CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216820Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DATE: 31-Jan-2023

TO: NDA 216820

FROM: Ravindra K. Kasliwal, Ph.D.,
Chemist, OPQ/ONDP/DNDP-3, Branch-6

SUBJECT: Correction to OPQ MDD memo filed on 1/3/2023 for NDA 216820.

The memo is to correct the NDA number from NDA 214993 to the correct NDA 21860, and to correct the drug product name from "(b) (4)" to "Kit for the preparation of technetium Tc99m mertiatide injection". The other aspects of the original memo are correct.

Ravindra Kasliwal

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Memorandum

DATE: 04-Jan-2023

TO: NDA 216820

FROM: Ravindra K. Kasliwal, Ph.D.,
Chemist, OPQ/ONDP/DNDP-3, Branch-6

SUBJECT: Correction to OPQ executive summary for NDA 216820.

The memo is to correct the statement (b) (4) (b) (4) in the summary rationale for recommendation (under Basis of Recommendation). The statement is corrected to "The only differences seen in the proposed and LD formulations is that the proposed drug product does not use sodium hydroxide for pH adjustment (they only use HCl), while the LD can use both HCl and NaOH for pH adjustment, and the hydration form of stannous chloride (the applicant uses stannous chloride dihydrate while the LD uses anhydrous stannous chloride). This correction does not change any assessment or OPQ recommendation.

Ravindra Kasliwal

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/s/

RAVINDRA K KASLIWAL
01/04/2023 01:40:12 PM

Memorandum

TO: NDA 214993

FROM: Ravindra K Kasliwal, Ph.D.
Review Chemist

SUBJECT: (b) (4) Daily dose for the drug product

(b) (4) after radiolabeling with technetium Tc 99m, is indicated for use in the diagnosis of congenital and acquired renal abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients aged 30 days and older. The product is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex. The (b) (4) dose for this radioactive drug product is 370 MBq (10 mCi) in adults and (b) (4) MBq (0.14 mCi)/kg) in pediatric patients. The (b) (4) mass amount of betiatide that can be injected is 1 mg. This is a one-time dose prior to imaging and there is no administration on a daily basis

Ravindra Kasliwal

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NDA Executive Summary

1. Application/Product Information

NDA Number.	**216820**
Applicant Name	Jubilant DraxImage Inc., dba Jubilant Radiopharma
Drug Product Name	Kit for the Preparation of Technetium Tc 99m Mertiatide
Dosage Form.	Injectable
Proposed Strength(s)	1 mg betiatide
Route of Administration	Intravenous
Maximum Daily Dose	Recommended dose in adult patients:185 MBq to 370 MBq (5 mCi to 10 mCi) as an intravenous bolus injection. Recommended dose in pediatric patients aged 30 days and older: 2.6 MBq/kg to 5.2 MBq/kg (0.07 mCi/kg to 0.14 mCi/kg) with a minimum dose of 37 MBq (1 mCi) as an intravenous bolus injection.
Rx/OTC Dispensed	Rx
Proposed Indication	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection, after radiolabeling with technetium-99m, is a radioactive diagnostic agent indicated for use in the diagnosis of congenital and acquired renal abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients aged 30 days and older. The product is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.
Drug Product Description	The proposed product Kit for the Preparation of Technetium Tc-99m Mertiatide Injection will be supplied as a sterile, pyrogen-free, (b) (4) white powder product in a (b) (4) (b) (4) The clear 10 mL glass vial is targeted to contain 1 mg of betiatide, 0.07 mg (minimum) stannous chloride dihydrate ($SnCl_2 \bullet 2H_2O$) and 0.2 mg (maximum) total tin expressed as stannous chloride dihydrate ($SnCl_2 \bullet 2H_2O$), 40 mg sodium tartrate dihydrate, 20 mg lactose monohydrate. Prior to lyophilization, hydrochloric acid is added for pH adjustment. The vial contents are sealed under argon. The 10 mL multi-dose vials are packaged as a carton of 5 vials.

	The product is used after reconstitution by the addition of sterile, pyrogen-free, isotonic sodium pertechnetate Tc 99m injection solution obtained from a commercially available technetium Tc 99m generator. After radiolabeling with sodium pertechnetate Tc 99m injection, each vial contains 740 MBq (20 mCi) to 3.70 GBq (100 mCi) of technetium Tc 99m mertiatide in 0.9% sodium chloride injection as a sterile, clear, and colorless solution. pH of the final solution is between 5 and 6.		
Co-packaged product information	None		
Device information:	None		
Storage Temperature/ Conditions	Before radiolabeling, store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protect from light. After radiolabeling with sodium pertechnetate Tc 99m injection, store vial upright in shielding to protect from radiation at room temperature 15°C to 30°C (59°F to 86°F).		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joe Leginus. Ph.D.	Sithamalli Chandramouli, Ph.D.
	Drug Product/ Labeling	Ravindra Kasliwal, Ph.D.	Danae Christodoulou, Ph.D.
	Manufacturing	Andrew Idzior, Ph.D.	Sateesh Sathigari, Ph.D.
	Biopharmaceutics	Nadia Ahmed, Ph.D.	Om Anand, Ph.D.
	Microbiology	David Bateman, Ph.D.	Marla Stevens-Riley, Ph.D.
	Other (specify):		
	RBPM	Anika Lalmansingh. Ph.D.	
	ATL	Ravindra Kasliwal, Ph.D.	

