Template

"Insert Your Institution Information Here"

[^{18}F]DCFBC: Master Production Record

For Synthesis of [^{18}F]-DCFBC: [^{18}F]DCFBC Injection

Purpose: This is the Master Production Record for synthesizing [^{18}F]-DCFBC, a fluorine-18 labeled radiopharmaceutical product for investigational use only.

REFERENCES & MATERIALS OVERVIEW

A. REFERENCES

1. **MBR-[^{18}F]DCFBC**, "[^{18}F]-DCFBC: [^{18}F]DCFBC Injection Master Batch Record "
2. **SAIC-Frederick-Q121,** "Chemical Purity by Visual Inspection**"**
3. **SAIC-Frederick -Q212**, "Gas Chromatography Analysis of Residual Solvents for [^{18}F]-fluoromisonidazole [^{18}F]FMISO, [^{18}F]DCFBC and [^{18}F]-fluoroestradiol [^{18}F]FES"
4. **SAIC-Frederick -Q113**, "Radionuclidic Identification by Half-Life Determination"
5. **SAIC-Frederick -Q114A,** "Alternative procedure for Bacterial Endotoxins by Limulus amoebocyte Lysate (LAL) Test Using the PTS (Portable Test System)"
6. **SAIC-Frederick -Q115**, "pH Testing of Final Product"
7. **SAIC-Frederick -Q117A**, " Alternative Procedure for the Sterility Test"
8. **SAIC-Frederick -Q110**, "Filter Integrity Test by Bubble Point"
9. **SAIC-Frederick -Q118A**, "An Alternate Test for the Detection of Kryptofix® [2.2.2]"
10. **Leidos-Q324**, "Chemical and Radiochemical Purity by HPLC for [^{18}F]DCFBC"
11. **SAIC-Frederick -Q012**, "Quality Systems Administration"
12. **SAIC-Frederick -Q015**, "Investigating Out of Specification QC Test Results"
13. **SAIC-Frederick -R004**, "Assigning Batch & Compounding Record Numbers to Production Runs"
14. **SAIC-Frederick -R005**, "Drug Product Complaints"
15. **SAIC-Frederick -R006**, "Product Labeling"
16. **SAIC-Frederick -R008**, "Good Documentation Practices"
17. **Leidos-R011**, "QC Testing, Review, & Final Release for [^{18}F]DCFBC"
18. **Form FQC-009**, "[^{18}F]DCFBC Final Product QC Test Results" Form
19. **Form R004-MBR-[18F]DCFBC-L**, "General Log for Assigning Unique Batch or Compounding Record Numbers"
20. **Form S-DCFBC**, "Supply Sheet for Production of [^{18}F]-DCFBC"
21. **PHOS30-L**, "Master Compounding Record for the Preparation of 30% ACN in phosphate buffer (pH 3.2)"
22. **ETH70-L**, "Master Compounding Record for Preparation of 70% Ethanol"
23. **KCO2-L**, "Master Compounding Record for the Preparation of 0.1M Potassium Carbonate"
24. **KRYP-L**, "Master Compounding Record for the Preparation of Kryptofix [2.2.2] Solution"
25. **TBAH-L**, "Master Compounding Record for the Preparation of 1.0 M TBAH Solution"

[^{18}F]DCFBC: DCFBC Injection Master Production Record Version: **V1**
Effective Date:_____12/11/2013__ Supersedes:

Author:_____ Date:_____ .
Signature

Regulatory Approval:_____ Date: _____ .
Signature

Procedure becomes effective on latest date of the two approval signatures above.
Procedure applies to [18F]DCFBC IND.

26. **ACN50-L,** "Master Compounding Record for the Preparation of 50% ACN Solution in Water with 0.1% of TFA"
27. **NABH-L**, "Master Compounding Record for the Preparation of NaBH4 Solution in Water"
28. **GCFES-L**, "Master Compounding Record for the Preparation of Gas Chromatography Standard Solution"

B. EQUIPMENT

Equipment Description
Biotage Microwave Reactor
HPLC Pump with Injector
Flow through UV Absorbance Detector
Vacuum Pump
Printer
HPLC Preparative Column (Atlantis T3 10 x 250 mm) (SS-Atlan)
Dose Calibrator (calibrated ion chamber)

C. REAGENTS/MATERIALS

GENERAL (Non-Inventoried per Batch) SUPPLIES
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, 500-2,000 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/solutions	Quantity
DCFBC supplies kit	1
[^{18}F]fluorobenzaldehyde Precursor	10.0 mg
Targeting ligand precursor	0.6-1.0 mg
Freshly prepared $NaBH_4$ solution	~0.5 mL
1.0 M TBAH solution	~ 0.2 mL
48% HBr solution	~2.0 mL
Prep. HPLC mobile phase	≥ 300 mL
Acetonitrile	4-5 mL
Water HPLC grade	30-40 mL

D. RESPONSIBILITIES

Each site should ensure that their operators have all of the required credentials and prerequisite training required to synthesize radiopharmaceuticals. Document all manufacturing control information on the corresponding Master Batch Record, **MBR-[^{18}F]DCFBC**.

