

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213227Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 131797

MEETING MINUTES

Radiomedix, Inc.
Attention: Ebrahim S. Delpassand, MD, FACNM
9701 Richmond Avenue, Suite 222
Houston, TX 77042

Dear Dr. Delpassand:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ⁶⁴Cu-DOTATATE [REDACTED] (b) (4).

We also refer to the telecon between representatives of your firm and the FDA on April 25, 2019. The purpose of the meeting was to obtain guidance regarding your upcoming NDA 505(b)(2) submission.

A copy of the official minutes of the 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 Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B (teleconference)

Meeting Category: Pre-NDA

Meeting Date and Time: April 25, 2019 at 3:00 p.m. (EST)

Meeting Location: White Oak Campus, Building 22, room 1348

Application Number: IND 131797

Product Name: ^{64}Cu -DOTATATE

Indication: Positron emission tomography (PET) imaging agent for the localization of somatostatin receptor positive neuroendocrine tumors (NETs).

Sponsor/Applicant Name: RadioMedix/Ebrahim S. Delpassand

Meeting Chair: Dr. Nushin Todd

Meeting Recorder: CAPT Diane Hanner

FDA ATTENDEES

OFFICE OF DRUG EVALUATION IV

- Charles Ganley, MD, Director, ODEIV
- Jagjit Grewal, MPH, Policy Advisor, OND Policy Staff

OFFICE OF NEW DRUGS / OFFICE OF DRUG EVALUATION IV/ DIVISION OF MEDICAL IMAGING PRODUCTS

- Alex Gorovets, MD, Deputy Director, DMIP, Division of Medical Imaging Products, (DMIP)
- Nushin Todd, MD, Clinical Team Leader, DMIP
- Brenda Ye, MD, Medical Officer, DMIP
- Cynthia Welsh MD, Medical Officer, DMIP (on detail) (by phone)
- Ronald Honchel, PhD, Pharmacology/Toxicology Reviewer, DMIP

- Michele Fedowitz, MD, associate Director for Labeling, DMIP (by phone)
- CAPT Diane Hanner, MPH, MSW, LSW, Senior Program Management Officer, DMIP

OFFICE OF NEW DRUGS PRODUCTS / DIVISION OF NEW DRUG PRODUCTS (DNDPII)

- Danae Christodoulou, PhD, Branch Chief, DNDPII
- Eldon Leutzinger, PhD, CMC Reviewer, DNDPII
- Ravindra K. Kasliwal, PhD, CMC Reviewer, DNDPII

OFFICE OF NEW DRUGS PRODUCTS/DIVISION OF MICROBIOLOGY ASSESSMENT

- Julie Nemecek, PhD, Microbiology Reviewer (by phone)

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY V

- Christy John, PhD, Clinical Pharmacology Team Leader, (DCP V)
- Edwin Chow, PhD, Clinical Pharmacology reviewer

OFFICE OF TRANSLATIONAL SCIENCES / OFFICE OF BIOSTATISTICS / DIVISION OF BIOSTATISTICS I

- Sungwon Lee, PhD, Biostatistics Reviewer, DBI
- Jyoti Zalkikar, Ph.D., Biostatistics Secondary Reviewer, DBI

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/OFFICE OF MEDICAL ERROR PREVENTION AND RISK MANAGEMENT /DIVISION OF RISK MANAGEMENT

- Brad Moriyama, Pharm D., Risk Management Analyst

SPONSOR ATTENDEES

- Ebrahim S. Delpassand, MD, Chairman & CEO, RadioMedix, Inc.
- David Ranganathan, PhD, Director CMC and Regulatory Affairs, RadioMedix, Inc.
- Izabela Tworowska, PhD, Chief Scientific Office, RadioMedix, Inc
- Nilesh Wagh, PhD, Scientist, RadioMedix, Inc

○ [REDACTED] (b) (4)

○ [REDACTED] (b) (4)

- Edward Porter, Vice President, Compliance, Curium Pharmaceuticals
- Katie Merkel, Manager, Regulatory Affairs, Curium Pharmaceuticals

○ [REDACTED] (b) (4)

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

1.0 BACKGROUND

The Sponsor requested a meeting on March 13, 2019, to obtain the Agency's feedback regarding their updated plans to their ^{64}Cu -DOTATATE, NDA submission. The Sponsor is seeking an indication for ^{64}Cu -DOTATATE as a diagnostic positron emission tomography (PET) imaging agent for management of neuroendocrine tumors (NETs). The Sponsor received Orphan Drug Designation for this drug and they have a Fast Track Designation. The meeting was granted on March 16, 2019, as a teleconference meeting and it was scheduled for April 25, 2019. On April 25, 2019, the Sponsor submitted responses prior to the meeting (Appendix A). The Sponsor's questions are listed below in *italics*, followed by the FDA's Response in **bold** font. The Meeting Discussion is indicated in ***bold italics*** below.

