

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203-155

SUPPL # 000

HFD # 160

Trade Name

Generic Name [11C] Choline

Applicant Name Mayo Clinic PET Radiochemistry Facility

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# .

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Frank Lutterodt
Title: Regulatory Project Manager
Date: August 28, 2012

Name of Office/Division Director signing form: Rafel Dwaine Rieves
Title: Division Director, Division of Medical Imaging Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

From: [Suggs, Courtney](#)
To: [Lutterodt, Frank A](#)
Cc: [Mathis, Lisa](#); [Addy, Rosemary](#); [Rieves, Dwaine](#); [Greeley, George](#)
Subject: NDA 203-155 11C Choline
Date: Friday, April 06, 2012 7:31:33 AM
Attachments: [1_Pediatric_Record.pdf](#)

Hi Frank,

The email serves as confirmation of the review for 11C Choline conducted by the PeRC PREA Subcommittee on April 4, 2012.

The Division presented a full waiver in pediatric patients because studies are impossible or highly impracticable for diagnostic PET (positron emission tomography) imaging for identification of local lymph node and distant recurrence of prostate cancer in patients following primary treatment failure and/or in patients and those who have failed one or more conventional imaging modalities for localization of recurrent prostate cancer because prostate cancer does not occur in the pediatric population

The PeRC agreed with the Division to grant a full waiver for this product.

The PeRC understand the development of this and similar products are evolving. The committee recommends the Division consider if this product would be beneficial for the imaging of other conditions in pediatrics and if a WR under BPCA would be appropriate.

The pediatric page is attached for 11C Choline.

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

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/s/

FRANK A LUTTERODT
08/31/2012

RAFEL D RIEVES
08/31/2012

Debarment Certification

Debarment Certification

Mayo Clinic PET Radiochemistry Facility certifies that we did not and will not use the services, in any capacity, of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Convictions

Mayo Clinic PET Radiochemistry Facility did not and will not use the services, in any capacity, of anyone convicted of a relevant offense within the last 5 years in connection with this application.



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Choline C-11 Injection.

We detected two areas within the proposed labeling that we think need clarification. Please consider these and submit a clean/redline version of your labeling as an amendment to your NDA as early as possible on September 11, 2012.

- 1) You added (b)(4) to the indication description of the drug's usefulness in a manner that may cause confusion since the indication is specifically for positron emission tomography (unqualified); by adding (b)(4) to the usefulness description, you may be inadvertently impacting potential reimbursement decisions by a perception that the drug is useful only when it is used in (b)(4)...was this your intent? In general, we regarded the data as sufficient to support (b)(4) "PET" (b)(4) and, while we do not object to your (b)(4) change, we want to be sure that you are aware of its potential implications. In general, we prefer to keep the modality as general as possible since technological improvements in modalities are fairly frequent and having more general labeling may help allay future concerns.
- 2) There is a typo in the clinical studies section/you correctly caught a typo for Table 5...which necessitates correcting another typo.

We include a track changes version here. Please examine these and resubmit the revised labeling as an amendment to your NDA.

If you have any questions, call Frank Lutterodt at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

RAFEL D RIEVES
09/10/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Choline C-11 Injection.

As mentioned in the telephone conversation on Friday, August 31, 2012, we have found a few typographical errors in the labeling text. Also, we request inclusion of a new sentence in the Nursing section/to note that the drug is not indicated for women.

We include a track changes and clean version here. Please examine these and resubmit the revised labeling as an amendment to your NDA. We hope to minimize typo/format errors.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

09/04/2012

From: Lutterodt, Frank A

Sent: Tuesday, September 04, 2012 10:38 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: final choline labeling- Please send back as an amendment to NDA 203-155

MEMORANDUM OF MEETING MINUTES

MEETING DATE: Friday, August 31, 2012
TIME: 9:00 AM EST
LOCATION: Teleconference
APPLICATION: NDA203-155
DRUG NAME: [¹¹C] -Choline
TYPE OF MEETING: NDA Teleconference

MEETING CHAIR: Dwaine Rieves

MEETING RECORDER: Frank Lutterodt

FDA ATTENDEES:

Rafel Dwaine Rieves, M.D., Director, DMIP
Robert Mello Ph.D., Microbiology Reviewer, NDMS
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Frank Lutterodt, M.S., Project Manager, DMIP

EXTERNAL CONSTITUENT ATTENDEES:

Joseph C. Hung, Ph.D., BCNP, FASHP, FAPhA, Professor of Pharmacy & Professor of Radiology, Director of Radiopharmaceutical Laboratories & Director of PET Radiochemistry Facility, Mayo Clinic

Mark Jacobson, Ph.D, PET Radiochemistry Coordinator, Mayo Clinic

Discussion:

This telephone conversation occurred on August 31, 2012, with the applicant of pending NDA 203-155. During the teleconference, there was discussion on the August 24th 2012 responses to the microbiology deficiencies. A problem still existed with the (b) (4) (i.e. media fill) where the applicant still does not substitute growth media for the product during the manipulations. FDA's position was explained in the light of the applicant's most recent submission.

