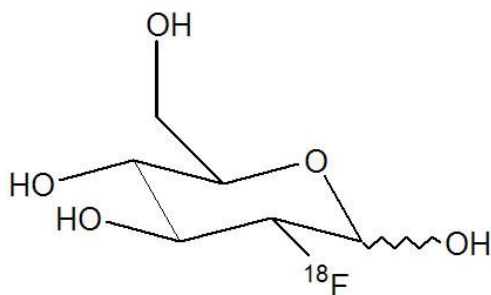


**Radiopharmaceutical Details:  $^{18}\text{F}$ -FDG****1. Name of Radiopharmaceutical (active ingredient)**

$^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose ( $^{18}\text{F}$ -FDG)

**2. Indicate the chemical structure for low molecular weight drug molecules**

(not required for antibodies, proteins, or polymeric agents)

**4. State specific details of techniques to analyze and quantify the compound**

(ex: spectrophotometer – make, settings, sample dilutions, etc.)

TLC MeCN/H<sub>2</sub>O, 95/5, silica.

**4b. Indicate the minimum detectable mass of the drug by HPLC analysis.**

Not applicable. No chemical analysis to quantify the FDG in the sample is routinely performed.

**5. Radioisotopes**

Fluorine-18

**6. Method of assaying radioisotope activity prior to administration**

(ex: Capintec ion chamber, gamma counter, or liquid scintillation counter; include details of make, setting, type of standard, etc.)

The amount of radioactivity in each unit dose is assayed prior to administration using a calibrated Capintec 712M dose calibrator dialed into a setting of 439. A daily constancy test is performed using an NIST traceable Cs-137 source. Accuracy, linearity and geometry testing is performed as required by the NRC or equipment manufacturer.

**7. Radionuclidic Purity**

(in %)

>99%

## 8. Significant radionuclidic impurities and means of assay

The radionuclide fluorine-18 is prepared using a cyclotron irradiation of oxygen-18 enriched water. Potential radionuclidic impurities are the very short half-life radionuclides oxygen-15 (half-life 2 minutes) and nitrogen-13 (half-life 10 minutes). The combination of the ion exchange and chromatographic columns used in the synthesis of  $^{18}\text{F}$ -FDG, together with the time used in the synthesis (> 1 hour), result in effectively no contamination of the final product with either of these radionuclides.

## 9. Radiochemical Purity

(in %)

>90%

## 10. Significant radiochemical impurities and means of assay

(ex: *Chromatographic techniques and procedure for analyzing radiochromatogram*).

The potential radiochemical impurities in  $^{18}\text{F}$ -FDG are free  $^{18}\text{F}^-$  and incompletely hydrolyzed intermediate. These are easily separated from the authentic  $^{18}\text{F}$ -FDG using silica gel thin-layer chromatography (TLC). A sample of the final product solution is spotted on a silica gel TLC plate. The plate is then developed using a 95:5 mixture of acetonitrile:water until the solvent has moved about three-fourths of the length of the plate. The chromatographic plate is allowed to dry and then scanned for the radioactivity. Radioactivity associated with the FDG ( $R_f$  approximately 0.4) is quantified by computer integration of radioactivity in regions across the plate. A permanent copy of the chromatogram and the integration report are attached to the Master Formula Card. Authentic FDG is co-spotted on the TLC plate for comparison.

## 11. Provide evidence that the tracer will be stable over period of storage prior to administration.

(Give details of storage conditions and on-going quality assurance procedures for sterility, apyrogenicity, and radiochemical purity.)

The short half-life of fluorine-18 (110 min) limits the storage of product to no more than six hours (three half-lives). Samples are kept at room temperature in the original multi-dose vial for no more than six hours.

## 14. Provide detailed information on how the pharmaceutical quality of the radioactive drug will be assured at the time of administration.

Include the following:

- pH
- Sterility
- Apyrogenicity

- **Identify (chemical and radiochemical purity)**
- **Concentration**

a. pH

A small amount of each batch of the final drug product will be spotted on Merck pH paper. The pH will be in the physiological range (4.5-7.5) and will be consistent from batch to batch.

b. Sterility

The product is delivered in a sterile multi-dose vial. No addition of liquid or aliquotting to another storage container is permitted. Individual doses are removed from this vial using aseptic techniques and only by trained pharmacy staff or nuclear medicine technicians.

During preclinical studies the final drug product was produced utilizing established synthesis procedures [See appended Master Formula Card]. When tested as described below the prepared batches were sterile. During clinical studies the radioactive drug product will be produced utilizing these established procedures and on a synthesis apparatus which will be appropriately maintained. Sterility tests will be routinely performed on batches of the drug product in an ex post facto manner utilizing residual samples.

An aliquot of the final drug products will be inoculated into each of the appropriate sterility test media and incubated according to USP recommendations:

- i. Fluid Thioglycollate Media (BBL, Division of Becton-Dickinson Co., Cockeysville, MD): 14 days at 30-35° C.
- ii. Soybean Casein Broth (BBL, Division of Becton-Dickinson Co., Cockeysville, MD): 14 days at 20-25° C.

Positive growth is indicated by cloudiness in the culture media. Results will be compared to positive and negative controls. The efficacy of utilizing a 0.22 µm membrane filter for terminal sterilization [See appended Master Formula Card] warrants release of the drug products for patient administration prior to results of sterility testing as stipulated by current USP

c. Apyrogenicity

An aliquot of the final drug product will be tested for the presence of bacterial endotoxin utilizing a Limulus Amebocyte Lysate (LAL) Test. The test is performed using a Charles River Endosafe-PTS Portable Testing System which is based on a kinetic chromogenic BET. The established USP endotoxin limit is 175 EU per dose for radiopharmaceuticals and is not exceeded.

d. Identify (chemical and radiochemical purity)

The main chemical contaminant of FDG is the mannose precursor which is non-toxic and therefore no analysis is done for this compound. Other possible chemical contaminants are the reagent Kryptofix and residual organic solvents. The presence of Kryptofix in the final FDG dose is analyzed by a spot test for amines, in comparison with standards of known concentration. The limit of Kryptofix in the dose formulation is 50 µg/mL, with

typical levels <5 µg/mL. Trace solvents in the final formulation are analyzed by gas chromatography employing a method comparable to that specified in the USP. Solvent levels are verified, by triplicate sample injections, to be <0.04% acetonitrile and <0.5% ethanol, based on comparisons of GC peak area with standards of known concentration.

e. Concentration

i. Mass Concentration (mass/volume)

The <sup>18</sup>F, and hence FDG, is only produced in trace amounts in this synthesis. Therefore, no mass analysis is routinely performed.

ii. Activity Concentration (activity/volume)

1-40 mCi/mL

iii. Specific Activity (activity per mass of drug)

Specific activity is not calculated for FDG, as no mass analysis is performed.

For questions or concerns, contact:

Brian Hockley  
Division of Nuclear Medicine  
(734) 615-2044  
Fax: (734) 615-2557  
Email: hockley@umich.edu