Production and Supplies of ^{99}Mo: Lessons Learnt and New Options within Research Reactors and Neutron Sources Community

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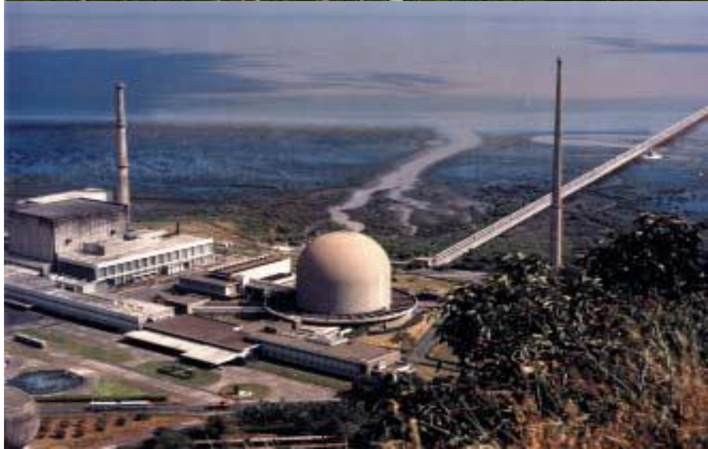


Outline of Presentation

- Importance of ^{99m}Tc and ^{99}Mo
- Fission moly industry: appreciation, challenges
- ^{99}Mo supply crisis – lessons (+ NEA findings)
- Alternate technologies to access ^{99}Mo
- Alternate separation methods to avail ^{99m}Tc
- MS interest in ^{99m}Tc and the IAEA support
- **Way forward**: some *personal* thoughts

Discovery of ^{99m}Tc generator, BNL, 1957

IAEA

Atoms for Peace: The First Half Century

1957–2007

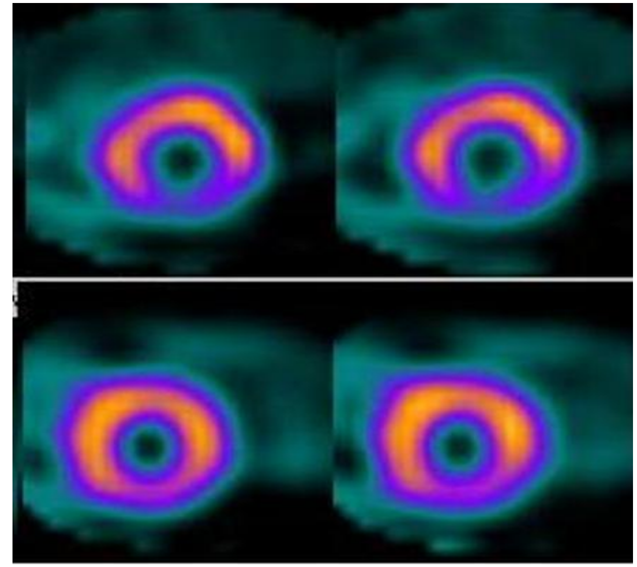
High Importance of ^{99m}Tc (6h) and ^{99}Mo (66h)

- Diagnostic imaging in nuclear medicine (NM) and ^{99m}Tc are synonymous over ~40 years.
- 90% of all NM studies involve such imaging; >80% use ^{99m}Tc, >**30 million studies per year** – ***1 study/sec*** (^{18}F ~10%; rest all 10%)
- ^{99m}Tc nuclear characteristics ($E\gamma$ 140.5 keV, 6 h) fit exceptionally well the imaging & dosimetry requirements.
- Versatile chemistry of Tc + multi-disciplinary synergy → specific products for imaging
- Easy, economic availability (until 2008)
- ^{99}Mo-^{99m}Tc generator for ^{99m}Tc supplies; gold-standard generator uses **fission-produced ^{99}Mo** (10^4Ci/g; 95% from HEU; stringent limits on RN impurities)

Major Applications of ^{99m}Tc Imaging

- imaging of (i) myocardial perfusion (cardiac patients) and (ii) bone mets (cancer patients)
- *other important uses*: SLND in breast cancer patients; prosthesis infection imaging in patients with joint replacement; renal function

^{99m}Tc reigning queen of radiopharmaceutical in NM → (fission) ^{99}Mo the queen mother!



Production of fission-produced ^{99}Mo (*fission moly*)

- worldwide requirement: ~12000 Ci (6-day Ci) per week (450-500 TBq) → 80-100 kCi at EOI
- 4 industrial producers, in Belgium, Canada, The Netherlands, South Africa, using 5 *aged* reactors, meet most of the world demands; 5th producer ANSTO uses the new OPAL reactor (*can produce more, if …*)
- a few other producers: ARG, IND, RF, … (PAK, EGY)
- ^{99}Mo shipped around the world every week, throughout the year. ^{99}Mo-^{99m}Tc generator manufacturers are there all over the world.