2. DISCUSSION

QUESTION 1:

No nonclinical studies have been performed with ^{64}Cu -DOTATATE. Instead, RadioMedix proposes to rely on data presented in the literature and on the FDA reviews of NETSPOT (^{68}Ga -DOTATATE; NDA #208547) and LUTATHERA (^{177}Lu -DOTATATE; NDA #208700), which are also DOTATATE-based radiopharmaceuticals and are approved for use. A summary of these data will be provided in Module 2.4. Module 2.6 will not be provided.

Does the Agency agree that this proposal is sufficient to support the filing of the NDA and that no further studies are necessary for the Division's review of the nonclinical section of the NDA?

FDA RESPONSE TO QUESTION 1:

You are proposing to reference information from the FDA publicly available reviews of Netspot and LUTATHERA for support of nonclinical safety in your planned NDA. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1) and 505(b)(2) NDAs. The FDA publicly available reviews do not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug. We note that nonclinical information described in the product labeling for NETSPOT and LUTATHERA are limited. However, you may be able to submit a 505(b)(2) NDA that relies upon the available published literature to support the nonclinical safety of your proposed product. See section 3.0 below for additional information on the 505(b)(2) regulatory pathway.

MEETING DISCUSSION - QUESTION 1:

None

QUESTION 2:

The full set of ADME/Pharmacology studies to support the filing of the NDA for ⁶⁴Cu-DOTATATE injection for the localization (b) (4) of NETs consists of the following:

- *A PK assessment of 6 patients in the Phase 3 study. Blood samples were analyzed at 1, 10, 30, 60, and 120 minutes. Urine samples were analyzed in three intervals post-injection of the study drug (⁶⁴Cu-DOTATATE); 0-60 minutes, 60-120 minutes, and 120-360 minutes.*
- *Imaging data found in the literature.*
- *A review of literature for PK/pharmacology data pertinent to ⁶⁴Cu-DOTATATE will be summarized in Module 2.7.2.*

Does the Agency agree that these data are sufficient to support the filing of the NDA and that no further studies are necessary for the Division's review of the clinical pharmacology section of the NDA?

FDA RESPONSE TO QUESTION 2:

Radiomedix's proposed clinical pharmacology studies and data to be included in the NDA submission as part of the clinical pharmacology package generally appear acceptable. However, the data submitted should include the following:

- 1. Address the following questions in the Summary of Clinical Pharmacology:**
 - a) What is the basis for selecting the dose and dosing regimen used in the trials intended to support your marketing application?**
 - b) What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?**
 - i. Provide any nonclinical data that showed Cu-DOTATATE is not metabolized by hepatic enzymes.**
 - c) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure (imaging results) or safety?**
- 2. Apply the following advice in preparing the clinical pharmacology sections of the original submission:**
 - a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**

- i. Particularly, provide data and chromatogram that showed ^{64}Cu -DOTATATE remained intact after 6 hours in plasma and urine.
- b) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with minimum and maximum values as appropriate.
- c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The individual subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - i. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - ii. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

MEETING DISCUSSION - QUESTION 2:

The Agency stated that available PK data, regardless of the limited amount of data, should be submitted in the NDA.

The Sponsor stated they excluded patients with renal or hepatic impairment and the literature is limited regarding these cohorts. The Agency stated that the Sponsor should document the lack of data in these groups when submitting the NDA.

QUESTION 3:

RadioMedix has completed the following clinical studies (full clinical study reports will be included in the NDA):

- *A Phase 3 open-label, single-dose, single-arm, single-center clinical trial using ^{64}Cu -DOTATATE PET-CT scan for imaging patients with known or suspected NETs. A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu -DOTATATE. A prospective analysis of this study was conducted with co-primary efficacy endpoints of the sensitivity and specificity of ^{64}Cu -DOTATATE based on the Standard of Truth.*
- *A retrospective analysis of 112 Danish patients with confirmed NETs of gastro-entero-pancreatic or pulmonary origin, by histopathology. All patients underwent both PET/CT with ^{64}Cu -DOTATATE and SPECT/CT with ^{111}In -DTPA-OC (Octreoscan®) within 60 days. The co-primary efficacy endpoints were sensitivity and specificity of ^{64}Cu -DOTATATE based on the Standard of Truth.*
- *A Phase 1 single-arm, single-dose, dose-ranging, non-comparative study. Twelve (12) patients were recruited with confirmed NET disease by histology or conventional anatomical and functional imaging modalities, including but not limited to magnetic*

resonance imaging (MRI), and/or computed tomography (CT), and/or, ^{18}F FDG PET/CT and/or ^{18}F NaF bone PET/CT and/or bone scintigraphy, and/or Octreoscan[®].

Appropriate dose of 4.0 mCi (b)(4) was determined.

In addition the following supportive studies are found in the literature:

- A prospective Phase 1 study in 14 Danish patients with a history of neuroendocrine tumors who underwent both PET/CT with ^{64}Cu -DOTATATE and SPECT/CT with the current routine imaging agent ^{111}In - diethylenetriaminepentaacetic acid–octreotide (DTPA-OC) (Octreoscan[®]).
- A head-to-head study where the diagnostic performance of ^{64}Cu -DOTATATE was compared with that of ^{68}Ga -DOTATOC in NET patients. Fifty-nine NET patients were scanned with both ^{64}Cu -DOTATATE and ^{68}Ga -DOTATOC PET/CT. 200 MBq of ^{64}Cu -DOTATATE was injected IV and a PET/CT scan was performed after 60 minutes. For the ^{68}Ga -DOTATOC scan 150 MBq was injected IV and PET/CT images were acquired after 45 minutes. The t-test for paired samples was used to compare SUVmax values for the two scans and for comparison of the tumor to background ratios.