Consults	None

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

Expiration dating period of 24 months at controlled room temperature (20°C to25°C) when protected from light is acceptable for JDI Kit for the Preparation of Technetium Tc 99m Mertiatide.

The radiolabeled product is to be stored at room temperature (15°C to 30°C) and must be used within 6-hour post-post radiolabeling.

b. Additional Comments for Action Letter:

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The proposed drug product refers to TechneScan MAG3™ approved under NDA 019882 on 06/15/1990 as the Listed Drug (LD) product. The only differences seen in the proposed and LD formulations is that the proposed drug product does not use sodium hydroxide for pH adjustment (they only use HCl), while the LD can use both HCl and NaOH for pH adjustment, and the hydration form of stannous chloride (the applicant uses anhydrous stannous chloride while the LD uses stannous chloride dihydrate). The Applicant has provided information and data to bridge the Listed Drug and the proposed drug product under 21 CFR 320.24 (b) (6). Based on the totality of the information provided, the proposed drug product, is adequately bridged to the listed drug (LD), NDA 019882 (TechneScan MAG3™) in accordance with 21 CFR §320.24(b)(6) and an in vivo pharmacokinetic study is not needed.

The applicant has provided adequate information, data, and controls (including specifications and analytical methods) for the betiatide active ingredient. A retest date of (b) (4) months is granted for betiatide (precursor) when stored a (b) (4)

The applicant has justified and qualified the quality of the components (including excipients) used in the drug product. Controls (including 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, elemental, and (b) (4) impurities) have been performed and satisfactory control strategies have been established.

The applicant provided an adequate information and validation data to support sterility of the proposed product. Manufacturing process and controls are adequately described. All facilities are acceptable based on compliance status, inspection history, and experience with the proposed operations.

Prescribing information (PI) contains adequate information for the radiolabeling and confirming the radiochemical purity (at the end user site) of the Kit. PI and labels are satisfactory.

Stability data covering 6-month period under accelerated conditions and up to 24 months under long term conditions for the three Lots are provided in this submission. Overall, the long term and accelerated stability data were all well within the proposed specifications and the data suggest that vial orientation does not affect any of critical quality attributes. JDI Mertiatide Kit is stable at room temperature, however, it must be protected from light (b) (4)).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

1. The drug product is photo-sensitive.
2. The proposed drug product is supplied as a lyophilized powder and is not intended for direct administration. The supplied drug product must be radiolabeled with sodium pertechnetate Tc 99m injection solution from a US marketed technetium Tc 99m generator, as directed, prior to administration.
3. (b) (4)
4.
5. JDI has committed to successfully conduct the Process Performance Qualification (PPQ) on (b) (4) L commercial scale batches of JDI Kit for the Preparation of Technetium Tc 99m Mertiatide prior to commercialization. These batches will be placed on long-term storage conditions (25±2°C/60±5% RH) as per the proposed post-approval stability protocol (table is described in SECTION 3.2.P.8.2 of submission #0010 dated 24-Oct-2022. Testing will be carried out on both the lyophilized vial and the reconstituted product.

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental

The applicant has requested categorical exclusion (section 1.12.14 of the NDA) from EA under 21 CFR 25.31 (a) because the use of the product will not result in increased use of the active ingredient when approved by the agency. Additionally, the applicant has indicated that to the best of their knowledge, no extraordinary circumstances indicate that the approval of this application may significantly affect the quality of the human environment.

Assessment: *{Adequate}*

The submitted application is a 505(b)(2) application, for an active ingredient that is already marketed. The use of active ingredient will likely substitute the use already occurs under previously approved applications and is not likely to add to the current use. The claim for categorical exclusion, therefore, under 21 CFR25.31(a) is justified and is acceptable.

Primary Environmental Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *12/14/2022*

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

Danae D. Christodoulou, Ph.D. *12/19/2022*

Ravindra Kasliwal

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Danae Christodoulou

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CHAPTER IV: LABELING

Prescribing information, Container and Carton labels submitted in amendment #0012 dated 13-Dec-2022 were reviewed.

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m MERTIATIDE INJECTION
Route(s) of administration	Adequate	for intravenous use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection: 1 mg betiatide as a lyophilized powder in 10 ml glass multiple-dose vial. Upon radiolabeling with technetium-99m, it contains up to 3,700 MBq (100 mCi) technetium Tc 99m mertiatide in approximately 10 mL volume at calibration time.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	This is not a tablet dosage form.

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

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.	Adequate	multiple-dose vial
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	Not applicable.

