BG75 30 Minute GMP – Varna Upgrade
Sveta Marina University Hospital, Varna, Bulgaria

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I. SUMMARY:

This white paper details the upgrade of the Sveta Marina University Hospital in Varna, Bulgaria to the 30 Minute configuration, termed BG75 30 Minute GMP. The existing BG System configuration at the Varna site was the 4.1.74 system release with a 45 [min] cycle time. A 30 minute GMP configuration was requested that would be able to produce at least 10 [mCi] of [^{18}F]FDG every 30 minutes to support site workflow. On January 15-19, 2015, the Varna site was successfully upgraded to the 30 minute configuration. The Radioisotope Generator (RIG) target was upgraded to the Tantalum Target 1.0 configuration[3] and the Chemistry Production Module (CPM) was upgraded with CO_2 gas cooling, large syringes for more efficient reagent pushes, and the 30 minute synthesis script. The data presented in this report shows that the upgrade was successful, achieving an average dose time of 29.8 [min] with an average dose of 14.1 [mCi]. Furthermore, the use of the Tantalum Target 1.0 during non-active CO_2 cooling has increased the average [^{18}F]FDG dose to 21 [mCi] in 45 [min] runs. The BG75 30 Minute GMP is now available for purchase.

II. BACKGROUND:

As a follow up to the 2014 SNM white paper on 30 minute proof of concept at UNC[1], the clinical site at Varna, Bulgaria was upgraded to the 30 minute configuration. The existing BG75 4.1.74 release at Varna had a 45 [min] cycle time. The desire to achieve a cycle time that is < 30 [min] is motivated by PET/CT workflow, which averages 1 patient every 30 [min] including preparation time and setup. In order to reduce the cycle time, a number of design changes needed to be implemented to remove 15 [min] from the synthesis. The Method section below details the design changes implemented and the Results section describes the performance of the 30 [min] system at ABT's clinical site at Varna in Q1 of 2015.

III. METHOD:

Figure 1 illustrates the improvements to various parts of the system for the 30 minute cycle time. The process of cooling the reaction vessel after evaporation is currently not controlled. Production cooling times are on the order of 5 minutes through conduction and convection through the atmosphere. Active CO_2 cooled air was implemented to reduce the cooling time from 5 minutes to < 1 minute (see Table 1). Figure 2 shows the active cooling block that has been optimized for air flow and thermal mass.

Synthesis Optimization

The production evaporation of the O-18 water, labeling of the F-18 to manostriflate and hydrolysis steps required to produce [^{18}F]FDG have not been optimized (e.g. temperature, time). A design of experiments was constructed to optimize the evaporation temperature and time, labeling temperature and time and hydrolysis time. Table 1 shows the results of the optimization.

Feature	HW LoE	SW LoE	Script LoE	Time Savings	Estimated Overall
Current Release				0	41
Large Syringe	Low	None	Med	2	39
Faster QC Injection	Low	None	Med	1	38
Active Cooling - Air	High	Low	Low	4	34
Evap Optimization - Time, Temp	None	None	High	2	32
Labeling Optimization - Time, Temp	None	None	High	1	31
Hydrolysis Optimization	None	None	Med	1	30
Target Unload via Rad Trace	None	None	Med	1	29
Faster Validate	None	None	Med	0.5	28.5

Figure 1. 30 Minute dose time reduction. The radioisotope generator (RIG) must produce at least 32 [mCi] in 25 [min] to achieve doses > 10 [mCi] for injection.

Table 1. Design of experiments around synthesis to optimize evaporation, labeling and hydrolysis time.

Process	BG75 4.2.1.78	BG75 30 Minute
Evaporation Temperature [°C]	110	130
Evaporation Time [min]	6	3.5
Labeling Temperature [°C]	80	80
Labeling Time [s]	120 + MeCN Evap	60 + MeCN Evap
Hydrolysis Time [s]	300	240
Cool Down Time [min]	5	< 0.5

Other Improvements

Larger syringes were employed to reduce the reagent addition time as shown in Figure 3 (Right). Improvements to the target load from the cycle time were also optimized. Finally, the QC injection was improved resulting in faster delivery of the QC sample to the QCM for analysis.

