

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 203-155	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: [¹¹ C] Choline Injection Dosage Form: Injection (10 – 20mCi (370 – 740 MBq)) Strengths: 4.0 – 33.1 mCi/mL		
Applicant: Mayo Clinic PET Radiochemistry Facility		
Date of Receipt: December 12, 2011		
PDUFA Goal Date: June 12, 2012		Action Goal Date (if different):
Proposed Indication(s): For diagnostic PET imaging for the identification of (b) (4) recurrence of prostate cancer in patients (b) (4)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
PET/CT with 11C-choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer. Garcia , et al, 2009, Spain, <u>Rev Esp Med Nucl</u>	Comparison of 11C-choline PET/CT detection of biochemical recurrence (BCR) data with 18F-FDG
Detection of local, regional, and distant recurrence in patients with PSA relapse after external beam radiotherapy using (11)C-choline positron emission tomography. Breeuwsma et al, The Netherlands, 2010, <u>Int J Rad Onc Biol Phys</u>	PET scan data from patients with recurrence/PSA relapse after External Beam Radiation Therapy (EBRT)
Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment”, Richter et al , Spain, 2010, <u>Molecular Imaging and Biology</u>	Biochemical prostate cancer dual tracer detection data from recurrent prostate cancer patients

*each source of information should be listed on separate rows

Please see attachment for 9 other publications that were referenced by the applicant

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
Answer: This application is a literature based NDA not based on a reference product but relying on published literature on the applicant’s proposed product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

[¹¹C] Choline Injection

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO



RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application does not rely on any listed product.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If “YES” to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If “NO”, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If “YES” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If “NO” or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

2.7.6 SYNOPSIS OF INDIVIDUAL STUDIES

The locations of the synopsis for Mayo Clinic's retrospective study and relevant literature that supports the intended indication of Choline C 11 Injection are shown in Table 1.

Table 1. Table of Synopses of Individual Studies

Study Title	Sponsor or Authors (year)	Location of CSR or Literature Reference
Choline C 11 positron emission tomography (PET) scan for patients with prostate cancer, with biochemical recurrence following failed initial treatment	Mayo Clinic PET Radiochemistry Facility	5.3.5.4
Evaluation of [11C]-choline positron-emission/computed tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer.	Rinnab L, Mottaghy FM, Blumstein NM, Reske SN, Hautmann RE, Hohl K, et al. (2007)	5.4
[(11)C]choline PET/CT in prostate cancer patients with biochemical recurrence after radical prostatectomy.	Rinnab L, Simon J, Hautmann RE, Cronauer MV, Hohl K, Buck AK, et al. (2009)	5.4
[11C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy.	Reske SN, Blumstein NM, Glatting G. (2008)	5.4
PET/CT with 11C-choline and 18F-FDG in patients with elevated PSA after radical treatment of a prostate cancer.	García JR, M. Soler M, Blanch MA, Ramírez I, Riera E, Lozano P, et al. (2009)	5.4
Detection of local, regional, and distant recurrence in patients with PSA relapse after external-beam radiotherapy using (11)C-choline positron emission tomography.	Breeuwisma AJ, Pruim J, van den Bergh AC, Leliveld AM, Nijman RJ, Dierckx RA, et al. (2010)	5.4
Is there a role for 11C-choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/mL.	Castellucci P, Fuccio C, Rubello D Schiavina R, Santi I, Nanni C, et al. (2010)	5.4

Study Title	Sponsor or Authors (year)	Location of CSR or Literature Reference
Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy.	Giovacchini, G, Picchio M, Coradeschi E, Bettinardi V, Gianolli L, Scattoni V, et al. (2010)	5.4
Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment.	Richter JA, Rodriguez M, Rioja J, Peuelas I, Mart-Climent J, Garrastachu P, et al. (2010)	5.4
Role of whole-body 18F-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer.	Pelosi E, Arena V, Skanjeti A, Pirro V, Douroukas A, Pupi A, et al. (2008)	5.4
[18F]fluorocholine PET/CT imaging for the detection of recurrent prostate cancer at PSA relapse: experience in 100 consecutive patients.	Cimitan M, Bortolus R, Morassut S, Canzonieri V, Garbeglio A, Baresic T, et al. (2006)	5.4
Evaluation of [(18)F]-choline PET/CT for staging and restaging of prostate cancer. Eur J Nucl Med Mol Imaging.	Husarik DB, Miralbell R, Dubs M, John H, Giger OT, Gelet A, et al. (2008)	5.4

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/s/

FRANK A LUTTERODT
08/31/2012

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 16, 2012

TO: Frank Lutterodt, M.S., Regulatory Project Manager
William Dickerson, M.D., Medical Officer
Division of Medical Imaging Products

FROM: John Lee, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D., Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
(Acting for Susan D. Thompson, M.D.
Acting Branch Chief, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations)

SUBJECT: Evaluation of Clinical Inspections

APPLICATIONS: NDA 203-155

APPLICANT: Joseph C. Hung, Ph.D.
Director, Radiochemistry Facility
Mayo Clinic, Rochester, MN

