ABT MOLECULAR IMAGING

in cooperation with

BG-75 Biomarker Generator

Technical Overview and Comparison

ABT BG-75 Biomarker Generator

The ABT Biomarker Generator (BG) is a revolutionary development in radiopharmaceutical production that delivers a single patient dose of PET radioisotopes and biomarkers on demand. The uniqueness of the BG is that it integrates the major hardware components required to produce and qualify PET biomarkers in a single, self-contained system that occupies a fraction of the space required by conventional systems (Figure 2) and is simple to operate. Three major components of radiopharmaceutical production are integrated into one functional unit that produces an individual patient "dose on demand."

- Compact, simple, efficient and self-shielded micro-cyclotron
- Microchemistry system for labeling FDG with the positron-emitting isotope, ^{18}F
- Automated quality control (QC) for verifying suitability for human injection

Comparison with Conventional PET Biomarker Production

Due to its small footprint and self-shielding, the ABT BG can be easily incorporated into an existing clinical or research setting, adjacent to PET imaging equipment if desired. By contrast, standard PET biomarker laboratories produce batches of positron-emitting isotopes in a conventional medical cyclotron, which poses a far greater radiation burden that requires significant physical containment of both the cyclotron and all downstream processing steps (Figure 2, Table 2). Typically, a concrete-reinforced bunker has to be specially built to contain the cyclotron, with separate "hot" labs dedicated to radiochemistry and QC, and several highly specialized staff to operate the cyclotron and perform subsequent functions. In comparison, the ABT BG is scaled for a single engineer/operator, occupies one-tenth the space, requires little infrastructure modification, and has embedded chemistry and QC processes that greatly simplify the entire radiopharmaceutical production cycle. These features translate into significantly less capital investment initially and lower ongoing operating costs compared to conventional PET biomarker laboratories (approximately 40 - 60% and 70% less, respectively; Table 2). Additionally, due to its self-contained design and lower energy, decommissioning the BG at the end of its useful life (15 - 20 years) is much simpler and far less costly (80% less) as well. Overall, the total cost of ownership for the ABT BG is less than one quarter that of conventional cyclotrons.

Figure 2. Comparison of space requirements for radiopharmaceutical production using the ABT Biomarker Generator (*left*) versus conventional systems (*right*). Due to its compact design, self-shielding, integrated microchemistry and automated QC systems, the BG requires less than one-tenth the space required for a standard PET biomarker lab with a conventional cyclotron. In conventional PET laboratories, production of positron-emitting radioisotopes, biomarker radiolabeling (chemical coupling or synthesis), and required QC functions are performed in physically separate spaces by approximately four highly skilled staff, using multiple pieces of equipment. Diagrams are drawn to scale.

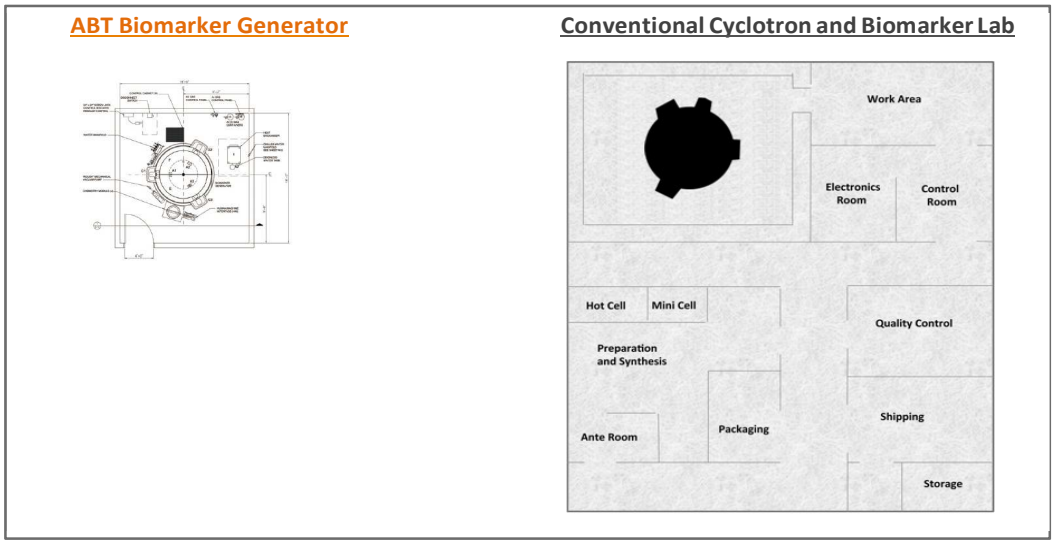

Table 2. Comparison of the ABT Biomarker Generator versus Conventional Cyclotrons

