PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Date of review: 11/20/06

5. MANUFACTURE OF DRUG SUBSTANCE

A. Batch Formula

The following components and their quantities are used in the production of each batch of [^{11}C]MePPEP for Injection:

Name of component	Component's function	Amount used
Desmethyl MePPEP	Substrate/starting material/ radiopharmaceutical precursor	1.0± 0.1 mg
[^{11}C]Iodomethane	Radiolabeling agent	0.1−1 Ci
N,N-Dimethylformamide	Reaction solvent	80 µL
Tetrabutylammonium hydroxide 0.5 M	Reaction Base	4.4 µL
HPLC column (Phenomenex Luna C-18)	Purify and anaylze product	1
Sodium Chloride Injection, USP, 10 mL vial	Formulation	1
Dehydrated Alcohol, Injection, USP, 1 mL ampule	Formulation	1
Polysorbate 80, N.F	Formulation	10 mg
Sterile empty vial, 10 mL	Product container	1
Filter (Millex MP; 0.22 µm; 25 mm)	Sterilization of product	1
Filter (Millex GV; 0.22 µm; 4 mm)	Sterile vent filter	1

NOTE: Upon scale-up, only the mCi amount of radioactive [^{11}C]carbon dioxide reagent is changed. The other components and their amounts remain as stated in the batch formula.

B. Production of Radionuclide

All radioactive [^{11}C]carbon dioxide is prepared at the NIH Cyclotron Facility. No other source of material is used for the production of [^{11}C]MePPEP for Injection.

C. Cyclotrons Used

The following cyclotrons are used for the production of [^{11}C]carbon dioxide radionuclide:

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Manufacturer	Model
General Electric	PETtrace
Cyclotron Corporation	CS-30
Japan Steel Works	JSW-1710

Specifications for Target Body

Target Data	JSW - 1710	CS-30	GE PETtrace # 1	GE PETtrace # 2
Target body material	Aluminum	Aluminum	Aluminum	Aluminum
Entrance target foil material	Aluminum	Aluminum	Havar	Havar
Target length, cm	30	25.4	25	10
Target volume, mL	212	129	75	11
Gas pressure, atm	5	17	10	25
Maximum proton energy, MeV	9	20	16.5	16.2
Maximum beam current, μA	30	25	50	30

D. Synthesis and Purification of the Drug Substance

Description of Radiosynthesis Equipment and Its Operation:

The descriptions of the radiosynthetic equipment and its cleaning and operation are provided in a copy of the SOP for the unit. See Document 5, SOP # MP201 and SOP # MP202.

Radiosynthetic Production Unit

Manufacturer: General Electric MS PET Systems AB

Model: GE PETtrace Methyl Iodide Micro Lab

Serial Number: 27740

In-Process Controls:

The radiosynthesis production unit continuously records data from its many transducers as part of each batch record attachment. The batch record provides all pertinent information for the control of the radiosynthesis.

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Post-Synthesis Procedures:

Descriptions of procedures used to prepare the production equipment, including any cleaning and purging procedures for a subsequent batch are provided in Document 5, SOP # MP 201 and MP 202.

6. MANUFACTURE OF DRUG PRODUCT

A. Production Operation

The production operation is initiated by manually loading the desmethyl MePPEP, dissolved in 0.080 mL of DMF and 4.4 µL of methanolic 0.5 M tetrabutyl ammonium hydroxide, into the Bioscan Autoloop module. [^{11}C]Carbon dioxide, produced from the cyclotron, is then converted into [^{11}C]iodomethane via the GE Micro-lab module. The [^{11}C]iodomethane is then swept into the Autoloop module and reacted with desmethylMePPEP to produce [^{11}C]MePPEP. The radiolabeled drug substance is purified with HPLC and the HPLC eluent removed by rotary evaporation. The purified [^{11}C]MePPEP is formulated in sterile saline for injection (USP, 0.9% w/v; 10 mL) containing Polysorbate 80 (N.F.; 10 mg) and dehydrated alcohol (USP; 0.9 mL) and sterile-filtered into a sterile, pyrogen-free dose vial. The final sterile vial, vent needle, product needle, and two sterile 0.22 µm filters are assembled in certified laminar flow sterile cabinet (in Room 10/B3C349) before attachment to the radiosynthesis unit.

The master production and control records that provide the exact procedures used in the controlled production of [^{11}C]MePPEP for Injection are provided in Document 2.

Attached to each batch of [^{11}C]MePPEP for Injection are (in this order):

1	**Production Batch Record**
2	**Quality Control Form:** - form contains summary of the quality control results - actual HPLC data
3	**Radiopharmacy Form:** - form contains summary of results (label, pyrogen testing, sterility testing)

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

B. Reprocessing of Drug Product

The PRSS does not reprocess [^{11}C]MePPEP for Injection.

7. CONTAINER/CLOSURE

The pre-sterilized, pre-sealed, pyrogen-free container/closure is obtained from Hospira, Inc. Full information on the container/closure along with its contents, sterilization procedures and sterility assurance are provided in the attached COA (Document 7).

