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Considerations regarding full cost recovery in direct production of ^{99m}Tc

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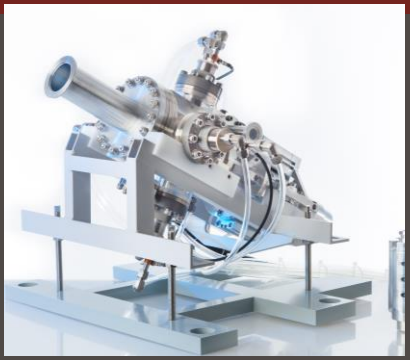
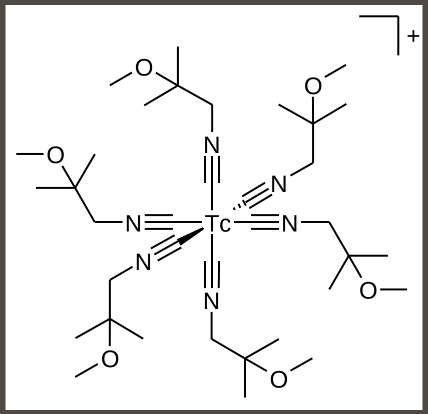
5) Centre for Probe Development and Commercialization





Direct Production of ^{99m}Tc

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery

Goals:

- Demonstrate routine, reliable, commercial-scale production of ^{99m}Tc via ^{100}Mo(p,2n) at multiple sites, multiple brands;
- Obtain regulatory approval for clinical use in humans;
- Establish a business plan;
- Disseminate, commercialize the technology

Hypothesis: Future production will be from variety of sources (neutron, proton, electron) and market driven

J. Beaver, H. Hupf, J Nucl Med 1971;12:739-741

Target Manufacturing

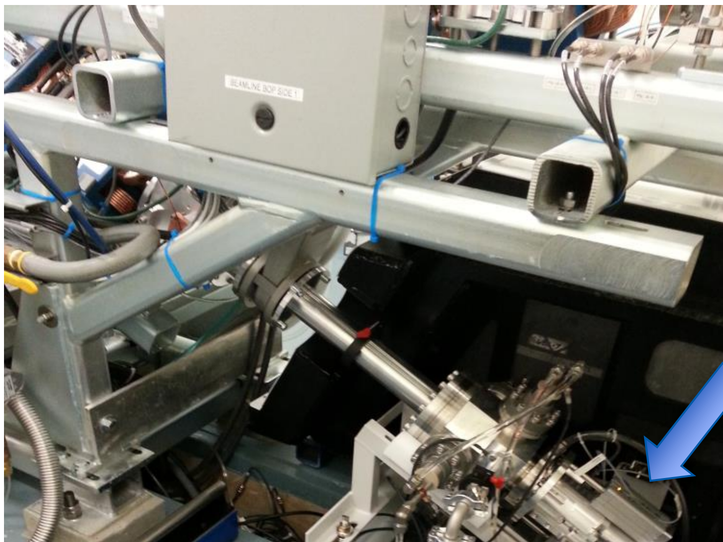
^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery

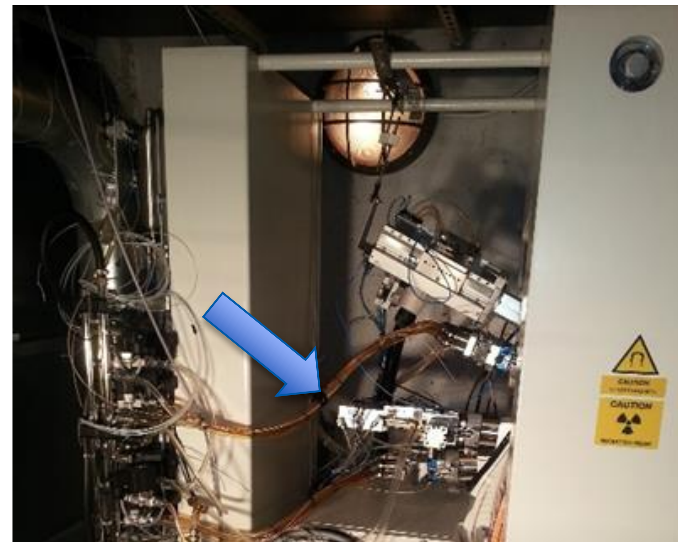
- Oblique and orthogonal targets
- Irradiations for six hours at max power
  - Oblique on ACSI TR19 (5.4 kW) & ACSI TR30 (@24 MeV) (10.8 kW)
    - 24 MeV, 450 µA, 6 hrs -> **1110 GBq** (30 Ci)
    - 18 MeV, 300 µA, 6 hrs -> **420 GBq** (11.3 Ci)
  - Orthogonal on GE PETtrace (2.1 kW)
    - 16.5 MeV, 130 µA, 6 hrs -> **170 GBq** (4.7 Ci)

Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022
Zeisler et al. WTTC 2014 & WTTC 2015 (wttc.triumf.ca)
Schaffer et al. Phys. Proc. 2015, 66, 383-395

Retrofit Existing Infrastructure

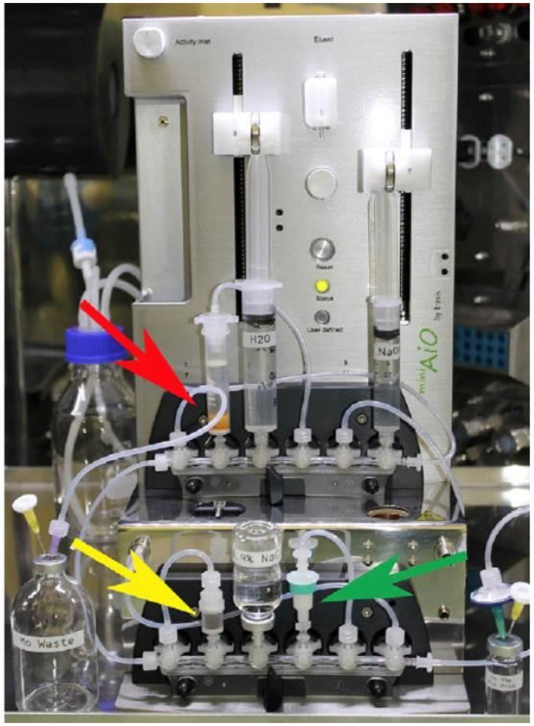
^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery





Purification of ^{99m}Tc

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery



- **SPE-based method:**
- **Process Time:** <90 min.
- **Efficiency**: 93%
- **Radiochemical Purity:** >99.99% TcO_4
- **Trace analysis:** <10 Bq Mo-99, <5 ppm Al^{3+}
- non-Tc impurities removed

Developed specifications and quality control tests.

Morley et al. Nuc. Med. Biol. 2012, 551-559

Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

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Radionuclidic Release Test

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	**Regulatory QA/QC**	^{100}Mo Recovery

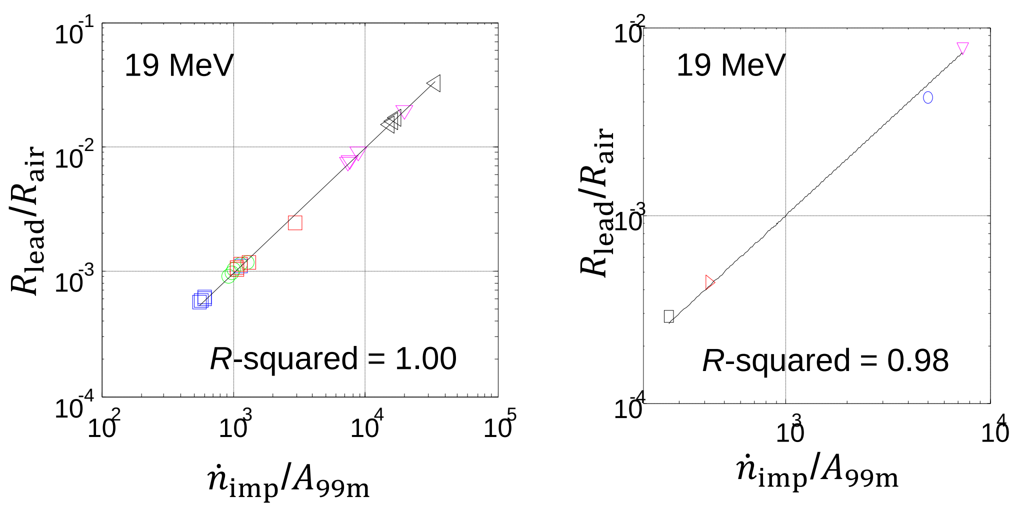
- Modified "moly shield" assay
  - Dose calibrator measurement of ^{99m}Tc-Pertechnetate sample with & without a 7mm thick lead shield
  - Ratio of generator pertechnetate measurements indicates content of ^{99}Mo since 140 keV emissions are highly attenuated
- Similarly, most impurities in direct-production have emissions > 140 keV

