

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

Date: August 27, 2012

From: Ravindra K. Kasliwal, Ph.D.
CMC Reviewer
Branch VII, DNDQA-III, ONDQA

Through: Ali Al-Hakim, Ph.D.
Branch Chief, Branch VII, DNDQA-III, ONDQA

Subject: NDA 203155; Choline C 11 Injection [Amendments dated 01-Aug-2012, and 03-Aug-2012]

FDA had sent an information request to the applicant on July 16, 2012, requesting updated validation information for two analytical procedures, TON 043C and TON043E. The updated validation reports VON 0005 and VON 0006 were provided in amendment dated 01-Aug-2012. Both these methods have been previously assessed and the applicant was asked to provide the accuracy (recovery) data for these methods.

The validation report VON 0005 for method TON 043E (radiochemical purity testing) shows that, at the detector sensitivity of (b) (4), the method is accurate (recovery ranges from (b) (4) to (b) (4)).

The method TON043E is suitable for determination of radiochemical purity.

The validation report VON 0006 for method TON 043C (Chemical purity testing for (b) (4) and choline) shows that the method is accurate (recoveries are between (b) (4) and (b) (4)) concentration solutions of (b) (4) and choline), linear (b) (4).

The method TON043C is suitable for quantitation of choline and (b) (4) in choline C 11 injection.

Additionally, the applicant has submitted an updated validation report (VON008) for the (b) (4) method TON043F) in amendment dated 03-Aug-2012. The data show that the (b) (4) in the specification limit level.

The recommendation made in the review number 1 is valid and the applicant has addressed the concerns related to the methods.

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/s/

RAVINDRA K KASLIWAL
08/27/2012

ALI H AL HAKIM
08/27/2012

NDA 203155

Choline C 11 Injection

Mayo Clinic PET Radiochemistry Facility (MCPRF)

Mayo Clinic

200 First Street SW

Rochester, MN 55905-0001

Ravindra K. Kasliwal, Ph.D.

Office of New Drug Quality Assessment

Division of Medical Imaging Products

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
III. Administrative.....	7
A. Reviewer's Signature.....	7
B. Endorsement Block.....	7
C. CC Block	7
Chemistry Assessment	8
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	8
S DRUG SUBSTANCE [Name, Manufacturer]	8
P DRUG PRODUCT [Name, Dosage form].....	29
A APPENDICES	46
R REGIONAL INFORMATION	46
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	47
A. Labeling & Package Insert	47
B. Environmental Assessment Or Claim Of Categorical Exclusion	48
III. List Of Deficiencies To Be Communicated.....	50

Chemistry Review Data Sheet

1. NDA 203155
2. REVIEW #: 1
3. REVIEW DATE: 11-Jul-2012 (revised 16-Jul-2012)
4. REVIEWER: Ravindra K. Kasliwal, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	12-Dec-2011
Amendment	08-Feb-2012
Amendment	13-Feb-2012
Amendment	2-Apr-2012
Amendment	10-Apr-2012
Amendment	05-Jun-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Mayo Clinic PET Radiochemistry Facility
Mayo Clinic
Address: 200 First Street SW
Rochester, MN 55905-0001
Representative: Joseph C. Hung, Ph.D., BCNP, Director of MCPRF
Telephone: 507-284-4140 (Dr. Hung); 507-266-2460 (Facility)
Fax: 507-266-2458

8. DRUG PRODUCT NAME/CODE/TYPE:

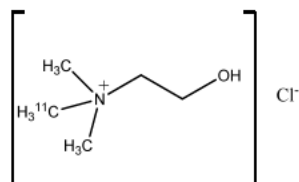
- a) Proprietary Name: N/A – None Proposed.
- b) Non-Proprietary Name (USAN): Choline C 11 Injection
- c) Code Name/# (ONDC only): Mayo clinic code 556
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: PET Imaging Agent
11. DOSAGE FORM: Injection
12. STRENGTH/POTENCY: 4 – 33.1 mCi /mL at End of Synthesis (EOS)
13. ROUTE OF ADMINISTRATION: Intravenous
14. Rx/OTC DISPENSED: X Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Chemical Formula: C₄¹¹CH₁₄ClNO⁺

