Linear Accelerator Production of Mo99/Tc99m in Canada

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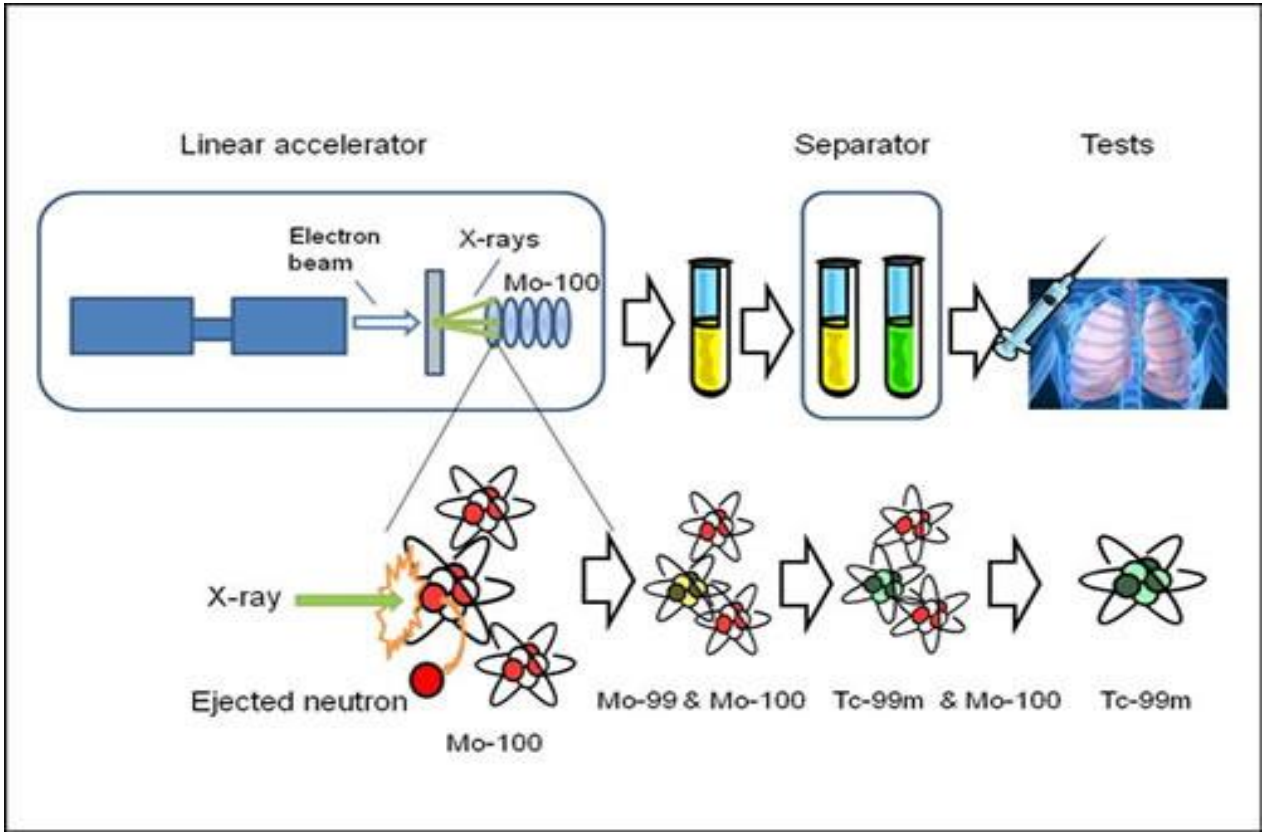
Linear Accelerator Process



Source: CLS

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PIPE Consortium

Partners

- Winnipeg Regional Health Authority/ Health Sciences Centre
- University of Winnipeg
- Acsion Industries

Collaborator/Contractors

- Canadian Light Source
- Mevex Corp
- MURR
- University Health Networks
- Thunder Bay Regional Hospital Research Centre
- NRC, Ottawa