- The applicant acknowledged FDA's position on the use of growth media in (b) (4). The applicant explained the history of their usage of (b) (4) instead of growth media. During the discussions the applicant did state that there are challenges in (b) (4)

(b) (4) FDA advised the sponsor to submit a justification on why this cannot be done.

- FDA agreed to review and comment on a courtesy copy of the revised [REDACTED] (b) (4) protocol which would be sent via email to the microbiology reviewer in advance of a formal submission to the NDA application.
- In response to the applicant's question concerning the conduct of new media fills and the submission of that new data, FDA agreed that the actual conduct of new media fills performed under the revised protocol should be scheduled as soon as possible but that data need not be submitted to the Agency during the current review cycle.
- It was agreed at the meeting that, for [REDACTED] (b) (4), it would be prudent for the applicant to amend the [REDACTED] (b) (4) validations in those submissions to include the use of growth media in place of drug product to ensure consistency among all of the drug product submissions.
- The applicant was informed that FDA will be sending the clean version of the package insert for [¹¹C] –Choline with edits of typographical errors and language in the pediatric section consistent with other therapeutic prostate cancer products. The applicant agreed to review and respond to the labeling in short order.

Drafted by Frank Lutterodt
Edited by Robert Mello, Ph.D., Microbiology Reviewer

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/s/

FRANK A LUTTERODT
09/12/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [11C] Choline Injection.

We are reviewing the Manufacturing and Clinical section of your submission and have the following comments and information requests. Please supply an amendment to your NDA as soon as possible to address the following items:

Manufacturing:

1. Your 6-month sampling frequency for viable monitoring of the (b) (4) production areas is not adequate to assure control of (b) (4) operations. Please adjust your viable environmental monitoring program to provide for the viable (microbial) sampling of (b) (4) during or at the conclusion of critical drug product (b) (4) manufacturing operations such as the assembly of the final product injection vial kit and the withdrawal of QA samples from the bulk drug vial at the (b) (4)

We advise you to review the following Agency 2011 Guidance: "PET Drugs — Current Good Manufacturing Practice (CGMP) (Small Entity Compliance Guide) which can be found online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM266640.pdf>

2. The media fill procedures used to validate the (b) (4) drug product are inadequate in that they:
 - a. do not represent all of the critical (b) (4) manufacturing processes
 - b. do not assess the full contents of the test vials
 - c. do not use growth medium to simulate the product solution

You should correct your media fill procedures to more closely simulate all of the critical (b) (4) manufacturing process including the assembly of the bulk drug vial (b) (4). Also, you should perform all steps using growth medium and incubate the entire contents of the test vials. For guidance on this topic, we refer you the Agency's 2012 guidance on this topic which may be obtained online at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273766.pdf>

Clinical:

We are currently finalizing our clinical and statistical reviews. In addition to reviewing the published literature and Mayo site data you submitted, we conducted our own published literature review—all focused upon obtaining the most verifiable clinical data. Our findings indicate that, when histopathology (cancer recurrence) is a comparator for PET findings, the PET findings indicate recurrent cancer in most patients with positive PET scans. This observation is based on four studies that we have identified from your submission plus our literature review. We summarize these findings in our draft label proposal. We have extensively revised the proposed labeling but we have also left certain items for you to address (as denoted in italics). Please review this labeling (in a separate document), address the items we cite and supply a revised label as an amendment to your NDA. If you propose alterations of the labeling text, please explain the basis for your proposal.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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/s/

RAFEL D RIEVES
08/16/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

We are reviewing the CMC section of your submission and have the following comments and information request:

1. Be advised that the test sample for finished product quality control testing (chemical and microbiological) must come from the final diluted sample. The proposal about dilution of individual doses as part of the reprocessing procedure is not acceptable, since the test sample for chemical and microbiological testing must come from the diluted dose. (b) (4)

(b) (4) This should be recorded in the batch record. Also, such an event (failing of (b) (4) test) is considered as an out of specification event and should be treated, investigated and corrected.