1.2 FULL PRESCRIBING INFORMATION

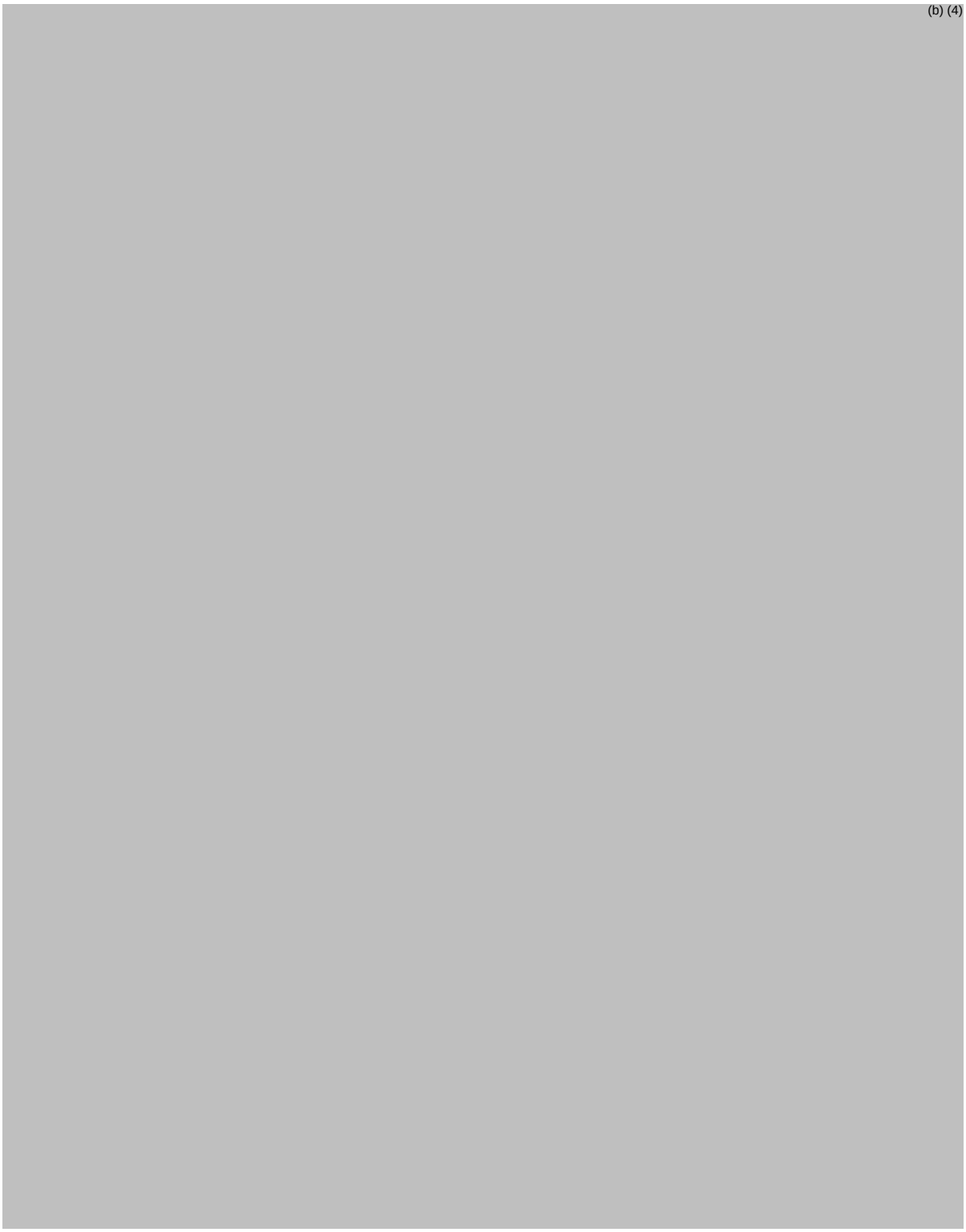
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	Section 2.4 describes drug preparation and handling. See description of the section below.

Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Section 2.5 describes Determination of Radiochemical Purity of Technetium Tc 99m Mertiatide See description of the section below the table.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Section 2.6 includes the following statement: Visually inspect the prepared Technetium Tc 99m Mertiatide Injection behind a lead glass shield for particulate matter and discoloration prior to administration. Only use solutions that are clear without visible particles.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	Adequate	The radiolabeled product will meet USP requirements.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	Adequate	It is included.
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with	Adequate	Appropriate radioactive warnings are included.

x numerical citation to "OSHA Hazardous Drugs".		

(b) (4)



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QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Inadequate	The dosage form is lyophilized powder for injection. It is not indicated in the section. We recommended. However, Dr. Kim Younsook (Associate Director of labeling for DIRM) indicted that it is not possible to include dosage form in this Kit preparation.
Strength(s) in metric system	Adequate	Strength is the amount of active ingredient betiatide that is present in the kit = 1 mg.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	Not a salt.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	White lyophilized powder in included.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	Not a tablet.

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Term multiple dose vial is included.

