An Update on Regulatory and Clinical Efforts en route to Commercialization of Cyclotron-Produced Tc-99m

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F Bénard[1], M Kovacs[1], T Ruth[1], **P Schaffer**[1,2]

1) The ITAP Consortium
2) ARTMS Products, Inc.

Sept. 13th, 2016

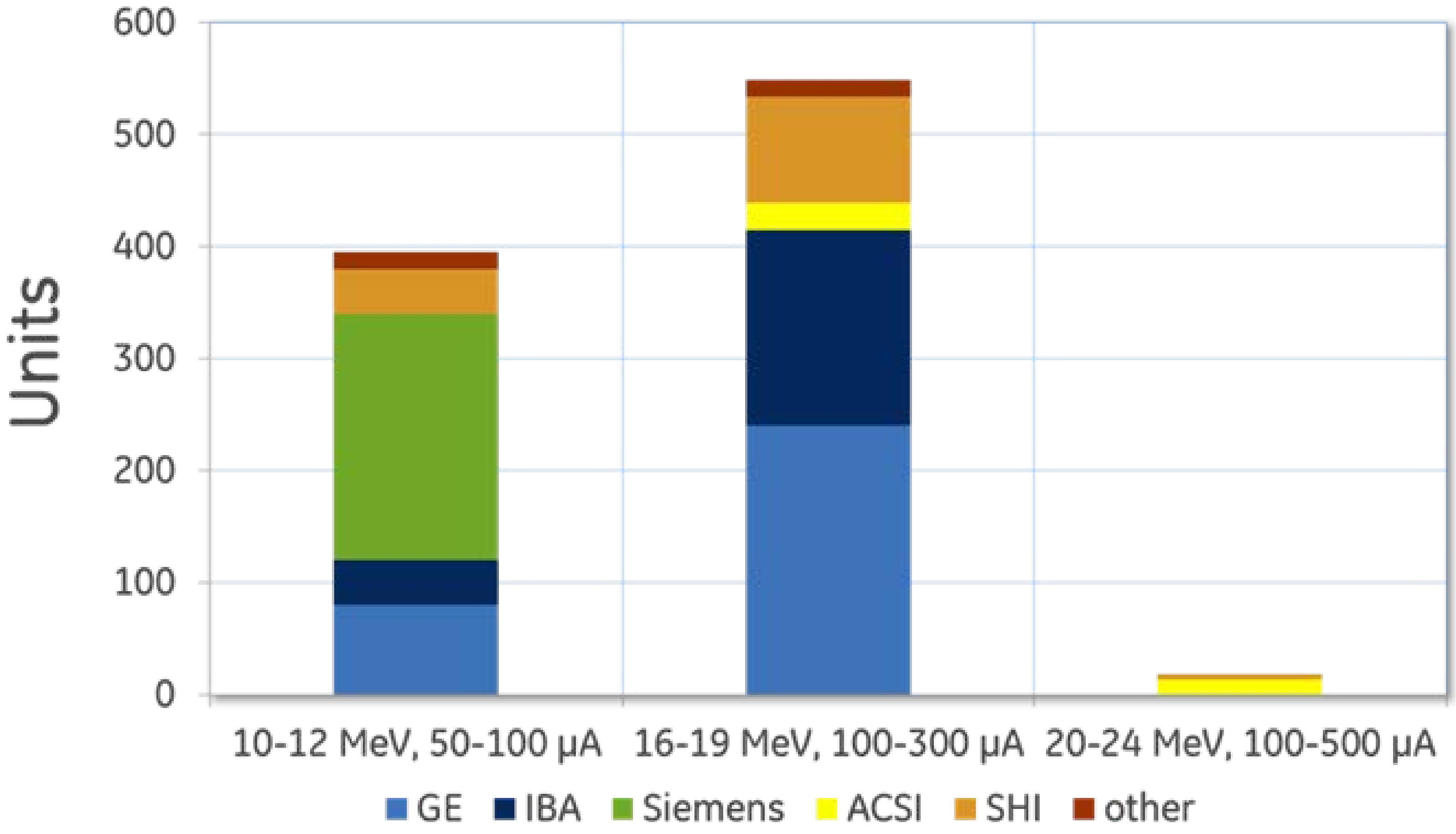
Current Supply Model

Reactor | Mo-99 Processer | Generator Manufacturer | Radiopharmacy | Clinic

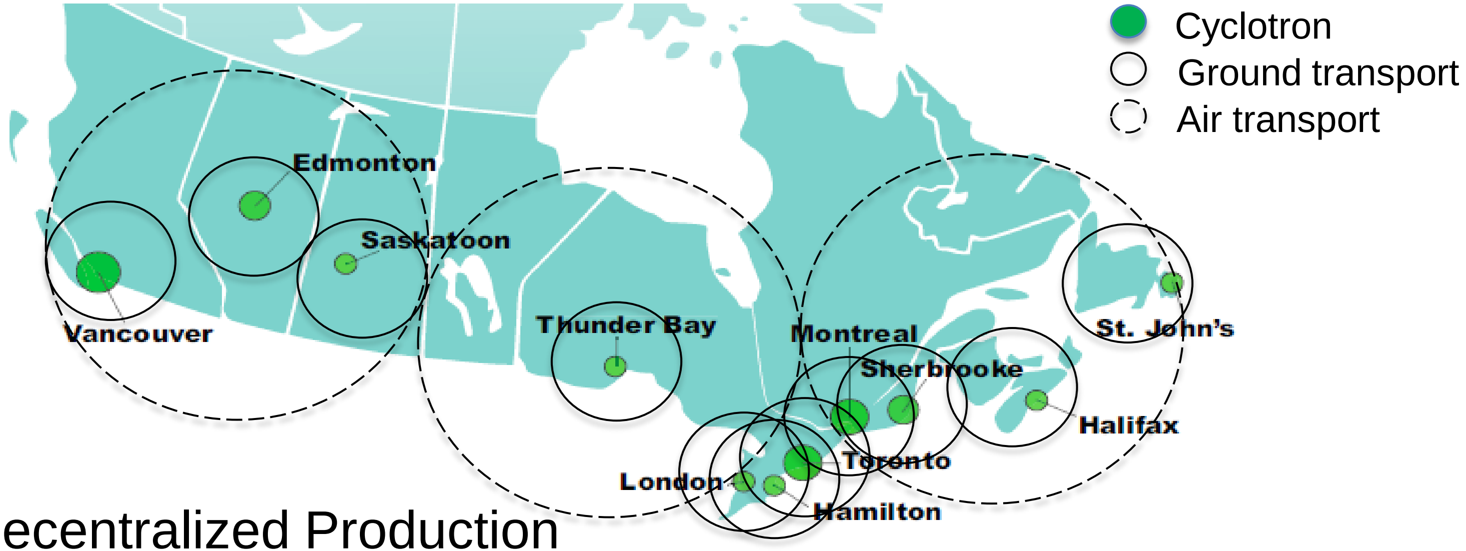
Our Philosophy

Cyclotron + ARTMS Technology   Radiopharmacy   Clinic

Cyclotrons by the Numbers



P Schaffer, F. Benard, A. Berstein et al. Phys Proc. 2015, 66, 383.



- Decentralized Production
  - ^{99m}Tc locally produced, locally used, competitively priced
  - Redundant supply to avoid widespread shortages
  - Fits with existing radiopharmacy distribution model
  - Complementary to:
    - other medical isotopes produced by cyclotrons (^{18}F)
    - other sources of ^{99m}Tc

2009 to Present: NRCan Mandate

^{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

Different Machines, Different Capabilities

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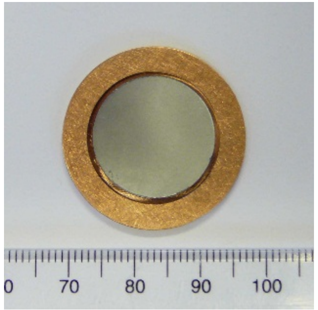
^{100}Mo Target | Cyclotron Modification | Optimize Irradiation | Purify $^{99m}TcO_4$ | Regulatory QA/QC | ^{100}Mo Recovery

