CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214993Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 16, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214993
Product Name and Strength:	Nephroscan (kit for the preparation of technetium Tc 99m succimer injection), 1 mg per vial
Applicant/Sponsor Name:	Theragnostics Inc. (Theragnostics)
OSE RCM #:	2021-1025-3
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Theragnostics Inc. (Theragnostics) submitted revised Nephroscan vial container label, carton labeling, diagnostic activity label and syringe label received on February 8, 2022 for Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) under NDA 214993. We reviewed the revised vial container label, carton labeling, diagnostic activity label, and syringe label for Nephroscan (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made from the Agency via email on February 2, 2022.

2 CONCLUSION

Theragnostics Inc. implemented all of our recommendations and we have no additional recommendations at this time.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DEVIN R KANE
02/16/2022 01:06:22 PM

HINA S MEHTA
02/16/2022 03:46:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Imaging and Radiation Medicine (DIRM)

Subject: Review of pediatric labeling for the Kit for the Preparation of Technetium Tc99m Succimer Injection.[1]

Applicant: Theragnostics, Inc.[2]

Application number: NDA 214993

Drug: NephroScan

[1] This review will refer to the drug product as "NephroScan"

[2] This review will refer to "Theragnostics, Inc." as the "Applicant"

Drug Class: Radioactive Diagnostic Agent

Proposed Indication: Use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients

Proposed Dosage Form: Injection

Route of administration: Intravenous

Proposed Dosing Regimen: Adult patients: 2 – 6 mCi (74 - 222 MBq)
Pediatric patients: 0.05 mCi/kg (1.85 MBq/kg) with a range of 0.5 – 2 mCi (19 – 74 MBq)

Consult Request:
DIRM requests DPMH to provide recommendations for pediatric use information in labeling based on the data included in the NDA submission to support pediatric approval of this product.

Materials Reviewed:

- The following documents entered into DARRTS under NDA 214993, May 19, 2021
  - Agreed Initial Pediatric Study Plan (iPSP), Module 1.9.4 (eCTD #0)
  - Annotated Draft Labeling Text, Module 1.14.1.2 (eCTD #0)
  - Approved Labeling Text for Listed Drug, Module 1.14.3.2 (eCTD #0)
  - Clinical Overview, Module 2.5 (eCTD #0)
  - Summary of Clinical Efficacy, Module 2.7.3 (eCTD #0)
  - Summary of Clinical Safety, Module 2.7.4 (eCTD #0)
  - Integrated Summary of Safety, Module 5.3.5.3 (eCTD #0)
  - Integrated Summary of Efficacy, Module 5.3.5.3 (eCTD #0)

- The following documents entered into DARRTS under NDA 214993
  - Information Request to Applicant, dated September 7, 2021
  - Information Request to Applicant, dated July 30, 2021
  - DPMH Pediatrics Consult Form dated June 11, 2021

- The following documents entered into DARRTS under IND 145176
  - Type C Meeting Minutes dated June 6, 2009

I. Background

A. Renal Parenchymal Disorders:

Renal parenchymal disorders encompass a group of diseases and disease processes that lead to renal injury. The processes are divergent in etiology and may or may not lead to a progressive reduction in renal function. In common clinical practice, renal parenchymal disorders refer to diseases associated with abnormalities or injuries that potentially cause irreversible damage to the renal tubulo-interstitium. In the pediatric age range, the most common causes of renal parenchymal disorders are congenital abnormalities of the kidneys and urinary tract (CAKUT) and acquired renal tubulointerstitial injury from acute infection and inflammation due to pyelonephritis.

B. Non-Invasive Imaging for Renal Parenchymal Disorders:

The presence of congenital developmental abnormalities in one or both kidneys can be delineated by renal ultrasound. However, renal ultrasound provides for gross anatomic detail and does not have the ability to delineate either finer acquired anatomical abnormalities such as acute intraparenchymal inflammation nor renal scarring in one or both kidneys. In addition, renal ultrasound cannot provide information on functional assessments of renal function.

For non-invasive imaging delineation of renal functional activity, nuclear medicine modalities are used as important options. Within nuclear imaging, the three most commonly used nuclear imaging agents for renal parenchymal functional assessment are technetium mercaptoacetyltriglycine (^{99}Tc-MAG3), technetium diethylene-triamine-pentaacetate (^{99}Tc-DTPA), and technetium 2,3 dimercaptosuccinic acid (^{99}Tc-DMSA [Tc99m succimer]). Due to its efficient extraction and excretion by the renal proximal tubular epithelium, ^{99}Tc-MAG3 is the imaging agent of choice for evaluation of a dilated upper urinary tract to diagnose the presence of obstruction.[3] TECHNESCAN MAG3 (^{99}Tc-MAG3) approved under NDA 019882 is indicated for use in the diagnosis of congenital and acquired abnormalities, renal failure, urinary tract obstruction, and calculi in adults and pediatric patients. It is a diagnostic aid in providing renal function, split function, renal angiograms, and renogram curves for whole kidney and renal cortex.[4] Due to its efficient glomerular filtration but lower tubular extraction, DRAXIMAGE DTPA

[3] O'Reilly P, Aurell M, Britton K, et al. Consensus on diuresis renography for investigating the dilated upper urinary tract. Radionuclides in Nephrourology Group. Consensus Committee on Diuresis Renography. J Nucl Med. 1996; 37(11): 1872-6.

