CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214993Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 214993

Integrated Quality Assessment

Table of Contents

RECOMMENDATION

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

NDA 214993
Assessment 1

Drug Product Name	NEPHROSCAN (Kit for the Preparation of Technetium Tc99m Succimer Injection)
Dosage Form	Powder for Injection
Strength	1 mg
Route of Administration	intravenous
Rx/OTC Dispensed	Rx
Applicant	Theragnostics Inc
US agent, if applicable	Sarah DeMare

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (0000)	19-May-2021	All
Amendment (0001)	16-Jul-2021	Drug Product, Manufacturing
Amendment (0002)	19-Jul-2021	Biopharmaceutics
Amendment (0006)	25-Aug-2021	Drug Product
Amendment (0008)	10-Sep-2021	Drug Product, Manufacturing
Amendment (0010)	14-Sep-2021	Microbiology, Drug Product, Manufacturing
Amendment (0012)	05-Oct-2021	Drug Product
Amendment (0014)	15-Oct-2021	Drug Product, Manufacturing
Amendment (0015)	18-Oct-2021	Manufacturing
Amendment (0017)	02-Nov-2021	Microbiology
Amendment (0018)	12-Nov-2021	Microbiology
Amendment (0019)	21-Dec-2021	Labeling
Amendment (0020)	23-Dec-2021	Microbiology, Manufacturing
Amendment (0021)	26-Jan-2022	Labeling
Amendment (0022)	26-Jan-2022	Microbiology
Amendment (0023)	08-Feb-2022	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Joseph Leginus	Su (Suong) Tran
Drug Product	Ravindra Kasliwal	Danae Christodoulou
Manufacturing	Andrew Idzior	Vidya Pai
Microbiology	George Arhin	Paul Dexter
Biopharmaceutics	Debasis Ghosh	Kimberly Raines
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Ravindra Kasliwal	
Laboratory (OTR)	NA	NA
Environmental	NA	NA

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	07-Mar-2007 By Mark B. Sassaman	(b) (4)
	III			Adequate	08-Feb-2022 By Ravindra Kasliwal	
	III			Adequate	31-Dec-2003 By Elizabeth Chikhale	
	III			Adequate	07-Jun-2021	

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

Document	Application Number	Description
NDA	017944	This is the listed drug. LOA dated 02-Jun-2020 is provided

2. CONSULTS: NONE

Discipline	Status	Recommendation	Date	Assessor

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The application is recommended for APPROVAL. Based on the OPQ review team's evaluation, there is sufficient information to assure the identity, strength, purity, quality, including sterility of the proposed drug product.

The approved expiration dating period for NEPHROSCAN (kit for the preparation of technetium Tc-99m succimer injection) shall be **18-months, when stored in a refrigerator at 2°C to 8°C (36°F to 46°F).**

All the listed manufacturing facilities have been deemed to be adequate based on the compliance status, a 704(a)(4) document review, inspection history, and experience with the proposed operations. In accordance with 21 CFR 25.31(b), the applicant has claimed a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20, which is justified and is acceptable.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product NEPHROSCAN (kit for the preparation of technetium Tc-99m succimer injection) will be supplied as a sterile, pyrogen-free, freeze-dried white powder product (b) (4) The clear 10 mL glass vial is targeted to contain 1 mg of succimer, 0.42 mg stannous (tin) chloride dihydrate, 0.1 mg ascorbic acid, 0.2 mg sodium hydroxide, and 0.02 mg hydrochloric acid. 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 up to 1,480 MBq (40 mCi) of technetium Tc 99m succimer in 0.9% sodium chloride injection as a sterile, clear, and colorless solution. pH of the final solution is between 3 and 3.5.

The Applicant submitted the proposed product as a 505(b)(2) application and references GE lyophilized Kit approved under NDA 017944, as the Listed Drug. Biopharmaceutics had determined that the applicant has established adequate scientific bridge (under 21 CFR 320.22(b)(6)) between the proposed product and the listed drug product.

The applicant has justified and qualified the quality of the components 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. The development data, process controls, and exhibit

batch records mitigate the risks posed by the proposed (b) (4) operations. The application has demonstrated adequate controls for sterility assurance. 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 totality of the presented stability data on the primary and supportive batches and the fact that each vial subsequent to radiolabeling is tested for acceptable radiochemical purity, supports the requested expiration dating period of **18-months, when stored in a refrigerator at 2°C to 8°C (36°F to 46°F).** Results of radiolabeling study indicate that when reconstituted as described in the PI, the **radiolabeled product is stable for up to 4 hours, at controlled room temperature 20° to 25°C (68° to 77°F);** excursions permitted to 15° to 30°C (59° to 86°F).

All the listed manufacturing facilities have been deemed to be adequate based on the compliance status, a 704(a)(4) document review, inspection history, and experience with the proposed operations.

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

Proposed Indication(s) including Intended Patient Population	NEPHROSCAN™ (Kit for the preparation of technetium Tc99m succimer injection), after radiolabeling with technetium Tc 99m, is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics patients including neonates.
Duration of Treatment	This is a one-time intravenously administered dose prior to imaging and there is no administration on a daily basis
Maximum Daily Dose	The maximum dose for this radioactive drug product is 222 MBq (6mCi) in adults and 1.85 MBq/kg (0.05 mCi/kg) in pediatric patients.
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

See drug substance chapter.

A retest date of (b) (4) months has been granted (b) (4)

Drug Product: Adequate

See drug product chapter.

Labeling: Adequate

The final revised labeling was submitted in amendment dated 08-Feb-2022 (#0023), which was adequate.

Manufacturing: Adequate

See manufacturing chapter.

The facilities are adequate based on the compliance status, a 704(a)(4) document review, inspection history, and experience with the proposed operations.

Biopharmaceutics: Adequate

See biopharmaceutics chapter.