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Objectives

To replace reactor technology with a cheaper, decentralized, more environmentally friendly, more secure supply of Mo99/Tc99m

Target Date – March 2016

PIPE Project

1. Accelerator (γ,n) and Reactor (n,γ) Production of Mo99
2. Mo99 processing & Tc99m generator extraction (quality Mo99 & Tc99m)
3. Radiopharmaceuticals and Evaluation
4. Cost and Recycling of Mo100
5. HC Regulatory Requirements
6. Business Model

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PIPE Funding

1. Non-Reactor Isotope Supply Program $4.5 million grant (2010-12), Natural Resources Canada. Total budget $8 million
2. Isotope Technology Acceleration Program $7.45 million loan (2012-2016), Natural Resources Canada. Total budget $11.7 million

NISP Funding Criteria 2010

- '.. most viable options for securing supplies of Tc-99m to the Canadian health system over the medium and long term'

Sustainable

- Viable for at least 15-20 yrs, and may begin producing in the short to medium time
- Meet a meaningful portion of the Canadian demand, but may or may not serve the U.S. or other markets
- Have a sound business model (± govt involvement)
- Be free of HEU because of non-proliferation

NISP Funding Criteria 2010

- '.. most viable options for securing supplies of Tc-99m to the Canadian health system over the medium and long term'

Secure

- Improve redundancy at all points in supply chain to avoid "single point of failure" of a linear supply chain;
- Diverse technologies to hedge against a failure
- Collocate irradiation and processing to minimize losses
- Ensure sufficient capacity for short-term outages of some sources.

Linear Accelerator - Advantages

- Electron linear accelerators are an existing technology, are generally simple and reliable to operate
- Photons produce fewer reaction channels, fewer undesired isotopes
- Technology doesn't need enriched uranium, there is minimal radioactive waste
- Accelerator licensing much easier than reactors (CNSC)
- Utilises current supply chain infrastructure for Mo99
- Geographical proximity to Canadian clients (reliability of supply and less decay loss)

Linear Accelerator - Challenges

- Power usage and target cooling – options are gas (helium) and water cooling
- 100Mo is only 9.6% in natural abundance, use of enriched 100Mo improves yield x10
- Established supply of enriched molybdenum-100
- Economics of enriched molybdenum-100; recycling is necessary
- Low-to-medium specific activity requires other technetium separation generator technologies

NISP 2010 Evaluation - LINAC

Pros	Cons
Technology: • The accelerator technology already exists and the power required is attainable with some development **Environmental:** • Generates minimal waste • Does not require enriched uranium **Regulatory:** • Licensing requirements for accelerators are significantly lower than for reactors **Benefits:** • A unique Canadian technology • Potential for creation of intellectual property and spin-off businesses	**Technology:** • Considerable R&D required to develop converter and targets to handle high power deposition • Substantial R&D for the target extraction, purification and recycling processes **Business:** • Cost of raw materials is high and could become prohibitive • New and less efficient generators would need to be manufactured; these may not be able to compete with the incumbents in the market, putting the business case at risk **Regulatory:** • Licensing of formulation kits could be onerous if the labelling yield and quality control tests are outside the monograph limits accepted by Health Canada • Licensing of a new type of generator

Summary Status PIPE Project

- Used a variety of accelerators/ product sources for technology development. Installed linear accelerator at CLS.
- Completed dissolution and extraction procedures for Mo99 targets
- Re-commissioned solvent generators - provided wealth of challenges and experience [Path = OLD > Refurbished > NEW]
- Consistently extracted pure Tc99m from Mo99 at >80% yields and successfully radiolabeled a range of radiopharmaceuticals
- Parallel-evaluated Mo99 from n,γ process (MURR), including radiopharmaceutical preparation
- Validated proof of concept recycling with <10% loss per cycle
- Held a pre-licensing meeting with Health Canada
- Renovated and licensed dedicated labs at containment level in Winnipeg (non-GMP)