A fast and simple dose-calibrator-based quality control test for the radionuclidic purity of cyclotron-produced ^{99m}***Tc***. Tanguay et al., Accepted for publication: Physics in Medicine and Biology.

Radionuclidic Release Test

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	**Regulatory QA/QC**	^{100}Mo Recovery

- Relate ratio to emissions per unit ^{99m}Tc activity
- Calibration provides a ***dosimetry-based*** release



calculation

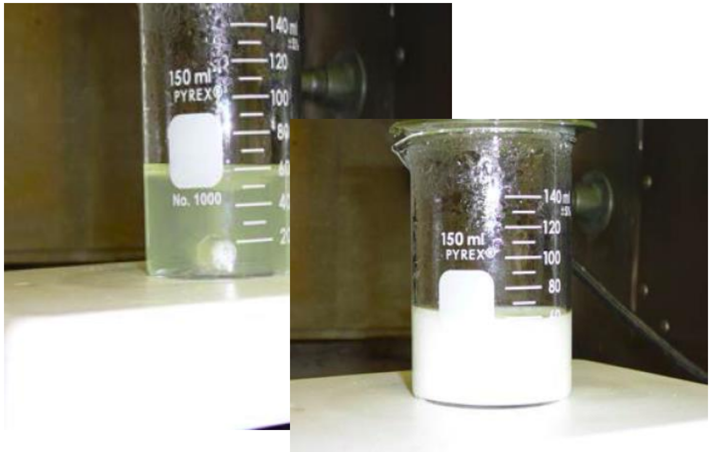
measurement

A fast and simple dose-calibrator-based quality control test for the radionuclidic purity of cyclotron-produced ^{99m}Tc. Tanguay et al., Accepted for publication: Physics in Medicine and Biology.

Recycling

^{100}Mo Target	Cyclotron Modification	Optimize Irradiation	Purify $^{99m}TcO_4$	Regulatory QA/QC	**^{100}Mo Recovery**

- High efficiency recovery process for multi-gram quantities of $^{100}MoO_4^{2-}$ required
- Some trace long-lived radionuclidic impurities
- Target dissolution waste stream (liquid, 10's of mL/batch)
- Original method: ion exchange
  >90% efficiency (non-optimized), large column volumes, slow
- Currently using acidic precipitation, thermal decomp. process
- Routine recovery yields >99%
- Analysis of recovered ^{100}Mo underway



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Status

- Hardware & Process is “locked down”
- Clinical Trial approved – patient recruitment starts w/c September 7
- Assembling New Drug Submission for Health Canada
- ARTMS™ formed to sell targets, target stations, hardware, and support for ^{99m}Tc-Pertechnetate producers