Molecular Weight: 138.63

Elemental Analysis: C, 42.60; H, 10.18; Cl, 25.57; N, 10.10; O, 11.54

Chemical Name: [¹¹C] Methyl-dimethyl-2-hydroxyethyl-ammonium.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)			(b) (4)	7	N/A		See Micro review for (b) (4)
	III			3	Adequate	26-July-2010	(b) (4) glass reviewed in connection with injectable product.
	III			1	Adequate	11-Jul-2012	Reviewed by Ravindra K. Kasliwal, Ph.D.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

Chemistry Review Data Sheet

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)**B. Other Documents:** None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not applicable.		
EES	Acceptable	20-Mar-2012	D. Smith, Office of Compliance
Pharm/Tox	Approval	20-Mar-2012	Ronald Honchel, Ph.D.
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	The product has 60 minute shelf life. The product methods validation can not be obtained and validation confirmed by FDA laboratories. This is not applicable for this product.		
OSE/DMEPA	No trademark is proposed.	01-May-2012	Kevin Wright, Pharm. D. completed label, labeling and packaging review.
EA	Claim for categorical exclusion is acceptable	11-Jul-2012	Ravindra K. Kalsiwal, Ph.D.
Microbiology	Pending		

The Chemistry Review for NDA 203155

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for approval action, provided the applicant satisfactorily addresses the listed CMC concerns and labeling. The microbiology reviewer's conclusion and recommendation is still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Choline C 11 chloride ($[^{11}\text{C}]$ Methyl-dimethyl-2-hydroxyethyl-ammonium) has a molecular weight of 138.63 g. The radionuclide ^{11}C has a half-life of 20.4 minutes and is a cyclotron-produced radionuclide that decays to boron-11 by positron emission. The ^{11}C radionuclide is produced (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED] (b) (4)

The total radioactivity used to manufacture one batch of drug product is approximately 40-331 mCi (1.48-12.247 GBq). Choline C 11 Injection is supplied in a glass vial containing 4.0-33.1 mCi/mL (0.148- 1.225 GBq/mL) of $[^{11}\text{C}]$ Choline in aqueous 0.9% sodium chloride solution (approximately 10 mL volume) in a 30 ml glass vial. The individual doses are dispensed under the practice of pharmacy by Mayo clinic. Because of the short physical half-life of ^{11}C , Mayo Clinic PET Radiochemistry Facility (MCPRF) has proposed , and which is acceptable, an

Executive Summary Section

expiration dating period of 60 minutes from the end of synthesis (EOS) calibration time when the drug product is stored at 22°C ± 5°C.

B. Description of How the Drug Product is Intended to be Used

Choline C 11 injection to be used as a diagnostic PET (positron emission tomography) imaging agent for identification of (b) (4) recurrence of prostate cancer in patients (b) (4)

The standard dosage is 20 mCi (0.740 GBq). A range of ±10% is applied to every dispensed standard dosage, which is within the ±20% variance allowed by the Nuclear Regulatory Commission for the determination of dispensed dosages. Individual dose of Choline C 11 injection is intravenously administered through a catheter and PET imaging is initiated immediately after administration. The imaging data are acquired for upto 15 minutes.

C. Basis for Approvability Recommendation

The application is recommended for an approval action for chemistry, manufacturing and controls (CMC) based on the following. The recommendation is contingent upon receiving acceptable recommendation from product quality microbiology (review is pending) and submission of acceptable labeling by the applicant.

- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug substance.
- Determination that sufficient information is provided in this New Drug Application, as amended, to ensure the identity, strength, quality, and purity of the drug product.
- The referenced drug master files (DMF) are adequate to support the product application.
- There are no major outstanding issues with specifications, methods and impurities.
- The stability of the product has been sufficiently demonstrated to support a 60 minute expiration dating period.

