CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210089Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) **210089**

Addendum to Integrated Quality Assessment

NDA 210089

Assessment 1 - addendum

Drug Product Name	Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection
Dosage Form	For injectable suspension
Strength	2.0 mg/vial
Route of Administration	Intravenous or Intraperitoneal
Rx/OTC Dispensed	Rx
Applicant	CIS Bio International
US agent, if applicable	Ed Porter, Curium US LLC.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Amendment (0018)	16-Mar-2020	Drug Product Labeling

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Office of Pharmaceutical quality recommends an approval action for the proposed new drug product in NDA 210089. The revised and labels (vial, 5-Vial kit, 30-vial carton, and radio assay label)and prescribing information (PI), as per our comments were submitted in amendment dated 3/16/2020 and are acceptable.

Application Technical Lead Name and Date:

Ravindra K. Kasliwal, Ph.D. *17-Mar-2020*

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
03/17/2020 11:09:51 AM

Office of Pharmaceutical Quality

New Drug Application (NDA) **210089**

Integrated Quality Assessment

Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 210089
Assessment 1

Drug Product Name	Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection
Dosage Form	For injectable suspension
Strength	2.0 mg/vial
Route of Administration	Intravenous or Intraperitoneal
Rx/OTC Dispensed	Rx
Applicant	CIS Bio International
US agent, if applicable	Ed Porter, Curium US LLC.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (003)	11-Jun-2019	All
Amendment (004)	12-Jun-2019	Drug Product
Amendment (006)	17-Jul-2019	Manufacturing Facility
Amendment (007)	26-Jul-2019	Manufacturing Facility
Amendment (008)	19-Sep-2019	Microbiology
Amendment (0012)	13-Nov-2019	Microbiology, Drug Product, Manufacturing
Amendment (0013)	10-Jan-2020	Drug Product
Amendment (0014)	27-Jan-2020	Manufacturing
Amendment (0015)	03-Feb-2020	Drug Product, Manufacturing
Amendment (0016)	14-Feb-2020	Drug Product
Amendment (0018)	02-Mar-2020	Drug product, Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	See consult chart	
Drug Product	Ravindra Kasliwal	Danae Christodoulou
Manufacturing	Laurie Nelson	Krishna Gosh
Microbiology	Dustin Thomas	Jesse Wells
Biopharmaceutics	Bryan Ericksen	Tapash Ghosh

Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Ravindra Kasliwal	
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 the proposed new drug product in NDA 210089, when the recommendations for Prescription Information (PI), Container and Carton labels have been implemented.

Basis for recommendation:

- The application was submitted as a 505(b)(2) NDA, citing NDA 017881 (Draximage®MAA) as the listed drug. The proposed drug product as well as the listed drug are supplied in multiple-dose vials. Biopharmaceutics has made a determination that even though the formulation (and component amounts) between the proposed new drug product and the listed drug are different the dose of the radiolabeled drug is equivalent, and these differences do not have an effect on safety or efficacy of the proposed drug product relative to the listed drug product.
- The applicant utilizes FDA-approved US sourced Albumin (b) (4) (b) (4) for the manufacture of macroaggregated (MAA) particles, and for use as an excipient in the drug product. (b) (4) (b) (4) and has been determined to be acceptable for use (CBER consult review).
- Components used for the drug product and their quality are adequate and have been qualified through successful manufacture and stability.
- 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 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, (b) (4) and elemental impurities) is adequate.
- Manufacturing and controls are adequately defined. The drug product manufacturing process and procedures are adequate for the manufacture of proposed sterile, (b) (4) (b) (4) lyophilized drug product.
- The drug product manufacturing facility was inspected and has an acceptable CGMP status for the manufacture of proposed sterile, (b) (4) lyophilized drug product. Other manufacturing, testing, labeling and packaging facilities have acceptable CGMP status.
- The drug product (kit) can be acceptably radiolabeled with sodium pertechnetate Tc 99m injection solution obtained from (b) (4)
- The available long-term stability data supports a **12-months expiration dating period for Pulmotech™MAA when stored at 2 to 25º C (36 to 77ºF)**.
- Radiolabeled product's stability data supports labeling statements "**radiolabel with ≤ 185 mCi of sodium pertechnetate Tc 99m injection in 2-13 mL volume**" and

"**Store radiolabeled product in a refrigerator at 2-8ºC and use within 18 hours of preparation**".

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product, Pulmotech™ MAA (Kit for the Preparation of Technetium Tc-99m Albumin Aggregated Injection), will be supplied as a sterile, (b) (4) white powder in a 15 mL clear glass vial in a nitrogen atmosphere. The glass vial is targeted to contain 2.0 mg of aggregated albumin, 0.22 mg total tin (as stannous (Sn^{2+}) and stannic (Sn^{4+}) chloride), minimum of (b) (4) mg stannous chloride (b) (4), 7.1 mg albumin human and 9.0 mg sodium chloride. Hydrochloric acid is added, as needed, to adjust the pH to 5.0 – 7.0. The 15 mL multi-dose vials will be supplied in either a 5-count clam shell or 30 count cartons.

The drug product, as supplied, is not intended for direct administration. The product is used after reconstitution (radiolabeling) (b) (4) as directed in prescribing information (PI). The radiolabeled product is to be prepared (b) (4) for human administration within 18 hours of preparation when stored in a refrigerator (2-8ºC). Since this is an injectable suspension product, the recommended needle size is 18 to 21-gauge needle for withdrawal and administration.

The macroaggregated albumin particles are manufactured from FDA-approved US sourced Albumin (b) (4)

(b) (4)

(b) (4)

HSA in its native and macroaggregated form is able to bind metal ions to form metal-protein complexes, which makes it suitable for labeling with radioactive sodium pertechnetate Tc-99m (Tc 99m ions). The proposed drug product formulation contains (b) (4) as well as in the insoluble macroaggregated form (active). To ensure that Tc 99m only binds to the macroaggregated form (b) (4), the company uses a proprietary process to manufacture MAA particles.