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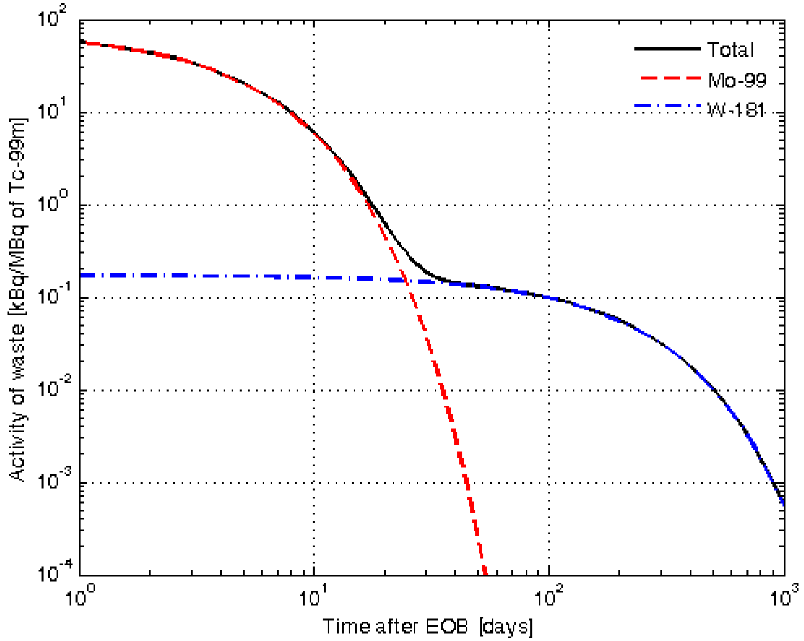
The Practice of Supply

Dissolved target solution

- ^{100}Mo solution samples (18 MeV) after removal of Tc
  - Gamma spec at ~ 30 days post irradiation

Isotope	Half life [hours]	Average Activity (kBq/MBq ^{99m}Tc)	Std Deviation (kBq/MBq ^{99m}Tc)
Mo-99	6.60E+01	7.19E+01	1.02E+02
W-181	2.91E+03	1.72E-01	3.03E-01
Zr-89	7.85E+01	2.48E-02	4.68E-02
Nb-95	8.40E+02	1.78E-03	3.03E-03
Nb-92m	2.44E+02	6.74E-04	1.23E-03
Zr-88	2.00E+03	4.94E-04	9.12E-04
Nb-95m	8.66E+01	4.03E-04	8.07E-04
Ta-182	2.75E+03	9.81E-05	1.56E-04
Y-91	1.40E+03	5.83E-05	1.17E-04
Y-88	2.56E+03	5.68E-05	1.04E-04
Nb-91m	1.46E+03	7.53E-06	1.51E-05
Tc-95m	1.46E+03	1.58E-06	1.84E-06

Preliminary



Irradiated target plate

- Expect some of the same radionuclides as the moly solution
  - from residual moly on the plate
- Will have radionuclides produced from Ta
  - plus those produced from trace elements in the Ta
  - Present experience indicates trace elements yield radionuclides that dominate ^{181}W

Isotope	Half life [hours]	Average Activity (kBq/MBq ^{99m}Tc)
W-181	2.91E+03	1.40E-04

