Wales Research and Diagnostic PET Imaging Centre

Feasibility Study on the Production of Technetium-99m on an IBA 18/9 Cyclotron Using a COSTIS Solid Target System

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Wales Research and Diagnostic PET Imaging Centre

- Based at the University Hospital of Wales
- Provide a routine clinical service for most of Wales using a GE 690 PET-CT Scanner
- Equipped with a Mediso pre clinical PET-CT scanner
- Have a GMP licensed production facility producing
  - FDG
  - FDOPA
  - Fallypride
  - Tau
- Equipped with an IBA 18/9 COSTIS solid target station for production of radiometals
  - ^{89}Zr
  - ^{48}V
  - ^{86}Y

IBA

Based in Belgium

Based on longstanding expertise, IBA RadioPharma Solutions supports hospitals and radiopharmaceutical distribution centers with their in-house radioisotopes production by providing them global solutions, from project design to the operation of their facility.

In addition to high-quality technology production equipment (cyclotron solutions, targetry systems, synthesizers, control systems, ...), IBA has developed in-depth experience in setting up (c)GMP radiopharmaceuticals production centers.

TRIUMF

Based in Vancouver

TRIUMF is one of the world's leading subatomic physics laboratories. It brings together dedicated physicists and interdisciplinary talent, sophisticated technical resources, and commercial partners in a way that has established the laboratory as a global model of success. Its large user community is composed of international teams of scientists, post-doctoral fellows, and graduate and undergraduate students.The University exists to create and share knowledge and to educate for the benefit of all.

Canada's national laboratory for particle and nuclear physics and accelerator-based science

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AIM

To determine whether it was possible to produce sufficient quantities of ^{99m}Tc using the $^{100}Mo(p,2n)^{99m}Tc$ reaction on an 18/9 IBA cyclotron equipped with a COSTIS solid target system using the targets developed by TRIUMF

PROJECT SET UP

Initial Meeting

First meeting in September 2016 at World Target and Target Chemistry conference at Los Alamos

Environmental Permitting Regulations

Needed to modify permit granted by Natural Resources Wales to enable work to proceed

Ionising Radiation Regulations

Needed to update Risk Assessments in areas where work was to be undertaken

Cyclotron Modification

Need to upgrade cyclotron

Enviromental Permitting Regulations

Initial Meeting

Target material is Enriched molybdenum

IBA Nirta Target Release Form

Target ID#: 0246

Mo-100 Batch#: BRZ20170501 (3/5) – not preprocessed

Test:	Acceptance Criteria:	QC Result:	Entered by:
Molybdenum Isotopic Composition (%)	Mo-92 ≤ 0.03% Mo-94 ≤ 0.03% Mo-95 ≤ 0.03% Mo-96 ≤ 0.03% Mo-97 ≤ 0.03% Mo-98 ≤ 4.85% Mo-100 ≥ 95%	*Enter enrichment used from batch record* Mo-92 0.003 % Mo-94 0.003 % Mo-95 0.003 % Mo-96 0.003 % Mo-97 0.003 % Mo-98 0.17 % **Mo-100** 99.815 % ☑ Passed ☐ Failed	V.H.
Properties of Sintered Molybdenum-100 Pellet:	Mass (0.9g ±5%) 0.855-0.945g	Mass: 0.9249 g ☑ Passed ☐ Failed	V.H.
	Diameter (12.3 – 12.7mm)	Diameter: 12.3 mm ☑ Passed ☐ Failed	V.H.
	Colour of molybdenum pellet	F (P) P P P F F ☑ Passed ☐ Failed	V.H.