The Applicant requested a waiver of bioavailability study for the proposed product (THG-Kit). Due to the qualitative and quantitative composition differences between the proposed product (THG-Kit) and the listed drug (GE Lyophilized Kit), the biowaiver under 21 CFR 320.22 was not applicable. Based on Agency's recommendation (Pre-IND meeting), the Applicant submitted information to establish a scientific bridge between its proposed product (THG kit) and listed drug (GE Lyophilized Kit) under 21 CFR 320.24(b)(6).

From a biopharmaceutics perspective, a scientific bridge (under 21 CFR 320.22(b)(6)) between the proposed product and the listed drug product has been sufficiently established.

Microbiology (if applicable): Adequate

See microbiology chapter

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	Manufacturing	High	(b) (4)	Acceptable.	Theragnostics has committed to implement a revised analytical procedure (b) (4) This update to the analytical procedure will be submitted with the first annual report.
(b) (4)	Manufacturing (b) (4) and container closure integrity.	High		Acceptable	(b) (4)
pH	Manufacturing	Medium		Acceptable.	

(b) (4)	Manufacturing, (b) (4) Container closure integrity	High	(b) (4)	Acceptable	(b) (4)
Stannous (Sn^{2+}) Chloride dihydrate content	Manufacturing, (b) (4)	High		Acceptable	
Succimer (DMSA) Content	Manufacturing, (b) (4)	High		Acceptable.	
Ascorbic Acid Content	Manufacturing	High		Acceptable	

D. List of Deficiencies for Complete Response

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

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

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

N/A

Application Technical Lead Name and Date:

Ravindra K. Kasliwal, Ph.D. *2/9/2022*

62 Pages have 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: Submission # 0019 dated 12/23/2021 and Submission #0021 dated 01/26/2022.

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	The established name is "(kit for the preparation of technetium Tc 99m succimer 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	Dosage form and strength statement is: For Injection: NEPHROSCAN contains 1 mg succimer as a lyophilized powder in a single dose vial. Upon radiolabeling with technetium Tc 99m, it provides a clear, colorless solution containing up to 1,480 MBq (40 mCi) technetium Tc 99m succimer in approximately 5 mL volume at calibration time. The word "white" should be added to before lyophilized powder
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	None

[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	The labeling indicates that "NEPHROSCAN contains 1 mg succimer as a lyophilized powder in a **single-dose vial**". **The word "white" should be added to before lyophilized powder**
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 a salt.

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	Drug Preparation and quality control instructions have been included in section 2.4 and 2.5, respectively. These have been reproduced below the table.

Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Subsequent to radiolabeling the product is radioactive, and is always kept in lead shielding. The "2.6 Administration" section indicates the following: Using a sterile shielded syringe, aseptically withdraw the prepared technetium Tc 99m Succimer Injection, and measure the radioactivity in the syringe using a dose calibrator, prior to administration. Ensure that the injected radioactivity is within ±10% of the recommended dose. Discard unused portion. Handle and dispose radioactive material in accordance with applicable regulations.
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	Subsequent to radiolabeling the product is radioactive, and is always kept in lead shielding. The required statement in "2.6 Administration" is modified to: Prior to use, visually inspect the prepared technetium Tc 99m Succimer Injection behind a lead glass shield. 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	None.
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	Adequate	Included in section 2.8 of the PI.
For hazardous products, include the statement *"DRUG X is a hazardous*	Adequate	Following aspects are included in PI: **Section 2.1 Radiation Safety – Drug Handling** After radiolabeling, handle technetium Tc 99m Succimer Injection with appropriate safety measures

drug. Follow applicable special handling and disposal procedures" with x numerical citation to "OSHA Hazardous Drugs".		to minimize radiation exposure [see Warnings and Precautions (5.2)]. Use waterproof gloves, effective radiation shielding, and other appropriate safety measures when preparing and handling technetium Tc 99m Succimer Injection. Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides. **Section 2.6**: Discard unused portion. Handle and dispose radioactive material in accordance with applicable regulations.

2.4 Drug Preparation

Prepare Technetium Tc 99m Succimer Injection according to the following procedure using asceptic technique:

a) Wear waterproof gloves.
b) Place the kit vial in lead shielding and disinfect the stopper (allow disinfectant to dry).
c) Use a sterile syringe to transfer 5 mL sodium pertechnetate Tc 99m injection obtained from a technetium Tc 99m generator with a maximum activity of 1,480 MBq (40 mCi) to the vial. The volume of sodium pertechnetate Tc 99m injection solution may be adjusted to 5 mL prior to adding to the kit vial using 0.9% sodium chloride injection, USP.
d) Use the same syringe to withdraw the appropriate gas volume from the vial for pressure compensation.
e) Lightly shake the vial to completely dissolve the powder. Ensure the stopper is well moistened.
f) Incubate the vial for 10 minutes at controlled room temperature 20°C to 25°C (68°F to 77°F).
g) Measure the product activity in a dose calibrator; complete the radiolabeled product vial label and affix to the vial shield.
h) Check radiochemical purity according to the method in 2.5 Radiochemical Purity Determination *[see Dosage and Administration (2.5)]*.
i) Use Technetium Tc 99m Succimer within 4 hours and store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