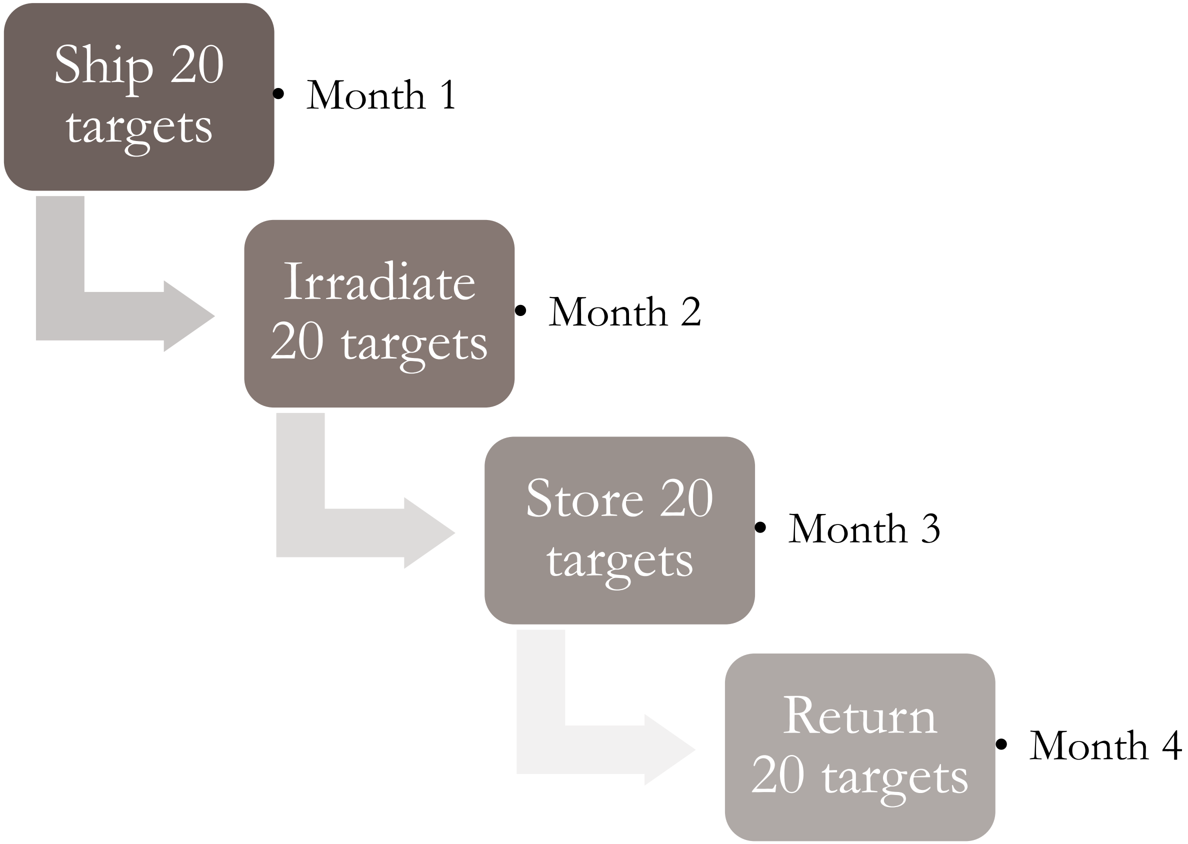
  - In process of acquiring gamma spectra

Recoverable Inventory

- An oblique plate (2 mm x 40 mm x 115 mm)
- Assume ~30 days of decay
- Irradiate 20 targets in 30 days
  - 1 per day * 5 days per week
- Accumulate 20 targets in 30 days that must be stored : 40 mm x 40 mm x 115 mm
- Each purification generates 100 mL of dissolved ^{100}Mo solution = 2 L of solution in same period

Inventory in circulation

- What stock is needed?
  - Per production batch, per site



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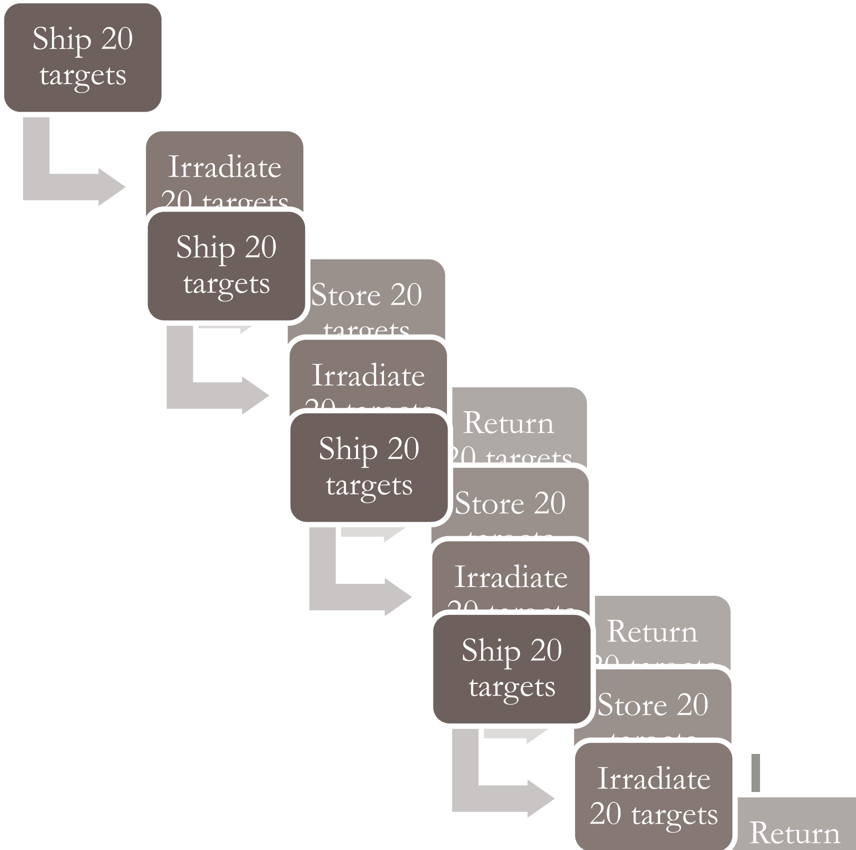
Inventory in circulation