[4] Found under TECHNESCAN MAG3 at Drugs@FDA.gov

(^{99}Tc-DTPA) approved under NDA 018511 is indicated for renal visualization, assessment of renal perfusion, and estimation of glomerular filtration rate in adult and pediatric patients.[5] ^{99}Tc-DMSA is a nuclear imaging agent that binds to sulfhydryl groups in proximal convoluted tubular epithelial cells with longer retention than other nuclear imaging agents.[6] Therefore, ^{99}Tc-DMSA concentrates to a higher degree in renal tubular epithelium making it an ideal agent for detection of renal cortical scarring and differential tubular functional assessment. The relied-upon Listed Drug (LD), MPI DMSA (^{99}Tc-DMSA) approved under NDA 017944, is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults.[7] In clinical practice, evaluation of renal parenchymal disorders using ^{99}Tc-DMSA imaging includes:

1. Diagnosis of acute pyelonephritis (APN)
2. Identification of renal scarring (RS)
3. Assessment of relative functioning renal mass (e.g. split renal function)
4. Identification of solitary or ectopic renal tissue
5. Delineation of horseshoe and pseudo-horseshoe kidneys

II. NDA 214993

A. Drug Product:

NephroScan is a kit for the preparation of technetium Tc99m succimer injection, which is a radioactive diagnostic agent proposed as an aid for the scintigraphic evaluation of renal parenchymal disorders in both adult and pediatric patients.[8] It contains the same active ingredient, dosage form, strength, and route of administration as the relied-upon LD, MPI DMSA. The differences between NephroScan and the LD are in two inactive ingredients. NephroScan contains less ascorbic acid (b) (4) and does not contain inositol (b) (4)

[5] Found under DRAXIMAGE DTPA at Drugs@FDA.gov

[6] Willis KW, Martinez DA, Hedley-Whyte ET, et al. Renal localization of 99mTc-stannous glucophetonate and 99mTc-stannous dimercaptosuccinate in the rat by frozen section autoradiography. The efficiency and resolution of technetium-99m. Radiat Res 1977; 69(3): 475-88.

[7] Found under MPI DMSA at Drugs@FDA.gov

[8] Ibid

B. Listed Drug

The MPI DMSA Kidney Reagent Kit was initially FDA approved on May 18, 1982, for use as an aid in the scintigraphic evaluation of renal parenchymal disorders only in adults.[9] This Kit is not approved for use in the pediatric population, and the initial adult approval predated the 2003 enactment of the Pediatric Research Equity Act (PREA). On October 15, 2014, the NDA holder withdrew from sale this Kit for reasons other than safety or effectiveness.

Since August 3, 2017, the Kit for the Preparation of Technetium Tc99m Succimer Injection (manufactured by ROTOP Pharma and with Market Authorization in Germany (ROTOP Kit)) has been imported for use in the United States under the Drug Shortages Program. The ROTOP Kit contains the same active ingredients (b) (4) (b) (4) as the NephroScan Kit put forward in the current NDA under review. Under the Drug Shortages Program, (b) (4) vials of the ROTOP Kit have been distributed within the United States for use in pediatric and adult patients.

C. Regulatory History of NephroScan:

There are currently no FDA-approved radiographic diagnostic agents for the scintigraphic evaluation of renal parenchymal disorders in pediatric patients. NDA 214993 for NephroScan was submitted on May 19, 2021, for approval through the 505(b)(2) pathway, with MPI DMSA as the LD. As a drug product with a new dosing regimen proposed for pediatric patients, NephroScan is subject to PREA study requirements, and the Applicant is required to provide an assessment in the pediatric population.

The Applicant submitted an Agreed Initial Pediatric Study Plan (iPSP) with the NDA proposing to provide evidence of safety and efficacy for use in pediatric patients from birth to less than 18 years of age from published literature. The Agreed iPSP submitted with the NDA did not include a plan to request a waiver or deferral of studies in any pediatric age groups. To support a potential indication in pediatric patients, the Applicant submitted published studies in pediatric and young adult patients from birth to 24 years of age assessing the diagnostic accuracy of Tc99m DMSA in the diagnosis and evaluation of APN, RS, and split renal function. The Applicant established a scientific bridge to justify reliance on Tc99m DMSA by showing the similarity between NephroScan and Tc99m DMSA (b) (4) (b) (4) The analyses included assessment of percent agreement, sensitivity, and specificity for these diagnoses/evaluations relative to imaging standards (e.g. magnetic

[9] Ibid.

resonance imaging (MRI), intravenous urography (IVU), ultrasound (US), and MAG3) as comparators. To provide evidence of the safety of NephroScan in the proposed pediatric population, the Applicant relied, in part, on the Agency's previous finding of the safety for Tc99m DMSA, with additional supportive evidence from:

- Clinical studies reported in the published literature
- Post-marketing experience from GE Healthcare for the LD, MPI DMSA
- Experience with non-FDA-approved technetium Tc99m succimer injection products (e.g., ROTOP Kit), imported in the United States under the Drug Shortages Program

D. Proposed Pediatric Labeling for NephroScan

In the proposed labeling for NephroScan, the Applicant includes pediatric specific information in Section 1, 2, and 8. The Applicant proposes to include "pediatrics" in the previously approved indication limited to only adults in Section 1. In sub-section 2.3 of labeling, the Applicant proposes a weight-based dosing regimen for pediatric patients from birth to less than 18 years of age. The weight-based dosing table provided in this sub-section of the Applicant's proposed labeling is consistent with the Society of Nuclear Medicine and Molecular Imaging (SNMMI) Dosing Guidelines, last updated in 2016.[10] This weight-based dosing guideline was used with the LD and in continued use for pediatric dosing with the imported ROTOP Kit. Dosing in pediatric patients weighing more than or equal to 39 kg matches the lowest proposed dose for adults. The difference in injected radioactivity for the SNMMI dosing guidelines and the ROTOP Kit dosing is relatively greatest at the lowest pediatric weights, and as weight increases the difference becomes smaller. Simulated exposures of Technetium and its excipients across the pediatric age range are similar in pediatric patients of disparate age and weight despite the differences in injected activity due to weight-based dosing. In sub-section (b) (4) of the proposed labeling, the Applicant includes a table (e.g. Table 2) estimating the radiation absorbed dose per injection in various organs and body tissues in a 70 kg adult and pediatric patients aged 1, 5, 10, and 15 years. The table is taken from the imported ROTOP Kit labeling used under the Drug Shortage Program and is derived from the International Commission on Radiological Protection (ICRP) report.[11]

[10] Treves ST, Gelfand MJ, Fahey FH, Parisi MT. 2016 Update of the North American Consensus Guidelines for Pediatric Administered Radiopharmaceutical Activities. J Nucl Med. 2016; 57(12): 15N-18N.

[11] Radiation dose to patients from radiopharmaceuticals (addendum 2 to ICRP publication 53). Ann ICRP. 1998 ;28(3): 1-126.