DRUG: Choline C 11 (no trade name)

NME: Yes

INDICATION: Enhancement of positron emission tomography (PET) in detecting prostate cancer with biochemical evidence of disease recurrence

REVIEW CLASSIFICATION: Priority

CONSULTATION REQUEST DATE: May 11, 2012

INSPECTION SUMMARY GOAL DATE: August 12, 2012

DMIP ACTION GOAL DATE: September 12, 2012

PDUFA DUE DATE: September 12, 2012

I. Background

Primary therapy for prostate cancer (surgery, radiation, and/or chemotherapy) may complicate post-therapy monitoring for disease recurrence using conventional imaging, typically bone scan (BS), computed tomography (CT), and/or magnetic resonance imaging (MRI). Therapy-induced tissue scarring makes it difficult to identify early disease recurrence, and early therapy for recurrent disease is often guided more by clinical suspicion than by objective imaging evidence.

NDA 203-155

Based on the clinical experience at Mayo Clinic (Rochester, MN) and supporting medical literature, the applicant (Joseph C. Hung, Ph.D.) claims that positron emission tomography (PET) using choline C 11 is effective in localizing early prostate cancer recurrence, particularly biochemical recurrence (BCR) with low but rising prostate-specific antigen (PSA) level within the 0.2 - 5.0 ng/mL range. A team of eight investigators at Mayo Clinic's Radiochemistry Facility documented their clinical experience as a retrospective patient chart review study. No study protocol was used, patients were not contacted, informed consent was not obtained, and the study was exempted from institutional review board (IRB) review. Mayo Clinic was the only study site. The applicant reports the following study findings and notes that they are consistent with those reported in the literature:

- Choline C 11 PET is 93% sensitive and 76% specific overall (after any primary therapy), and 95% sensitive and 86% specific after radical retropubic prostatectomy (RRP). For the Mayo Clinic patient population, positive predictive value (PPV) and negative predictive value (NPV) were 89% and 82%, respectively.
- In about one-third of the patients with BCR, choline C 11 PET (61 of 176 patients, 35%) was clinically useful in detecting treatable lesions that were otherwise not identified using conventional imaging (88% sensitivity, 94% PPV). In about one-half of these patients (35 of 61 patients, 57%), the identified lesions were surgically resected.
- In comparison with conventional imaging, choline C 11 PET increased the rate of recurrent lesion detection by 30%. One adverse event (AE) was noted during the chart review, a mild self-limited injection site reaction that resolved uneventfully without treatment.

Based on these study findings, along with those published in the literature, the applicant proposes that choline C 11 PET is indicated for "identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

" This NDA, supported by literature reports in addition to the retrospective study (pending publication), is considered a 505(b)(2) application under Federal Food, Drug, and Cosmetic Act.

Study Medication

Choline C 11 is used clinically as a PET radiopharmaceutical, currently most commonly in evaluating prostate cancer. PET identifies metabolic activity and is unaffected by tissue scarring.

- Choline is an essential nutrient important to cell structure and function, including cholinergic neurotransmission, transmembrane signaling, and lipid metabolism. Studies to date indicate that choline is not mutagenic and has no developmental toxicity. Choline kinase activity is up-regulated in cancer cells, and administered choline accumulates preferentially in cancer over normal cells.

- Carbon-11 is a radioisotope produced artificially in a cyclotron which decays to boron-11 by positron emission with a decay half-life of 20 minutes. When conjugated to choline, carbon-11 permits PET imaging of tissues that preferentially accumulate choline, including prostate cancer tissue. At Mayo Clinic, the study medication Choline C 11 Injection is manufactured at the center's Radiochemistry Facility (b) (4)

PET Image Acquisition and Interpretation

Choline C 11 PET was performed using a Discovery RX or 690 integrated scanner (General Electric Medical Systems; Waukesha, Wisconsin) using standard methods in conjunction with low-dose (scout) CT to delineate the anatomic region of interest.

- Immediately following intravenous infusion of choline C 11, PET was performed using 3-minute acquisitions to obtain three-dimensional images from the orbits to the upper thighs.
- Choline C 11 images were viewed and interpreted by a team of physicians experienced in interpreting PET images. Image interpretation at a special display station allowed simultaneous visualization of PET, CT, and/or fused images in transverse, coronal, and sagittal sections.

Retrospective Chart Review Study

Mayo Clinic investigators reviewed the medical records of 231 consecutive prostate cancer patients evaluated with choline C 11 PET (254 scans) between September 2007 and November 2010. The review findings in a subgroup of 176 patients were documented as a retrospective study entitled "Choline C 11 positron emission tomography (PET) scan for patients with prostate cancer with biochemical recurrence following failed initial treatment."