Electrophoretic deposition

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

Press-Sinter-Braze

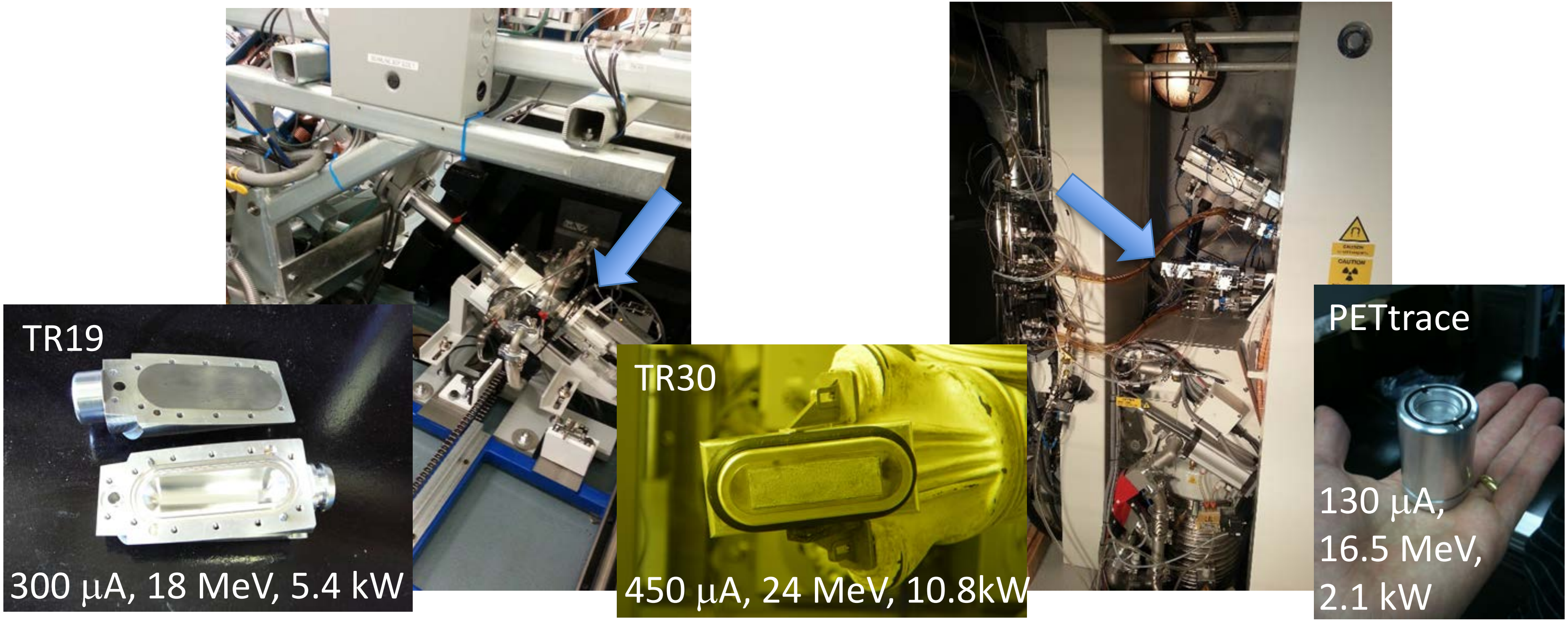


Schaffer et al. Phys. Proc. 2015,66,383.
Zeisler et al. WTTC 2014

- Maximize ^{99m}Tc production, minimize impurities: ^{100}Mo purity, target thickness, irradiation energy/time
- Reduce density, balance thermal conductivity

