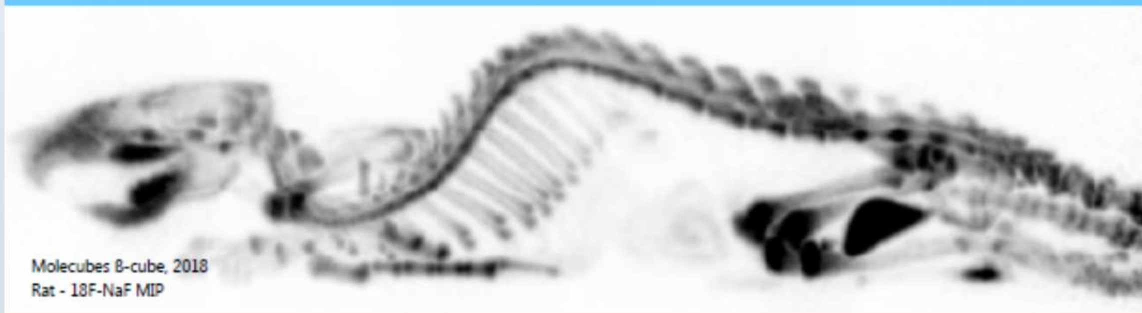
Which (new) supply sources for Mo/ Tc ?

Geets Jean- Michel - IBA Radiopharma Solution
AIPES Innovation WG



7th International Symposium on Medical Radioisotopes

The changing landscape

May 9, 2019

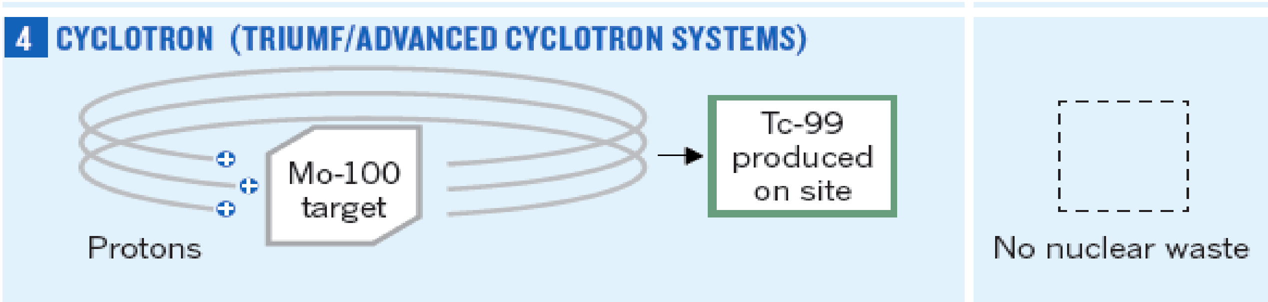
- The estimated **Mo-99 production capacities** of the current irradiators are:

Reactors	Countries	Targets	Operating weeks / year	Irradiation capacities / week [6-day Ci]	Irradiation capacities / year [6-day Ci]	End of operation
BR2	Belgium	HEU/LEU	21	6 500 – 7 800	136 500 – 163 800	> 2026
HFR	The Netherlands	HEU/LEU	39	6 200	241 800	2026
SAFARI	South Africa	LEU	44	3 000	130 700	2030
LVR-15	Czech Republic	HEU	30	3 000	90 000	2028
MARIA	Poland	LEU	36	2 200	79 200	2030
OPAL	Australia	LEU	43	3 500 (2019)	150 500 (2019)	2057
RA-3	Argentina	LEU	46	400	18 400	2027

Ref: Nuclear Energy Agency, NEA/SEN/HLGMR (2018)3, August 2018, www.oecd-nea.org

PRODUCTION OF TC^{99M} WITH CYCLOTRONS

^{100}Mo (p,2n) ^{99m}Tc & all other (p,xn) products



Direct Tc99m production with proton 22-24 MeV

- Canadian government promoted strategy to develop alternative sources in which it has invested a lot

Robust high-yield ~1 TBq production of cyclotron based sodium [^{99m}Tc]pertechnetate☆