2.5 Radiochemical Purity Determination

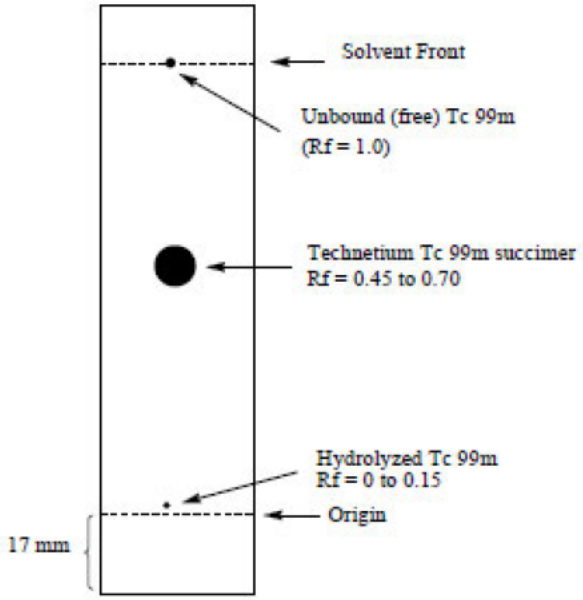
Determine the radiochemical purity of Technetium Tc 99m Succimer Injection as follows:

a) Activate a 65 × 95-mm silica gel thin-layer chromatographic (TLC) plate by heating at 100°C to 110°C (212°F to 230°F) for 30 minutes.
b) Cool the silica gel TLC plate and immediately apply 1 microμL of Technetium Tc 99m Succimer Injection about 17 mm from one end of the TLC plate and allow to dry. If necessary, the Technetium Tc 99m Succimer Injection solution may be diluted with 0.9% sodium chloride injection USP, to a radioactive concentration of 18.5 MBq to 370 MBq (0.5 mCi to 10 mCi) per mL.

c) Develop the TLC plate over a period of about 30 to 45 minutes by ascending chromatography, using a solution of n-butanol saturated with 0.3 N hydrochloric acid (*see Note 1*). Air-dry the developed TLC Plate.

d) Determine the radioactive distribution on the TLC plate by scanning the chromatogram with a radiochromatographic scanner having a suitably collimated radiation detector.

e) The radioactivity associated with technetium Tc 99m succimer is at Rf between 0.45 and 0.70, hydrolyzed Tc 99m is located at the origin (Rf 0 to 0.15) and the unbound Tc 99m is located at the solvent front (Rf 1.0)



$$Rf = \frac{\text{Distance (from origin) reaveled by solute (Tc 99m compound)}}{\text{Distance (from origin) travelend by solvent (n-butanol /3N HCl)}}$$

f) Calculate radiochemical purity using the following formula:

$$\textit{Percent (\%) Raciochemical Purity} = \frac{\textit{Technetium Tc 99m succimer activity}}{\textit{Total activity (Tc 99m succimer + HR Tc 99m + Unbound Tc 99m)}} \times 100$$

g) Technetium Tc 99m Succimer Injection preparation with not less than 85% radiochemical purity is suitable for administration. Discard preparation with less than 85% radiochemical purity.

Note 1: To prepare the n-butanol saturated with 0.3 N hydrochloric acid solution, place 50 mL of 0.3 N HCl and 50 mL of n-butanol in an Erlenmeyer flask. Place the mixture in an ultrasonic bath for 2 hours, during which time the solution heats up to about 50°C. Cool the solution to room temperature. After about 30-45 minutes the phase separation of the mixture will complete. Collect the upper phase of the mixture and discard the lower phase. The solution is stable for up to 7 days when stored at controlled room temperature 20°C to 25°C (68°F to 77°F).

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

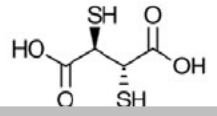
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s):	Adequate	The dosage form is (Powder) For Injection.
Strength(s) in metric system:	Adequate	Strength is 1 mg/mL
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	None.
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	The labeling indicates that "upon radiolabeling with technetium Tc 99m, it provides up to 1,480 MBq (40 mCi) technetium Tc 99m Succimer Injection as a clear, colorless solution in approximately 5 mL volume at calibration date and time".
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	The labeling indicates that "NEPHROSCAN contains 1 mg succimer as a lyophilized powder in a single-dose vial". **The word "white" should be added to before lyophilized powder**

Section 11 (DESCRIPTION)

11.1 Chemical Characteristics

NEPHROSCAN is a sterile, single-dose kit for the preparation of Technetium Tc 99m Succimer Injection a radioactive diagnostic agent, for intravenous use.

The active ingredient, succimer is meso-2,3-dimercaptosuccinic acid with a molecular weight of 182.22 g/mol. The chemical structure of succimer is shown below. Subsequent to radiolabeling with sodium pertechnetate Tc 99m, the active moiety technetium TC 99m succimer is obtained in situ.



(b) (4)

In addition, after radiolabeling with sodium pertechnetate Tc 99m injection, each vial contains up to 1,480 MBq (40 mCi) of technetium Tc 99m succimer in 0.9% sodium chloride injection as a sterile, clear, and colorless solution. pH of the final solution is between 3 and 3.5.

11.2 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 3.

Table 3 Principal Radiation Emission Data for Technetium Tc 99m

Radiation/ Emission	Mean % / Disintegration	Mean Energy (keV)
Gamma 2	89.07	140.5

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 4.

Table 4 Physical Decay Chart for 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

11.3 External Radiation

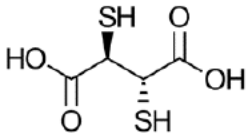
The specific gamma ray constant for technetium Tc 99m is 0.78 R/hr-mCi at 1 cm. The first half value layer is 0.017 cm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000. Table 5 displays the radiation attenuation by lead shielding.

Table 5 Radiation Attenuation by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0.02	0.5
0.08	0.1
0.16	0.01
0.25	0.001
0.33	0.0001

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	**NEPHROSCAN** is a sterile, single-dose **kit for the preparation of Technetium Tc 99m Succimer Injection** a radioactive diagnostic agent, **for intravenous use**.
Dosage form(s) and route(s) of administration	Adequate	
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 active ingredients. Use USP/NF names in alphabetical order.	Adequate	The active ingredient, succimer is meso-2,3-dimercaptosuccinic acid with a molecular weight of 182.22 g/mol. The chemical structure of succimer is shown below. Subsequent to radiolabeling with sodium pertechnetate Tc 99m, the active moiety technetium Tc 99m succimer is obtained in situ.
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	(b) (4) [redacted] In addition, after radiolabeling with sodium pertechnetate Tc 99m injection, each vial contains up to 1,480 MBq (40 mCi) of technetium Tc 99m succimer in 0.9% sodium chloride injection as a sterile, clear, and colorless solution. pH of the final solution is between 3 and 3.5.