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QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	There is no proprietary name. The established name "Kit for the Preparation of Technetium Tc 99m Mertiatide Injection" is used only.
Dosage form(s) and route(s) of administration	Adequate	For intravenous use is included.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	Not a salt.
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Each 10 mL vial contains 1 mg betiatide, 20 mg lactose monohydrate, 40 mg sodium tartrate dihydrate, 0.07 mg (minimum) stannous chloride dihydrate and 0.2 mg (maximum) total tin expressed as stannous chloride dihydrate. Prior to lyophilization, hydrochloric acid is added for pH adjustment. The vial contents are sealed under argon. After radiolabeling with sodium pertechnetate Tc 99m injection, each vial contains up to 3,700 MBq (100 mCi) of technetium Tc 99m mertiatide in 0.9% sodium chloride injection in approximately 10 mL volume as a sterile, clear, and colorless solution with a pH between 5 and 6.

For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	See above.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Alcohol is not present.
Sterility statement (if applicable)	Adequate	Sterile nature of the drug is included.
Pharmacological/Therapeutic class	Adequate	Term radioactive diagnostic agent is included in the description.
Chemical name, structural formula, molecular weight	Adequate	The active ingredient, betiatide, is N-[N-[N-[(benzoylthio) acetyl]glycyl]glycyl] - glycine and has a molecular weight of 367.38 g/mol. After reconstitution with sodium pertechnetate Tc 99m injection, the radioactive agent technetium Tc 99m mertiatide (disodium[N-[N-[N-(mercaptoacetyl) glycyl]glycyl] glycinato (2-) -N,N′,N″,S‴]oxotechnetate (2-)) is formed in situ. Structures are included.
If radioactive, statement of important nuclear characteristics.	Adequate	Information is included in section 11.2
Other important chemical or physical properties (such as pKa or pH)	Adequate	The pH of the radiolabeled product is described. “pH between 5 and 6”

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	Not an oral product.
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	Adequate	Radiolabeled product meets the USP monograph requirements.

QUALITY ASSESSMENT

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Kit for the Preparation of Technetium Tc 99m Mertiatide Injection is included. Supplied as a white lyophilized powder is included.
Strength(s) in metric system	Adequate	1 mg betiatide is included.
Available units (e.g., bottles of 100 tablets)	Adequate	10 mL vial as a carton of 5 vials is included.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	White lyophilized powder is included.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	Not a tablet.
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.	Adequate	Multiple-dose 10 mL vial is included.

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Before radiolabeling, store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protect from light. After radiolabeling with sodium pertechnetate Tc 99m injection, store vial upright in shielding to protect (b) (4) from radiation at room temperature 15°C to 30°C (59°F to 86°F). Use within 6 hours of radiolabeling. Dispose of unused Technetium Tc 99m Mertiatide Injection in compliance with the regulations of the government agency authorized to license the use of this radionuclide. This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Before radiolabeling, store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature] and protect from light. After radiolabeling with sodium pertechnetate Tc 99m injection, store vial upright in shielding to protect (b) (4) from radiation at room

		temperature 15°C to 30°C (59°F to 86°F). Use within 6 hours of radiolabeling.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	Product is injected in hospitals, imaging centers and not dispensed to a patient.

1.2.5 Other Sections of Labeling: None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Following is included: Manufactured for: Jubilant DraxImage Inc., dba Jubilant Radiopharma™ 16 751 TransCanada Highway Kirkland, Quebec H9H 4J4 Canada 1-888-633-5343 www.jubilantradiopharma.com

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): NONE

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	Not a salt.
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	Displayed on PDP
NDC	Adequate	
Lot number and expiration date	Adequate	(b) (4)

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	(b) (4) [redacted]
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, and these products require a “Not for direct infusion” statement.	Adequate	(b) (4) [redacted]
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	See above.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Alcohol is not present.

QUALITY ASSESSMENT

Linear Bar code	Choose an item.	

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	NDA number in indicated on the PDP.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Product is injected in hospitals, imaging centers and not dispensed to a patient.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	The vial is lyophilized powder vail for injection. It is sealed with aluminum crimp seal.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	The Kit is not a USP monograph product. The radiolabeled product meets USP monograph requirements. The radioassay label meets the USP monograph label requirements. The statements that in making dosage calculations, correction is to be made for radioactive decay, and also indicates that the radioactive half-life of 99mTc is 6.0 hours are included in PI.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

QUALITY ASSESSMENT

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Prescribing Information, container, carton and radioassay labels are adequate from a product quality perspective.

