[^{11}C]PBR28 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: 08/22/05

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]PBR 28 for injection:

Name of component	Component's function	Amount used
Desmethyl-PBR 28	Substrate starting material – radiopharmaceutical precursor	1.0 ± 0.1 mg
[^{11}C]methyl iodide	Radiolabeling agent	100 to 1000 mCi
N,N-Dimethylformamide	Reaction solvent	80 µL
Tetrabutylammonium hydroxide 0.5 M	Reaction Base	4 µL
HPLC column	Separate product	1
Sodium Chloride for Injection, (USP; 10 mL vial)	Formulation	1
Sterile vial, 10 mL	Product container	1
Filter (MP; 0.22 µm; 25 mm; Millex)	Sterilization	1
Filter (GV; 0.22 µm; 4 mm; Millex)	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 Radionulide

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]PBR 28.

C. Cyclotrons Used

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

Manufacturer	Model

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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 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 radiosynthetic 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 radiosynthetic process.

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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-PBR 28 dissolved in 0.080 mL of DMF and 4 µL of 0.5 M methanolic 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 methyl iodide Micro-lab module. The [^{11}C]iodomethane is then swept into the Autoloop module and the radiolabeling reagent is reacted with desmethyl-PBR 28 to produce [^{11}C]PBR 28. The radiolabeled drug substance is purified by HPLC and the HPLC eluent removed by rotary evaporation. The purified [^{11}C]PBR 28 is formulated in Sterile Saline for Injection (USP, 0.9% w/v; 10 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 a sterile cabinet (certified laminar flow sterile cabinet in RM B3C-313) 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]PBR 28 are provided in document 2.

Attached to each [^{11}C] PBR 28 batch (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)

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NOTE: ***DOCUMENT 2 – [^{11}C]PBR28 FOR INJECTION: MASTER BATCH RECORD***

Reagents/solvents/supplies	Lot/Exp
N,N-Dimethylformamide, anhydrous	
Desmethyl-PBR 28 (precursor to PBR 28); 1.0 mg;	
HPLC column (semi-prep, Luna; 10 µm;10 mm x 250 mm; Phenomenex)	
HPLC column (analytical, Onyx, 10 µm; 4.6 mm x 100 mm; Phenomenex)	
Water, HPLC grade	
Acetonitrile, HPLC grade	
Ammonium formate	
Tetrabutyl ammonium hydroxide (1.0 M in methanol)	
Ethyl Alcohol, USP 200 Proof	
Sterile vial 10 mL; 1 each	
Sterile Saline for Injection; 10 mL	
Sterile Millex-GV filter (vent filter, 0.22 µm pore size; 4 mm diameter); 1 each	
Sterile Millex-MP filter (sterilization filter, 0.22 µm pore size; 25 mm diameter); 1 each	
Sterile needle (21 gauge; 2 inches long) for sterile filtration; 1 each	
Sterile needle (20 gauge; 1.5 inches long) for sterile vent; 1 each	

Material	Function	Actual weight	Volume	Date of Preparation/SOP #
N,N-Dimethylformamide	Solvent	N/A	0.080 mL	Bottle opened on _____
0.01 M Ammomium formate in 1 L of HPLC grade water, pH adjusted	Aqueous mobile phase for preparative HPLC	N/A	1 L	SOP # GP101
A/B = 70/30 v/v; A = 0.01 M ammonium formate in 1 L of HPLC grade water; B is acetonitrile	Isocratic mobile phase for analytical HPLC	N/A	1 L	SOP # GP101
Accepted Desmethyl-PBR 28	Precursor (1.0 ± 0.1 mg)	mg	N/A	SOP # GP101

