CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214993Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 145176

MEETING MINUTES

Theragnostics Inc.
Attention: Sarah DeMare
Product Development Champion
Facet Life Sciences, Inc., US Agent Contact for Theragnostics
6122 Stone Wolfe Dr.
Glen Carbon, IL 62034

Dear Ms. DeMare:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Technetium Tc99m Succimer Injection.

We also refer to the meeting between representatives of your firm and the FDA on October 1, 2019. The purpose of the meeting was to discuss and gain Agency's concurrence on the content and format of the proposed 505(b)(2) NDA.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at 301-796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND

Meeting Date and Time: October 1, 2019 at 3:30 pm
Meeting Location: WO, Building 22, Conference Room 1309

Application Number: PIND 145176
Product Name: Technetium Tc-99m Succimer Injection

Indication: For use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics
Sponsor Name: Theragnostics Inc. represented by in the US by Facet Life Sciences

Meeting Chair: Libero Marzella, M.D., Ph.D.
Meeting Recorder: Modupe Fagbami, Regulatory Project Manager

FDA ATTENDEES
Libero Marzella, M.D., Ph.D., Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
August Hofling, M.D., Ph.D., Clinical Team Leader, DMIP
Stephanie Coquia, M.D., Clinical Reviewer, DMIP
Jonathan Cohen, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Jagjit Grewal, Policy Advisor, OND Policy Staff, OMPT/CDER/OND
Ravindra Kasliwal, Ph.D., CMC Reviewer; OPQ/ONDP/DNDPII/NDPBVI
Carattini Maritere, Ph.D., CMC Micro Reviewer, OMPT/CDER/OPQ/OPF/DMA/MABIII
Haber Martin, Ph.D., CMC Reviewer, OMPT/CDER/OPQ/ONDP/DNDAPI/NDBII
Amy Taylor, M.D., Medical Officer, OMPT/CDER/OND/ODEIV/DPMH
Okpo Eradiri, Ph.D., Branch Chief, OMPT/CDER/OPQ/ONDP/DB/BBII
Leo Zadecky, R.Ph., M.S., Drug Shortage Staff; OMPT/CDER/OCD/DSS
Anissa Davis-Williams, R.N., B.S.N., M.P.H. RPM, OMPT/CDER/OND/ODEIV/DPMH
Modupe Fagbami, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES:

Greg Mullen, Ph.D., CEO and President, Theragnostics Inc. / Theragnostics Ltd.
Dana Blue, Regulatory Consultant to Theragnostics Inc., Facet Life Sciences
Sarah DeMare, US Agent Contact and Regulatory Consultant to Theragnostics Inc., Facet Life Sciences
(b) (4) Consultant to Theragnostics (b) (4)

BACKGROUND:

The Sponsor, Theragnostics Inc. requested this Type B, Face to Face meeting through Facet Life Sciences to discuss and gain Agency's concurrence on the content and format of their proposed 505(b)(2) NDA.

Technetium Tc-99m Succimer Injection is indicated for use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adults and pediatrics. Technetium Tc-99m Succimer Injection will be administered as a single, intravenous (IV) dose containing up to (b) (4)

Note: The Sponsor has not conducted any nonclinical or clinical studies on 99mTc-DMSA for use in the imaging of the kidneys but intends to rely on the data provided in the most recent label for the GE Healthcare product (NDA 0179944, approved 5/18/1982, but currently not in the market) as well as data reported in the peer-reviewed scientific literature.

FDA sent Preliminary Comments to Theragnostics Inc. through Facet Life Sciences, Inc., on September 27, 2019.

DISCUSSION

Question 1

Does FDA agree that Theragnostics product qualifies for a biowaiver?

Clinical Safety and Efficacy

Theragnostics has not performed any clinical studies on their Kit for the Preparation of Technetium Tc99m Succimer Injection. Theragnostics intends to support the clinical section of the NDA by performing a literature search.

