Producing Medical Isotopes with Electron Linacs

Presentation to
2015 CAP Congress

By

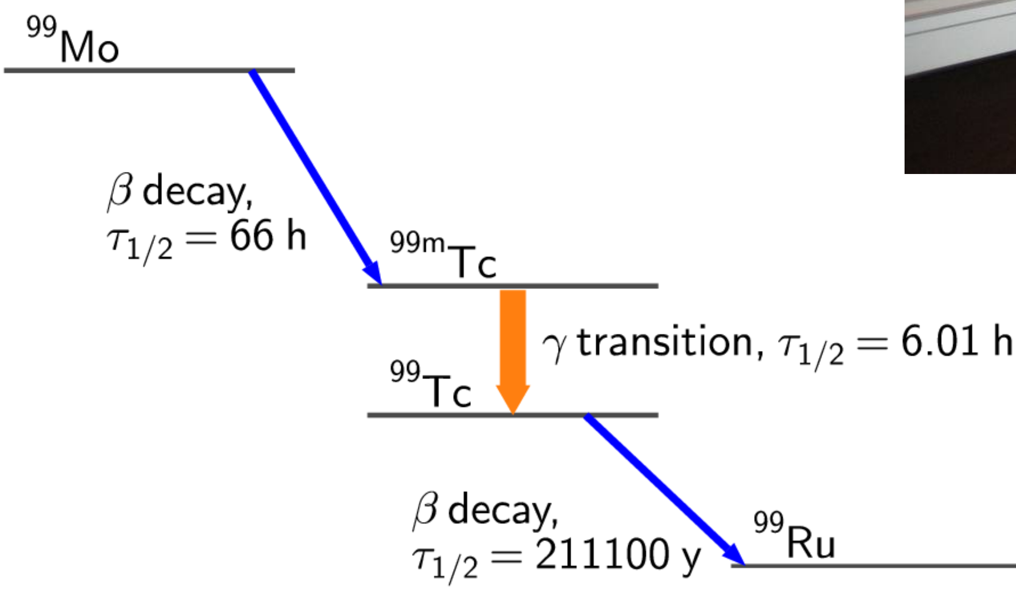
Mark de Jong (Canadian Light Source Inc.)
2015 June 16

Canadian Light Source Centre canadien de rayonnement synchrotron | Ten Years of Discovery

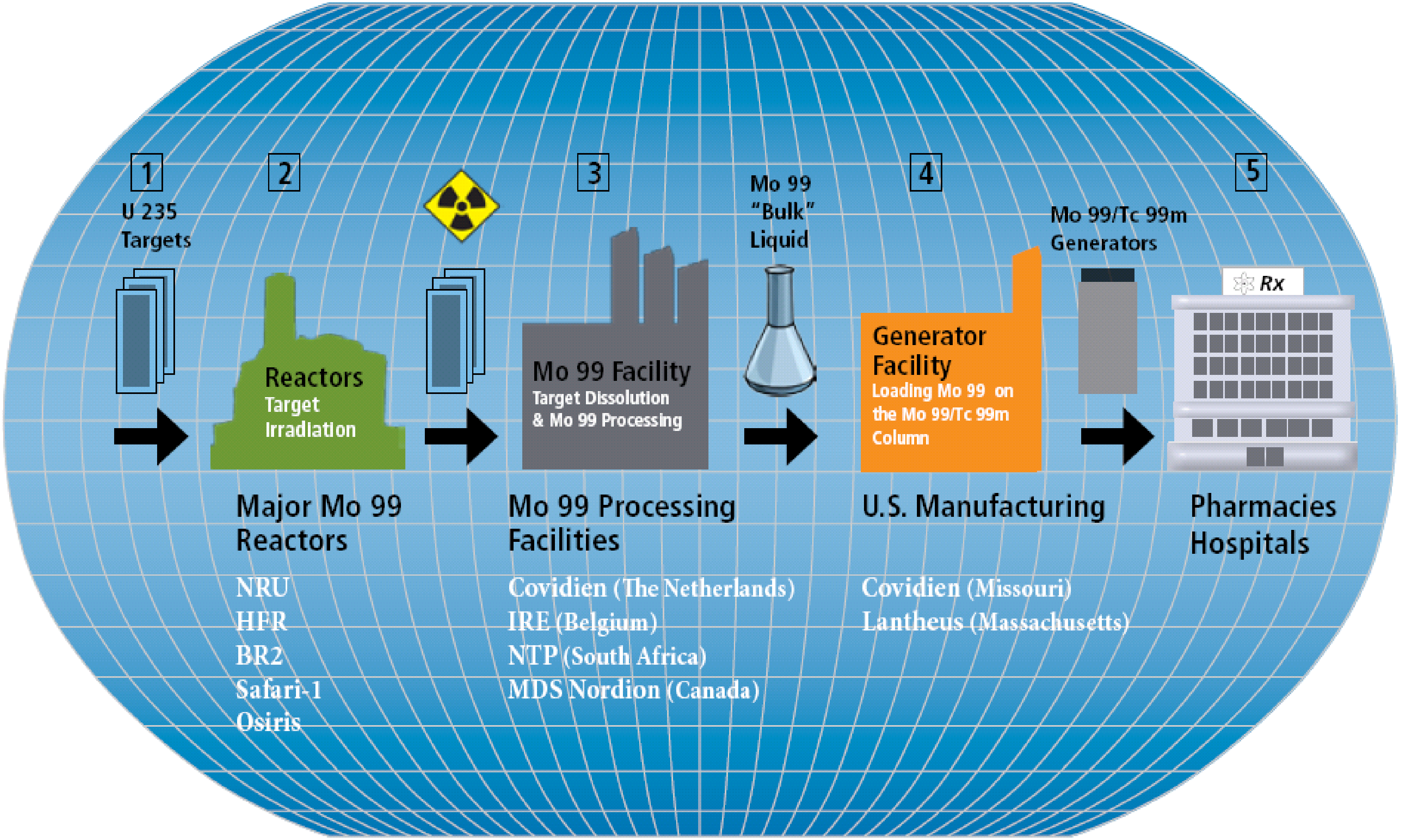
The Goal: ^{99m}Tc

^{99m}Tc:

- 140 keV γ-ray, 6 hr half life
- Used for ~80 % of nuclear medicine diagnostic imaging
- Canada – about 5500 procedures per day



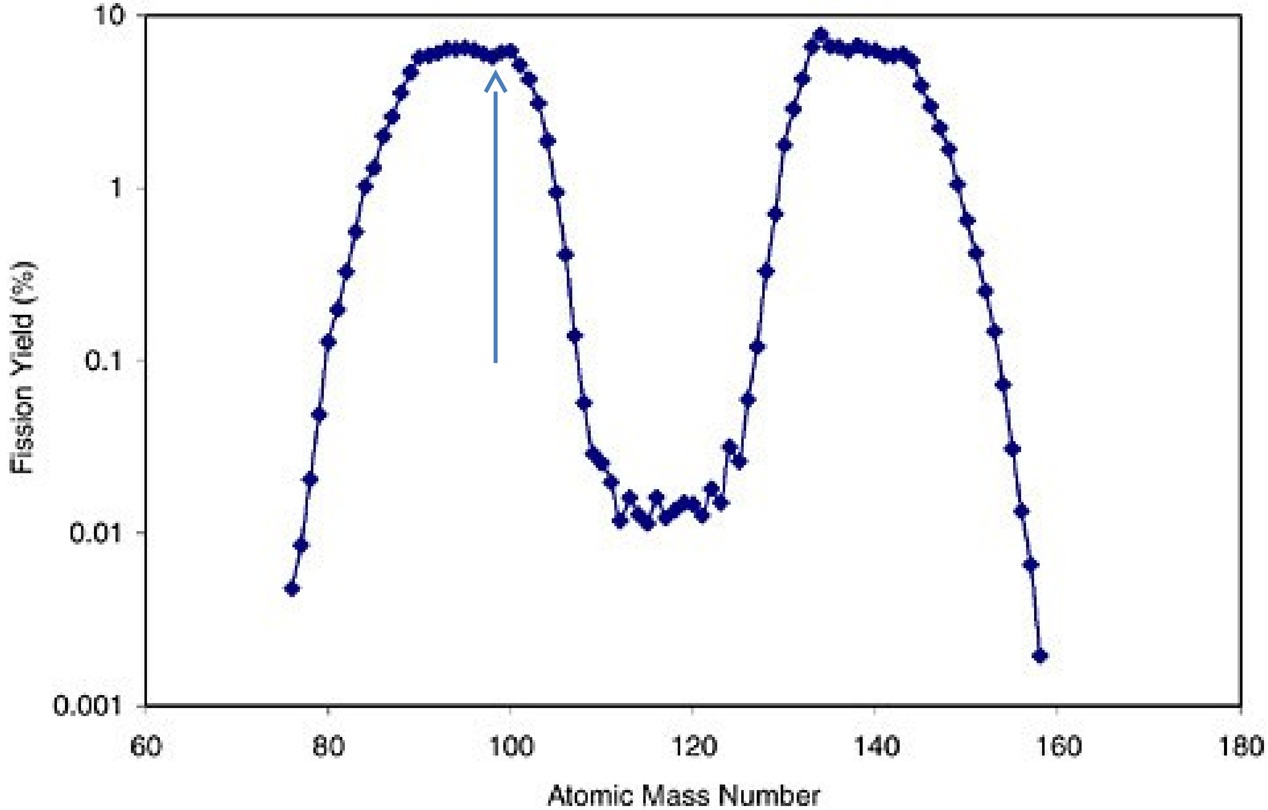
Current Production Method



Current Production Method

Mo-99 via U-235 fission:

- Mo-99 at peak of fission mass distribution
- ~ 6 % of fissions yield Mo-99
- Half life of 66 hrs



Issues with Current Production Method

- Major production reactors are old, with growing availability issues
  - No shut-down should be longer than 4 days!
  - Two major shut-downs at NRU, and similar issues at HFR
  - NRU scheduled for permanent shut-down in 2018

- Most current production uses highly enriched ^{235}U (HEU)
  - Nuclear proliferation concerns
  - Significant on-going “consumption” of HEU
  - Significant accumulation of high-level fission waste

- Conversion to LEU an option but:
  - Lower efficiency
  - More waste
  - Significant cost increase likely

- Major producing countries (e.g., Canada and Netherlands) not willing to continue to subsidize production for use in other countries

NRCan NISP Program for Accelerator Production ^{99}Mo / ^{99m}Tc

- Non-reactor-based Isotope Supply Program (NISP)
  - announced 2010 June 2 – ended 2012 March 31
  - $35M total funds available
  - Demonstrate feasibility of “commercial-scale” production
  - Two approaches funded:
    - Proton cyclotron production of ^{99m}Tc using ^{100}Mo(p, 2n)
    - Electron linac production of ^{99}Mo using ^{100}Mo(γ, n)

- Four projects funded:
  - two cyclotron-based:
    - ACSI + U of Alberta + U of Sherbrooke
    - TRIUMF/UBC + BC Cancer Agency + Lawson Health Research Institute (U Western Ontario) + CPDC (McMaster U)
  - two linac-based
    - Canadian Light Source Inc. (U of Saskatchewan) + NRC (Ottawa, Montreal)
    - Prairie Isotope Production Enterprise (PIPE)
      - Winnipeg Regional Health Authority + Acsion Industries + U of Winnipeg

NRCan ITAP Program for Accelerator Production ^{99}Mo / ^{99m}Tc

- Isotope Technology Acceleration Program (ITAP)
    - announced 2012 June – ends 2016 March 31
    - $25M total funds available to cover up to 65% of expenses
    - Secure Health Canada approval of accelerator-sourced ^{99m}Tc
    - Two approaches funded:
        - Proton cyclotron production of ^{99m}Tc using ^{100}Mo(p, 2n)
        - Electron linac production of ^{99}Mo using ^{100}Mo(γ, n)

