Template Provided By:

Cancer Imaging Program

National Cancer Institute

Standard Operating Procedure

GEN-Q212

Gas Chromatography Analysis of Residual Solvents for [^{18}F]FMISO and [^{18}F]FES

1. **Purpose:** To describe the quality control procedure to determine residual solvents by gas chromatography for the final [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) and [^{18}F]Fluoroestradiol ([^{18}F]FES) product solutions.

2. **Scope:** Gas Chromatography is used to determine the amount of residual solvents in the final product. This procedure will be performed at all of the sites manufacturing [^{18}F]FMISO and [^{18}F]FES. This quality control procedure is one of the lot release tests performed on the final products. The test must be completed and passed prior to releasing the lot for human administration.

3. **Responsibilities:** 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 28, ‹467› Organic Volatile Impurities
   - **4.2** USP 28 ‹621› Chromatography
   - **4.3** USP 28 ‹821› Radioactivity
   - **4.4** USP 28 ‹823› Radio-pharmaceuticals For Positron Emission Tomography—Compounding.
   - **4.5** **Gen-Q015**, “Investigating Out of Specification QC Test Results”
   - **4.6** FDA Draft Guidance PET Drug Products—Current Good Manufacturing Practice (CGMP)—September 2005 (CDER)
   - **4.7** FDA Guidance for Industry ICH Q3C—Tables and List (November 2003 Revision 1)

SOP**: GEN-Q212** Date:_____

Printed Name	Signature	Date
Author:		
Regulatory Approval:		

Cancer Imaging Program, *Confidential--Use and restriction of this document is set forth in Transfer Agreement executed with the National Cancer Institute (NCI).*

5. **Forms**
   - **Form FQC-010**, [^{18}F]FMISO Final Product QC Test Results Form
   - **Form FQC-005**, [^{18}F]FES Final Product QC Test Results Form
   - **Form IOS-001**, Investigating Out Of Specification QC Test Results 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.

   6.2. The allowable level for acetone is less than 5,000 ppm. Acetone is a Class 3 solvent; this class of solvents includes solvents not known as a human health hazard at levels normally accepted in pharmaceuticals. This limit is based upon the FDA's Guidance for Industry ICH Q3C—Tables and List (November 2003 Revision 1), page 7, which states; "amounts of these residual solvents [Class 3] of 50 mg per day or less (corresponding to 5000 ppm for 10 mL of injectate) would be acceptable without justification".

7. **Materials and Equipment**

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

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

   7.3. Hydrogen, UHP grade when using FID

   7.4. Helium UHP grade.

   7.5. External standard mixture stock solutions: acetone 50,000 ppm, and acetonitrile 4,000 ppm in FMISO or FES preparative mobile phase with dilutions of 1/2, 1/4, 1/8 and 1/16.

   7.6. Gas liquid chromatography column: AT^{TM}-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 76°C @ 40°C/min and hold at 76°C for one minute.
   - Then perform a second temperature ramp from 76° to 150°C @ 20°C/min held at 150°C for 1.5 minutes.

   8.1.2 The injector temperature should be 225°C.

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

   8.1.4 <u>For Flame Ionization Detection (FID)</u>: set up the detector with the appropriate hydrogen flow.

Cancer Imaging Program, *Confidential--Use and restriction of this document is set forth in Transfer Agreement executed with the National Cancer Institute (NCI).*

8.1.5 <u>For Mass Spectrometers (MS)</u>: 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 M/Z

8.1.6 The detector signal to noise must be greater than 10:1 for the maximum allowable concentration for each solvent when injecting 0.5 µL of the analyte with an on column flow of 1.0 mL/min of helium and a split ratio of 100:1 (shunted : on column).

8.2 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 values for calculating the standard curve.

8.3 The retention times should be approximately 2.3 minutes for acetone (k' approximately 0.5), 3.4 minutes for ethanol (k' approximately 1.2), 4.5 minutes for acetonitrile (k' approximately 1.9), 4.7 minutes for water (k' approximately 2.0).

8.4 Sample standard chromatograms for FMISO and FES solutions are shown in Figures 1a and b, and 2a and b, respectively. For a valid analysis all standards, including water and ethanol, must be analytically separable with a resolution > 1.5.

8.5 Inject duplicate samples of 0.5 - 1 µL of the product sample to be tested.

8.6 Determine the concentrations of acetone and acetonitrile in the final product.

8.7 A batch **passes** this test for residual solvents -*when there is* **less than 5,000 ppm of acetone and less than 400 ppm of acetonitrile**, **in both samples of the final solution** for injection.

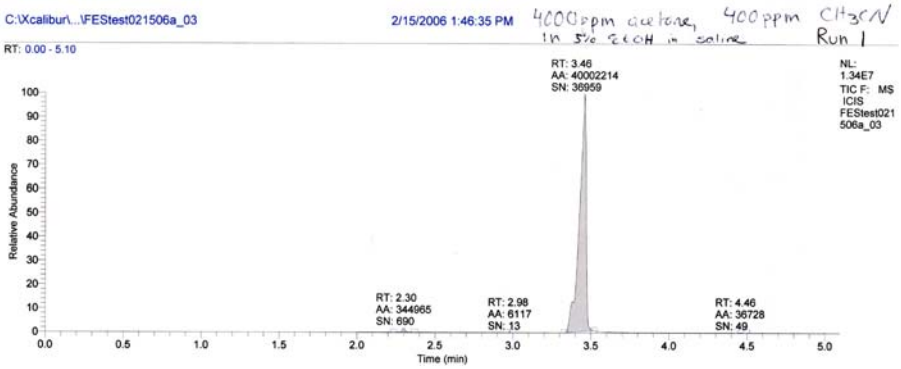

Figure 1a. Gas chromatogram of a standard solution containing 4,000 ppm of acetone (retention time 2.30 min) and 400 ppm of acetonitrile (retention time 4.46 minutes) in the FMISO preparative mobile phase. The peak with a 3.5 min retention time is from ethanol in the mobile phase. The peak at 2.98 min is a methanol impurity in the non patient ethanol used for this test run. The chromatogram is ended just before water elutes.