First the entire process is (b) (4)

(b) (4)

The mechanism of action for Tc-99m MAA products is attributed to the controlled size of the particles that become trapped in the first capillary bed encountered, creating a temporary blockade of terminal arterioles/capillaries in the lung. For diagnostic efficacy it is important to administer sufficient number of particles to accurately map the flow of blood through the lungs. For reasons of safety, it is also important to control the particle size and to inject a sufficiently small number of particles to avoid major interruptions of blood flow through the lung and a lung with marked pulmonary perfusion deficiency.

It is believed that, in the lung of an adult there are approximately 280 billion capillaries and 300 million arterioles. Following injection of ^{99m}Tc MAA, which typically contain about 350,000 particles, and depending on the particle size distribution relative to regional blood flow, roughly one out of every one million capillaries (diameter < 20 μm) and one out of every 1,000

arterioles (= 0.1%) (diameter > 20 μm) is likely to become temporarily occluded. Too small macroaggregates (< 10 μm) won't block blood vessels of the lungs while too large macroaggregates (> 150 μm) may lead to an increase of the pulmonary arterial pressure. For the currently approved product, the recommended number of particles injected to an adult range from 200,000 – 700,000 (DraxImage MAA Prescribing Information). Therefore, even if the maximum number of particles were injected under the least favorable assumption of a diameter > 20 μm for all particles, about 700,000 out of 300,000,000 = 0.23% of the arterioles in an otherwise normal healthy adult lung would be occluded by the particles.

Each 15 mL vial is filled with (b) (4) Drug Product. The vial is partially stoppered with a 20-mm grey (b) (4) stopper, and sealed (b) (4) with a 20-mm flip top aluminum orange Overseal. (b) (4)

The most critical quality attributes, besides microbiological controls, are the size and number of particles, (b) (4) and radiochemical purity of the product. (b) (4)

The proposed product is not photo-sensitive, and the clear glass container closure system has been shown to be suitable for maintaining the quality and sterility the drug product. The applicant has provided 12-month long term stability data (both for refrigerator storage and for controlled room temperature storage), along with the statistical analysis report, that supports the proposed **12 months expiration date for Pulmotech MAA when stored at 2 to 25º C (36 to 77 ºF).** Results of radiolabeling study indicate that when reconstituted with 2-13 mL volume and radioactivity (b) (4), the radiolabeled product is stable for 24 hours. The radiolabeled product is to be stored in a **refrigerator (2 to 8ºC (36º to 46ºC) and the product proposed labeling recommends a use period of 18 hours**, which is acceptable.

The first Tc 99m MAA drug product was approved by agency in 1976. Since then the Agency has approve 9-NDAs for this drug product. Although the drug product NDAs, except for the DRAXIMAGE NDA (N 017881) have been discontinued, none has been discontinued or withdrawn for safety reasons. Therefore, safety and effectiveness as well as the conditions of use for Tc 99m MAA have been well established. CIS Bio has marketed a comparable drug product (called Pulmocis) in the EU market since 1993. The proposed product will be the second Tc 99m MAA product in the market, once approved.

Proposed Indication(s) including Intended Patient Population	Technetium Tc 99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients. Technetium Tc 99m Albumin Aggregated Injection also may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (b) (4) shunt patency.
Duration of Treatment	One time use prior to imaging.

Maximum Daily Dose	The recommended intravenous dose for the average (70 kg) ADULT patient for lung imaging is 37 to 148 megabecquerels (1 to 4 millicuries) of Technetium Tc 99m Albumin Aggregated Injection. The recommended intraperitoneal dosage used in the average patient (70 kg) for peritoneovenous (b) (4) shunt patency evaluation is 37 to 111 megabecquerels (1 to 3 millicuries). The recommended percutaneous transtubal (b) (4) dosage for the average patient (70 kg) is 12 to 37 megabecquerels (0.3 to 1 millicurie) in a volume not to exceed 0.5 mL. The recommended number of particles per single injection is 200,000 to 700,000 with the suggested number being approximately 350,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 to 1.9 mL. In PEDIATRIC patients, the suggested intravenous dose for perfusion lung imaging is 0.925 to 1.85 MBq per kilogram (25 to 50 μCi/kg) of body weight; a usual dose is 1.11 MBq per kilogram (30 μCi/kg), except in newborns, in whom the administered dose should be 7.4 to 18.5 MBq (200 to 500 μCi). The number of particles will vary with age and weight of the pediatric patient
Alternative Methods of Administration	Intravenous, intraperitoneal, percutaneous

B. Quality Assessment Overview

Drug Substance: Adequate

In the NDA 210089, Albumin (Human) (b) (4) in the manufacturing of Drug Substance, Albumin Aggregated, and (b) (4)

The information provided for Albumin (Human) (b) (4) is adequate to assure quality and safety of the lots manufactured by (b) (4)

Drug Product: Adequate

The applicant has justified and qualified the quality of the components used in the drug product. Controls (specifications) for critical quality attributes have been established, the acceptance criteria have been adequately justified and analytical methods have been verified to be suitable for the assessment of the respective quality attribute. Assessment of risk of presence of impurities (organic, inorganic and elemental) have been performed and satisfactory control strategies have been established. The proposed product is not

photo-sensitive, and the clear glass container closure system has been shown to be suitable for the drug product. The applicant has provided 12-month long term stability data (both for refrigerator storage and for controlled room temperature storage), along with the statistical analysis report, that supports the proposed 12 months expiration date for Pulmotech MAA when stored at 2 to 25º C (36 to 77 ºF). Results of radiolabeling study indicate that when reconstituted with 2-13 mL volume and radioactivity of (b) (4) (b) (4) the radiolabeled product is stable for 24 hours. The radiolabeled product is to be stored in a refrigerator at 2 to 8ºC (36º to 46ºC) and the product proposed labeling recommends a use period of 18 hours, which is supported by data which is acceptable.