2. Provide results of accuracy studies (mass / counts recovery studies) for the radiochemical purity method (TON043M) and for chemical purity method (TON043C).
3. The proposed vial label is not acceptable. The vial label must contain at a minimum, the approved name of the drug product (Choline C 11 Injection), identifying lot or control number, the name of manufacturer, and radioactivity symbol. The other required can be deferred to elsewhere in the labeling (shield label and insert). Provide revised mock up of the vial label (including the colors, if any) that contains such information.
4. The Shield label is not acceptable. Provide revised mock up of the shield label (including the colors, if any) that contains such information.
 - Place drug's NDC code in the upper left hand corner of the sticky label.

- Remove or significantly reduce prominence of Mayo Clinic graphic in the upper left corner of the sticky label.
- The Radioactivity symbol can be placed in the upper right corner of sticky label.
- The name of the drug product “Choline C 11 Injection” should be placed prominently, so that it is the most prominent item on the sticky shield label.
- Place statement “For intravenous use” below strength statement below the drug product name on the sticky label.
- Place strength statement “Contains ____ mCi (or MBq) @ _____” under the route of administration. Here the information inserted should be the end of synthesis assay and time of assay.
- Place statement [REDACTED] ^{(b) (4)} on the sticky label.
- Place statement “Contains: 0.9% Sodium Chloride Injection, USP” on the stick label.
- Place statement “Rx Only” on the sticky label.
- Clearly label lot number with date. For example “Lot # _____, Date: MM/DD/YYYY”.
- Add storage statement “store at controlled room temperature, 25°C (77°F)”.
- Add name and address of the manufacturer in the bottom of the sticky label.
- In the part B of the shield label, the prominence of Mayo Clinic graphic should be reduced; the name and address of the manufacturer should be relocated to the bottom portion of the label; the name of the drug product should be changed to Choline C 11 Injection and should be placed so that it is the most prominent item on the label; the other information revised to be consistent with the sticky label.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FRANK A LUTTERODT

07/19/2012

From: Lutterodt, Frank A

Sent: Monday, July 16, 2012 9:18 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: CMC Comments and Request: Mayo Choline NDA 203155



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional CMC information requests:

1. You indicate that Choline C 11 Injection may be reprocessed if a batch fails to meet specifications due to (1) (b)(4) integrity test (MC-C11-Q184); (2) Appearance—particulates in the final product formulation (MC-C11-Q180); and (3) (b)(4) (MC-C11-Q182). You have, however, not provided the details of reprocessing and testing procedures. Provide these procedures. While reprocessing due to failure of (b)(4) integrity test and due to presence of particulate material in the product may be reasonable (if information and supporting data are provided), reprocessing due to failure in (b)(4) is not acceptable and should be withdrawn from the NDA file. Additionally, the QC should be performed on reprocessed product. Provide these details.
2. You have proposed acceptance criteria for (b)(4) impurity in the drug product to be (b)(4). You also indicate that (b)(4) in the final drug product ranges between approximately (b)(4). We ask that the specification acceptance criterion of (b)(4) be reduced. Provide revised specification sheet for the drug product.
3. You did not provide details (actual procedure) regarding the preparation of standard solution, test solution and mobile phase solution as well as quality (b)(4) used in the radiochemical identity test procedure (TON 043B). Provide updated procedure which includes this information as well as a representative HPLC chromatogram.
4. You did not provide any method details and procedure description for the radionuclidic purity method. Even though the method is outsourced to an external vendor, the details need to be provided in the application. Provide details radionuclidic purity determination method.

5. In the test for radiochemical purity test (TON-043E), you have indicated that the system suitability testing is not applicable. The system suitability testing ensures that the equipment is functioning properly and should be included in the method. Provide amended method that includes system suitability testing. You may use the 3 standard solution replicates of standard solution of choline chloride and determine % RSD, and have acceptance criteria, based on peak areas of the standard solution as part of the system suitability testing. Additionally, provide details of the preparation of solutions and representative chromatograms for the system suitability test and test solution.
6. For the (b) (4) determination method, provide preparation of reference and test solutions and representative chromatograms for the system suitability test and test solution.
7. In the chemical purity determination method, the system suitability testing acceptance criteria are not specified and should be specified for each aspect. Further, the % RSD for three replicates of standard injection of (b) (4) is extremely broad and should be (b) (4). We generally recommend % RSD criteria of (b) (4). Additionally, provide preparation of solutions and representative chromatograms for the system suitability test and test solution. Provide amended method description and information.
8. You have not provided validation data (results of validation studies) for the drug product analytical methods in the NDA. Provide these.