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Enviromental Permitting Regulations

Needed to determine product radionuclides, daughter radionuclides and likely yields from nuclear reaction

Nuclear reactions modelled in silica

Main channel - $^{100}Mo(p,2n)^{99m}Tc$

Also - $^{100}Mo(p,pn)^{99}Mo \rightarrow {}^{99m}Tc$

Also need to account for other reactions on ^{100}Mo and other Mo isotopes

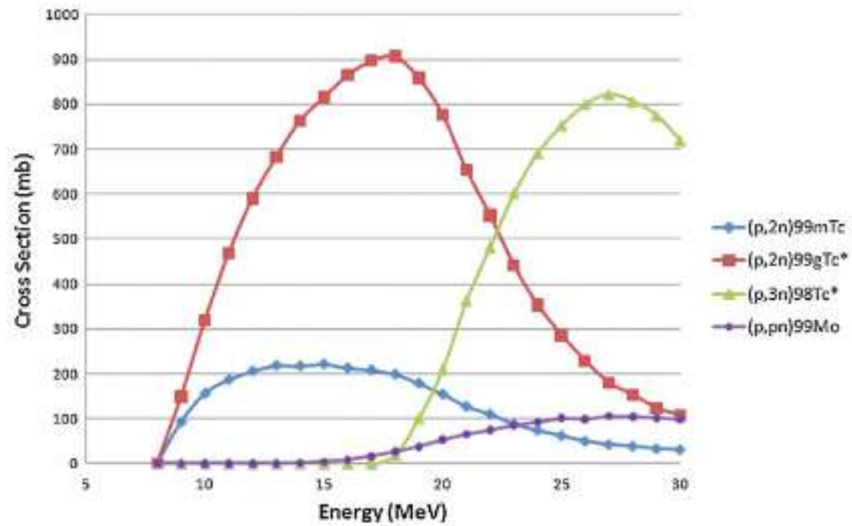

Figure 2. Excitation functions corresponding to the ^{100}Mo+p reaction products with the highest cross sections in the investigated energy range. Stable isotopes are marked by an asterisk.

Celler et al, Phys Med Biol 56 (2011); 5469-5484

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Enviromental Permitting Regulations

There will be some (p,n) reactions produced during irradiation

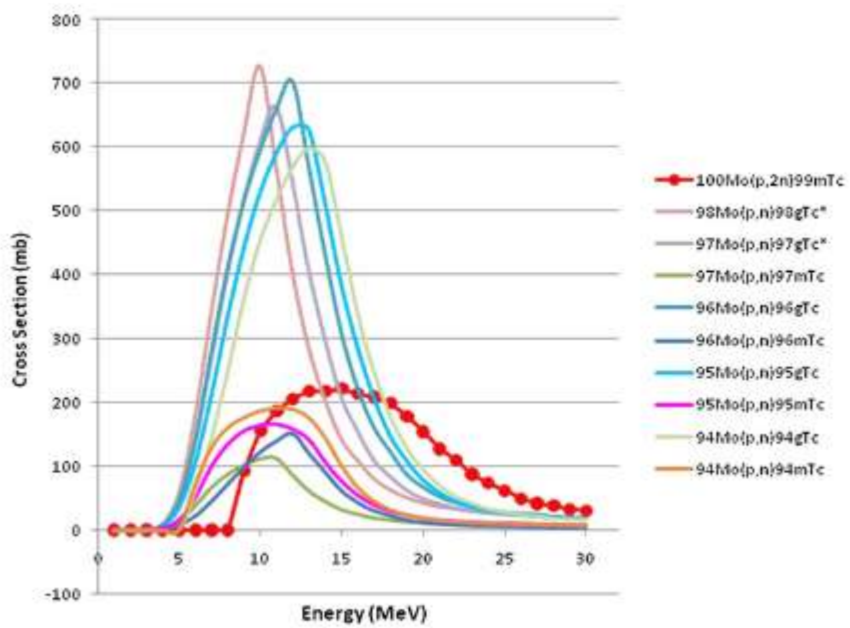

Figure 3. Comparison of the ^{100}Mo(p,2n)^{99m}Tc excitation function to the six other technetium isotopes (isomeric and ground states) which are produced through the (p,n) reaction. The excitation function for ^{99m}Tc is marked with red circles and stable isotopes are marked by an asterisk.