The literature search will be performed for published clinical papers relevant to ^{99m}Tc-DMSA for the indication of use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients. Literature will be summarized in the appropriate Modules 2.7 sections.

Search parameters will include pharmacodynamics (PD), absorption, distribution, metabolism, and excretion (ADME), toxicity, efficacy, and safety of DMSA. The search will cover February 2007 (date of the last labeling update for MPI DMSA Kidney Reagent) through 6 months prior to NDA submission.

FDA Response:

No, we do not agree. Your proposed product does not meet the criteria for biowaiver as described at 21 CFR 320.22. Under 21 CFR 320.24(b)(6), however, FDA can consider the establishment of a scientific bridge between your proposed drug product and the listed drug. For this purpose submit in your NDA supporting data and information to demonstrate that any differences in active and inactive ingredients between the proposed and listed drug products do not contribute to differences in their in vivo performance. Provide, in a side-by-side comparison table, relevant physicochemical characteristics of both drug products and discuss why any differences would not alter the relative in vivo disposition kinetics of the drug. Literature data and information may be used to support bridging.

Meeting Discussion:
The Sponsor reiterated that there are no differences in the active ingredient, between the Sponsor product and the listed drug except one inactive ingredient. The Sponsor stated that the strongest indicator of equivalence in the in vivo performance is the physiological distribution test performed at release.

The Agency stated that while the physiological distribution model can be supportive, it is not definitive in establishing the scientific bridge. The Agency then requested a side by side comparison of relevant physicochemical properties of both drug products in tabular format and discuss any differences in relation to disposition kinetics of the drug.

The Sponsor will also provide scientific justification by citing the literature and/or use data generated from in-house experiments.
The Agency requested the Sponsor to include in the pharmaceutical development section a discussion about inositol and suggested that the formulation comparison and justification should be included in the biowaiver section, as well as in the Module 2 summaries.

Question 2

Does FDA agree with Theragnostics' approach to support the clinical section of the NDA based solely on literature?

FDA Response:

If you are able to provide an adequate scientific bridge between your product and the listed drug as described above, you may be able to rely in part on FDA's previous findings of safety and effectiveness for Tc99m-DMSA in adults (NDA 017944).

However, since there are differences in the proposed formulation, population of use, and dose between your product and the listed drug, your literature search should include citations of any publication date that describe:

- **studies of Tc99m-DMSA use in pediatric patients,**
- **studies specifically involving use of your formulation, and**
- **studies specifically using your proposed adult and pediatric dosing regimens.**

In addition to the above citations, your literature search should include any other studies of Tc99m-DMSA in adults that were published since FDA approval. You must provide adequate justification to establish that reliance upon the published literature is scientifically appropriate. See the "505(b)(2) Regulatory Pathway" section below for additional information.

Meeting Discussion:
The Sponsor stated that there was no difference between their formulation and the GE formulation. The Agency responded that literature specifically using the Sponsor's formulation would not be required if the Sponsor provides adequate scientific justification (as per Question 1 discussion) that the Sponsor's changes to the inactive ingredients do not affect the safety and efficacy of the product or its in vivo performance.

Question 3

Does FDA agree with Theragnostics' approach to the clinical literature search?

FDA Response:

See above.
Meeting Discussion: There was no meeting discussion on this item.

a. Proposed Dose

The dose for the previously approved GE product was 74-222 MBq (2-6 mCi) for an average patient (70kg). Theragnostics is proposing to label their product with the dosing information (b) (4) The proposed dose is as follows:

(b) (4)

(b) (4)

[redacted]

Question 4

Does FDA agree with Theragnostics' proposed dose?

FDA Response:

The proposed dose appears reasonable. However, you must provide adequate information to support the proposed dose. Non-US labeling or non-US regulatory authority assessments may not be relied upon as these are neither FDA's findings related to a listed drug, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature. (b) (4)

[redacted]

Meeting Discussion: There was no meeting discussion on this item.