Sub-section 8.4 of the proposed labeling includes the following language:

(b) (4)

III. Discussion

Published industry guidance on the incorporation of pediatric information into human prescription drug product labeling notes that inclusion of pediatric use information in relevant sections of labeling is required when data support use of a drug for a pediatric indication.[12,13] The labeling guidance recommends discussion of pediatric use information in the *Pediatric Use* sub-section (e.g. sub-section 8.4) and in other sections of labeling as appropriate.[14]

Proposed labeling relevant to the pediatric indication(s) anticipated to be approved by DIRM for NephroScan does not currently include detailed information in sub-section 8.4 (b) (4) from the submitted published studies providing supportive evidence for dosing, safety, and efficacy. Review of labeling in drug products with pediatric indication(s) approved, at least in part, from submission of published studies reveals inclusion of details of the pivotal published studies serving as the basis for approval provided in both sub-section 8.4 (b) (4)

IV. Conclusions

In general, the pediatric use information in labeling proposed by the Applicant for NephroScan is consistent with the content and format required under regulations and recommended in the pediatric labeling guidance. Ideally, information for labeling relevant to pediatric indication(s) should include a high-level summary of the basis for approval in sub-section 8.4 with cross-reference to more detailed information from data considered pivotal by the Division to support pediatric approval (b) (4)

[12] 21 CFR 201.57(c)(9)(iv)(B), (C), and (D).

[13] Found at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-information-incorporated-human-prescription-drug-and-biological-products-labeling-good.

[14] Ibid.

(b) (4)

a reasonable approach for NephroScan labeling is to provide a more detailed summary of the basis for approval of the pediatric indication from submitted published studies in sub-section 8.4. If the basis for approval relies on the extrapolation of efficacy from the approved adult indication with supportive evidence for dosing, safety, and efficacy from published literature, providing a description of the primary studies from which this evidence was drawn should be included in sub-section 8.4.

V. Recommendations:

DPMH recommends the following modifications for the pediatric relevant sections to the proposed NephroScan labeling:

- In sub-section 8.4, modify the pediatric use statement at the beginning of the subsection to mirror the language in the Indication statement in Section 1 of labeling.
- Given the lack of adequate and well-controlled trials supporting pediatric use of this product, describe the basis for pediatric approval in sub-section 8.4, using alternative language as permitted under 21 CFR 201.57(c)(9)(iv)(G) such as the following: “Use in the pediatric population is supported by…”.
- The basis for pediatric approval should ideally consist of language reflecting the pivotal data sources, analyses, or both that supported the proposed pediatric dosing, safety, and efficacy of the product. If the Division relied on extrapolation of efficacy established in adults from adequate and well-controlled trials, then this language should be conveyed in sub-section 8.4. If the Division relied on certain key publications and/or analyses of available published data/studies to support dosing and safety of NephroScan at the proposed dosing in the pediatric population, include a summary of these (patient populations, diseases/conditions evaluated) in sub-section 8.4. The number of studies submitted supporting the safety and efficacy of the proposed pediatric indication(s) should not be enumerated in sub-section 8.4.
- Include in sub-section 8.4 any pivotal statistical analyses conducted by DIRM on the submitted published studies that inform pediatric use and that served as an important basis for finding NephroScan to be safe and effective for the approved pediatric indication(s).
- Avoid references to “clinical experience” or “clinical practice guidelines” throughout labeling. Including recommendations from clinical practice guidelines in labeling is not consistent with the evidentiary standard required for approval of

drug and biological products. Furthermore, clinical practice guidelines may include recommendations that are not rooted in evidence from adequate and well-controlled studies when these studies do not exist for a particular topic within the disease under consideration. Additionally, both clinical experience and recommendations in clinical practice guidelines change over time. Clinical practice guidelines are regularly updated in many disease states as understanding of a disease and its treatment evolve. Including references to “clinical experience” and/or “clinical practice guidelines” in labeling may make labeling outdated and in need of regular revision as guidelines change. For these reasons, FDA-approved labeling should not include references to “clinical experience” or “clinical practice guidelines”.

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/s/

SHAMIR TUCHMAN
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MONA K KHURANA
02/09/2022 01:16:55 PM

JOHN J ALEXANDER
02/09/2022 05:25:11 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 28, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 214993
Product Name and Strength:	Nephroscan (kit for the preparation of technetium Tc 99m succimer injection), 1 mg per vial
Applicant/Sponsor Name:	Theragnostics Inc. (Theragnostics)
OSE RCM #:	2021-1025-2
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Theragnostics Inc. (Theragnostics) submitted revised Nephroscan carton labeling (back panel) received on January 26, 2022 for Nephroscan (kit for the preparation of technetium Tc99m succimer injection) under NDA 214993. We reviewed the revised carton labeling (back panel) for Nephroscan (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations made via email on January 11, 2022 to update the manufacturer's information on the back panel of the proposed carton labeling.

2 CONCLUSION

Theragnostics Inc. implemented all of our recommendations and we have no additional recommendations at this time.

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/s/

DEVIN R KANE
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HINA S MEHTA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 6, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214993
Product Name and Strength:	Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) 1 mg per vial
Applicant/Sponsor Name:	Theragnostics Inc. (Theragnostics)
OSE RCM #:	2021-1025-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Theragnostics Inc. (Theragnostics) submitted revised Nephroscan kit vial label, carton labeling, diagnostic label, and syringe label received on December 21, 2021 for Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) under NDA 214993. We reviewed the revised kit vial label, carton labeling, diagnostic label, and syringe label for Nephroscan (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kane, D. Label and Labeling Review for Nephroscan (NDA 214993). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 13. RCM No.: 2021-1025.

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HINA S MEHTA
01/07/2022 05:21:08 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/23/21

To: Modupe Fagbami**,** Regulatory Project Manager, Division of Medical Imaging Products (DMIP)

From: James Dvorsky, Team Lead
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for NephroScan (kit for the preparation of technetium Tc99m succimer injection)

NDA: 214993

In response to DMIP's consult request dated 6/11/21, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for NephroScan.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DMIP on 12/22/21 and have no comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on 12/21/21, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact James Dvorsky at (301) 796-2655 or james.dvorsky@fda.hhs.gov.