Celler et al, Phys Med Biol 56 (2011); 5469-5484

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Enviromental Permitting Regulations

Also will see (p,2n) reactions as well

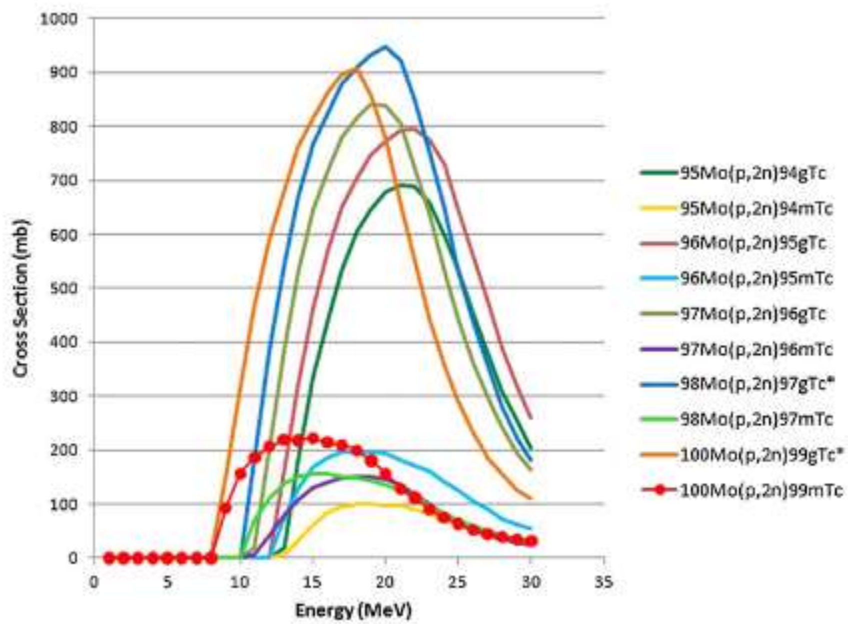

Figure 4. Comparison of the ^{100}Mo(p,2n)^{99m}Tc excitation function to the other radioactive and stable technetium isotopes (isomeric and ground states) which are produced through the (p,2n) reaction. The excitation function for ^{99m}Tc is marked with red circles and stable isotopes are marked by an asterisk.

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Enviromental Permitting Regulations

Wide range of radionuclidic impurities generated

Needed to determine product radionuclides daughter radionuclides and likely yields from nuclear reaction