- Major study objectives were to determine: (1) sensitivity and specificity of choline C 11 PET in identifying prostate cancer recurrence, and (2) PPV and NPV of choline C 11 PET result as applicable to the patient population at Mayo Clinic.
- Subject selection: (1) primary therapy for prostate cancer; (2) follow up monitoring using conventional imaging, histopathology of biopsy and/or surgical resection specimen, and choline C 11 PET; (3) BCR of prostate cancer defined as (a) after RRP, two or more elevated PSA \geq three months apart, (b) after radiation or cryoablation, a rise in PSA of > 2 ng/mL above the nadir, or (c) after primary androgen deprivation therapy, any steady rise in PSA
- The results of choline C 11 PET were compared with those of the accepted (truth) standard defined as conventional imaging and/or tissue histopathology:
 - Positive PET result: considered true positive (**TP**) if recurrent disease confirmed by histopathology or conventional imaging, or if PSA decreased $> 50\%$ following irradiation of choline-avid lesions; otherwise, false positive (**FP**)
 - Negative PET result: considered true negative (**TN**) if disease not seen by histopathology and conventional imaging; otherwise, false negative (**FN**)
- The applicant refers to efficacy analyses as efficacy endpoints: (1) sensitivity = $TP / (TP + FN)$, (2) specificity = $TN / (TN + FP)$, (3) PPV = $TP / (TP + FP)$, and (4) NPV = $TN / (TN + FN)$. The following efficacy endpoints (data tabulations) were collected from patient charts:
 - Raw efficacy endpoints : *petrst* (choline C 11 PET scan result; negative or positive), *biopsy* (histopathology result of biopsy), and *resect* (histopathology result of resection specimen)
 - Interpreted efficacy endpoints: *disease* (histopathologically confirmed disease recurrence status, TN or TP) and *concl* (conclusion about choline C 11 PET scan result: TP, TN, FP, or FN)

II. INSPECTION RESULTS

Inspected Entity	Study Description Number of Patients	Inspection Dates	Outcome Classification
Eugene D. Kwon, M.D. Joseph C. Hung, Ph.D. Radiochemistry Facility Mayo Clinic 200 First Street SW Rochester, MN 55905	Retrospective review of patient charts 176 patients with biochemical evidence of prostate cancer recurrence	June 25 - 29, 2012	Pending (Preliminary NAI)

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, minor deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This inspection outcome classification is based on preliminary communication with the field investigator. The final inspection report has not been received from the field office and OSI's review of the report remains pending as of this clinical inspection summary.

What was inspected:

- **Patients:** The study population consisted of 176 patients with prostate cancer in BCR after failed primary therapy and evaluated using conventional imaging and/or histopathology and choline C 11 PET. Study records for 70 patients with negative conventional imaging were selected at random for review and verification of study data.
- **Data Verification:** Patient charts (source documents) could not be reviewed by the FDA because informed consent from subjects had not been obtained, including consent for FDA review. Therefore, data collection forms (DCFs) could not be reviewed against source documents.
- The data listed in Data Tabulations 1 and 2 (provided by DMIP) were consistent with those on DCFs, to include choline C11 PET scan date, patient age, and data variables:
 - Data Tabulation 1 (PET_1CN3): Primary data set
 - Data Tabulation 2 (PET_1CN5): Additional data, including assessment of TPs
- **Definition of negative conventional image:** A conventional image was considered to be negative if it failed to show a lesion suggestive of cancer recurrence in a patient with rising PSA.
 - CT: no lesions suggestive of cancer recurrence between chest and pelvis
 - MRI: no lesions suggestive of cancer recurrence anywhere
 - BS: no local concentration of contrast agent (hot spots)
- Typical clinical trial elements were not applicable to this IRB-exempt retrospective patient chart review study. The following study elements were not evaluated:
 - Subject eligibility, randomization, investigational treatment, protocol deviations, subject discontinuations, concomitant medication use, informed consent, management of adverse events and adverse event reporting, test article accountability, study monitoring, and IRB oversight
 - Verification of source data in patient charts: Information in a patient chart is legally confidential. Informed consent was not obtained to permit the review by regulatory authorities.

General observations and comments:

No deficiencies were observed and a Form FDA 483 was not issued. Data reported in the NDA (Data Tabulations 1 and 2) were consistent with those on DCFs. All data on DCFs appeared to be internally consistent. Comparable data included:

- Raw co-primary efficacy endpoints: *petrslt* (choline C 11 PET scan result; negative or positive), *biopsy* (histopathology result of biopsy), and *resect* (histopathology result of resection specimen)
- Interpreted efficacy endpoint data: *disease* (histopathologically confirmed disease recurrence status; true negative or true positive) and *concl* (conclusion for choline C 11 PET scan result; true positive, true negative, false positive, or false negative)

Assessment of data integrity:

Lacking subject informed consent, patient charts are legally confidential and could not be audited to verify accurate data transfer from patient charts to DCFs. Therefore, OSI can only determine that the data reported in the NDA were consistent with those on audited DCFs.

Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be forwarded to DMIP if conclusions change upon receipt and review of the final inspection report.

