BG75 1.0 Enhanced GMP Design
[18F]FDG Production with Yield Optimization

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I. SUMMARY:

This white paper describes the new ABT Biomarker Generator (BG) platform for radiopharmaceutical development, termed the BG75 1.0 Enhanced GMP design. This design is compliant with international [18F]FDG GMPs and pharmacopeia surrounding the production of PET radiopharmaceuticals. This design has three different target configurations for the Radioisotope Generator 2.0[3] (RIG), and contains new Chemistry Production Module (CPM) hardware required for yield optimization and 30 minute cycle time[1]. The CPM also has a new Chemistry Control Unit (CCU) that monitors QC function to ensure that a safe dose is produced. As part of the system design, a risk assessment was performed to ensure that all aspects of the design had been reviewed and analyzed for safe operation and a safe [18F]FDG dose. The Discovery Dose Synthesis Card is available for use with this design that gives researchers the ability to develop novel tracers using the flexible Discovery development environment. The system will be available for purchase on July 1, 2015[4-6].

II. BACKGROUND:

The BG75 30 Minute configuration, which is currently available for purchase, produces a safe and effective dose of [18F]FDG on a sterile card. The purpose of this project is to add the necessary features to the BG75 platform to make it compliant with Good Manufacturing Practice (GMP) requirements. The addition of all GMP features will ensure that the system can be used for clinical injection internationally in multiple environments. Furthermore, the hardware and scripts associated with the [18F]FDG synthesis have been upgraded to optimize [18F]FDG yield and produce batches of [18F]FDG dispensed into a vial for easier dose splitting.

The novelty of the BG75 system from a GMP standpoint is the automation of the chemistry synthesis, QC processing and automation of the system as a whole through the Human Machine Interface (HMI). The methodology employed by ABT is to analyze the system from a GMP perspective and ensure that the system meets all pharmaceutical regulatory requirements and is supported by the appropriate verification and validation and a risk management file. In this way, the system has been tested and its design has been documented according to ISO 13485 and 9001 standards. The sections below describe the architecture of the system and the regulatory strategy associated with documenting the design and ensuring GMP compliance. The BG75 2.0 Enhanced GMP system will follow the 1.0 release and add multiple-tracer workflow and DSCs for [18F]NaF and [18F]FMISO[3].

III. SYSTEM CONFIGURATION AND WORKFLOW:

The software has three modes of operation: a Discovery Mode that can be used for preclinical research and new tracer development, Routine Clinical Mode and GMP Clinical Mode. F-18 can be produced in all modes. Figure 1 illustrates the differences between these modes. Discovery Mode does not check for a valid QC file or enforce the daily System Suitability Test (SST). Discovery Cards shown in Figure 3 (Right) do not contain purification columns and are designed to distribute to a vial for HPLC based purification. The Routine Clinical and GMP Clinical Modes of operation are to be used for clinical injection of [18F]FDG. The GMP 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 and bringing it back up in another mode.