Isotope	$T_{1/2}$	Decay products (with their $T_{1/2}$)	Reaction	Cross section (mb)					
				10 MeV	16 MeV	19 MeV	20 MeV	24 MeV	30 MeV
43-Tc-93	2.75 h	→ Mo-93 (4.0×10^3 yr) → Nb-93*	Mo-92 (p,γ)	5.56	1.08	0.68	0.54	0.13	0.014
			Mo-94 (p,2n)	0	322	576	615	610	285.5
			Mo-95 (p,3n)	0	0	0	0	66.1	340.8
43-Tc-93m	43.5 min	77% →Tc-93 (2.75 h) → Mo-93 (4.0×10^3 yr) → Nb-93* 23% → Mo-93 (4.0×10^3 yr) → Nb-93*	Mo-92 (p,γ)	2.00	0.19	0.09	0.06	0.01	0.003
			Mo-94 (p,2n)	0	48.5	100	101	73.6	29.1
			Mo-95 (p,3n)	0	0	0	0	4.79	31.2
43-Tc-94	293 min	→ Mo-94*	Mo-94 (p,n)	452	338	129	96.2	33.9	16.7
			Mo-95 (p,2n)	0	442	645	680	597	204
			Mo-96 (p,3n)	0	0	0	0	40.7	378.6
43-Tc-94m	52 min	→ Mo-94*	Mo-94 (p,n)	187	67.2	24.2	19.0	11.1	7.48
			Mo-95 (p,2n)	0	84.3	100.0	98.4	71.0	27.7
			Mo-96 (p,3n)	0	0	0	0	5.55	46.7
43-Tc-95	20 h	→ Mo-95*	Mo-94 (p,γ))	1.54	0.7	0.49	0.39	0.08	0.02
			Mo-95 (p,n)	528	285	108	78.2	30.2	15.9
			Mo-96 (p,2n)	0	573	747	773	730	259
			Mo-97 (p,3n)	0	0	0.41	15.8	300	552
43-Tc-95m	61 d	4% →Tc-95g (20 h) → Mo-95* 96% → Mo-95*	Mo-94 (p,γ))	0.86	0.24	0.14	0.10	0.02	0.007
			Mo-95 (p,n)	165	54.7	23.3	18.6	11.4	7.6
			Mo-96 (p,2n)	0	186	197	193	142	53.6
			Mo-97 (p,3n)	0	0	0.03	1.69	57.3	82.1
43-Tc-96	4.28 d	→ Mo-96*	Mo-96 (p,n)	594	222	88.1	68.0	33.4	19.4
			Mo-97 (p,2n)	0	720	841	837	532	163.3
			Mo-98 (p,3n)	0	0	0	0.95	276	601
43-Tc-96m	51.5 min	98% →Tc-96 (4.28 d) → Mo-96* 2% → Mo-96*	Mo-96 (p,n)	122	42.6	14.9	11.1	5.5	3.2
			Mo-97 (p,2n)	0	140	150	145	80.0	24.0
			Mo-98 (p,3n)	0	0	0	0.20	50.1	96.5
43-Tc-97*	4.2×10^6 yr	→ Mo-97*	Mo-97 (p,n)	608	154	61.7	48.5	26.2	16.6
			Mo-98 (p,2n)	0	825	933	948	648	182.2
43-Tc-97m	91.4 d	96% →Tc-97 (4.2×10^6 yr) →Mo-97* 4% → Mo-97*	Mo-97 (p,n)	111	24.6	13.1	11.4	8.23	5.74
			Mo-98 (p,2n)	0	156	143	135	82.9	30.7
43-Tc-98*	4.2×10^6 yr	→ Ru-98*	Mo-98 (p,n)	728	110.0	51.9	43.7	28.5	18.9
			Mo-100 (p,3n)	0	0	101	210	691	723
43-Tc-99*	2.1×10^5 yr	→ Ru-99*	Mo-100 (p,2n)	318.4	864	858.9	777.8	356.3	110.3
43-Tc-99m	6.01 h	→ Tc-99g (2.1×10^5 yr) → Ru-99*	Mo-100 (p,2n)	157	213.5	179.8	155.8	74.9	31.9

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Enviromental Permitting Regulations

^{99m}Tc dominates

Significant quantities of ^{99}Mo produced

Trace amounts of other impurities produced

^{97m}Tc has 91 day half life. Decays by isomeric transition and emits a gamma ray at 97 keV

Table 5. Calculated thick target saturated yields (MBq μA^{-1}) for the dominant radioactive products. Enriched and natural molybdenum targets were irradiated with proton energies 16–10 MeV, 19–10 MeV and 24–10 MeV.

