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Cancer Imaging Program

National Cancer Institute

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Master Batch Record

MBR-[^{18}F]FLT-_____

For Synthesis of 3'-Deoxy-3'-[^{18}F]Fluorothymidine: [^{18}F]FLT Injection

Approval Signatures:

Printed Name	Date	Signature	Date
Author:			
Supervisor:			
Regulatory Affairs/QA:			

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

Synthesis Batch Record

3'-Deoxy-3'-[^{18}F]Fluorothymidine Batch Number: **MBR-[^{18}F]FLT-_____**

Manufacturing Date: _____ Expiration Date: _____

EQUIPMENT

Equipment Description	Internal Tracking Number/ Identification	Manufacturer	Verified By (Initials)
Nucleophilic Synthesis Module with glassware			
Cyclotron			
HPLC Pump with Injector			
Flow through UV Absorbance Detector			
Vacuum Pump			
Computer with Nucleophilic Synthesis Module Software installed			
Printer			
Shielding for Nucleophilic Synthesis Module / Hot Cell			

GENERAL (Non-Inventoried per Batch) SUPPLIES

Supply Description	Verified By (Initials)
Appropriate Safety Wear including radiation badges, lab coat, safety glasses, shielding	
Gloves	
Container for Solvent Waste, 200-2,000 mL bottle	
Liquid Nitrogen or Liquid Argon	
Helium or Nitrogen Gas 30-150 psig supply on and > 500 psi in tank or sufficient cryogen	
Compressed Air 70-150 psig supply on with sufficient tank or compressor capacity	

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

INVENTORIED SUPPLIES (may vary with synthesis module)

Supply Description	Internal Tracking Number/ Identification	Quantity	Verified By (Initials)
Sterile Syringe, 1 mL, no silicone or latex (for Vial 1-6 additions and ^{18}F Sep Cartridge wash)		8	
Disposable Needles 23 or 25G x > 2½" long (fill Vials 1-6)		6	
Sterile Vent Filter 0.2 µm Millex SLGS V25 5F	**SS-SVF-_____**	4	
Alumina N Light Sep-Pak Cartridge	**SS-SPC-_____**	1	
[^{18}F] Separation Cartridge	**SS-FSC-_____**	1	
Sterile Disposable Syringes, 10 mL no silicone or latex (for acetone)		1	
Sterile Disposable Syringes: 1-0.5 mL (QC sample), 1-1 mL (conc saline), 1-10 mL (Alumina wash), 2-5 mL (QC sample, ethanol clean)		5	
Sterilizing Filter 0.2 µm	**SS-SPF-_____**	2	
Sterile Vented Filter Needle	**SS-VFN-_____**	1	
Empty Sterile Vial, 10 mL to 30 mL	**SS-SBV-_____**	1	
Sterile Disposable Needles 22G or smaller		8	
HPLC Preparative Column (Luna C_{18} 10 x 250 mm with guard)	**SS-LUN-_____**	1	
Alcohol Swabs		qs	

REAGENTS/SOLUTIONS

Reagent	Internal Tracking Number/ Identification	Quantity	Verified By (Initials)
Ethyl Alcohol, absolute USP	**SS-ETH-_____**	qs	
SWFI, Sterile Water for Injection	**SS-WFI-_____**	qs	
Kryptofix® [2.2.2]	**SS-KRY-_____**	15 ± 2 mg	
K_2CO_3	**SS-KCA-_____**		
NaOH, USP	**SS- NAH-_____**		
[^{18}F] Precursor, 5'-*O*-Benzoyl-2,3'-anhydrothymidine	**SS-BAT-_____**	10 ± 1 mg	
Dimethyl Sulfoxide (DMSO), anhydrous	**SS-DMS-_____**	1.0 ± 0.05 mL	
Sodium Dihydrogen Phosphate, Monobasic, USP	**SS-DPM-_____**		
Sodium Phosphates for Injection, USP	**SS-NAP-_____**	1 vial	
Acetonitrile, USP	**SS-ACN-_____**	1.0 ± 0.05 mL	
23.4% Sodium Chloride Solution, for dilution, USP (234 mg/mL)	**SS-NCC-_____**	1 vial	
Acetone, spectrophotometric grade	**SS-ACT-_____**	qs to clean unit	
$H_2{}^{18}O$, Target material	**SS-O18-_____**	1.0 – 5.0 mL	