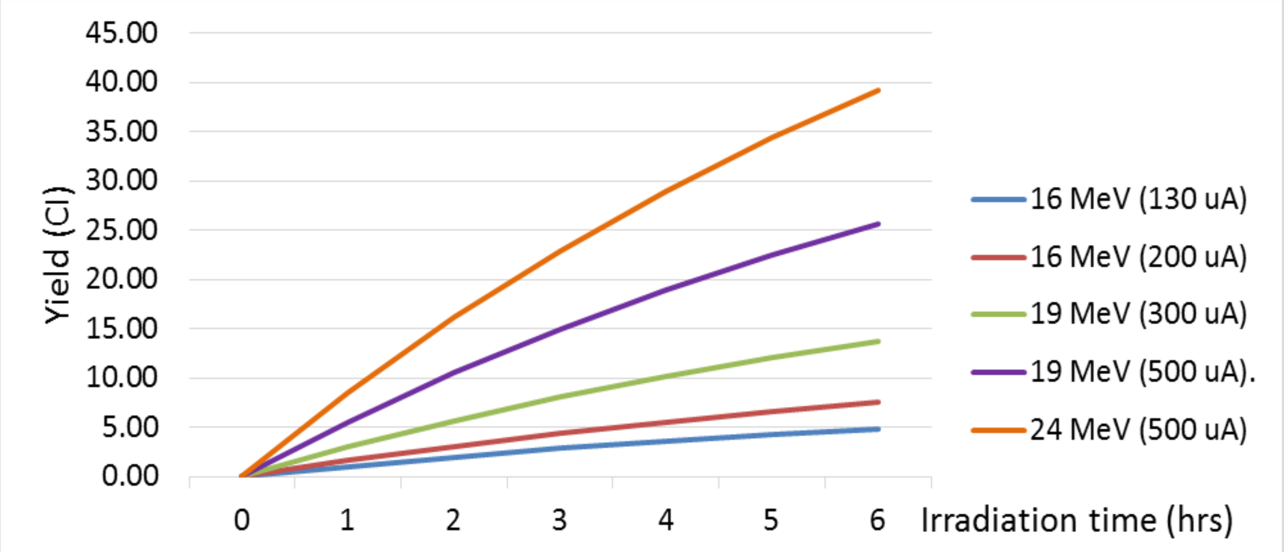
Cyclotron Retrofit

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



Real and Projected Yields of ^{99m}Tc

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

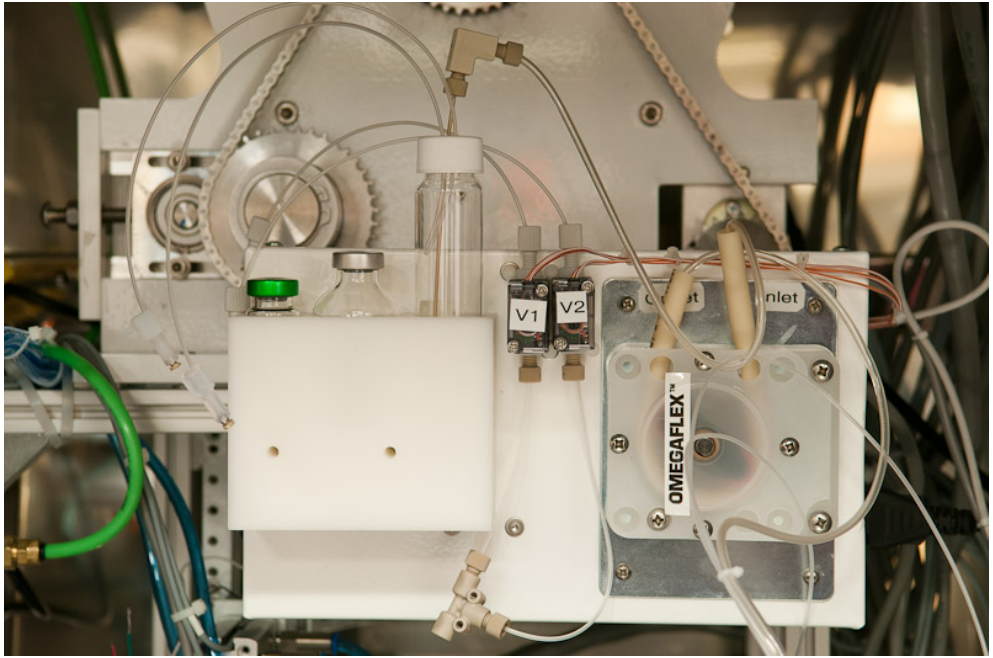


GE PETtrace
16.5 MeV, 130 μA
Theoretical 4.9 Ci (6h)
Achieved 4.7 Ci
Expected Sat^n: 75.6 mCi/μA

TR19
18 MeV, 300 μA
Theoretical 15.4 Ci (6h)
Achieved 15.0 Ci (@ 300 μA)
Expected Sat^n: 103 mCi/μA

TR30 (@24 MeV)
24 MeV, 500 μA
Theoretical 39 Ci (6h)
Achieved ~32 Ci (@ 450 μA)
Expected Sat^n: 156.8 mCi/μA