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/s/

JAMES S DVORSKY
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
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Food and Drug Administration
Silver Spring, MD 20993
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Division of Pediatrics and Maternal Health Review

Date: October 15, 2021 **Date consulted:** June 11, 2021

From: Catherine Roca, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health (DPMH)

To: Division of Imaging and Radiation Medicine (DIRM)

Drug: NEPHROSCAN (Kit for the Preparation of Technetium Tc99m Succimer Injection)

NDA: 214993

Applicant: Theragnostics, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214993
- DPMH Consult Request dated June 11, 2021. DARRTS Reference ID 4810215

- DPMH Consult Review Kit for the Preparation of Technetium Tc99m Exametazime Injection, NDA 208870, Carrie Ceresa, Pharm D., MPH, Clinical Analyst, March 29, 2017. DARRTS Reference ID 4076476[1]
- DPMH Consult Review for Draximage DTPA (Kit for preparation of technetium Tc99m Injection, NDA 18511, Carrie Ceresa Pharm D., MPH, November 13, 2017. DARRTS Reference ID 4180141.[2]
- DPMH Consult Review Technegas (technetium Tc99m) labeled carbon aerosol for inhalation, Jane Liedtka, MD, Medical Officer, November 16, 2020. DARRTS Reference ID 4702466[3]

Consult Question: Provide assistance with labeling.

INTRODUCTION AND BACKGROUND

On May 19, 2021, Theragnostics, Inc. submitted a new 505(b)(2) NDA for NEPHROSCAN (Kit for the Preparation of Technetium Tc99m Succimer Injection) for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics. DIRM consulted DPMH on June 11, 2021 to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- NEPHROSCAN (Technetium Tc99m Succimer Injection) is a 505(b)(2) application that relies on the safety and efficacy data referenced in MPI DMSA Kidney Reagent NDA 017944, which was approved for use in the United States on May 18, 1982 as an aid in the scintigraphic evaluation of renal parenchymal disorders. MPI DMSA Kidney Reagent was discontinued from marketing by the manufacturer, for reasons other than safety issues. On October 15, 2014, Technetium Tc99m Succimer injection (DMSA) was placed on the FDA Drug Shortage List. On August 3, 2017, FDA granted Theragnostics Inc., permission to import DMSA drug product under the drug shortage program.
- On May 19, 2021, pursuant to the FDA's recommendation, Theragnostics submitted the 505(b)(2) NDA to obtain approval for NEPHROSCAN.
- NEPHROSCAN was granted priority review on June 2, 2021

DPMH has conducted reviews for three previous radiolabeled technetium Tc99m products. See these reviews (noted above under "Materials Reviewed") for "Drug Characteristics," "Radiation Units and Conversions," "Radiation Exposure and Pregnancy," "Guidelines on Radiopharmaceuticals and Pregnant Women, American College of Radiology (ACR)," "Case Reports of Exposures to Technetium during Pregnancy," and literature review up to November 16, 2020 in PubMed.

[1] The Kit for the Preparation of Technetium Tc99m Exametazime Injection review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.
[2] The Draximage DTPA (Kit for preparation of Technetium Tc99m Injection review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.
[3] The Technegas (Technetium Tc99m) labeled carbon aerosol for inhalation review was part of the materials reviewed but was not a source relied upon for the labeling recommendations below.

Evaluation of Kidney Disease During Pregnancy[4]

Parenchymal kidney disease can occur from acute conditions, such as pyelonephritis, or be the result of scarring from chronic kidney disease. Acute kidney disease or injury during pregnancy is uncommon in high-income countries. Radionucleotide studies using technetium Tc99m succimer provide visualization of focal renal parenchymal abnormalities and assessment of a difference of kidney function between the two kidneys; it is not used often in the evaluation of renal disease in adults. However, it is commonly used in the evaluation of pediatric renal disease, since it has less radiation exposure than CT scanning.

According to the American College of Radiology Practice Parameters for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation,[5] all radiopharmaceuticals used for diagnostic purposes (except potentially Iodine-131) have short half-lives and low administered activities that result in low radiation risks and expose the fetus to less than 0.50 mGy. The practice parameters do not require routine pregnancy testing prior to performing renal scans with technetium Tc99m.[6]

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been conducted with Technetium Tc99m succimer injection.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature through July 2021 using the PubMed database and the search terms, "technetium Tc99m," and "pregnancy," "maternal," and "fetal." The result of the search was three relevant papers noted in the Applicant's Table 2 below. (Note that the included publications also include one pertaining to lactation.)

[4] UpToDate, "Radiologic assessment of renal disease," and "Acute kidney injury in pregnancy." accessed September 2, 2021.

[5] ACR-SPR Practice Parameter for Imaging Pregnant of Potentially Pregnant Adolescents and Women with Ionizing Radiation. Revised 2018 (Resolution 39), pp1-23.

[6] ACR-SPR Practice Parameter for Imaging Pregnant of Potentially Pregnant Adolescents and Women with Ionizing Radiation. Revised 2018 (Resolution 39), p5. Table 2.

Table 2 Summary of Publications Reviewed

Article Country	Study Design	No. Exposed / Unexposed	Results and Conclusions
Stabin and Breitz, 2000 Brazil/USA	Theoretical study based on literature results evaluating breast milk.	N/A	Based on all the data, peak concentration in breast milk is 3 hours post-injection. If activity is found, it is most likely free pertechnetate (unchelated). Table 3 provides estimated possible infant radiation doses from ingestion of radiopharmaceuticals. Refer to Section 1.1.1.1 for additional information.
Saunders et al., 2002 United Kingdom	Theoretical study based on data derived from nonclinical studies evaluating fetal development.	N/A	Most of activity from Tc99m DMSA in Stage 3 fetal organs came from maternal organs as there was only 0.14% placental transfer. At Stage 1, 0.007% of DMSA activity was translocated to fetus, though that increased slightly over the measurement period. Maternal bladder contributed 43.3% to total fetal body dose at Stage 1, and 25.7% at Stage 3. Refer to Section 1.1.1.2 for additional information. 2.7.2 Summary of Clinical Pharmacology Studies, Table 23 provides calculations to the fetus at first and third trimester.
Balan et al., 1997 United Kingdom	Retrospective (fetal development)	82 pregnant women to 40 MBq of Tc99m MAA. Those with abnormal scan also received Tc99m carbide.	Calculated uterine radiation dose was 6.3 mGy/MBq (0.2 mSv) and 3 mGy/MBq (0.3 mSv) for V/Q, respectively. The total fetal dose values were calculated to be below the threshold value for severe mental retardation. Refer to Section 1.1.1.3 for additional information.