In accordance with 21 CFR 25.31(a), Cis Bio International has claimed a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20, which is justified and is acceptable.

Labeling: Inadequate

The labeling comments, related to prescribing information and the container and carton labels, cited in the labeling review should be sent to the applicant.

Manufacturing: Adequate

The Kit is manufactured at CIS Bio International (b) (4) the finished drug product is labeled at Curium US LLC in Maryland Heights, MO, US and final product release is performed. Curium is also identified as an alternative final product testing site.

The manufacturing procedures are adequately defined and verified to confirm that they are adequate for the manufacture of the proposed lyophilized, proposed drug product. All the listed manufacturing facilities have been found to have acceptable CGMP status.

Biopharmaceutics: Adequate

The application was submitted as a 505(b)(2) NDA, citing NDA 017881 (Draximage® MAA) as the listed drug. The proposed drug product as well as the listed drug are supplied in multiple-dose vials. Biopharmaceutics has made a determination that even though the formulation (and component amounts) between the proposed new drug product and the listed drug are different, the dose of the radiolabeled drug is equivalent, and these differences do not have an effect on safety or efficacy of the proposed drug product relative to the listed drug product.

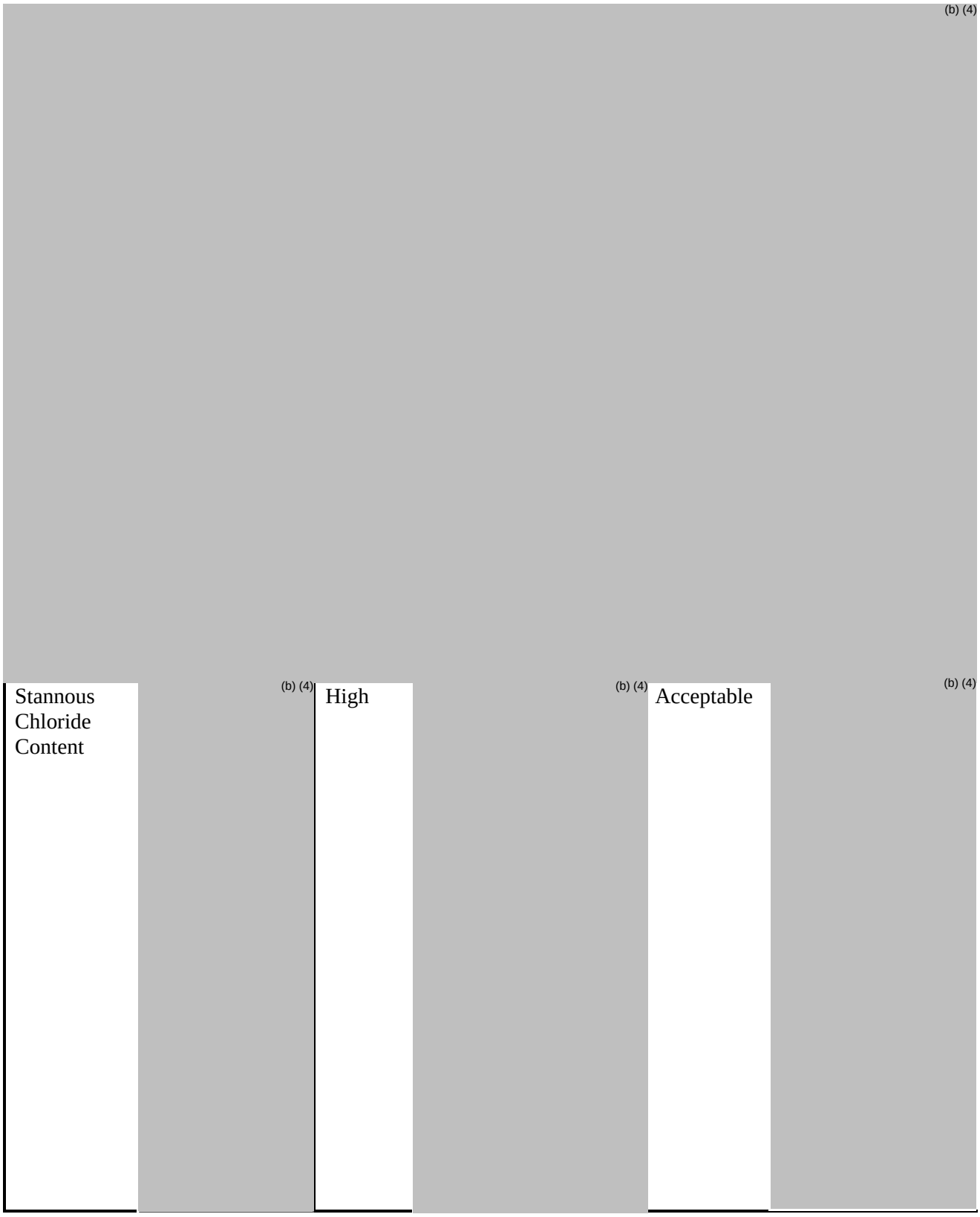
Microbiology: Adequate

Manufacturing procedures have been determined to be adequate for the manufacture of sterile, (b) (4) lyophilized drug product. The container closure system has been found to be adequate to maintain sterility throughout the shelf life of the proposed drug

product. The proposed drug product is a multiple dose vials (b) (4) . However, on the basis of microbiology assessment the (b) (4) radiolabeled product can be stored and used for up to 18 hours when stored in a refrigerator (at 2-8°).