Parameter	ABT Biomarker Generator	Conventional Medical Cyclotron
Laboratory Footprint	300 square feet (30 m^2)	3,300 square feet (330 m^2)
Placement	Flexible	Multiple constraints: bunker for cyclotron; physically separate chemistry and QC "hot" labs
Weight	24 tons	50 - 65 tons
Shielding	Self-contained (exposure <1 mR/hour)	Bunker for cyclotron; chemistry hot cells required
Radiation Profile	<1 mR/hr at 1 meter	Exposure = 2 mR/hr at room boundary
Additional Equipment	$50,000	$750,000
Build Out Costs	<$150,000	$1 - 3m
Build Out Time	<6 months from construction start	> 18 months from construction start
Operating Power	<5 kW	35 kW
HVAC Requirements	2.5 KW	40 KW
Target Beam Current*		40 - 60 µA
Internal Cyclotron Targets*	3	4 - 8
Dose Quantity Production	Single	Batch
Repetitive Production Cycle	40 minutes	3 hours
Quality Control	Integrated and automated	Requires separate QC Lab and personnel
Regulatory Burden	Lower due to less radiation exposure	Higher due to high radiation production
Environmental Requirements	Laminar flow hood for using closed card chemistry synthesis with Integrated dispensing	Clean room requirements due to open synthesis and dispensing
Personnel	1 - 1.5 FTE	3 - 5 FTE
System Pricing	$2.5m	$1.9m - $2.2m
Operating Expenses	$175k/year	$600k/year
Decommissioning Costs	<$100K	>>$500K
Total Project Price	$2.7m	$4.0m - $6.0m

The many advantages of FDG production using the ABT Biomarker Generator versus conventional systems include space, staffing, operational complexity, and system lifecycle costs (Figure 2 and Table 2), which make it particularly well suited for emerging PET/CT markets. Capital investment for the BG is 40 - 60% less than for conventional systems and ongoing operating costs are 70% less (Table 2). Because the BG-75 is a low energy self-shielded, stand-alone unit, decommissioning costs at the end of its useful life are 80% less than a conventional PET biomarker laboratory.

Virtually all PET cyclotron makers have partnered with specialty radiochemistry and QC equipment manufacturers to market a total solution for PET biomarker production. Unlike the ABT system, though, these conventional radiochemistry systems require significant user intervention and are not fully integrated with isotope production or QC processes. The ABT BG-75 is the first and only competitor in this space to automate PET biomarker chemistry and QC capability.

Table 3. Comparison Of Radiochemistry And Quality Control Using the ABT Biomarker Generator and Conventional Systems

Parameter	ABT Biomarker Generator	Conventional
Environmental Requirements	Closed card based synthesis requiring only laminar flow hood	Open system requires Class C environment for synthesis module and class A for dispensing
Shielding Requirements	No hot cell required/self-shielded CPM	Hot Cells required for production and dispensing.
Dose Production	Individual Dose	Batch production
Validated Automated FDG Quality Control	Provided	Not available
Specialized Staffing	1 Technician	1 Radio-chemist 1 Pharmacist 1 Cyclotron operator

Technology Overview

Mini-Cyclotron Particle Accelerator

The accelerator component of the ABT BG-75 is a low- energy, 7.5 mega electron-volt (MeV) positive-ion cyclotron that accelerates protons (H^+) to one-eighth the speed of light. The accelerated protons "bombard" a small volume of "heavy" water (the target). When bombarded by high-energy protons, the ^{18}O in a small fraction of the water molecules is converted to a short half-life isotope of fluorine, ^{18}F.

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To protect personnel and equipment from radiation generated by the high-energy proton bombardment, the ABT BG-75 cyclotron employs an innovative shield that opens vertically, which affords both a small footprint and ease of service (Figure 3). The entire cyclotron system, including shielding, weighs 45,000 lb. (20,500 kg.) and requires minimal facility modification compared to other medical accelerators (Table 2).

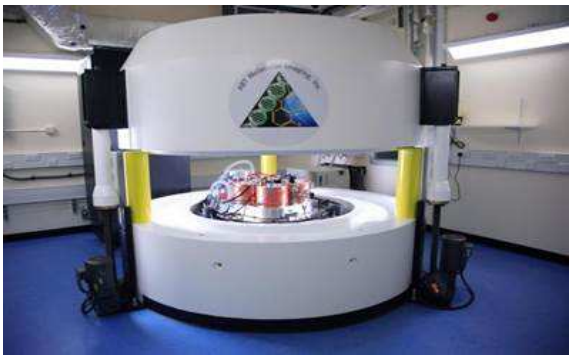


Figure 3. ABT Biomarker Generator mini---cyclotron, with vertical shields lifted.