- Effect on inventory of manufacturer and producer?
- Cascades to 80 targets in circulation
  - Assume
    - 1 – 1.5 g of ^{100}Mo per target
    - $500 per g ^{100}Mo
  - Up to $60K of ^{100}Mo alone in circulation per single batch producer



Summary

- Target technology proven and adaptable for all cyclotron systems
- Direct-production in clinical trials with commercial scale (Ci) batch sizes
- New Drug Submission for Canadian Market Authorization being assembled this fall
- ^{100}Mo targets are available from a manufacturer near you…

Acknowledgements

- **The Team:**

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Canada

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LAWSON HEALTH RESEARCH INSTITUTE

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a place of mind UBC

Thank you!
Merci

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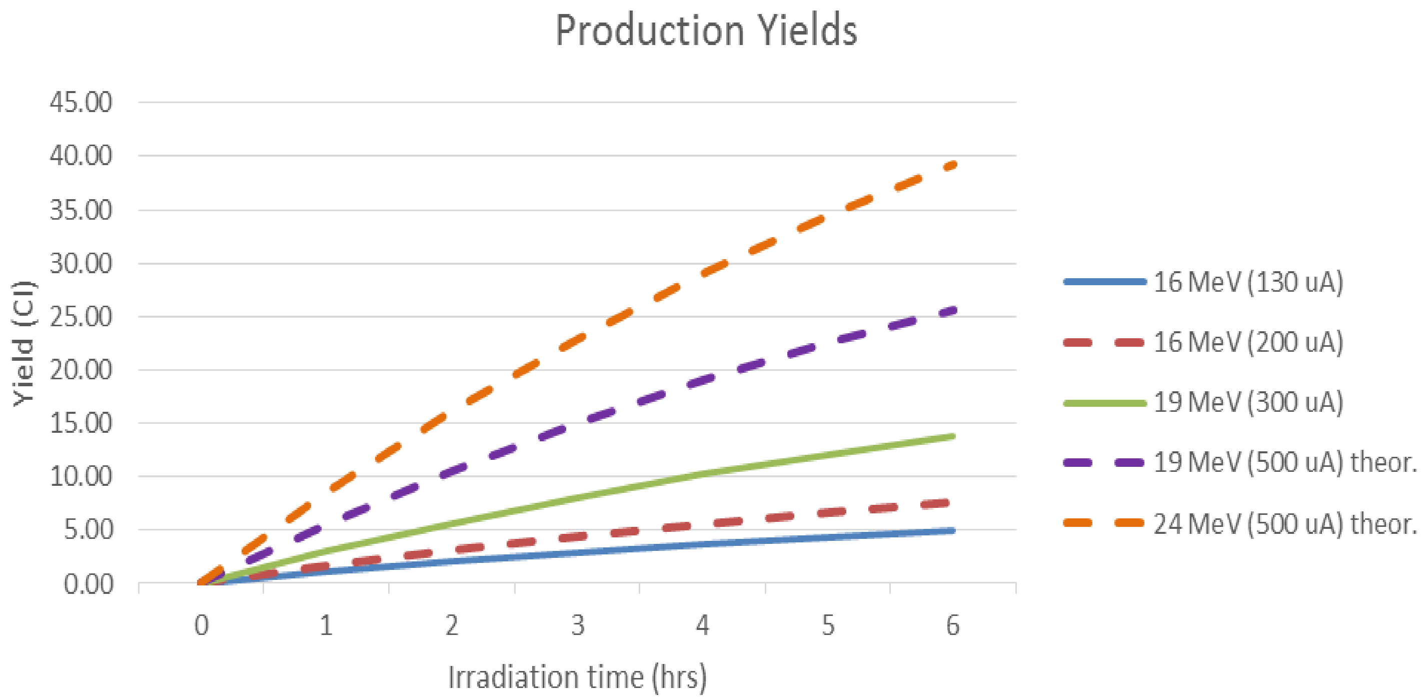
Real and Projected Yields of ^{99m}Tc