		99.54% Enriched Mo			97.39% Enriched Mo			Natural Mo		
Product	$T_{1/2}$	16 MeV	19 MeV	24 MeV	16 MeV	19 MeV	24 MeV	16 MeV	19 MeV	24 MeV
Radioactive technetium isotopes										
^{99m}Tc	6.01 h	**2809**	**4235**	**5765**	**2748**	**4144**	**5640**	**272**	**410**	**558**
^{97m}Tc	91.4 d	6.35	9.51	15.8	41.2	69.7	108	468	734	1125
^{96m}Tc	51.5 min	0.034	0.054	1.38	0.178	0.295	8.62	339	470	710
^{96g}Tc	4.28 d	0.164	0.270	7.40	0.862	1.50	46.4	1914	2332	3782
^{95m}Tc	61 d	0.140	0.175	0.224	0.143	0.226	0.392	463	738	1198
^{95g}Tc	20 h	0.561	0.707	0.920	0.507	0.819	1.59	1640	2693	4765
^{94m}Tc	52 min	0.134	0.204	0.304	0.122	0.172	0.242	252	394	604
^{94g}Tc	293 min	0.512	0.912	1.65	0.450	0.735	1.24	975	1793	3357
^{93m}Tc	43.5 min	0.009	0.044	0.108	0.009	0.043	0.105	16.8	79.9	196
^{93g}Tc	2.75 h	0.055	0.245	0.709	0.054	0.240	0.688	102	446	1293
Radioactive other elements										
^{99}Mo	65.9 h	27.9	220	1222	27.3	215	1196	2.70	21.3	118
^{93m}Mo	6.9 h	0.0000	0.0002	0.004	0.0000	0.0002	0.004	0.006	0.372	6.51
^{91}Mo	15.5 min	0.004	0.103	0.57	0.0034	0.009	0.476	9.85	256	1413
^{97}Nb	72.1 min	43.4	94.3	179	42.5	92.3	175	4.20	9.13	17.3
^{96}Nb	23.4 h	10.3	76.0	377	10.1	74.3	369	1.00	7.31	36.5
^{95m}Nb	3.6 d	0.027	0.061	0.119	0.173	0.382	0.751	1.62	3.57	7.03
^{95}Nb	35 d	0.358	0.800	1.38	2.25	5.02	8.68	21.0	47.0	81.1
^{94m}Nb	6.3 min	0.019	0.219	1.33	0.120	1.38	8.36	12.9	33.7	111
^{92m}Nb	10.2 d	0.013	0.021	0.035	0.009	0.016	0.037	27.0	53.2	120
^{91m}Nb	60.9 d	0.009	0.030	0.094	0.008	0.026	0.077	18.34	66.5	215.2
^{89m}Nb	66 min	0.0004	0.002	0.004	0.0003	0.001	0.004	1.00	4.24	10.7
^{89}Nb	2.0 h	0.002	0.014	0.062	0.002	0.012	0.052	5.07	35.0	154
^{90}Nb	14.6 h	0.0000	0.0001	0.014	0.0000	0.0001	0.014	0.0005	0.233	25.2
^{93m}Nb	16 yr	0.0006	0.0014	0.0034	0.003	0.007	0.019	7.15	15.4	32.6
^{88}Zr	83.4 d	0.0000	0.0003	0.014	0.0000	0.0002	0.012	0.0043	0.649	34.9

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Enviromental Permitting Regulations

Open source ^{99m}Tc increased from 2.1 GBq to 500 GBq on permit

Other radionuclides, excluding alpha emitters increased from 0.3 GBq to 100 GBq

NRW did not approve the irradiation of a natural Molybdenum target

Table 4. The calculated number of nuclei of ^{99m}Tc and other reaction products obtained at EOB for 3, 6, 9, and 12 h irradiation of 99.54% enriched thick molybdenum target with 16–10 MeV, 19–10 MeV and 24–10 MeV protons with 200 μA current. Additionally, the percent ratios of ^{99m}Tc to all technetium, to stable technetium, to all radioactive technetium and to the sum of all radioactive isotopes are listed.

	3 h	6 h	9 h	12 h
	Proton energy = 16 MeV			
^{99m}Tc	5.13E+15	8.75E+15	1.13E+16	1.31E+16
Total stable Tc	2.06E+16	4.27E+16	6.59E+16	8.99E+16
Total other radioactive Tc	1.72E+13	3.38E+13	5.00E+13	6.60E+13
Total radioactive other	1.26E+14	2.12E+14	2.87E+14	3.59E+14
^{99m}Tc/all technetium	19.9%	17.0%	14.6%	12.7%
^{99m}Tc/all stable technetium	24.9%	20.5%	17.2%	14.6%
^{99m}Tc/all radioactive technetium	99.7%	99.6%	99.6%	99.5%
^{99m}Tc/all radioactive isotopes	97.3%	97.3%	97.1%	96.9%
	Proton energy = 19 MeV			
^{99m}Tc	7.74E+15	1.32E+16	1.71E+16	1.99E+16
Total stable Tc	3.58E+16	7.38E+16	1.13E+17	1.54E+17
Total other radioactive Tc	2.85E+13	5.59E+13	8.26E+13	1.09E+14
Total radioactive other	7.24E+14	1.32E+15	1.71E+15	1.99E+15
^{99m}Tc/all technetium	17.8%	15.2%	13.1%	11.4%
^{99m}Tc/all stable technetium	21.6%	17.9%	15.1%	12.9%
^{99m}Tc/all radioactive technetium	99.6%	99.6%	99.5%	99.5%
^{99m}Tc/all radioactive isotopes	91.1%	90.4%	89.5%	88.5%