Does the Division agree that the clinical studies demonstrate adequate efficacy and safety to support the filing of an NDA for the proposed indication?

FDA RESPONSE TO QUESTION 3:

We agree no additional clinical studies are needed. Regulatory decision-making such as filing determination will be made after review of the submitted NDA.

MEETING DISCUSSION - QUESTION 3:

None

QUESTION 4:

RadioMedix proposed to summarize the safety data from the retrospective Denmark study, prospective Phase 1 study, prospective Phase 3 study, and literature data and provide the information in Module 2, section 2.7.4. "Summary of Clinical Safety" instead of presenting in 5.3.5.3 "Reports of Analyses of Data" from more than One Study, as an integrated summary of safety (ISS). The Division agreed to this approach in the written responses dated February 22, 2019.

As further clarification, the presentation of safety data from the Denmark study and from supporting literature will be in the form of written summaries. The presentation of data from the prospective Phase 1 study will be in the form of written summaries as well as in-text data listings. (b)(4)

RadioMedix does not intend to submit "integrated" safety datasets and intends to submit data summary, only. Will this be acceptable to the Agency?

FDA RESPONSE TO QUESTION 4:

- a) We understand the limitation of safety assessment from literature-based studies, therefore, we agree with your proposal of presenting safety written summaries from the Denmark study and from supporting literature.
- b) Regarding your prospective Phase 1 study (RMX-17-22) and Phase 3 study (RMX-18-22), please clarify the file type of your proposed “in-text data listing”. We infer these to be patient level safety data. We expect patient-level data to be presented in SDTM and ADaM formats, and SAS programs as you have submitted for the Denmark study in your 2/5/2019 submission to IND 131797. Please confirm.
- c) We do not agree with your proposal [REDACTED] (b) (4).
[REDACTED] For the pivotal Phase 3 study (RMX-18-22), we expect the safety information to be presented in the form of written summaries (clinical study report including summary tables) as well as patient-level data (in SDTM and ADaM formats and SAS programs).
- d) We expect an integrated safety assessment (submitted either in module 2, clinical summary of safety, or module 5, integrated summary of safety) based on the *total safety population* of all these clinical studies.

MEETING DISCUSSION - QUESTION 4:

The Agency reiterated that safety data from all the clinical studies, including the literature, be submitted for review. The Agency stated an integrated assessment of safety on the total safety population (on all the clinical studies conducted by the Sponsor) is required. The Sponsor should provide descriptions and analyses of the cases (including those in the Phase 1 study) in an overall safety assessment. The Sponsor may list limitations of safety assessment (e.g. limitation of safety information from the literature, small number of subjects from the Phase 1 study) in the overall safety assessment. The safety information can be placed either in Module 2, Summary of Clinical Safety, or in Module 5, Integrated Summary of Safety.

QUESTION 5:

⁶⁴Cu-DOTATATE drug product involves [REDACTED] (b) (4).
[REDACTED] ⁶⁴Cu-DOTATATE will be commercially manufactured at Curium Pharma.

[REDACTED] (b) (4).
[REDACTED]).

(b) (4)

In order to ensure the completeness at time of filing the CMC to the RadioMedix NDA, an overview of the RadioMedix approach to the Module 3 NDA is provided.

Does the Division agree with the proposal for the content of the NDA Sponsor Module 3 when Type II DMF(s) are available for cross-reference?

FDA RESPONSE TO QUESTION 5:

Your proposal for the content in the module 3 of the NDA, when type II DMFs are cross referenced, is acceptable, with the following additional information. The drug substance for the proposed product will be the ^{64}Cu complex of the dotatate peptide. In the NDA, you will need to provide structure characterization data for the drug substance. This may be accomplished by correlating the well characterized reference standard lot with the radioactive drug by orthogonal means. Please note that the NDA should have enough information to support labeling the product and to assure that any future changes to the CMC are appropriately submitted to the NDA. Also, please ensure that your contract manufacturer ^{(b) (4)} incorporates cross -references to other DMFs (e.g., type III container closure DMFs).

MEETING DISCUSSION - QUESTION 5:

The Agency stated that a collection of characterization data ^{(b) (4)} may be sufficient ^{(b) (4)}

The Agency also noted that an additional section in the drug substance section may be incorporated to provide the ^{(b) (4)} characterization data.

QUESTION 6:

RadioMedix could not locate established/generic names for two recently approved radiopharmaceuticals, NETSPOT (ki for the preparation of gallium Ga 68 dotatate injection, NDA 208547) and LUTATHERA[®] (lutetium Lu 177 dotatate, NDA 208700) injection, in the current edition of USP Dictionary of USAN and International Drug Names.