Abbreviations: DMSA = dimercaptosuccinic acid; MAA = macroaggregated albumin; N/A = not applicable; No. = number of; Tc99m = technetium 99m; USA = United States of America; V/Q= ventilation-perfusion.

The above table is taken from the Applicant's Efficacy Information Amendment, dated July 28, 2021, page 4.

Reviewer's Comments:

The studies located by the applicant have been previously reviewed by DPMH. One paper was related to lactation and will be reviewed in the lactation section of this review. The paper by Saunders[7] was a theoretical model, with no cases of infant exposure. Only one paper included infant exposures; no adverse pregnancy outcomes were reported. However, as noted in the American College of Radiology Practice Parameters for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation,[8] radiation exposure to the fetus is very low (less than 0.50 mGy), such that the practice parameters do not require routine pregnancy testing prior to performing renal scans with technetium 99m.[9]

[7] Saunders M, et al. Model-based comparison of maternal and foetal organ doses from 99m Tc pertechnetate, DMSA, DTPA, HDP, MAA and MAG3 diagnostic intakes during pregnancy. Eur J Nucl Med. 2002.29:1365-1373.
[8] ACR-SPR Practice Parameter for Imaging Pregnant of Potentially Pregnant Adolescents and Women with Ionizing Radiation. Revised 2018 (Resolution 39), pp1-23.
[9] ACR-SPR Practice Parameter for Imaging Pregnant of Potentially Pregnant Adolescents and Women with Ionizing Radiation. Revised 2018 (Resolution 39), p5. Table 2.

DPMH Review of the Literature
DPMH performed a search of the published literature from November 2020 until September 2021 to update previous DPMH literature reviews. The PubMed and Embase databases were queried using the following search terms, "technetium Tc99m," and "pregnancy," "spontaneous abortion," "stillbirth," "congenital malformations," and "pregnancy outcomes."
No new relevant publications were located in the search.

Studies reviewed in previous DPMH consults indicate that data on pregnancy outcomes following technetium Tc99m exposure are insufficient to determine a drug-associated risk of spontaneous abortion or major birth defects. A case report found in previous reviews indicated that technetium Tc99m crosses the placenta and is taken up by the fetal liver with smaller amounts in the abdomen likely due to biliary excretion.[10]

LACTATION
Nonclinical Experience
Information was not provided regarding the presence of technetium Tc99m in animal milk.

Review of Literature
Applicant's Review of the Literature
The Applicant performed a search of the published literature through July 2021 using the PubMed database and the search terms, "technetium Tc99m," and "lactation." The search resulted in one paper that is briefly described in the Applicant's Table 2 (above, under the pregnancy subheading).

DPMH Review of Literature
DPMH has conducted reviews for three previous technetium Tc99m products. See these reviews (noted under "Materials Reviewed") for information regarding technetium Tc99m use and lactation including input from LactMed[11] and several Radiology Regulatory Associations. The recommendations varied somewhat from "No need to interrupt breastfeeding" to a recommendation for a "12-24 hour interruption depending on the dose used." DPMH conducted a new review of published literature using PubMed regarding technetiumTc99m and breastfeeding and lactation from 2020 through August 2021.

No new relevant publications were identified in the search.

Hale's[12] rates technetium Tc99m succimer as, L3-limited data-probably compatible, and makes reference to requiring only a 4-hour interruption with technetium Tc99m succimer (DMSA):

[10] Maguire C, et al. Hepatic uptake of technetium-99m HM-PAO in a fetus. J Nuclear Med. 1990;31:237-239.
[11] http://toxnet nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[12] Hale's Medications & Mothers' Milk (halesmeds.com), accessed September 2, 2021.

"The American Academy of Pediatrics (AAP) and the International Commission on Radiological Protection recommend different periods of breastfeeding cessation depending on which formulation of Tc-99m is used (see list below).[13, 14,15]

For the following salts do not breastfeed for 4 hours:
DMSA, DTPA, DISDA, ECD, Gluconate, Glucoheptonate, HM-PAO, Sulfur Colloids, MAG3, MIBI, PYP, phosphonates (MDP)< Technegas, tetrofosmin."

Reviewer comment:
Previous DPMH reviews (in consultation with clinical pharmacology) for technetium Tc99m products have recommended withholding breastfeeding for 4 hours. However, during the labeling discussions with the Division, the health physicist noted that the recommendations have been revised by the Advisory Committee on Medical Uses of Isotopes Subcommittee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials.[16] Current guidelines recommend the following: "For 99mTc-labeled radiopharmaceuticals, rather than radiopharmaceutical-specific interruption period, a single 24-hour interruption period is recommended." Labeling will be revised to align with current guidelines.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No reproductive studies in animals were performed.

Review of Literature

Applicant's Review of the Literature

The Applicant performed a search of the published literature through July 2021 using the PubMed database and the search terms, "technetium Tc99m," and "fertility, "male fertility," or "female fertility."

No relevant studies were found in the search.

DPMH Review of the Literature

DPMH performed a search of the published literature November 2020 until September 2021 to update previous DPMH literature reviews. The PubMed and Embase databases were queried using the following search terms, "technetium Tc99m," and "fertility," "infertility," and "hormonal contraception."

No new relevant publications were located in the search.

[13]Sachs HC, Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: and update on selected topics. Pediatrics. 2013:132(3):e796-809.
[14] International Commission on Radiologic Protection. Annex D. Recommendations on breast-feeding interruptions. Annals of the ICRP. 2008;38(1-2):163-84.
[15] Stabit MG. Radiating dose concerns for the pregnant and lactating patient. Semin Nucl Med. 2014;44:479-88.
[16] Dilsizian V, et al. Advisory Committee on Medical Uses of Isotopes (ACMUI) Subcommittee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials, final report submitted Jan. 31, 2019.

Reviewer comment:
The Applicant performed an adequate search of the literature. No relevant data were found in any of the literature searches.