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Key operation	Check	Comment/SOP #
Check all gas valves are open and that pressure on regulators are 60, 12, and 22 p.s.i. for nitrogen, helium, and hydrogen, respectively		
Test 32 karat Beckman HPLC data acquisition interface box, UV, and PIN diode detector by making it wait for trigger and then initiate data collection		
6-way valve in NEMA box is set to hot-cell # 3 and 3-way valve is on “cryo” position		
Check gas collection valve is on “fill” position		
Heating bath is filled with water and set to 80 ˚C		
Dry-ice traps are ready		
All transfer tubings (20 mL column, HPLC fraction collection line, saline inlet) are cleaned with USP ethanol and flushed dry		SOP # MP201.6
10 mL syringe containing sterile saline for injection, USP hooked to end of saline addition line		
Verify balance accuracy (acceptable range 9.9 – 10.1) of a 10 g NIST calibrated standard weight		Record weight _____ g
Sterile filtration unit is installed		SOP # MP201.7
Run prep sequence on GE Microlab MeI box		SOP # MP201.5
Check flow in RMA, RMB, RMC		SOP # MP201.5
Clean and dry the Bioscan auto loop		SOP # MP201.3
Check integrity of GE MeI box by running leak check 1		SOP # MP201.4
Confirm solvent selector switch is set to PBR28 prep column		
Equilibrate the preparative column with acetonitrile-0.01 M ammonium formate (47: 53 v/v) at 8 mL/min. Pressure should be about 2.8 k p.s.i.		SOP # MP201.8
Equilibrate the analytical column with acetonitrile-0.01 M ammonium formate (30:70 v/v) at 6 mL/min.		SOP # MP201.8
Check for leaks on preparative and analytical columns at operating flow rates		
Inject PBR 28 standard and clean analytical port		SOP # QA303.2 and # QA303.3

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Turn down the flow on preparative and analytical systems to 0.567 and 0.234 mL/min, respectively		SOP # MP201.8
Verify vacuum integrity. Turn on pump; gauge should read at least 28 inches of mercury (67 mBar).		
Dissolve precursor in 80 µL of DMF. Add 4 µL of 0.5 M tetrabutyl ammonium hydroxide in methanol *ca.* 3 min before E.O.B.		SOP # GP101
Allow the reaction to proceed in the loop for 3.0 min.		

Filter integrity test performed at 45 p.s.i		SOP # GP102
		P = Pass F= Fail (circle one)

Cyclotron, run #	
End of bombardment	
Beam current	µA
Bombardment time	min
Empty vial weight (g):_____(W_0); vial weight after removal of QC sample (g): _____ (W_1)	Calculated volume (mL) = $W_1 – W_0$ = _____ mL
Final formulated product	mCi at
Production chemist	Signature:

B. Reprocessing of PET Drug Product

The PET Radiopharmaceutical Sciences Section of the Molecular Imaging Branch of NIMH does not reprocess [^{11}C]PBR 28.

7. CONTAINER/CLOSURE

The pre-sterilized, pre-sealed, pyrogen-free container/closure is obtained from Abbott laboratories. Full information on the container/closure along with its contents sterilization procedures and sterility assurance is provided in the attached certificate of analysis (COA).

Name and Address of Supplier	Abbott Laboratories Inc.200 Abbott Park Rd. Abbott, IL

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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 [11C]PBR 28 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 the standard operating procedure entitled, "SOP # QA301: Post-filtration sampling for QC."

B. Regulatory Specifications, Procedures, and Testing Schedules

Each batch of [11C]PBR 28 for injection will meet the following specifications during its entire shelf life (see below). We commit that any batch that fails to meet the acceptance criteria will not be released. We also commit that FDA will be notified of any changes to the approved application.

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 alternate 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.

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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 ± 1.0 min in comparison to standard injection of PBR 28	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Radiochemical purity	NLT[1] 95 % [^{11}C]PBR 28	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 (PBR 28 equivalent)[3]	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Assay (radioconcentration)	2.0 mCi to 25 mCi /mL at EOS[4]	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 3 and Document 5 SOP #QA 302.	Test performed on 3 validation runs.
pH	4.5−7.5	pH paper See Document 3	Test completed before release of drug product

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Specific radioactivity	No carrier added [^{11}C]PBR 28 NLT 500 Ci/mmol at EOS	HPLC QC Procedure See Document 3.	Test completed before release of drug product
Sterility testing	Sterile	NIH Microbiology Bldg 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 prior to 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 completion of test.

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