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

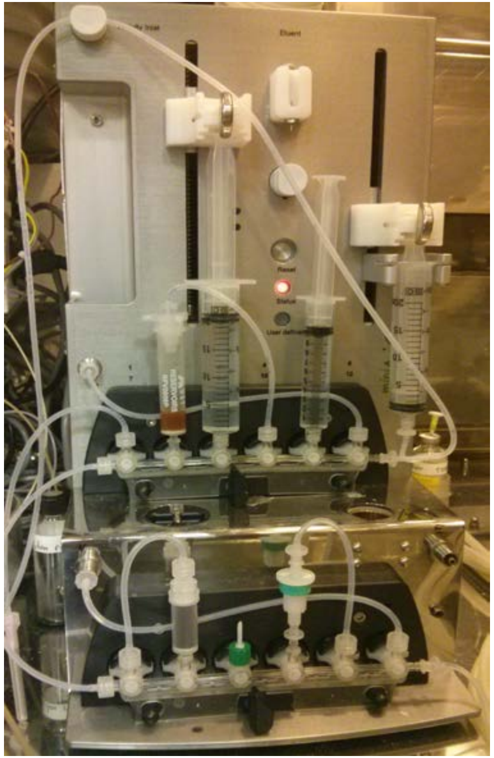


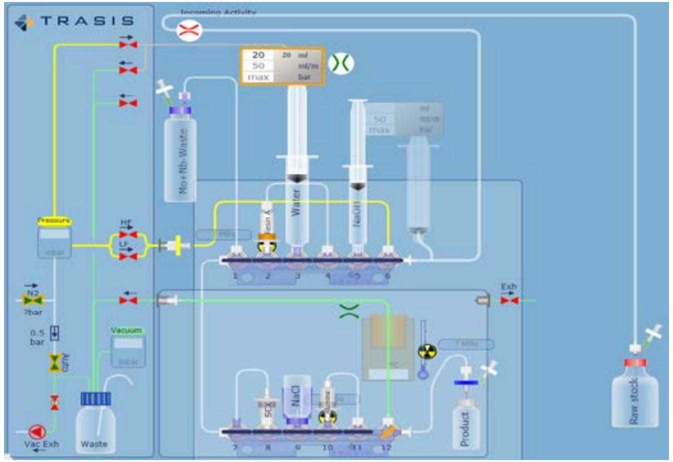
- **Target Dissolution**
  - Target transfers pneumatically for dissolution
  - 30% H_2O_2 circulated with peristaltic pump
  - 5M NaOH added and circulated
  - 45 minutes
  - Transferred to processing module for MoO_4^{2-} / TcO_4^- separation

Morley et al. Nuc. Med. Biol. 2012, 551-559
Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Purification of ^{99m}Tc

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





Purification:

- Solid-phase extraction
- Process Time: ~45 min.
- Efficiency: 92.7 ± 1.1%
- Final Product: $Na[^{99m}TcO_4]$
- GMP compliant

Morley et al. Nuc. Med. Biol. 2012, 551-559
Bénard et al., J. Nucl. Med. 2014, 55, 1017-1022

Isotopic Impurities	Nuclear Impurities	Chemical Impurities

Isotopic Impurities

Isotope	Content (%)
^{100}Mo	99.815
^{98}Mo	0.17
^{97}Mo	0.003
^{96}Mo	0.003
^{95}Mo	0.003
^{94}Mo	0.003
^{92}Mo	0.003

