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TEST RESULTS FOR MOBILE PULSAR® SYSTEM

Introduction

Cyclomedical Applications Group, LLC, has maintained a strict independence in relationships with equipment manufacturers in order to properly advise clients in the choice of production, quality control, and safety equipment, laboratory design, and operation for PET radiopharmaceutical manufacture. As the designer and contract operator of the Wisconsin Medical Cyclotron, LLC, a commercial [^{18}F]FDG production center near Milwaukee, Wisconsin, Cyclomedical is very familiar with all aspects of cyclotron based production. Because there is an increasing demand for PET radiopharmaceuticals in less populated areas where a large production center may not be economically justified, we undertook an independent evaluation of the performance of a linear accelerator-based system which has the advantages of lower installation cost and complexity and lower relocation cost should that become necessary in the future.

Cyclomedical Applications Group (Cyclomedical) negotiated an agreement between AccSys Technology, Inc. (AccSys), the manufacturer of the PULSAR®-7 linear accelerator, and Wisconsin Medical Cyclotron (WMC) for the evaluation tests. Cyclomedical received no compensation from either party for this independent evaluation.

AccSys PULSAR -7 production system

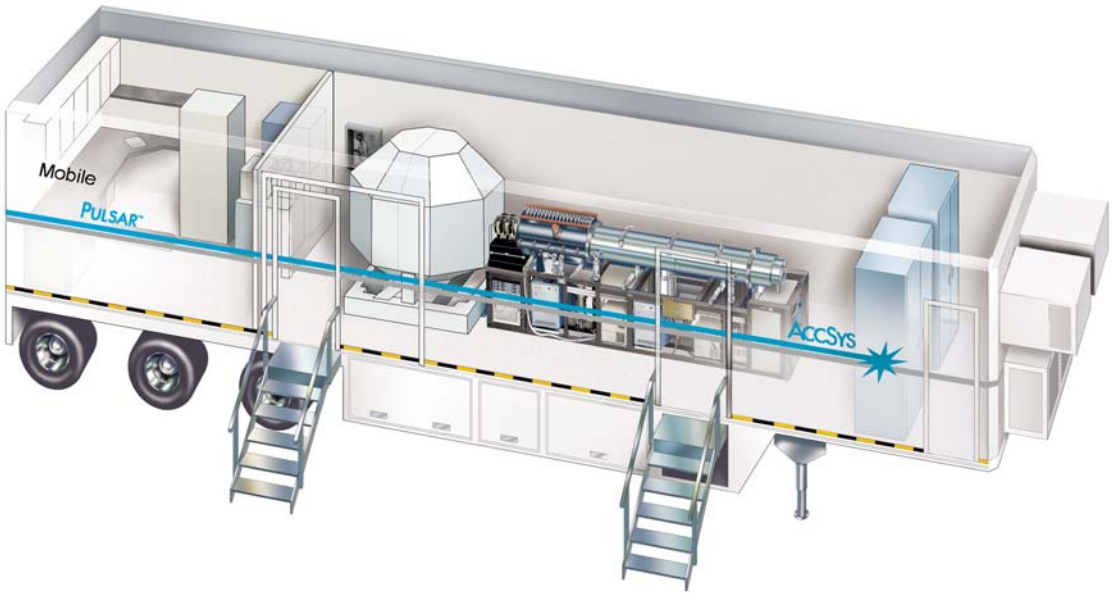
The AccSys PULSAR® -7 is a radiofrequency linear proton (H^+) accelerator system for PET radionuclide production and consists of the following:

- H^+ duoplasmatron Ion Source (to 30 keV)
- Radio frequency quadrupole (RFQ) first stage accelerator (to 3.5 MeV)
- Drift tube linac (DTL) second stage accelerator (to 7 MeV)
- Shielded PET radionuclide target system
- PC-based control system

The accelerator, with the beam transport line, is approximately 18.3 feet long, and weighs approximately 3 tons. The target system shield weighs approximately 9 tons.
For a complete description of the PULSAR®-7, see attachment 1.