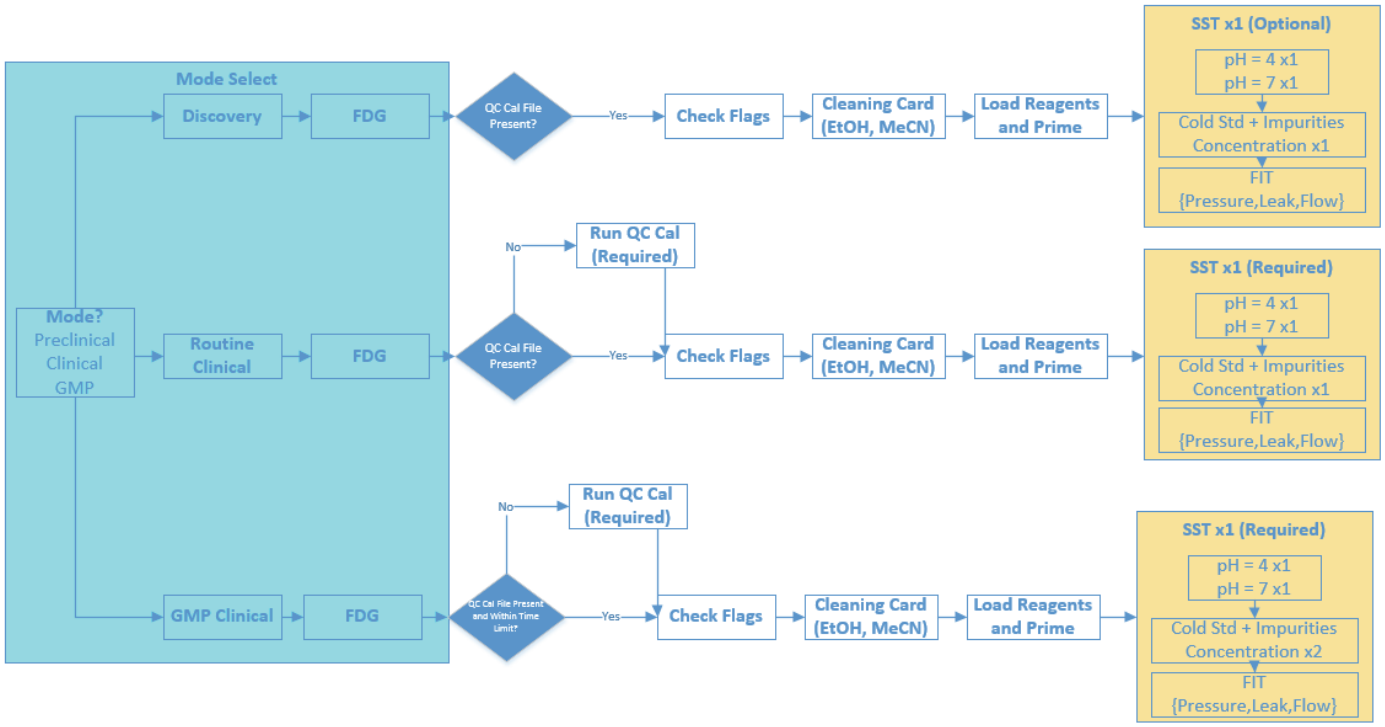

Figure 1. The three modes of operation of the BG75 1.0 Enhanced GMP system: GMP Clinical, Routine Clinical, and Discovery Mode.

Table 1 below describes the system configuration differences between the BG75 30 Minute and BG75 1.0 Enhanced GMP configurations. The differences between the two system configurations are the CPM and software for GMP compliance including 21 CFR Part II. The RIG 2.0 is compatible with both configurations.

Table 1. 30 Minute versus BG75 1.0 Enhanced GMP system configuration.

Subsystem	BG75 30 Minute	BG75 1.0 Enhanced GMP
Software	4.2.2.1	4.3
Chemistry Production Module (CPM)	0.5	1.0
Radioisotope Generator (RIG)	1.0 or 2.0[3]	2.0[3]
RIG Target	High Flow Stainless Steel Tantalum Target 1.0 Tantalum Target 2.0	High Flow Stainless Steel Tantalum Target 1.0 Tantalum Target 2.0

IV. RESULTS:

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) (see Figure 2). 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. The CPM contains three major subsystems, the chemistry card system (CCS), the quality control module (QCM) and the chemistry control unit (CCU). The CCS includes the reagent metering system and is the location of the disposable dose synthesis card. The QCM contains all quality control hardware and tubing. Both the CCS and the QCM are shielded appropriately to minimize exposure to the operator. Both the CCS and the QCM are controlled by the CCU, which commands and monitors all the CPM equipment. Finally, the HMI communicates through Ethernet with the ACU and the CCU and displays the information on the user interface. The reagent kits for [18F]FDG/[18F]NaF come in 8 and 16 batch kits. Each tracer comes with

quality control stands for quality control system calibration and daily system suitability tests. The software has three modes of operation: a Discovery Mode that can be used for preclinical research and new tracer development, Routine Clinical Mode and GMP Clinical Mode. F-18 can be produced in all modes.