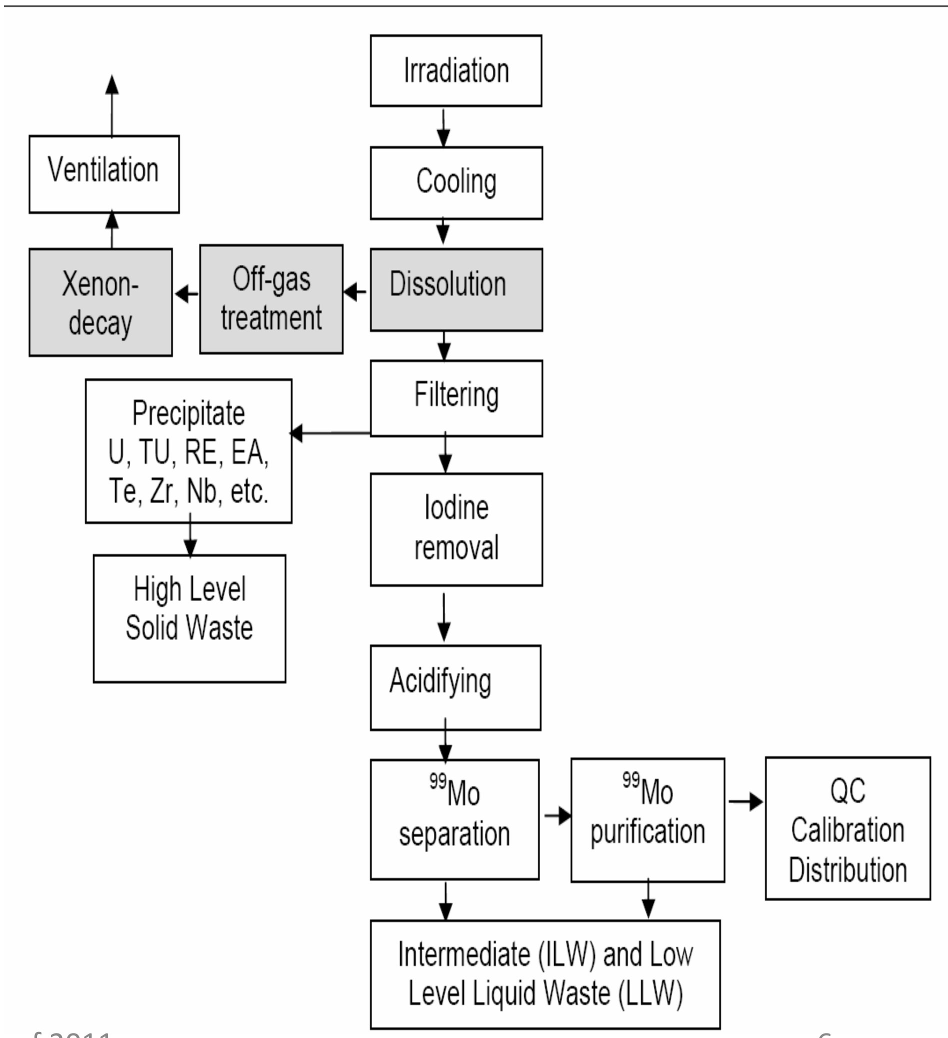
Fission-Moly Production: Salutations to Technology Developers & Industries

- 80-100 kCi ^{99}Mo/w of 10^4-10^3 Ci/g → ~50 g Mo/w; i.e. 2.5kg Mo/y!
- **since 1980: >50kg ^{99}Mo!**
- waste activity:60-100X
- U targets - irradiation in RR
- BNL: acid dissolution & alumina + (AECL-MDSN, Canada); ANL scheme (LEU)
- KFK: alkali dissolution & chelex ion-exchange + wide use: Covidien; IRE; NTP.