Ionising Radiation Regulations

Risk assessments did not show any significant additional risk

Each irradiation expected to produce between 50-100 GBq of ^{99m}Tc

Shielding in all areas designed for 200 GBq of ^{18}F

Cyclotron Modification

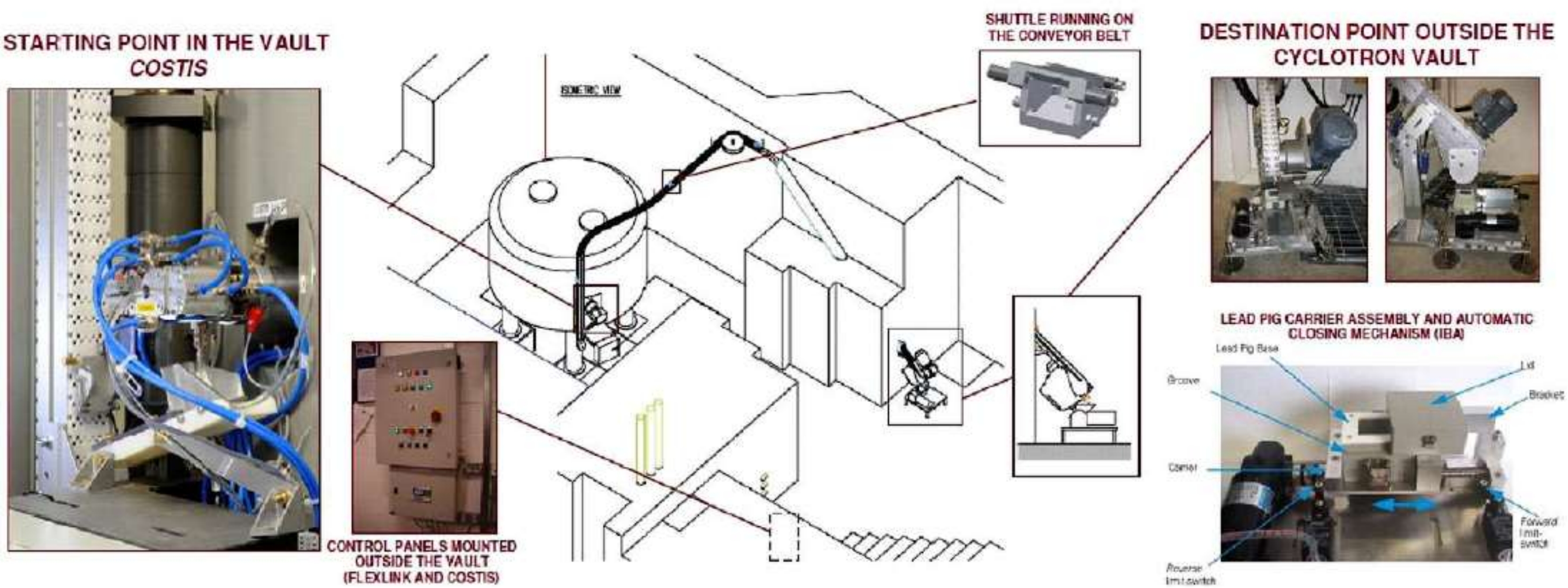
Needed to upgrade target water cooling to allow current to increase from 40 μA to 55 μA

Needed to remove Helium cooling from front of target and replace with vacuum. Achieved with a simple click and connect fitting.

Test of Target Loading and Unloading

In November 2016, we received a natural Mo target to ensure the system could load and unload the target disks

Original target slightly too big to maintain vacuum on target. Diameter reduced from 12.5 mm to 12 mm. Target loading and unloading repeated with new target successfully.