Primary Labeling Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *16-Dec-2022*

Secondary Assessor

Danae D. Christodoulou, Ph.D. *16-Dec-2022*

Ravindra Kasliwal

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Danae Christodoulou

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see Chapter VI (Biopharmaceutics) of the NDA IQA Guide

Product Information	Kit for the Preparation of Technetium Tc 99m Mertiatide- Lyophilized Powder for Solution
NDA Number	216820
Assessment Cycle Number	1
Drug Product Name/ Strength	Kit for the Preparation of Technetium Tc 99m Mertiatide/Betiatide 1mg/10 mL vial
Route of Administration	Injection
Applicant Name	Jubilant DraxImage Inc., dba Jubilant Radiopharma (JDI)
Therapeutic Classification/ OND Division	CDER/OND/OSM/DIRM
RLD/RS Number	NDA 019882
Proposed Indication	Diagnosis of congenital & acquired abnormalities, renal failure, urinary tract obstruction, & calculi in adults & pediatric patients. Diagnostic aid in providing renal function, split function, renal angiograms, & renogram curves for whole kidney & renal cortex

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant, Jubilant DraxImage Inc., has submitted NDA 216820 for the marketing approval of Kit for the Preparation of Technetium Tc 99m Mertiatide, which when reconstituted using the Tc-99m generated on site makes an intravenous solution. The reconstituted intravenous solution is used as a renal imaging agent for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients.

The proposed drug product refers to Technescan MAG3™ approved under NDA 019882 on 06/15/1990 as the Listed Drug (LD) product. (b) (4) (b) (4) (b) (4) Therefore, this application was deemed not suitable to be filed via the 505 (j) pathway. In the current submission to the FDA, the

(b) (4)

Applicant has claimed that the 505 (b) (2) pathway is more appropriate for this application. Therefore, the Applicant has submitted this NDA 216820 for their proposed drug product.

The vials of both the proposed drug product and the LD contain the sterile, non-radioactive ingredients to produce the Technetium Tc-99m Mertiatide injection when reconstituted with sodium pertechnetate Tc99m Injection, USP. The Applicant has claimed that Betiatide is the API precursor, and during reconstitution, the betiatide is converted into mertiatide, which forms the Mertiatide-Technetium Tc99m complex. The Applicant has also claimed that the difference between the proposed drug product and the LD is a difference in the hydration form of stannous chloride. However, based on the formulations of the proposed drug product in comparison to the LD, it is noted that both drug products use stannous chloride dihydrate as per the manufacturing formula and process. This Reviewer has noted that the only differences seen in the formulations is that the proposed drug product does not use sodium hydroxide for pH adjustment (they only use HCl), while the LD can use both HCl and NaOH for pH adjustment.

The Applicant has provided information and data (side-by-side comparative tables of the formulations, a side by side comparison of the finished product composition, a comparison of the reconstituted product kits, comparisons of the conditions of use, and comparisons of the physical and chemical attributes between the Listed Drug product and the proposed drug product) to bridge the Listed Drug and the proposed drug product under 21 CFR 320.24 (b) (6).

The very minor differences in the formulation are not expected to demonstrate differences in the in vivo drug performance. However, it is noted that the Applicant had originally conducted comparative studies between three batches of the proposed drug product in comparison to one batch of a reference listed drug approved in Canada, which this Reviewer found not acceptable. Therefore, the Applicant was recommended, via an IR, to conduct testing using a US-FDA approved reference drug product. In response to the FDA's IR, the Applicant provided physiochemical comparisons using the US-FDA approved Listed Drug product.

Based on the totality of the information provided, the proposed drug product, NDA 216820 (Kit for the Preparation of Technectium Tc 99m Meriatide Lypholized Powder for Solution) for intravenous administration is adequately bridged to the listed drug (LD), NDA 019882 (Technescan MAG3™) in accordance with 21 CFR §320.24(b)(6) and an in vivo pharmacokinetic study is not needed.

From a Biopharmaceutics perspective, NDA 216820 for Kit for the Preparation of Technetium Tc 99m Mertiatide Lyophilized Powder for Solution is recommended for APPROVAL.

List of Submissions Being Assessed (table):

Document(s) Assessed	Date Received
NDA-215395-ORIG-1 (Seq 0003)-Original NDA-215395-ORIG-1 (Seq 0007)-IR Response	03/30/2022 08/11/2022

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

B.12 BRIDGING OF FORMULATIONS

Assessment: ***{Adequate}***

The Applicant has proposed a waiver of in-vivo bioavailability and bioequivalence studies. In the Agency's General Advice Letter (Dated 02/15/22), the FDA provided recommendations on how to bridge the proposed drug product to the listed drug product. Since the formulation is not considered Q1/Q2 per OGD, the Applicant could not be granted a biowaiver. However, to support the Applicant's waiver request and per the FDA's recommendations, the Applicant has provided information/data to bridge the Listed Drug and the proposed drug product under 21 CFR 320.24 (b) (6). To support this bridging, the Applicant has provided side-by-side comparative tables of the formulations, a side by side comparison of the finished product composition, a comparison of the reconstituted product kits, comparisons of the conditions of use, and comparisons of the physical and chemical attributes between the Listed Drug product and the proposed drug product.