DISCUSSION AND CONCLUSIONS

Pregnancy

The findings from the available data found in published literature with technetium Tc99m succinate and use in pregnant women are insufficient to evaluate for a drug-associated risk for major birth defects or miscarriage, however, radiation exposure to the fetus from technetium Tc99m succimer is expected to be low (less than 0.50 mGy). No adverse fetal effects have been identified for diagnostic procedures that involve exposure to less than 50 mGy.

Technetium Tc99m succinate was originally approved in 1982, so it is likely that there have been a number of fetal exposures since that time, yet there are few published adverse events reported. A pregnancy registry is not recommended.

Lactation

Limited date from case reports indicate that technetium Tc99m is present in breast milk. Technetium Tc99m succinate is used for renal imaging in infants; exposure to the infant via breast milk is expected to be lower. However, exposure of a breastfed infant to radiation from technetium Tc99m can be minimized by discontinuing breastfeeding for 24 hours according to current guidelines. Instructions for discontinuing breastfeeding and pumping and discarding of breastmilk for a minimum of 24 hours will be included in labeling.

Females and Males of Reproductive Potential

There are no human or animal data available on the effects of technetium Tc99m succinate on fertility or the effects on hormonal contraception. Practice parameters for technetium Tc99m succinate do not require pregnancy testing or contraception. This subsection will not be included in labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------USE IN SPECIFIC POPULATIONS----------

- Lactation*:* Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for at least 24 hours after technetium Tc99m succimer injection administration. (8.2)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with technetium Tc99m succimer injection use in pregnant women are insufficient to evaluate for a drug-associated risk for major birth defects and miscarriage. Animal reproduction studies with technetium Tc99m succimer have not been conducted. Although all radiopharmaceuticals have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose, the radiation exposure to the fetus from technetium Tc99m succimer is expected to be low (less than 0.50 mGy) *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Human Data

No adverse fetal effects of radiation risks have been identified for diagnostic procedures involving less than 50 mGy, which represents less that 10mGy fetal doses.

8.2 Lactation

Risk Summary

Technetium Tc99m succimer is present in breast milk. There are no data on the effects of technetium Tc99m succimer on the breastfed infant or the effects on milk production. Technetium Tc99m succimer has been used used for imaging infants with renal disease; exposure via breastmilk is expected to be lower. Based on clinical guidelines, exposure of technetium Tc99m succimer to a breastfed infant may be minimized by advising a lactating woman to temporarily breastfeeding and to pump and discard breast milk for a minimum of at least 24 hours after administration of technetium Tc99m succimer injection. The developmental and health benefits of breastfeeding should be considered along with a mother's clinical need for technetium Tc99m succimer injection, any potential adverse effects on the breastfed child from technetium Tc99m succimer injection or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

Lactation

Advise a lactating woman to temporarily discontinue breastfeeding and to pump and discard breast milk for at least 24 hours after technetium Tc99m succimer injection administration to minimize radiation exposure to the breastfed infant. *[see Use in Specific Populations (8.2)]*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHERINE A ROCA
10/15/2021 09:47:15 AM

MIRIAM C DINATALE
10/15/2021 10:52:32 AM

LYNNE P YAO
10/22/2021 09:18:19 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 13, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214993
Product Name, Dosage Form, and Strength:	Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) 1 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Theragnostics Inc. (Theragnostics)
FDA Received Date:	May 19, 2021
OSE RCM #:	2021-1025
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Theragnostics Inc. (Theragnostics) submitted a 505(b)(2) application under NDA 214032 for Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) on May 19, 2021. Nephroscan, after radiolabeling with technetium Tc 99m, is a radioactive diagnostic agent proposed for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics. We evaluated the proposed Nephroscan prescribing information (PI), vial container label, carton labeling, diagnostic label, and syringe label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

NDA 214993 relies upon the listed drug MPI DMSA Kidney Reagent (kit for the preparation of technetium Tc 99m succimer injection) which was approved under NDA 017944 on May 18, 1982. NDA 017944 is discontinued per Drugs@FDA and was previously marketed in single-dose vials containing 1 mg of dimercaptosuccinic acid. The proposed product will be available in the same presentation as the reference product.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Theragnostics Inc. (Theragnostics) submitted a 505(b)(2) application to obtain marketing approval of Nephroscan (kit for the preparation of technetium Tc 99m succimer injection) on May 19, 2021. We note the proposed Nephroscan product has the same active ingredient (kit

for the preparation of technetium Tc 99m succimer), strength (1 mg) in single dose vials, dosage form (for injection), route of administration (intravenous), recommended dose (74 MBq to 222 MBq (2 mCi to 6 mCi)), preparation steps, and beyond use time following reconstitution (4 hours) as the reference listed drug, MPI DSMA Kidney Reagent. We note MPI DSMA Kideny Reagent (NDA 017944) it is not currently marketed by the Sponsor, GE Healthcare Inc.

We performed a risk assessment of the proposed prescribing information (PI), vial container label, carton labeling, diagnostic label, and syringe label for Nephroscan to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI, container label, carton labeling, diagnostic label, and syringe label for Nephroscan identified areas of vulnerability that may lead to medication errors. For the Division we recommend using the same units and unit presentations throughout the PI. For the Applicant we recommend defining the format of the expiration date, aligning the information presented on the container label, carton labeling, diagnostic label, and syringe label with the information in the PI for consistency, and including a recommended dosage statement. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Nephroscan prescribing information (PI), vial container label, carton labeling, diagnostic labeling, and syringe label identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Theragnostics Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We note the use of the symbol "-" in order to represent the word "to" for the recommended dosage ranges. We recommend removing the use of the symbol and replacing it with its intended meaning of "to".

b. As currently presented, there are numeric values presented without being immediately followed by the appropriate units. We recommend including the appropriate units after all numeric values in order to prevent any confusion.

c. We note the recommended dosing ranges are presented in terms of millicuries with the megabecquerel equivalent values presented in parenthesis. We recommend displaying the recommended dosages in terms of megabecquerels with the millicurie equivalent values presented

in parenthesis to prevent confusion and for consistency with other products.

d. As currently presented, the second bullet under dosage and administration states "Instruct patients to drink a sufficient amount of water before administration (b) (4) . We recommend removing this bullet from the highlights of dosage and administration as this information is not needed here.