Nonclinical Questions

b. Nonclinical Studies on Active Ingredient

Theragnostics has not performed any nonclinical studies on their Kit for the Preparation of Technetium Tc99m Succimer Injection. Theragnostics intends to rely on data from the nonclinical biodistribution data obtained during product release. This test is

performed, at a minimum, on each new batch of active substance produced and after every 10 finished product batches. Additionally, Theragnostics intends to support the nonclinical section of the NDA by performing a literature search.

The literature search will be performed for published nonclinical papers relevant to ^{99m}Tc-DMSA for the indication of use as an aid in the scintigraphic evaluation of renal parenchymal disorders in adult and pediatric patients. Literature will be summarized in the appropriate Module 2.6 sections.

Search parameters will include PD, ADME, and toxicity of DMSA. The search will cover February 2007 (date of the last labeling update for MPI DMSA Kidney Reagent) through 6 months prior to NDA submission.

Question 5 Does FDA agree with Theragnostics' approach to support the nonclinical section of the NDA based solely on literature?

FDA Response:

Yes, we agree. Please ensure that all cited nonclinical literature is included in the NDA and organized according to relevant section. Summaries should be included for each citation.

Meeting Discussion: There was no meeting discussion on this item.

Question 6

Does FDA agree with Theragnostics' approach to the nonclinical literature search?

FDA Response:

Yes, we agree.

Meeting Discussion: There was no meeting discussion on this item.

Chemistry, Manufacturing, and Controls Questions

c. (b) (4) Specification

The proposed commercial specification (b) (4) is provided in Table 1.

Table 1 (b) (4) **Specification**

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(b) (4)

d. Lyophilized Kit Specification

The proposed commercial specification for the lyophilized kit is provided in Table 2. The product complies with the Ph. Eur. 0643 monograph for Technetium (^{99m}Tc) succimer injection.

Table 2 Lyophilized Kit Specification

Test	Method	Acceptance Criteria
Appearance of lyophilizate* Particulate contamination	Visual Ph. Eur. 2.9.20	White or white-yellowish solid, free from visible particles
Solubility	-	The lyophilizate dissolves completely (b) (4)
Appearance after reconstitution*	Ph. Eur. 2.2.1/ 2.2.2 (b) (4)	Clear, colorless solution
Identification		
[^{99m}Tc]Technetium-Succimer injection solution (b) (4)	Ph. Eur 0643	(b) (4)
$SnCl_2x2H_2O$ (total Sn content)	Ph. Eur. 2.2.25	(b) (4) nm
pH*	Ph. Eur. 2.2.3	(b) (4)
Assay (Succimer)*	Ph .Eur. 2.2.25	(b) (4) mg/vial
$SnCl_2x2H_2O$ (total Sn content)	Ph. Eur. 2.2.25	(b) (4) mg/vial

Test	Method	Acceptance Criteria
$SnCl_2x2H_2O$ (Sn^{2+})*	Ph. Eur. 2.2.19	(b) (4) mg/vial
Ascorbic acid	Ph. Eur. 2.2.29	(b) (4) mg/vial
(b) (4)		
Sterility*	Ph. Eur.2.6.1	Sterile
Endotoxin Content	Ph. Eur. 2.6.14	(b) (4) IU/vial
Identification		
[^{99m}Tc]Technetium-Succimer injection solution (b) (4)	Ph. Eur. 0643, Ph. Eur. 2.2.27	[^{99m}Tc]Technetium-Succimer (b) (4)
Radiochemical Purity*	Ph. Eur. 0643	
10 minutes after labeling		(b) (4) %
4 hours after labeling		(b) (4) %
Content of Pertechnetate Ions	Ph. Eur. 0643	
10 minutes after labeling		(b) (4) %
4 hours after labeling		(b) (4) %

Test	Method	Acceptance Criteria
Physiological Distribution in Rats*§	Ph. Ur. 0643	(b) (4)
Leak Test	Visual Ph. Eur. 3.2.9	

*Tests performed on stability.