Microchemistry

The microchemistry component of the ABT BG greatly simplifies the workflow associated with radiopharmaceutical production by miniaturizing and automating the chemical processes for biomarker radiolabeling, which otherwise would require a dedicated technician, radio-chemist, radio-pharmacist, and "hot" chemistry lab. The ABT microchemistry system is programmable and capable of producing many one or two-step ^{18}F radiochemistry processes, using two consumables developed and sold by ABT:

- Reagent Kit, containing chemicals for the radiolabeling reaction
- Sterile, disposable, single-use Dose Synthesis Card containing production components (Figure 4; described further in Consumables section below)

The ABT BG microchemistry unit sits adjacent to the BG cyclotron shield or an adjacent room, functionally integrates with the cyclotron, and is self-shielded (Figure 5). Once the radioactive isotope is generated in the cyclotron, it is pumped to the microchemistry system, where a series of automated valves, pumps, and heaters execute the chemistry methods necessary for incorporating the isotope into the biomarker molecule. When the cycle is complete, a single dose of radiopharmaceutical is delivered to a syringe ready for patient injection (**Figure 4**), and a small sample is delivered to the automated QC System for qualification testing.

Figure 4. ABT Biomarker Generator Dose Synthesis Card (DSC) for generating a single dose of ^{18}FDG radiopharmaceutical. This ABT---consumable consolidates multiple, separate subcomponents of conventional radiochemistry systems into a single disposable item.

Automated QC

ABT's QC module is the first and only integrated, automated QC system commercially available for PET biomarkers. Occupying a footprint much smaller than traditional lab equipment, the system uses embedded methods, micro-sensors and small-scale analytics (HPLC, radiation detector, pH meter) to perform most of the tests as required by US and EU pharmacopeia standards to qualify radiopharmaceuticals for human injection:

- pH
- Filter integrity
- Residual volatile organics
- Radiochemical purity

The only manual tests are those for Endotoxins, sterility and radionuclide purity. When complete, the system produces a QC record for each dose generated. The whole process occurs automatically in less than 20 minutes, replacing traditional systems that require five or more pieces of large test equipment and at least 45 minutes of hands-on time by one or more specially trained technicians.

Figure 5. ABT Biomarker Generator integrated microchemistry and QC modules.

Consumables

As mentioned above, the Reagent Kits and Dose Synthesis Cards are used by the microchemistry system to produce the radiopharmaceutical (Table 3). A single Reagent Kit is sufficient for a day's worth of production, yielding multiple doses from a single kit. Two Reagent Kit sizes are available based on the customer's dose volume needs. The Dose Synthesis Card, however, is designed for single use per dose, and comes sterile-packed with syringe attached (Figure 4). Contained within the Dose Synthesis Card are the chemical reaction vessel, purification column and the majority of the wetted pathways used during the production process. This level of integration eliminates the need for extra setup, assembly and cleaning required for maintaining sterility on traditional chemistry systems.

Regarding QC consumables, standard reagents are required to both periodically calibrate the QC system detectors (QC Calibration Standards) and perform daily verification that the QC system is within specification (QC Suitability Standards). Packaged standards streamline the typical preparation required for the staff to qualify the required analytical equipment, are more cost---effective than bulk reagents, and come with a certificate of quality from ABT. Because each lot of reagents is pre---qualified by ABT, our proprietary system relieves an ongoing regulatory burden for the user.

Table 3. Consumables Used with the ABT Biomarker Generator

Consumable	Usage	Sizes
Dose Synthesis Card	1/dose	One
Reagent Kit	1/day	8 - dose; 12 - dose
QC Suitability Standards	1/week	One
QC Calibrations Standards	1/month	One

System Controls and Software

The ABT BG uses networked components to monitor and control the accelerator, chemistry, and QC functions as well as provide user interaction. Each major subcomponent of the BG runs independently with unique software and supporting firmware specific to its specialized purpose. ABT's design philosophy for the BG software is to reduce operator burden and simplify the workflow by automatically leading the operator through startup, production, and shutdown. Unlike conventional PET radiopharmaceutical production, the BG operator is not required to monitor beam production, nor complex chemical synthesis. The BG operator screen is simplified with minimal user interaction, while in-process FDG production is limited to just three user button clicks. Interlocks and in-process failures are automatically presented to the operator, as are options for recovery, where appropriate.

Figure 6. Complete BG-75 System in single room Configuration.

Regulatory

Cyclotrons with integrated chemistry module(s) are regulated in the U.S. and Europe as laboratory equipment, and are not considered to be medical devices. Applicable design standards and testing to certain safety directives such as IEC 61010, EMC Directive, Low Voltage Directive apply to product safety to receive a CE Mark to market in Europe. In the U.S., the FDA has also promulgated guidance for PET drug production that will require such production to be compliant with the FDA's good manufacturing practice (GMP) regulations as defined in 21 CFR 212 for clinical use of registered drugs. In the emerging markets, each country, generally under the guidance of the Minister of Health, treats regulatory approvals differently; however, most jurisdictions model their regulatory standards after either the U.S. or European pharmacopeia methods.