Cancer Imaging Program, *Confidential--Use and restriction of this document is set forth in Transfer Agreement executed with the National Cancer Institute (NCI).*

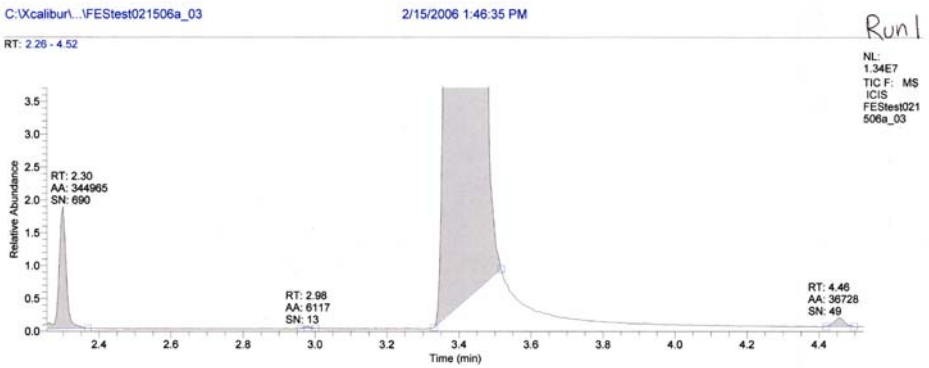

Figure 1b shows an expanded view of the chromatogram shown in figure 1a. There was no attempt to accurately determine the ethanol peak.

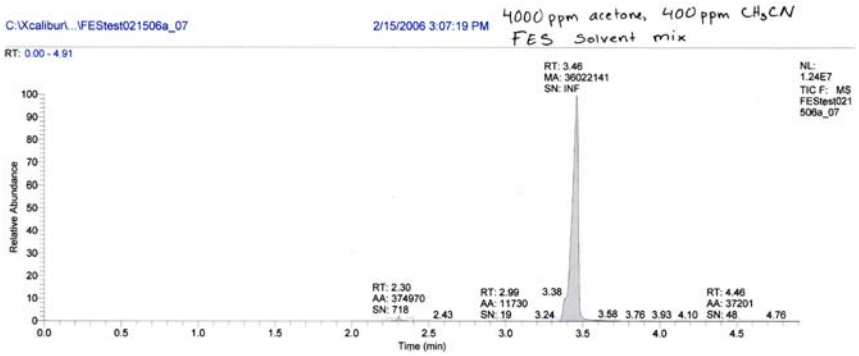

Figure 2a. Gas chromatogram of a standard solution containing 4,000 ppm of acetone (retention time 2.30 min) and 400 ppm of acetonitrile (retention time 4.46 minutes) in the solution used for the FES product. The peak with a 3.5 min retention time is from ethanol in the mobile phase. The chromatogram is ended just before the water elutes.

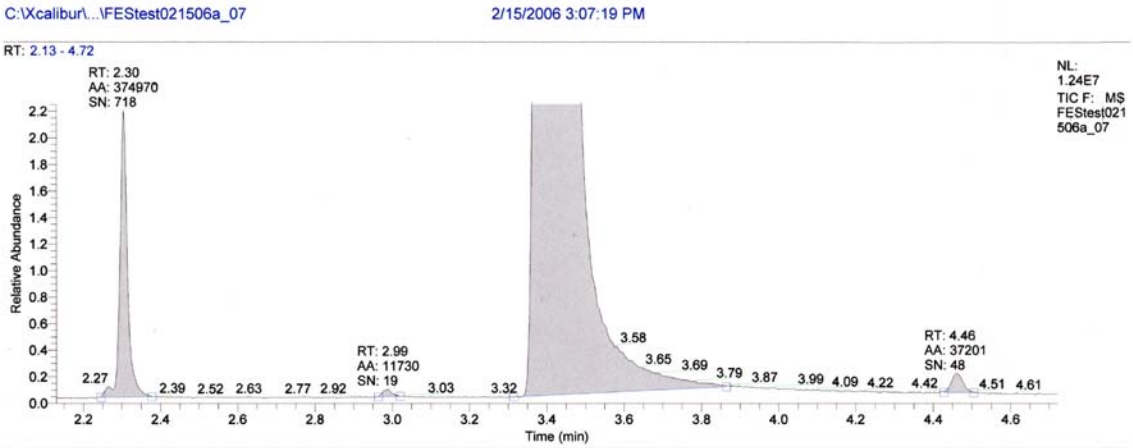

Figure 2b shows an expanded view of the chromatogram shown in figure 2a.

Cancer Imaging Program, *Confidential--Use and restriction of this document is set forth in Transfer Agreement executed with the National Cancer Institute (NCI).*