III. OVERALL ASSESSMENT OF FINDINGS

Based on literature reports and one retrospective study, the applicant submitted this 505(b)(2) application. A limited inspection of the retrospective study was performed. Lacking subject informed consent, patient charts could not be reviewed as source documents. The data reported in the NDA were reviewed against DCFs. No significant deviations were observed and a Form FDA 483 was not issued. Data Tabulations 1 and 2 in the NDA were consistent with audited study records.

Note: The review of the final inspection report has not been completed and the final inspection outcome classification remains pending. The observations noted above are based on preliminary communications with the field investigator and a preliminary review of the inspection report. An addendum to this clinical inspection summary will be forwarded to DMIP if the final classification changes from the pending classification or if additional observations of clinical or regulatory significance are discovered after completing the review of the final inspection report.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Susan Leibenhaut, M.D.
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Janice Pohlman, M.D., M.P.H.

Team Leader

(Acting for Susan D. Thompson, M.D.

Acting Branch Chief

Good Clinical Practice Assessment Branch

Division of Good Clinical Practice Compliance

Office of Scientific Investigations)

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/s/

JONG HOON LEE
08/16/2012

SUSAN LEIBENHAUT
08/16/2012

JANICE K POHLMAN
08/16/2012

DSI CONSULT: Request for Clinical Inspections

Date: May 9, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
John Lee M.D. Medical Officer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *William Dickerson, M.D., Medical Officer, DMIP*
Alexander Gorovets, M.D., Team Leader, DMIP
Rafel Dwaine Rieves M.D., Director, DMIP

From: *Frank Lutterodt, M.S. Regulatory Health Project Manager/DMIP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-203-155
Applicant: Mayo Clinic Radiochemistry Facility (Joseph Hung, Ph.D.):
Drug Proprietary Name: None, Generic name is Choline C 11
NME or Original BLA: Yes
Review Priority: Priority

Study Population includes < 17 years of age: No
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Choline C 11 Injection is indicated for diagnostic PET imaging for the identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

PDUFA:
Action Goal Date: September 12, 2012
Inspection Summary Goal Date: One month prior to action goal date

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Mayo Clinic/Dr. Joseph Hung/Rochester, MN/telephone 507-284-2511/or 507-284-4107/email at jhung@mayo.edu	none	176	As above

The sponsor supplied clinical data in the form of a study report that consisted of analyses of information extracted from medical records. Patients' charts were consecutively selected for the review if they underwent a choline C 11 PET scan at Mayo Clinic within the time interval September 2007 through November 2010. The study was titled "Choline C11 positron emission tomography (PET) scan for patients with prostate cancer, with biochemical recurrence following failed initial treatment". A clinical protocol was not used to extract the information and the sponsor does not purport that Good Clinical Practice expectations apply to the study in the same manner as they would for a study that used a protocol and/or a prospective design. Instead, the sponsor states, "The data presented to support this NDA were collected in compliance with GCP standards to the extent that the institution and regulatory agencies required for a retrospective chart review." Patients did not provide consent to study participation, were not contacted and the planned study was exempted from IRB review. The sponsor did use "data collection forms" that contained the following information (for each patient):

ID	Accession Number	Study Date	Agent	History	Date of birth
Date of Diagnoses	Age at Treatment	PSA @ dx	Clinical state	Gleason Score	Type of Treatment
Pathologic stage	LN stage	Adjuvant therapy	Type of Adj Treatment	Time to biochem failure	PSA at time of PET
PSA trend	PSADT (months)	PSA velocity (ng/mL/mo)	ADT@PET	Reason for PET	Findings of PET
Additional Imaging Findings	Targeted Biopsy (Y/N)	Path of Biopsy	Treatment	Metastatectomy (Y/N)	Path at Resection
Extent of Lymphadenectomy	# LN Removal	# LN (+)	PSA at last follow-up	PT status DF/alive/dead/recurrence	

Appendix 7 of the study report contains a listing of patients by birth date. The data collection forms were not submitted to the NDA; instead data tabulation sets (SAS data sets) were supplied.

Subsequently, the sponsor submitted the following information:

Study ID	Convention imaging	CT scan	Time from CT Scan to Choline PET Scan	Bone Scan	Time from Bone Scan to Choline PET Scan
MRI	Time from MRI to Choline PET scan	Prostacint Scan	Time from Prostacint Scan to Choline PET Scan	Biopsy	Resection
Location of first recurrence	Location of second recurrence	Location of third recurrence	Selective Radiation to choline avid lesions	More than 50% reduction in PSA	Confirmed Disease
PET result	Conclusion				

III. Site Selection/Rationale

Mayo Clinic is the sole clinical site.

Rationale for DSI Audits

A specific efficacy concern based on review of site specific efficacy data. Specifically, the review team requests DSI to examine the data collection forms and medical records for a representative number of patients in order to verify that the information in the form is correct, with respect to the medical record source document as well with the data tabulation set supplied to FDA. We recommend DSI to select representative patients from among the 75 patients in whom “conventional imaging was negative.” Dr. Lan Huang (OBS) can supply a list of randomly selected patients (by ID number and birthday) if necessary. Additionally, we can supply a copy of the data tabulation set supplied by the sponsor.