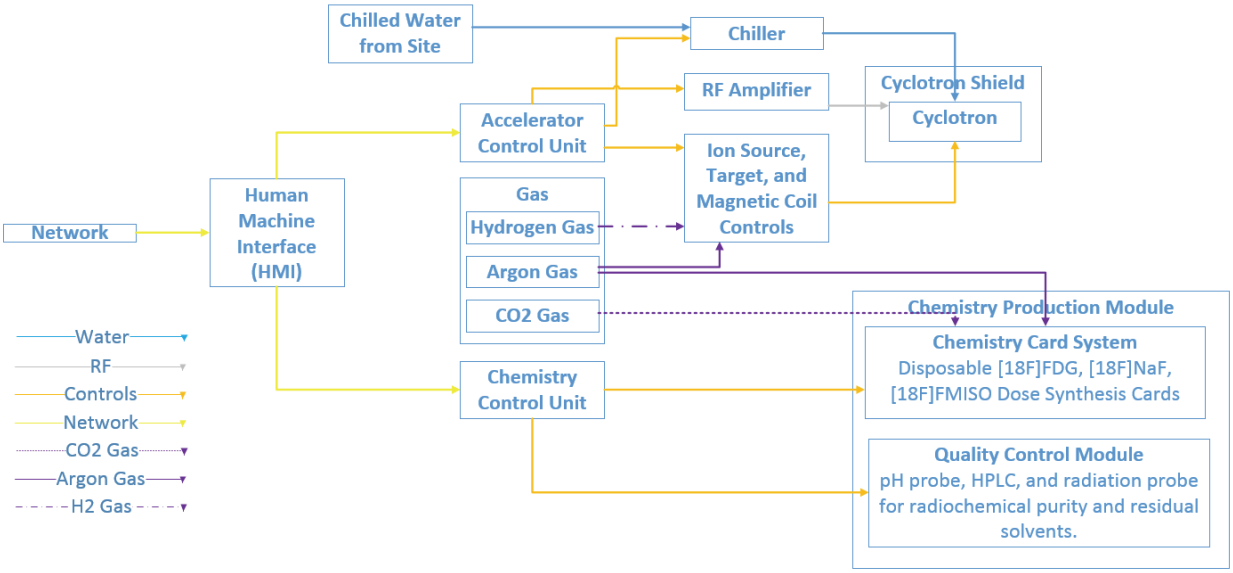

Figure 2. High level system architecture for the BG75 1.0 Enhanced GMP system showing how the Human Machine Interface controls the RIG and CPM through the Accelerator Control Unit (ACU) and Chemistry Control Unit (CCU).

Dose Synthesis Cards for the BG75 1.0 Enhanced GMP

The dose synthesis cards for the BG75 1.0 Enhanced GMP are shown in Figure 3. The existing [18F]FDG syringe card will be available along with an [18F]FDG batch card that has a syringe needle and vial for dose-splitting batch production. The Discovery card contains the same material as the [18F]FDG card with the exception that the purification column is removed. The Discovery card is to be used for new-tracer development.

