BG75 [^{18}F] Multi-Tracer CPM

Automated [^{18}F]FDG/NaF/FMISO/FLT Production & QC

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I. SUMMARY:

This white paper presents the design of the BG75 Multi-tracer (MT) Chemistry Production Module (CPM) system, which is based off of the BG75 1.0 and 2.0 Enhanced CGMP systems[1,2]. The software has been updated from v4.2.3.7 to v5.0 to add multiple tracer workflow for [^{18}F]FDG/NaF/FMISO/FLT. [^{18}F]NaF and [^{18}F]FMISO have been automatically produced at multiple sites including the ABT factory. The [^{18}F]FLT dose synthesis card is under development. All tracers are produced in an international CGMP manner. Though no pharmacopeia exists for [^{18}F]FMISO/[^{18}F]FLT, ABT is committed to partnering with sites to develop the necessary document for their Internal Review Board (IRB). The BG75 MT CPM 2.0 system with FDG/NaF production is available for purchase now and will be available for purchase in with [18F]FMISO production September 1, 2016, and [^{18}F]FLT in June of 2017.

II. BACKGROUND:

The BG75 MT CPM has been developed in line with ABT's philosophy of Dose on Demand® production with solid phase extraction (SPE) purification. The system can be brought up in a [^{18}F]FDG/NaF mode, [^{18}F]FMISO mode, or [^{18}F]FLT mode at the start of day. The MT CPM also supports up to 3 CPMs attached the RIG to allow for each CPM to produce CGMP radiopharmaceuticals on demand with little interruption to routine [^{18}F]FDG workflow.

III. SYSTEM CONFIGURATION AND WORKFLOW:

The software has three modes of operation: (1) Explorer Mode that can be used for new tracer development, (2) a Preclinical Mode for preclinical research, and (3) CGMP Clinical Mode for human injection. F-18 can be produced in all modes. Figure 1 illustrates the differences between these modes. Explorer Mode does not check for a valid QC file or enforce the daily System Suitability Test (SST). Discovery Cards do not contain purification columns and are designed to distribute to a vial for HPLC based purification. The CGMP Clinical mode of operation is to be used for clinical injection of PET Radiopharmaceuticals. The CGMP Clinical Mode enforces a valid QC calibration file within 3 months of the run date and two SST residual solvent injections. The mode of operation is chosen at the start of the day. The mode can be changed by shutting down the system (45 minute procedure) and bringing it back up in another mode if multiple MT CPMs are not available on site.

IV. SYSTEM ARCHITECTURE:

The system can be broken into the following three major subsystems: the radioisotope generator (RIG, e.g. cyclotron), the chemistry production module (CPM) and the human machine interface (HMI). The RIG is controlled by the accelerator control unit (ACU), which is an embedded FPGA that monitors ion source current, target current, target water delivery and transfer and RF frequency and power. A typical site layout is shown in Figure 2 with both and an [^{18}F]FDG and a [^{18}F]FMISO CPM.