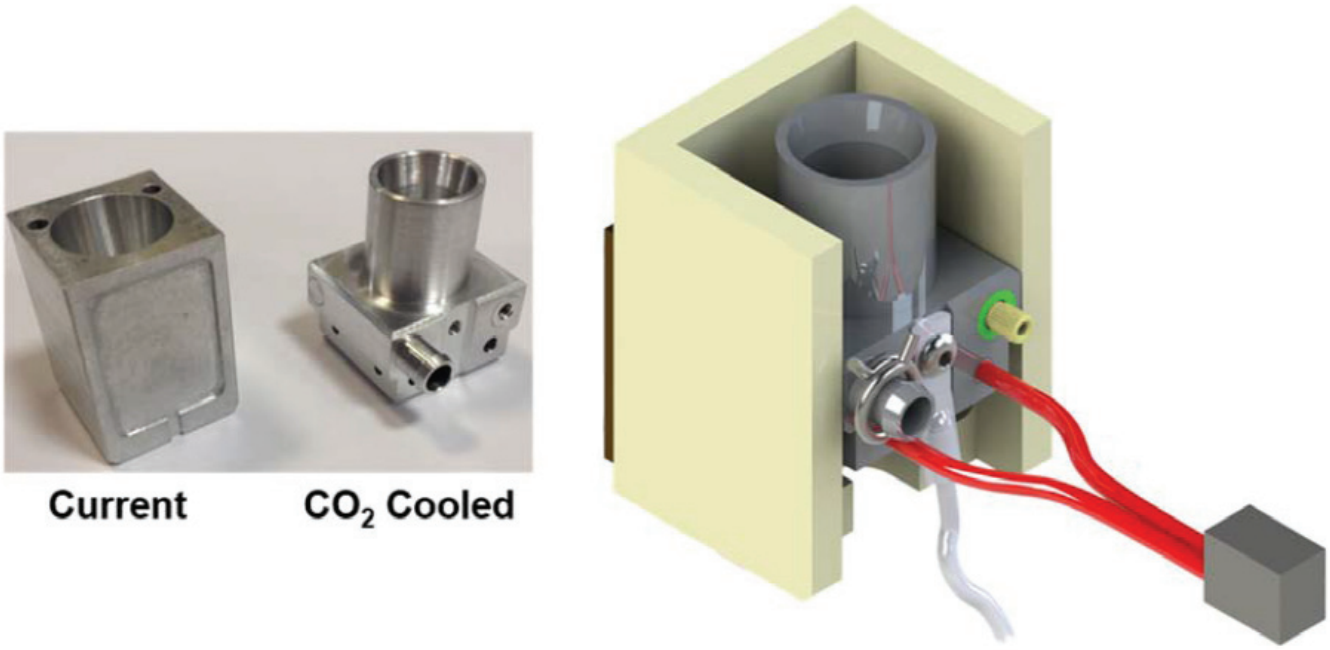

Figure 2. Active cooling block used to cool the temperature of the reaction chamber. It has a lower mass, an internal chamber for CO_2 cooling and results in improved heater mounting.

