



BG75 2.0 Enhanced GMP Design

Dose on Demand [¹⁸F]FDG, [¹⁸F]NaF, and [¹⁸F]FMISO Multi-tracer Workflow

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I. SUMMARY:

This white paper presents the design of the BG75 2.0 Enhanced GMP system, which has the same hardware as the BG75 1.0 Enhanced [¹⁸F]FDG GMP¹ system with the addition of the [¹⁸F]NaF and [¹⁸F]FMISO dose synthesis cards. The software will also be updated from v4.3 to v5.0 to add multiple tracer workflow. [¹⁸F]NaF and [¹⁸F]FMISO have been automatically produced at multiple sites including the ABT factory. [¹⁸F]NaF and FMISO will be produced in an international GMP manner. Though no pharmacopeia exists for [¹⁸F]FMISO, ABT will develop a Drug Master File (DMF) to support site specific [¹⁸F]FMISO imaging. The system will be backwards compatible with all BG75 1.0 Enhanced GMP Dose Synthesis Cards including [¹⁸F]FDG and Discovery cards and the Radioisotope Generator 2.0². The BG75 2.0 Enhanced GMP system with NaF production will be available September 1, 2015 for purchase and with FMISO production December 1, 2015 for purchase.

II. BACKGROUND:

Immediately following the release of the BG75 1.0 Enhanced GMP system for [¹⁸F]FDG production¹, the BG75 2.0 Enhanced GMP integration and verification and validation testing with [¹⁸F]NaF and [¹⁸F]FMISO will commence³⁻⁵, as the only difference between the BG75 1.0 and 2.0 designs is the software and the addition of the GMP [¹⁸F]NaF and [¹⁸F]FMISO cards. The benefits of using [¹⁸F]NaF in medicine are in the study of bone cancer and bone metastases associated with prostate cancer. 10 mCi of [¹⁸F]NaF has been shown to have higher accuracy, higher sensitivity and greater differentiation compared to 30 [mCi] of Tc-99⁶. Combined [¹⁸F]FMISO PET imaging and IMRT has been shown to improve the delivery of higher radiation therapy doses to hypoxic regions⁷. The following sections of this document illustrate the necessary hardware and software updates and the current design progress made toward the including of [¹⁸F]NaF and [¹⁸F]FMISO on the BG75 2.0 Enhanced GMP system.

III. SYSTEM CONFIGURATION AND WORKFLOW:

The major difference between the BG75 1.0 Enhanced GMP and the BG75 2.0 Enhanced GMP is the multi-tracer workflow. The multi-tracer workflow allows for the Human Machine Interface (HMI) to distribute F-18 to an [¹⁸F]FDG CPM and an [¹⁸F]FMISO CPM. Even with the addition of two CPMs, the footprint of the BG75 system does not change, as illustrated in Figure 1, which shows a potential site layout with two CPMs.

IV. RESULTS:

The BG75 2.0 Enhanced GMP CPM has been built in the ABT factory and is in the hardware and software integration phase. [¹⁸F]NaF validation runs will begin in July followed by [¹⁸F]FMISO runs scheduled to start in September. The sections below describe the state of the DSCs, yields and regulatory strategy.

Dose Synthesis Cards for the BG75 2.0 Enhanced GMP

Figure 2 describes the DSCs that are available with the BG75 2.0 Enhanced GMP system. All cards from the BG75 1.0 Enhanced GMP are compatible with the 2.0 GMP system with the addition of the [¹⁸F]NaF and [¹⁸F]FMISO cards. The [¹⁸F]FMISO DSCs will be available with an up to 8 dose reagent kit. Both [¹⁸F]NaF and [¹⁸F]FMISO will have the associated cold standards for QC calibration and daily System Suitability Testing (SST).