Can the Division provide guidance on the requirements for USAN for radiopharmaceuticals such as ^{64}Cu -Dotatate Injection?

FDA RESPONSE TO QUESTION 6:

As noted, the drug substance for the proposed product will be the ^{64}Cu complex of the dotatate peptide. In the NDA, provide a USAN name for the drug substance.

The link regarding the Procedure for United States Adopted Names is below.

<https://www.ama-assn.org/about/united-states-adopted-names/procedure-usan-name-selection>

MEETING DISCUSSION - QUESTION 6:

The Agency stated that the Sponsor should file the USAN as soon as possible as it will be needed for review of product labeling.

QUESTION 7:

^{64}Cu -DOTATATE received Fast Track Designation on December 19, 2018. As such, the product is eligible for a Rolling Review. Due to the timing of completion of the CMC information for this application, RadioMedix proposes to submit the entire Toxicology, Clinical Pharmacology, and Clinical modules of the NDA followed by a separate submission of the entire CMC module.

Does the Division agree that a rolling review as proposed would be appropriate for this application?

FDA RESPONSE TO QUESTION 7:

A Rolling review for your application may be possible. However, you have not provided a schedule for submission of each portion of your planned NDA. You should submit an amendment to your IND with your request for rolling review as detailed in the [FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics](#) (see Appendix 2: Process for Rolling Review). If a rolling review is granted, note that the Agency is not obligated to start review prior to receipt of a complete application.

MEETING DISCUSSION QUESTION 7:

The Sponsor stated that each NDA Module will be submitted in entirety. The Sponsor was informed that if a rolling review were to be granted, anything outside the agreed upon schedule would be considered a late submission.

QUESTION 8:

Should the Division agree to a rolling review for the NDA, the Sponsor proposes that the establishment section of the 356H form is left blank when submitting the initial application (i.e., Toxicology, Clinical Pharmacology, and Clinical modules). The 356H form will be updated

with the appropriate establishment information (including inspection readiness) for the product when the CMC Module is submitted.

Does the Division agree that the approach to site information on the 356H form is appropriate for a rolling review?

FDA RESPONSE TO QUESTION 8:

No. If granted a rolling review status, you should not leave the 356H form blank until the CMC Module has been submitted. Please identify the establishment Information (Item 29) in the form with the initial submission. If the site is not ready for inspection, please check the No box in item 29 and provide the date when it will be ready.

MEETING DISCUSSION QUESTION 8:

The Agency reiterated that form 356H must be completed and the Sponsor should indicate on the form when the sites will be ready for inspection. The Sponsor was also informed that the sites must be ready for inspection at time of filing the CMC modules (final submission).

2.0 IMPORTANT MEETING LANGUAGE

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 16, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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 related to 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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: <http://www.fda.gov/ectd>.

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 <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. 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 <http://www.regulations.gov>).

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 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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>4.</i>	

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.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or

marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no additional issues identified that required further discussion.

5.0 ACTION ITEMS

No issues have been identified that require further actions.

6.0 ATTACHMENTS AND HANDOUTS

Attachment A (below) – Contains the Sponsor Responses (received April 25, 2019) to the FDA Responses

Appendix (A)

The Sponsor's reply to the FDA Responses were received on Thursday, April 25, 2019, at 11:35 a.m. and are included below:

QUESTION 1:

No nonclinical studies have been performed with ⁶⁴Cu-DOTATATE. Instead, RadioMedix proposes to rely on data presented in the literature and on the FDA reviews of NETSPOT (⁶⁸Ga-DOTATATE; NDA #208547) and LUTATHERA (¹⁷⁷Lu-DOTATATE; NDA #208700), which are also DOTATATE-based radiopharmaceuticals and are approved for use. A summary of these data will be provided in Module 2.4. Module 2.6 will not be provided.

Does the Agency agree that this proposal is sufficient to support the filing of the NDA and that no further studies are necessary for the Division's review of the nonclinical section of the NDA?

FDA RESPONSE TO QUESTION 1:

You are proposing to reference information from the FDA publicly available reviews of Netspot and LUTATHERA for support of nonclinical safety in your planned NDA. "Full reports of investigations" of safety and effectiveness are required to be submitted for approval of 505(b)(1)

and 505(b)(2) NDAs. The FDA publicly available reviews do not constitute full reports of investigations. See 21 C.F.R. 314.430(e)(2). A 505(b)(2) applicant that seeks to rely upon the Agency's finding of safety and/or effectiveness for a listed drug may rely on FDA's finding of safety and effectiveness as reflected in the FDA-approved labeling for the listed drug. We note that nonclinical information described in the product labeling for NETSPOT and LUTATHERA are limited. However, you may be able to submit a 505(b)(2) NDA that relies upon the available published literature to support the nonclinical safety of your proposed product. See section 3.0 below for additional information on the 505(b)(2) regulatory pathway.

RadioMedix Response:

We plan to submit a 505(b)(2) and rely on available published literature to support the nonclinical safety of ⁶⁴Cu-DOTATATE.