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 of lyophilized powder, Meltback.	Lyophilization cycle; (b) (4) Container closure integrity.	High	(b) (4)	Acceptable	(b) (4)
Headspace Oxygen Content	(b) (4)	High		Acceptable	


(b) (4)
Stannous Chloride Content
(b) (4)
High
(b) (4)
Acceptable
(b) (4)

	(b) (4)				
Number of macro-aggregates (MAA) per vial	Improper heating and or stirring during the macroaggregate manufacturing process; (b) (4)	High	(b) (4)	Acceptable	Excessive adverse events related to pulmonary occlusion in non-susceptible patients may be due to administration of excessive number of MAA particles.
Size of the macro-aggregates		High		Acceptable	Excessive adverse events related to pulmonary occlusion in non-susceptible patients may be due to administration of excessive number of large MAA particles; Inordinate amount of background activity in images may be due to the excessive number of small particles in the radiolabeled product.
Radiochemical purity		High		Acceptable	Poor radiochemical purity may manifest itself in poor images during the diagnostic procedure.

	[redacted] (b) (4)		[redacted] (b) (4)		
Sterility		High		Acceptable	[redacted] (b) (4)

	(b) (4)		(b) (4)		

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

Deficiencies are listed in labeling Review.

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. *6/18/2020 (revised 3/12/2020)*

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	28-Aug-2009 by Olen M Stephens, Ph.D.	(b) (4)
	III			Adequate	NA	
	III			Adequate	2/11/2020	

B. OTHER DOCUMENTS: *IND, Listed Drug, RS, Approved NDA*

Document	Application Number	Description
BLA	102366	Albumin (Human) 25%, Trade name: AlbuRx25
Pre-IND	132108	Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection
NDA	017842	Technescan MAA

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	None			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	None			
Drug Substance (CBER): Elena Karnaukhova	Complete	The information provided for Albumin (Human) (b) (4) is adequate to assure quality and safety of the lots manufactured by (b) (4) (b) (4) manufacturer).	9/4/2019	Elena Karnaukhova, Ph.D.

Ravindra Kasliwal

Digitally signed by Ravindra Kasliwal
Date: 3/12/2020 01:28:23PM
GUID: 508da7220002a0e4e2c176d5eddcbe42

FOOD AND DRUG ADMINISTRATION

Center For Biologics Evaluation and Research

MEMORANDUM

From: Elena Karnaukhova, Ph.D.; LBVB, DBCD, OBRR, CBER; (240) 402-9621

Subject: ICCR# 00011353, a Consult Reviewer Memo for Albumin (Human) (b) (4) used in the manufacture of the Kit for Preparation of Technetium Tc 99m Albumin Aggregated Injection, NDA 210089

Through: Abdu Alayash, Ph.D., Chief; LBVB, DBCD, OBRR, CBER; (240) 402-9350

Anika Lalmansingh, RBPMBI, DRBPMI, OPRO, OPQ, CDER; (240) 402-0356

To the file: NDA BN210089

Recommendation: From the standpoint of Albumin (Human) (b) (4) quality and safety, there are no issues identified or questions that may need a clarification from the company or be further discussed at this time.

SUMMARY

Submission Receipt Date: 6/11/2019

Date of Consult Request: 6/18/2019

Application: NDA 210089

Applicant: Cis Bio International

Product: Pulmotech MAA Kit for Preparation of Technetium Tc 99m Albumin Aggregated Injection

Indication: Technetium Tc 99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients. It also may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (b) (4) shunt patency.

ICCR Subject: Albumin (Human) (b) (4)

Background

On June 11, 2019 Cis Bio International submitted a 505(b)(2) NDA for Pulmotech MAA Kit for Preparation of Technetium Tc 99m Albumin Aggregated Injection. The lead review organization is Office of Pharmaceutical Quality (OPQ), CDER. The product Pulmotech MAA Kit for Preparation of Technetium Tc 99m Albumin Aggregated Injection described in this application is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients, and it also may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (b) (4) shunt patency.

Summary of Albumin (Human) 25% Assessment

The scope of this consult review is limited to Albumin (Human) (b) (4) (b) (4) which is used in the manufacture of the Pulmotech MAA Kit for Preparation of Technetium Tc 99m Albumin Aggregated Injection (NDA 210089).

I have looked through the information provided in the NDA 210089 for the quality of Albumin (Human) (b) (4). To manufacture the proposed Albumin Aggregated Injection the applicant utilizes FDA-approved US sourced Albumin (Human) 25% (AlbuRx® 25) which is manufactured by CSL Behring AG (Bern, Switzerland; BLA 102366, US License 1767).

In the NDA 210089, Albumin (Human) (b) (4) (b) (4)

On my evaluation, the information provided for Albumin (Human) (b) (4) in this NDA is consistent with that of FDA-approved Albumin (Human) 25% (AlbuRx® 25, BLA 102366) and adequate to assure quality and safety of the lots manufactured by (b) (4) The test results for the lots of Albumin (Human) (b) (4) referred to in this submission were conducted by a sub-contractor laboratory (b) (4) and found to be well within the product specification requirements and in accordance with the albumin USP monograph, 21 CFR 640.82, Sterility Tests <71> and Bacterial Endotoxins Test <85>.

In my opinion, from the standpoint of Albumin (Human) (b) (4) quality and safety, there are no questions that may raise an issue, need a clarification from the company or should be discussed at this time.

Review comments to be communicated to applicant

There are no outstanding review issues with regards to Albumin (Human) (b) (4)

62 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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	Pulmotech™ MAA	Acceptable by OSE
Established name(s)	kit for the preparation of technetium Tc 99m albumin aggregated injection	Acceptable. This is consistent with CDER labeling for Tc 99m kits.
Route(s) of administration	Intravenous and intraperitoneal	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.	(b) (4) 2 mg Albumin Aggregated as a lyophilized powder (b) (4)	Revise to: Pulmotech MAA multiple-dose vial contains 2 mg of albumin aggregated. Upon radiolabeling with sodium pertechnetate Tc 99m injection solution, it provides an injectable suspension of technetium Tc 99m albumin aggregated. (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	Multiple-dose vials

1.2 FULL PRESCRIBING INFORMATION

The section 2.3 supplied by applicant should be changed to:

2.3 Directions for Preparation

Procedural Precautions

- Perform all transfer and vial stopper entries using aseptic techniques.
- Wear waterproof gloves during the entire preparation procedure and during subsequent patient dose withdrawals from the Pulmotech MAA vial.
- Make all transfers of sodium pertechnetate Tc 99m injection solution during the preparation procedure with an adequately shielded syringe.
- Keep the **Radioactive Preparation** in the Dispensing Vial Shield described below (with cap in place) during the useful life of the **Radioactive Preparation.** Make all withdrawals and injections of the **Radioactive Preparation** with an adequately shielded syringe.