We request the inspector to determine at least the following:

- that the patient underwent a C 11 Choline PET scan on the purported date
- that the purported age is correct

-try to determine the criteria the sponsor used to determine “conventional imaging was negative”—these criteria are not apparent and appear to rely solely upon information that was entered into the “additional imaging findings” on the data collection form or some other ad hoc data extraction form
- that all the variables are on data collection forms and on the medical records and that they match

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): single center study that may have labeling implications

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *Mayo Clinic—only site.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Mr. Frank Lutterodt at 301-796-4251 or Dr. Bill Dickerson (301-796-4219) or Dr. Alex Gorovets at 301-796-1736.

Concurrence: (as needed)

_____ Medical Team Leader
_____ *BD* _____ Medical Reviewer
_____ *DR* _____ Division Director (for foreign inspection requests or requests
for 5 or more sites only)

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/s/

RAFEL D RIEVES
05/09/2012

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

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

Memorandum

Date: 5/8/2012

To: Frank Lutterodt, Regulatory Project Manager
Division of Hematology Products

From: James Dvorsky, Regulatory Reviewer
Division of Professional Drug Promotion

Subject: Comments on draft labeling (Package Insert) for NDA 203155, Choline C 11 Injection

In response to your labeling consult request on February 28, 2012, we have reviewed the draft Package Insert for Choline C 11 Injection and have the following comments. Note that these comments are based upon the May 8, 2012 version of the label.

Package Insert Labeling:

Section	Statement	Comment
12.2 Pharmacodynamics		(b) (4)
12.2 Pharmacodynamics		

(b) (4)

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/s/

JAMES S DVORSKY
05/08/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: May 1, 2012

Reviewer: Kevin Wright, PharmD
Division of Medication Error and Prevention Analysis

Team Leader Yelena Maslov, PharmD
Division of Medication Error and Prevention Analysis

Division Director Carol Holquist, RPh.
Division of Medication Error and Prevention Analysis

Drug Name and Strength(s): Choline C-11 Injection
148 MBq to 1225 MBq (4 mCi to 33.1 mCi)

Application Type/Number: NDA 203155

Applicant/sponsor: Mayo Clinic PET Radiochemistry Facility

OSE RCM #: 2011-4611

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed vial label, shield, sticky, and insert labeling for Choline C-11 under NDA 203155 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Choline C-11 Injection is currently under review by the Division of Medical Imaging Products (DMIP). DMEPA was consulted by DMIP to review labels and labeling for this product. Choline C-11 is manufactured at the Mayo Clinic's PET Radiochemistry Facility. The self life (60 minutes) of this product limits the distribution of this product to internal clinic use only.

1.2 REGULATORY HISTORY

The Applicant submitted labels and labeling for Choline C-11 under NDA 203155 submitted on December 12, 2011. This submission is pursuant 21 CFR 212 on current good manufacturing practices (CGMP) for positron emission tomography (PET) drugs. More specifically, this regulation seeks to ensure the safety, identity, strength, purity and quality of PET drugs.

1.3 PRODUCT INFORMATION

The following product information is provided in the December 12, 2011 original submission.

- Active Ingredient: Choline C-11
- Indication of Use: Diagnostic PET (positron emission tomography) imaging for identification of (b) (4) recurrence of prostate cancer in patients (b) (4)
(b) (4)
- Route of Administration: Intravenous
- Dosage Form: Solution for Injection
- Strengths: 148MBq/mL to 1225 MBq/mL (4mCi/mL to 33.1 mCi/mL)
- Dose and Frequency: 370 MBq to 740 MBq (10 mCi to 20 mCi)
- How Supplied: Single dose 30 mL vial
- Storage: Store at controlled room temperature, 25 C (77 F). Permitted temperature excursions between 15 to 30 C (59 F to 86 F). Solution expires (b) (4) minutes after end of synthesis (EOS).
- Container and Closure System: 30 milliliter glass vial.

2 METHODS AND MATERIALS REVIEWED

DMEPA reviewed the Choline C-11 labels and package insert labeling submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Vial Labels submitted December 12, 2011 (Appendix A)
- Shield Labeling submitted December 12, 2011 (Appendix B)
- Stick Label submitted December 12, 2011 (Appendix C)
- Insert Labeling submitted December 12, 2011 (no image)

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESMENT

- Our analysis of the labels and labeling considered the distribution system of this product, and product expiry. We noted several deficiencies in the labels and labeling that may lead to confusion:
 - Vial label uses a  ^{(b) (4)}
 The primary identifier for this product is Choline C-11. Consequently, the name, 'Choline C-11', should appear on the vial label for ease of product identification.
 - Additionally, this label does not include product information such as strength at calibration and product expiration. This information should appear on the immediate container to ensure the accuracy of the dose in the event the vial is separated from the shield.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI: 2004.

