Updated specifications for IND #76,042
[F-18]FMISO, [F-18]fluoromisonidazole

Test	Current Specifications	Original Filed Specifications
Radiochemical Purity (TLC):	R_f >0.5 Purity ≥ 95%	R_f >0.5 Purity ≥ 95%
Residual Solvent Levels:	Acetone ≤ 5000 ppm Acetonitrile ≤410 ppm	Acetone < 5000 ppm Acetonitrile < 400 ppm
Radionuclidic Purity:	Measured half-life 100 – 120 minutes	Measured half-life 100 – 120 minutes
Bacterial Endotoxin Levels:	< 175 EU per dose	< 175 EU per dose
pH:	4.5-8.0	6-8
Sterility:	Negative/no growth, must also pass filter integrity test	no growth observed in 14 days
Residual Kryptofix® [2.2.2]:	< 50 µg/ mL Kryptofix®	< 50 µg/ mL Kryptofix®
Radiochemical Purity (HPLC):	≥ 95%	> 95%
Chemical Purity (HPLC):	FMISO ≤ 15 µg/dose Other compounds ≤35µg/dose	FMISO < 15 µg/dose other < 35 µg / dose Specific impurities:~ 4.0min ≤ 3 µg/mL ~6.0 min ≤ 4 µg/mL
Chemical Purity (particulates):	Clear and Colorless	Clear and Colorless
The drug solution is stored at room temperature in a septum sealed, sterile, pyrogen-free glass vial with an **expiration** time of **12 hours**		

The specifications that have been updated are for pH and acetonitrile. The purity specifications have been clarified to ≥ instead of > to avoid ambiguity. These changes are not considered major and will not increase risk to the patient.

Justification for these changes is to align these specifications with similar FDA approved PET radiopharmaceuticals and the ICH guidelines. Many sites are now preparing FMISO with pre-filled cassettes and automated synthesis instruments that were designed in compliance with these newer published limits.

1. Acetonitrile is listed in the Guidance for Industry, QC3 – Tables and List, Revision 2, February 2012 as a class 2 solvent with a concentration limit of 410 ppm. Acetone is a class 3 solvents and limited to 5000 ppm so no specification change is needed for them.

2. FDA approved labeling for two very similar radiopharmaceuticals, F-18 FDG and NaF F-18, has both drugs specified at pH 4.5-8. To be consistent with these drugs, we have changed the F-18 FMISO specification to 4.5-8.[1]

[1] FLT now has a monograph in the European Pharmacopeia with a pH specification of 4.5-8.5. There is no USP monograph