- Three projects funded:
    - two cyclotron-based
        - ACSI
        - TRIUMF
    - one linac-based
        - PIPE with CLSI linac production support

Linac Project Team

- Canadian Light Source Inc.
- National Research Council (NRC)
- Winnipeg Health Sciences Centre
- Acsion Industries Ltd.
- University of Winnipeg

- With support from:
  - Mevex Corp.
  - University of Ottawa Heart Institute
  - NorthStar Medical Radioisotopes LLC
  - University Health Network (U of Toronto)

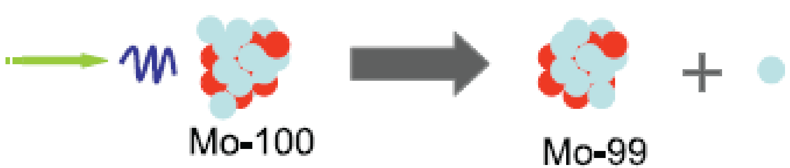
- Project Funding:
  - Natural Resources Canada (NRCan) – NISP and ITAP
  - Province of Saskatchewan – Crown Investment Corp.
  - Project Team members

Linac Production of ^{99}Mo

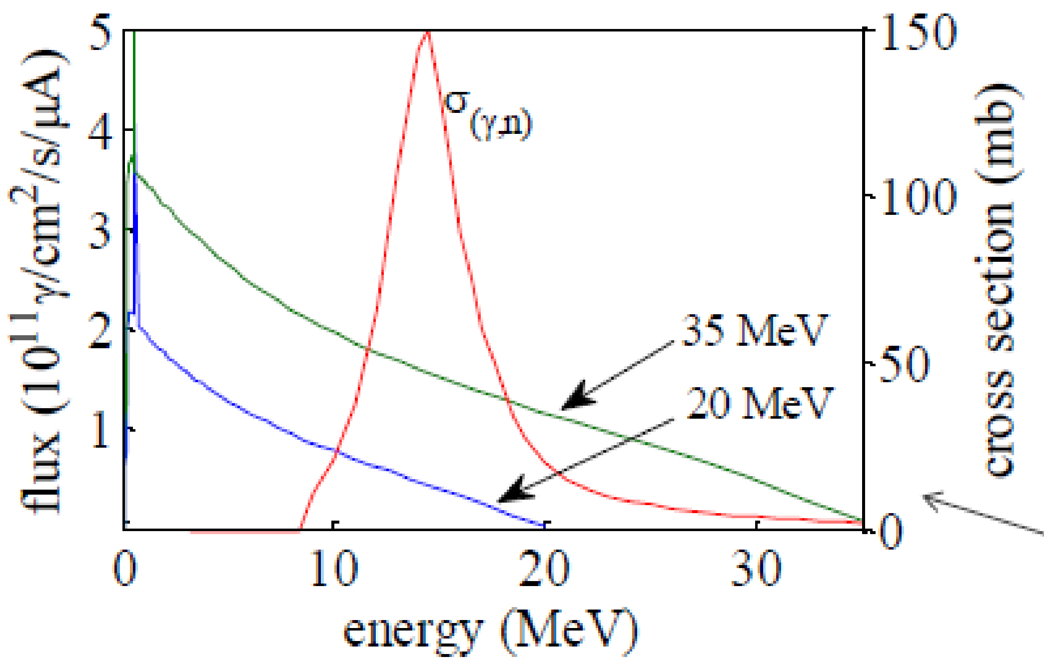
- Photo-nuclear reaction on ^{100}Mo:
  - $^{100}Mo\ (\gamma, n)\ ^{99}Mo$

- Natural Mo is 9.63% ^{100}Mo
- Available with enrichments of > 95 %
- Known for more than 40 years
- Photons produced via

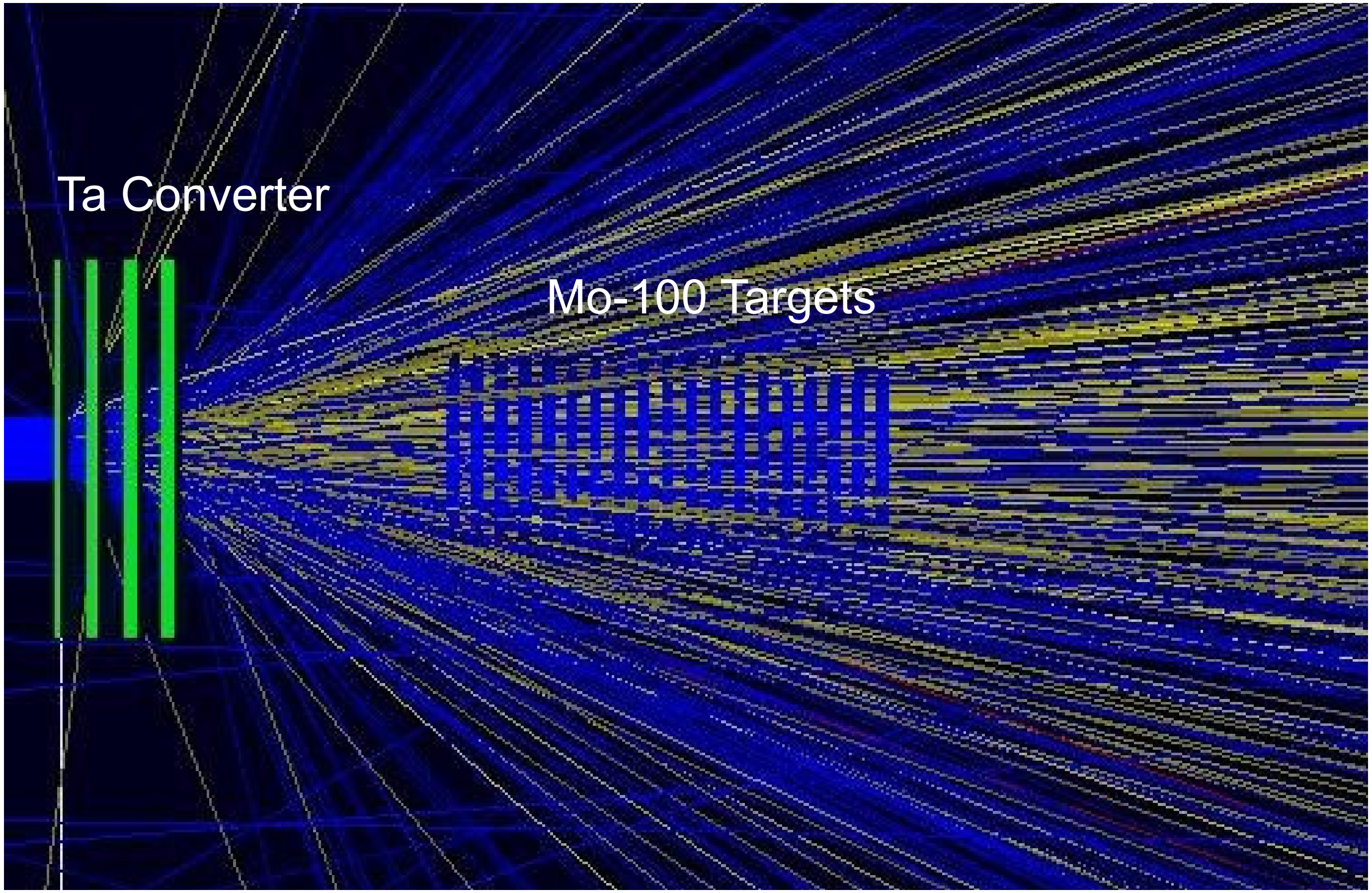
Bremsstrahlung using high-energy electrons from linear accelerator ⇨ high-energy X-rays



