOTATATE Injection), 4 mCi/vial is recommended for **APPROVAL.**

APPENDIX I

(b) (4)

Parnali Chatterjee

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	213227
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Copper Cu 64 Dotatate/4.0 mCi
Route of Administration	Intravenous
Applicant Name	RadioMedix, Inc.
Therapeutic Classification/ OND Division	DMIRM
Manufacturing Site	Curium US LLC 2703 Wagner Place Maryland Heights, MO 63043 USA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
eCTD 0004	**1/3/2020**

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission provides for the initial marketing of the sterile PET drug product, Copper Cu 64 Dotatate. All information related to sterility assurance and product manufacturing is covered under DMF (b) (4); reviewed and deemed adequate in D (b) (4) M01R01.docx, dated 19 June 2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
Quality microbiology review D (b) (4) M01R01.docx, dated 19 June 2020 for the sterility assurance information related to the manufacture of Copper Cu 64 Dotatate Injection at the Curium US LLC facility.

S DRUG SUBSTANCE

The drug substance is non-sterile; therefore, the drug substance is not reviewed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Module 3.2.P.1, Description and Composition of the Drug Product.pdf)
(Module 3.2.P.7, Container Closure System.pdf)

- **Description of the drug product –** sterile solution supplied in a single-use vial containing 1 mCi/mL (4 mCi/vial) of copper Cu-64 dotatate.

- **Drug product composition –**

Component	Function	Quantity per 1 mL	Quantity per vial
Copper Cu-64 dotatate	Drug substance/API	1.00 mCi	4.0 mCi
(b) (4)			(b) (4)
Ascorbic acid	(b) (4)	40 mg	160 mg
Dehydrated alcohol (ethanol)		0.05 mL (v/v)	0.2 mL
Sterile WFI			(b) (4)
Sodium Hydroxide		As needed for pH adjustment (pH 5.5-7.5)	
Hydrochloric Acid			

- **Container closure system –**

Item	Description	Supplier
Vial		(b) (4)
Stopper		
Closure		

Assessment: ***Adequate***

The applicant provided adequate information regarding the drug product composition and primary container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

The container closure integrity testing is referenced to DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

Container closure integrity testing was reviewed and deemed adequate in quality microbiology review D(b) (4)M01R01.docx, dated 19 June 2020.

Antimicrobial Effectiveness Testing

Not applicable; the drug product is package in single-use vials.

P.3 MANUFACTURE

P.3.1 MANUFACTURERS

(Module 3.2.P.3.1, Manufacturer(s).pdf)

Curium US LLC
2703 Wagner Place
Maryland Heights, MO 63043

FEI: 1946929
DUNS: 557570652

P.3.3 DESCRIPTION OF THE MANUFACTURING PROCESS AND PROCESS CONTROLS

Overall Manufacturing Operation

(Module 3.2.P.3.3, Description of Manufacturing Process and Process Controls.pdf)

The manufacture of the drug product is covered under DMF (b) (4) (LOA dated 3 December 2019). A brief description of the manufacturing process is provided below for reference purposes.

(b) (4)

(b) (4)

Assessment: *Adequate*

The proposed manufacturing process for Copper Cu 64 Dotatate was reviewed and deemed adequate in quality microbiology review D(b) (4)M01R01.docx, dated 190 June 2020.

(b) (4) ***Manufacturing Process***
Buildings and Facilities

Facility information, including environmental monitoring, is referenced to DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The facility information and environmental monitoring program were reviewed and deemed adequate in quality microbiology review D(b) (4)M01R01.docx, dated 19 June 2020.

Sterilization/Depyrogenation of containers, closures, equipment and Components – See P.3.5

P.3.5 PROCESS VALIDATION AND/OR EVALUATION

(b) (4) ***Manufacturing Process***
Drug Product Solution (b) (4)

The (b) (4) validation studies are referenced to DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The (b) (4) validation studies were reviewed and deemed adequate in quality microbiology review D(b) (4)M01R01.docx, dated 19 June 2020.

(b) (4)

Information (b) (4) is referenced to DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The proposed (b) (4) were reviewed and deemed adequate in quality microbiology review D (b) (4) M01R01.docx, dated 19 June 2020.

Sterilization/Depyrogenation of Containers, Closures, Equipment and Components

All sterilization/depyrogenation process validation information is covered under DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The sterilization/depyrogenation process validation information was reviewed and deemed adequate in quality microbiology review D (b) (4) M01R01.docx, dated 19 June 2020.

(b) (4) ***Procedures and Specification***

(b) (4) procedures and results are covered under DMF (b) (4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The (b) (4) was reviewed and deemed adequate in quality microbiology review D (b) (4) M01R01.docx, dated 19 June 2020.

P.5 CONTROL OF DRUG PRODUCT

P.5.1 SPECIFICATION

(Module 3.2.P.5.1, Specifications.pdf)

Test	Analytical Method	Acceptance Criteria
(b) (4)	N/A**	Pass

Sterility*	(b) (4), per USP <71>	Sterile
Bacterial Endotoxins	(b) (4) per USP <85>	≤ (b) (4) EU/mL
(b) (4)		

Assessment: *Adequate*

The applicant did not include the test method (b) (4) in the release specification; however, release testing is performed by the DMF holder and the product release specification was reviewed and deemed adequate in D (b) (4) M01R01.docx, dated 19 June 2020. Therefore, additional information will not be requested at this time.