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LINAC Mo99 Production

PROOF OF CONCEPT

Acsion Industries, MB
10MeV, 2kW, 2010/11
115km

Mevex Corp, ON
20MeV, 20kW, 2011
2050km

National Research Council, ON
35MeV, 2kW, 2011-13
2050km

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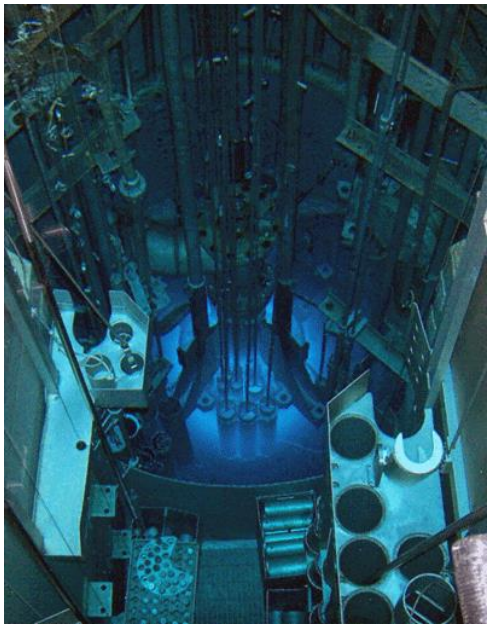
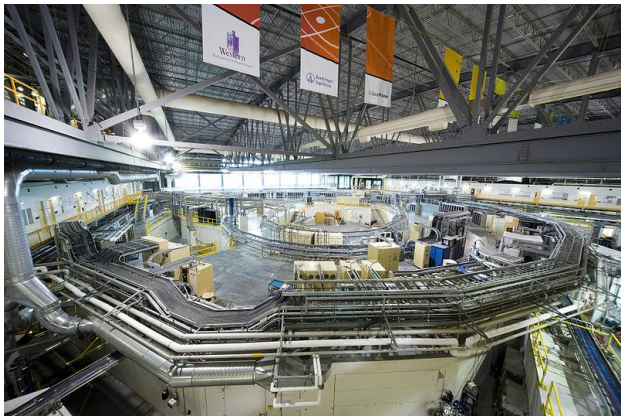
LINAC Mo99 Prodcution

MURR, MO
10MW, 2013-4
1500km

Canadian Light Source, SK
35MeV, 40kW, 2014-, 800km





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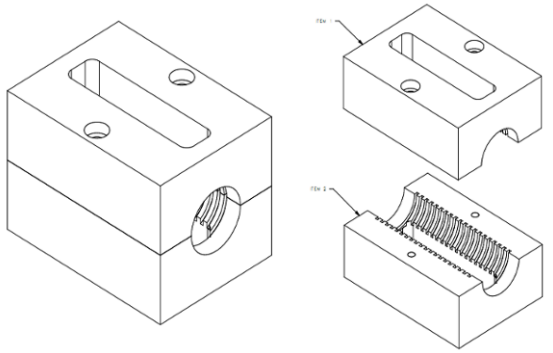
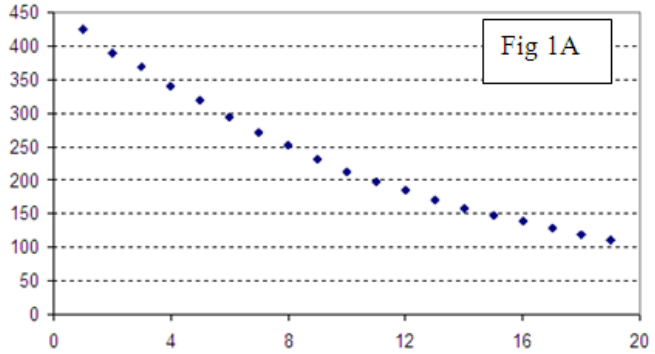
LINAC Mo99 Production