QUESTION 2:

The full set of ADME/Pharmacology studies to support the filing of the NDA for ⁶⁴Cu-DOTATATE injection for the localization (b) (4) of NETs consists of the following:

- A PK assessment of 6 patients in the Phase 3 study. Blood samples were analyzed at 1, 10, 30, 60, and 120 minutes. Urine samples were analyzed in three intervals post-injection of the study drug (⁶⁴Cu-DOTATATE); 0-60 minutes, 60-120 minutes, and 120-360 minutes.
- Imaging data found in the literature.
- A review of literature for PK/pharmacology data pertinent to ⁶⁴Cu-DOTATATE will be summarized in Module 2.7.2.

Does the Agency agree that these data are sufficient to support the filing of the NDA and that no further studies are necessary for the Division's review of the clinical pharmacology section of the NDA?

FDA RESPONSE TO QUESTION 2:

Radiomedix's proposed clinical pharmacology studies and data to be included in the NDA submission as part of the clinical pharmacology package generally appear acceptable. However, the data submitted should include the following:

3. Address the following questions in the Summary of Clinical Pharmacology:
 - d) What is the basis for selecting the dose and dosing regimen used in the trials intended to support your marketing application?

Radiomedix Response:

An open-label, single-dose, dose-ranging study was conducted to identify the lowest amount of administered ^{64}Cu -DOTATATE dose to obtain a diagnostic quality image. This study will be discussed in the NDA.

- e) What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - i. Provide any nonclinical data that showed Cu-DOTATATE is not metabolized by hepatic enzymes.

Radiomedix Response:

In the NDA, we will provide the results from the PK study, which was performed as recommended by the FDA during the October 4, 2016 Pre-IND meeting. This study provides urine (at 0-60 minutes, 60-120 minutes, and 120-360 minutes) and blood (at 1, 10, 30, 60, and 120 minutes) recovery information. In addition, data from the literature will be provided, which includes absorbed dose information (standardized uptake values) in tissues and organs. No other PK data are available.

Due to the low dose of ^{64}Cu -DOTATATE administered in the clinical studies (4 mCi), bioanalytical assays are unable to characterize the pharmacokinetics of the product beyond the data collected in the PK study. Analysis of additional information such as intact parent drug, free ^{64}Cu and ^{64}Cu moieties is extremely challenging if not impossible due to the half-life of ^{64}Cu (12.7 hours) and the very low levels of radioactivity that will be present in the blood.

Does the Division agree that additional PK information beyond that described will not be required due to the reasons presented?

- f) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure (imaging results) or safety?

Radiomedix Response:

No drug-drug interaction data were collected in the clinical studies. Although there are theories that somatostatin and its analogs competitively bind to somatostatin receptors and may affect efficacy, these products were excluded from the clinical trials. Thus, these analyses are not available. RadioMedix plans to propose language in the labeling to discontinue any use of somatostatin or analog products prior to dosing with ^{64}Cu -DOTATATE.

In regards to intrinsic factors and their influence on safety, due to the small number of adverse events, an analysis would not provide meaningful information. There were a total of 10 adverse events experienced by 6 subjects in studies RMX-17-22 and RMX-18-22 (total population of 71). All of these were considered to be unrelated to the study drug. In

addition, there were no clinically significant changes in lab parameters or vital signs in both studies.

The data collected for imaging results showed sensitivity and specificity in identifying disease from image scans as $\geq 90\%$ for Study RMX-18-22. Thus, due to the extremely high image quality overall, analyzing sex, race, disease and organ dysfunction would not provide meaningful information.

Does the Division agree that extrinsic and intrinsic analyses are not required due to the reasons provided?

4. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
 - d) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - i. Particularly, provide data and chromatogram that showed ^{64}Cu -DOTATATE remained intact after 6 hours in plasma and urine.

Radiomedix Response:

The validation report for the HPLC chromatographic method used for the PK study will be provided in the NDA. Chromatograms for each patient will be included.

- e) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with minimum and maximum values as appropriate.
- f) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The individual subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - iii. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - iv. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

Radiomedix Response:

Please see our response to 1(c) above.

QUESTION 3:

RadioMedix has completed the following clinical studies (full clinical study reports will be included in the NDA):

- A Phase 3 open-label, single-dose, single-arm, single-center clinical trial using ^{64}Cu -DOTATATE PET-CT scan for imaging patients with known or suspected NETs. A total of 63 subjects were injected with a mean dose of 4.11 mCi of ^{64}Cu -DOTATATE. A prospective analysis of this study was conducted with co-primary efficacy endpoints of the sensitivity and specificity of ^{64}Cu -DOTATATE based on the Standard of Truth.
- A retrospective analysis of 112 Danish patients with confirmed NETs of gastro-entero-pancreatic or pulmonary origin, by histopathology. All patients underwent both PET/CT with ^{64}Cu -DOTATATE and SPECT/CT with ^{111}In -DTPA-OC (Octreoscan®) within 60 days. The co-primary efficacy endpoints were sensitivity and specificity of ^{64}Cu -DOTATATE based on the Standard of Truth.
- A Phase 1 single-arm, single-dose, dose-ranging, non-comparative study. Twelve (12) patients were recruited with confirmed NET disease by histology or conventional anatomical and functional imaging modalities, including but not limited to magnetic resonance imaging (MRI), and/or computed tomography (CT), and/or, ^{18}F FDG PET/CT and /or ^{18}F NaF bone PET/CT and/or bone scintigraphy, and/or Octreoscan®. Appropriate dose of 4.0 mCi (b) (4) was determined.