Nuclear Impurities

Chemical or Common Name	Structure	Origin
^{94g}Tc pertechnetate	$^{94g}TcO_4^-$	$^{94}Mo(p,n)^{94g}Tc$ $^{95}Mo(p,2n)^{94g}Tc$
^{95m}Tc pertechnetate	$^{95m}TcO_4^-$	[illegible]
^{95g}Tc pertechnetate	$^{95g}TcO_4^-$	$^{95}Mo(p,n)^{95g}Tc$ $^{96}Mo(p,2n)^{95g}Tc$
^{96m}Tc pertechnetate	$^{96m}TcO_4^-$	$^{96}Mo(p,n)^{96m}Tc$ $^{97}Mo(p,2n)^{96m}Tc$
^{96g}Tc pertechnetate	$^{96g}TcO_4^-$	$^{96}Mo(p,n)^{96g}Tc$ $^{97}Mo(p,2n)^{96g}Tc$
^{97m}Tc pertechnetate	$^{97m}TcO_4^-$	$^{97}Mo(p,n)^{97m}Tc$ $^{98}Mo(p,2n)^{97m}Tc$
^{97g}Tc pertechnetate	$^{97g}TcO_4^-$	$^{97}Mo(p,n)^{97g}Tc$ $^{98}Mo(p,2n)^{97g}Tc$
^{98}Tc pertechnetate	$^{98}TcO_4^-$	$^{100}Mo(p,3n)^{98}Tc$
^{98g}Tc pertechnetate	$^{98g}TcO_4^-$	$^{98}Mo(p,n)^{98g}Tc$
^{99g}Tc pertechnetate	$^{99g}TcO_4^-$	$^{100}Mo(p,2n)^{99g}Tc$
^{91}Mo	$^{91}MoO_4^{2-}$	$^{92}Mo(p,pn)^{91}Mo$
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
^{100}Mo	$^{100}MoO_4^{2-}$	Unreacted starting material[1]
^{89}Nb	$^{89}NbO_2$	$^{92}Mo(p,\alpha)^{89}Nb$
^{89m}Nb	$^{89m}NbO_2$	$^{92}Mo(p,\alpha)^{89m}Nb$
^{90}Nb	$^{90}NbO_2$	$^{94}Mo(p,\alpha n)^{90}Nb$
[illegible]	[illegible]	[illegible]
^{91m}Nb	$^{91m}NbO_2$	[illegible] $^{94}Mo(p,\alpha)^{91m}Nb$ $^{95}Mo(p,\alpha n)^{91m}Nb$
^{92m}Nb	$^{92m}NbO_2$	$^{95}Mo(p,\alpha)^{92m}Nb$ $^{96}Mo(p,\alpha n)^{92m}Nb$
^{93m}Nb	$^{93m}NbO_2$	$^{96}Mo(p,\alpha)^{93m}Nb$ $^{97}Mo(p,\alpha n)^{93m}Nb$
^{94m}Nb	$^{94m}NbO_2$	$^{97}Mo(p,\alpha)^{94m}Nb$ $^{98}Mo(p,\alpha n)^{94m}Nb$
^{95}Nb	$^{95}NbO_2$	$^{98}Mo(p,\alpha)^{95}Nb$
^{95m}Nb	$^{95m}NbO_2$	$^{98}Mo(p,\alpha)^{95m}Nb$
^{96}Nb	$^{96}NbO_2$	$^{100}Mo(p,\alpha n)^{96}Nb$
^{97}Nb	$^{97}NbO_2$	$^{100}Mo(p,\alpha)^{97}Nb$
^{88}Zr	$^{88}ZrO_2$	$^{92}Mo(p,\alpha n)^{88}Zr$
^{107}Cd	^{107}CdO	$^{107}Ag(p,n)^{107}Cd$
[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
^{67}Zn	^{67}ZnO	$^{67}Cu(p,n)^{67}Zn$

Tc impurities

Mo impurities

Other reactions

Target backing

Chemical Impurities

Element	Content (ppm)
Mn	0.1
Cr	1.16
Cu	5
Fe	16
Sn	1.8
Ni	0.5
Si	15
Na	6
Mg	1
Ti	0.26
Al	2.16
Co	0.1
Zn	1
W	14

J. Tanguay *et al*, *Phys Med Biol.* 2015 Nov 7 ; **60**(21) pp 8229-47

Rapid Impurity Assessment

Option 1: Gamma spectroscopy

- Requires samples at multiple time points (i.e. over many days)
  - Accurate and precise but not fast
  - Requires analysis of complicated emission spectra

Option 2: Dose calibrator with lead shield

- Compare air and shielded samples
- Similar method currently used to test for moly breakthrough in generator-produced ^{99m}Tc[1,2]
- Establish a regulatory limit based on less than 10% increased dose at expiry

1. H. H. Lo *et al.*, *Radiology*, 93(5), 1969.
2. P. Richards and M. O'Brian, *J. Nucl. Med.*, 10(7), 1969.

Patient Dose Considerations

- Cumulative dose increase over pure $^{99m}TcO_4^-$
  - ➢ Proposed limit: <10% over pure ^{99m}Tc
- Worst case scenario: thick target, 12 hr bombardment, dose at 24 hr > EoB
  - ➢ Proposed 18 hr shelf life

			Dose increase (%)		
			16 MeV	18 MeV	24 MeV
Mo Isotope	Sample 1	Sample 2	Sample 1 vs. Sample 2	Sample 1 vs. Sample 2	Sample 1 vs. Sample 2
92	0.005	0.003	5.4 vs. 1.7	5.7 vs. 1.7	69.5 vs. 6.0
94	0.005	0.003			
95	0.005	0.003			
96	0.005	0.003			
97	0.01	0.003			
98	2.58	0.17			
100	97.39	99.815			