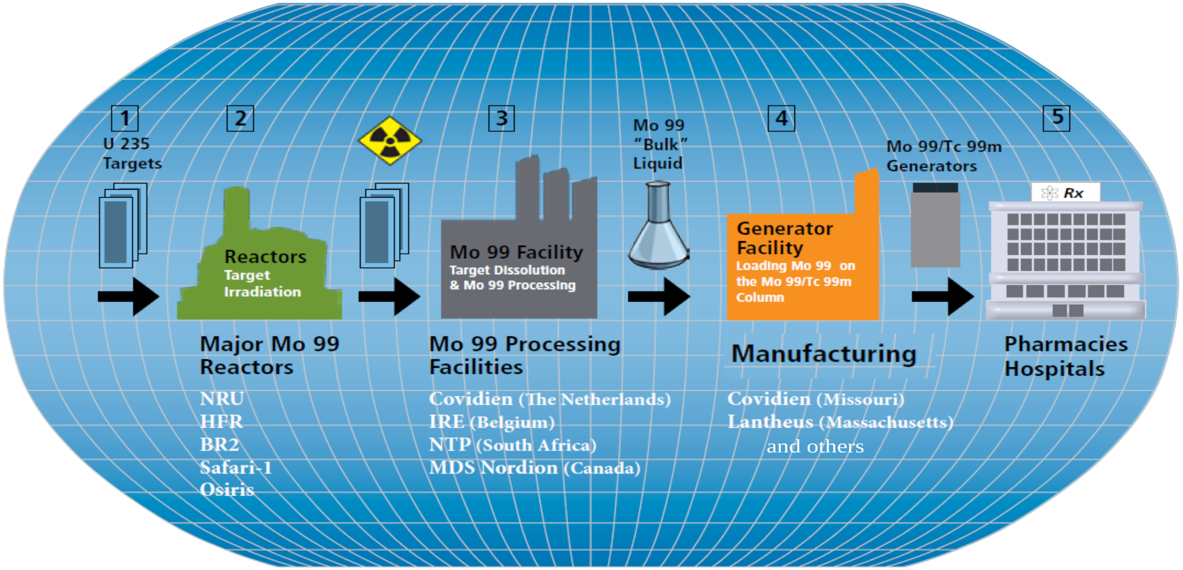
- CNEA-INVAP, Argentina

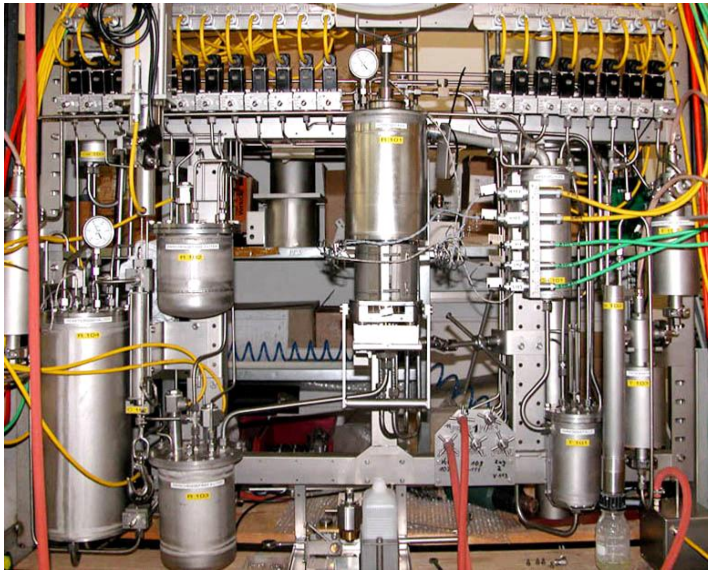
- ANSTO & EAEA (INVAP process)

- ROMOL of ITD - GSG: $NaOH+NaNO_3$ (PINSTECH; D'grad-RF)



Complex chain of ^{99}Mo/^{99m}Tc supplies & stages





- ^{99}Mo consignments: Recipients - generator producers (large 10-20; others 50-80) in several countries; use within 8-20 hours

- corporate entities, e.g. Lantheus, Covidien
- small/medium producers, e.g. CGM/Chile; Monrol/Turkey
- national labs, e.g. IPEN/Brazil; AEOI/Iran

- generator production → supplies of generators
- ^{99m}Tc generator consignments: Recipients (several 1000s) - radiopharmacy service providers OR hospitals in every part of the world (use 1-2 week) - corporate entities / nuclear pharmacies; - individual hospitals

^{99}Mo Supply Crisis 12/2007-Q3/2010 - Main Lessons

- highly optimise the use of all produced ^{99}Mo and capacity of ^{99m}Tc generators – *demand-side management* (*post-crisis reduction: ~25% activity demand!*)
- mutual back-up plans – reserve capacity, both irradiation and processing - long-term sustainability aspects (including transport issues) – *supply-side management*
- complex supply chain + unsustainable economic model for reactor services and ^{99}Mo production - *NEA Report on economic aspects of ^{99}Mo supply chain*
- ^{99}Mo cost is a tiny fraction in final cost of patient service → additional cost of ^{99}Mo should not impact cost to patients (1%) - *reimbursement rates & national healthcare management*
- emerging interest in & need to encourage *alternate technologies* to produce ^{99}Mo and avail ^{99m}Tc

NEA's HLG-MR report findings on economic aspects of ^{99}Mo supply chain (1 of 2)

<u>historical market development vis-à-vis economic sustainability – a legacy impact</u>

- reactor irradiation prices set too low to support infrastructure development [0.26ε irradn. cost for ^{99}Mo (0.11%) in radiopharma price → 0.33-2.39ε (0.14-0.97%)]
- commercialisation reinforced low prices and created market power
- analysis - calculations confirm → economic structure inadequate; ^{99}Mo industry unsustainable
- government support sustained the industry; they are (will be) re-examining level of subsidies to reactors

NEA's HLG-MR report findings on economic aspects of ^{99}Mo supply chain (2 of 2)

- LEU conversion necessary, but not supported by market
- additional capacity can increase supply, but not an economic panacea

- Changes required for economic sustainability:

- changes to address market, policy and technological failures
- prices to increase, but the impact on end users is small
- reserve capacity needs to be funded

- The recommendations and options cited include:

- defining government role in financially supporting industry
- paying for full costs of ^{99}Mo production & reserve capacity

- Policy Approach: 6 Principles + supporting recommendations

Alternate Technologies for Production of ^{99}Mo & ^{99m}Tc

Scale of production, 6-day Ci: **large (>1000 Ci)**; medium (100-1000 Ci); *small (<100 Ci)*

- Reactor vis-à-vis Accelerator usage
- 'Fission' vis-à-vis 'Activation' (by n/γ/p) method
- Post-production process technologies
- Status: concept level to demonstrated capability
- Non-fission, non-reactor route for medium scale production would be ideal!
- *Related Issues*: FDA approval of product; recycle-reuse of enriched targets – GMP compliance need

Alternate Technologies for Production of ^{99}Mo & ^{99m}Tc

fission-based, using (reactor) neutrons

- Aqueous homogeneous reactor (AHR) – B&W/USA (old patent), *IAEA-CRP related to AHR feasibility in progress*
- Target Fuelled Isotope Reactor (TFIR) – proposal of Sandia National lab/USA – concept: using fuel elements as targets & recovery of fission isotopes
- Sub-critical Hybrid Intense Neutron Emitter (SHINE Medical Technologies): Low energy D accelerator for D-T reaction & making use of neutrons produced for fission of LEU salt solution - Phoneix Nucl labs; Univ of Wisconsin-Madison & Morgridge Inst for Research; LBNL&LANL; TechSource Inc. (US tech dev funding)

aspects: technology development – large investment – replication – ‘fission still’

