Template Provided By:

Cancer Imaging Program
National Cancer Institute

Master Batch Record For Synthesis of [^{18}F]-Fluoromisonidazole: [^{18}F]FMISO Injection

[^{18}F]Fluoromisonidazole Batch Number: MBR-[^{18}F]FMISO-_____

Manufacturing Date: _____ Expiration Date (12 hrs EOS): _____

Equipment Description	Internal Tracking Number/ Identification	Manufacturer	Verified By (Initials)
Nucleophilic Synthesis Module System with glassware			
Cyclotron with F18 target			
HPLC Pump with Injector			
Flow through UV Absorbance Detector			
Vacuum Pump			
Computer with Nucleophilic Synthesis Module Software installed			
Printer			
HPLC Preparative Column (Econosphere C_{18} 10 x 250 mm)	SS-ECO-_____		

GENERAL SUPPLIES	Verified By (Initials)
Appropriate Safety Wear including radiation badges, lab coat, safety glasses, shielding, gloves	
2 beakers. One for filter integrity test, one for clean up.	
Graduated cylinder to measure HPLC flow with stopwatch	
Container for Solvent Waste, 200-2,000 mL bottle	
Cryogen: dry ice/solvent mixture, Nitrogen $_{liq}$, or Argon $_{liq}$	
Helium, Argon, 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	

Reagents / Compounded Solutions	Internal Tracking Number/ Identification	Quantity	Verified By (Initials)
FMISO supplies kit	SS-FMISO-_____	1	
FMISO Precursor, 1-(2'-nitro-1'-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulfonyl-propanediol	SS-NIT-_____	5 ± 1 mg	
Acetonitrile, USP	SS-ACN-_____	2.0 ± 0.2 mL	
Acetone, spectrophotometric grade	SS-ACT-_____	qs to clean unit	
$H_2{}^{18}O$, Target material	SS-O18-_____	1.0 – 5.0 mL	
70% Vol. Ethanol	ETH70-_____	≥ 500 mL	
(95:5) Water for injection: Ethanol	W5ETH-_____	~ 1 L	

GEN-Manufacture of [^{18}F]FMISO Using A Nucleophilic Synthesis Module Date: _____

Author:_____**Date:**_____ .

Regulatory Approval:_____**Date:** _____ .

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

I. Maintenance and Cleaning of the Nucleophilic Synthesis Module	Performed By Initial
I.1 Conditioning the Preparative HPLC Column (Requires ~30 min)	
I.1.1. N_2, He or Ar supply pressure _____ psi (30–150). Air pressure_____ psi (70–150).	_____
I.1.2. Module power on.	_____
I.1.3. Software initialized, enter user name and password.	_____
I.1.4 Add ≥ 300 mL of 70% ethanol, to eluent bottle 2 and ≥ 500 mL of preparative mobile phase (5% ethanol in water for injection) to eluent bottle 1	_____
70% Ethanol Compounding Record: ETH70-_____	
Volume added: _____mL (≥ 300 mL)	
5% Ethanol Mobile Phase:	
Volume added: _____ mL (≥ 500 mL)	
I.1.5. Make certain that the Econosphere preparative HPLC column is installed.	_____
I.1.6 Select manual operation from the software menu and switch the injector to inject position.	_____
I.1.7. Open the He or N_2 eluent purge. Turn the valve to eluent 2 (70% ethanol). Set pump flow to 5 (mL/min), _____, Let it run for > 10 minutes, _____ (minutes run).	_____
I.1.8. Set pump flow to 0 (mL/min), _____, Turn the valve back to eluent 1 (5% ethanol)	_____
I.1.9. Set pump flow to 5 (mL/min), _____, Let it run for > 10 minutes, _____ (minutes run). Check that the flow is steady. Measured flow after ~10 minutes _____ (mL/min). Set the pump flow to 0 (mL/min), _____ and close the He, Ar or N_2 eluent purge.	_____
I.1.10. Go to the module software and select manual stop.	_____
I.2. Perform Maintenance on 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. Remove the used ^{18}F separation and purification columns from the synthesizer.	_____
I.2.2. Empty the ^{18}O water vial, dry it and reattach it to the synthesizer.	_____
I.2.3. Remove, empty and replace the cold trap.	_____
I.2.4. Fill the dewar with new cryogen. Reattach clean cold trap.	_____
I.2.5. Empty the v-vial and reattach it to the synthesizer.	_____
I.2.6. Empty the waste bottle. Verify that the appropriate lines from are attached to the waste bottle.	_____
I.2.7. Inspect or replace the Reaction Vessel	_____
I.2.8. Record the equipment maintenance in the equipment history log book, on **Form EQ-001**.	_____
I.3. 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.3.1. Nitrogen or Helium tank pressure _____ psi (≥ 500 or liq), supply pressure _____ psi (30 – 150). Air supply pressure _____ psi (70 – 150).	_____
I.3.2. Module power on. Vacuum pump switch turned on.	
I.3.3. Computer on.	_____
I.3.4. Module software initialized. Enter username and password.	_____
I.3.5. Document the equipment cleaning in the equipment history log on **Form EQ-001**.	_____

