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Standard Operating Procedure

GEN-Q112

Gas Chromatography Analysis of Residual Solvents

Approval Signatures:

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

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Gas Chromatography Analysis of Residual Solvents

1. **Purpose:** To describe the quality control procedure for analyzing residual solvents in the final product solution of 3'-deoxy-3'-[^{18}F]Fluorothymidine ([^{18}F]FLT) using Gas Chromatography.

2. **Scope:** Gas Chromatography is used to determine the amount of residual solvents in the final product. This procedure will be performed at the *manufacturing sites* synthesizing [^{18}F]FLT under the *Sponsor's* IND. This quality control procedure is one of the lot release tests performed on the final product and it must be completed prior to releasing the lot for human administration.

3. **Responsibilities:**
   3.1. *Manufacturing Sites*: To follow this procedure as written and to ensure that all results, control information, and raw data are documented as specified in dedicated Quality Control Laboratory Notebooks and recorded on the appropriate testing forms.

4. **References**
   4.1 USP, ‹467› Organic Volatile Impurities
   4.2 Channing M.A., Huang B.X., Eckelman W.C.: Analysis of residual solvents in 2-[^{18}F]FDG by GC, Nuclear Medicine and Biology 28(2001) 469-471.
   4.3 USP 26 ‹621› Chromatography
   4.4 USP 26 ‹821› Radioactivity
   4.5 USP 26 ‹823› Radiopharmaceuticals For Positron Emission Tomography—Compounding
   4.6 Machulla H.J. et al. Procedure for Routine Synthesis of [^{18}F]FLT in High Activities. *J. Nucl. Med.* **2001**, 42 *(5)*, 257P.
   4.7 J.R. Grierson, A.F. Shields, Radiosynthesis of 3'-Deoxy-3'-[^{18}F]fluorothymidine: [^{18}F]FLT for imaging of cellular proliferation *in vivo*, Nucl. Med. Biol. 27 (2000) 143-156.
   4.8 **GEN-Q015**, "Investigating Out of Specification QC Test Results"
   4.9 FDA Draft Guidance PET Drug Products—Current Good Manufacturing Practice (CGMP)—June 2002 (CDER)
   4.10 FDA Guidance for Industry ICH Q3C—Tables and List (November 2003 Revision 1)
   4.11 Kateman G., Buydens L. Quality Control in Analytical Chemistry, second ed. John Wiley & Sons, Inc. New York. 1993. 317 p.

5. **Forms**
   - **Form FQC-001**, "[^{18}F]FLT Final Product QC Test Results" Form I
   - **Form IOS-001**, "Investigating Out Of Specification (OOS) QC Test Results Form"

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- **GCS-L-,** "Master Compounding Record: Preparation of GC Standard Solution"
- **Form Q112**, "Preparation of GC Dilutions from Standard Solution Form"

6. Policies

6.1. The permissible level of acetonitrile in the final product is less than or equal to 400 ppm. This value is the same as that for the USP permissible level of acetonitrile in 2-[^{18}F]FDG which may not exceed 400 ppm.

6.2. The allowable levels for both, acetone, and DMSO, are less than 5000 ppm. [Both of these are Class 3 solvents; this class of solvents includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. Therefore this limit is based upon the FDA's Guidance for Industry ICH Q3C—Tables and List (November 2003 Revision 1), page 7, where it considers 5,000 ppm in 10 mL i.e., 50 mg or less per day, of these Class 3 residual solvents as an acceptable limit, without additional justification.]

7. Materials and Equipment

7.1. Gas Chromatography System with Flame Ionization Detector (FID) and / or Mass Spectrometer (MS) Detector

7.2. Chromatography Sample Injection Syringe with injector an Auto-sampler system

7.3. Hydrogen, UHP grade if using FID

7.4. Helium UHP grade

7.5. **GCS-L,** (Master Compounding Record for "Preparation of GC Standard Solution"), External standard mixture stock solution: acetone 50,000 ppm, dimethylsulfoxide (DMSO) 50,000 ppm, and acetonitrile 4,000 ppm in FLT mobile phase (92:8, 0.15 M PBS USP: ethanol USP) with dilutions of 1/2, 1/4, 1/8 and 1/16.

7.6. Gas liquid chromatography column: AT™-WAX column, 30m in length, 0.25mm ID, 0.25 µm (Alltech Associates, Inc. Deerfield, Ill. or equivalent)

8. Procedures

8.1 Set up the GC with the Following Conditions:

8.1.1 <u>Oven Temperature Program of the Following</u>:

- Initial Temperature of 40°C held for 1 minute.
- Then ramp from 40° to 56°C @ 15°C/min and hold at 56°C for one minute.
- Then perform a second temperature ramp from 56° to 190°C @ 20°C/min held at 190°C for 1.5 minutes.

8.1.2 The injector temperature should be 225°C.

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8.1.3 Use helium as the carrier gas with a column flow rate of 1 mL/min.

8.1.4 For Flame Ionization Detection (FID): set up the detector with the appropriate flow of hydrogen for the detector.

8.1.5 For Mass Spectrometers (MS): use electron impact @ 70eV with an ion source temperature of 200°C, a transfer line temperature of 275°C and a scan range of 15 – 100.

8.1.6 For either detector, the signal to noise must be greater than 10:1 for the maximum allowable concentration for each solvent when injecting 0.5 µL of the solvent with a split ratio of 100:1 shunted to on column respectively, *i.e.* the split flow is 100 mL/min of helium carrier gas through the column.

8.2 Prepare fresh dilutions (1/2, 1/4, 1/8 and 1/16) of the **GCS-L-####**, GC Standard Solution as indicated on **Form Q112**, "Preparation of GC Dilutions from Standard Solution Form."

8.3 Inject 0.5 µL - 1.0 µL of each of the five prepared concentrations of the external standard mixture on the GC Column to obtain the values for calculating the standard curve.

8.4 The retention times should be approximately 2.2 minutes for acetone (k' approximately 0.4), 3.1 minutes for ethanol (k' approximately 1.0), 3.9 minutes for acetonitrile (k' approximately 1.5), 4.7 minutes for water (k' approximately 2.1), and approximately 8.8 minutes for DMSO (k' approximately 4.7).

8.5 A sample chromatogram is shown in Q112 appendix. All standards, including water and ethanol, must be analytically separable with a resolution > 1.5 for a valid analysis.

8.6 Inject duplicate samples of 0.5 µL of the product sample to be tested.

8.7 Determine the concentration of acetone, acetonitrile, and DMSO in the final product.

8.8 This batch **passes** this analysis of residual solvents *if there is* **less than 5,000 ppm of acetone**, **and less than 5,000 ppm of DMSO**, **and less than 400 ppm of acetonitrile**, **in both samples of the final solution** for injection.

8.9 If the batch of final product fails to meet any one of the criteria outlined in step 8.7 above, initiate an Out of Specification (OOS) investigation as outlined in **GEN-Q015**, "Investigating Out of Specification QC Test Results," and record the results on **Form IOS-001**, "Investigating Out Of Specification (OOS) QC Test Results Form."

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REVISION HISTORY

Version Number	Description	Reason for Revision	Date	Author
V0	Original Record	Revised NCI-Q112 Version January 25, 2005 to create the new SOP.	March 1, 2005	Teresa R. Zuber

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