5 RECOMMENDATIONS

Based on this information request sent to the Applicant, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

A. Vial Label

- a. Presentation of product name on the label should be consistent with the presentation of the product's name in the package insert. Thus, consider revising the name from [REDACTED]^{(b) (4)} to read, "Choline C-11 Injection".
- b. Clearly label the lot number with date. For example Lot # 110930-T and MMM/DD/YYYY.
- c. If space permits, add the route of administration statement, "For Intravenous Use".
- d. If space permits, add the statement, "Rx Only".

B. Shield Labeling

- a. Increase the prominence of the product name, Choline C-11 Injection.
- b. Decrease the prominence of the Mayo Clinic graphic and the facility's information to help ensure that the name of the product is the most prominent item on the shield labeling.
- c. Delete all trailing zeroes that appear throughout the insert labeling. Trailing zeroes (e.g. '1.0') are considered dangerous abbreviations². As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve error prone trailing zeroes in the labeling of products.
- d. Relocate the radioactive materials warning to the upper portion of the labeling for better visibility.
- e. Change the statements [REDACTED]^{(b) (4)} to "Expiration Date & Time" and [REDACTED]^{(b) (4)} to Calibration Date & Time.
- f. Add statement, "For Intravenous Use Only".

C. Sticky Label

- a. Decrease the prominence of the Mayo Clinic graphic.
- b. Clearly label the lot number with date. For example Lot # 110930-T and MMM/DD/YYYY.
- c. Eliminate all trailing zeroes from the vial shield labeling (e.g. 500.00 mCi change to 500 mCi)
- d. Add the statement "Calibration Date & Time".

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 01/03/2012.

- e. Change the strength presentation to read as follows,
[REDACTED]^{(b) (4)} As currently presented, the strength and concentration presentations are very confusing and may be misinterpreted. As a result, the wrong dose may be administered.
- f. Add statement, “For Intravenous Use Only”.

D. Insert Labeling

1. General Comments

- a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice’s List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.³ As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
- Revise all instances of trailing zeroes appear in Section 11.2 (Physical Characteristics), and Section 14 (Clinical Studies). Trailing zeros are dangerous dose designations that could be misinterpreted as a 10 fold dose if the trailing zero is not seen (e.g., 2.0 ng/mL may be misinterpreted as 20 ng/mL in Section 14).
 - We note the use of the abbreviations throughout the insert labeling. Prior to the use of these abbreviations, the Applicant should provide the intended meaning to mitigate confusion and misinterpretation [e.g. Positron Emission topography-computed topography (PET/CT), kiloelectron volt (keV), millimeter (mm), and microgram per plate (µg/plate).

2. Highlights of Prescribing Information

- Revise the usual dose statement, [REDACTED]^{(b) (4)} to read ‘370 MBq to 740 MBq (megabequerel) (10 mCi to 20 mCi (millicurie))’ throughout the highlights of prescribing information.

³ <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 10/28/2009.

- Revise the statement, ‘intiate imaging immediately after administration of Choline C-11 Injection and acquire static emission images 0-15 minutes from the time of injection to read intiate imaging immediately after administration of Choline C-11 Injection and acquire static emission images 0 to15 minutes from the time of injection.
- Revise the statement of strength, [REDACTED] (b) (4) to read Choline C-11 Injection contains 148 MBq to 1225 MBq per milliliter (4 mCi to 33.1 mCi per milliliter).

3. Section 2: Dosage and Administration

- Revise the statement: [REDACTED] (b) (4) to ‘The recommended dose is 370 MBq to 740 MBq (10 mCi to 20 mCi) as an intravenous infusion’.
- Revise Table 1 to read left to right in chronological order.

If you have further questions or need clarifications, please contact Sandra Griffith, project manager, at 301-796-2445.

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

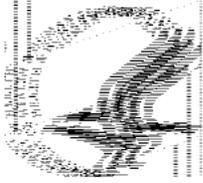
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/s/

KEVIN WRIGHT
05/01/2012

YELENA L MASLOV
05/01/2012

CAROL A HOLQUIST
05/02/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Labeling Review

Date: March 19, 2012 **Date Consulted:** December 13, 2011

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT, Acting Team Leader – Maternal Health
Pediatric and Maternal Health Staff

Hari Cheryl Sachs, MD, Team Leader – Pediatrics
Pediatric and Maternal Health Staff

Lisa Mathis, MD, OND Associate Director,
Pediatric and Maternal Health Staff

To: Division of Medical Imaging Products (DMIP)

Drug: Cholin C11 Injection, NDA 203155

Sponsor: Mayo Clinic PET Radiochemistry Facility

Subject: Pregnancy, Nursing Mothers, and Pediatric Use Labeling

Materials Reviewed:

- Draft Choline C11 Labeling, dated December 12, 2011
- PREA Waiver Request, dated December 12, 2011

Consult Question:

Please review the pregnancy, nursing mothers, and pediatric use subsections of Choline C11 Injection labeling.