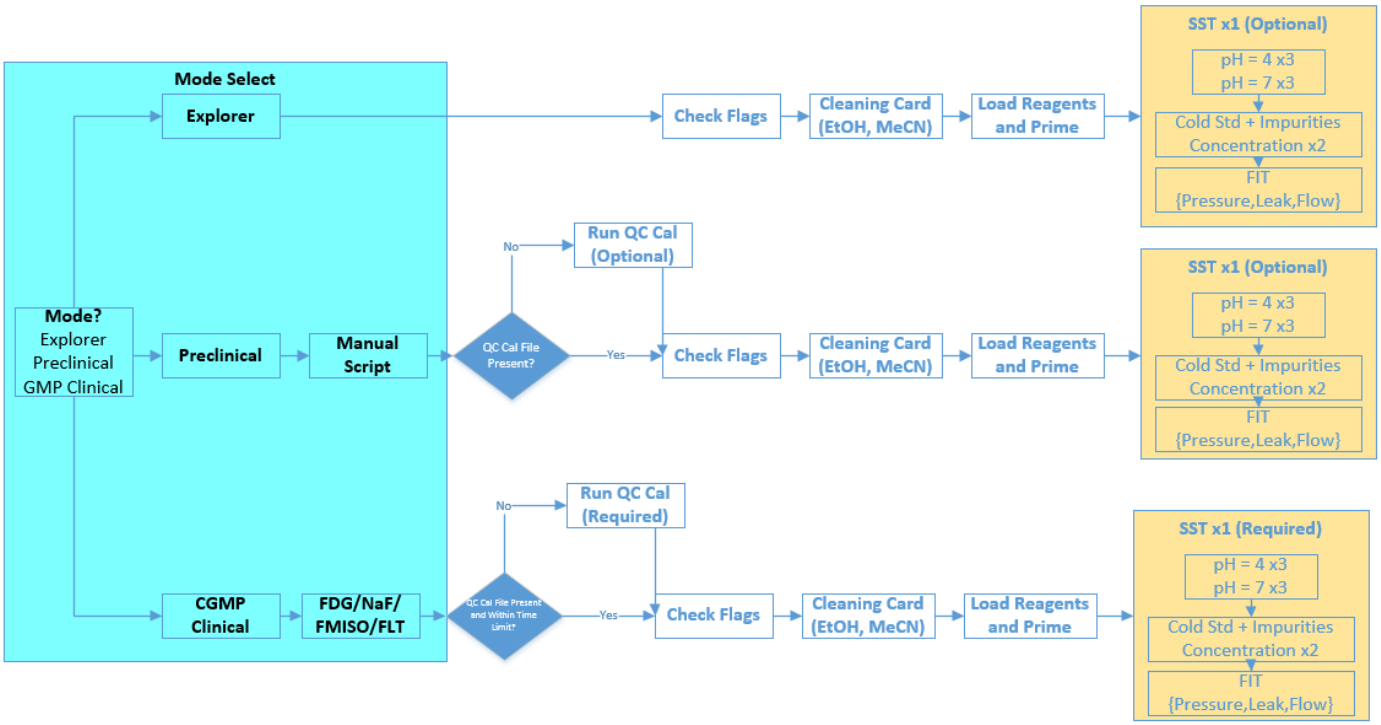

Figure 1. The three modes of operation of the BG75 MT CPM 2.0 system: Explorer, Preclinical, and CGMP Clinical.

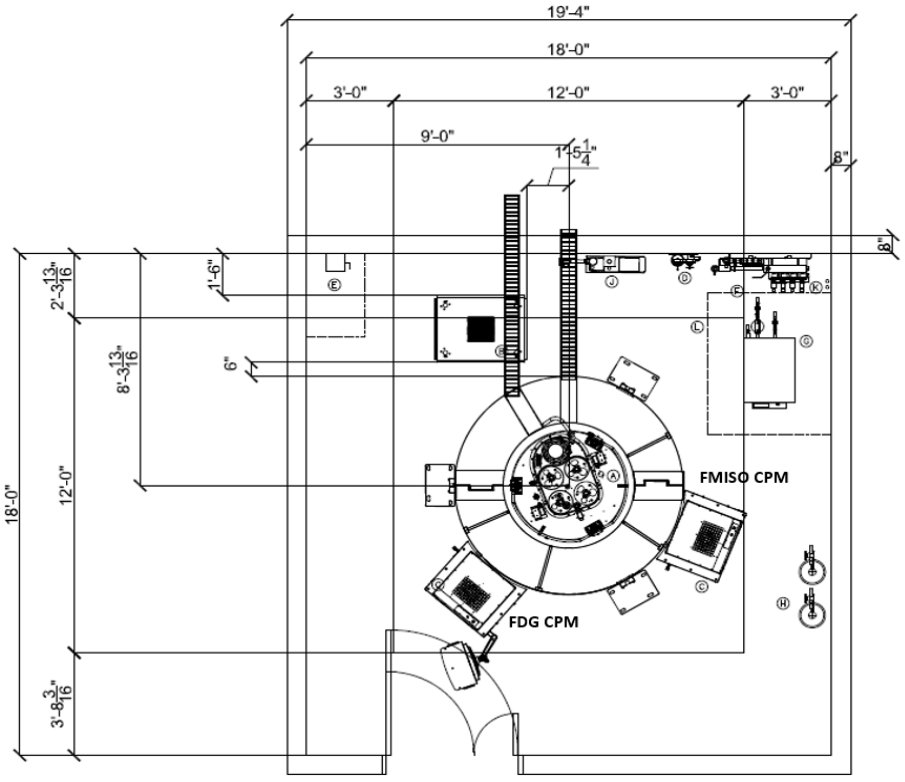

Figure 2. Site Layout showing multiple CPMs for [18F]FDG and [18F]FMISO CPMs.

[18F] Chemistry Card System (CCS)

The Chemistry Production Module (CPM) has been updated with the latest pinch valves to improve reliability. Figure 3 describes the DSCs that are currently available with the BG75 MT CPM CGMP system. The [18F]FDG/FMISO/FLT DSCs will be available with an up to 8 dose reagent kit. All reagents will have the associated residual solvents and cold standards kits for QC calibration and daily System Suitability Testing (SST).