P.5.2 ANALYTICAL PROCEDURES

Assessment: See Section P.5.1

P.5.3 VALIDATION OF ANALYTICAL PROCEDURES

Endotoxins

Method suitability testing for the endotoxins test is covered under DMF (b) (4) (LOA dated 3 December 2019).

Based on the proposed endotoxins specification and the prescribing information, the maximum endotoxins dose administered to patients is calculated below:

Maximum dosage per hour: 4 (b) (4) % mCi in a single injection
Strength: 1 mCi/mL in 10 mL single dose vial
Endotoxins specification: ≤ (b) (4) EU/mL
The drug product is not intended for pediatric administration.

Maximum dose volume x Endotoxins spec = (b) (4) mL x (b) (4) EU/mL = (b) (4) EU/dose.

The maximum endotoxins dose at the proposed maximum endotoxins specification and maximum dose as calculated by this reviewer is within the USP <85> recommendation of NMT (b)(4) EU/dose.

Assessment: *Adequate*

Endotoxins method suitability testing was reviewed and deemed adequate in D(b)(4)M01R01.docx, dated 19 June 2020. Additionally, the applicant has met regulatory expectations for the endotoxins test acceptance criteria.

Sterility

Method suitability testing for the sterility test is covered under DMF (b)(4) (LOA dated 3 December 2019).

Assessment: *Adequate*

All information related to the sterility test was reviewed and deemed adequate in quality microbiology review D(b)(4)M01R01.docx, dated 19 June 2020.

P.7 CONTAINER CLOSURE

Assessment: See Section P.1

P.8 STABILITY

P.8.1 STABILITY SUMMARY AND CONCLUSION

(Module 3.2.P.8.1, Stability Summary and Conclusion.pdf)

Stability testing was performed on three drug product batches at long-term storage condition (25 ± 2°C/60 ± 5% RH).

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	(b)(4) per USP <85>	≤ (b)(4) EU/mL
Sterility	(b)(4), per USP <71>	Sterile

(b) (4)	Not provided	Pass

Proposed testing schedule for the exhibit batches is as follows:

Stability storage conditions: 25 ± 2°C/60 ± 5% RH

Test	Time (Days) (b) (4)
Bacterial Endotoxin	
Sterility	
(b) (4)	

Proposed expiry: 48 hours when stored at room temperature

Assessment: *Adequate*

The test method for the (b) (4) test was not provided; however, this information was provided in DMF (b) (4) as part of the stability summary and conclusion, and was reviewed and deemed adequate in D(b) (4)M01R01.docx, dated 19 June 2020.

P.8.2 POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT

(Module 3.2.P.8.2, Post-Approval Stability Protocol and Stability Commitment.pdf)

The product stability specification includes the following microbiological tests:

Test	Test Method	Acceptance Criteria
Bacterial Endotoxins	(b) (4), per USP <85>	≤ (b) (4) EU/mL
Sterility	(b) (4), per USP <71>	Sterile
(b) (4)	Not provided	Pass

The testing schedule in the post-approval protocol is as follows:

Stability storage conditions: 25 ± 2°C/60 ± 5% RH

Test	Time (Days) (b) (4)
Bacterial Endotoxin	
Sterility	
(b) (4)	

Post Approval Stability Commitment

The applicant stated that, per DMF (b)(4), one lot will be placed in the stability program.

Assessment: *Adequate*

The post-approval stability protocol is covered under DMF (b)(4); this information was reviewed and deemed adequate in D(b)(4)M01R01.docx, dated 19 June 2020.

P.8.3 STABILITY DATA

(Module 3.2.P.8.1, Stability Summary and Conclusion.pdf)

The stability program is managed by the drug product manufacturer, Curium US LLC, and is covered under DMF (b)(4) (LOA dated 3 December 2019). The applicant provided the following summary:

Long-term stability studies were performed for three registration batches (064-X19003, 064-X19004 and 064-X19005). The provided results, up to the 2 day expiry, demonstrated that endotoxins and sterility specifications were met.

Assessment: *Adequate*

The stability data were reviewed and deemed adequate in D(b)(4)M01R01.docx, dated 19 June 2020.

APPENDICES – N/A

R REGIONAL INFORMATION

Executed Batch Records

The executed batch records are covered under DMF (b)(4) (LOA dated 3 December 2019).

Assessment: *Adequate*

The executed batch records were reviewed and deemed adequate in D(b)(4)M01R01.docx, dated 19 June 2020.

Comparability Protocols

Assessment: Not applicable.

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

2.A. Prescribing Information

Store at room temperature (25°C). The product is not diluted prior to administration.

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology that is provided in the product labeling.

Post-Approval Commitments

Assessment: See Section P.8.2.

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable.

Primary Microbiology Assessor Name and Date:
Laura R. Wasil, Ph.D.; 22 June 2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Julie Nemecek, Ph.D.; 22 June 2020

Laura Wasil

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Julie Nemecek

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Ravindra Kasliwal

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Date: 8/24/2020 08:31:17AM
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAVINDRA K KASLIWAL
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