Please supply a response as soon as possible, preferably within 3 business days.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FRANK A LUTTERODT
05/24/2012

From: Lutterodt, Frank A
Sent: Tuesday, May 22, 2012 8:09 AM
To: 'Hung, Joseph C., Ph.D.'
Subject: CMC Information Request



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional CMC information requests:

1. You indicate that Choline C 11 Injection may be reprocessed if a batch fails to meet specifications due to (1) (b)(4) integrity test (MC-C11-Q184); (2) Appearance—particulates in the final product formulation (MC-C11-Q180); and (3) (b)(4) (MC-C11-Q182). You have, however, not provided the details of reprocessing and testing procedures. Provide these procedures. While reprocessing due to failure of (b)(4) integrity test and due to presence of particulate material in the product may be reasonable (if information and supporting data are provided), reprocessing due to failure in (b)(4) is not acceptable and should be withdrawn from the NDA file. Additionally, the QC should be performed on reprocessed product. Provide these details.
2. You have proposed acceptance criteria for (b)(4) impurity in the drug product to be (b)(4). You also indicate that (b)(4) in the final drug product ranges between approximately (b)(4). We ask that the specification acceptance criterion of (b)(4) be reduced. Provide revised specification sheet for the drug product.
3. You did not provide details (actual procedure) regarding the preparation of standard solution, test solution and mobile phase solution as well as quality (b)(4) used in the radiochemical identity test procedure (TON 043B). Provide updated procedure which includes this information as well as a representative HPLC chromatogram.
4. You did not provide any method details and procedure description for the radionuclidic purity method. Even though the method is outsourced to an external vendor, the details need to be provided in the application. Provide details radionuclidic purity determination method.

5. In the test for radiochemical purity test (TON-043E), you have indicated that the system suitability testing is not applicable. The system suitability testing ensures that the equipment is functioning properly and should be included in the method. Provide amended method that includes system suitability testing. You may use the 3 standard solution replicates of standard solution of choline chloride and determine % RSD, and have acceptance criteria, based on peak areas of the standard solution as part of the system suitability testing. Additionally, provide details of the preparation of solutions and representative chromatograms for the system suitability test and test solution.
6. For the (b) (4) determination method, provide preparation of reference and test solutions and representative chromatograms for the system suitability test and test solution.
7. In the chemical purity determination method, the system suitability testing acceptance criteria are not specified and should be specified for each aspect. Further, the % RSD for three replicates of standard injection of (b) (4) is extremely broad and should be (b) (4). We generally recommend % RSD criteria of (b) (4). Additionally, provide preparation of solutions and representative chromatograms for the system suitability test and test solution. Provide amended method description and information.
8. You have not provided validation data (results of validation studies) for the drug product analytical methods in the NDA. Provide these.

Please supply a response as soon as possible, preferably within 3 business days.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

05/22/2012

From: Lutterodt, Frank A

Sent: Tuesday, May 22, 2012 8:09 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: CMC Information Request



NDA 203,155

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your December 12, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

On April 17, 2012, we received your April 17, 2012 submission. We have determined that this information constitutes a major amendment to this application, as described in our telephone conversation with you on May 8, 2012. The receipt date for the submission was within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 12, 2012.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 22, 2012.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director,
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
05/10/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional request:

1. We note that you propose to [REDACTED] (b) (4). The instructions regarding hormonal therapies are not similarly specific -- no time frame for "avoid" is given. Was there consistency in the length of time (prior to imaging) for discontinuation of hormonal therapies? If there was not consistency, how was the timing of pre-dose discontinuation determined, and do you have data on each patient's concomitant hormonal therapy and timing of discontinuation?

This information is important to help us review your proposed labeling; please supply a response as soon as possible, preferably within 3 business days.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

05/04/2012

From: Lutterodt, Frank A

Sent: Thursday, May 03, 2012 7:28 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: Drug-Interaction IR NDA 203155 [11C] Choline



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional requests:

1. Sections **12.1 Mechanism of Action** and **12.2 Pharmacodynamics** of the proposed package insert do not describe the mechanism by which C11-choline allows selective distribution/visualization of lesions. What property of C11-choline causes selective distribution? Please revise section 12.1 to describe the mechanism by which C11-choline allows effective imaging of lesions, or state that the mechanism of action is unknown. The statements should be supported by data or literature references.