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	Alcohol is not present as an inactive ingredient.
Sterility statement (if applicable)	Adequate	NEPHROSCAN is a **sterile**, single-dose kit for the preparation of Technetium Tc 99m Succimer Injection a radioactive diagnostic agent, for intravenous use.
Pharmacological/Therapeutic class	Adequate	NEPHROSCAN is a sterile, single-dose kit for the preparation of Technetium Tc 99m Succimer Injection a **radioactive diagnostic agent**, for intravenous use.
Chemical name, structural formula, molecular weight	Adequate	The active ingredient, succimer is meso-2,3-dimercaptosuccinic acid with a molecular weight of 182.22 g/mol. The chemical structure of succimer is shown below. 
If radioactive, statement of important nuclear characteristics.	Adequate	Physical Characteristics Details regarding technetium 99m are provided in section 11.2.
Other important chemical or physical properties (such as pKa or pH)	Adequate	The pH of the radiolabeled solution that is injected is described.

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	This is an injectable drug product.

Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	Description section does not contain promotional statements.
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	None

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

How Supplied

(b) (4)

Storage and Handling

Store NEPHROSCAN in a refrigerator at 2° to 8°C (36° to 46°F) in original carton. Do not freeze.

After radiolabeling, store Technetium Tc 99m Succimer Injection upright, shielded, for up to 4 hours, at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). *[see Dosage and Administration (2.4)]*.

This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

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	For injection is included.
Strength(s) in metric system	Inadequate	**Strength 1 mg Succimer should be added.**
Available units (e.g., bottles of 100 tablets)	Adequate	Carton of 5 single dose vials is indicated.
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Indicates "white lyophilized powder".
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	Single dose vial is indicated.

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" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Store NEPHROSCAN in a refrigerator at 2° to 8°C (36° to 46°F) in original carton. Do not freeze. After radiolabeling, store Technetium Tc 99m Succimer Injection upright, shielded, for up to 4 hours, at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). *[see Dosage and Administration (2.4)]*.

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	Store NEPHROSCAN in a refrigerator at 2° to 8°C (36° to 46°F) in original carton.
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	None.
Include information about child-resistant packaging	N/A	Health care personal injects the product in hospital setting prior to the imaging procedure.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenteral, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

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	**Distributed by:** Theragnostics, Inc. 150 Grossman Drive Braintree, MA 02184 1-617-286-7479

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

None. Health care personal injects the product in hospital /imaging center setting prior to the imaging procedure.

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Comments: The vial label should be revised as follows:

1. Add the word "Sterile" on the upper right side (above proprietary name) of the label.
2. Relocate "Single-Dose Vial. Discard Unused Portion" to appear after or below the "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc99m Injection (USP)".
3. Add storage statement, e.g., "Store refrigerated" or "Store refrigerated at 2° to 8°C (36° to 46°F)".

Carton Labeling

PRINCIPLE DISPLAY PANEL:

BACK PANEL:

The Carton Labeling should be revised as follows:

1. **Back Panel:**

   a. Revise the quantitative statement label from, (b) (4) to "Each vial contains 1 mg succimer, 0.1 mg ascorbic acid, USP, 0.42 mg stannous chloride dihydrate, 0.02 mg hydrochloric acid, and 0.2 mg sodium hydroxide."

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	Adequate	Established name, "Kit for the Preparation of Technetium Tc 99m Injection" is provided below the proprietary name in both container and carton label.
Special preparation instructions (if applicable)	Adequate	Detailed preparation in quality control instructions are provided in PI. The label indicates "**For intravenous use only** after radiolabeling with Sodium Pertechnetate Tc99m Injection (USP) (b) (4)". Further the container label will also contain the statement "Recommended Dosage: See Prescribing Information.".

Storage and handling information (if applicable)	Adequate	The storage statement is present in the carton label. We have recommended that the vial (container) label also contain the storage statement.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	See below.
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	The container label is small to contain quantitative composition. In the carton able the inactive ingredients are not in alphabetical order, and HCl and NaOH are not included. We are asking that the carton labeling be revised .
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Caron label has the information. Container label only contains name of the manufacturer.

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	Established name, "Kit for the Preparation of Technetium Tc 99m Injection" is provided below the proprietary name in both container and carton label. Prominence is acceptable.
Strength(s) in metric system	Adequate	Label indicates "1 mg succimer".
Route(s) of administration	Adequate	For intravenous use is indicated: "**For intravenous use only** after radiolabeling with Sodium Pertechnetate Tc99m Injection (USP) (b) (4) "
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	N/A	It is a lyophilized powder.
"Rx only" displayed on the principal display	Adequate	Rx Only is indicated on the PDP
NDC	Adequate	NDC is indicated on the PDP.
Lot number and expiration date	Adequate	The Lot (number) and Exp. Date are included.

[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	Instructions should be revised as follows: "**Store refrigerated at 2° to 8°C (36° to 46°F) in original carton.** Do not freeze. After radiolabeling, store upright (b) (4) (b) (4) excursions permitted to 15° to 30°C [59° to 86°F]) (b) (4) Do not use and discard 4 hours after reconstitution.".
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	Single dose vial is indicated on PDP.
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.	Inadequate	In carton label, HCL and NaOH are not listed, and the inactive ingredients are not in alphabetical order.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Space for barcode is indicated on the back panel.