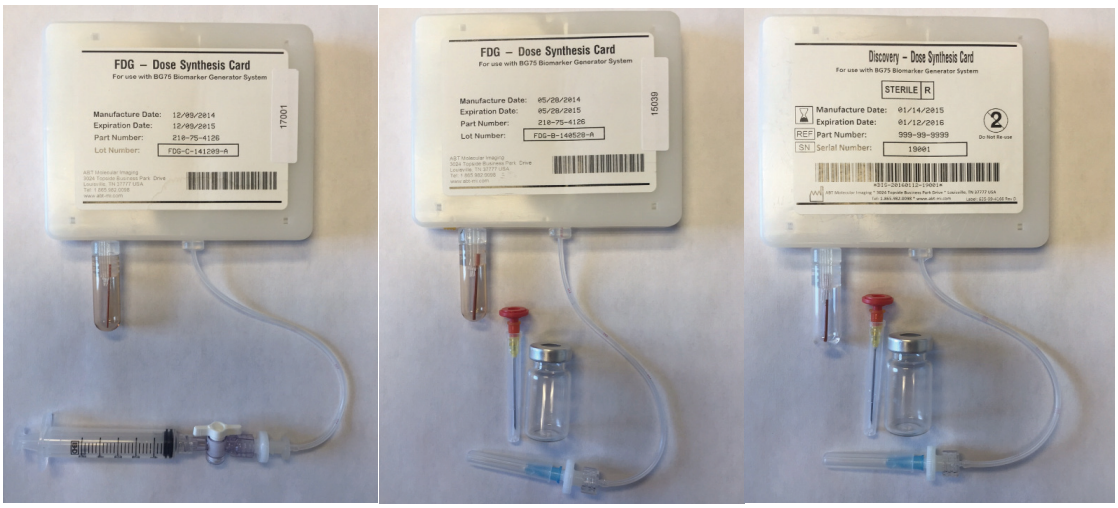

Figure 3. Dose Synthesis Cards (DSC) available for the BG75 1.0 Enhanced GMP system. (Left) [18F]FDG Enhanced GMP Syringe card for individual doses, (Middle) [18F]FDG Enhanced GMP Batch card that dispenses into a vial for dose splitting and (Right) Discovery Card that dispenses to a vial for HPLC purification.

[18F]FDG Yields with Yield Optimization

A new feature of the BG75 1.0 Enhanced GMP system is yield optimization hardware and scripts. The yield optimization is based on the addition of a vacuum pump to the Chemistry Card System (CCS). The vacuum pump performs the essential function of removing air from the reactor after azeotrope evaporation to ensure a water-free reactor for the rest of synthesis. The improvement in yield can also been seen in the chemistry plots. The addition of the vacuum pump also necessitated optimizing the label temperature and times for the synthesis script.

The addition of yield optimization along with the target options available for the RIG 2.0, results in the following [18F]FDG yields in Table 2.

Table 2. [18F]FDG Yield with different target configurations in 1 [hr].

Radio-Tracer	High Flow Stainless Steel [mCi]	Tantalum Target 1.0 [mCi]	Tantalum Target 2.0 [mCi]
[18F]FDG	16-20	28-32	46-54