SHINE: concept and plans

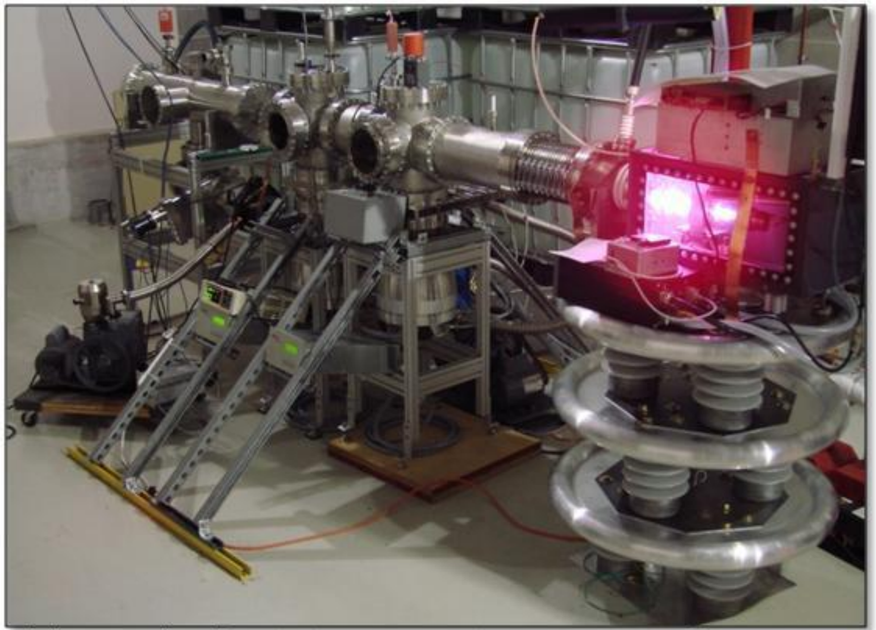


Figure 1: Prototype neutron source for SHINE ^{99}Mo production system

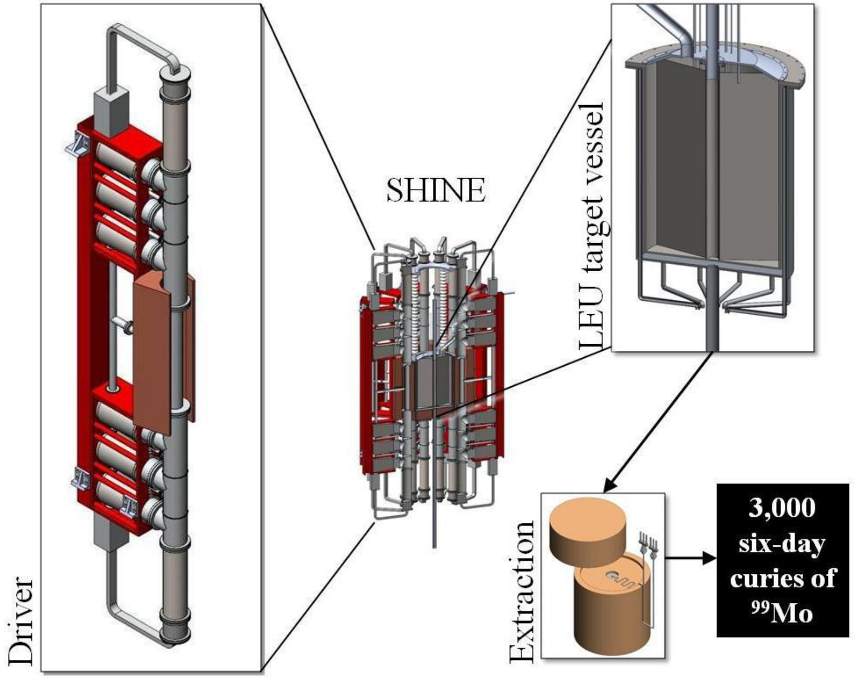


Figure 2: The PMI ^{99}Mo production process using SHINE

Alternate Technologies for Production of ^{99}Mo & ^{99m}Tc

activation-based, using neutrons

- utilization of BWR (~35 in US) for high purity Mo metal activation - use of traversing in-core probe (TIP) like system (GE-Hitachi, USA); 6-day irradiation, manufacturing facility in US east coast planned; use of new concept gel generator system (TD funding)
- ^{98}Mo(n,γ) with neutrons from reactors or other intense neutron sources & revisit of older methods OR explore new methods - most practicable; many utilisable RR world over [aim 100s of Ci]
- ^{98}Mo(n,γ) and off-line mass separation of ^{99}Mo (enrichment): team/company in S- Africa
- fast neutron reaction (n,2n) on enriched ^{100}Mo target (e.g. IFMIF)

multi-nucilidic Mo: *14.84% 92; 9.25% 94, 15.92% 95; 16.68% 96 ; 9.55% 97;* ***24.13% 98; 9.63% 100***

Prospects of n, gamma (‘activation’) moly

Natural MoO_3 target

- σ for (n,γ): 0.13 b
- σ with n epithermal: ~6.5 b
- ^{99}Mo of 0.2 - 1 Ci/g (RR flux dependent) - India, RF, …
- compacted powder targets – efficient use of RR positions
- compatible with alternate separation schemes
- gel, multi-column, high affinity adsorbent, electrochemical cell … merit attention