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	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Health care personal injects the product in hospital setting prior to the imaging procedure.
No text on Ferrule and Cap Overseal unless a cautionary statement is required.	N/A	

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Inadequate	There is a USP monograph for the radiolabeled product: technetium Tc 99m Succimer Injection". The applicant has provided labels for the radiolabeled vial and for the syringe in which the patient dose is drawn. We have recommended changes to those labels to be in conformance with the USP requirement.
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.	Inadequate	The pH of the proposed product is 3-3.5. The pH of the radiolabeled product in the monograph is 2-.0-3.0. In the radiolabeled product vial and the syringe label, we are asking the applicant to include pH statement indicating the difference.
And others if space is available.	Adequate	Detailed preparation in quality control instructions are provided in PI. The Carton label indicates "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc 99m Injection, USP". See package insert for reconstitution & dosing instructions.

ITEMS FOR ADDITIONAL ASSESSMENT

Radiolabeled Product Vial Label:

(b) (4)

[redacted]

Revise the Radiolabeled Product Vial Label as follows:

1. Revise word [redacted] (b) (4) to "Calibration".
2. Since the proposed product is different from the USP monograph product in terms of pH, this difference must be stated on radiolabeled product label. Include statement "pH is between 3 – 3.5".

Syringe Label:

Revise the Syringe label as follows:

1. We recommend that the statement [redacted] (b) (4) be deleted from the label.
2. In the light area of the label, also include the following:
   a. Revise [redacted] (b) (4) to "Calibration ____Time____ Date"
   b. Space for "Activity Amount" (expressed as total megabecquerels (microcuries or millicuries) and concentration as megabecquerels (microcuries or millicuries) per mL at the time of calibration of syringe dose) of the radioactivity in the syringe.
   c. Space for beyond-use time as the following format, "Discard after: ___Time Date".

Assessment of Carton and Container Labeling: *Inadequate*

Overall Assessment and Recommendation:

The container, carton, radiolabeled vial, and syringe labeling is currently **Inadequate** and should be revised as follows:

1. Revise the quantitative statement on the back panel of the carton label from, [redacted] (b) (4) to "Each vial contains 1 mg succimer, 0.1 mg ascorbic acid, USP, 0.42 mg stannous chloride dihydrate, 0.02 mg hydrochloric acid, and 0.2 mg sodium hydroxide."

2. Revise the container (vial label) as follows:
   a. Add the word "Sterile" on the upper right side (above proprietary name) of the label.

b. Relocate "Single-dose vial. Discard Unused Portion" to appear below the "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc99m Injection (USP) b[redacted]" statement.
c. Add storage statement, e.g., "Store refrigerated" or "Store refrigerated at 2° to 8°C (36° to 46°F)".

3. Revise the Radiolabeled Product Vial Label as follows"
   a. Revise the word [redacted] to "Calibration".
   b. Since the proposed product is different from the USP monograph product in terms of pH. This difference must be stated on radiolabeled product label. Include statement "pH is between 3 – 3.5".

4. Revise the Syringe label as follows:
   a. We recommend that the statement [redacted] be deleted from the label.
   b. In the light area of the label, also include the following:
      i. Revise [redacted] to "Calibration Time Date"
      ii. Space for "Activity Amount" (expressed as total megabecquerels (microcuries or millicuries) and concentration as megabecquerels (microcuries or millicuries) per mL at the time of calibration of syringe dose) of the radioactivity in the syringe.
      iii. Space for beyond-use time as the following format, "Discard after: Time Date".

Primary Drug Product Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *2/2/2022*

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

Danae D. Christodoulou, Ph.D. *2/2/2022*

Ravindra Kasliwal

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Danae Christodoulou

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Date: 2/02/2022 09:35:55AM
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ADDENDUM TO NDA 214993 LABELING REVIEW

IN the previous product quality labeling review, the container, carton, radiolabeled vial, and syringe labeling was found to be **Inadequate** for the reasons listed below. An IR was sent to the applicant (02-Feb-2022). The applicant submitted the response and revised labeling in amendment dated 08-Feb-2022. Following is the assessment of the response:

FDA Comment:

1. Revise the quantitative statement on the back panel of the carton label from, (b) (4) (b) (4) (b) (4) to "Each vial contains 1 mg succimer, 0.1 mg ascorbic acid, USP, 0.42 mg stannous chloride dihydrate, 0.02 mg hydrochloric acid, and 0.2 mg sodium hydroxide."

Response: The applicant submitted the revised carton label that contains the requested composition statement.

(b) (4)

Assessment: ADEQUATE

FDA Comment:

2. Revise the container (vial label) as follows:

   a. Add the word "Sterile" on the upper right side (above proprietary name) of the label.
   b. Relocate "Single-dose vial. Discard Unused Portion" to appear below the "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc99m Injection (USP) (b) (4)" statement.
   c. Add storage statement, e.g., "Store refrigerated" or "Store refrigerated at 2° to 8°C (36° to 46°F)".

Response: The applicant submitted the revised container label that contains the requested information.

(b) (4)

Assessment: ADEQUATE

FDA Comment:

3. Revise the Radiolabeled Product Vial Label as follows:
   a. Revise the word (b) (4) to "Calibration".
   b. Since the proposed product is different from the USP monograph product in terms of pH. This difference must be stated on radiolabeled product label. Include statement "pH is between 3 – 3.5".

Response: The applicant submitted the revised radiolabeled product vial label that contains the requested information.

(b) (4)

Assessment: ADEQUATE

FDA Comment:

4. Revise the Syringe label as follows:
   a. We recommend that the statement [redacted] (b) (4) be deleted from the label.
   b. In the light area of the label, also include the following:
      i. Revise [redacted] (b) (4) to "Calibration____Time____ Date"
      ii. Space for "Activity Amount" (expressed as total megabecquerels (microcuries or millicuries) and concentration as megabecquerels (microcuries or millicuries) per mL at the time of calibration of syringe dose) of the radioactivity in the syringe.
      iii. Space for beyond-use time as the following format, "Discard after: ___Time ___Date".