III. Administrative**A. Reviewer's Signature**

Ravindra K Kasliwal, Ph.D.

B. Endorsement Block

Chemist Name: Ravindra K. Kasliwal, Ph.D. / Date See-DARRTS

Chemistry Branch Chief Name: Ali Al-Hakim, Ph.D. / Date-See DARRTS

Project Manager Name: Frank Lutterodt / Date – see DARRTS

1.CC Block

See DARRTS

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/s/

RAVINDRA K KASLIWAL
07/17/2012

ALI H AL HAKIM
07/17/2012

Initial Quality Assessment (IQA)
Branch VII

Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging Products (DMIP)

NDA: **203115**

Applicant: Mayo Clinic PET Radiochemistry Facility (MCPRF), Mayo Clinic, 200 First Street SW,
Rochester, MN 55905-0001

Stamp Date: 05-Dec-2011

PDUFA Date: 12-Jun-2012 (Priority)

Trademark: None

Established Name: Choline C 11 Injection

Laboratory Code: None

Dosage Form: Injection solution

Route of Administration: Intravenous Injection

Dose: 10 – 20mCi (370 – 740 MBq)

Strength: 4.0 – 33.1 mCi/mL

Indication: Choline C 11 Injection is indicated for (b) (4)

[REDACTED]

CMC Reviewer: Ravindra K. Kasliwal, Ph.D.

	YES	NO
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ONDQA Fileability:	X	
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Comments for 74-Day Letter	X	
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Summary and Critical Issues:

A. Summary

Background Summary

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 (b) (4)

[REDACTED]

Choline C 11 Injection will be manufactured by Mayo Clinic PET Radiochemistry Facility, Rochester, MN. This submission is provided entirely in eCTD (electronic Common Technical Document) format.

On November 30, 2011, FDA granted a barrier-to-innovation waiver of application fee to the applicant for this NDA. A copy of this letter is provided. The FDA letter had stated that the “Mayo Clinic’s Choline C 11 injection would be considered a new molecular entity.” Additionally, FDA’s Division of Medical Imaging Products (DMIP) stated,

“...visualization of recurrent cancer is a clinically important imaging claim and would likely be given a priority review.” As such, the applicant has requested that a “Priority Review” be granted for their 505(b) (2) NDA on Choline C 11 Injection.

(b) (4)

(b) (4)

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(b) (4)

NDA FILING CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		

2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		The NDA is e-CTD.
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			Not applicable.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Listed in drug substance manufacturing facilities section.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)			Not applicable. The radioactive drug substance is manufactured in-situ during the manufacture of the drug product.

8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		The sites are identified in the drug substance section of the application.
9.	Is additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		The testing sites are identified in the manufacturing facilities section in the drug substance section.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		The radioactive drug substance is manufactured in-situ during the manufacture of the drug product.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		The radioactive drug substance is manufactured in-situ during the manufacture of the drug product.
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?		X	The drug product is choline C 11 injection in 0.9% sodium chloride solution. No other formulations are indicated. Information is being requested from applicant.
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	It is being requested. However this is a short shelf life product (60 minutes), so methods validation by the labs may not be practicable.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		The micro section is part of the module 3 of the e-CTD.

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		X	DMF for closure formulation is not provided. It is not clear if the DMF (b) (4) referenced DMF for closure formulation.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)			(b) (4)	10-May-2001	Should be reviewed by Micro

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable.
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	See the comments that should be forwarded to the applicant in 74-day letter of before.

{See appended electronic signature page}

Ravindra K. Kasliwal, Ph.D.
 CMC Reviewer
 Branch VII
 Division of New Drug Quality Assessment-III
 Office of New Drug Quality Assessment

12-Jan-2012

{See appended electronic signature page}

Ali Al-Hakim, Ph.D.
 Branch Chief
 Branch VII
 Division of New Drug Quality Assessment-III
 Office of New Drug Quality Assessment

12-Jan-2012

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/s/

RAVINDRA K KASLIWAL
01/12/2012

ALI H AL HAKIM
01/12/2012