In the side-by-side comparison table of the LD and proposed drug product formulations, the Applicant has claimed that the differences between the two drug products are the hydration form of one of the excipients in the formulation, stannous chloride (see Table A1 in the Appendix). However, based on this Reviewer's assessment of the drug product and conversations with the drug product Reviewer, it is noted that both drug products use the same dihydrate form of stannous chloride. The only differences noted between the formulations are that the LD uses both HCl and NaOH for pH adjustment whereas the Applicant only uses HCl (does not use NaOH). The proposed drug product formulation is shown in Table 1. The formulations are comparable, and the slight formulation differences are not expected to impact the in vivo performance of the drug product.

Table 1: Composition of the Proposed Drug Product

Ingredients	Product Composition	Batch Formula	% w/w	Function	Quality Standard
	Amount per unit (mg/vial)	Amount per batch size (b) (4)			
Active Substance					
Betiatide	1 mg	(b) (4)		Precursor for Tc99m Mertiatide	Professed
Excipients					
Stannous Chloride Dihydrate	0.2 mg	(b) (4)		(b) (4)	NF/ Ph.Eur.
Sodium Tartrate Dihydrate	40 mg				NF
Lactose Monohydrate	20 mg				NF/ Ph.Eur/JP
Water for Injection	(b) (4)			(b) (4)	NF/ Ph.Eur./BP
Hydrochloric Acid				pH adjustment	NF
Argon				(b) (4)	(b) (4)
Total theoretical Weight					

The Applicant has provided a side-by-side comparison table of the finished product compositions of the proposed drug product and the LD. Once the proposed product is formulated, it is lyophilized into a cake. As shown in Table 2, the Applicant has claimed that the proposed lyophilized drug product is quantitatively and qualitatively the same as the LD in the lyophilized form.

Table 2: Comparison of LD and proposed drug product in Lyophilized Form

Comparison Lyophilized Powder for Solution (Amount of each ingredient present in the lyophilized product composition-each 10 ml vial)				Comparison statement
Ingredients	**Function**	**RLD* Technescan MAG3™ (NDA 019882) CURIUM US LLC**	**Kit for the Preparation of Technetium Tc 99m Mertiatide- JDI**	
Betiatide,	Active Pharmaceutical Ingredient	1 mg	1 mg	*Same amount is present – See section 5 below*
Minimum- Stannous Chloride Dihydrate ($SnCl_2 \cdot 2H_2O$)	(b) (4)	0.05 mg	(b) (4) mg	(b) (4) *section 5 below*
Maximum- Total tin as Stannous Chloride Dihydrate $SnCl_2 \cdot 2H_2O$)		0.2 mg	0.2 mg	*Same amount is present - See section 5 below*
Sodium Tartrate Dihydrate		40 mg	40 mg	*Same amount is present - See section 5 below*
Lactose monohydrate		20 mg	20 mg	*Same amount is present - See section 5 below*

*RLD composition from the FDA's approved package insert.

The Applicant has provided a comparison between the reconstituted products (both the LD and the proposed drug product) and noted that the proposed drug product's reconstitution and labeling procedure is the same as the LD. Furthermore, the total Tc 99m radioactivity and volume of Tc99m is equivalent to the LD, per the drug product reviewer. Additionally, the Applicant has demonstrated that the pH of the proposed drug product is the same as the LD (between pH 5.0-6.0) and that the amount of (b) (4) (b) (4) (b) (4) is well controlled via proposed release and stability specifications, consistent with the LD labelling. Furthermore, the Applicant has noted that the proposed drug product and the LD have the same indications, the same patient dosing and radioactivity, and the same route of administration, dosage form, and strength. The Applicant has also noted that both the proposed drug product and LD have similar radiochemical purity results (RCP). Per the drug product reviewer, the proposed product and the LD have the same radioactive dose, same dose, and same radiochemical purity, and are therefore equivalent per the drug product reviewer.

In addition, the Applicant provided comparisons of the physical and chemical attributes of three batches of the proposed drug product (Registration Batches #0B134, #0C260, and #0F641) in comparison to one batch of the LD (Batch #09620003). As shown in Table 3, the comparisons of the drug product before reconstitution include appearance, identification of betiatide, betiatide assay, uniformity of dosage units, product impurities, stannous chloride, total tin content, sodium tartrate content, (b) (4) elemental impurities, particulate matter. All comparisons demonstrated similarity between the proposed drug product and the LD. Furthermore, the Applicant has noted that the LD has higher particulate matter and unknown impurities than the proposed drug product. However, it is noted that the Applicant's "reference" drug product was not a US-FDA approved drug product since it was sourced from Canada. Therefore, the Applicant was recommended via IR to use the US-FDA approved Listed Drug for the comparative studies. In response to the FDA's IR, the Applicant has provided comparisons using the US-FDA approved LD.