The ABT BG is designed to operate in accordance with USP compounding (Chapter <823>) and PET USP monograph requirements, which set process and legal standards for PET drug compounding. The Biomarker Generator's embedded production and testing methods and its integrated hardware tremendously simplify all of these processes required to be cGMP compliant. In addition, the point-of-use philosophy by default means there is no distribution or marketing so the chain of custody is never broken from production to patient injection. In some jurisdictions, customers have been able to incorporate the Biomarker Generator in their on-site pharmacy operations and utilize their existing pharmacy guidelines.

CUSTOMER PROFILE

Customer Profile October 2013

Sveta Marina University Hospital
Varna, Bulgaria

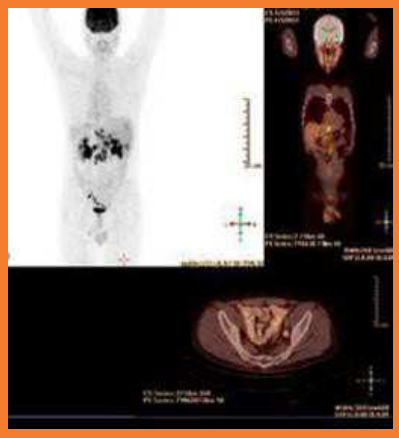
Clinical ^{18}F-FDG implementation

Following initial installation in April, 2013, Sveta Marina University Hospital has produced over 700 clinical ^{18}F-FDG doses utilizing ABT's "Dose on Demand™" Biomarker Generator. The ABT System provides the first fully integrated solution, combining a compact 7.5 MeV cyclotron, card based micro-chemistry, and automated quality control, for single-dose ^{18}F-FDG production.

Sveta Marina University Hospital is the largest diagnostic and consultative medical university complex in Varna, and the first facility in Bulgaria to implement in house biomarker production. Their experience demonstrates the clinical utility, and ease of implementation, of ABT's Biomarker Generator System.

Simplifying in-house production

Sveta Marina constructed a compact building adjacent to the hospital's Nuclear Medicine Department to house the ABT System. No special shielding was required, and the hospital utilized existing staff to operate the system. The PET production center was up and running within seven months from the start of construction, and within 3 months of system delivery, demonstrating the site planning and logistic advantages of installing the "Dose on Demand™" Biomarker Generator.



"The Biomarker Generator enabled us to produce our own supply of FDG, making our operations much more efficient and cost effective."

Reducing ^{18}F-FDG costs, and increasing availability

Prior to the installation of the ABT System, Sveta Marina Hospital established PET/CT Services by importing ^{18}F-FDG from a neighboring country via air travel, dramatically limited scheduling availability, and increasing the cost to perform PET/CT studies. The ABT solution provided cost effective in-house production of ^{18}F-FDG, on demand access, and unlimited PET/CT scheduling availability.

Dr. Pavel Bochev
Director of Nuclear Medicine
Sveta Marina University Hospital

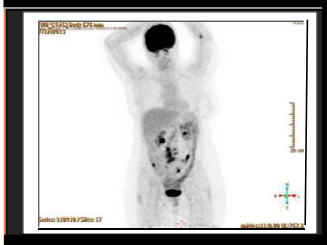
Q: What was your purpose for implementing?

"We needed a more reliable FDG supply, and a conventional cyclotron was not economically feasible. The ABT Biomarker Generator System enabled us to produce our own supply of FDG, making our operations much more efficient and cost effective. We now operate five days per week, and complete 6-8 PET/CT scans per day."

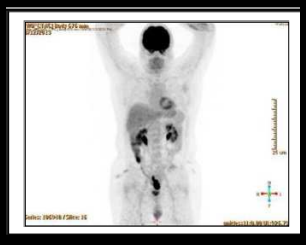
Q: What has been your experience?

"We were able to fully implement the ABT solution within three months of shipment, and utilize our existing staff, which is an important advantage of the system. ABT assisted our team throughout the process, and to date, we have scanned over 700 patients utilizing the system. The clinical images produced using the Biomarker Generator, and our advanced PET/CT Scanner, proved to be an excellent combination for our hospital."

Clinical Studies



Diagnosis: Rectal Cancer
Dose: 7mCi FDG
Equipment: Gemini TF PET/CT
Time/bed position: 90sec.



Diagnosis: Colorectal Cancer
Dose: 5mCi FDG
Equipment: Gemini TF PET/CT
Time/bed position: 90sec.

"The clinical images produced using the Biomarker Generator, and our advanced PET/CT Scanner, proved to be an excellent combination for our hospital."

ABT Molecular Imaging, Inc.

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