E. PRE-PRODUCTION SETUP

Setting up of preparative HPLC system

a) HPLC system power on. Computer on and Windows software initialized.
b) Add ≥ 300 mL of mobile phase (**PHOS30-L-)** to the eluent bottle
c) Make certain that the Atlantis T3 prep C-18 HPLC column (**SS-Atlan**) is installed.
d) Run the method previously set for this purification. Check that the flow is steady.
e) Make sure the column is clean and there is no unusual UV absorption until 30 min.

Production area clearance and setup

a) Inspect the production area. Assure all extraneous materials and labels have been removed.
b) Verify materials, supplies and equipment required for synthesis are in place and properly organized.
c) Set the oil-bath temp. to 120 °C and turn on the stirring system.
d) Turn on the biotage microwave reactor.

F. RADIOSYNTHESIS

1. Elute [^{18}F]fluoride from QMA cartridge to a microwave glass vial (Biotage) using K_2CO_3 (0.15 mL, **KCO2-L-**) and K222 (0.9 mL, **KRY-L-**) mixture.

2. Azeotropically dry the eluted solution at 120 °C on under vacuum and gentle flow of N_2 for 8 min.

3. Transfer ~1 mL of acetonitrile 2 times to the reaction vial in 6 min of interval and continue the drying process until all the solvent is evaporated.

4. Dissolve 10 mg of precursor with ~ 0.7 mL of ACN and transfer to the dried reaction vial.

5. Microwave the reaction mixture at 100 °C for 4 min.

6. Transfer ~0.2 mL of $NaBH_4$ solution (**NABH-L-**) and stir the mixture for 5 min.

7. Transfer ~ 2 mL of HBr (**SS-HBR**) to the vented reaction vial.

8. Microwave the reaction mixture at 100 °C for 3 min.

9. Dilute the reaction mixture with 4-5 mL of water.

10. Remotely pass the diluted reaction mixture through an activated C-18 Plus Sep-Pak (SS-PSP).

11. Wash the Sep-Pak with 5-10 mL of water (**SS-HGW**)..

12. Dry the Sep-Pak by gentle flow of N_2 for 3 min.

13. In a new reaction vial transfer ~ 0.6 mg of targeting ligand (**SS-PEP**) in ~ 0.2 mL of water.

14. Transfer ~ 0.15 mL of 1.0 M TBAH solution (**TBAH-L-**) to the new reaction vial.

15. Elute the trapped activity of C-18 Plus Sep-Pak to the new reaction vial using ~ 1.5 mL of acetonitrile.

16. Microwave the reaction mixture at 80 °C for 3 min.

17. Dilute the reaction mixture with 3-4 mL of water (**SS-HGW**).

G. PURIFICATION

18. Remotely transfer the diluted reaction mixture on to the prep HPLC column (**SS-Atlan**).

19. Elute the HPLC column at a flow rate of 4 mL/min. Observe the elution and collect fraction containing [18F]DCFBC based on the retention time (~ 11min) of the observed radiation peak.

20. Dilute the collected product with 20 mL of water (**SS-HGW**)..

21. Remotely pass the diluted product through a C-18 Light Sep-Pak (**SS-LSP**).

22. Wash the Sep-Pak with 5 mL of sterile water (**SS-WFI**)..

23. Dry the Light Sep-Pak with 5 mL of air.

H. STERILE FILTRATION AND FORMULATION

24. Connect the Light Sep-Pak cartridge with a 30 mL vented (**SS-VFN**) sterile vial (**SS-SBV**) through a 0.2 micron sterile filter (**SS-SPF**).

25. Elute the [^{18}F]DCFBC product from Light Sep-Pak to sterile vial using 1.0 mL of absolute ethanol (USP) followed by 14 mL of 0.9% saline (**SS-NSI**).

26. Detach the product vial from sterile filter and assay the product. Record the assay results with time.

27. Record the specific concentration of the product.

28. Perform bubble point test of the sterile filter following standard procedure (**SAIC-Frederick-Q110**).

29. Aseptically draw ~ 400 µL of the product for QC tests

I. POST-SYNTHESIS CLEAN UP OF PREP HPLC SYSTEM

a) Replace the mobile phase bottle of the HPLC system by 70% absolute ethanol in water (>

300 mL).

b) Transfer ~ 4 mL 70% ethanol mobile phase to the injection vial of HPLC.

c) Run the HPLC system for 30 min at 4 mL/min flow rate.

d) Keep the HPLC system (injector and column) under 70% ethanol solution until next production.