Enriched ^{98}Mo traget

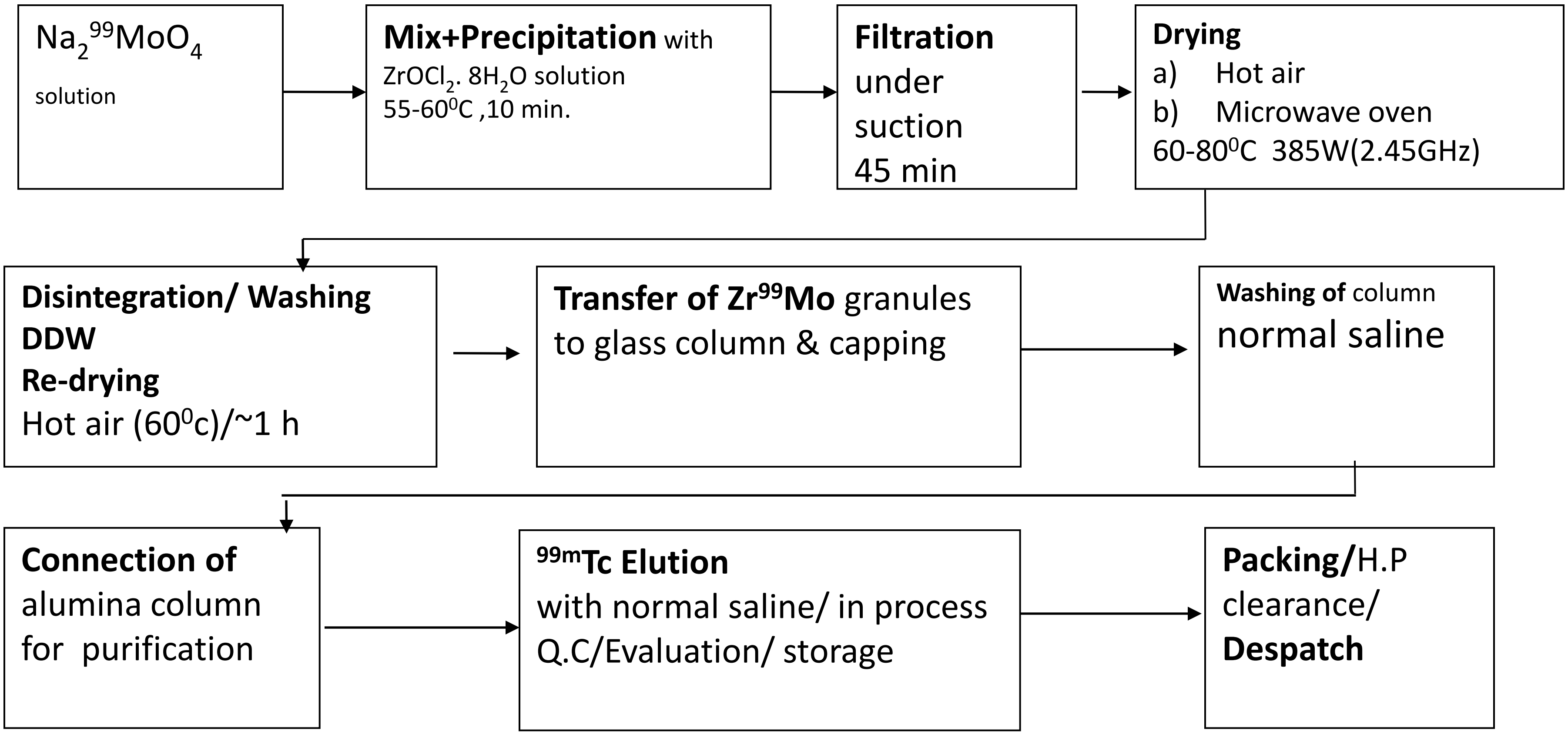
- ^{98}Mo nat abun 24.13%
- 4 times higher enrichment
- order of magnitude higher yield & sp act (epithermal)
- recovery-reuse of targets
- ^{99}Mo of >>2 Ci/g
- large-bed alumina column generator for distribution of ^{99m}Tc: INP, Uzbekistan
- *systems on LHS applicable*

Technologies for utilising 'activation' ^{99}Mo

*KEY: **chemistry** based solutions! revisit and adopt separation methods for ^{99m}Tc suited to activation ^{99}Mo (e.g. n,γ) - specific activity 0.2-1 Ci/g*

- **MEK extraction** (India, RF - vast experience) – automated plant system by Atommed-Rosatom, RF
- zirconium molybdate **gel generator** (India, Kazakhstan)
- **post-elution concentration** of ^{99m}Tc from large (alumina) column
- **multi-column ion-exchange** chromatography - automated module - to adsorb or extract ^{99m}Tc and recover ^{99}Mo for recycling; then re-elute and purify ^{99m}Tc (Northstar, USA) - basis: Indian work (Chattopadhyay et al.)
- use of **high affinity adsorbent for Mo**: poly titanium oxochloride (PTC), nano zirconia, polymeric zirconium compound (PZC) (Australia, India, Japan)
- **electrochemical separation** of ^{99m}Tc in BARC-India