Procedure for the preparation of Technetium Tc 99m Albumin Aggregated

1. If Pulmotech MAA vials are stored in the refrigerator, remove a vial and allow the contents to come to room temperature for approximately 5 minutes.
2. Remove the protective disc from the Pulmotech MAA vial and swab the rubber septum with an alcohol swab or a suitable bacteriostatic agent to disinfect the surface.
3. Place the vial in a suitable dispensing vial shield fitted with a shielded cap.
4. Calculate the amount of sodium pertechnetate Tc 99m injection solution (2 mL to 13 mL) to be added to the Pulmotech MAA vial. During or prior to addition of technetium Tc 99m solution do not vent the Pulmotech MAA vial. In choosing the amount of technetium Tc 99m radioactivity to be used in the preparation of technetium Tc 99m albumin aggregated ensure that the radioactive dose will contain the desired number of MAA particles, while taking into account the number of patients, administered radioactive dose, radioactive decay. The recommended **maximum amount** of technetium Tc 99m to be added to the Pulmotech vial is 6.85 GBq (**185 mCi).** Calculate (see section 2.1) the amount of radioactivity per vial required to be added to maintain the number of particles per dose within a recommended range [for adults 200,000 to 700,000, and for pediatric patients as per **Table 1**].
5. After adding sodium pertechnetate Tc 99m injection solution to the Pulmotech MAA vial in the dispensing vial shield (with cap in place), mix the contents by agitation and allow to stand for a minimum of 15 minutes at room temperature. Once prepared the product will have a turbid white appearance. (b) (4)
6. Assay the product in a suitable dose calibrator and record the activity of the technetium Tc 99m albumin aggregated, total suspension volume, number of Tc 99m MAA particles, radioactive concentration, time and date of preparation, onto the radio-assay information label and attach it to the dispensing vial shield. . 0.9% sodium chloride injection solution may be used as a diluent to achieve the desired number of particles and radioactivity.
7. Prior to withdrawing a dose, gently agitate the contents of the radiolabeled Pulmotech MAA vial to

resuspend any settled technetium Tc 99m albumin aggregated particles. Failure to mix the reaction vial contents adequately before use may result in a non-homogenous suspension with a resulting non-uniform distribution of radioactivity in the lung. Withdrawals for administration must be made aseptically using a sterile needle (18 to 21 gauge) and syringe. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from the vial, the contents should not be replaced with air.

8. Store the radiolabeled Pulmotech MAA vial in the dispensing vial shield in a refrigerator at 2° to 8°C (36° to 46°F). Use radiolabeled Pulmotech MAA within 18 hours from the time of preparation. Discard unused product.

Section 3 (DOSAGE FORMS AND STRENGTHS)

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

2 DOSAGE FORMS AND STRENGTHS

Pulmotech MAA multiple-dose vial contains 2 mg of albumin aggregated as lyophilized powder. Radiolabeling with sodium pertechnetate Tc 99m injection solution provides an injectable suspension of technetium Tc 99m albumin aggregated. The radioactive dose for an adult is intended to contain 200,000 particles to 700,000 particles of technetium Tc 99m albumin aggregated with the target dose of approximately 350,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 mL to 1.9 mL.

2.3.1 Section 11 (DESCRIPTION)

Recommend revising the description section (11) to:

Pulmotech MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection), when prepared with sodium pertechnetate Tc 99m injection, provides Technetium Tc 99m Albumin Aggregated Injection. Pulmotech MAA contains macroaggregates of U.S.-licensed human serum albumin (non-reactive when tested for hepatitis B antigen (HB_SAg) by enzyme immunoassay). The macroaggregated albumin (MAA) is obtained by heat denaturation of stannous chloride treated human serum albumin under controlled conditions.

Upon radiolabeling with sodium pertechnetate Tc 99m injection solution, the stannous reduced Tc99m binds to the aggregated albumin to provide technetium Tc 99m albumin aggregated. The particle size distribution of the aggregated albumin is such that not less than 90 percent are 10 to 90 microns in size. There are no aggregated albumin particles greater than 150 microns in size.

Pulmotech MAA is provided as a 15 mL multiple dose glass vial containing white lyophilized powder. The contents of the vial are under nitrogen. Each vial contains 2 mg of albumin aggregated, 7.1 mg of albumin human (soluble), 0.22 mg of maximum total tin (as $SnCl_2 \cdot 2H_2O$), 0.1 mg (minimum) stannous chloride, and 9 mg of sodium chloride. Hydrochloric acid is added for pH adjustment and the pH of the reconstituted solution is between 5 and 7. The kit does not contain any bacteriostatic agent.

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

11.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours.[4] The

principal photon that is useful for detection and imaging is listed in **Table 5**.

Table 5 – Principal Radiation Emission Data[4]

Radiation	Mean % per Disintegration	Energy (keV)
Gamma-2	89.07	140.5

11.2 External Radiation

The specific gamma ray constant for Technetium Tc 99m is 0.78 R/mCi-hr at 1 cm. The first half-value thickness of lead (Pb) for Technetium Tc 99m is 0.017 cm. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in **Table 6**. For example, the use of 0.25 cm of Pb will decrease the external radiation exposure by a factor of about 1000.