This information is important to help us review your proposed labeling; please supply a response as soon as possible, preferably within 3 business days.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

04/17/2012

From: Lutterodt, Frank A

Sent: Tuesday, April 17, 2012 3:39 PM

To: 'Hung, Joseph C., Ph.D.'

Subject: RE: Information Request



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional requests:

1. The retrospective study report unclearly defines “biochemical recurrence.” Based on the totality of the information, it appears you defined biochemical recurrence (BCR) as the following, based upon the primary therapy:
 - For patients who had surgical therapy (RRP or any type of minimally invasive ablative surgery), BCR was defined as post-therapy PSA value > 0.2 ng/mL on two PSA laboratory determinations obtained at least 3 months apart;
 - For patients who had radiation and/or cryotherapy, BCR was defined as at least one post-therapy PSA laboratory determination that was > 2 ng/mL higher than the post-therapy PSA nadir;
 - For patients who ADT, BCR was defined as post-therapy PSA laboratory values that consistently increased over time.

If our understanding (as stated above) is not correct, supply a corrected version of these BCR definitions. If our statement is correct, please confirm. Additionally, identify the “normal” PSA values for your clinical site.

2. We anticipate labeling (section 14) to focus upon the results from the subset of 75 patients in whom “conventional imaging” was negative. Of these 75 patients, we understand 35 had negative PET scans and 40 had positive PET scans. We request better characterization of these 75 patients, as follows:
 - a. Please complete the following table:

	Total, n = 75	Pos PET, n = 40	Neg PET, n = 35
Age (median/range)			
PSA at time of scan (median/range; identify numbers of missing)			
Initial therapy (if available; identify numbers of missing)			

- b. Supply a scatter plot of patient PSA values at time of scan (Y axis) by PET scan result (Neg/Pos).
 - c. Develop tables that show the distribution of patients by PET scan outcome (Neg/Pos) when categorized by PSA value tercile, quartile, quintile (i.e., when the group range of PSA values at time of PET scan are categorized into 3, 4 and 5 components, n = 75).
3. For the 35 patients with negative conventional imaging and negative PET Scans please provide follow-up clinical data. We understand that 31 of these patients are reported to have no recurrence; how was the lack of recurrence verified? Specifically, supply information on the duration of follow-up for these 31 patients and the type of evaluations performed over the follow-up time period. We understand 4 of the 35 patients had recurrence verified by biopsy. Please explain decision to biopsy and what was biopsied in the face of negative conventional imaging and negative PET scans.
 4. For the 40 patients with negative conventional imaging and positive PET Scans please provide follow-up clinical data on the 11 un-confirmed, and 5 false positive cases (based on biopsy).

This information is important to help us review your proposed labeling; please supply a response as soon as possible, preferably within 5 business days.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT
04/17/2012

From: Lutterodt, Frank A
Sent: Friday, April 13, 2012 2:36 PM
To: Lutterodt, Frank A; 'Hung, Joseph C., Ph.D.'
Subject: RE: Information Request

This is a follow-up to the previous information request which was inadvertently sent with an omission.



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following additional requests:

1. The retrospective study report unclearly defines “biochemical recurrence.” Based on the totality of the information, it appears you defined biochemical recurrence (BCR) as the following, based upon the primary therapy:
 - For patients who had surgical therapy (RRP or any type of minimally invasive ablative surgery), BCR was defined as post-therapy PSA value > 0.2 ng/mL on two PSA laboratory determinations obtained at least 3 months apart;
 - For patients who had radiation and/or cryotherapy, BCR was defined as at least one post-therapy PSA laboratory determination that was > 2 ng/mL higher than the post-therapy PSA nadir;
 - For patients who ADT, BCR was defined as post-therapy PSA laboratory values that consistently increased over time.

If our understanding (as stated above) is not correct, supply a corrected version of these BCR definitions. If our statement is correct, please confirm. Additionally, identify the “normal” PSA values for your clinical site.

2. We anticipate labeling (section 14) to focus upon the results from the subset of 75 patients in whom “conventional imaging” was negative. Of these 75 patients, we understand 35 had negative PET scans and 40 had positive PET scans. We request better characterization of these 75 patients, as follows:
 - a. Please complete the following table:

	Total, n = 75	Pos PET, n = 40	Neg PET, n = 35
Age (median/range)			
PSA at time of scan (median/range; identify numbers of missing)			
Initial therapy (if available; identify numbers of missing)			

b. Supply a scatter plot of patient PSA values at time of scan (Y axis) by PET scan result (Neg/Pos).