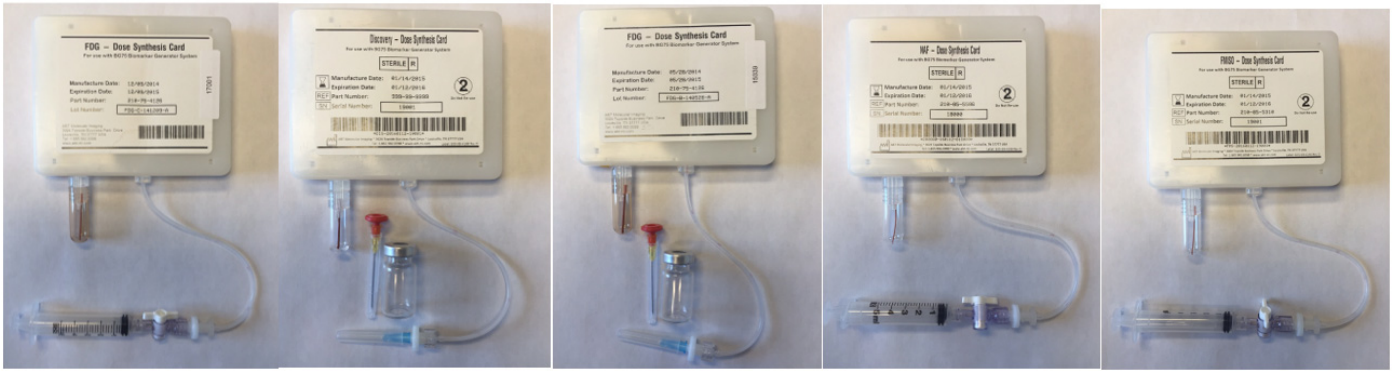

Figure 3. Dose Synthesis Cards (DSC) currently available for the BG75 2.0 Enhanced GMP system. (Left) [18F]FDG DSC 2.0 Syringe, (Left Middle) [18F]FDG Discovery DSC, (Middle) FDG DSC 2.0 Vial, (Right Middle) [18F]NaF DSC 2.0 Syringe, and (Right) [18F]FMISO DSC 2.0 Syringe.

Using support from 1R44CA195813-01 - Automatic Production and Quality Control of Tumor Proliferation PET Radiotracer FLT, an FLT card has been developed based off of the EU approved precursor (DMTr-Boc-Nosyl) for use with the MT CPM 2.0 (see Figure 3). Successful solid phase extraction purification has been achieved with both Alumina N Basic in conjunction with a C-18 column and Alumina A Acidic in conjunction with a tC-18 column. Alumina B, tC-18, and C-18 with trap and release were not capable of achieving radiochemical purities > 95 [%].

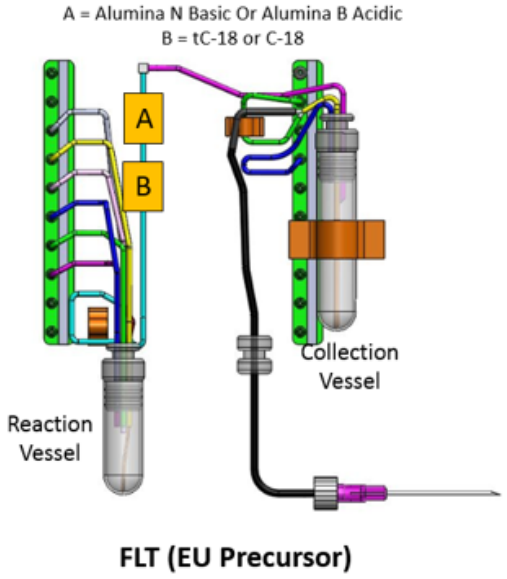

Figure 4. Prototype [18F]FLT dose synthesis cards for the EU based precursor. The EU based precursor has been developed with solid phase extraction which is more easily integrated into our current chemistry production module (CPM) architecture.

The synthesis parameters for [18F]FLT are shown in Table 1.

Table 1. Synthesis and purification chemistry scripts for [18F]FLT using the EU labeling precursor.