Table 6 – Radiation Attenuation by Lead Shielding

Shield Thickness(Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

To correct for physical decay of this radionuclide, the fractions that remain at selected time intervals after the time of calibration are shown in **Table 7**.

Table 7 – Physical Decay Chart: Technetium Tc 99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

*Calibration Time

2.3.2 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Recommend following for this section:

16.1 How Supplied

Pulmotech MAA (kit for the preparation of technetium Tc 99m albumin aggregated injection) is supplied either as a 5-vial clam shell (NDC 69945-139-20) or as a carton of 30 vials (NDC 69945-139-40).

Each 5-vial kit contains 5 multiple dose Pulmotech MAA vials, 1 prescribing information and 5 radio assay information labels. Each 30-vial carton contains 30 multiple dose Pulmotech MAA vials, 1 prescribing information and 30 radio assay information labels.

16.2 Storage and Disposal

Store Pulmotech MAA (kit for the preparation of Tc 99m albumin aggregated injection) at 2° to 25°C (36° to 77ºF) before preparation (radiolabeling).

After, preparation with sodium pertechnetate Tc 99m injection, store radiolabeled technetium Tc 99m albumin aggregated Injection in a refrigerator at 2° to 8°C (36° to 46ºF).

Do not use and discard radiolabeled Pulmotech MAA at 18 hours after preparation.

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 (b) (4) 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

Following are general comments (taking DMEPA comments into account) that should be sent to the applicant:

1. Decrease the prominence of the statement "Rx Only" by de-bolding as this information appears more prominent than the rest of the information on the principal display panel.

2. To increase readability, a unit-of-measure should follow each numeric dose designation'. Include, 'MBq', 'mcCi' and 'mCi' after each numeric value pertaining to strength and dosage throughout.

3. To increase readability and reduce clutter, use abbreviations for units of measure where appropriate (replace megabecquerels with MBq, etc.)

3.1 Container Label

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

1. The container label for the vial does not have an NDC number. Place the NDC number on the vial label. We recommend upper left of trademark of the vial label. The vial label should contain the NDC number with the package code (i.e., the last 2 digits) assigned to the vial presentation which should be different from the package codes for the cartons containing 5 and 30 vials respectively.

2. Include statement “Sterile, Multiple-Dose Vial” on the label. We recommend upper right of the Pulmotech MAA trademark.

3. Revise the recommended dosage statement to “Dosage: See prescribing information” as dose is variable and per 21 CFR 201.55.

4. Revise the storage statement to, “Before radiolabeling, store at 2^{o} to 25^{o}C (36^{o} to 77^{o}F). After radiolabeling, store shielded in refrigerator at 2^{o} to 8^{o}C (36^{o} to 46^{o}F). Use within 18 hours.”

5. Revise the route of administration statement to, “**For intravenous and intraperitoneal use** after radiolabeling with sodium pertechnetate Tc 99m”. The statement “For intravenous and intraperitoneal use” should be bolded.

Carton Labeling

5-Vial Clam Shell Labeling:

(b) (4)

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

1 Revise the statements (b) (4) to:

Dosage: See prescribing information
Prepare technetium Tc 99m aggregated albumin injection as described in prescribing information.

2 Revise the "Kit Contains" statement to:

5sterile, multiple-dose Pulmotech MAA vials.
5 radio assay information labels.
1 Prescribing Information.

3 The net quantity and package type are currently missing on the principal display panel (PDP) per 21 CFR 201.51. (See also Draft Guidance: Container and Carton, April 2013 (lines 731-733, 764-766)). Include the net quantity of "5 Multiple-dose vials" on the PDP.

4 Revise the route of administration statement to, "**For intravenous and intraperitoneal use** after radiolabeling with sodium pertechnetate Tc 99m". The statement "For intravenous and intraperitoneal use" should be bolded.

5 Revise the quantitative statement " (b) (4) " to

Each Pulmotech MAA vial contains:
mg Albumin Aggregated
7.1 mg Albumin Human
0.22 mg (maximum) stannous chloride
0.1 mg (minimum) stannous chloride
9 mg sodium chloride
Hydrochloric acid for pH adjustment
Sealed under nitrogen

6 Revise the storage statement to, “Before radiolabeling, store at 2° to 25°C (36° to 77°F). After radiolabeling, store shielded in refrigerator at 2° to 8°C (36° to 46°F). Use within 18 hours of radiolabeling.”

30 Vial Carton Labeling:

(b) (4)

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

1. The net quantity and package type are currently missing on the principal display panel (PDP) per 21 CFR 201.51 (See also Draft Guidance: Container and Carton, April 2013 (lines 731-733, 764-766)). Include the net quantity of "30 Multiple-Dose Vials" on the PDP.

2. Revise the route of administration statement to, "**For intravenous and intraperitoneal use** after radiolabeling with sodium pertechnetate Tc 99m". The statement "For intravenous and intraperitoneal use" should be bolded.

3. Revise the storage statement to, "Before radiolabeling, store at 2° to 25°C (36° to 77°F). After radiolabeling, store shielded in refrigerator at 2° to 8°C (36° to 46°F). Use within 18 hours of radiolabeling."
4. Revise the statement "(b) (4)" to "Dosage: See prescribing information" per 21 CFR 201.55. Additionally, remove the "(b) (4)" statement as dosage is variable.

5. Revise the "Carton Contains" statement to:

   30 sterile, multiple-dose Pulmotech MAA vials.
   30 radio assay information labels.
   1 Prescribing Information.

6. Revise the quantitative statement "(b) (4)" to

   Each Pulmotech MAA vial contains:
   2 mg Albumin Aggregated
   7.1 mg Albumin Human
   0.22 mg (maximum) stannous chloride
   0.1 mg (minimum) stannous chloride
   9 mg sodium chloride
   Hydrochloric acid for pH adjustment
   Sealed under nitrogen

7. The location of the Lot and Expiration date is currently missing. Include / identify the Lot and Expiration date on the carton.