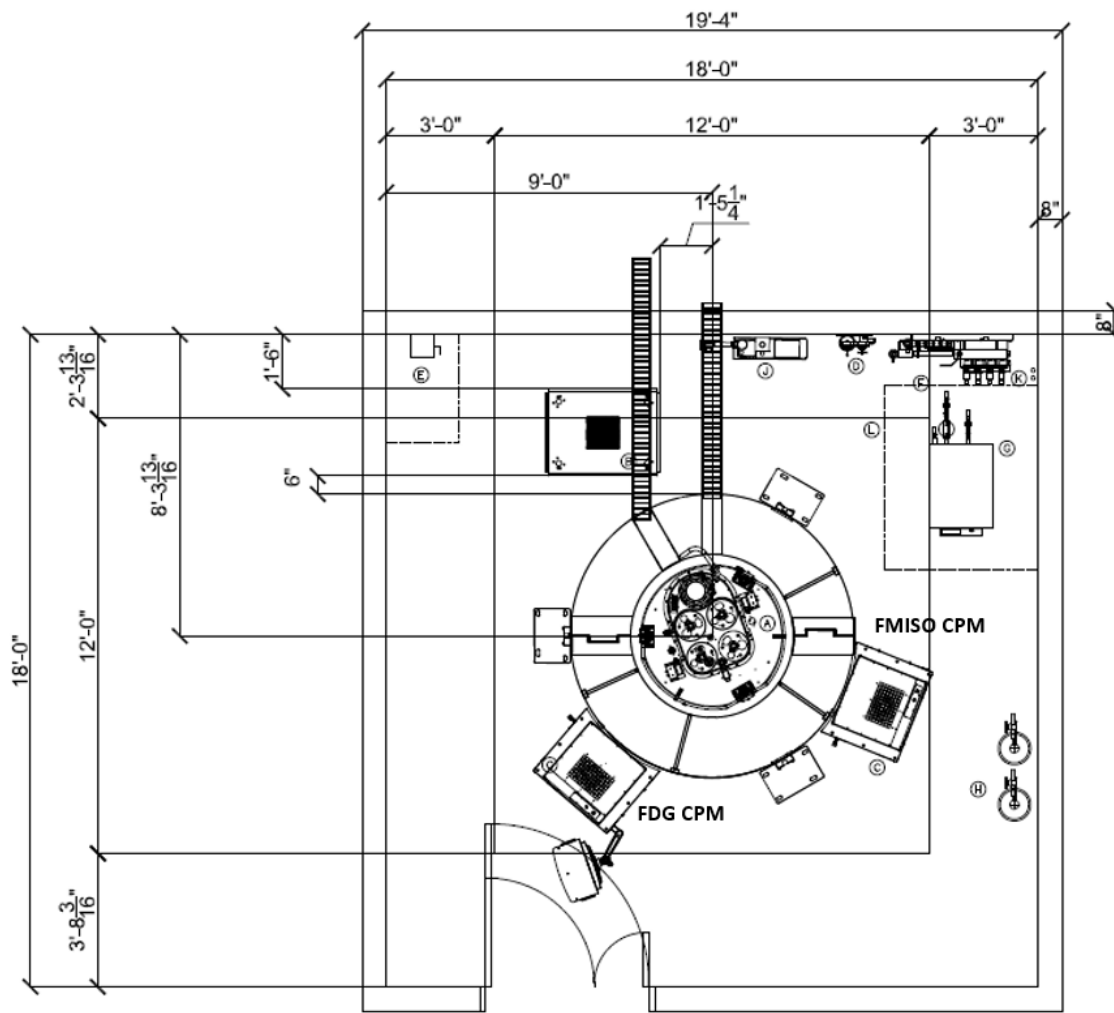
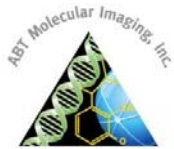


Figure 1. Site Layout showing multiple CPMs for [¹⁸F]FDG and [¹⁸F]FMISO CPMs.



Figure 2. Dose Synthesis Cards (DSC) currently available for the BG75 2.0 Enhanced GMP system. (Left) [¹⁸F]FDG Enhanced GMP Syringe card for individual doses, (Left Middle) [¹⁸F]FDG Enhanced GMP Batch card that dispenses into a vial for dose splitting,



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(Middle) Discovery Enhanced GMP DSC that dispenses to a vial for HPLC purification, (Right Middle) [¹⁸F]NaF Enhanced GMP DSC, and (Right) [¹⁸F]FMISO GMP Enhanced DSC.

[¹⁸F]FDG, [¹⁸F]NaF, and [¹⁸F]FMISO Yields with Yield Optimization

Automatic FMISO synthesis and purification on [¹⁸F]FMISO DSCs have been achieved at two sites (ABT and UNC) in the past two months. The [¹⁸F]FMISO card shown in Figure 2 has been optimized for [¹⁸F]FMISO yield and the purification column has been optimized for radiochemical purity. Table 1 describes the [¹⁸F]FMISO production in the ABT factory. The improvement in the decay corrected yield starting on April 23th was achieved by optimizing the labeling temperature and time from 110 [°C] and 9 [min] to 100 [°C] and 7 [min].