The PULSAR®-7 tested at WMC was in a mobile configuration, mounted in a Medical Coaches 48 ft semi-trailer (see attachment 2). The trailer, containing all systems necessary for production of [^{18}F]FDG, was relocated from its manufacturing site in Pleasanton, CA, to

an outside parking space adjacent to the WMC facility in West Allis, Wisconsin. Power was supplied in the form of a standard mobile unit 220 volt 3 phase outside connector. The semi-trailer was located on the asphalt parking area without an additional parking pad or support. On-board equipment included a radiopharmaceutical synthesis module (GE MX_{FDG}) in a shielded mini-cell. This system, as shown at a recent Society of Nuclear Medicine Annual Meeting, included a complete quality control testing laboratory and patient dose preparation equipment; however, for the purposes of the evaluation tests, [^{18}F]FDG qualification and unit dose preparation were performed in the WMC facility.



The WMC radioactive materials license was amended to include this unit at the facility address for the duration of the three month test. Radioactive materials license requirements included a lockable chain-link fence around the trailer.

Radiation Safety

Radiation exposure was measured at the trailer surface at three different levels above the parking lot surface during full beam bombardment of the ^{18}F production target. These data are shown on the following page. All measurements are total radiation (neutrons and gamma rays) and are given in mr/hr.

Radiation exposure at trailer surface (mr/hr)

Full beam on [$^{18}O]H_2O$ target

8.5 ft. from ground

0.4	0.5	0.6	0.7	1.2	1.7	1.7	2.6	3.1	3.3	1.7	1.3	0.4	0.4	0.3	0 .2	
						Streetside										
0.3	Lab end													Power supply end		0.2
						Curbside										
0.2	0.2	0.2	0.3	0.5	0.9	1.4	1.8	3.7	4.3	2.3	1.2	0.5	0.5	0.2	0.2	

5.3 ft. from ground

0.4	0.5	0.6	0.7	1.2	1.7	1.6	2	2.6	1.6	1.4	0.8	0.4	0.3	0.3	0 .3	
						Streetside										
0.3	Lab end													Power supply end		0.3
						Curbside										
0.2	0.2	0.2	0.3	0.3	0.9	1.1	1.5	1.5	1.6	0.8	0.6	0.2	0.3	0.3	0.3	

1.0 ft. from ground

0.6	0.6	0.6	0.6	0.5	0.5	0.9	1	1.5	0.9	0.7	0.4	0.3	0.3	0.3	0 .3	
						Streetside										
0.4	Lab end													Power supply end		0.3
						Curbside										
0.2	0.2	0.2	0.3	0.4	0.9	0.8	1.1	0.7	0.6	0.4	0.4	0.4	0.4	0.4	0.3	

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[^{18}F]F- and [^{18}F]FDG manufacture

The PULSAR®-7 arrived from California in Milwaukee, Wisconsin at the Wisconsin Medical Cyclotron facility on Sunday, August 27, 2006. A test beam was obtained on Tuesday, August 29. After final site preparation and radiation safety evaluation, the ten week production trial started on Monday, September 11, 2006 under a test protocol that called for daily production and qualification of two batches of [^{18}F]FDG. WMC quality control validation began on September 15.

Seventy eight ^{18}F production runs were performed over forty three production days. Seventy two [^{18}F]FDG batches were produced.

The results of all runs are shown in the summary table, attachment 3.

Explanation of tabulated data

Target body

Two target bodies, one made of silver and one made of niobium were evaluated for the [^{18}O]H_2O target system, each with an ^{18}O water capacity of 0.35ml. This configuration is referred to as a "thin target" in which the majority of protons in the beam are brought to rest in the target body and not in the [^{18}O]H_2O. (The number of protons that actually react with the ^{18}O in any bombarding system is a very small percentage of the protons in the incident beam). The small deposition of energy in the water itself therefore reduces the cooling requirement and, theoretically, the thin target has little affect on yield because the energy of the beam after it passes through the thin water layer is reduced below that necessary to induce the ^{18}O(p,n)^{18}F nuclear reaction. The performance of these target bodies are shown both combined and separately in the data plots. Neither target was serviced (rebuilt) during the trial.

SOB

Start **O**f **B**ombardment means the time when the target irradiation began.

Beam Current (I)

The target system uses a support grid over the titanium (commonly used in target windows) target window to aid in cooling the window and as a window support for the pressurized target (approximately 315 psi). The measured beam current is the average charge per unit time deposited in the target while the current shown in he table is a calculated current in the [^{18}O]H_2O itself; it is the target current adjusted by

the 65% transmission of beam through the grid. The drift tube Linac produces a pulsed beam with a pulse length of 125 sec at a repetition rate of about 85 Hz. The actual production beam is, therefore, about 9 mA with a 1% duty cycle.