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FRANK A LUTTERODT

04/13/2012

From: Lutterodt, Frank A

Sent: Thursday, April 12, 2012 5:18 PM

To: 'Hung, Joseph C., Ph.D.'

Subject: Information Request



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

We are reviewing the CMC section of your submission and have the following comments and information request:

- Provide revised acceptance specifications for the future lots of choline chloride reference standard. The acceptance criteria must also include at least confirmation of identity by NMR / IR spectroscopy by MCRF. Provide a reference spectrum with the identity of future lots will be compared. Additionally, we could not locate representative certificate of analyses (COA) from supplier in section 3.2.S.5, as indicated. Provide COA and spectroscopy data for the reference standard lot which is currently used by your facility.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

04/06/2012

From: Lutterodt, Frank A

Sent: Friday, April 06, 2012 11:13 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: Information Request for NDA202218



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Our review of your NDA 203155 for Choline C11 injection is ongoing and we have the following Information Requests:

1. Clinical Usefulness

The Clinical Studies section of the proposed labeling states that the use of your drug leads to [REDACTED] (b) (4). [REDACTED] (b) (4)”. Please explain your calculation of [REDACTED] (b) (4)” and indicate location of any supporting data.

Abbreviated Clinical Study Report (5.3.5.4.1), page 27 of 36, (RRP Patients Only) states, among other things, that “the clinical usefulness was 31%.” We understand that you calculated “clinical usefulness” as the number of clinically useful PET scans / total number of PET scans, but please explain how you defined “clinical usefulness” and calculated it being at 31%. (Please also indicate the location of any supporting data).

2. PSA cut-off

The Clinical Studies section of the proposed labeling states that the [REDACTED] (b) (4) [REDACTED] Please explain the basis for this statement and indicate location of any supporting data.

Abbreviated Clinical Study Report (5.3.5.4.1), page 27 of 36, (RRP Patients Only) states that the “PSA cut-off for likelihood of having a positive scan for the RRP patients was lower (1.7 ng/mL) than the cutoff used for all patients (2.0 ng/mL).” Please explain the basis for this statement and indicate location of any supporting data.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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FRANK A LUTTERODT

04/03/2012

From: Lutterodt, Frank A

Sent: Tuesday, April 03, 2012 8:29 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: RE: Responses to Information Request for Choline C 11 Injection -

From: Lutterodt, Frank A
Sent: Tuesday, March 27, 2012 3:01 PM
To: 'Hung, Joseph C., Ph.D.'
Subject: Information Request for [11C] choline

Dear Dr. Hung:

We refer you to your NDA for [11C] Choline, please provide responses to the following regarding your label:

- Please comment on your ability to adjust the presentation of information, placement of information and add color contrast (see attachment).
- Please clarify the use of the "sticky" label.
- Please describe the information that is captured in the barcode.

Regards,

Frank

--

Frank Lutterodt, M.S. | Regulatory Health Project Manager | Division of Medical Imaging Products
Office of Drug Evaluation IV | Center for Drug Evaluation and Research | Food and Drug Administration
10903 New Hampshire Avenue, Room 2381 | Silver Spring, MD 20993 Phone: (301) 796.2050 • Fax: (301) 796.9849 |
Frank.Lutterodt@fda.hhs.gov

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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FRANK A LUTTERODT
04/03/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

We refer to your NDA 203155 for C11-Choline and, specifically, to the retrospective study titled "Choline C11 PET for patients with biochemical recurrence following failed initial treatment". Our review is ongoing and we have the following Information Requests:

1. In relation to the SOT (STANDARD OF TRUTH) used for data analyses in this study, please provide a clear definition of "true positive" and "true negative" and identify corresponding variables in the submitted analysis sets.
2. For each patient in this study, provide the following information:
 - Pathology: POS or NEG (either by biopsy or by surgical resection)
 - "Conventional" Imaging: POS or NEG
 - Indicate the type of "conventional" imaging used
 - Indicate the timing of the "conventional" imaging in relation to the timing of Choline-PET imaging
 - Radiation therapy (RT) for recurrence: POS or NEG
 - Of those who received RT for recurrence, 50 % decrease in PSA: POS or NEG
 - Identify the localization of recurrence by Choline PET according to the categories in the proposed indication statement: "local", "lymph node", or "distant". Please clearly define each category
3. Please use "xpt format" for data submission in response to this information request.