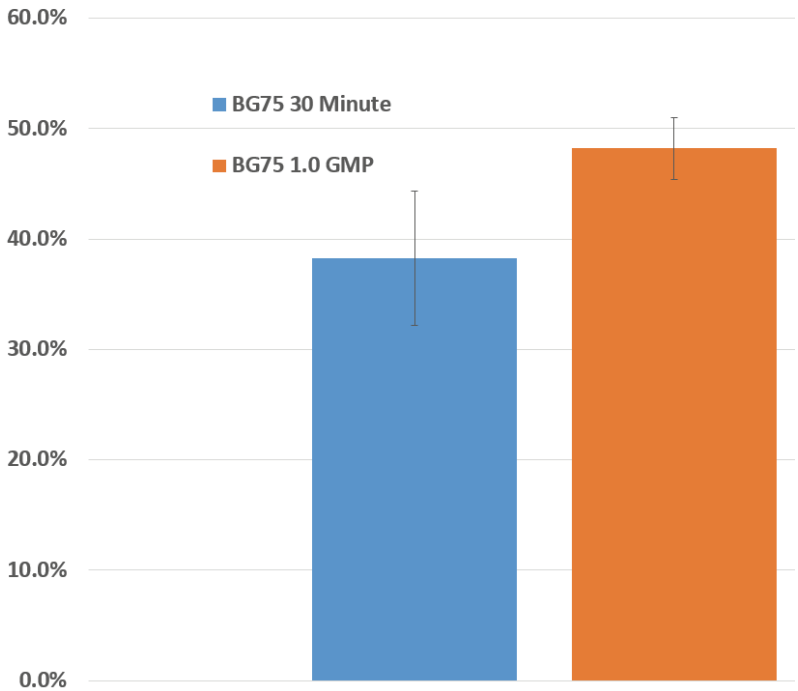

Figure 4. Dose in Syringe for vacuum yield optimized BG75 1.0 Enhanced GMP compared to the existing BG75 30 Minute release. The addition of vacuum improves the Decay Corrected Yield (DCY) by removing the residual water after azeotrope evaporation.

Chemistry Production Module (CPM)

The Chemistry Production Module (CPM) has been updated with the latest pinch valves to improve reliability and movement of the QC draw loop up to the Chemistry Card System (CCS). The movement of the QC draw loop results in a more reliable QC draw and push to the Quality Control Module (QCM). The new QC draw schematic is shown in Figure 5.

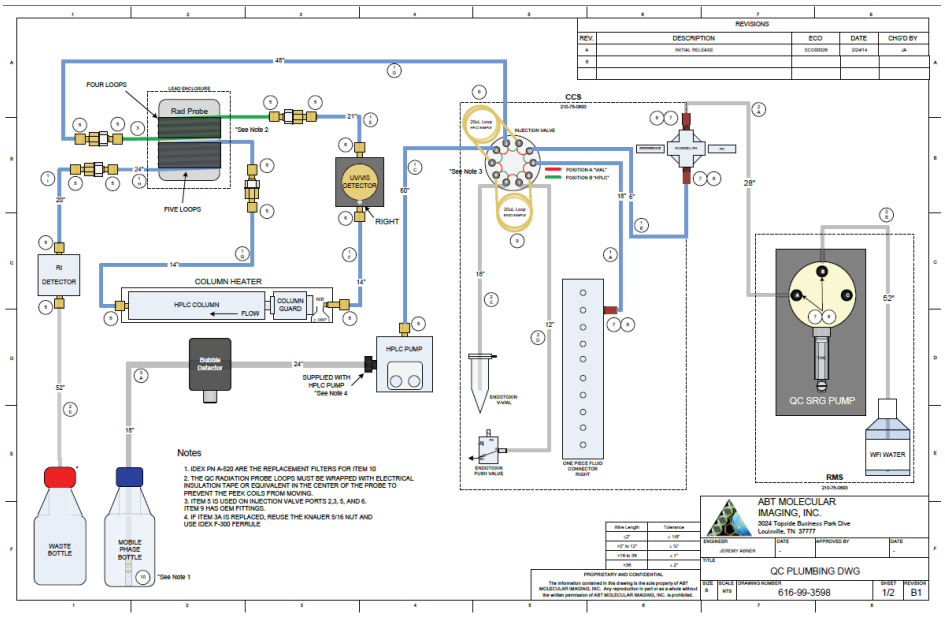

Figure 5. New QC Load Loop Architecture that allows for more efficient and contamination free QC draw (Patent Pending 14/618,772).

PET Production Suite (PPS)

The PET Production Suite provides a number of CPM enclosure configurations to suit site specific requirements. The three CPM enclosures shown in Figure 6 support the Discovery, Routine Clinical and Enhanced GMP Clinical Modes of operations. ABT has partnered with GermFree® to produce a biosafety cabinet that is fully upgradable to the BG75 1.0 Enhanced GMP CPM and provide a Class 100 environment with particle monitoring for sterility inoculation and manual QC tests.