In addition the following supportive studies are found in the literature:

- A prospective Phase 1 study in 14 Danish patients with a history of neuroendocrine tumors who underwent both PET/CT with ^{64}Cu -DOTATATE and SPECT/CT with the current routine imaging agent ^{111}In - diethylenetriaminepentaacetic acid–octreotide (DTPA-OC) (Octreoscan®).
- A head-to-head study where the diagnostic performance of ^{64}Cu -DOTATATE was compared with that of ^{68}Ga -DOTATOC in NET patients. Fifty-nine NET patients were scanned with both ^{64}Cu -DOTATATE and ^{68}Ga -DOTATOC PET/CT. 200 MBq of ^{64}Cu -DOTATATE was injected IV and a PET/CT scan was performed after 60 minutes. For the ^{68}Ga -DOTATOC scan 150 MBq was injected IV and PET/CT images were acquired after 45 minutes. The t-test for paired samples was used to compare SUVmax values for the two scans and for comparison of the tumor to background ratios.

Does the Division agree that the clinical studies demonstrate adequate efficacy and safety to support the filing of an NDA for the proposed indication?

FDA RESPONSE TO QUESTION 3:

We agree no additional clinical studies are needed. Regulatory decision-making such as filing determination will be made after review of the submitted NDA.

[Radiomedix Response:](#)

[We thank the Division for their response.](#)

QUESTION 4:

RadioMedix proposed to summarize the safety data from the retrospective Denmark study, prospective Phase 1 study, prospective Phase 3 study, and literature data and provide the information in Module 2, section 2.7.4. “Summary of Clinical Safety” instead of presenting in 5.3.5.3 “Reports of Analyses of Data” from more than One Study, as an integrated summary of safety (ISS). The Division agreed to this approach in the written responses dated February 22, 2019.

As further clarification, the presentation of safety data from the Denmark study and from supporting literature will be in the form of written summaries. The presentation of data from the prospective Phase 1 study will be in the form of written summaries as well as in-text data listings. [REDACTED] (b) (4)

RadioMedix does not intend to submit “integrated” safety datasets and intends to submit data summary, only. Will this be acceptable to the Agency?

FDA RESPONSE TO QUESTION 4:

- e) We understand the limitation of safety assessment from literature-based studies, therefore, we agree with your proposal of presenting safety written summaries from the Denmark study and from supporting literature.

Radiomedix Response:

We thank the Division for their response.

- f) Regarding your prospective Phase 1 study (RMX-17-22) and Phase 3 study (RMX-18-22), please clarify the file type of your proposed “in-text data listing”. We infer these to be patient level safety data. We expect patient-level data to be presented in SDTM and ADaM formats, and SAS programs as you have submitted for the Denmark study in your 2/5/2019 submission to IND 131797. Please confirm.

Radiomedix Response:

We confirm that patient-level data presented in SDTM and ADaM formats and SAS programs will be provided [REDACTED] (b) (4)

patient-level data is provided in the study report in tables and listings.

Does the Division agree [REDACTED] (b) (4)

g) We do not agree with your proposal [REDACTED] (b) (4)

[REDACTED] For the pivotal Phase 3 study (RMX-18-22), we expect the safety information to be presented in the form of written summaries (clinical study report including summary tables) as well as patient-level data (in SDTM and ADaM formats and SAS programs).

Radiomedix Response:

For Study RMX-18-22, patient-level data will be provided as described above.

h) We expect an integrated safety assessment (submitted either in module 2, clinical summary of safety, or module 5, integrated summary of safety) based on the *total safety population* of all these clinical studies.

Radiomedix Response:

The studies which provide safety data that can be integrated are RMX-17-22 (Phase 1) and RMX-18-22 (Phase 3). Since 4 patients from the 4 mCi cohort of Study RMX-17-22 were included in the analysis for Study RMX-18-22, there are only an additional 8 subjects of which 1 experienced 2 adverse events to integrate with Study RMX-18-22. These adverse events were not related to the drug in Study RMX-17-22 and there were no clinically significant changes in lab parameters or vital signs. Thus, integrating the data would not provide meaningful information.

Does the Division agree that an ISS is not necessary based on the reasons described?

QUESTION 5:

⁶⁴Cu-DOTATATE drug product involves [REDACTED] (b) (4)
[REDACTED] ⁶⁴Cu-DOTATATE will be commercially manufactured at Curium Pharma.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

In order to ensure the completeness at time of filing the CMC to the RadioMedix NDA, an overview of the RadioMedix approach to the Module 3 NDA is provided.