INTRODUCTION

On December 12, 2011, The Mayo Clinic PET Radiochemistry Facility submitted a new drug application (NDA 203155) for Choline C11 Injection for the proposed indication of diagnostic PET imaging for identification of (b) (4) recurrence of prostate cancer in patients (b) (4).

(b) (4). The Sponsor submitted an application for orphan designation on March 4, 2011, and the final determination is pending.

DMIP consulted the Pediatric and Maternal Health Staff (PMHS) to review the proposed pregnancy, nursing mothers, and pediatric use labeling.

BACKGROUND

Choline C11 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with PET imaging localization of recurrent prostate cancer. Choline is a dietary supplement and Choline C11 is similar to natural choline with the exception of one radioactive Choline C11 atom. Choline C11 Injection is a radio-labeled analog of choline, an endogenous substrate that is an essential component of phospholipids of the cell membrane, and as such is involved in synthesis of the structural components of cell membranes, as well as modulation of trans-membrane signaling. The activities of phospholipids (i.e., increased uptake of choline) have a role in aberrant cell proliferation and transformation that occurs in tumor cells.¹

PROPOSED LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION



Reviewer Comment: This information may be deleted as no information is provided for pediatric use and there is no indication that includes lactating women.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

(b) (4) with ¹¹C choline. It is (b) (4) not known whether Choline C11 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Choline C11 Injection should be given to a pregnant woman only if clearly needed.

¹ See draft labeling submitted December 12, 2011

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for radiation exposure to nursing infants from Choline C11 Injection, use alternative infant nutrition sources (e.g., stored breast milk or infant formula) for 8 hours (>10 half lives of radioactive decay for ¹¹C isotope) after administration of the drug or avoid use of the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of Choline C11 Injection has not been established in pediatric patients, [REDACTED] (b) (4)

Reviewer Comment: Lacking safety and effectiveness information, no cross-reference should be provided to the dosage and administration section. In addition, the reference to mechanism of action, dosimetry and adult studies is unnecessary.

17 PATIENT COUNSELING INFORMATION

[REDACTED] (b) (4)
Instruct [REDACTED] patients to [REDACTED] (b) (4)

Reviewer Comment: This information may be deleted as there is no indication that includes lactating women.

DISCUSSION AND CONCLUSIONS

The administration of radiopharmaceuticals to a pregnant or nursing woman results in the transfer and absorption of radionuclides to the embryo, fetus, or human milk-fed child from maternal tissues through placental transfer or through breast milk.² Potential effects of radiation on the fetus depend on the fetal stage of development and the magnitude of the radiation dose.

The rate of clearance of radioactivity from breast milk depends on the physical half life (radioactive half-life), and the general recommendation for radiopharmaceuticals is to pump and discard breast milk for 10 half-lives³ after drug administration before resuming nursing, and using alternative nutrition sources for infants during this time (e.g., stored human milk, formula).

Pregnancy and Nursing Mothers Labeling

Until the Pregnancy and Lactation Labeling Rule (PLLR) publishes, the Maternal Health Staff (MHS) is using a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. The Pregnancy and Nursing Mothers section of labeling should describe available animal and human data in a manner that allows clinicians, who are prescribing medication for pregnant patients and female patients of reproductive potential, to balance the

² Risica S, Fattibene F., Mazzei C., Nuccetelli C, Rogani A. Radionuclides in pregnancy and breastfeeding. Microchemical J. 73 (2002) 251-264

³ Stabin MG, Breitz H. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med 2000; 41:863-873

benefits of treating the patient with the potential risks to the mother, fetus and/or infant. PMHS-maternal health labeling recommendations comply with current regulations but incorporate “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). Usually the first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management.

No human pregnancy data or animal data is available for Choline C11 Injection, so the fetal radiation dose and potential harm from this product is unknown. Pregnancy labeling was revised to reflect the lack of information on the use of Choline C11 Injection during pregnancy.

No data is available on the excretion of Choline C11 in breast milk; however, radiopharmaceuticals are transferred to breast milk after administration. Nursing Mothers labeling was revised to reflect the need to pump and discard breast milk for 10 half-lives after Choline C11 Injection administration.

Pediatric Use Labeling

The Pediatric Use subsection of labeling should clearly describe what is known and what is unknown about use of a drug in children, including limitations of use. This subsection should also highlight any differences in efficacy or safety in children versus the adult population. For products with pediatric indications, pediatric use information should be placed in the specific sections of labeling as warranted. 21 CFR 201.57(c)(9)(iv) describes the appropriate pediatric use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

Pediatric studies have not been conducted with Choline C11 Injection; therefore, the Pediatric Use subsection of labeling should reflect that safety and effectiveness have not been established in the pediatric population. ¹¹C Choline radiation dosimetry has been calculated for all age groups using referenced biodistribution data along with the Organ Level Internal Dose Assessment Code (OLINDA) software. However, the pediatric Use subsection should not contain a cross-reference to the dosimetry data lacking safety and efficacy data in the pediatric population.