PETtrace Process Validation Batch Analysis

Process Validation Batch No.		1509011	1509025	1510005
Batch Size (EOS) (GBq)		35.3	51.7	37.0
Final Product Amount at EOB (GBq)		N/A41.2	N/A61.1	N/A43.5
Estimated Yield (%) (decay-corrected)		100	135	89
Membrane filter integrity (≥ 50 psi)		62	61	65
Specification	**Acceptance Criteria**	**Results**		
Visual Appearance	Clear, colorless solution, free from visible particulates	Conforms	Conforms	Conforms
pH	4.5 to 7.5	7.5	7.0	7.5
Radionuclidic purity	Isotopes other than ^{99m}Tc contribute an emission rate < 6,000 emissions/ sec/MBq of ^{99m}Tc	34	52	53
Radionuclidic identity	Half-life between 5.72 and 6.32 hours	5.81	5.84	5.83
Radiochemical purity	≥ 95%	100	100	100
Radiochemical identity	Rf = 0.8 – 1.0	1.0	1.0	1.0
Aluminum content	≤ 10 μg/mL of solution (10 ppm)	<10	<10	<10
Hydrogen peroxide content	≤ 50 mg/L of solution (50 ppm)	0	0	0
Molybdenum content	≤ 30 μg/mL of solution (30 ppm)	0	0	0
Radioactivity concentration	(≤ 27.8 GBq/mL)	1.83	2.58	1.84
Bacterial endotoxins[2]	≤ 17.5 EU/mL	<2.5	<2.5	<2.5
Sterility[2]	No growth	No growth	IP[3]	IP[3]

TR19 Clinical Batch Analysis

Impurity	$T_{1/2}$	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8
Tc-93m	43.5m	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Tc-93g	2.75h	16.4±0.7	7.7±0.8	27±2	22.5±0.7	4.1±0.2	9.9±0.4	3.7±0.2	35±2
Tc-94m	52m	<LOD	<LOD	220±20	140±18	71±9	87±9	110±10	<LOD
Tc-94g	4.88h	21.6±0.8	30±2	33±2	29±1	17.3±0.6	16.5±0.6	23±1	31±1
Tc-95m	61d	0.088±0.004	0.077±0.008	0.15±0.01	0.140±0.005	0.083±0.002	0.056±0.001	0.076±0.004	0.120±0.003
Tc-95g	20h	15.1±0.6	17.7±0.8	25±1	21±1	12.8±0.8	10.3±0.5	16.3±0.8	21.1±0.7
Tc-96m	51.5m	<LOD	<LOD	560±70	580±83	<LOD	<LOD	<LOD	<LOD
Tc-96g	4.28d	3.7±0.1	7.3±0.3	6.4±0.3	6.1±0.3	3.4±0.2	4.80±0.08	4.0±0.2	4.9±0.1
Tc-97m	91.4d	4.2±0.2	4.0±0.2	6.0±0.2	8.6±0.4	4.5±0.2	4.2±0.1	4.4±0.2	4.7±0.1
Mo-99*	65.9h	0.57±0.02	0.73±0.04	0.05±0.01	0.31±0.06	0.32±0.01	0.172±0.009	0.51±0.03	<LOD
Re-181	20h	2.0±0.2	<LOD	2.0±0.1	4.2±0.8	3.31±0.09	4.3±0.5	3.8±0.4	5.2±0.6
Re-182m	12.7h	2.3±0.1	0.77±0.09	3.4±0.4	5.7±0.4	5.3±0.5	4.3±0.3	3.1±0.3	5.3±0.5
Re-183	70d	0.024±0.001	0.018±0.001	0.056±0.001	0.072±0.003	0.043±0.002	0.054±0.002	0.046±0.002	0.086v0.002
Re-184	38d	0.005±0.001	0.004±0.001	0.008±0.001	0.018±0.008	0.012±0.001	0.013±0.001	0.017±0.001	0.026±0.001
Total (Bq/MBq)		**66±1**	**68±2**	**877±73**	**816±86**	**122±9**	**141±9**	**168±12**	**107±3**
Radionuclidic Purity (%)		**99.99**	**99.99**	**99.91**	**99.92**	**99.99**	**99.99**	**99.98**	**99.99**
QRT Ratio		**194**	**420**	**249**	**158**	**182**	**145**	**246**	**365**
Dose Increase (%) At expirey		**0.25**	**0.38**	**0.41**	**0.41**	**0.23**	**0.27**	**0.27**	**0.32**
Yield (GBq)		17.0	34.8	19.7	36.0	19.5	21.3	29.8	20.5