8. You did not indicate the location of barcode on the 30-vial carton label. Indicate the location of barcode on the carton label.

Radio-Assay Label:

(b) (4)

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

1. Revise the "(b) (4)" to "Discard after: ___ Hour ____ Date."

2. Include a statement "Number of technetium Tc99m MAA particles: ___ " This is the number of MAA particles for the lot provided on the vial label.

3. Revise the storage statement to "Store shielded in refrigerator at 2º to 8ºC (36º to 46ºF)."

Overall Assessment and Recommendation:

The labeling is currently inadequate and should be revised as indicated for each section.

Primary Labeling Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *2/10/2020*

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

Danae D. Christodoulou, Ph.D. *2/14/2020*

Ravindra Kasliwal

Digitally signed by Ravindra Kasliwal
Date: 2/24/2020 09:40:47AM
GUID: 508da7220002a0e4e2c176d5eddcbe42

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 2/24/2020 09:44:46AM
GUID: 5050dd27000012a4c69bfc70b47660b7

59 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

QUALITY ASSESSMENT

BIOPHARMACEUTICS

Product Background:

NDA: 210089-ORIG-1

Drug Product Name / Strength: Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection 2 mg

Route of Administration: Injection

Applicant Name: CIS Bio International

Review Summary: Adequate

The proposed formulation and LD are not exactly Q1/Q2, the proposed product does not qualify for a waiver of in vivo bioavailability studies for your NDA submitted through the 505(b)(2) pathway per 21 CFR 320.22 (b)(1)(i, ii). However, as per the CMC evaluation, the proposed product is considered similar to the listed drug (LD) in terms of macroaggregated albumin content, stannous chloride content, particle size, particle number and other critical quality attributes. Therefore, based on the information provided, FDA considers that a "bridge" between the proposed drug product to the Listed Drug (LD) has been established per 21 CFR 320.24(b)(6).

The NDA 210089 for Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection 2 mg is adequate from the biopharmaceutics perspective.

List Submissions being reviewed (table):

06/11/2019	NDA 210089/Sequence 0003/Original Submission

Concise Description Outstanding Issues Remaining:

None

Bridging of Formulations

Reviewer's Assessment: *Adequate*

According to the batch analysis document in Module 3.2.P.5.4, all three exhibit batches were manufactured at the same site. Therefore, this section is not applicable and no bridging of formulations is necessary.

Biowaiver Request

Reviewer's Assessment: *Adequate*

Supportive data are provided in Module 1.12.15. See \\cdsesub1\evsprod\nda210089\0003\m1\us\112-other-correspondence\request-for-waiver-of-in-vivo-bioavailability-studies.pdf

CFR 320.24(b)(6) was cited, with justification and supporting data demonstrating that the differences between the proposed product and the LD do not contribute to difference in *in vivo* performance. DraxImage MAA is the LD for this 505(b)(2) application. The applicant for the proposed Cis Bio International Tc-99m MAA kit is requesting approval for the same two indications for use as Draximage MAA, that being for intravenous injection for perfusion imaging of the lungs and for evaluation of (b) (4) shunt patency following intraperitoneal injection. In both indications, the Cis Bio International Tc-99m MAA will be either delivered directly to the systemic venous circulation or to the intraperitoneal fluid space.

The following aspects were evaluated in terms of product similarity: compendial specifications, a qualitative and quantitative drug formulation comparison, and a dosage strength comparison. Through this evaluation, each one of these comparisons determined the products to be sufficiently similar.

In M-003-19-8003 CHEM the proposed product is referred to as Curium Albumin Aggregated Injection. A formulation comparison with other similar products are presented in Table 6.

Table 6. Formulation Comparison – Critical Formulation Components for Albumin Aggregated Injection

Component	(b) (4)
Particle Size	
Particles per vial	
Macroaggregated Albumin (MAA)	
Stannous chloride	

Although several other products are listed here, the only relevant comparison is between Curium Albumin Aggregated Injection and the LD.

Macroaggregated Albumin

Macroaggregated Albumin was compared in Table 7.

Table 7. Formulation Comparison – Critical Quality Attributes for Albumin Aggregated Injection

	Quantity per Vial mg	Number of Particles	mass / million particles	Mass of MAA per dose	Doses Per Vial
DRAXIMAGE					
mass MAA (mg)	2.5	3 million	(b) (4)		
		8 million			
CURIUM					
Mass MAA (mg)	2	2 million			
		4 million			

Although the overall mass of MAA is higher in the listed drug relied upon, so too are the overall number of particles. Ultimately the mass of MAA delivered normalized over a dose of 350,000 particles is between (b) (4) for DraxImage MAA and the Curium proposed product respectively. The range of MAA administered in the proposed product falls within the range of the LD.

Stannous Chloride

(b) (4)

This is not expected to have an impact on the safety of the product (b) (4)

Particle Size

The mechanism of localization of the albumin aggregated radiopharmaceutical is by capillary blockade. The particle size of perfusion lung imaging agents may have undesirable effects on pulmonary localization and is therefore considered a critical quality attribute of the drug product. In the finished drug product, the primary mechanism for controlling particle size by visually inspecting a sample of the product reconstituted with saline and the proportion of particles within a specific size range is reported. For the LD, 90% of the particles must fall between 10-70 µm. For the proposed Curium AAI product, the specific particle range complies with the USP compendia whereby 90.0% are between 10-90 µm. (b) (4)

(b) (4)

Particle Number

The number of injected particles in MAA is important in terms of both image quality and toxicity. Too few injected particles may result in degradation of lung images. The number of particles necessary for an artifact-free scan in normal individuals is >60,000 the recommended dose for 99mTc-MAA in adults is 200,000-700,000, with the suggested number being 350,000. Both the LD and the proposed Curium product is prepared in a multi-dose format and therefore the number of particles required are one of the considerations when preparing a patient dose and determining the strength dose to be administered. Since this is a parameter that is determined by the prescribing physician based on the labeled number of particles per vial, the impact of the reported difference in particle numbers per vial is negligible. Depending on the number of particles in a lot of the proposed product, between 6 and 11 patient doses containing 350,000 particles can be prepared. This is in comparison to the LD with which 9 to 23 doses of the same potency can be administered..