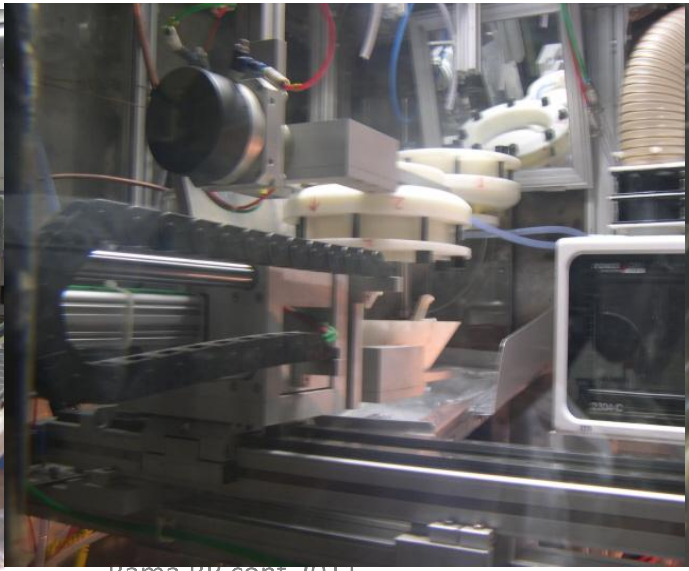
^{99}Mo as part of Column! Flow-chart for Preparation of Zirconium Molybdate - ^{99}Mo Gel for ^{99m}Tc Generator

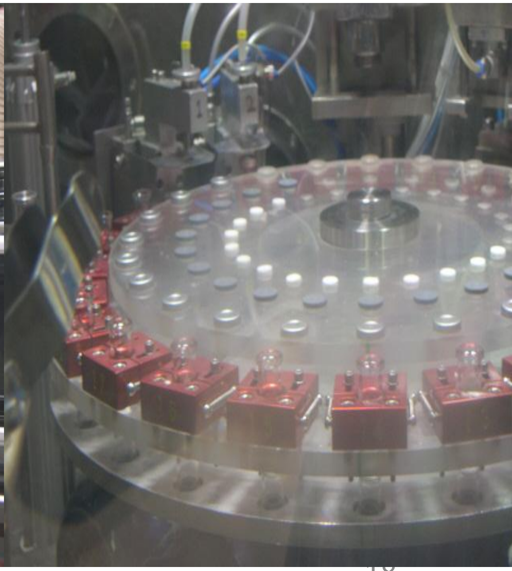


Rama RR conf 2011

^{99m}Tc generator *Geltech* based on zirconium molybdate - ^{99}Mo gel (ZrMo) column: India

- Alumina capacity for Mo: ~20 mg/g
- ^{99}Mo as component of column matrix: ZrMo gel: 25-30% Mo
- **(n,γ)^{99}Mo: 0.2-1 Ci/g**
- 6-9 g ZrMo column use; upto 0.5 Ci (18.5 GBq)
- BRIT >200 batches; >2300 gen supply



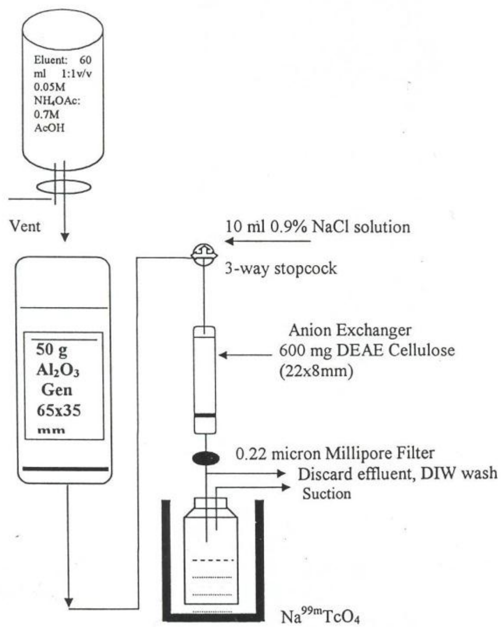


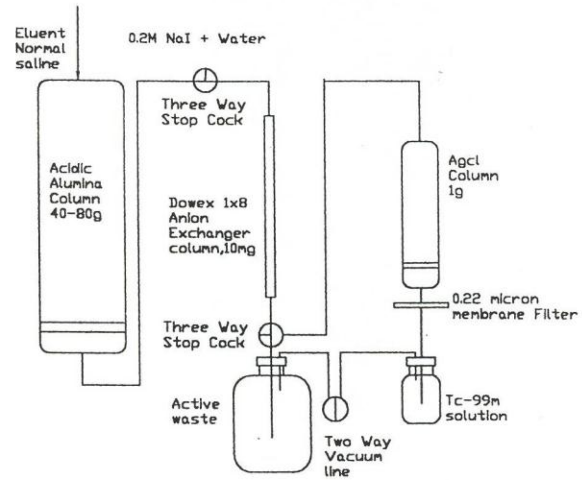
Value of post-elution concn systems for 'no-carrier-added (nca)' TcO_4^-

- acidic alumina column chromatography: *Gold standard*
- fission produced ^{99}Mo of very high sp acty required
- Mo adsorption capacity **20mg/g** → large column to use (n,γ)^{99}Mo
- ORNL development of post-elution concn of ReO_4^- linked to ^{188}W-^{188}Re generator – trigger for adoption for TcO_4^- and use of 'jumbo' alumina column with (n,γ)^{99}Mo
- *basis*: trap nca TcO_4^- (sub μM) of large volume on anion exchanger & re-elute in a small volume
- academic pursuit at BRIT-India - papers and PhD thesis work (Sarkar et al.) → assume significance during ^{99}Mo supply crisis!
- high value utility for adoption in several alternate approaches (including in accelerator-cyclotron) of production of ^{99}Mo and ^{99m}Tc

Development of Post-Elution Concentration (PELCON) Strategies for ‘nca’ Pertechnetate