^{100}Mo Target	Cyclotron Modification	**Optimize Irradiation**	Purify $^{99m}TcO_4$	Regulatory QA/QC	^{100}Mo Recovery

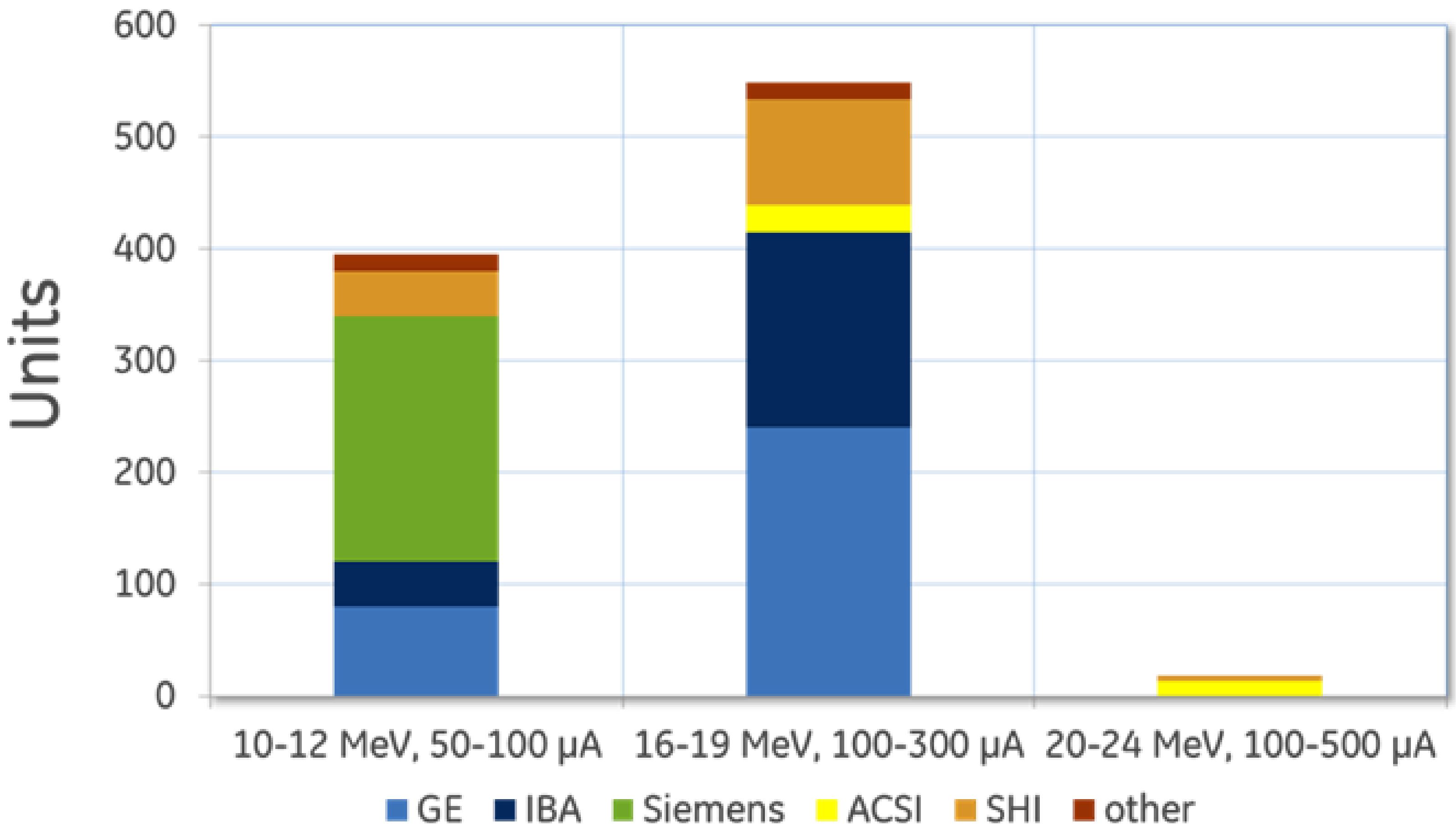


GE PETtrace
16.5 MeV, 130 μA
Theoretical 4.9 Ci (6h)
Achieved 4.7 Ci
Sat^{n}: 75.6 mCi/μA

TR19
18 MeV, 300 μA
Theoretical 15.4 Ci (6h)
Achieved 11.3 Ci (@ 240 μA)
Sat^{n}: 103 mCi/μA

TR30 (@24 MeV)
24 MeV, 500 μA
Theoretical 39 Ci (6h)
Achieved ~32 Ci (@ 450 μA)
Sat^{n}: TBD

Cyclotrons By the Numbers



Estimated global cyclotron numbers by various manufacturers (with data from ACSI, GE, IBA and Siemens, Sumitomo data estimated)

Schaffer et al. Phys. Proc. in press (2014).

Mo elemental composition

Vendor		Isoflex		Trace Sciences		Isoflex		Isoflex
CoA #		4939		74		42-01-100-3857		42-01-100-4178
Element		ppm		ppm		ppm		ppm
Mn	<	0.1		0.3		1	<	5
Cr		1.16		0.2		1	<	5
Cu		5	<	0.6		10	<	5
Fe		16		6		20	<	5
Sn		1.8				1	<	5
Ni		0.5		0.8		1	<	5
Si		15				70		20
Na		6		164		1	<	5
Mg		1		6.09		5	<	5
Ti		0.26	<	0.07		20	<	5
Al		2.16		8		20	<	5
Co	<	0.1	<	0.01		1	<	5
Zn	<	1		0.3		2		10
W		14			<	100	<	5
Ag			<	0.02				
Ba				0.8				
Be			<	0.01				
Ca				470				
Cd				1.46				
Pb			<	0.06				
Sb			<	0.01				
Se			<	0.04				
Sr			<	0.3				
V			<	0.01				
sum	< %	0.006408		0.06591		0.0253		0.009