Exploit "giant dipole resonance" around 15 MeV in most heavy nuclei



Photon Shower (EGS++)



Electrons and photons above 14 MeV shown

Why Electron Linacs?

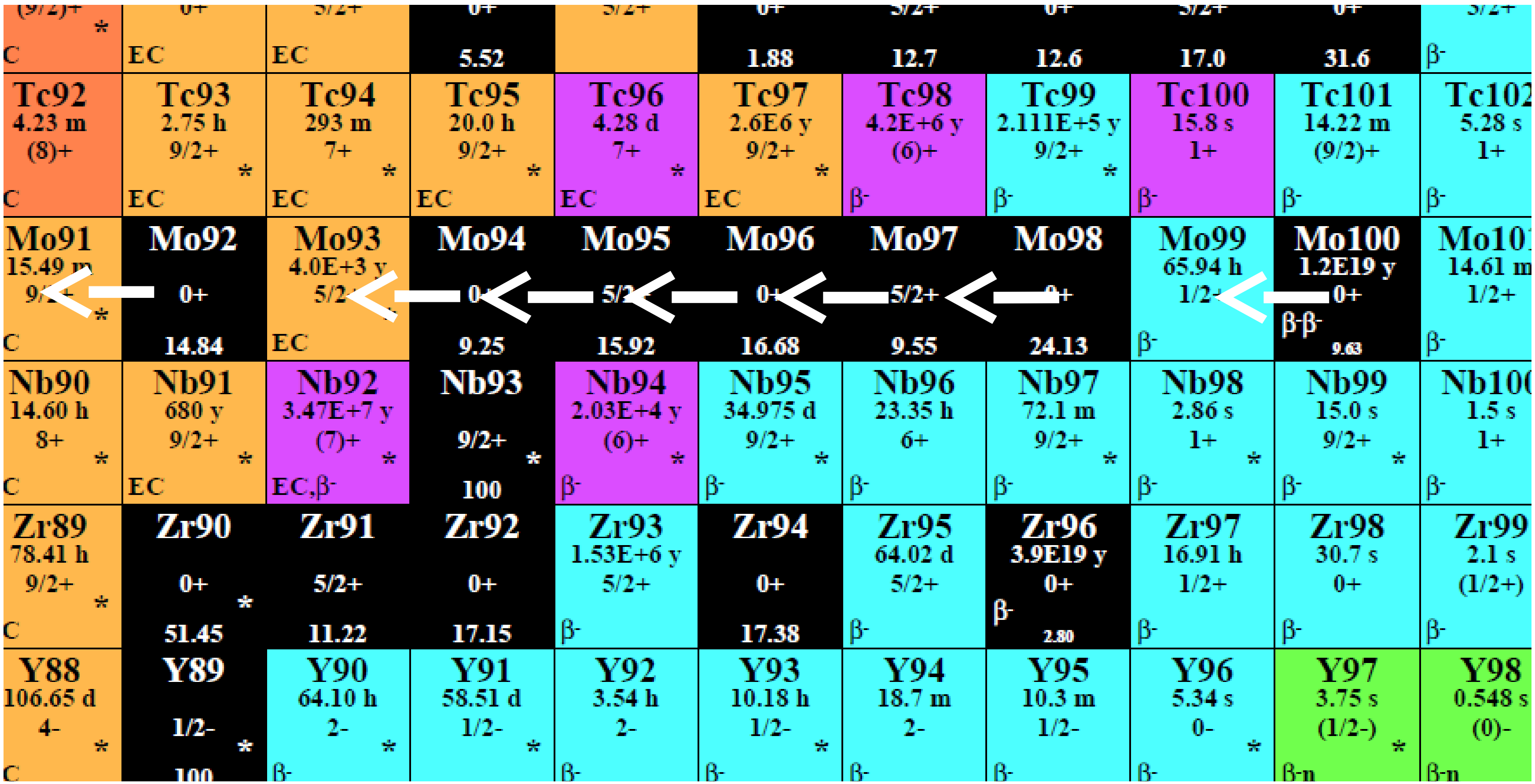
- Disadvantages:
  - Lower cross-sections (electromagnetic vs nuclear interactions)
  - Fewer reaction channels, especially for positron emitters
  - More difficult to make carrier-free radio-isotopes

