

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203155Orig1s000

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

Positron Emission Tomography (PET) Products

06 September 2012

NDA: 203-155/N-000

Drug Product Name

Proprietary: none

Non-proprietary: Choline C-11 Injection

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
24 August 2012	24 August 2012	24 August 2012	24 August 2012
06 September 2012	06 September 2012	n/a	n/a

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
12 December 2011	1	14 August 2012

Applicant/Sponsor

Name: Mayo Clinic PET Radiochemistry Facility
(MCPRF)

Address: Mayo Clinic
200 First Street SW
Rochester, MN 55905-0001

Representative: Joseph C. Hung, PhD, BCNP
Director of MCPRF

Telephone: 507-284-4104

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from a microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** New Drug Application 505(b)(2)
 2. **SUBMISSION PROVIDES FOR:** Marketing Authorization
 3. **MANUFACTURING SITE:** Mayo Clinic PET Radiochemistry Facility (MCPRF)
Mayo Clinic
200 First Street SW
Rochester, MN 55905-0001
 4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Injection; intravenous; 4-33.1mCi/mL @ end of synthesis (EOS). The bulk drug is collected into (b) (4) type I molded glass vials sealed with (b) (4) stoppers.
 5. **METHOD(S) OF STERILIZATION:** Sterile (b) (4) station.
 6. **PHARMACOLOGICAL CATEGORY:** Positron Emission Tomography (PET) Radiodiagnostic Imaging Agent
- B. **SUPPORTING/RELATED DOCUMENTS:**
- C. **REMARKS:**
- The NDA amendment was submitted in eCTD format.
 - On 16 August 2012 a microbiology information request was transmitted to the applicant concerning deficiencies in environmental monitoring and media fill support of (b) (4). The applicant responded on 24 August 2012 but the information provided did not fully address the original deficiencies. A T-con between the applicant and the Division (including this reviewer) was held on 31 August 2012 to clarify the requirements to satisfy the deficiencies in the applicant's media fill program.
 - The applicant submitted an additional amendment concerning the media fills on 06 September 2012.

Filename: N203155N000R2.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability - Recommend Approval**
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology -** Sterile collection vials are assembled in an (b) (4) environment. The assembled collection vial is prepared with (b) (4) that penetrate the vial's sterile seal. (b) (4) for sterility and bacterial endotoxins testing. The product vial and samples are placed in a protective device (b) (4) for storage and transfer.

- B. Brief Description of Microbiology Deficiencies - None**
- C. Assessment of Risk Due to Microbiology Deficiencies - N/A**

III. Administrative

- A. Reviewer's Signature:** _____
Robert J. Mello, Ph.D.
Senior Microbiology Reviewer
- B. Endorsement Block:** _____
David Hussong, Ph.D.
Director, New Drug Microbiology Staff

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/s/

ROBERT J MELLO
09/07/2012

DAVID HUSSONG
09/07/2012

The reviewer has provided a recommendation for approval based on an evaluation of the applicant's risk assessment and corrected procedures. I concur that the microbiology procedures and controls are appropriate for approval.

Product Quality Microbiology Review

Positron Emission Tomography (PET) Products

14 August 2012

NDA: 203-155/N-000

Drug Product Name

Proprietary: none

Non-proprietary: Choline C-11 Injection

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
12 December 2011	12 December 2011	13 December 2011	15 December 2011
08 February 2012	08 February 2012	n/a	n/a
13 February 2012	13 February 2012	n/a	n/a
05 June 2012	05 June 2012	n/a	n/a

Submission History (for amendments only): N/A

Applicant/Sponsor

Name: Mayo Clinic PET Radiochemistry Facility
(MCPRF)

Address: Mayo Clinic
200 First Street SW
Rochester, MN 55905-0001

Representative: Joseph C. Hung, PhD, BCNP
Director of MCPRF

Telephone: 507-284-4104

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval pending the receipt of additional information.

Product Quality Microbiology Data Sheet

- A.
1. **TYPE OF SUBMISSION:** New Drug Application 505(b)(2)
 2. **SUBMISSION PROVIDES FOR:** Marketing Authorization
 3. **MANUFACTURING SITE:** Mayo Clinic PET Radiochemistry Facility (MCPRF)
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200 First Street SW
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 5. **METHOD(S) OF STERILIZATION:** Sterile (b) (4) station.
 6. **PHARMACOLOGICAL CATEGORY:** Positron Emission Tomography (PET) Radiodiagnostic Imaging Agent
- B. **SUPPORTING/RELATED DOCUMENTS:**
- DMF (b) (4)
 - DMF (b) (4)
 - DMF (b) (4)
- C. **REMARKS:**
- The NDA was submitted in eCTD format.
 - The submission was initially granted Priority Review status with a PDUFA goal date of 12 June 2012.
 - An NDA Amendment dated 17 April 2012 was classified as a major amendment submitted within 3 months of the PDUFA goal date. Therefore, in a letter dated 10 May 2012, the Applicant was notified that the PDUFA goal date was being extended to 12 September 2012.
 - The 08 February 2012, 13 February 2012 and 05 June 2012 submissions were responses to both microbiology and chemistry information requests.

filename: N203155N000R1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability** - The application is recommended for approval pending the receipt of additional information.
- B. Recommendations on Phase 4 Commitments and/or Agreements** - N/A