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II. Pre-Synthesis Setup for Manufacturing [^{18}F]FMISO Using Nucleophilic Synthesis Module (takes ~20 min) (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.)	**Performed By Initial**
II.1. Prepare the ^{18}F Separation Cartridge (**SS-FSC**), use two 1 mL non lubricated syringes with short needles Slowly wash cartridge with 1 mL of ethanol (**SS-ETH**). Slowly wash cartridge with 1 mL of sterile water (**SS-WFI**) do not blow out, wait five minutes. Push air through the column to expel the residual water.	_____ _____ _____
II.2. Prepare the Sterile product vial assembly: (regular syringes and needles) Use aseptic technique in the laminar air flow hood to do the following tasks: Label the empty product sterile vial (**SS-SBV**) with " [^{18}F]-FMISO" batch number. SWAB vial. Insert a venting filter needle (**SS-VFN**) into the empty sterile vial (**SS-SBV**). Add 0.40 mL of concentrated saline (**SS-NCC**) to the vial using a 0.5 mL syringe. Reswab. Insert a sterilizing filter (**SS-SPF**) with a ≤ 22G needle into the final product empty sterile vial.	_____ _____ _____ _____ _____
II.3. Make certain the ^{18}F target line is hooked up to the automation unit	
II.4. Prepare 0.1 M K_2CO_3 Solution (Use 1 cc nonlubricated syringe and long needle) Transfer 0.50 ± 0.05 mL 0.1 M K_2CO_3 (**KCO2-L**) to box vial 1.	_____
II.5. Kryptofix® [2.2.2] addition: (Use 3 cc nonlubricated syringe and long needle) Transfer 2.0 ± 0.2 mL of Kryptofix® [2.2.2] (**KRYP-L**) 15 mg/ 2 mL in acetonitrile to box vial 2.	_____
II.6. HCl addition: (Use 3 cc nonlubricated syringe and long needle) Transfer 2.0 mL ± 0.2 mL of 0.5N HCl (**HCL-L**) to box vial 4	_____
II.7. Sodium bicarbonate addition: (Use 3 cc nonlubricated syringe and long needle) Aseptically transfer 2.5 ± 0.2 mL of sodium bicarbonate solution (**SS-BIC**) to vial 5.	_____
II.8. FMISO precursor addition: (Use 3 cc nonlubricated syringe and long needle) Aseptically, transfer 2.0 ± 0.2 mL FMISO precursor (**SS-NIT**, 5 mg) in CH_3CN to vial 6.	_____
II.9. Run the FMISO Program: (NOTE: 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**

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III. Manufacturing [^{18}F]FMISO Using 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.)	**Performed By Initial**
III.1. Synthesize [^{18}F]FMISO	_____
III.1.1. Start the Synthesis Program.“”	_____
III.1.2. Deliver the $^{18}F^-$ activity to the synthesis box. **$^{18}F^-$ Delivery: Start Time:** _____ **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. **Synthesis: Start Time:** _____ **Stop Time:** _____ (time of day) **Quantity of ^{18}F Delivered:** _____mCi	_____
III.1.4. HPLC Collection: start collection when the FMISO peak starts on the Radioactivity trace. **HPLC Fraction Started:** _____ minutes (Retention Time) End the [^{18}F]FMISO product collection. **HPLC Fraction Stopped:** _____ minutes (Retention Time)	_____
III.1.5. Remove the shielded [^{18}F]FMISO product vial assembly from the hot cell if necessary.	
III.1.6 Remove the sterilizing filter from the [^{18}F]FMISO product vial.	_____
III.1.7. Verify the assigned batch number, sign and date the printout, and attach it to this batch record.	_____

IV. Post-Synthesis	**Performed By Initial**
IV.1. Withdraw Samples for Quality Control Testing	
IV.1.1. Assay the [^{18}F]FMISO prodict using a calibrated ion chamber. **Final Product Assay: _____ mCi Time of End of Synthesis (EOS): _____** (time of day)	_____
IV.1.2. Particulate test of the final product as per **Gen-Q121**, (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.	_____
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 $\lambda = \ln(2)/109.8$ 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** **(5-16 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-010** as they are obtained.	_____
IV.1.8. Attach all manufacturing variances to the batch record. Record the # of variances reported here, _____.	_____
IV.1.9. Attach appropriate labels to the product vial. Also attach exact copies of the labels placed on the final product dose vials (syringes) below in the batch record for documentation of the labeling that was used for doses for this batch of product.	_____
IV.1.10. Perform final review and release of QC Test Results as per **NCI-R209**.	_____
IV.1.11. Record final sterility results on **Form FQC-010** once they are available	_____

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

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Place Copies of Labels Here

(if extra room is needed put labels on the back of this sheet)

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

V.1. Cleaning the HPLC Injector & Column

V.1.1. Attach the lines to the waste bottle.

V.1.2. Add ethanol (**SS-ETH**, 4 mL) to Synthesis Module HPLC loading vial _____ mL through the V14

V.1.3. Change eluent bottle 1 to contain > 200 mL of 70 % Ethanol (**ETH70-L**), _____ mL.

V.1.4. Start the HPLC FMISO cleaning program.

V.1.5. Verify the cleaning program is complete.

V.1.6. **Attach a new sterile filter (SS-SPF) on the product HPLC outlet**

V.1.7. Sign and date printout, and attach it to the batch record. Document any work on the equipment in the equipment history log book on **Form EQ-001**.

V.2. Cleaning the Nucleophilic Synthesis Module System (reagent and reaction vials) (Sponsor to provide following manufacturer's instruction.

Performed By: _____ **Date:** _____ **Checked By:** _____**Date:**_____

Signature *Signature*

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We certify that [^{18}F]-Fluoromisonidazole Production Batch **MBR-[^{18}F]FMISO-_____** was prepared according to the Manufacturing Instructions in the Manufacturing Production Record **MPR-[^{18}F]FMISO**. 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-R209**, "QC Testing, Review, and Final Release for [^{18}F]FMISO" 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** or **Gen-Q117A**.

_____ 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-R209**, "QC Testing, Review, and Final Release for [^{18}F]FMISO," 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: _____

Final Sterility Results: _____ Pass _____ Fail

Final Status of [^{18}F]-Fluoromisonidazole Production Batch **MBR-[^{18}F]FMISO-_____**:

_____ 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 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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