- Advantages:
  - Photons are more penetrating => thicker targets, windows
  - Photons are "cheap"
  - Electron linacs are generally simpler and more reliable (compared to cyclotrons)
  - Fewer reaction channels
    - Fewer undesired isotopes
    - Less radioactive waste

- Relatively unexplored option!
  - Few low-energy research electron linacs still operating
  - Most are low current / power except for industrial linacs below 10 MeV

Reaction Channels

- Arrows show (γ, n) reactions on Mo isotopes
- (γ, p) produces Nb isotopes which decay to Mo

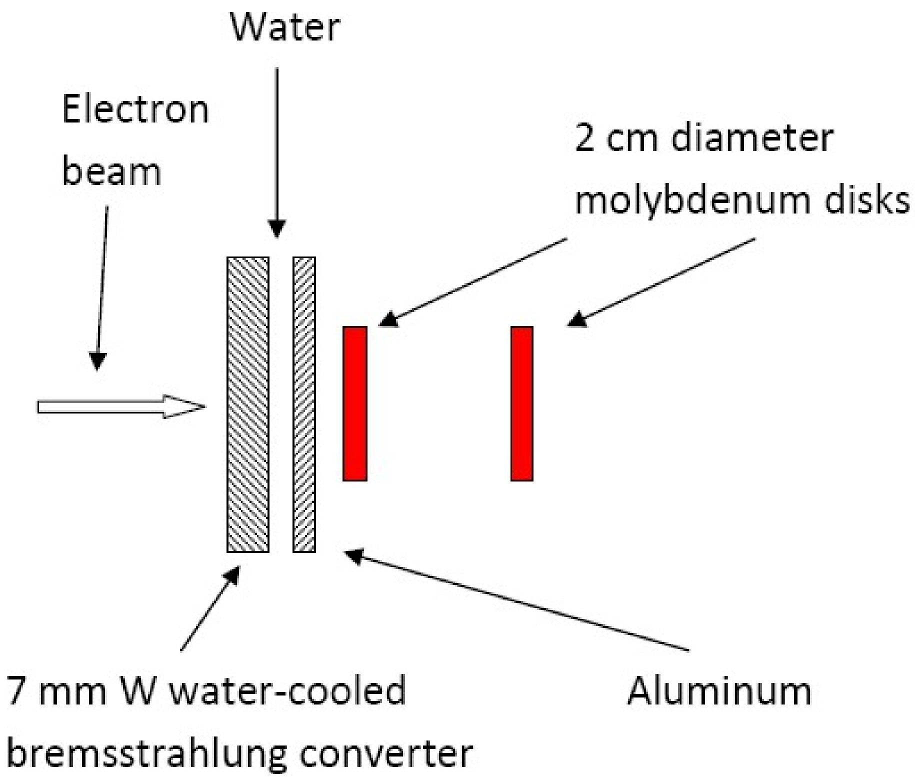


Linac Project Scope - 1

- Develop a fabrication method for ^{100}Mo targets (NRC and Acsion)
- Low-power testing (< 2 kW) of ^{100}Mo target to validate production yield estimates (done at NRC in Ottawa)
  - Evaluate the quality of the ^{99}Mo produced and the ^{99m}Tc separation process, performed by Radiopharmaceutical Research Group at HSC
- Development of a suitable recycling process to recover the ^{100}Mo after irradiation and ^{99m}Tc separation for future targets (NRC and Acsion)