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Photographs of the Mo target on a copper backing

Target Irradiations

In February 2017, we undertook 6 target irradiations with representatives with TRIUMF and IBA

3 x 1 hour at 50 μA
3 x 6 hour at 50 μA

Targets were unloaded, transferred to a research hot cell and measured in a Capintec CRC 25R dose calibrator

Repeated measurements were taken using data logging software

Activities were decay corrected to End of Beam assuming a 6 hour half life

No attempts were made to measure gamma spectrum

Targets were visually assessed for damage post irradiation

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Log of a 6 hour irradiation demonstrating stable cyclotron performance

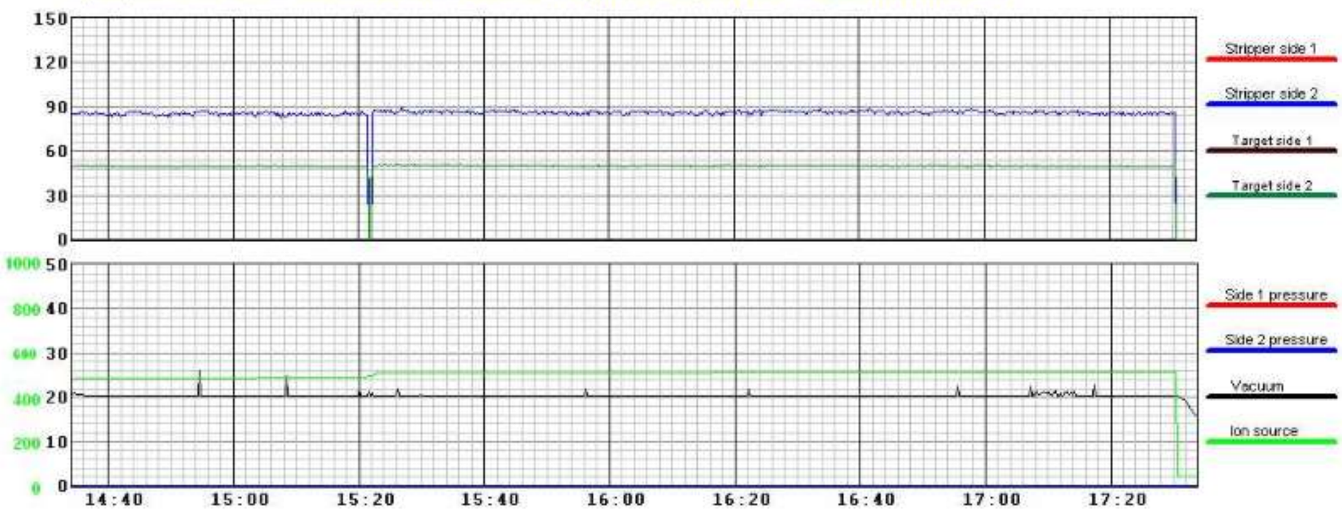
ESC | CYCLONE 18/9 Logbook | (Auto- Print request)

"Beam On" Time : 11 : 26 : 11 "Beam Off" Time : 17 : 30 : 28 Total Irradiation time : 06 : 01 : 30 Operator Name : MANAGER Date : 10/02/2017

Source Parameters :		Coils Power supply parameters :		Dee Voltage parameters :	
Maximum Set point :	517.1 mA	Set point at Beam start-up :	139.0 A	Set point at Beam start-up :	34.1 KV
Set point value at Beam Stop :	517.1 mA	Set point at Beam stop :	139.8 A	Set point at Beam stop :	34.1 KV

Type : H - Single Beam	Side 1	Side 2
	Side 2/ Side 1 ratio at beam stop :	0.0
Port number, target number, volume	0	7 Cust. Target 7
Requested target current		0.0 µA
Maximum target current		52.8 µA
Integrated target current		300.01 µA.hr
Requested integrated current		300.00 µA.hr
Extraction at Beam Stop		62.05 %

Input your comments here : Tc-99m CYCLOTRON PRODUCTION (MG, AD, SM) for TRIUMF target 0246 REUSED test.