Please provide written response by Tuesday, February 28, 2012.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

02/27/2012

From: Lutterodt, Frank A

Sent: Friday, February 24, 2012 1:11 PM

To: 'Hung, Joseph C., Ph.D.'

Subject: Clinical Information Request



NDA 203-155

FILING COMMUNICATION

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) dated December 12, 2011, received December 12, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for [¹¹C] Choline Injection.

We also refer to your amendments dated February 6, 8, 13, and 23, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Medical Imaging Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
02/24/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

We are reviewing your submission and have the following clinical pharmacology comments and information requests:

- 1) We did not find any references to drug-drug interaction for [11-C]Choline except for colchicine (Roef MJ, et al., Nucl Med Com. 2010;31:1075-7) . The authors of this article discuss that other antimitotic therapies using agents such as paclitaxel or docetaxel may also produce compromised [11-C]choline PET images. Do you agree with this conclusion? If not, please explain.
- 2) In addition to colchicine, NDA section 2.7.2.3.7 Drug-Drug Interaction Studies identifies a number of other potential interactions. Please provide references in support of these drug-drug interactions.
- 3) Can it readily be ruled out that a meal rich in choline, or other lipids that are constituents of cell membranes, would alter image quality? At your institution, is imaging always performed in a fasted state?

Please provide written response by Thursday, February 23, 2012.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

02/22/2012

From: Lutterodt, Frank A

Sent: Tuesday, February 21, 2012 6:28 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: FW: Clinical Pharmacology Information Request - NDA 203-155



NDA 203-155

PRIORITY REVIEW DESIGNATION

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) dated December 12, 2012, received December 12, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for [¹¹C] Choline Injection.

We also refer to your submissions dated February 6 and 8, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 12, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 15, 2012.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 24, 2012.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301)796-4251.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director,
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
02/10/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

We are reviewing your submission and have the following comments and information requests:

The submission contains numerous references to documents and procedures but very little actual data on the microbial controls supporting the (b) (4) manufacturing process. To adequately assess the manufacturing process and the microbial quality of the finished drug product, the following information request should be conveyed to the applicant.

Please provide the following additional information:

1. The three (3) most recent media fill validation reports (including procedures and results).
2. Results of container-closure studies that demonstrate that the drug product vial closure system remains an effective barrier to microbial ingress following removal of the various needles used during filling and subsequent sampling of the final drug product container.
3. A description of the (b) (4) testing program sampling plan along with action levels performed during the filling process (include the sample locations, method of collection, frequency of sampling, volume of air sampled).
4. A description of the (b) (4) Integrity Test Method and Post-Use Integrity Test Limits.
5. A description of the endotoxin test method and the assay validation.
6. A description of the sterility test methods. Also, provide copies of the bacteriostasis/fungistasis reports (including results) generated using the drug product.
7. Clarify the meaning of Table 2.3.P.2.5.1 in Section 2.3.P.2.5. The table headings are inconsistent with the table entries.
8. A description of the sterilization processes for reusable, sterile components.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

02/08/2012

From: Lutterodt, Frank A

Sent: Wednesday, February 08, 2012 4:07 PM

To: 'Hung, Joseph C., Ph.D.'

Subject: Microbiology Information Request

Record of Telephone Conversation

NDA: 203-155/Choline C 11

Telephone call date: January 23, 2012

Speakers:

Joseph Hung and colleagues from Mayo Clinic
FDA representatives: Frank Lutterodt, Dwaine Rieves, Bill Dickerson, Jyoti Zalkikar, Alex Gorovets, Lan Huang, Louis Marzella, Lucie Yang

FDA called the sponsor to obtain clarification regarding the retrospective study performed at Mayo in support of the NDA. Specifically, FDA discussed certain GCP topics with the sponsor who verified that they had a systematic procedure in place for their retrospective study, that is was exempt from IRB review and they will provide datasets to allow FDA to verify the data.

The sponsor provided the following email the day after the phone call:

Dear Dr. Rieves:

On behalf of my colleagues at Mayo who have worked on the Choline NDA, I would like to express our sincere gratitude to you and your team to take time from your busy schedules to talk to us yesterday. I think we had a very productive teleconference - thank you very much for your candid comments and suggestions, as well as valuable guidance!