Table 3: Physiochemical comparisons of LD vs proposed drug product before Reconstitution

Test	Acceptance Criteria (Release)	Jubilant DraxImage Lot (s)			RLD Lot (s)	
					Canadian	US
		0B134	0C260	0F641	09620003	09621006
Description	(b) (4)	Conforms	Conforms	Conforms	Conforms	Conforms
Appearance		Conforms	Conforms	Conforms	Conforms	Conforms
(b) (4) of Betiatide		Conforms	Conforms	Conforms	Conforms	Conforms
(b) (4) of Betiatide		Conforms	Conforms	Conforms	Conforms	Conforms
Betiatide Assay		(b) (4)				
Uniformity of Dosage Units (UDU) (Weight Variation)	AV NMT 15.0 Meets USP <905> Requirements					
Impurities and Degradation Products	(b) (4)					
	Individual impurities:	(b) (4)				
Stannous Chloride Content (expressed as $SnCl_2 \cdot 2H_2O$)	(b) (4)	(b) (4)				
Total Tin Content(expressed as $SnCl_2 \cdot 2H_2O$)						
Sodium Tartrate Content						
		(b) (4)				
Bacterial Endotoxins	(b) (4)	(b) (4) EU/ml	(b) (4) EU/ml	(b) (4) EU/ml	Not tested*	Not tested*
Elemental Impurities	Meet USP <232> requirements	Conforms	Conforms	Conforms	Conforms	Not tested*
Sterility	Sterile	Sterile	Sterile	Sterile	Not tested*	Not tested*
Particulate Matter**	(b) (4)	(b) (4) particles/vial	particles/vial	particles/vial	particles/vial	particles/vial
		(b) (4) particles/vial	particles/vial	particles/vial	particles/vial	particles/vial

The Applicant has also conducted comparative testing of the reconstituted proposed drug product vs reconstituted LD with respect to clarity of solution and completeness, pH, 99mTc-Mertiatide identity, radiochemical purity, and osmolality. All comparisons demonstrate similarity between the proposed drug product and the LD. See Table 4.

Table 4: Physiochemical comparisons of LD vs proposed drug product after Reconstitution

Test	Acceptance Criteria (Release)		Jubilant DraxImage Lot (s)			RLD Lot (s)	
			0B134	0C260	0F641	Canadian 09620003	US 09621006
Tests on the Reconstituted Product							
Note: Test performed at reconstitution and at 6 hours post-reconstitution							
Clarity of Solution and Completeness	(b) (4)	T: 0 h	Conforms	Conforms	Conforms	Conforms	Conforms
		T: 6 h	Conforms	Conforms	Conforms	Conforms	Conforms
		T: 0 h	Conforms	Conforms	Conforms	Conforms	Not tested*
		T: 6 h	Conforms	Conforms	Conforms	Conforms	Not tested*
pH	5.0 – 6.0 (4 ml reconstitution volume)	T: 0 h	5.4	5.4	5.4	5.8	Not tested*
		T: 6 h	5.4	5.4	5.4	5.7	5.6
	5.0 – 6.0 (10 ml reconstitution volume)	T: 0 h	5.4	5.5	5.4	5.8	Not tested*
		T: 6 h	5.4	5.5	5.4	5.7	Not tested*
Identity	(b) (4)		Conforms	Conforms	Conforms	Conforms	Conforms
Radiochemical Purity	(b) (4)	T:0 h	(b) (4)				
		T:6 h					
		T:0 h					
		T:6 h					
		T:0 h					
		T:6 h					
Osmolality (Freezing Point Depression)	USP <785> Method 4 mL Reconstitution: Report percent difference to RLD		400 mOsm/kg	402 mOsm/kg	397 mOsm/kg	395 mOsm/kg	392 mOsm/kg
	USP <785> Method 10 mL Reconstitution: Report percent difference to RLD		329 mOsm/kg	330 mOsm/kg	329 mOsm/kg	330 mOsm/kg	323 mOsm/kg

Finally, the Applicant conducted physical property testing on the lyophilized powder of the LD in comparison to the proposed drug product including identification via FTIR and powder X-ray diffraction, and LOD on the lyophilized powder. See Table 5. These comparisons demonstrate similarity between the proposed drug product and the LD, per the drug product reviewer. For further details, see the Drug Product Review.

Table 5: Physiochemical comparisons of LD vs proposed drug product on the Lyophilized Powder

Test	Acceptance Criteria (Release)	Jubilant DraxImage Lot			RLD Lot
		0B134	0C260	0F641	09620003
Fourier Transform Infrared Spectroscopy (FTIR)	USP <1856> FTIR bands and absorption frequencies identical and (b) (4) of RLD frequencies Overlay correlation threshold (b) (4) as compared to RLD	IR bands and absorption frequencies (b) (4) cm^{-1} of RLD frequencies. Correlation Threshold: > 0.99	IR bands and absorption frequencies (b) (4) cm^{-1} of RLD frequencies. Correlation Threshold: > 0.99	IR bands and absorption frequencies (b) (4) cm-1 of RLD frequencies. Correlation Threshold: > 0.99	Characteristic bands observed	Characteristic bands observed
X-Ray Diffraction (XRD)	USP <941> XRD Diffraction patterns correspond to RLD	Diffraction patterns correspond to an amorphous material. XRD diffraction pattern correspond to RLD	Diffraction patterns correspond to an amorphous material. XRD diffraction pattern correspond to RLD	Diffraction patterns correspond to an amorphous material. XRD diffraction pattern correspond to RLD	Diffraction patterns correspond to an amorphous material.	Diffraction patterns correspond to an amorphous material.
(b) (4)						

From a Biopharmaceutics perspective, based on the total information submitted above, the data supports the Applicant's claim that the two parenteral drug products are comparable, and the slight differences, in pH adjusters, as discussed above are not likely to impact the in vivo performance of the proposed drug product. From a biopharmaceutics perspective, bridging is established between the proposed product and the LD. For reference, bridging information and data are included in: Request for waiver of in vivo BA or BE studies and Comparisons with US RLD.