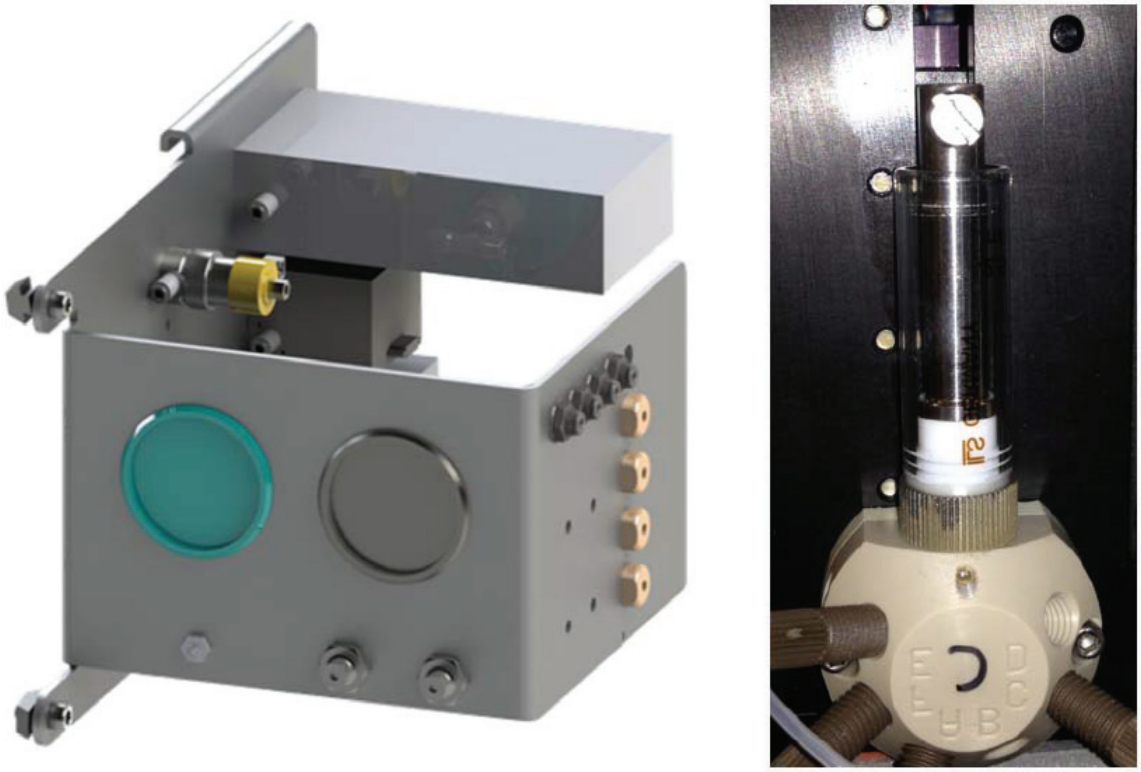

Figure 3. (Left) The gas manifold was updated with active cooling components. (Right) Syringe size was increased from 250µL & 500µL syringes to 1.0mL & 2.5mL. This reduces the number of strokes and therefore reduces the time for each injection. All syringes are now larger than their highest respective process requirement. Air chase can be metered with reagent to reduce injection strokes.

IV. RESULTS:

The 30 Minute upgrade at Varna was executed successfully over 4 days from January 15-19, 2015. The target upgrade was accomplished in 1 day which included breaking vacuum on the cyclotron, installing the Tantalum Target 1.0, optimizing the target position in height and angle with respect to the beam and performing validation runs. Figure 4 below illustrates the improvement in target yield for a 45 [min] run at 4.5 [uA] of beam on target. A target current of 4.5 [uA] was chosen to be able to compare to the high flow stainless steel target that will burst at currents > 5 [uA]. The Tantalum Target 1.0 can produce F-18 at beam strengths up to 6.5 [uA].

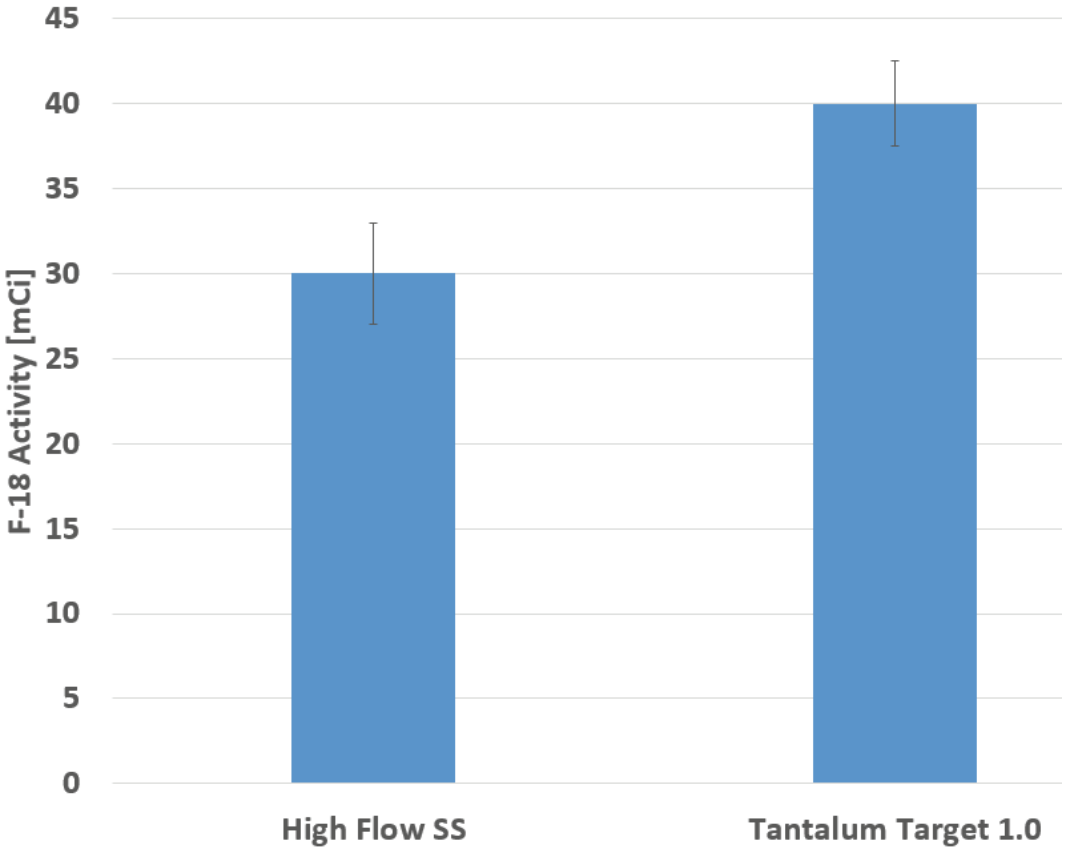

Figure 4. Stainless steel (SS) target yield versus 30 Minute Tantalum Target 1.0 yield in a 45 [min] run at Varna for the same target current of 4.5 [uA]. The Tantalum Target 1.0 can produce more if run at 6.5 [uA].