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

Solutions	Specification	Compounding Record Number (if applicable)	Quantity
70% Vol. Ethanol	Compounded from USP reagents	**ETH70-_____**	500 mL
(92/8) Sodium Phosphate 10 mM/ Ethanol	Compounded from USP reagents	**HBS-_____**	> 750 mL
0.04 M K_2O_3 solution	High purity carbonate in USP water for injection	**KCO-_____**	0.5 mL
Kryptofix® [2.2.2] solution (15mg in 1 mL acetonitrile)	Anhydrous CH_3CN, reagent grade [2.2.2]	N/A	1.0 mL
1% NaOH	Compounded from USP/NF reagents	**NAH-SOLN-_____**	0.35 mL
0.2N Sodium Dihydrogen Phosphate	Compounded from USP reagents	**DHP-_____**	0.75 mL

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

I. Maintenance and Cleaning of the Nucleophilic Synthesis Module

(Initial all blanks when the step is performed as listed, add values or "no" where appropriate.)

STEP	Performed By Initial/Date
I.1. Perform Maintenance on the Nucleophilic Synthesis Module. I.1.1. Remove the used ^{18}F separation and the purification columns from the synthesizer. I.1.2. Empty the ^{18}O water vial, dry it and reattach it to the synthesizer. I.1.3. Remove and empty the cold trap. I.1.4. Fill the dewar with new liquid nitrogen or argon and replace the cold trap. I.1.5. Empty the v-vial and reattach it to the synthesizer. I.1.6. Empty the waste container.	
I.1.7. Inspect or replace the Reaction Vessel I.1.8. Record the equipment maintenance in the equipment history log book, on **Form EQ-001**.	
I.2. Cleaning the Nucleophilic Synthesis Module (Sponsor to complete this section as per the specific Nucleophilic Synthesis Module's Cleaning procedure outlined in the manufacturer's manual not inconsistent with clinical manufacturing for human administration.) I.2.1. Nitrogen or Helium tank pressure _____ psi (≥ 500 or liq), supply pressure _____ psi (30 – 150). Air supply pressure _____ psi (70 – 150). I.2.2. Synthesis Module power on. Vacuum pump switch turned on. I.2.3. Computer on. I.2.4. Module software initialized. Enter username and password. I.2.5. I.2.6. I.2.7. I.2.8 I.2.9. I.2.10.Document the equipment cleaning in the equipment history log on **Form EQ-001**.	

Performed By: _____ **Date:** _____
Signature

Checked By: _____ **Date:** _____
Signature

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

II. Pre-Synthesis Setup for Manufacturing [^{18}F]FLT Using Synthesis Module

STEP	Performed By Initial/Date
II.1. Conditioning the HPLC Column (Requires ~1 hour) II.1.1. Add ≥ 200 mL of 70% ethanol, (**ETH70-L**), to eluent bottle 2 and ≥ 500 mL of fresh preparative mobile phase (**HBS-L,** 92% 0.01 M Phosphate 8%Ethanol) to eluent bottle 1. **70% Ethanol Compounding Record: ETH70-_____** **Volume Added: _____ mL (**≥ 200 mL**)** **Mobile Phase Compounding Record: HBS-_____** **Volume Added: _____ mL (**≥ 500 mL**)** II.1.2. On Module software go to the menu bar and select manual operation. Switch the injector to the inject position. II.1.3. Open the He or N_2 eluent purge. Turn the valve to eluent 2 (70% ethanol). II.1.4. Set pump flow to 4 (mL/min), _____, Let it run for > 10 minutes, _____ (minutes run). II.1.5. Set pump flow to 0 (mL/min), _____, Turn the valve back to eluent 1 (**HBS-L**). II.1.6. Set pump flow to 3 (mL/min), _____, Let it run for ~ 4 minutes, _____ (minutes run). Then set the pump flow to 6 (mL/min), _____, Let it run for > 20 minutes, _____ (minutes run). Check that the flow is steady. After 10-15 minutes check the flow rate of the HPLC column _____ (mL/min) to ensure that it is running properly. II.1.7. Close the He or N_2 eluent purge, pump flow to 0 (mL/min), _____. II.1.8. On the Module software, go to the menu bar and select manual stop.	
II.2. Prepare the ^{18}F Separation Column (SS-FSC) II.2.1. Slowly wash column with 1 mL of ethanol (**SS-ETH**), _____ mL. II.2.2. Slowly wash column with 1 mL of Sterile Water for Injection (**SS-WFI**), wait five minutes, _____ mL, _____ min. II.2.3. Push air through the column to expel the residual water.	
II.3. Prepare the Sep-pak® Alumina N Light Cartridge (SS-SPC) Wash the column with 10 mL of Sterile Water for Injection (**SS-WFI**), _____ mL. Expel the residual water.	
II.4. Prepare Precursor Solution (5'-*O*-benzoyl-2,3'-anhydrothymidine: DMSO) Transfer 1 mL of DMSO (**SS-DMS**) to FLT precursor (**SS-BAT**) vial, _____ mL. Ensure thorough mixing prior to transferring from the vial.	