Production Step	EU Precursor
Precursor	DMTr-Boc-Nosyl
Azeotrope Evaporation	100 [°C], 6 [min], Vacuum
Labeling	65 [°C], 9 [min], Sealed reactor
MeCN Evaporation	65 [°C], 5 [min], Vacuum
Hydrolysis/Condensation	110 [°C], 2 [min], Vacuum
Purification	HPLC

The proof of concept with automated [18F]NaF[8] 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/NaF/FMISO/FLT 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 [mCi]
[18F]FDG	20-24	35-40	55-60[1]
[18F]NaF	35-40	60-65	110-120[1]
[18F]FMISO	10-14	16-20	25-30[1]
[18F]FLT	N/A	3-5	7-10[1]

[1]Estimated production.

[18F] Quality Control Module (QCM)

The movement of the QC draw loop results in a more reliable QC draw and push to the Quality Control Module (QCM). The QCM also includes semi-automation of the dose strength and RNP test by integrating the output from a dose calibrator into the dose record. This feature is optional.

PET Production Suite (PPS)

The PET Production Suite provides a number of CPM enclosure configurations to suit site specific requirements. The addition of the QC test cart for manual QC testing ensures that sterility inoculation and endotoxin testing are performed in a CGMP manner (see Figure 5).

System Optional Installation Kit (SOIK)

The BG75 MT CPM also comes with other optional equipment to suit siting and manual Quality Control Testing needs.

Table 3. Components of the System Optional Installation Kit (SOIK).

Installation and Siting
Power Transformer
CPM UPS
RIG UPS
Indoor/Outdoor Chiller
Radiation Safety
L-Block (25x reduction in γ)
RIG Equipment
Target Cleaning Kit
3rd Party QC Equipment
Charles River
MCA
Survey Meter
Digital Area Monitor (for cyclotron and chemistry room)
5cc Syringe Shield
Syringe Carrier
Personal Dosimeters
Dose Calibrator

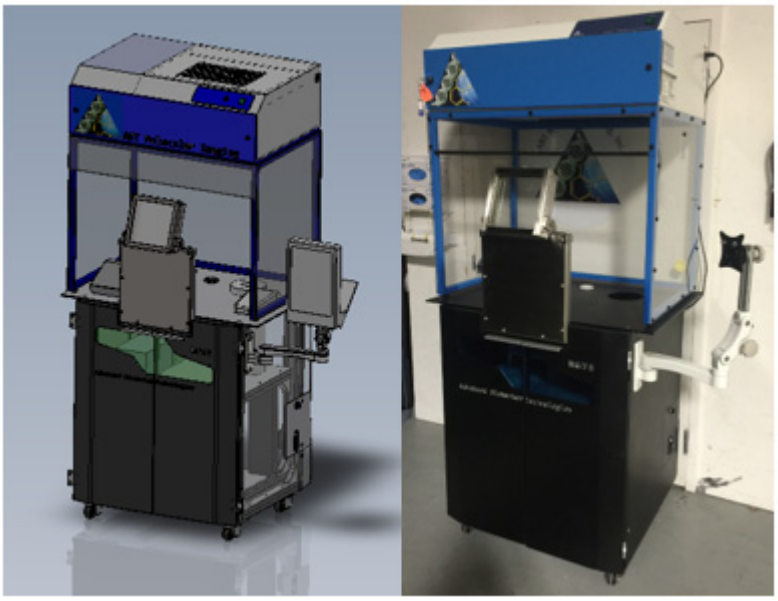

Figure 5. Model and actual QC test cart used for manual QC testing. The QC test cart provides an ISO Class 5 environment for sterility inoculation and endotoxin testing.

Regulatory Strategy

ABT's existing BG system has achieved certification to inject clinical patients in Sveta Marina University Hospital in Varna, Bulgaria and Owen Kane in St. Petersburg, Russia. Under these certifications the sites have successfully injected more than 3,000 patients with [18F]FDG produced at 3 sites with the BG system since installation. The hospitals have never failed a sterility test.

A Drug Master File (DMF) is available for [18F]FDG/NaF. A DMF equivalent will be available for [18F]FMISO/FLT and will require site specific IRB approval.

V. CONCLUSIONS:

The BG75 MT CPM system has been presented in this white paper. The design has been developed in accordance with ISO 13485 and 9001 standards, which include design inputs, verification, validation and a risk management file. The first MT CPM will be installed at Newcastle University in Q1 of 2017.

VI. REFERENCES:

1) White Paper - BG75 1.0 Enhanced GMP - FDG. Baltimore, MD. 2015. http://abt-mi.com/en/resources
2) White Paper - BG75 2.0 Enhanced GMP - FDG NaF and FMISO. Baltimore, MD. 2015. http://abt-mi.com/en/resources