Simultaneous with the target upgrade, the existing Chemistry Production Module (CPM) was upgraded to the 30 Minute configuration. This upgrade took 1 day, followed by 1 day for QC calibration and 2 days of validation runs. Table 2 summarizes the performance of the 30 minute cycle time at Varna.

Table 2. 30 Minute Validation data from Varna on January 15th-18th, 2015.

Date	Activity	Dose Time
1/15/2015	12.30	31.25
1/15/2015	13.24	29.41
1/15/2015	13.52	30.26
1/15/2015	12.80	26.63
1/15/2015	11.55	28.08
1/15/2015	11.81	30.59
1/16/2015	17.57	30.35
1/16/2015	15.67	31.35
1/17/2015	11.85	27.90
1/17/2015	13.15	32.05
1/18/2015	17.00	30.43
1/18/2015	18.43	29.10
Average	**14.1**	**29.8**
STD	**2.4**	**1.6**

A benefit of using the Tantalum Target 1.0 in conjunction with 30 minute cycle time is the ability to increase the standard [^{18}F]FDG dose for a 45 [min] cycle time, which is the standard workflow at Varna. Figure 5 compares the standard workflow [^{18}F]FDG runs for the High Flow Stainless Steel target and the Tantalum Target 1.0 showing an average dose improvement from 14 to 21 [mCi].

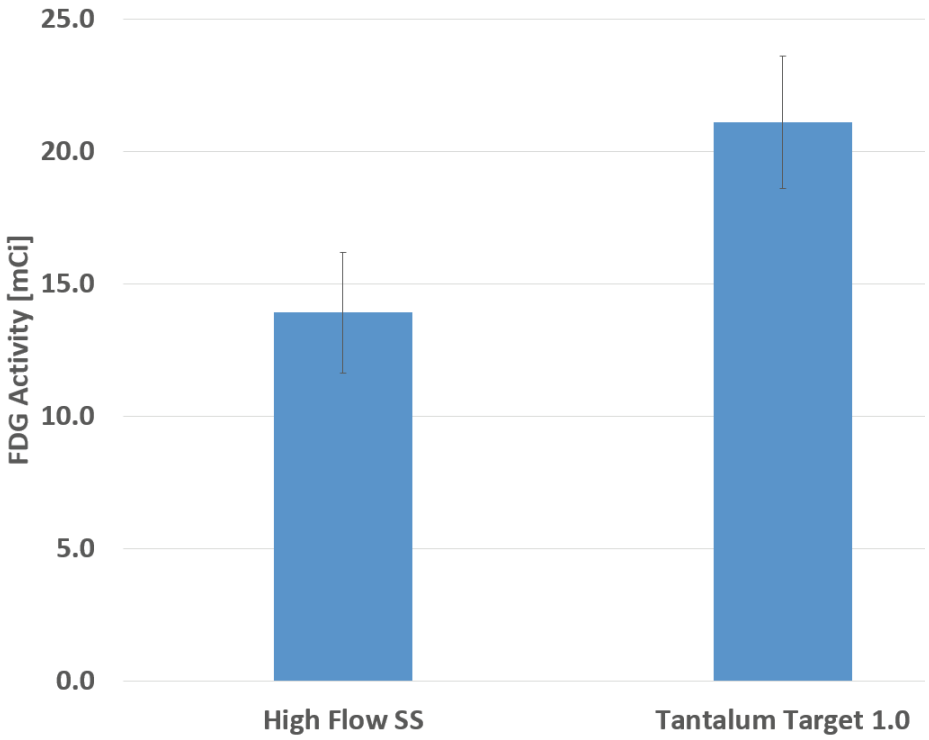

Figure 5. Non-active cooling yield before and after 30 minute upgrade.

The next system major BG system release will occur on July 1, 2015 and will be titled the BG75 1.0 Enhanced GMP system[2]. The BG75 1.0 Enhanced GMP will also be capable of the 30 minute cycle time and will feature Good Manufacturing Process (GMP) compliance.

V. CONCLUSIONS:

The BG75 30 Minute configuration was a successful upgrade at Varna. The 30 minute cycle time was validated on site with an average yield of 14.1 [mCi] and average cycle time of 29.8 [min]. The addition of the Tantalum Target 1.0 increased the standard cycle time yield from an average of 14 to 21 [mCi]. The Varna site has been running with the 30 Minute upgrade for 5 months. The 30 Minute configuration is released and available for purchase.

VI. REFERENCES:

1) White Paper - 30 Minute Cycle Time, SNM, St. Louis, MO. 2014. http://abt-mi.com/en/resources
2) White Paper - BG75 1.0 Enhanced GMP, SNM, Baltimore, MD. 2015. http://abt-mi.com/en/resources
3) White Paper - RIG 2.0, SNM, Baltimore, MD. 2015. http://abt-mi.com/en/resources