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

STEP	Performed By Initial/Date
II.5. Prepare Sterile Product Vial Assembly Label the empty product sterile vial (**SS-SBV**) with "[^{18}F]FLT" and the Master Batch Number. Use aseptic technique, in a laminar flow hood to insert a sterilizing filter with a ≤ 22G needle into the final product empty sterile vial. Insert a venting filter needle into the empty sterile vial. Add 0.50 to 0.60 mL of concentrated saline for dilution, USP (**SS-NCC**) to the vial, _____ (mL added).	
II.6. Run the FLT Program (<u>NOTE</u>: Ensure that the target line is attached to the synthesizer.) Select the METHOD for the Synthesizer to use. *This section is the list of prompts for the specific computer program and the adding of reagents prior to starting the synthesis—the sponsor should provide this depending on which nucleophilic synthesis module they choose to utilize.*	

Preparation	Answer

Performed By: _____ **Date:** _____
Signature

Checked By: _____ **Date:** _____
Signature

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III. Manufacturing [^{18}F]FLT Using the Nucleophilic Synthesis Module

STEP	Performed By Initial/Date
III.1. Synthesize [^{18}F]FLT III.1.1. Press the "**START"** button. III.1.2. Deliver the $^{18}F^-$ activity to the synthesis box. **$^{18}F^-$ Delivery Start Time: _____** (time of day) **$^{18}F^-$ Delivery Time Complete: _____** (time of day) III.1.3. Verify cyclotron transfer of ^{18}O water (**SS-O18**) with $^{18}F^-$ process ^{18}F fluoride is complete. Press the "**okay button for the prompt: "Click okay after F^- is delivered from cyclotron.**" **Synthesis Start Time: _____** (time of day, cyclotron clock) III.1.4. HPLC Collection: Press the "**COLLECT**" when the FLT peak appears on the Radioisotope display. **HPLC Fraction Started: _____** minutes (Retention Time) Press the "**STOP COLLECT**" to end the collection. **HPLC Fraction Stopped: _____** minutes (Retention Time) III.1.6. Remove the [^{18}F]FLT product vial assembly from the hot cell if necessary and transfer it behind the shield.	

Performed By: _____ Date: _____
Signature

Checked By: _____ Date: _____
Signature

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

IV. Post-Synthesis

STEP	Performed By Initial/Date
IV.1. Withdraw Samples for Quality Control Testing **IV.1.1.** Assay using the Dose Calibrator **Final Product Assay: _____ mCi** **Time of End of Synthesis (EOS): _____** (time of day) **IV.1.2.** Particulate test of the final product (describe), _____. **IV.1.3.** Perform an integrity test of the sterile product filter as per **GEN-Q110**. Record the results of the filter integrity test here, _____ psi. Remove and discard the vent filter. **IV.1.4.** Sample Withdrawn for QC Testing: _____ mL (0.5 mL) **Assay of Quality Control Sample: _____ mCi at _____** (time of day). Calculated EOS Activity: $\frac{\text{Sample mCi}}{e^{-\lambda t}}$ = **_____ mCi (EOS)** $e^{-\lambda t}$ **= _____ where λ = ln(2)/109.8 and t = (Assay Time – EOS) in minutes** **IV.1.5.** Calculated Specific Concentration: $\frac{\text{mCi (EOS)}}{\text{mL sample}}$ = **_____ mCi/mL** Calculated Final Product Volume: $\frac{\text{Final Product Assay}}{\text{Calculated Specific Concentration}}$ = **_____ mL (12-17 mL)** **IV.1.6.** Sterility and Reserve Samples Withdrawn: _____ mL (2.0 mL) **IV.1.7.** Record the results of the QC release tests on **Form FQC-001** as they are obtained. **IV.1.8.** Attach all manufacturing variances to the batch record and record the number of variances reported here, _____.	