Mo	>%	99.99359		99.9341		99.975		99.991

Ta elemental composition

	HTA 11402045	HTA11402058	HTA11112188
Element	% composition	% composition	% composition
C	0.0032	0.0040	0.0048
N	0.0006	0.0000	0.0029
O	0.0092	0.0092	0.0108
H	0.0005	0.0006	0.0012
Fe	0.0006	0.0008	0.0008
Mo	0.0008	0.0008	0.0033
Ni	0.0005	0.0007	0.0005
Si	0.0002	0.0005	0.0037
Ti	0.0003	0.0003	0.0005
W	0.0198	0.0238	0.0039
Nb	0.0492	0.0586	0.0210
Ta	99.9151	99.9007	99.9466

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Economics

- Assessments of 16, 19 and 24 MeV operations
- Activity-based costing model with 3 phases:

  i) plate manufacturing and Mo-100 recycling
  ii) irradiation, dissolution and purification
  iii) target plate and Tc-99m distribution + indirect
- Activities: Materials, salaries/benefits, power/utilities, equipment, waste, process failure and training.
- Indirect costs: wages, admin(sales, general), regulatory and capital.
- Amortization for most lab equipment was 3 to 7 years (usually 7), except cyclotron (25 years) and building (40 years)
- Production rate: 2.8 GBq/uA at saturation
- Injected doses: 20 mCi;
- ^{100}Mo: $0.50/mg
- Activity losses: 65%, average wait time of 9hrs between EOB and injection
- Comparable cost/dose to subsidized generator ^{99m}Tc