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – Sterile collection vials are assembled in an (b)(4) environment. The assembled collection vial is prepared with (b)(4) for sterility and bacterial endotoxins testing. The product vial and samples are placed in a protective device (b)(4) for storage and transfer.
- B. Brief Description of Microbiology Deficiencies** - The proposed (b)(6) month frequencies for viable environmental monitoring cannot assure that the microbial integrity of the (b)(4) manufacturing area is being maintained during routine manufacturing operations. Also, the media fill program is inadequate in that it does not simulate all production operations, it does not use microbial growth media in place of drug product and not all of the simulated product is incubated.
- C. Assessment of Risk Due to Microbiology Deficiencies** - N/A

III. Administrative

- A. Reviewer's Signature:** _____
Robert J. Mello, Ph.D.
Senior Microbiology Reviewer
- B. Endorsement Block:** _____
David Hussong, Ph.D.
Director, New Drug Microbiology Staff

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/s/

ROBERT J MELLO

08/14/2012

DAVID HUSSONG

08/14/2012

This review identifies two issues that the applicant should address prior to approval of the application.

PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

NDA Number: 203-155 **Applicant:** Mayo Clinic PET Radiochemistry Facility (MCPRF) **Submit Date:** 12/12/2011

Drug Name: [¹¹C] Choline Injection; 4-33.1 mCi/ml EOS **NDA Type:** 505(b)(2) **Received Date:** 12/12/2011

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		Section 3.2.P.2.5, and Section 3.2.P.8
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Section 3.2.P.3.3, and Sections 3.2.S.2.2, -3 and -4
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?		X	Insufficient information provided to validate (b) (4) procedures
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?		X	Product is not preserved. Container closure integrity studies were not submitted.
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		Section 3.2.P.5.1
7	Has the applicant submitted the results of analytical method verification studies?	X		Section 3.2.P.5.3.2.5 (pages 9-10), but information is insufficient
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?	-	-	Not applicable
9	Is this NDA fileable? If not, then describe why.	X		The submission is fileable but additional information is required to complete the review.

Additional Comments: The submission is fileable.

In order to complete a substantive review of the submission, additional information will be requested from the applicant (see below). DMF (b) (4) was

referenced for the preparation and [REDACTED] (b) (4) of the empty, [REDACTED] (b) (4) sterile collection vials, and it will be reviewed as part of the submission.

Robert J. Mello, Ph.D.
Senior Review Microbiologist

Date

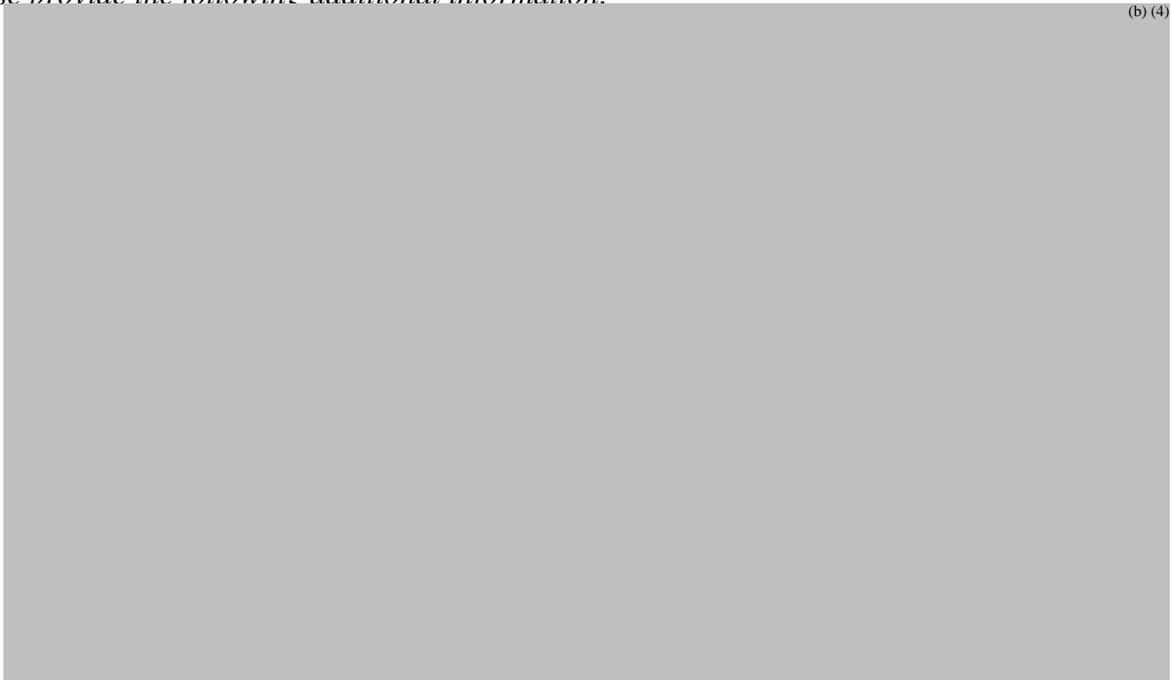
David Hussong, Ph.D.
Director, OPS/NDMS

Date

Product Quality Microbiology Assessment

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

Please provide the following additional information:



[END]

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/s/

ROBERT J MELLO
01/10/2012

DAVID HUSSONG
01/10/2012