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

STEP	Performed By Initial/Date
IV.1.9. Attach appropriate labels to the product vial. Also attach exact copies of the labels placed on the final product vials below in the batch record for documentation of the labeling that was used for this batch of product. **Place Labels Here** **IV.1.10.** Refer to page 12. **IV.1.11.** Refer to page 12.	

Performed By: _____ **Date:** _____
Signature

Checked By: _____ **Date:** _____
Signature

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

V. Post-Synthesis Clean-Up of [^{18}F]FLT System

STEP	Performed By Initial/Date
V.1. Cleaning the HPLC Injector & Column **V.1.1.** Attach the lines to the waste container. **V.1.2.** Add ethanol (4 mL) to Synthesis Module HPLC loading vial _____ mL. **V.1.3.** Change out eluent bottle 1 containing the preparative mobile phase (**HBS-L**), 92% 0.01 M Phosphate 8% Ethanol) to a new eluent bottle 1 containing > 200 mL of 70 % Ethanol (**ETH70-L**), _____ mL. **V.1.4.** Start the HPLC ethanol cleaning program. **V.1.5.** Verify the cleaning program is complete. **V.1.6.** Document in the equipment history log book on **Form EQ-001**. **V.1.7.** Close down the Synthesis Module program. **V.1.8.** Shut down the computer. **V.1.9.** Shut down power to the module.	

Performed By: _____ **Date:** _____
Signature

Checked By: _____ **Date:** _____
Signature

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

We certify that 3'-Deoxy-3'-[^{18}F]Fluorothymidine Production Batch **MBR-[^{18}F]FLT-_____** was prepared according to the Manufacturing Instructions in the Manufacturing Production Record **MPR-[^{18}F]FLT**. Any additional manufacturing modifications have been captured along with the appropriate control information as outlined in **GEN-M120**, "Documentation of Manufacturing Variances, and attached as appropriate.

_____ The QC release tests are complete and this batch of product has been preliminarily released according to GEN-R009, "QC Testing, Review, and Final Release" for administration to human subjects. Final approval will be complete once the results of the Final product Sterility Testing have been met and reviewed as per GEN-Q117.

_____ The QC release tests are complete and this batch of product will not be released, as it has failed to meet at least one or more of the specifications outlined in GEN-R009, "QC Testing, Review, and Final Release," and the OOS investigation as per GEN-Q015 could not rule out the possibility of product quality issues.

Date of Batch Completion: _____

Manufacturing Operator: _____ Date: _____
Signature

Manufacturing Manager: _____ Date: _____
Signature

Date Final Sterility Results Received: _____

_____ Pass _____ Fail

Final Status of 3'-Deoxy-3'-[^{18}F]Fluorothymidine Production Batch **MBR-[^{18}F]FLT-_____**:

_____ Final approval and release has been granted.

_____ After careful review and consideration of the QC release testing and OOS investigation, this batch of product *cannot* be granted final approval and release; and therefore cannot be administered or used for any further testing, if it passed all but the sterility tests previously. Notify all doctors of previously treated patients within 24 hours if the sterility test does not pass specification.

Manufacturing Manager: _____ Date: _____
Signature

QA/Regulatory Affairs: _____ Date:_____
Signature

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Manufacture of [^{18}F]FLT Using a Nucleophilic Synthesis Module

REVISION HISTORY

Version Number	Description	Reason for Revision	Date	Author
V0	Original Record	Original Record generated from original MBR to create generic record.	March 1, 2005	Teresa R. Zuber

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