Response: The applicant submitted the revised radiolabeled product vial label that contains the requested information.

(b) (4)

[redacted]

Assessment: ADEQUATE

Conclusion: The revised labeling submitted on 08-Feb-2022 (#0023) is adequate from a product quality perspective.

Primary Assessor Name and Date:

Ravindra K. Kasliwal, Ph.D. *2/9/2022*

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

Danae D. Christodoulou, Ph.D. *2/9/2022*

Ravindra Kasliwal

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Danae Christodoulou

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CHAPTER VI: BIOPHARMACEUTICS

Assessor's Summary:

The Applicant submitted a 505(b)(2) application to obtain market approval for NephroScan (Kit for the preparation of Technetium Tc99m Succimer Injection; also referred to as THG-Kit within this document). The NephroScan is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics. This 505(b)(2) NDA submission references listed product, GE lyophilized Kit, approved under NDA 017944.

The Applicant requested a waiver of bioavailability study for the proposed product (THG-Kit). Due to the qualitative and quantitative composition differences between the proposed product (THG-Kit) and the listed drug (GE Lyophilized Kit), the biowaiver under 21 CFR 320.22 is not applicable. Based on Agency's recommendation (Pre-IND meeting), the Applicant submitted information to establish a scientific bridge between its proposed product (THG kit) and listed drug (GE Lyophilized Kit) under 21 CFR 320.24(b)(6).

The listed drug contains inositol (b) (4) (Table 1). The proposed drug, (b) (4) does not contain inositol. (b) (4) (b) (4) The listed drug contains higher amounts of (b) (4) (ascorbic acid) compared to the proposed product. (b) (4) (b) (4) (b) (4) (b) (4) the level of ascorbic acid appears to be adequate in the proposed product. So, lower amount of ascorbic acid in THG-Kit compared to Listed drug will not affect the quality of the product. (b) (4) (b) (4) The physiochemical properties like pH, osmolality and radiochemical purity are found to be similar or adequately controlled for both listed drug and proposed product. From a biopharmaceutics perspective, a scientific bridge (under 21 CFR 320.22(b)(6)) between the proposed product and the listed drug product has been established. However, as there are changes in inactive ingredients, we defer to Pharmacology/Toxicology and Clinical Pharmacology for the final decision of this bridging in case there are safety and efficacy concerns.

- *Highlight the documents being assessed in this most recent assessment using the tabular format below.*

Document(s) Assessed (SN-#)	Date Received
• **Original NDA (0000)** • **Amendment (0001)** • **Request for biowaiver (0002)**	• **19-May-2021** • **16-Jul-2021** • **19-Jul-2021**

➢ *Include a summary of the biopharmaceutics assessment, at a minimum, consider the following information:*

The Applicant requested a biowaiver for the proposed product. From a perspective of biopharmaceutics assessment, the scientific bridge under 21 CFR 320.24 (b)(6) between the proposed product (THG-Kit) and listed drug (GE Lyophilized Kit) has been established.

5. Biowaivers/Biostudies

- *Biowaiver Requests:* The Applicant submitted a biowaiver request and established scientific bridging under 21 CFR 320.24(b)(6).
- *IVIVC: [Summarize any IVIVC proposals and indicate if approved or not approved]: NA*

➢ *Add the Risk Assessment table under the Assessment Summary section.:*

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #	Comments
One of the critical formulation variables is the amount of ascorbic acid (b) (4)	**High**	**Compared to RLD (GE Lyophilized Kit) ascorbic acid amount is lower in the proposed product (Kit).**	**Low**	(b) (4)

Sn(II) to Sn(IV).				(b) (4)

Highlight Key Issues from Last Cycle and Their Resolution: NA

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

B.1 BCS DESIGNATION

Assessment: NA

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: NA

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: NA

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QBD

Assessment: NA

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS –*In-Vitro Alcohol Dose Dumping*

Assessment: NA

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: NA

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: NA

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: NA

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: NA

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: NA

B.11 EXTENDED-RELEASE DOSAGE FORMS –*Extended-Release Claim*

Assessment: NA

B.12 BRIDGING OF FORMULATIONS

Assessment: *NA*

B.13 BIOWAIVER REQUEST *(if applicable, otherwise delete)*

Assessment: ***Adequate***

In eCTD Module 1.12.15, the Applicant requested a waiver of in vivo studies. During a Pre-IND meeting in Oct 2019, the Applicant asked the Agency if the proposed product qualifies for a biowaiver. The Agency indicated that the proposed product does not meet the criteria under 21 CFR 320.22 for biowaiver. However, the Agency recommended that the Applicant may consider establishment of a scientific bridge (under 21 CFR 320.22(b)(6)) between the proposed product and the listed drug. Based on communication with the Agency, the Applicant provided information to establish a scientific bridge between Test (THG Kit) and Reference (GE Lyophilized

Kit, NDA 017944-S011) drug products. The scientific bridge is established based on data to demonstrate that any difference in active and inactive ingredients between the proposed and listed drug product do not contribute towards the difference of in vivo activity of the product. Following is the formulation comparison of the proposed Kit and Listed Drug Kit:

Table 1. Tc99m Succimer Injection Formulations Comparisons

Ingredient	Use	Quantity per Vial			
		GE Liquid Kit	GE Lyophilized Kit	THG Kit	ROTOP Kit*
Meso-2,3-dimercaptosuccinic acid	Active	(b) (4)	1.0 mg	1.0 mg	1.0 mg
Stannous Chloride dehydrate ($Cl_2H_4O_2Sn$)	(b) (4)		0.42 mg	0.42 mg	(b) (4)
Ascorbic Acid			0.70 mg	0.1 mg	
Inositol			50.0 mg	--	
Sodium Hydroxide	Adjustment of pH (b) (4)		Not specified	0.2 mg	
Hydrochloric Acid	Adjustment of pH (b) (4)		Not specified	0.02 mg	
Nitrogen			--	--	