B. 13 BIOWAIVER REQUEST

Assessment: *{Adequate/Inadequate}*

Since the formulations of the proposed drug product and the LD are not Q1/Q2 per OGD, this Application is not eligible for a biowaiver.

Primary Biopharmaceutics Assessor's Name and Date: Nadia Ahmed, PharmD 12/06/22

Secondary Assessor Name and Date (and Secondary Summary, as needed): Om Anand, PhD 12/06/22

Appendix:

BIOPHARMACEUTICS DEFICIENCIES Sent to the Applicant via IR (Dated 07/28/22):

1. We note that in your comparative physiochemical studies between the proposed drug product and the Listed Drug (LD), you have used a drug product that is not the US-FDA approved for your comparisons. Submit comparative studies and corresponding information/data using the US-FDA approved Listed Drug and your proposed drug product for further assessment.

Summary of Applicant's Response to IR (Dated 8/12/22): In response to the Agency's IR, the Applicant has provided comparisons using the US-FDA approved drug product.

Table A1: Applicant's Formulation Comparison Table between LD and proposed drug[2]

Ingredients	Chemical formula	RLD	JDI proposed Formulation				IID Maximum Potency per Unit Dose
		Amount per unit (quantity/ mL)	Amount per unit (quantity/ mL)	Unique Ingredient Identifier (UNII)	Function	Quality Standard	
Active Ingredient							
Betiatide	$C_{15}H_{17}N_3O_6S$	1 mg	1 mg	9NV2SR34P8	Precursor for Tc99m Mertiatide	Professed	Not applicable
Inactive Ingredients							
Stannous Chloride Anhydrous	$SnCl_2$	0.17 mg	--	R30H55TN67	Reducing Agent	NF/Ph.Eur.	0.05 mg
Stannous Chloride Dihydrate*	$SnCl_2 2H_2O$	--	0.2 mg	1BQV3749L5			0.25 mg
(b) (4)							
Water For Injection	H_2O		(b) (4)	Not applicable	(b) (4)	NF/ Ph.Eur./BP	Not applicable

(b) (4)

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	216820
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Kit for the preparation of Technetium Tc 99m Mertiatide
Route of Administration	Intravenous injection
Applicant Name	Jubilant DraxImage Inc., dba Jubilant Radiopharma
Therapeutic Classification/ OND Division	Division of Medical Imaging Products
Manufacturing Site	Jubilant DraxImage Inc., dba Jubilant Radiopharma 16751 Trans Canada Highway, Kirkland, QC, Canada, H9H 4J4
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

The drug product is (b) (4) (b) (4) yophilized.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0003	March 30, 2022
eCTD Seq #0006	June 24, 2022
eCTD Seq #0008	September 9, 2022

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

Remarks: The drug product is supplied as kit with five non-radioactive 10 mL reaction vials containing the lyophilized drug product, five radio assay information labels and five sterile venting needles.

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

Supporting Documents:

DMF (b) (4) (type V)- (b) (4) doc, dated August 2, 2022. (b) (4) (b) (4) (b) (4) (adequate)

DMF (b) (4) (type III)- (b) (4) docx, dated August 2, 2022. (b) (4) (b) (4) (b) (4)

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** The Tc 99m Mertiatide kit includes five 10 mL multi-dose reaction vials with lyophilized drug product, five radio assay information labels for the reconstituted product and five sterile venting needles ((b) (4) Each needle is received pre-sterilized in its final packaging.

- **Description of drug product kit components:**

Component	Description	Manufacturer
Vials	Five 10 mL vials containing lyophilized drug product (see below)	Jubilant DraxImage Inc., dba Jubilant Radiopharma
Labels	Five radio assay labels to be added once the drug product is radiolabeled.	
Venting needles	Five 20 gauge x 1.5" (b) (4) (b) (4) venting needles with (b) (4) filter, (b) (4) (b) (4)	(b) (4)

- **Drug product composition:**

Ingredient	Content per vial
Betiatide	1 mg
Stannous chloride dihydrate, USP	0.2 mg
Sodium tatrate dihydrate, NF	40 mg
Lactose monohydrate, USP	20 mg
Water for Injection, USP	Removed during lyophilization
Hydrochloric acid, NF	For pH adjustment

- **Description of primary container closure system:**

Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Cap		

Adequate

Reviewer's Assessment:
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.2, SEQ0003, Microbiology)

(b) (4)

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