2. Dosage Forms and Strengths

a. We note there are numeric values greater than 1,000 that are presented without the use of a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the value. Revise "1480" to read "1,480".

b. As currently presented, the strength is presented in terms of millicuries with the megabecquerel equivalent values presented in parenthesis. We recommend displaying the strength in terms of megabecquerels with the millicurie equivalent values presented in parenthesis.

c. We note the highlights of dosage forms and strengths only contains information regarding the reconstituted vial of Nephroscan. We recommend revising this section to read "Nephroscan single-dose vials contains 1 mg meso-dimercaptosuccinic acid as a lyophilized powder. Upon radiolabeling with sodium pertechnetate Tc 99m, it provides a 5 mL solution with up to 1,480 MBq (40 mCi) of technetium Tc 99m succimer at calibration date and time.".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. We note the use of the symbol "-" throughout Section 2 to represent the word "to". We recommend removing the use of the symbol throughout Section 2 and replacing it with its intended meaning of "to".

b. As currently presented, numeric values are presented in Section 2 without being followed by their respective units. We recommend including the appropriate units after all numeric values presented in Section 2.

c. We note the use of trailing zeros used in Section 2. We recommend removing the use of trailing zeros in order to avoid ten-fold misinterpretation of numeric values.

d. We note Section 2.3 provides the recommended dosage for Nephroscan for adult and pediatric patients in terms of millicuries with the megabecquerel equivalent value in parenthesis. We recommend

displaying the recommended dosage of Nephroscan for adults and pediatric patients in terms of megabecquerels with the millicurie equivalent value in parenthesis to prevent confusion and consistency with other products.

e. As currently presented, Section 2.4 Drug Preparation contains the information [redacted] (b) (4) We recommend removing this information from Section 2.4 as it is not necessary to be presented here.

f. We note in step (d) of the preparation instructions under Section 2.4 the units “GBq” (gigabecquerel) are used, whereas the units “MBq” (megabecquerel) are used in the rest of the PI. We recommend presenting the values in terms of “MBq” instead of in “GBq”. Revise “1.48 GBq” to read “1,480 MBq”.

g. We note step (g) of the preparation instructions under Section 2.4 states to [redacted] (b) (4) We recommend including the approved room temperature range in order to avoid any confusion.

h. We note the use of the symbol “µ” in Section (b) (4) to represent “micro” for “microliters”. We recommend removing the use of the symbol and replacing it with its intended meaning of “micro”. We recommend presenting the units for “microliters” as “microL”.

i. As currently presented in Section (b) (4) temperature values are presented in terms of degrees Celsius without being followed by the Fahrenheit equivalent value in parenthesis. We recommend providing the Fahrenheit equivalent value in parenthesis after all Celsius temperatures.

2. Section 3: Dosage Forms and Strengths

a. As currently presented, the dosage form of Nephroscan is not provided in Section 3. We recommend including the dosage form as the first piece of information in Section 3. Revise to read:

b. We recommend revising Section 3 Dosage Forms and Strengths to read:

“Nephroscan is supplied as a single-dose vial containing a lyophillized powder of 1 mg meso-dimercaptosuccinic acid, 0.42 mg stannous chloride dihydrate, 0.1 mg ascorbic acid, 0.2 mg sodium hydroxide, and 0.02 mg hydrochloric acid. After reconstitution and radiolabeling with technetium Tc-99m, the vial contains 5 mL of a sterile solution of technetium Tc-99m succimer injection with a strength up to 1,480 MBq (40 mCi) of technetium Tc 99m succimer at calibration date and time.”.

3. Section 16: How Supplied/Storage and Handling

a. We recommend including subheadings in Section 16 in order to increase the prominence of the important information provided in the section. We recommend including one subheading for "How Supplied" for how supplied information and one subheading for "Storage and Handling" for the storage and handling information.

b. We note Section 16 lacks a description of the contents of each Nephroscan vial, as well as a physical description of the product. We recommend revising the first part of the section to read "Nephroscan is supplied as single-dose vial for the preparation of technetium Tc 99m succimer. Each vial contains 1 mg meso-dimercaptosuccinic acid, 0.42 mg stannous chloride dihydrate, 0.1 mg ascorbic acid, 0.2 mg sodium hydroxide, and 0.02 mg hydrochloric acid as a lyophillized powder. Nephroscan vials are supplied in cartons with 5 vials per carton (NDC 71083-0020-5).".

c. As currently presented, Section 16 contains the statement (b) (4) Additionally, Section 16 also contains the statement (b) (4) (b) (4) We recommend removing these statements as they are not required in this section of the PI.

d. We note the radionuclide is not supplied with the Nephroscan vials. We recommend including the statements "The radionuclide is not part of the carton. Before reconstitution and radiolabeling with Tc-99m, the contents of this kit are not radioactive" underneath the how supplied information.

e. We note the use of the symbol "-" to represent the word "to" in the storage information. We recommend removing the use of the symbol and replacing it with its intended meaning of "to". Additionally, we note there are numeric values presented in the storage information that are not immediately followed by their respective units. We recommend including the appropriate units after all numeric values.

f. As currently presented, the first line of the storage information reads (b) (4) We recommend revising these statements to read "Store Nephroscan at 2° to 8°C (36° to 46°F) in original carton. Do not freeze."

g. We note after reconstitution and radiolabeling Nephroscan is to be stored (b) (4) We recommend revising this information to read "After reconstitution and radiolabeling [*see Dosage and Administration (2)*], store technetium Tc 99m succimer injection upright with appropriate shielding to protect from radiation at 20° to 25°C (68° to 77°F, excursions permitted to 15° to

30°C [59° to 86°F]) (see USP Controlled Room Temperature). Do not use and discard 4 hours after reconstitution".