For your information, we will organize the requested data that we have used for the statistical analyses, as well as the statistical analysis methods/definitions that we have employed to generate the final outcome in eCTD format. We plan to submit the requested information (including the statement of financial disclosure and statement about GCP compliance issue) either the 1st or 2nd week of February via FDA's e-submission gateway. Since this e-submission will cover all of the requested items, we will NOT forward any CD containing these materials to you. Please advise me as to whether this is acceptable or not.

Once again, many thanks for your kind support and encouragement for our Choline NDA project!

Warmest regards,

Joe

Joseph C. Hung, Ph.D., BCNP, FASHP, FAPhA

Professor of Pharmacy & Professor of Radiology

Director of Radiopharmaceutical Laboratories & Director of PET

Radiochemistry Facility

Mayo Clinic

200 First Street SW

Rochester, MN 55905-0001

Phone: (507) 284-4104; Fax: (507) 266-4461

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/s/

RAFEL D RIEVES
02/03/2012



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [¹¹C] Choline Injection.

We are reviewing the CMC section of your submission and have the following comments and information requests:

1. We noticed that the test result data for only one batch of choline C 11 injection drug product is provided. Provide release test result data for a minimum of three batches of choline C 11 injection drug product.
2. We noticed that the stability data for only one batch of choline C 11 injection drug product is provided. Provide release stability data for a minimum of three batches of choline C 11 injection drug product.
3. You have not provided information on the type of closure used in the container closure system that is used for finished product. Provide information on the type of closure (e.g., type of (b)(4) formulation used), quantitative composition of the formulation, and information that the formulation meets the USP chapter <661>, USP chapter <87> and USP chapter <88>), and type of crimp seal used.
4. In the analytical procedures used complete details of the procedures appear to be lacking. Each procedure should include the following, as appropriate: (1) the analytical supplies and their quality used; (2) all the equipment and the settings used during the performance of the procedure; (3) the preparation of test, standard, and analytical solutions; (4) detailed description of the test procedure; (5) exact calculations performed in quantitative procedures; (6) the recording of the results; and (7) the system suitability test(s) performed. Provide updated details of the analytical procedures.

5. Indicate whether or not the proposed C 11 injection drug product formulation is representative of the formulations used in human subjects during the investigation (IND) studies. Additionally, we note that over 100 batches have been made for this product at your facility. Provide a tabular summary of the radiochemical purity results for the batches used in clinical studies.
6. Provide copies of method validation package.
7. You have listed [REDACTED] (b) (4). Be advised that since this molecule forms the [REDACTED] (b) (4)
 - a. The identity of each lot of [REDACTED] (b) (4) should be confirmed upon receipt by IR or GC method. Provide the identity test specification of this material.
 - b. Provide the GC method used for confirmation of purity specified in the manufacturer's certificate of analyses (COA).
 - c. You have indicated that [REDACTED] (b) (4) is obtained from [REDACTED] (b) (4) and is [REDACTED] (b) (4). Provide the [REDACTED] (b) (4) procedure, test procedure (the GC method), and test results obtained for the [REDACTED] (b) (4) product.
 - d. The submitted COA for [REDACTED] (b) (4) is from [REDACTED] (b) (4). Provide a more recent COA. Also, clarify what is the expiration dating period for this material and how is it established.

We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

01/17/2012

From: Lutterodt, Frank A

Sent: Thursday, January 12, 2012 4:42 PM

To: 'Hung, Joseph C., Ph.D.'

Cc: Lowe, Val, M.D.; Kwon, Eugene D., M.D.; Hartman, Karen A.

Subject: RE: NDA 203-155



NDA 203-155

INFORMATION REQUEST

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for [^{11}C] Choline Injection.

We are reviewing the Statistics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Submit or locate the following:

- Analysis datasets and raw datasets of the pivotal study (in xpt or sas format) with define.pdf.,
- the sub-group analyses results by age.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT

01/17/2012

From: Lutterodt, Frank A

Sent: Tuesday, January 10, 2012 9:29 AM

To: 'Hung, Joseph C., Ph.D.'

Subject: RE: NDA 203-155



NDA 203-155

NDA ACKNOWLEDGMENT

Mayo Clinic, PET Radiochemistry Facility, (MCPRF)
Attention: Joseph C. Hung, Ph.D, BCNP
Director of Mayo Clinic
PET Radiochemistry Facility
200 First Street SW
Rochester, MN 55905-0001

Dear Dr. Hung:

We have received your New Drug Application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: [¹¹C] Choline Injection

Date of Application: December 12, 2011

Date of Receipt: December 12, 2011

Our Reference Number: NDA 203-155

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 10, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

FRANK A LUTTERODT
12/19/2011