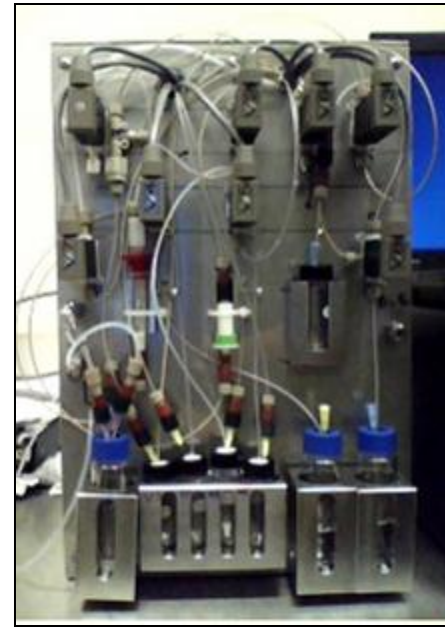
Schematic of post-elution concentration based novel ^{99m}Tc delivery system- present work





SCHEMATIC OF CONCENTRATION OF Tc-99m PERTECHNETATE USING STRONG ANION EXCHANGER AND AgCl COLUMN.

Radiochemical Separation Process in Emerging Alternate Technologies for ^{99m}Tc: NorthStar Generator



$^{98}Mo(n,\gamma)^{99}Mo$ [$^{100}Mo(\gamma,n)^{99}Mo$; $^{100}Mo(p,2n)^{99m}Tc$

- oxidative dissolution Mo target → solution of MoO_4^{--}/TcO_4^- → trap nca TcO_4^- on anion exchange column - ($^{98/100}Mo$ recovery for reuse); re-elution & purification. [other (similar) methods also available]

basis: Indian work of Chattopadhyay et al.

Potential of two more separation options

high affinity adsorbent for Mo

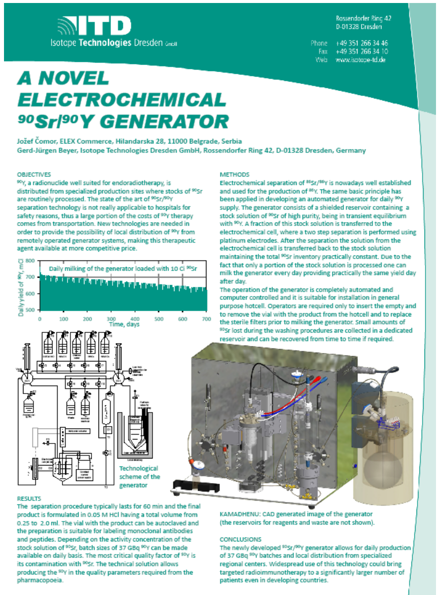
aim: order of magnitude higher capacity than <u>20mg/g</u> of alumina to use 1-2Ci/g ^{99}Mo

index: performance reliability, ease, reproducibility, meet regulatory needs *(GMP, FDA)*

- poly titanium oxo chloride (PTC) India, Vietnam-Australia; <u>80mg/g</u>
- nano-zirconia (<u>140mg/g</u>); nano-ceria (India)
- polymeric zirconium compound (PZC; Japan)

electrochemical separation (BARC)

- *genesis*: ^{90}Y separation from ^{90}Sr *(fully automated generator system now available)* → TcO_4^- deposition on Pt for separation from $^{99}MoO_4^{--}$ in electrochemical cell



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A NOVEL ELECTROCHEMICAL ^{90}Sr/^{90}Y GENERATOR

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OBJECTIVES

^{90}Y, a radionuclide well suited for endoradiotherapy, is distributed from specialized production sites where stocks of ^{90}Sr are routinely processed. The state of the art of ^{90}Sr/^{90}Y separation technology is not really applicable to hospitals for safety reasons, thus a large portion of the costs of ^{90}Y therapy comes from transportation. New technologies are needed in order to provide the possibility of local distribution of ^{90}Y from remotely operated generator systems, making this therapeutic agent available at more competitive price.

Technological scheme of the generator

METHODS

Electrochemical separation of ^{86}Sr/^{86}Y is nowadays well established and used for the production of ^{86}Y. The same basic principle has been applied in developing an automated generator for daily ^{90}Y supply. The generator consists of a shielded reservoir containing a stock solution of ^{90}Sr of high purity, being in transient equilibrium with ^{90}Y. A fraction of this stock solution is transferred to the electrochemical cell, where a two step separation is performed using platinum electrodes. After the separation the solution from the electrochemical cell is transferred back to the stock solution maintaining the total ^{90}Sr inventory practically constant. Due to the fact that only a portion of the stock solution is processed one can milk the generator every day providing practically the same yield day after day.

The operation of the generator is completely automated and computer controlled and it is suitable for installation in general purpose hotcell. Operators are required only to insert the empty and to remove the vial with the product from the hotcell and to replace the sterile filters prior to milking the generator. Small amounts of ^{90}Sr lost during the washing procedures are collected in a dedicated reservoir and can be recovered from time to time if required.

KAMADHENU: CAD generated image of the generator (the reservoirs for reagents and waste are not shown).

RESULTS

The separation procedure typically lasts for 60 min and the final product is formulated in 0.05 M HCl having a total volume from 0.25 to 2.0 ml. The vial with the product can be autoclaved and the preparation is suitable for labeling monoclonal antibodies and peptides. Depending on the activity concentration of the stock solution of ^{90}Sr, batch sizes of 37 GBq ^{90}Y can be made available on daily basis. The most critical quality factor of ^{90}Y is its contamination with ^{90}Sr. The technical solution allows producing the ^{90}Y in the quality parameters required from the pharmacopoeia.