Does the Division agree with the proposal for the content of the NDA Sponsor Module 3 when Type II DMF(s) are available for cross-reference?

FDA RESPONSE TO QUESTION 5:

Your proposal for the content in the module 3 of the NDA, when type II DMFs are cross referenced, is acceptable, with the following additional information. The drug substance for the proposed product will be the ^{64}Cu complex of the dotatate peptide. In the NDA, you will need to provide structure characterization data for the drug substance. This may be accomplished by correlating the well characterized reference standard lot with the radioactive drug by orthogonal means. Please note that the NDA should have enough information to support labeling the product and to assure that any future changes to the CMC are appropriately submitted to the NDA. Also, please ensure that your contract manufacturer ^{(b)(4)} incorporates cross -references to other DMFs (e.g., type III container closure DMFs).

RadioMedix Response:

We thank the Division for providing us with the additional Module 3 considerations for the NDA.

We would like to seek clarification on the characterization requirements ^{(b)(4)}

does the agency agree that the identity of the Cu-dotatate complex is sufficiently demonstrated.

QUESTION 6:

RadioMedix could not locate established/generic names for two recently approved radiopharmaceuticals, NETSPOT (kit for the preparation of gallium Ga 68 dotatate injection, NDA 208547) and LUTATHERA[®] (lutetium Lu 177 dotatate, NDA 208700) injection, in the current edition of USP Dictionary of USAN and International Drug Names.

Can the Division provide guidance on the requirements for USAN for radiopharmaceuticals such as ^{64}Cu -Dotatate Injection?

FDA RESPONSE TO QUESTION 6:

As noted, the drug substance for the proposed product will be the ^{64}Cu complex of the dotatate peptide. In the NDA, provide a USAN name for the drug substance.

The link regarding the Procedure for United States Adopted Names is below.

<https://www.ama-assn.org/about/united-states-adopted-names/procedure-usan-name-selection>

RadioMedix Response:

RadioMedix is in the process of initiating the USAN application procedure. Does the Division require a copy of the USAN application within the NDA.

QUESTION 7:

⁶⁴Cu-DOTATATE received Fast Track Designation on December 19, 2018. As such, the product is eligible for a Rolling Review. Due to the timing of completion of the CMC information for this application, RadioMedix proposes to submit the entire Toxicology, Clinical Pharmacology, and Clinical modules of the NDA followed by a separate submission of the entire CMC module.

Does the Division agree that a rolling review as proposed would be appropriate for this application?

FDA RESPONSE TO QUESTION 7:

A Rolling review for your application may be possible. However, you have not provided a schedule for submission of each portion of your planned NDA. You should submit an amendment to your IND with your request for rolling review as detailed in the [FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics](#) (see Appendix 2: Process for Rolling Review). If a rolling review is granted, note that the Agency is not obligated to start review prior to receipt of a complete application.

Radiomedix Response:

We plan to submit an amendment to the IND with a request for rolling review. This will include a schedule for submission of each portion of the planned NDA.

QUESTION 8:

Should the Division agree to a rolling review for the NDA, the Sponsor proposes that the establishment section of the 356H form is left blank when submitting the initial application (i.e Toxicology, Clinical Pharmacology, and Clinical modules). The 356H form will be updated with the appropriate establishment information (including inspection readiness) for the product when the CMC Module is submitted.

Does the Division agree that the approach to site information on the 356H form is appropriate for a rolling review?

FDA RESPONSE TO QUESTION 8:

No. If granted a rolling review status, you should not leave the 356H form blank until the CMC Module has been submitted. Please identify the establishment Information (Item 29) in the form with the initial submission. If the site is not ready for inspection, please check the No box in item 29 and provide the date when it will be ready.

Radiomedix Response:

We thank the Division for their response. RadioMedix will follow the written advice provided to avoid refuse to receive issues.

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/

LIBERO L MARZELLA
05/23/2019 05:19:31 PM



IND 131797

**MEETING REQUEST-
WRITTEN RESPONSES**

Radiomedix, Inc.
Attention: Ebrahim S. Delpassand, MD, FACNM
9701 Richmond Avenue, Suite 222
Houston, TX 77042

Dear Dr. Delpassand:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{64}Cu -DOTATATE (b) (4)

We also refer to your submission dated January 8, 2019, containing a meeting request. The purpose of the requested meeting was to provide the Sponsor with guidance regarding their clinical analysis of (b) (4)

Further reference is made to our Meeting Granted letter dated January 15, 2019, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 8, 2019, background package.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C

Meeting Category: Guidance

Application Number: IND 131797

Product Name: ⁶⁴Cu-DOTATATE [REDACTED] (b) (4)

Indication: Diagnostic agent for the localization of somatostatin receptor positive neuroendocrine tumors (NETs)

Sponsor/Applicant Name: RADIOMEDIX

Regulatory Pathway: 505(b)(2)

1.0 BACKGROUND

The Sponsor requested a meeting on January 8, 2019, to obtain the Agency's feedback regarding their updated plans to their ⁶⁴Cu-DOTATATE clinical development program. The Sponsor noted that two clinical studies (a dose-assessment study and an adequate and well-controlled safety-efficacy study) conducted by RadioMedix in Houston. The meeting was granted on January 15, 2019, as a Written Response Only.