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[b] Sherbrooke Molecular Imaging Center, Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke (CRCHUS), Sherbrooke, QC, Canada

- **NEW infrastructure**
- **NEW cyclotron**
- 400 µA solid target

- 26 Ci EOB
- 19 Ci EOS (eob+3h)
- 18h shelf-life (purity)

A R T I C L E I N F O

Article history:
Received 5 December 2017
Received in revised form 27 February 2018
Accepted 27 February 2018

Keywords:
[^{99m}Tc]pertechnetate
Cyclotron
GMP
High yield
High-current targets
Solid target

A B S T R A C T

This paper presents the irradiation and processing of high-current ^{100}Mo targets at the University of Alberta (UofA) in a GMP compliant setting. For purpose of comparison with a second production facility, additional studies at Centre Hospitalier Universitaire de Sherbrooke (CHUS) are also described.
Introduction: More than 70% of today's diagnostic radiopharmaceuticals are based on ^{99m}Tc, however the conventional supply chain for obtaining ^{99m}Tc is fragile. The aim of this work was to demonstrate reliable high yield production and processing of ^{99m}Tc with medium-energy, high-current, cyclotrons.
Methods: We used two cyclotrons (TR-24, Advanced Cyclotron Systems, Inc) for irradiations with 22 MeV or 24 MeV incident energy and 400 µA current up to a maximum of 6 h. The irradiated ^{100}Mo was dissolved using peroxide, basified using ammonium carbonate, and purified using a PEG-based solid phase extraction technique.
Results: High-yield productions with 22 MeV (400 µA, 6 h) yielded an average isolated [^{99m}Tc]TcO_4^- yield of 878 GBq ± 99 GBq (23.7 Ci ± 2.7 Ci) decay corrected to EOB, n = 8 (isolated saturation yield: 4.36 ± 0.49 GBq/µA). Irradiations with 24 MeV (400 µA, 6 h) resulted in an average isolated [^{99m}Tc]TcO_4^- yield of 993 GBq ± 100 GBq (26.8 Ci ± 2.7 Ci) decay corrected to EOB, n = 7 (isolated saturation yield: 4.97 ± 0.50 GBq/µA). These yields corresponds to 600–700 GBq (16–19 Ci) of [^{99m}Tc]TcO_4^- at release (i.e. 3 hour post-EOB). For all tested batches, the QC results were within the recently published specifications in the European Pharmacopoeia.
Conclusion: Reliable near-TBq production yields for ^{99m}Tc can be obtained using medium-energy cyclotrons.
Advances in knowledge and implications for patient care: This work presents evidence that medium-energy high-current cyclotrons can provide high yields of [^{99m}Tc]TcO_4^- with radionuclidic impurities levels within the specifications of the existing European Pharmacopoeia monograph, indicating that this technology can have a share in the future ^{99m}Tc supply market.