PREA

The Sponsor submitted a request for waiver of pediatric studies because conducting the necessary studies would be impossible or highly impracticable because prostate cancer is a disease that occurs predominately in the adult population. This waiver request will be discussed at PeRC; however, PMHS agrees that a waiver of pediatric studies is appropriate for the submitted indication. (b) (4).

DMIP could consider issuing a Written Request for Choline C11 if they believe there is a public health benefit of obtaining studies in children. A review of medical literature did not identify current off label use of Choline C11 in the pediatric population.

RECOMMENDATIONS

See the attached labeling for PMHS recommended revisions to the pregnancy, nursing mothers, and pediatric use subsections of Choline C11 Injection labeling.

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Appendix A – PMHS Tracked – Changes Revisions of Choline C11 Injection Labeling

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/s/

JEANINE A BEST
03/20/2012

HARI C SACHS
03/20/2012

LISA L MATHIS
03/27/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203-155 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: NONE Established/Proper Name: [¹¹C] Choline Dosage Form: Injection (10 – 20mCi (370 – 740 MBq)) Strengths: 4.0 – 33.1 mCi/mL		
Applicant: Mayo Clinic PET Radiochemistry Facility Agent for Applicant (if applicable): N/A		
Date of Application: December 12, 2011 Date of Receipt: December 12, 2011 Date clock started after UN: N/A		
PDUFA Goal Date: June 12, 2012	Action Goal Date (if different):	
Filing Date: February 10, 2012	Date of Filing Meeting: January 11, 2012	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication: Choline C 11 Injection is indicated for diagnostic PET imaging for the identification of (b) (4) recurrence of prostate cancer in patients following (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Barrier to Innovation waver granted

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>			X	The applicant did not propose a proprietary name. Only established name is being used
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>			X	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (Vial Shield)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)				
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>			X	

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2/8/2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 11, 2012

BLA/NDA/Supp #: (b) (4)

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: [11C]Choline

DOSAGE FORM/STRENGTH: 10-20 mCi

APPLICANT: Mayo Clinic PET Radiochemistry Facility

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

BACKGROUND:

The application is submitted as a 505(b) (2) new drug application (NDA) to obtain approval to market Choline C 11 Injection for the diagnostic PET (positron emission tomography) imaging for identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

Manufacturing of Choline C 11 Injection will be at Mayo Clinic PET Radiochemistry Facility, Rochester, MN. On November 30, 2011, FDA granted a barrier-to-innovation waiver of application fee to the applicant for this NDA. The Choline C 11 injection is considered as a new molecular entity." A "Priority Review" was granted for this 505(b) (2) NDA on Choline C 11 Injection and the applicant's (b) (4)

This submission is provided entirely in eCTD (electronic Common Technical Document) format.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Frank Lutterodt	Y
	CPMS/TL:	Kyong Kang	Y
Cross-Discipline Team Leader (CDTL)	Alexander Gorovets		Y
Clinical	Reviewer:	William Dickerson	Y
	TL:	Alexander Gorovets	Y
Social Scientist Review (for OTC products)	Reviewer:		N
	TL:		N

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		N
	TL:		N
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		N
	TL:		N
Clinical Pharmacology	Reviewer:	Christy John	Y
	TL:	Gene Williams	Y
Biostatistics	Reviewer:	Lan Huang	Y
	TL:	Jyoti Zalkikar	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ronald Honchel	Y
	TL:	Adebayo Laniyonu	N
Statistics (carcinogenicity)	Reviewer:		N
	TL:		N
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		N
	TL:		N
Product Quality (CMC)	Reviewer:	Ravindra Kasliwal	Y
	TL:	Ali Al Hakim	N
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Robert Mello	Y
	TL:	Bryan Riley	N
CMC Labeling Review	Reviewer:		N
	TL:		N
Facility Review/Inspection	Reviewer:	Zhong Li	Y
	TL:		N
OSE/DMEPA (proprietary name)	Reviewer:		N
	TL:		N

OSE/DRISK (REMS)	Reviewer:	
	TL:	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N
	TL:	N
Bioresearch Monitoring (OSI)	Reviewer:	N
	TL:	N
Controlled Substance Staff (CSS)	Reviewer:	N
	TL:	N
Other reviewers	Rafel Dwaine Rieves (Director, DMIP) Charles Ganley (Office Director)	Yes Yes (TCON)
Other attendees	Carrie Ceresa, PM, PMHS Mildred Wright, PM, PMHS Sandra Griffith, Safety PM, OSE	

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Charles Ganley</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<p>REGULATORY CONCLUSIONS/DEFICIENCIES</p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
<p>ACTIONS ITEMS</p>	
<p><input type="checkbox"/></p>	<p>Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).</p>
<p><input type="checkbox"/></p>	<p>If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).</p>
<p><input type="checkbox"/></p>	<p>If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

Frank Lutterodt

February 10, 2012

Regulatory Project Manager

Date

Kyong Kang

February 10, 2012

Chief, Project Management Staff

Date

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

FRANK A LUTTERODT
02/10/2012

KYONG A KANG
02/13/2012