Bombardment time (t)

For runs up to September 29, the bombardment time, t, is the uninterrupted minutes of target bombardment. After that date, the bombardments were broken into two successive runs of approximately equal length with target refill between bombardments, and with each target delivered to the same synthesis unit. The successive bombardments decreased the probability of low yields that might be caused by water boil-off during long irradiations, but has almost no affect on production yields.

Saturation ($1-e^{-\ t}$)

The production of radioactivity, A, during a charged particle irradiation is given by

$$A = n \quad I(1-e^{-\ t})$$

where n is the number of target nuclei (e.g., ^{18}O), is the reaction probability (called the reaction cross section), I is the beam current, is the decay constant of the product (e.g., ln(2)/109.7 = 0.0063 for ^{18}F) and t is the length of bombardment.

The quantity ($1-e^{-\ t}$) is called the saturation factor; that is, it describes the exponential build-up of radioactive product as a function of the length of bombardment. Thus, when t is very long ($e^{-\infty} = o$), the equation reduces to

$$A = n \quad I$$

and this quantity is called the saturation yield. Dividing the actual yield from a bombardment by the saturation factor gives the saturation yield which, being independent of the length of bombardment, is useful in comparing data from runs of different bombardment duration.

EOB

End **O**f **B**ombardment time.

QMA (^{18}F)

The irradiated target water containing the induced ^{18}F after bombardment was passed via a delivery tube to the General Electric MX_{fdg} synthesizer. The first stage in the synthesis is the isolation of the [^{18}F]Fluoride from the target water accomplished by passing the water through a Waters QMA anion exchange cartridge from. A radiation detector behind the QMA cartridge measured the ^{18}F isolated. This assay is used as the EOB yield of ^{18}F. While the calibration of the synthesizer's in-process detector was inexact, the detector response is very consistent over the range of activities encountered.

Reactor (^{18}F)

The ^{18}F fluoride adsorbed on the QMA cartridge is eluted from the cartridge into the reactor (reaction vessel) during the second stage of the synthesis by passage of the eluting solution, Kryptofix-carbonate. A detector near the reactor monitors the activity in the reactor during the next several stages of the synthesis. Since the liquid levels in the reactor vary during synthesis, affecting the detector geometry, the detector response varies also. The number shown in the table is the assay immediately after the eluting solution has been delivered to the reactor.

C-18 hydrolysis

After the ^{18}F labeling of the FDG precursor (mannose triflate) in the reactor, the reactor solution is passed through a trapping cartridge, C-18, which removes the labeled intermediate from the reaction solution. A radiation detector behind the C-18 monitors the trapped activity. The cartridge is first washed to remove impurities and then the ^{18}F labeled intermediate is hydrolyzed to produce [^{18}F]FDG. The hydrolyzing solution added to the cartridge is such a small volume that the activity remains in the field of view of the C-18 detector. This assay of [^{18}F]FDG remaining on the cartridge after hydrolysis is shown in the table. The synthesizer run sheets in Attachment 4 show the detector responses of these detectors during all phases of synthesis.

Assay

The dose calibrator assay at EOS performed on board the AccSys trailer.

EOS

The **E**nd **O**f **S**ynthesis is the time of dose calibrator assay of the [^{18}F]FDG final product after it has been removed from the C-18 cartridge, buffered, diluted, and transferred to the final product vial.

WMC

All quality control tests were performed by Wisconsin Medical Cyclotron personnel in the WMC facility. The tests were performed according to USP requirements for [^{18}F]FDG.

Performance Calculations

Chemistry at EOS represents the radiochemical yield of [^{18}F]FDG, data decay corrected to end of synthesis, C-18 assay/QMA assay, expressed as a percentage. Calibration of these in-process detectors is inexact but consistent and linear over the range of use. A plot of these data is shown in attachment 3.

Saturation ^{18}F at EOB is the assay of the QMA cartridge (QMA (^{18}F)), decay corrected for the time of delivery of the 18F from the target to the synthesizer, divided by the saturation factor, $(1-e^{-\ t})$.

Production rate (mCi/ A) is the saturation activity divided by the beam current. This quantity allows comparison of all data (i.e., data obtained at various conditions of beam current and bombarding time) for consistency of operation. Plots of production rates as a function of bombardment number are given for both target bodies together and for silver and niobium targets, individually, in attachment 3.