Impurities are in Bq/MBq of ^{99m}Tc. LOD is limit of detection

Summary

- Regulatory process well underway
  - Pre-CTA consultations with Health Canada
    - Issue: Tc-99m approved in Canada as a medical device
    - Overall sentiment: 2 small patient cohorts, data for 3 different kit formulations (cationic, anionic, neutral)
  - Current status: CTA and REB approvals in Vancouver, London; Hamilton on standby
  - 60 patient trial: 29/30 bone completed, 1/30 thyroid
  - Pre-NDS discussions underway
  - Full NDS submission anticipated end of 2016

Moving Forward…

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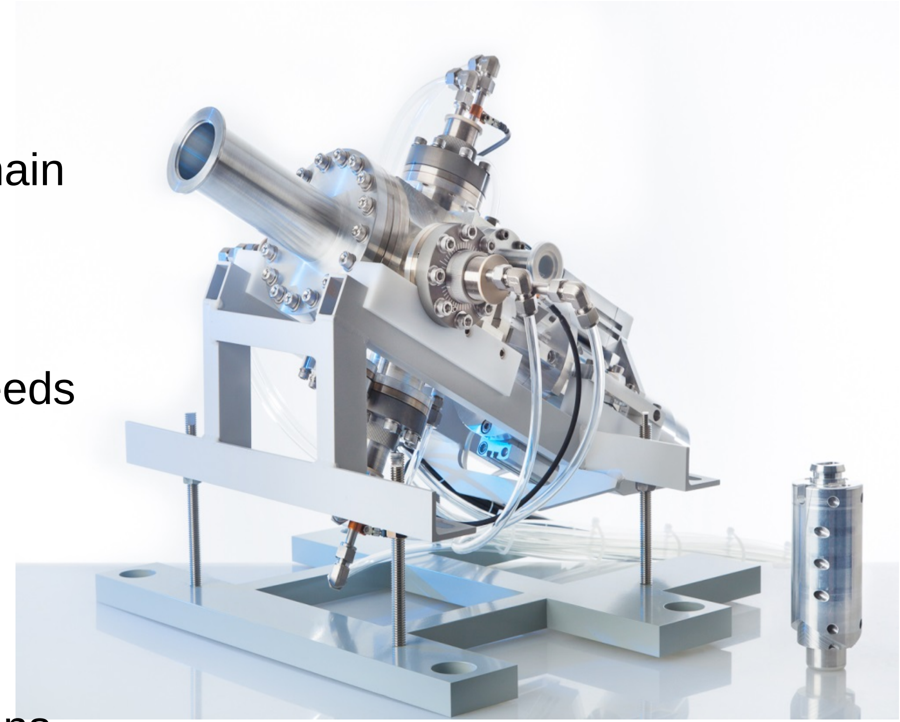
ARTMS Value Proposition

ARTMS™ Products Inc.

- Reliable, 'green' supply of ^{99m}Tc
  - Reduces reliance on HEU
  - Avoids single point of failure supply chain
- Supply independence and logistical compatibility
  - Local control, responsive to market needs
  - Well-suited for geographically concentrated patient populations
- Multiple revenue sources
- Competitive team, technology
  - Protected by multiple patent applications



ARTMS ^{99m}Tc Production System

Milestones and Deliverables

2009-2011	2012-2014	2015-2016	2017 +
R&D	Prototype and Testing	Clinical & Marketing	Approval and Sales

- Next 6 – 12 months:
  - Complete clinical trial in Canada and submit New Drug Submission
  - Obtain ISO 9001 certification and establish routine production capacity
  - Establish market development partnership with non-Cdn provider
- Next 12 – 24 months:
  - Establish OEM supply contract with global cyclotron manufacturer
  - Establish licencing/partnering arrangement in additional jurisdictions

Summary

- Regulatory
  - Nearing NDS submission
- Commercialization
  - Sole license issued to ARTMS Products Inc.
  - Advanced discussions underway with BC health service provider
  - ARTMS has nearly completed seed funding round, negotiations with first customer
- Emerging shift in ^{99m}Tc production
  - Reactor-based supply and processing likely to maintain sufficient capacity, next 2 years are critical
  - Several alternatives in development (n, p^+ and e^-/γ)
  - Full cost recovery must be implemented
    - Despite this, cyclotron produced Tc-99m is price competitive today

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  PIs: F. Bénard, T. Ruth, A. Celler, J. Valliant, M. Kovacs,

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- **Finances/Admin**
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Natural Resources Canada Ressources naturelles Canada

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TRIUMF

ARTMS™ Products Inc.

Thank you!
Merci!

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