§Test performed in case of a new batch active substance or after 10 produced finished product batches.

Question 8

Does FDA have any comments regarding the proposed commercial specification for the lyophilized kit?

FDA Response:

We have following comments regarding the specifications:

- **Specifications for the (b) (4) content, also to be evaluated during stability, should be incorporated in the lyophilized kit specifications.**
- **Limits for the potential API degradation products be incorporated in the specifications.**
- **Risk analysis for the presence of (b) (4) potential elemental impurities should be conducted, and if necessary specifications should be incorporated.**
- **Tests for solubility, (b) (4) and ascorbic acid content should also be evaluated during stability.**

Additionally, we also recommend that as part of the drug product container closure qualification studies, an assessment of the container closure be performed to evaluate that it does not introduce potential interfering impurities, such as elemental impurities, in the drug product.

The microbiological tests (bacterial endotoxins per Ph. Eur. 2.6.14 and sterility test per Ph. Eur.2.6.1) proposed for the drug product appear reasonable.

However, the acceptability of the test methods and specifications will be determined upon submission of the NDA.

Please note that the maximum endotoxins patient dose will be determined from the sum of endotoxins exposure from the lyophilized drug product and generator eluate, as well as any additional kit components that come into direct contact with the product. The maximum endotoxins patient dose should not exceed 175 EU/dose, per USP <85>.

Meeting Discussion:
The Sponsor discussed including in the specification a test (b) (4) **The Sponsor asked if this would be sufficient to address Agency's concern regarding** (b) (4) **content, such that a separate test would not be required.**
The Agency stated that they would prefer a (b) (4) **test added to the specification.**
The Agency confirmed that bullet point 2 was specific (b) (4) (b) (4)
The Sponsor agreed with bullet points 3 and 4 and agreed to perform the container closure assessment.

NDA Registration Batches APPEARS THIS WAY ON ORIGINAL

Table 3 describes the 3 batches that will be used to support the 505(b)(2) application, including the available stability data for each batch. Batches that provide supportive data are described in Table 5. Each batch was manufactured according to the procedure described in **Error! Reference source not found.**, and tested according to the specification in Table 2. Stability tables with all available data to date are provided in Section **Error! Reference source not found.**.

Table 3 NDA Registration Batches

Lot Number	Date of Manufacture	Available Stability Data		(b) (4)
		Storage Condition	Data Available	
EP 02 17 16 3	19 April 2017	5°C ± 3°C	21 months	
		25°C ± 2°C	6 months	

EP 02 17 18 5	05 May 2017	5°C ± 3°C	21 months	(b) (4)
		25°C ± 2°C	6 months	
EP 02 17 18 2	02 May 2017	5°C ± 3°C	21 months	
		25°C ± 2°C	6 months	

Question 9

Does FDA agree that the 3 batches referenced above will be sufficient to support the 505(b)(2) application?

FDA Response:

We are not able to make such an assessment at this time as batches are reviewed in conjunction with the acceptable specifications. We have the following comments regarding the stability batches:

In general, registration and stability data for the three batches, which represent commercial manufacturing (site, scale and process), manufactured using the three separate API batches should be submitted in the application. A minimum of 12-month long term and 6-month accelerated data are expected to be submitted. Supportive data may be submitted as appropriate.

Meeting Discussion:
The Sponsor proposed to manufacture 3 new batches, using 3 different lots (b) (4) (b) (4) that would be designated as NDA registration batches. These batches would be placed on an ICH stability program and tested per the amended specification. In order to expedite submission of the NDA, the Sponsor proposed to include in the NDA the 18 to 21 months of data referred to in the background package, along with a reduced amount of stability data on the new batches, which was likely to be 3 months of data at both long term and accelerated considerations at the time of submission. The Sponsor would provide a commitment to supplement the application with each stability timepoint as soon as the data are available, until the 12-month data point. Subsequent timepoints would be submitted in an annual report. The Sponsor will include (b) (4) ascorbic acid, and solubility testing at a later timepoint and the container closure would be the same.
The Agency will accept the suggested approach based on data available because the product is on the drug shortage list. Additionally, the Agency would like to see how trend analysis, and submitting with 3 months of stability data will impact the expiry date. The Agency also agreed that the Sponsor could supplement during NDA review with stability data.

e. NDA Registration Batch Stability Data

The NDA registration batches, described in Table 3, were tested according to the protocol presented in Table 4. Stability data to date is presented in Section **Error! Reference source not found.**. In addition, 1 supportive stability batch is available, as described in Table 5.