NRC (Ottawa) - INMS

-Proof-of-concept work using 35 MeV, 3 kW linac at INMS



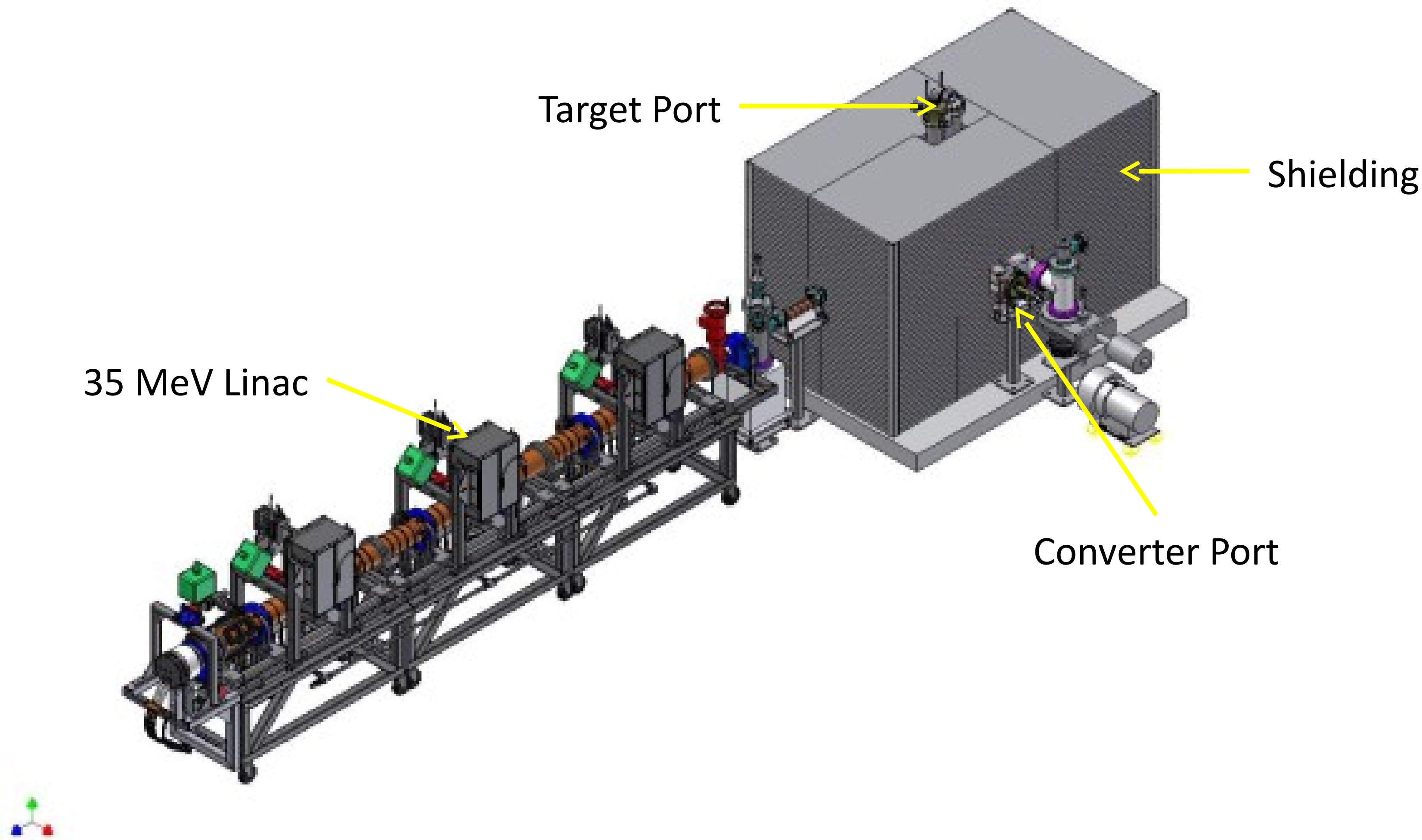
Linac Project Scope - 2

- Install 35 MeV, 40 kW, linac in an existing underground experimental hall at CLS
  - Linac based on industrial high-power systems developed by Mevex
  - Design & build bremsstrahlung converter and Mo target system
    - must handle > 30 kW beam power
    - design remote handling system for loading shipping casks

- Develop nuclear substance laboratory for target manufacture and recycling production facility for ^{100}Mo targets
    - Targets are sintered disks of molybdenum metal powder
    - 15 mm dia x 1 mm thick, ~ 85 – 90 % maximum density
    - ^{100}Mo is ~95 – 97% enrichment, primarily for yield

- Irradiated targets are shipped to Winnipeg HSC for ^{99}Mo dissolution and ^{99m}Tc extraction
    - HSC takes the lead on preparation of NDA for linac-sourced ^{99m}Tc to submit for Health Canada approval

Isotope Linac and Target Assembly

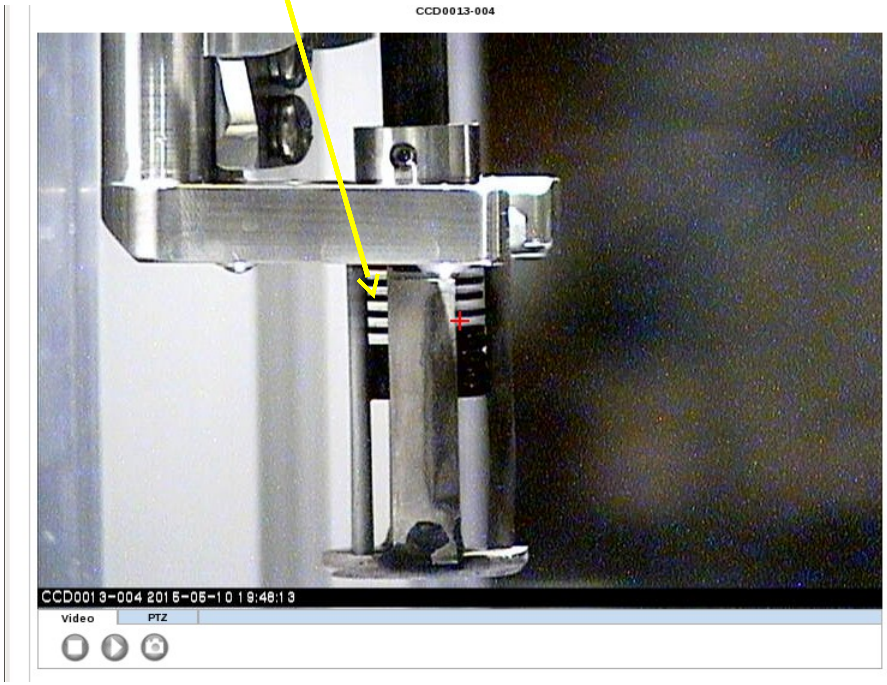


Linac Isotope Production Facility

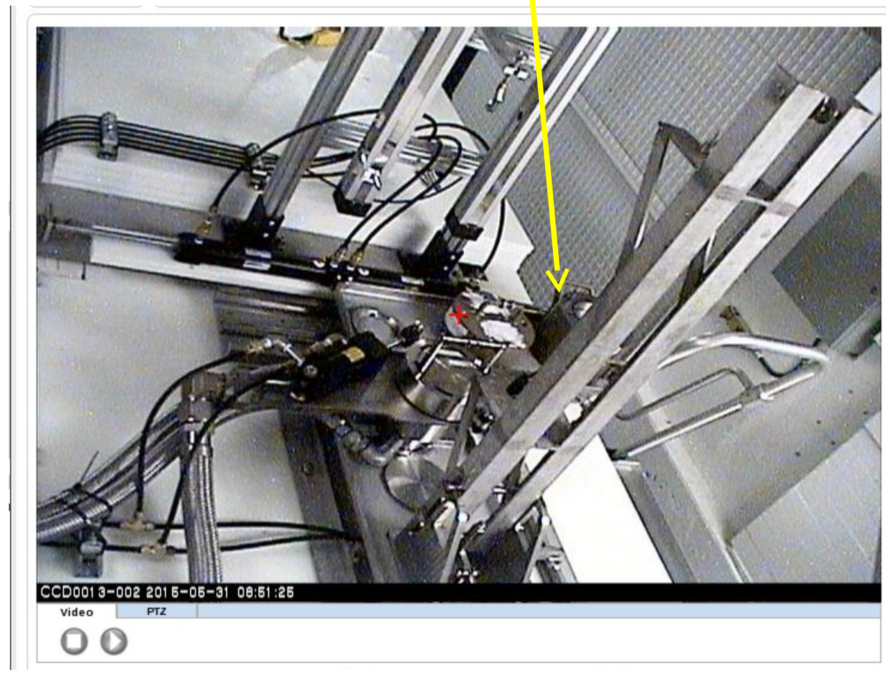
Targets and Remote Handling

Mo target disks

Shipping Cask



Target Holder with 9 disks



Remote handling facility

LINAC ^{99}Mo Shipment

The Medical Isotope Project's particle accelerator shoots high-energy X-rays at molybdenum-100, seen here. The X-rays knock out a neutron to create molybdenum-99, which decays into the medically useful isotope technetium-99m. (David Stobbe / Stobbe Photography)