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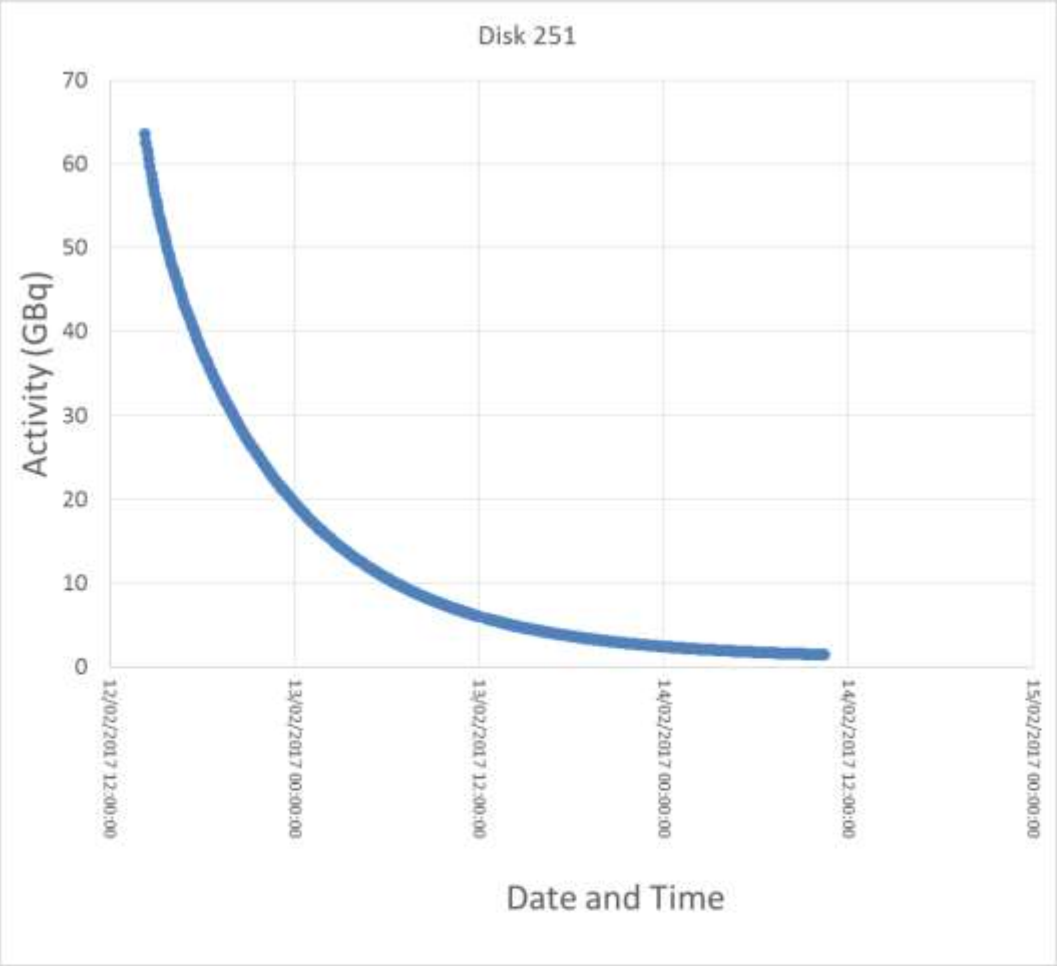
Results

The 1 hour irradiations produced 13.5 ± 1.4 GBq of ^{99m}Tc

The 6 hour irradiations produced 63±6 GBq of ^{99m}Tc

Activity measurements 4 days later on 6 hour irradiation targets showed < 500 MBq present

No visual evidence of significant target degradation post irradiation



Conclusion

It is possible to produce 60 GBq of ^{99m}Tc on an IBA 18/9 cyclotron equipped with a COSTIS solid target system using the targets designed and produced by TRIUMF without large amounts of long lived impurities

With a modified cooling system, it is possible to use up to 50 μA without target degradation or melting