The average production rate over all runs and the average beam current over all runs were used to generate an experimental data-based theoretical calculation of EOB ^{18}F activity that might be expected from the PULSAR®-7 under these experimental conditions. The error bars are one standard deviation from the production rate mean.

Attachment 5 shows the system problems that resulted in lost bombardments, down days, and yields that were low due to attributable causes. The average production of [^{18}F]FDG per day and per run are also shown.

Discussion

Figure 1, attachment 3, shows the batch production of [^{18}F]FDG for all runs in the trial. Note that, while the incident beam currents are fairly uniform, the lengths of bombardment vary over more than a factor of three, affecting the yields by more than a factor of two. These data also vary according to a number of factors that are not related to the PULSAR® -7 itself; for example, there were three target problems having to do with improper target water loads and with pressure leak during bombardment. There were also two synthesizer problems that resulted in one low yield and one failed synthesis.

A better measure of accelerator performance is shown in Figure 2, the ^{18}F production rate, which normalizes data for different lengths of bombardment and is not affected by the performance of the synthesizer. It is affected by the performance of the target, however, and more dramatically for this trail by inconsistencies in accurately defining the true average beam current over the length of bombardment. Much of the data scatter in figure 2 (and in Figures 3 and 4 which show Niobium and Silver target production rates separately), is due to off-and-on beam during long bombardments, many of which were caused by a marginally sized cooling system chiller, a problem which is being rectified in the unit tested. Close inspection of the data reveals that adding the recorded length of bombardment to the Start of Bombardment for all runs does not always yield a time that coincides with the End of Bombardment time defined by the ^{18}F activity measurement on the QMA separation cartridge. Taking account of these data taking inconsistencies, the PULSAR®-7 demonstrated a reasonable accelerator and target performance over the trial period.

Target performance in relation to synthesis yields in a system that uses a beam pulsed at over 9 mA is also an area of major concern. Figure 5 shows all synthesis yields as measured by the ratio of [^{18}F]FDG on the C-18 cartridge to ^{18}F activity on the QMA cartridge of the synthesizer. With the exception of a few mechanical problems with the synthesizer, the data demonstrate the suitability of [^{18}F]Fluoride for [^{18}F]FDG production. Figure 6 shows the independence of synthesis yields to amounts of ^{18}F produced, demonstrating that long bombardments of either target do not adversely affect synthesis results.

In Figure 7 we have shown the expected ^{18}F production as a function of bombardment time for the PL-7 under the experimental conditions of this trial. The yield was calculated from the production equation using the average production rate and the average beam current over all runs. A one hour bombardment should yield 634 mCi ^{18}F and a two hour bombardment 1068 mCi. This production rate was lower than that which we had observed at the AccSys

factory demonstration using a fixed PULSAR®-7. **(Note: This yield data was read from the QMA detector, which has now been shown to be low by ~20%)** The fixed PULSAR®-7 has routinely produced over a Ci/hr. The lower production rate was most likely caused by the marginal chiller in the mobile system which restricted power to lower sustained beam currents, and which caused interrupted bombardments. The alignment of the beam on the target might also have been offset by a small amount, resulting in a beam transmission through the grid of less than 65% used in the calculations. The ability of the PULSAR®-7 to supply [^{18}F]FDG for limited scale distribution using these experimentally verified production rates is shown in attachment 6.

Conclusion

AccSys Technology, Inc. has demonstrated in this trial the ability to transport the PULSAR®-7 in a mobile van over a long distance and produce a proton beam on target within one day, achieve a 94% ^{18}F production batch reliability, to perform multiple daily bombardments of several hours duration, and to produce [^{18}F]fluoride suitable for [^{18}F]FDG manufacture. The [^{18}F]FDG production yields were adequate for small scale distribution over a limited distribution radius, and the product met quality standards.

Although it may be possible to use the PULSAR®-7 as a truly **mobile** radioisotope producer, Cyclomedical Applications Group's evaluation of the mobile PULSAR®-7 was primarily for a **re-locatable** accelerator. We believe that this has been successfully demonstrated. Using a better cooling system would almost certainly result in very acceptable reliability.

In fact, upon return to the factory, the trailer cooling system was rebuilt and solid operation of the unit achieved for several weeks before it was shipped to a customer.


Mobile
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PET Isotope Production Lab
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