- Acsion Industries
  - <1 GBq
- NRC
  - 4-6 GBq
- MURR
  - 250 GBq
- CLS*
  - Up to 1850 GBq





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LINAC Mo99 Production

- CLS linear accelerator specifications
  - Max 35 MeV, 40 kW
  - To be operated at 20 MeV, 20 kW
  - Commissioned 2014
- Mo100(γ,n)Mo99 threshold 9.8 MeV
- Bremstrauhlung converter is tantalum
- Natural and enriched molybdenum targets have been used
- Targets are water cooled – radiolysis challenges

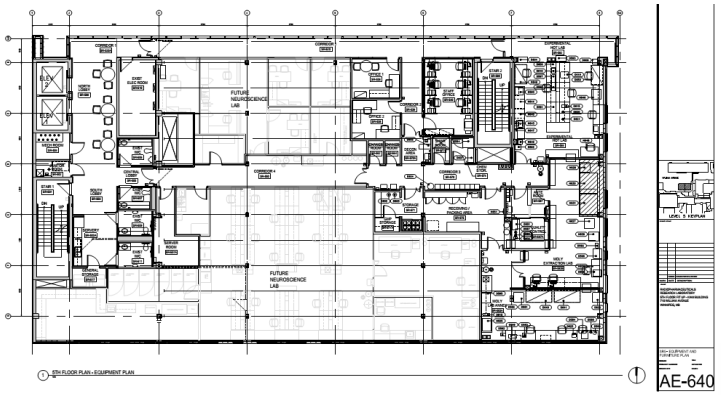
Reactor Mo98(n,γ)Mo99 Prod

- Relative yield compared to HEU (HEU efficiency is 100%)
  - Natural MoO_3 7.1%; Enriched (98%) MoO_3 29%; Natural metal Mo 23%; Enriched (98%) Mo metal 92% *(NEA/OECD 2010)*
- Amounts ordered by PIPE ~6Ci/ shipment, travel <24 hrs
- Low specific activity (0.2 - 1 Ci/g) similar to that of LINAC production – good surrogate in evaluation of generator technology. Fission sp activity 10^3-10^4 Ci/g
- Targets 25.4x1mm natural Mo discs

Molybdenum Processing

JBRC

KIAM



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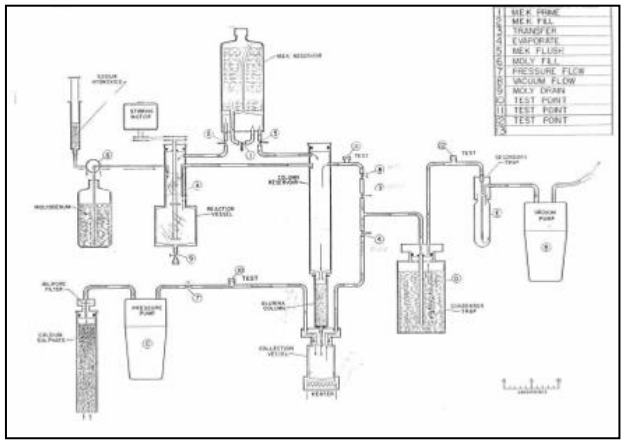
Molybdenum Processing

- Dissolution goal is within 1hr, then drying
- Tested solvents - HCl acid, HNO_3-H2SO4 acid, HNO_3 acid, HNO_3 + HF acid
- Studied influence of heating on dissolutions
- **Very efficient dissolution in 30% hydrogen peroxide**
- Final dissolution in 5M NaOH is instant
- Time limiting step is Mo drying (~ 1 hr) –important for H2O2 content

Mo99/Tc99m Solvent Generator

- Earlier models in used for 2 decades in Winnipeg with fission Mo99
- Automated, with scheduled run capability
- Fully self-shielded for Tc99m extraction
- MEK-5M NaOH separation, Tc99m is passed passing through an alumina column for final purification
- Tc99m product is terminally sterilized by filtration
- Complete operation, calibration and maintenance user manuals available