2.0 QUESTIONS AND RESPONSES

QUESTION 1:

Radiomedix proposes to pool the sensitivity and specificity data from the retrospective Denmark study and the prospective Phase 3 trial and present the information in Module 2, section 2.7.3 Summary of Clinical Efficacy instead of presenting in Module 5.3.5.3 Reports of Analyses of Data from More than One Study, as an integrated summary of efficacy (ISE). Does the Agency agree?

FDA RESPONSE TO QUESTION 1

We do not object to placing the information in Section 2.7.3. Summary of Clinical Efficacy as an integrated summary of efficacy (ISE), instead of presenting in Section 5.3.5.3 Reports of Analyses of Data from More than One Study.

However, sensitivity and specificity results from pooled data of the retrospective Denmark study and the prospective phase 3 study (RMX-18-22) would not be informative. We refer you to the meeting minutes of the 10/4/2012 tele-conference for discussion of the clinical development requirements of ⁶⁴Cu-DOTATATE. Data from the prospective phase 3 study under the special protocol assessment agreement will be reviewed as a main source of confirmatory evidence for approval of the study drug and data from the retrospective Denmark study as supportive evidence.

QUESTION 2:

Radiomedix proposes to pool the safety data from the retrospective Denmark study, prospective Phase 1 study, prospective Phase 3 study, and literature data and present the information in Module 2, section 2.7.4 Summary of Clinical Safety instead of presenting in 5.3.5.3 Reports of Analyses of Data from More than One Study, as an integrated summary of safety (ISS). Does the Agency agree?

FDA RESPONSE TO QUESTION 2

Yes. However, complete clinical study reports, should be submitted in Module 5.

ADDITIONAL FDA COMMENTS

We suggest you request a PreNDA meeting ahead of your planned NDA submission to ensure your submission contains the necessary information for our review.

3.0 IMPORANT MEETING INFORMATION

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide

feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

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 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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/s/

LIBERO L MARZELLA
02/22/2019 03:50:22 PM



IND 131797

**MEETING REQUEST-
WRITTEN RESPONSES**

Radiomedix, Inc.
Attention: Ebrahim S. Delpassand, MD, FACNM
9701 Richmond Avenue, Suite 222
Houston, TX 77042

Dear Dr. Delpassand:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ^{64}Cu -DOTATATE [REDACTED] (b) (4)

We also refer to your submission dated April 10, 2018, containing a meeting request. The purpose of the requested meeting was to discuss the development of the Sponsor's clinical database.

Further reference is made to our Meeting Granted letter dated April 16, 2018, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your April 10, 2018, background package.

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C

Meeting Category: Guidance

Application Number: IND 131797

Product Name: ^{64}Cu -DOTATATE [REDACTED] (b) (4)

Indication: Diagnostic agent for the localization of somatostatin receptor positive neuroendocrine tumors (NETs)

Sponsor: **RADIOMEDIX**

1.0 BACKGROUND

The Sponsor requested a meeting on April 10, 2018, to obtain the Agency's feedback regarding their updated plans to their ^{64}Cu -DOTATATE clinical development program. The Sponsor noted that two clinical studies (a dose-assessment study and an adequate and well-controlled safety-efficacy study) conducted by RadioMedix in Houston, will be supported by the published clinical literature from the University of Copenhagen. The meeting was granted on April 16, 2018, as a Written Response Only.

2.0 QUESTIONS AND RESPONSES

QUESTION #1

Considering the strengths and limitations associated with source data availability at the Rigshospitalet, University of Copenhagen does the Agency have advice on how to enhance the regulatory and clinical usefulness of the information contained in published studies of clinical experience at the site, as well as our plans to reanalyze investigator-supplied data tabulations for the largest clinical study?

FDA Response to QUESTION #1

We reiterate our previous responses and refer you to the meeting minutes from the October 4, 2016 teleconference. The second paragraph on page 3 of the minutes references the two studies conducted at the University of Copenhagen in a total of 112 patients and states "In addition, we request that you analyze the source data to which you state you have obtained access and present the results as a study report including datasets. In particular,

please clarify and describe the methodology utilized in Pfeifer et al for image interpretation, provide patient narratives for the 12 patients who were negative for disease, and provide information on how the lesions were verified as true positive.”

QUESTION #2

Does the overall clinical data development plan/program appear reasonable (i.e., two prospective studies at the Houston site, published reports of studies, a reanalysis of a 2015 published report, literature update and citation to the experience with ⁶⁴Cu-DOTATATE)?

FDA Response to QUESTION #2

No. we do not agree. We refer you to our response to clinical question #1 from the October 4, 2016, meeting minutes for a summary of our recommendations.

Additionally, we will be scheduling a teleconference meeting with you to provide additional guidance on the source data needed and to answer any clarifying questions you may have.

3.0 IMPORANT MEETING INFORMATION

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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. 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: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies,

CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

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06/13/2018