Conclusion

The LD and the proposed US-based Curium product are quantitatively and qualitatively similar in the critical formulation components. The quantity of MAA in each product are within the same range, and the particle characterization (i.e. size and number) are not significantly different and therefore the products are expected to function similarly. One difference is that the proposed Curium product could potentially contain more stannous than the LD. Both values are reported in their specifications as a minimum quantity therefore it is difficult to accurately assess the difference. This difference does not pose a risk to the safety of the finished drug product and could result in improved radiochemical purity (i.e. efficacy) in that conversion of free pertechnetate is expected to be greater in the proposed formulation.

As the proposed formulation and LD are not exactly Q1/Q2, the proposed product does not qualify for a waiver of in vivo bioavailability studies for your NDA submitted through the 505(b)(2) pathway per 21 CFR 320.22 (b)(1)(i, ii). However, as per the CMC evaluation, the proposed product is similar to the LD in terms of macroaggregated albumin content, stannous chloride content, particle size, particle number and other critical quality attributes. Therefore, based on the information provided, FDA considers that a “bridge” between the proposed drug product to the Listed Drug (LD) has been established per 21 CFR 320.24(b)(6).

QUALITY ASSESSMENT

The NDA 210089 for Technetium Tc 99m Albumin Aggregated Injection / 2 mg is adequate from Biopharmaceutics perspective.

Primary Biopharmaceutics Reviewer Name:

Bryan Ericksen, Ph.D.

Secondary Reviewer Name:

Tapash Ghosh, Ph.D.

Bryan Ericksen

Digitally signed by Bryan Ericksen
Date: 2/14/2020 01:18:20PM
GUID: 59285fba002134adea4d6f405770a2b2

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 2/14/2020 01:47:36PM
GUID: 508da7230002a2433ddcef616ca190df

CHAPTER VII: MICROBIOLOGY
IQA NDA Assessment Guide Reference

Product Information	
NDA Number	210089
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Kit for the Preparation of Technetium Tc-99m Albumin Aggregated Injection 2 mg/vial
Route of Administration	Intravenous and intraperitoneal
Applicant Name	Cis Bio International
Therapeutic Classification/ OND Division	OND/ODEIV/DMIP
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
NDA 210089 0003 (3)	**06/11/2019**
0011	**09/19/2019**
0012	**11/13/2019**

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

Remarks: The submission is in the eCTD format, some figures and tables have been copied from the original application. The amendment dated 09/19/2019 is in response to an IR sent 08/29/2019. The amendment dated 11/13/2019 is in response to the IR sent 10/04/2019.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None

Supporting Documents: D(b) (4)M14R01.doc (11/14/2018) and D(b) (4)M15R01.doc (05/13/2019, adequate) for review of DMF (b) (4) (b) (4)a1.pdf (10/25/2007, adequate) for review of (b) (4) method.

S Drug Substance

Drug substance is non-sterile and not reviewed – N/A

P.1 Description of the Composition of the Drug Product

Description of drug product – Sterile, (b) (4) product supplied under (b) (4) nitrogen atmosphere. The product consists of white lyophilized powder

in a 15mL multi-dose glass vial. The 15mL glass vials are packaged into 5 count clam shell or 30 count carton. The product is used after reconstitution with sterile, (b) (4) pertechnetate solution with the USP 42 monograph. The reconstitution solution is packaged separately from the product. Once reconstituted, the product has a beyond use date of 18 hours at 2-8°C.

Drug product composition –

Ingredient	Quantity Required for Finished Batch	Amount Per Vial	Function
Albumin aggregates	(b) (4)	2 mg	(b) (4)
Stannous Chloride (b) (4)		0.1 mg	
Albumin Human (b) (4) (b) (4) USP		7 mg	
Sodium Chloride, USP		9 mg	
Hydrochloric Acid, NF		q.s.	
Nitrogen, EP		q.s.	
		(b) (4)	

Description of container closure system –

Component	Description	Manufacturer	Item Code
Vial	15 mL Glass Vial (b) (4)	(b) (4)	
Stopper	(b) (4) Grey (b) (4) Closure		
Seal	20 mm Flip-off Crimp Seal		

Reviewer's Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity
(3.2.P.8.3 RD-03-03-028R (b) (4) Container Closure Integrity; 3.2.P.5.2, (b) (4))

The container/closure system used for validation was identical to production: 15 mL glass (b) (4) vial with 20 mm (b) (4) rubber stopper (b) (4) ; 20 mm aluminum (b) (4) crimp (b) (4)

Study/Report # and date: (b) (4) Version 1.0 10/10/2018
Test method: (b) (4)

(b) (4)

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Reviewer's Assessment: ***Adequate***

The labeling provides adequate storage, dosing, and reconstitution information. Hold time study supports 18 hour in use time.

List of deficiencies: N/A

Primary Microbiology Assessor: Dustin Thomas, Ph.D. 02/28/2020

Secondary Microbiology Assessor: Yan Zheng, Ph.D. 02/28/2020

Tertiary Microbiology Assessor: Jesse Wells, Ph.D. 02/28/2020

Jesse Wells

Digitally signed by Jesse Wells
Date: 3/03/2020 10:57:38AM
GUID: 508da70b00028ea901ac6652677f7d00

Dustin Thomas

Digitally signed by Dustin Thomas
Date: 3/03/2020 11:09:34AM
GUID: 5a9d7e03000dc17a5f2fc069bb182920

Yan Zheng

Digitally signed by Yan Zheng
Date: 3/03/2020 10:59:50AM
GUID: 58ca9ce301e697996a209b08cf0d70b6

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
03/12/2020 02:48:31 PM