4.2 RECOMMENDATIONS FOR THERAGNOSTICS INC.

We recommend the following be implemented prior to approval of this NDA:

A. Vial Container Label

1. We note the use of a trailing zero on the proposed vial container label for the amount of dimercaptosuccinic acid in each vial. We recommend removing the use of trailing zero. Revise "1.0 mg" to "1 mg".
2. Consider revising the statement "Single-Dose Vial" to read "Single-Dose Vial. Discard Unused Portion" to minimize risk of the entire contents of the vial being given as a single dose.
3. As currently presented, the proposed vial container label reads (b) (4) We recommend revising these statements to read "For intravenous use only after radiolabeling with Sodium Pertechnetate Tc 99m Injection (USP)".
4. We note the proposed vial container label contains a placeholder for the expiration with a proposed format of "mmmyyyy". FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

B. Carton Labeling

1. We note the use of a trailing zero on the proposed principal display panel and back panel of the carton labeling for the amount of dimercaptosuccinic acid in each vial. We recommend removing the use of trailing zero. Revise "1.0 mg" to "1 mg".
2. As currently presented, the proposed principal display panel of the carton labeling reads (b) (4) We recommend revising these statements to read "For intravenous use only after rradiolabeling with Sodium Pertechnetate Tc 99m Injection (USP)".
3. We note the statement (b) (4) is presented on the principal display panel of the proposed carton labeling. We recommend revising this statement to read "5 Single-Dose Vials. Discard Unused Portion".

4. As currently presented, the storage information presented on the proposed back panel of the carton labeling does not align with the storage information presented in the proposed prescribing information (PI). We recommend revising the storage information presented on the back panel of the carton labeling to align with the information presented in the PI. Revise to read "Store refrigerated at 2° to 8°C (36° to 46°F) in original carton. Do not freeze.
   After reconstitution and radiolabeling, store upright in appropriate shielding to protect from radiation, at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C [59° to 86°F]) (see USP Controlled Room Temperature). Do not use and discard 4 hours after reconstitution.".
5. We note the statement (b) (4) (b) (4) We recommend revising this statement to read "Recommended Dosage: See Prescribing Information.".
6. We note the proposed back panel of the carton labeling contains a placeholder for the expiration with a proposed format of "mmmddyyyy". FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a slash or a hyphen be used to separate the portions of the expiration date.

C. Diagnostic Label

1. We note the proposed diagnostic label states (b) (4) We recommend revising this statement to read "See Prescribing Information before use".
2. As currently presented, the "Rx Only" statement (b) (4) (b) (4) We recommend (b) (4) the "Rx Only" statement (b) (4) and prominently displaying the statement on its own line.
3. We note the storage information presented on the proposed diagnostic label differs from the information presented in the prescribing information. We recommend revising the storage information to align with the storage information presented in the prescribing information. Revise the storage information to read "Store upright in appropriate shielding to protect from radiation, at 20° to 25°C (68° to 77°F, excursions permitted to 15° to 30°C [59° to 86°F]) (see USP Controlled Room Temperature). Use within4 hours".
4. We note the placeholder line (b) (4) We recommend revising this line to read "Discard After: _____Time _____Date".

5. We note the placeholder line for [redacted] Since [redacted] is not defined elsewhere on the label, we recommend spelling out [redacted] We recommend revising this line to read [redacted]

D. Syringe Label

1. We note that Nephroscan must be used within 4 hours of reconstitution. We recommend including this information on the syringe label. Revise the syringe label to include the statement "Do not use and discard 4 hours after reconstitution".

2. As currently presented, the proposed syringe label contains the statement [redacted] We recommend revising this statement to read "See prescribing information before use".

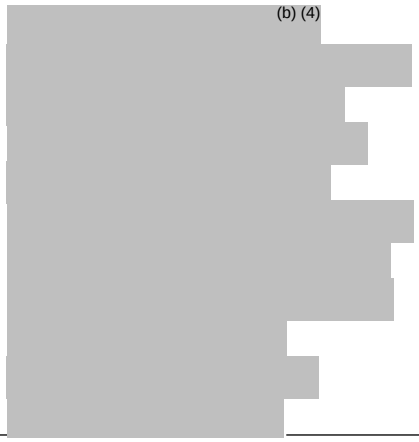
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nephroscan received on May 19, 2021 from Theragnostics Inc., and the listed drug (LD).

Table 2. Relevant Product Information for Nephroscan and the Listed Drug		
Product Name	Nephroscan	MPI DMSA Kidney Reagent[a] (NDA 017944)
Initial Approval Date	N/A	May 18, 1982
Active Ingredient	kit for the preparation of technetium Tc 99m succimer injection	
Indication	To be used as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatric patients.	
Route of Administration	Intravenous	
Dosage Form	For Injection	
Strength	1 mg	
Dose and Frequency	Adults: 74 MBq to 222 MBq (2 mCi to 6 mCi) administered as an intravenous bolus injection. Pediatric: 0.05 mCi/kg of body weight (1.85 MBq/kg) with a range of 19 MBq to 74 MBq (0.5 mCi to 2 mCi) administered as an intravenous bolus injection.	The suggested dose range for slow I.V. administration to be employed in the average patient (70 kg) for renal parenchymal imaging is 74 MBq to 222 MBq (2 mCi to 6 mCi) technetium Tc99m succimer injection.
How Supplied	5 vial carton containing Single-dose vials of 1 mg meso-dimercaptosuccinic acid, 0.42 mg stannous chloride dihydrate, 0.1 mg ascorbic acid, 0.2 mg sodium hydroxide, and 0.02 mg hydrochloric acid.	Vials containing a freeze-dried mixture of 1 mg dimercaptosuccinic acid, 0.42 mg stannous chloride dihydrate [0.38 mg (minimum) stannous chloride dihydrate ($SnCl \cdot 2H_2O$) and 0.46 mg (maximum) total tin expressed as stannous chloride dihydrate ($SnCl \cdot 2H_2O$)], 0.7 mg ascorbic acid, and 50 mg inositol.

[a] MPI DSMA Kidney Reagent [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 JUL 14. Available from: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

Storage	(b) (4)  (b) (4) 	Store the kit at 2° to 8°C (36° to 46°F) and protect from light.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Nephroscan labels and labeling submitted by Theragnostics Inc..

- Vial Container Label received on May 19, 2021
- Carton Labeling received on May 19, 2021
- Diagnostic Label received on May 19, 2021
- Syringe Label received on May 19, 2021
- Prescribing Information (Image not shown) received on May 19, 2021, available from \\CDSESUB1\evsprod\nda214993\0000\m1\us\draft-labeling-text.pdf

G.2Label and Labeling Images

- Vial Container Label

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

DEVIN R KANE
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