* Also referred to as Theragnostics Imported Kit.
(b) (4)

GE drug product formulation (GE Liquid Lit) was initially approved under NDA 017944 and later (NDA 017944-S-011), GE submitted a CBE-30 supplement to add a new manufacturer and formulation change from liquid to lyophilized product (GE lyophilized Kit). As evidenced from Table 1, GE lyophilized Kit is different from existing GE liquid formulation because lyophilized product contains new inactive ingredients like ascorbic acid and inositol. In 2014, GE ceased commercial distribution of GE Kit and Tc99m DMSA Injection was placed on drug shortage list. Having received the grant from the Agency under unapproved drug to address shortage the Applicant imported the Kit of the preparation of Tc99m Succimer Injection which was manufactured by ROTOP Pharmaka of Germany. In Table 1, the product is indicated as ROTOP Kit. In this submission, the Applicant proposed THG Kit (b) (4)

Inositol: (b) (4)
(b) (4)

(b) (4)

(b) (4) Essentially, (b) (4)

(b) (4) inositol has no role in the bioperformance of the product.

Ascorbic Acid: (b) (4)

(b) (4)

(b) (4) So, the lower amount of ascorbic acid has no detrimental effect on the bioperformance of the product.

Physicochemical Properties: The Applicant did not provide side-by-side physicochemical properties. Following summary is based on this submission and FDA database (Listed Drug):

pH: (b) (4)

The Applicant proposed a specification for the THG Kit. A comparative pH data was summarized below in Table 2.

Table 2. Physicochemical Property (pH) Comparison

Kit	Proposed Specification for THG Kit	Approved Specification for GE Lyophilized Kit*
pH	3.0-3.5 (batch data: 3.0, 3.1, 3.1)	(b) (4) (batch data 2.78, 2.86)

*FDA database

Osmolality: Osmolality is a measure of the dissolved particles in fluid. The Ref product contains 50 mg inositol. According to Sec 1.12.5. Appendix 1 Reconstitution Instruction comparison, the lyophilized product should be reconstituted with 5 mL sodium pertechnetate Tc99m (USP monograph on sodium pertechnetate injection) . However, not more than 40 mCi should be transferred to the vial. However, the concentration of the generator eluate may be adjusted to 5 mL using 0.9% sodium chloride solution for injection. So, final concentration of inositol in 5 mL solution would be 1% w/v or 0.27 mmol (MW of inositol 180.16). So, the change of osmolality due to the presence or absence of 50 mg inositol would be insignificant.

Radiochemical Purity: According to Sec 1.12.5. Appendix 1 Reconstitution Instruction comparison, radiochemical purity should be tested for final solution for both THG Kit and GE lyophilized Kit.

From a biopharmaceutics perspective, a scientific bridge (under 21 CFR 320.22(b)(6)) between the proposed product and the listed drug product has been established. However, as there are changes in inactive ingredients, we defer to Pharmacology/Toxicology and Clinical Pharmacology for the final decision of this bridging in case there are safety and efficacy concerns.

Primary Reviewer: Date:
Debasis Ghosh, Ph.D. 10/22/2021

Secondary Reviewer: Date:
Kimberly Raines, Ph.D. 10/22/2021

Debasis Ghosh

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Kimberly Raines

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FDA U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
NDA Number	214993
Assessment Cycle Number	1
Drug Product Name / Strength	Kit for the Preparation of Technetium Tc99m Succimer Injection
Route of Administration	Intravenous injection
Applicant Name	Theragnostics Inc
Manufacturing Site	ROTOP Pharmaka GmbH Bautzner Landstrasse 400 01328 Dresden, Germany
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☒ Depyrogenation Validation Data
☒ Product Sterility Assurance	☒ Product Release and/or Stability Specifications
☒ Media Fill Data	☒ Validation for Product Release and/or Stability Test Method
☒ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: N/A

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

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
May 19, 2021	May 19, 2021	N/A	May 24, 2021
September 14, 2021[1] (eCTD sequence # 10)	September 14, 2021	N/A	September 15, 2021
November 2, 2021[2] (eCTD sequence # 17)	November 2, 2021	N/A	November 3, 2021
November 12, 2021[3] (eCTD sequence #18)	November 12, 2021	N/A	November 12, 2021
December 23, 2021[4]	December 23, 2021	N/A	January 3, 2022

(eCTD sequence # 20)			
January 26, 2022[5] (eCTD sequence # 22)	January 26, 2022	N/A	January 27, 2022

[1]Response submission to the Agency's August 17, 2021 CMC Information Request Letter
[2]Response submission to the Agency's October 21, 2021 CMC Information Request Letter
[3]Unsolicited Amendment adding an alternate stopper for use with the THG kit
[4]Response submission to the Agency's December 8, 2021 CMC Information Request Letter
[5]Response submission to the Agency's January 19, 2022CMC Information Request Letter

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

Concise Description of Outstanding Issues: See Microbiology List of deficiencies at the end of this review.

Supporting Documents:

- DMF (b) (4) (b) (4)

Remarks: eCTD. The firm seeks Priority Review designation based on Drug Shortage.

The Agency notes that the original NDA submission lacked significant information needed for the product quality microbiology review of a sterile drug product (e.g. Container Closure Integrity Test, Bacterial Retention Study, sterilization and depyrogenation validations for equipment and components, etc were not addressed in the submission). The Agency provided comments to the applicant to address specific information needs. Further, the applicant was referred to the same FDA guidance documents that were previously provided in response to Pre-NDA Meeting (IND 145176) submitted 8/1/19:

- Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064983.htm (b) (4)

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The drug product, Kit for the Preparation of Technetium Tc99m Succimer Injection (or THG Kit) is a white, sterile lyophilized powder for injection.