Name and address of supplier	Hospira Inc. 275 North Field Drive, Lake Forest, Illinois 60045
NDC/List number	5816-11
Container	Flip-top – Vial - Glass (LF)
Representative COA and acceptance criteria	COA (Document 7)

8. CONTROLS FOR THE FINISHED DOSAGE FORM

A. Sampling Procedures

Each batch of [^{11}C]MePPEP for Injection will be produced in one vial. A description of the amount of volume that is withdrawn from the finished drug product container and how it is distributed among individual tests is provided in SOP # QA301, “Post-filtration Sampling for QC”.

B. Regulatory Specifications, Procedures, and Testing Schedules

Each batch of [^{11}C]MePPEP for Injection will meet the following specifications during its entire shelf life (see below). We assure that any batch that fails to meet the acceptance criteria will not be released. We also assure that FDA will be notified of any changes to the approved application.

[^{11}C]MePPEP FOR INJECTION: CHEMISTRY, MANUFACTURING AND CONTROLS

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Date of review: 11/20/06

Note: The following tests are related to a commonly used production method. In the event that the production method does not use a component listed below or uses an alternative method of production or produces additional impurities, appropriate tests, acceptance criteria, procedures, and a testing schedule that is more appropriate for such production should be proposed.

Test	Acceptance criteria	Procedures	Testing schedule
Radionuclidic identity	The measured half-life is between 18–22 min	Measurement of a sample in a dose calibrator over 20 min period.	Test completed annually or before use of new target design
Radiochemical identity	Retention time ± 0.5 min in comparison to standard injection of MePPEP	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Radiochemical purity	NLT[1] 95 % [^{11}C]MePPEP	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Chemical Purity	For the injection NMT[2] 1.0 μg of impurity MePPEP equivalent[3]	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Radioconcentration Assay	2.0 mCi to 25 mCi /mL at EOS[4]	Sample measured in ionization chamber (dose calibrator) See Document 3.	Test completed before release of drug product
Residual solvents:	Acetonitrile: NMT 0.04% (w/v). Ethanol: NMT 10% (w/v)	Gas chromatography with flame ionization detection. See Document 5 SOP # QA 302.	Test performed on each batch. Drug product may be released before test completion

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

pH	4.5−7.5	pH paper See Document 3	Test completed before release of drug product
Specific radioactivity	NLT 500 Ci/mmol at EOS	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Sterility testing	Sterile	NIH Microbiology Building 10 Clinical Center	Bactec Test initiated as soon feasible. Typically, less than 24 hours after release of drug product
Membrane filter integrity	Sterile 0.22 µm filters are used once. Each membrane tested by bubble point test.	Pressure gauge transducer. No bubbles at 45 p.s.i See Document 5: SOP # GP102.	Test completed before release of drug product
Bacterial endotoxins (LAL)	Less than 2.5 EU/mL	LAL test kit procedure (see Document 4: Radiopharmacy Form)	Test performed on each batch. Drug product may be released before test completion.

1. NLT = No less than
2. NMT = No more than
3. i.e. < 10% impurity of maximum allowed dose of 10.0 µg
4. EOS = End of synthesis

9. MICROBIOLOGICAL VALIDATION

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Data provided in Document 9 (Validation Runs) show that [^{11}C]MePPEP for Injection is obtained in a sterile and pyrogen-free form, when prepared according to this application and the submitted batch production record.

10. STABILITY AND BATCH DATA

A. Expiry Dating Period

Expiry-dating period is 1 h from EOS for [^{11}C]MePPEP for Injection stored at controlled room temperature (note: refer to USP for controlled room temperature definition).

B. Stability Data/Batch Data

Complete release and stability data were obtained on three batches of [^{11}C]MePPEP for Injection, prepared at the upper range of the proposed radioconcentration and stored at controlled room temperature. See Document 9: Validation Runs.

Also for each stability batch:

- The batch was stored in the same container/closure as it was produced.
- All tests indicated in the specification section were performed at release.
- The appearance and radiochemical purity were also evaluated at the end of the proposed expiry period.

11. VIAL AND OUTER PACKAGING LABELS

Proposed vial and outer packaging labels are shown in Document 5: SOP # QA 304. Each batch will be labeled with a lot number, compound name, volume and assay and will contain the statement: "Caution: New Drug Limited by Federal Law to Investigational Use".

12. ENVIRONMENTAL ASSESSMENT

In accordance with 21 CFR 25.31(b), the PRSS claims a categorical exclusion from the environmental assessment requirements of 21 CFR 25.20 for approval of [^{11}C]MePPEP for

PET Radiopharmaceutical Sciences Section,
Molecular Imaging Branch,
National Institute of Mental Health,
National Institutes of Health,
Bldg. 10, Rm. B3 C338,
Bethesda, MD 20892

Injection on the basis that the estimated concentration of [^{11}C]MePPEP at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, no extraordinary circumstances exist.