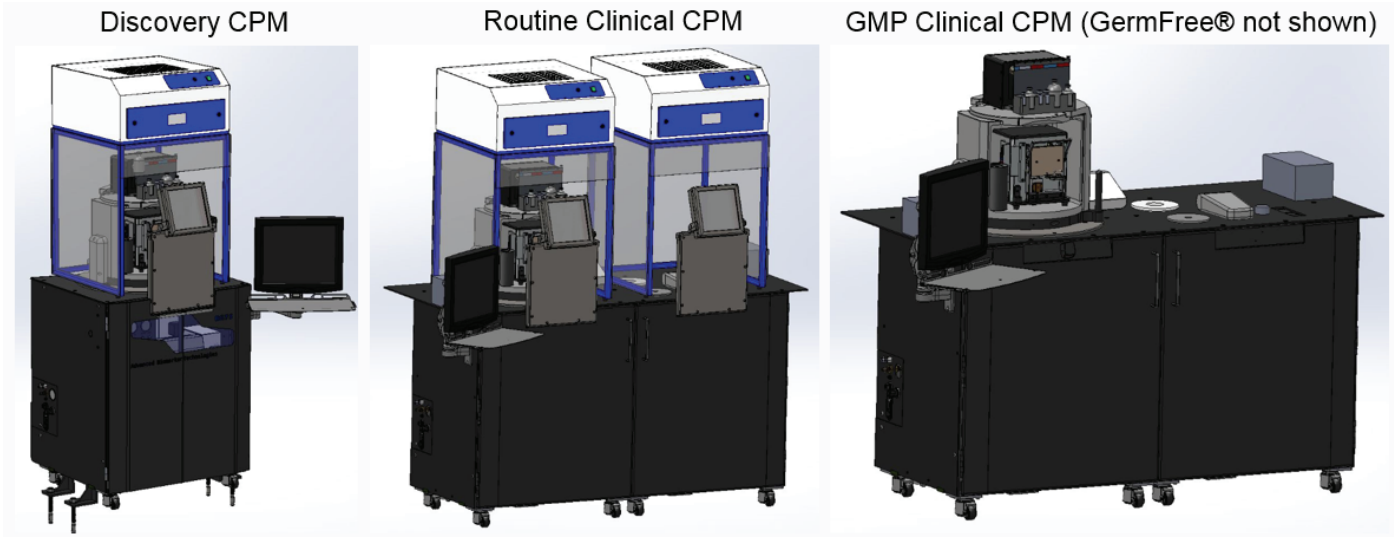

Figure 6. The different CPM enclosure configuration options. (Left) The Discovery Mode configuration is used for novel tracer development and preclinical workflow. (Middle) The Routine Clinical configuration includes the addition of a customized CPM cart for manual QC equipment and a laminar flow hood. (Right) The GMP Clinical configuration has a custom GermFree® ISO Class 100 hood with particle monitoring for the most stringent international GMP sites.

System Optional Installation Kit (SOIK)

The BG75 1.0 Enhanced GMP also comes with other optional equipment to suit siting and manual Quality Control Testing needs. The equipment in the table below is compatible with the Discovery, Routine and GMP Clinical configurations.

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

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 by the BG system since installation. The hospitals have never failed a sterility test.

After the release of this project, the system will be compliant with all international GMP and the associated pharmacopeias for [18F]FDG and [18F]NaF. The system will also be compliant with the associated monographs for FMISO as it is not universally accepted for reimbursement. ABT will submit Drug Master Files (DMF) for [18F]FDG and NaF in the United States and United Kingdom. Using the DMFs, ABT will pursue clinical injections for [18F]FDG and [18F]NaF at our existing sites at the University of North Carolina and Newcastle University. The DMF is estimated to be complete by August of this year. ABT will also be perusing clinical NaF injection certification in Varna, Bulgaria, and FMISO injections at our site in Owen Kane, St. Petersburg, Russia, which already has approval for clinical FMISO injections.