Mo99/Tc99m Solvent Generator



Mo-99/Tc-99m MEK extraction Generator at the Health Sciences

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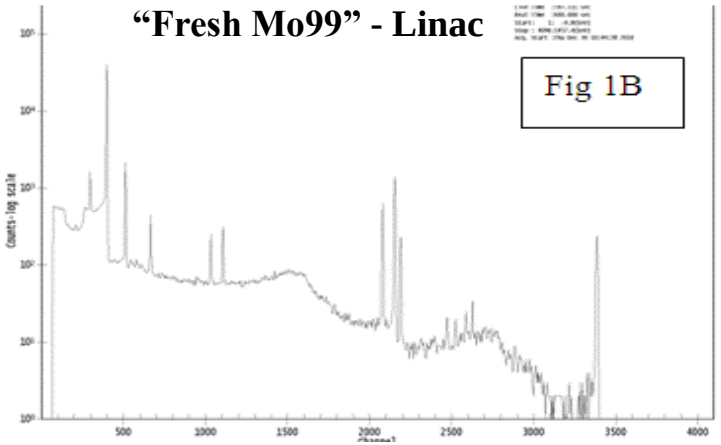
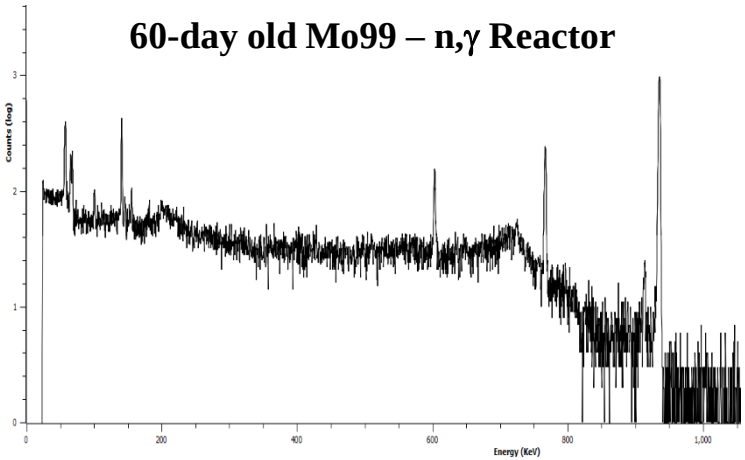
QC-Mo99-HPGe Spectroscopy





- Tc99m and Mo99m peaks in accelerator-enriched Mo100
- 60-day old accelerator Mo99 is decayed to background
- Long lived radionuclides in reactor Mo98(n,γ)Mo99 are Nb95 (765 KeV, 35d), Nb92 (934, 912 KeV, 10d), Ta182 (65, 68, 100, 1121,1221 KeV, 114d)

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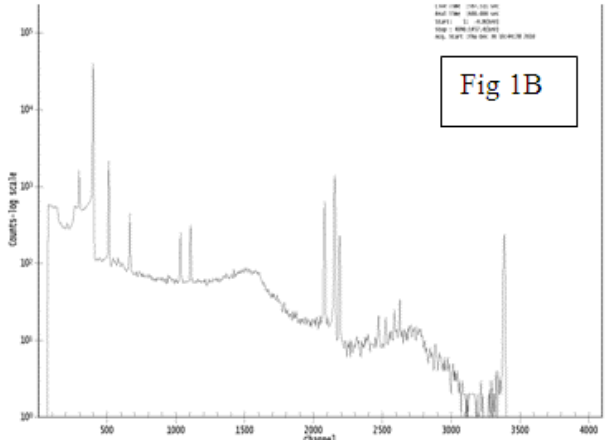
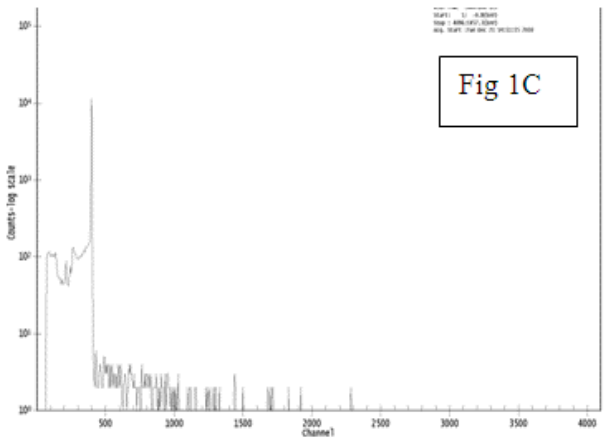
QC-Tc99m-HPGe Spectroscopy