^{99}Mo Processing

- Dissolution goal is within 1hr, then drying
- Tested solvents - HCl acid, HNO_3-H_2SO_4 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 H_2O_2 content

Mo99/Tc99m Separation Generator

- Earlier models in used for 2 decades in Winnipeg with fission Mo99
- MEK-5M NaOH separation
- Automated, programmable for scheduled runs
- Fully self-shielded up to 250GBq
- Tc99m is passed through alumina column for final purification
- Tc99m product is terminally sterilized by filtration
- Complete operation, calibration and maintenance user manuals available

^{99}Mo/^{99m}Tc Separation Generator

J Radioanal Nucl Chem

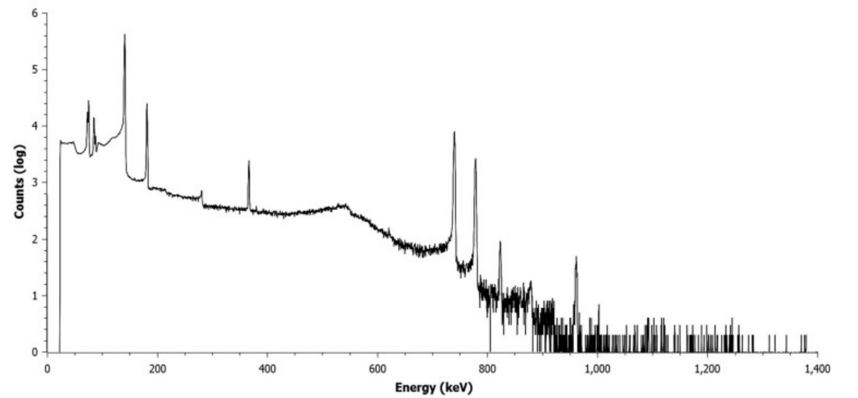


Fig. 2 HPGe spectrum obtained for irradiated enriched ^{100}Mo disks. The spectrum shows peaks attributable only to ^{99}Mo (peaks at 140, 180, 366, 739, 777, 822 and 960 keV)

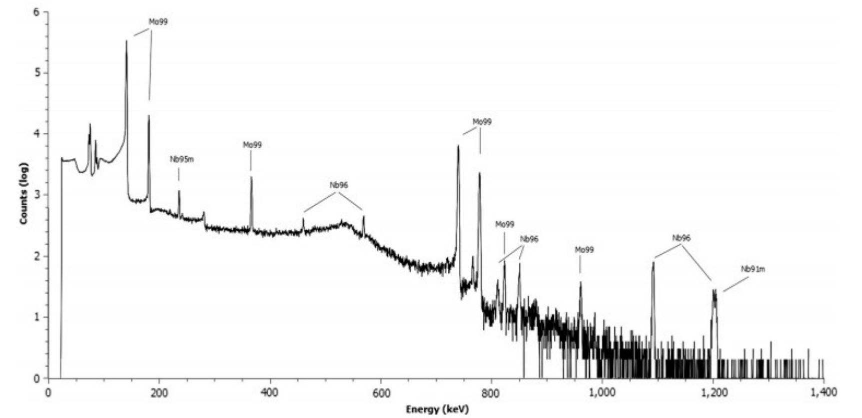


Fig. 3 HPGe spectrum obtained for irradiated natural molybdenum disks at 15 days. The spectrum shows peaks attributable to ^{99}Mo (at 140, 180, 366, 739, 777, 822 and 960 keV) as well as impurity peaks of ^{91m}Nb, ^{92m}Nb, Nb and ^{95m}Nb ($t_{1/2}$ = 60.86 days, 10.15 days, 86.6 h, 35.15 days, respectively)