The table of contents of the Drug Master File, shown in Figure 7, represents a milestone in PET radiopharmaceutical production from a regulatory perspective as it is the first automated radioisotope production,

synthesis, purification and quality control system in the world for [18F]FDG production. The safety and efficacy of the device is based on a risk assessment developed under ISO 13485 design controls as shown in Figure 8.

Figure 7. Drug Master File (DMF) Table of Contents. DMF shall be complete by August 2015.

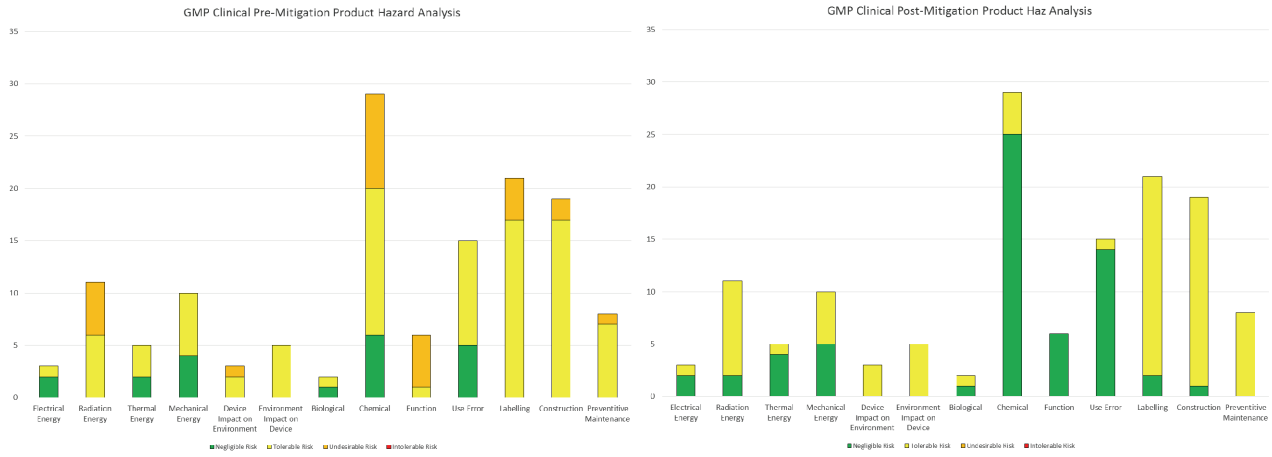

Figure 8. (Left) Pre and (Right) Post mitigation risk after implementing and verifying the design of the BG75 1.0 Enhanced GMP.

The [18F]FDG DSC will go through appropriate extractables and leachables testing with isopropyl alcohol (IPA) and acetonitrile (MeCN).

V. CONCLUSIONS:

The BG75 1.0 Enhanced GMP 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 BG75 1.0 Enhanced GMP has been successfully developed and tested with yield optimization in-house at ABT's factory in Knoxville, TN. The Drug Master File has been developed for the BG75 1.0 Enhanced GMP system and will be referenced by aNDA and MHRA submissions at our USA and UK sites. The system will be available for purchase on July 1, 2015.

VI. REFERENCES:

1) White Paper - 30 Minute Upgrade at Varna, Baltimore, MD. 2015. http://abt-mi.com/en/resources
2) White Paper - BG75 2.0 Enhanced GMP, Baltimore, MD. 2015. http://abt-mi.com/en/resources
3) White Paper - RIG 2.0, Baltimore, MD. 2015. http://abt-mi.com/en/resources
4) Automated Radiopharmaceutical Production and Quality Control System, 14/618,795, Submitted March 6, 2015, ABT Molecular Imaging, Inc. Knoxville, TN
5) Automated Quality Control System, 14/618,772, Submitted March 6, 2015, ABT Molecular Imaging, Inc. Knoxville, TN
6) Dose Synthesis Card, 14/618,732, Submitted March 6, 2015, ABT Molecular Imaging, Inc. Knoxville, TN. http://abt-mi.com/en/resources