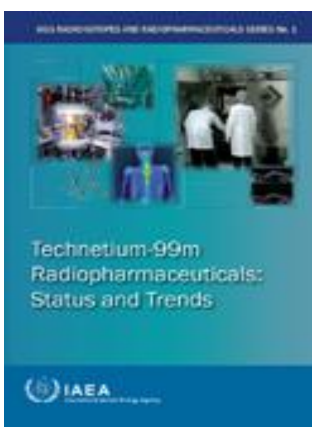
CONCLUSIONS

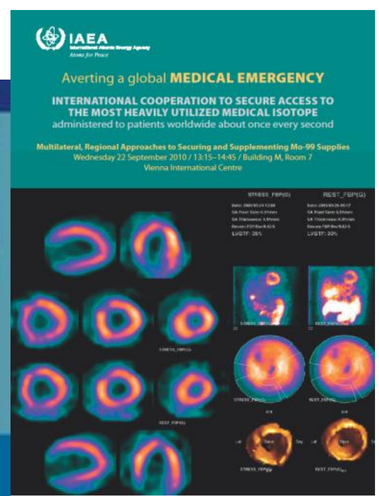
The newly developed ^{90}Sr/^{90}Y generator allows for daily production of 37 GBq ^{90}Y batches and local distribution from specialized regional centers. Widespread use of this technology could bring targeted radioimmunotherapy to a significantly larger number of patients even in developing countries.

IAEA Member States' Access to ^{99m}Tc

- IAEA support to MS in NM → ^{99}Mo-^{99m}Tc generators; import / domestic production
- ^{99m}Tc generators (0.2 to >1 Ci) produced by national labs (10 - 250+ per week); distributed production
- supplies of 'bulk moly' available from the few main manufacturers (? 2008-2010)

- Past national TC Projects in several MS: e.g. Bangladesh, Iran, Pakistan, Syria, Vietnam





^{99m}Tc Generator Production Facility in MS: IAEA Support under TC Projects

IAEA Seminar in October 1986: Model - Local generator production using imported fission-produced ^{99}Mo!

BGD/2/010: Upgrading Technetium-99m Generator Production Facilities at National Nuclear Centre (2003-2007)
EGY/2/008: Production of Tc-99m gel generators for nuclear medicine (2000-2006)
SYR/2/004: Upgrading Technetium-99m Generator Production (and labelling compounds) (2003-2009)
TUR/2/015: Strengthening of Radioisotope Production Facility at Cekmece Nuclear Research Centre (2005-2009)

PHI/6/021: Setting Up a Facility for the Production of Molybdenum-99/Technetium-99m Generators (since 2009)

Path to Securing & Sustaining ^{99}Mo-^{99m}Tc Supplies

- strengthen existing ^{99}Mo-^{99m}Tc production-supply chain; large producers' role vital – ***near-future needs***
- facilitate enhanced use of existing capacity of suitable RR & processing facilities – ***eye on medium term***
- foster/support conversion to LEU targets – ***political will***
- ***diversity - defence in depth***: support alternate methods for further supplementing and securing supplies

  - reactor and accelerator routes

  - use of non-HEU targets

RR needed *for other isotopes:* ***^{131}I, ^{192}Ir, ^{60}Co, …***

Paradigm Shift Needed

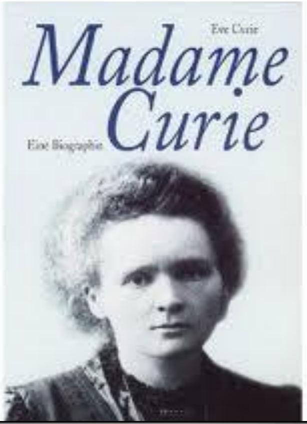
- moving away from fission moly dependence and 6-day Ci paradigm → *cleaner, greener & least decay loss*
- ^{18}FDG model around the world to trigger 'beyond alumina column generators' era of ^{99m}Tc
- KEY: advances in process module automation → adopt apt separation schemes for ^{99}Mo & ^{99m}Tc

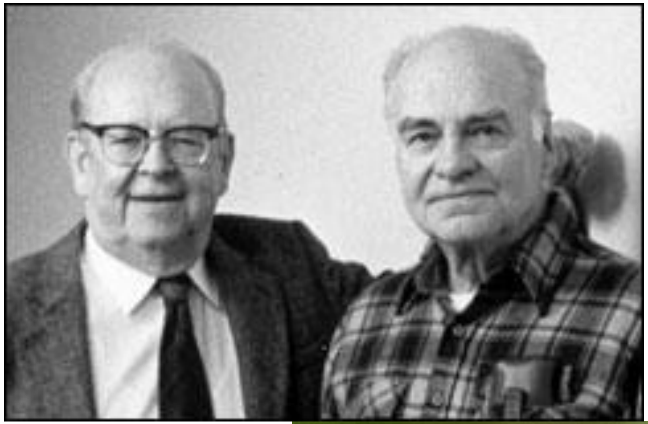
- foster novel ^{99m}Tc delivery systems and distribution of separated ^{99m}Tc

- support RR & other intense radiation source for multi-centric production of ^{99}Mo (several 100s of Ci scale)
- ***energy security analogy:*** *no single energy source can meet world needs!*
- *coal power ~ fission moly;* ***nuclear power ~ 'activation' moly***

IYC 2011 to celebrate the achievements of chemistry & its contributions to the well-being of humankind

- Professional Expertise: domestic ^{99}Mo & ^{99m}Tc generators & products in India
- IAEA Programme Manager: fostering accessibility of medical isotopes: ^{99}Mo-^{99m}Tc





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Thank You All