J Radioanal Nucl Chem

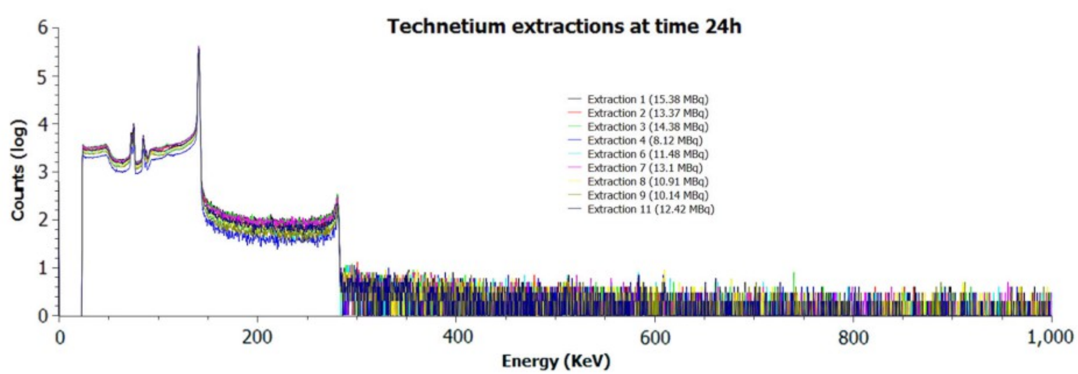
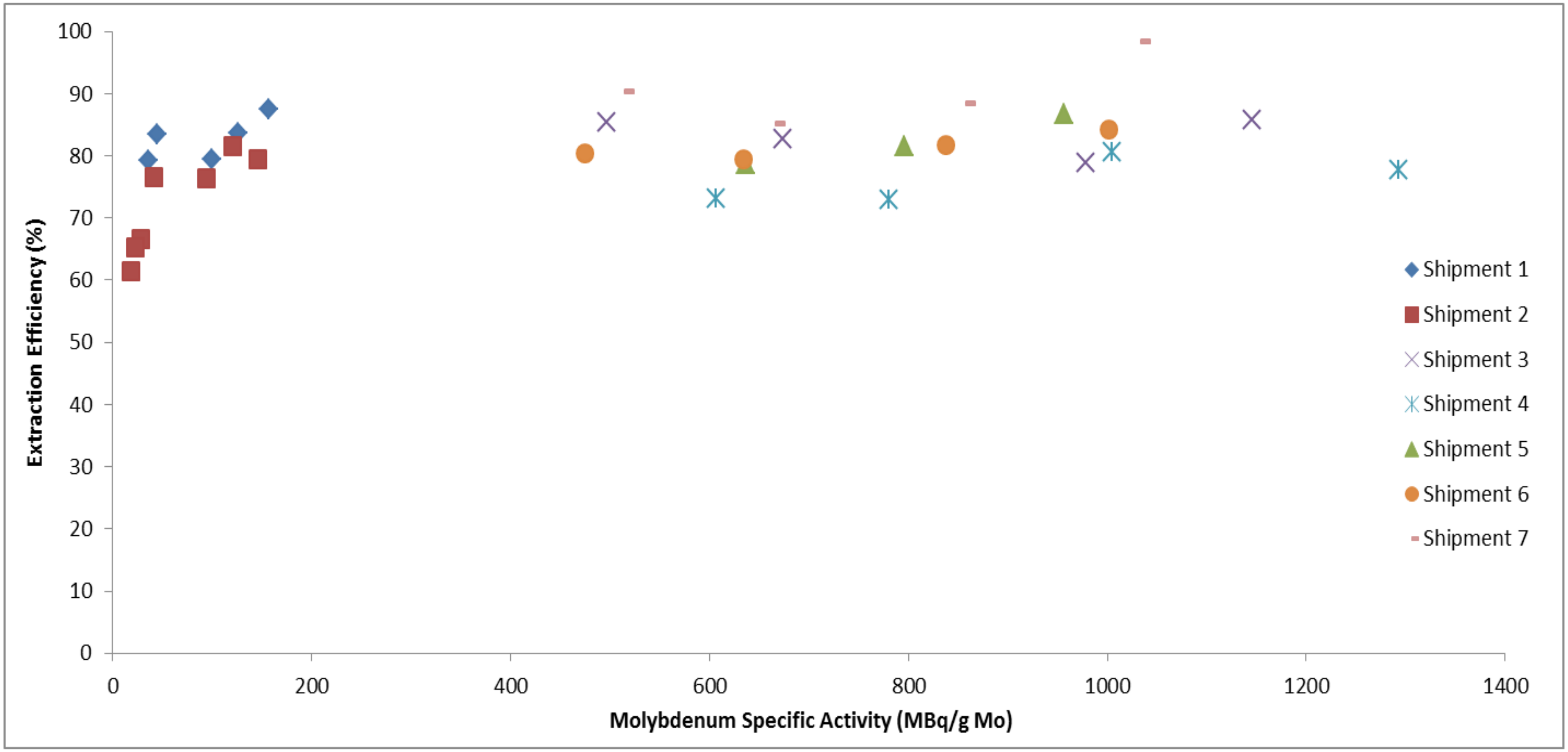


Fig. 4 Spectra obtained for the ^{99m}Tc-pertechnetate from the solvent generator. Only peaks attributable to ^{99m}Tc are seen, ^{99m}Tc radionuclidic purity even after 24 h (when longer-lived impurities would have shown increased prominence)

Extraction Efficiency vs Specific Activity



Evaluations and Licensing

- Radiopharmaceuticals prepared:
  - Tc99m-Pertechnetate
  - Tc99m-MDP
  - Tc99m-Sestamibi
  - Tc99m-DTPA
  - Tc99m-Tetrofosmin*
- Pharmacopeial QC testing parameters and standards
- Stability studies over the useful life of radiopharmaceutical as per product monograph, up to 24 hr

Summary Licensing

- **LINAC-sourced, solvent generator separated Tc99m sodium pertechnetate meets USP requirements for comparable SA neutron-capture produced Tc99m**

- **Solvent generator separated Tc99m sodium pertechnetate meets USP specifications for impurities MEK**

Current Status

- Started linac operations in August 2014
  - Trial irradiations from October 2014 through February 2015
    - 6 natural molybdenum disks in each trial
    - **3.5 GBq** and **2.83 GBq** (~48 h at 10 kW)
    - **1.86 GBq** (~24 h at 10 kW)
    - All measurements in Winnipeg at ~36 h after EOB
  - Weekly shipments since mid-April 2015
    - 9 natural molybdenum disks, 72h at 15 kW
    - **21.9 ± 1.2 GBq** delivered per run ⇨ **34.0 GBq average at EOB**
    - All measurements in Winnipeg at ~40 h after EOB
  - Plan to switch to ^{100}Mo targets in July 2015
    - ~100 to 300 GBq per shipment using ^{100}Mo targets
- Ultimately, production will be sufficient to support the provinces of Manitoba and Saskatchewan (population ~2.25M)

Future Plans

- Perform animal SPECT-CT studies and clinical trials to support Health Canada approval
- Complete new GMP-compliant processing and distribution facility in Winnipeg
- Optimize the ^{100}Mo target recycling and logistics
- Examine commercial feasibility of national production using two to four 100kW electron linacs, each with multiple target stations
- Explore production possibility for other isotopes
- Explore international commercial opportunities for technology