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Table 4 Stability Protocol for NDA Registration Batches

Storage Condition	Timepoint (Months)						
	0	3	6	9	12	15	21
5°C ± 3°C	(b) (4)						
25°C ± 2°C							

(b) (4)

Table 5 Supportive Batches

Lot Number	Manufacture Date	Available Stability Data		(b) (4)
		Storage Condition	Data Available	
EP 02 17 30 3	26 July 2017	40°C ± 2°C for 5 days, then 5°C ± 3°C	15 months	
		40°C ± 2°C for 10 days, then 5°C ± 3°C	15 months	

Question 10

Does FDA agree that the stability data provided will be sufficient to support the 505(b)(2) application?

FDA Response:
See response to question 9 above.

Meeting Discussion: There was no meeting discussion on this item.

Question 11

Does FDA have any additional comments regarding the chemistry, manufacturing and controls for the kit for the preparation of ^{99m}Tc Succimer Injection?

FDA Response:

a. **The NDA should contain an analysis of the stability data as per the ICH guidelines.**

b. **All U.S. commercially available technetium Tc-99m generators should be qualified for radiolabeling the kit and data presented in the pharmaceutical development section of the NDA.**

c. **In the specification for identification of technetium Tc 99m succimer, you have indicated** (b) (4) **Please clarify** (b) (4) **under the test conditions.**

d. **Please note that we expect that validation data for Ph. Eur. methods will be included in the NDA.**

e. **For additional information necessary to describe the microbiological control of your manufacturing process in support of an NDA application, see the following guidances:**
   - (b) (4)
   - ***Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products***

Meeting Discussion:
The Sponsor stated that for the lyophilized kit all analytical methods have been validated. For the radiolabeled product, testing has been performed according to the product specific European Pharmacopeia monograph; therefore, validation has not been performed. The Sponsor asked if this would be acceptable. Because the Agency does not have access to the European Pharmacopeia validation reports; therefore, to the extent possible, the Sponsor should perform verification.
   - (b) (4)
   - ***Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products***

f. Regulatory and Procedural Questions

g. NDA Table of Contents

The proposed table of contents to support the 505(b)(2) application is provided in **Error! Reference source not found.**. APPEARS THIS WAY ON ORIGINAL

Question 12

Does FDA have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

FDA Response:

The Integrated Summaries of Efficacy and Safety (ISE and ISS) are required sections of the NDA. If you intend to use the Module 2 summaries to replace the ISE and ISS sections, we recommend including cross references to the appropriate summary documents in Module 2 and your rationale for them in the required ISE and ISS sections for Module 5.

Meeting Discussion: There was no meeting discussion on this item.

h. Regulatory Route

FDA has previously reviewed and approved a Kit for the Preparation of Technetium Tc99m Succimer Injection (NDA 017944-MPI DMSA Kidney Reagent). Theragnostics has not conducted any nonclinical or clinical studies in support of our NDA. Instead, Theragnostics intends to rely on FDA's acceptance of the efficacy and safety of Kit for the Preparation of Technetium Tc99m Succimer Injection and summarize information available in the public domain. Although the active ingredient, dosage form, strength, route of administration, intended use, and labeling are anticipated to be identical between Theragnostics' product and the previously approved product, the inactive ingredients are slightly different with regards to the quantity of ascorbic acid, (b) (4) (b) (4) and the absence of inositol, (b) (4) Therefore, the absence of inositol in the Theragnostics kit formulation would not be expected to adversely affect the safety or efficacy of the drug product.