Table 1. [¹⁸F]FMISO yields from the BG75 2.0 Enhanced GMP prototype at ABT April 16 to 29 with Tantalum Target 1.0⁹.

Date [MM:DD:YYYY]	Starting Activity [mCi]	Dose in Syringe [mCi]	Start Time [HH:MM]	End Time [HH:MM]	DCY [%]
4/16/2015	45.0	10.1	14:56	15:29	27.7%
4/17/2015	79.9	16.7	9:35	10:11	26.2%
4/17/2015	69.9	16.3	10:17	10:53	29.3%
4/17/2015	44.9	10.6	10:59	11:35	29.7%
4/23/2015	45.9	8.8	11:28	12:10	25.0%
4/23/2015	32.7	8.4	13:59	14:38	32.7%
4/27/2015	39.3	10.4	12:02	12:50	35.7%
4/27/2015	39.0	11.8	13:39	14:12	37.3%
4/27/2015	45.7	11.5	15:07	15:41	31.2%
4/29/2015	38.8	10.0	10:47	11:22	32.0%

The proof of concept with automated [¹⁸F]NaF⁸ and [¹⁸F]FMISO production now allows ABT to retire design risk on the residual solvent testing with the Quality Control Module (QCM). Table 2 below illustrates the production for [¹⁸F]FDG, [¹⁸F]NaF and [¹⁸F]FMISO with the various target configurations.

Table 2. [¹⁸F]FDG, [¹⁸F]NaF, and [¹⁸F]FMISO Yields with different target configurations in a 1 [hr] run.

Radio-Tracer	High Flow Stainless Steel [mCi]	Tantalum Target 1.0 [mCi]	Tantalum Target 2.0 ⁺³ [mCi]
[¹⁸ F]FDG	16-20	28-32	46-54
[¹⁸ F]NaF	30-35	55-60	90-100
[¹⁸ F]FMISO	8-12	14-18	23-27

⁺The Tantalum Target 2.0 will be available Q4 of 2015.

Regulatory Strategy

A Drug Master File (DMF) for [¹⁸F]NaF will be available in December 2015 for reference. A DMF equivalent will be available for [¹⁸F]FMISO in March 2016 and will require site specific IRB approval. Both the [¹⁸F]NaF and [¹⁸F]FMISO will go through appropriate extractables and leachables testing with isopropyl alcohol (IPA) and acetonitrile (MeCN) to support a [¹⁸F]NaF release of September 1, 2015 and a [¹⁸F]FMISO release December 1, 2015.



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V. CONCLUSIONS:

The BG75 2.0 Enhanced GMP design was presented in this white paper illustrating that risk retirement of [^{18}F]NaF and [^{18}F]FMISO synthesis and quality control is complete. The system will support [^{18}F]FDG, [^{18}F]NaF, [^{18}F]FMISO and Discovery cards. The software is in the process of being developed for multiple tracer workflow. DMFs will be available for both [^{18}F]NaF and [^{18}F]FMISO to support clinical imaging. The BG75 2.0 Enhanced GMP system with NaF production will be available September 1, 2015 for purchase and with [^{18}F]FMISO production December 1, 2015 for purchase.

VI. REFERENCES:

- 1) White Paper - BG75 1.0 Enhanced GMP, Baltimore, MD. 2015. <http://abt-mi.com/en/resources>
- 2) White Paper - RIG 2.0, Baltimore, MD. 2015. <http://abt-mi.com/en/resources>
- 3) Automated Radiopharmaceutical Production and Quality Control System, 14/618,795, Submitted March 6th, 2015, ABT Molecular Imaging, Inc. Knoxville, TN
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- 5) Dose Synthesis Card, 14/618,732, Submitted March 6th, 2015, ABT Molecular Imaging, Inc. Knoxville, TN
- 6) Sodium Fluoride PET Bone Imaging: A Clinical Reality - Susan Kirk Molecular Imaging Siemens Healthcare Knoxville TN USA.
- 7) Hypoxia Imaging with [F-18] FMISO-PET in Head and Neck Cancer: Potential for Guiding Intensity Modulated Radiation Therapy in Overcoming Hypoxia-Induced Treatment Resistance, Hendrickson, K et al. Radiother Oncol. 2011 Dec; 101(3): 369–375.
- 8) White Paper – NaF at UNC, St. Louis, MO 2014. <http://abt-mi.com/en/resources>
- 9) Automated Manufacture of [^{18}F]FMISO in the BG 75 system. Synthesis and Purification using Solid Phase Extraction, 1001, SNMMI 2015, Baltimore, MD.