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QC-Tc99m-Other Tests

- Molybdenum breakthrough (both radionuclidic and chemical –ICP spectrometry)
- Radionuclidic purity (HPGe spectroscopy)
- pH
- MEK solvent content
- Alumina breakthrough (chemical)

Tc99m Radiopharmaceuticals

- Tc99m-Sestamibi
- Tc99m-Macroaggregated Albumin
- Tc99m-MDP
- Tc99m-DTPA
- Tc99m-Sulphur Colloid

- Pharmacopeial QC testing parameters and standards
- Performed stability studies 0 hr, 2 hr, 4hr and 24 hr

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Upcoming PIPE Milestones

- Operational CLS linear accelerator and supply of Mo99 - 2014
  - Optimize yields, troubleshoot
- Commission automated target handling and process
- Separate stream for Mo99/Tc99m from n,γ technology
- Perform animal SPECT-CT studies and human clinical trials
- Complete centralized GMP-compliant processing and distribution facility in Winnipeg
- Optimize 100Mo target recycling and logistics
- Develop appropriate end-user generator technology*
- Provide a complete, scalable accelerator business model, including equipment, facilities, logistics and licensed product

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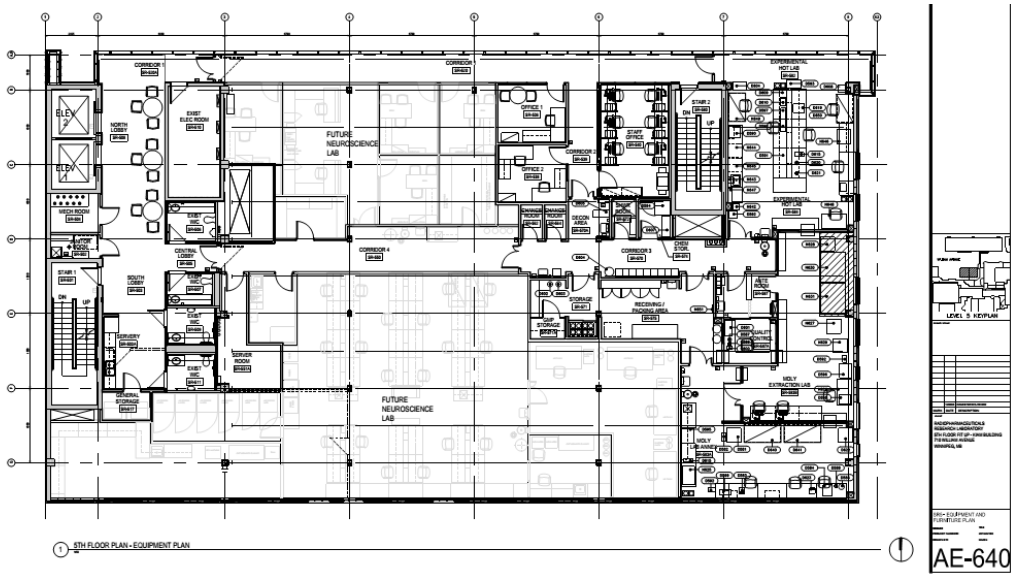

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