Note to Reviewer: The lyophilized powder is reconstituted with sodium pertechnetate at radiopharmacies to achieve the dosage form, Technetium Tc99m Succimer Injection (Tc99m DMSA Injection) for administration to patients.

- **Drug product (THG Kit) composition –**

Ingredient	Quantity per vial	Function
Meso-DMSA, in-house	1.0 mg	Active Pharmaceutical Ingredient
Sn(II) Chloride dihydrate, Ph. Eur	0.42 mg	(b) (4)
(b) (4)-Ascorbic Acid, USP, Ph.Eur	0.1 mg	
Sodium Hydroxide, NF, Ph. Eur	0.2 mg	Adjustment of pH
Hydrochloric Acid, NF, Ph. Eur	0.02 mg	(b) (4) (b) (4) Adjustment of pH (b) (4)

- **Description of container closure system –**
THG Kit is packaged in 10 mL colorless, (b) (4) glass vial closed with a (b) (4) stopper and sealed with an aluminum crimp overseal (3.2.P.7 Container Closure System)

Component	Description	Manufacturer/Supplier
Container	10 mL neutral colorless (b) (4) glass vial	(b) (4)
Closure	(b) (4) mm (b) (4) rubber stopper	
Overseal	20.3 mm Aluminum crimp seal	

***Note to Reviewer**: The 11/12/21 submission adds a new stopper to the THG Kit due to supply chain problems with the initial proposed stopper. The new (b) (4) stopper has the identical dimensions to the originally proposed stopper (11/12/21; P.7 p. 5/9). See Section P.3.5 below for depryogenation and sterilization review for both stoppers.

Reviewer's Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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NDA214993 Nephroscan –

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEPHROSCANTM safely and effectively. See full prescribing information for NEPHROSCAN

consulting for pediatric dosimetry

Reviewer: Kish Chakrabarti, Ph.D., FAAPM, DIRM/CDER

Introduction:

Indication for use:

NephroScan, after radiolabeling with technetium Tc 99m, is a radioactive diagnostic agent indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics.

Technetium Tc 99m is a pure gamma emitter with 140 keV energy peak and 6-h half-life. The radio diagnostic agent Tc99m DMSA binds to the cortical region of kidneys. Gamma scintigraphy is used to image the renal cortices for the detection of small focal lesions such as pyelonephritic scars.

Technetium Tc99m Succimer Injection (Tc99m DMSA Injection) was initially approved on 18 May 1982 (NDA 017944-MPI DMSA Kidney Reagent) for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults. The product was discontinued by the manufacturer (GE Healthcare [GEHC]) for commercial reasons. It was placed on the FDA Drug Shortage List on 15 October 2014. On 03 August 2017, the FDA granted Theragnostics Inc. (Theragnostics) permission to import DMSA drug product manufactured by ROTOP Pharmaka GmbH under the drug shortage program (Theragnostics Imported Kit).

Comments are on radiation dosimetry and lactation labeling:

(b) (4) Radiation Dosimetry

The recommended **pediatric dose** is 0.05 mCi/kg (1.85 MBq/kg) with a range of 0.5-2.0 mCi (19-74 MBq).
In adults, the recommended amount of radioactivity to be administered for renal parenchymal imaging is 2-6 mCi (74-222 MBq).

The estimated absorbed radiation doses for an average adult reported in the GE Kit PI, 2007. Similar radiation exposure is reported in the ROTOP DMSA PI, 2019 based on the International Commission on Radiological Protection (ICRP) publication 80.

(b) (4)

The sponsor **Theragnostics has not conducted biopharmaceutics studies with Tc99m DMSA** or any **dosimetry measurements using animal or human data**. Usually, 5 or more patients are used for average dose and standard deviations estimations. The calculated doses on weight and activity based on ICRP 80 are listed in the labeling.

Justification for accepting the protocol and labeling without dosimetry data:

This is a known radio tracer used as a **diagnostic agent** indicated as an aid for the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients. To remove this product from the Drug Shortages List, FDA recommended Theragnostics submit an NDA.

Theragnostics states that FDA has previously determined that Tc99m DMSA is safe and effective for this purpose in adults. The sponsor further states that extensive scientific literature on Tc99m DMSA demonstrates that Tc99m DMSA is also safe and effective for this indication in the pediatric population and is in fact clinically recognized as the diagnostic gold standard worldwide for both **pediatric and adult patients.**

The sponsor may thus be allowed to market the product without dose and biopharmaceutics study data.

As per ICRP 118 report, *"In the urinary tract, the kidneys are the most sensitive organ, and the bladder and the ureters are more resistant (deduced from radiotherapeutic experience, usually with 5 years of follow-up). The threshold dose for the human kidney is approximately 7–8 Gy acute dose, approaching 20 Gy for doses given as multiple 2-Gy fractions. For late reactions in the bladder and the ureters, the threshold total fractionated (2-Gy fractions) dose is _50 Gy."*

Therefore, for both adult and pediatric patients, the doses delivered are safe.

8.2 Lactation

Risk Summary

The sponsor states:

NRC Sub-Committee has adopted the widely used 0.1-rad dose limit in formulating guidelines for the discontinuation of breast feeding for lactating mothers. For 99mTc-labeled radiopharmaceuticals, rather than a radiopharmaceutical-specific interruption period. **a single 24-hour interruption period is recommended.**

References:

1. ICRP Publication 80 3.6.1
2. ICRP Publication 118
3. U.S. Nuclear Regulatory Commission, Regulatory Guide 8.39 Revision 1, Release of Patients Administered Radioactive Materials, April 2020, accessed May 11, 2020 via https://www.nrc.gov/docs/ML1923/ML19232A081.pdf.

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