Table 6 Comparative Formulation

Ingredient	Use	MPI DMSA Kidney Reagent	Kit for the Preparation of Technetium Tc99m Succimer Injection
		Quantity per vial	
Meso-2,3-dimercaptosuccinic acid	Active	1.0 mg	1.0 mg
Stannous Chloride dihydrate	(b) (4)	0.42 mg	0.42 mg
Ascorbic Acid		0.70 mg	0.1 mg
Inositol		50.0 mg	--
Sodium Hydroxide	Adjustment of pH	Not specified	0.2 mg
Hydrochloric Acid	(b) (4) Adjustment of pH	Not specified	0.02 mg
Nitrogen	(b) (4)	--	--

Based on these considerations, Theragnostics intends to submit our NDA for Kit for the Preparation of Technetium Tc99m Succimer Injection via the 505(b)(2) regulatory route in early 2020.

Question 13

Does FDA agree that a 505(b)(2) application is the most appropriate regulatory route**?**

FDA Response:

Given the differences in formulation and conditions of use (e.g., pediatric use) between your proposed product and the listed drug, submission of an NDA pursuant to the 505(b)(2) regulatory pathway is appropriate. Your intention to rely, in part, on FDA's previous findings of safety and effectiveness for technetium Tc99m succimer kit (NDA 017944) and published literature appears acceptable. See the "505(b)(2) Regulatory Pathway" section below for additional information.

Meeting Discussion: There was no meeting discussion on this item.

Proposed Label APPEARS THIS WAY ON ORIGINAL

Theragnostics plans to provide product labeling identical to the most recent GE Healthcare label (**Error! Reference source not found.**). Updates will be made to this label, as appropriate, based on information found in the literature (search criteria provided in Section 0 and Section b).

Question 14

Does FDA agree with providing product labeling identical to the most recent GE Healthcare label?

FDA Response:

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- **The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products**
- **The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential**
- **Regulations and related guidance documents**
- **A sample tool illustrating the format for Highlights and Contents, and**
- **The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.**
- **FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.**

1 **http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm**
2 **http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm**

Meeting Discussion: There was no meeting discussion on this item.

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08415 9.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09330 7.htm

i. Pediatric Requirements

The Pediatric Research Equity Act (PREA) requires NDAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment. Theragnostics Kit for the Preparation of Technetium Tc99m Succimer Injection is essentially identical to the previously approved MPI DMSA Kidney Reagent. The formulation has the same dosage form, strength and route of administration as MPI DMSA Kidney Reagent, with minor differences in inactive ingredients as described in Table 6. As such, Theragnostics does not believe they are required to conform to PREA requirements for this product.

Question 15

Does FDA agree with Theragnostics' assessment that PREA is not applicable for the Kit of the Preparation of Technetium Tc99m Succimer Injection?

FDA Response:

No. We do not agree. You are proposing a new dosing regimen, and are, therefore, subject to PREA's requirement for a pediatric assessment. You should plan on submitting an iPSP as described in the PREA requirements section below. Your iPSP needs to include a plan for an assessment with justification of the proposed dosing regimen and safety of your product in pediatric patients based on existing information (e.g., literature and safety experience with your imported product). Once your iPSP has been submitted, you will receive comments on your plan. The adequacy of the data submitted to support pediatric dosing will be determined after review of your NDA.

Meeting Discussion: There was no meeting discussion on this item.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and

design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[4] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[4] https://www.fda.gov/media/88173/download

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[6] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[7] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[8] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[7] https://www.fda.gov/media/88173/download
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Additional information can be found at FDA.gov.[9]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[12]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[13]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used

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[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[10] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[11] https://www.fda.gov/media/109533/download
[12] http://www.fda.gov/ectd
[13] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[14] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[15]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see

[14] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[15] http://www.regulations.gov

also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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/

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