J.D. Andersson et al. / Nuclear Medicine and Biology 60 (2018) 63–70

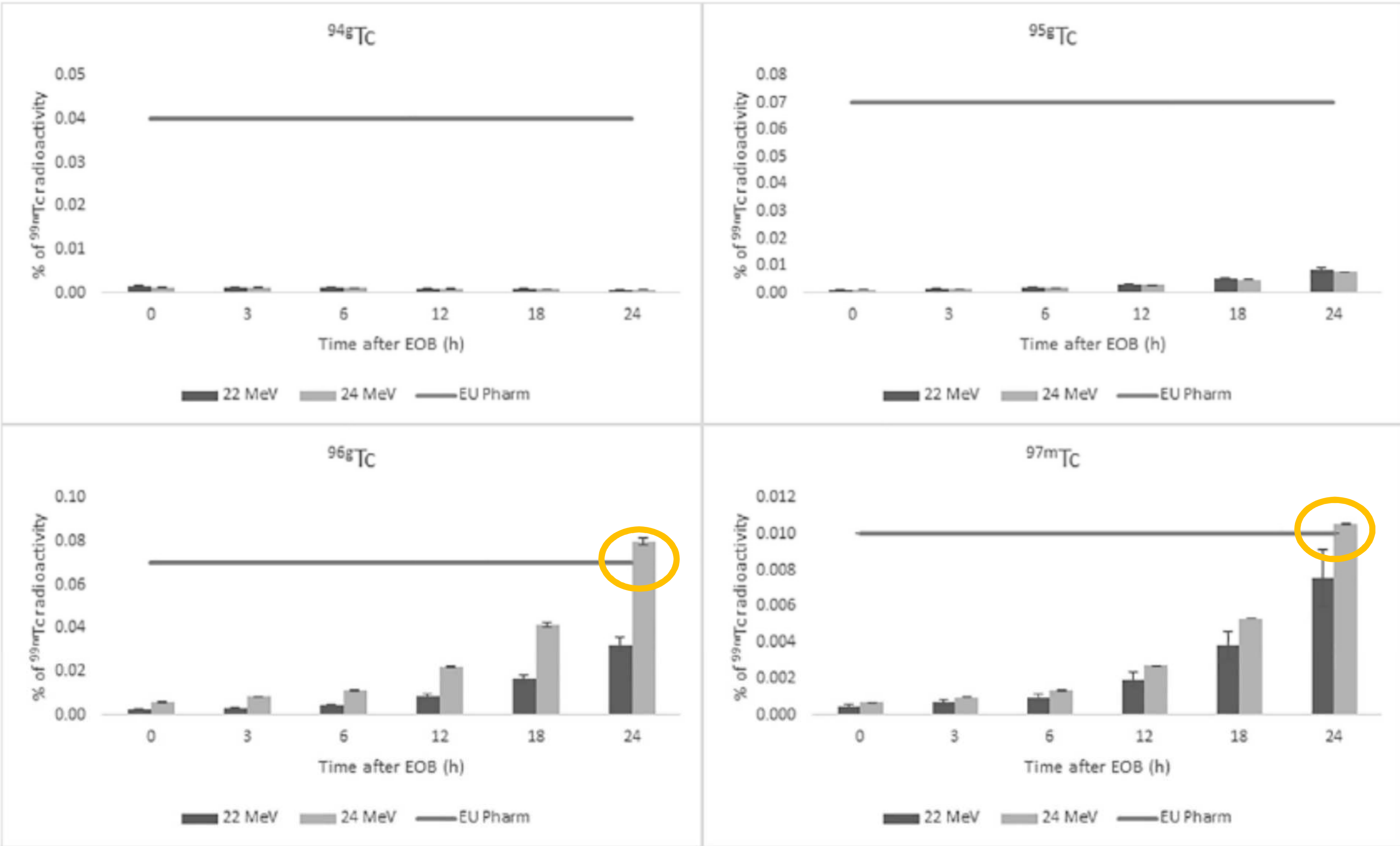


Fig. 5. Select radionuclidic impurities expressed as a percentage of ^{99m}Tc radioactivity and the change of contribution over time. Data from 6 h irradiations at 400 μA and 22 MeV (UofA, N = 8) or 24 MeV (CHUS, N = 7).

J.D. Andersson et al. / Nuclear Medicine and Biology 60 (2018) 63–70

WW Cyclotrons installed fleet ~ 1310

+210 IBA PET cyclotons installed worldwide

+ **310** GE HC PetTrace
+ **60** SHI HM-18

18 MeV proton

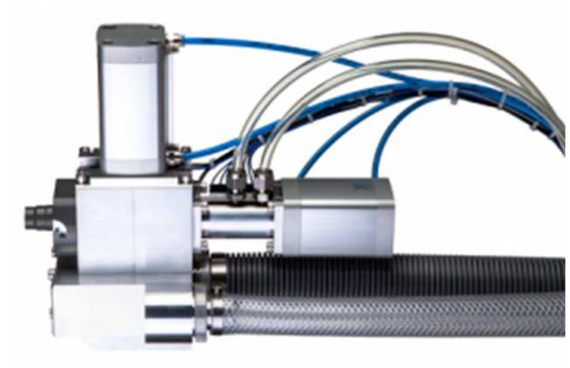
Cyclone® 30

Cyclone® 70

Existing cyclotron fleet Ep: 16 – 18 MeV mainly

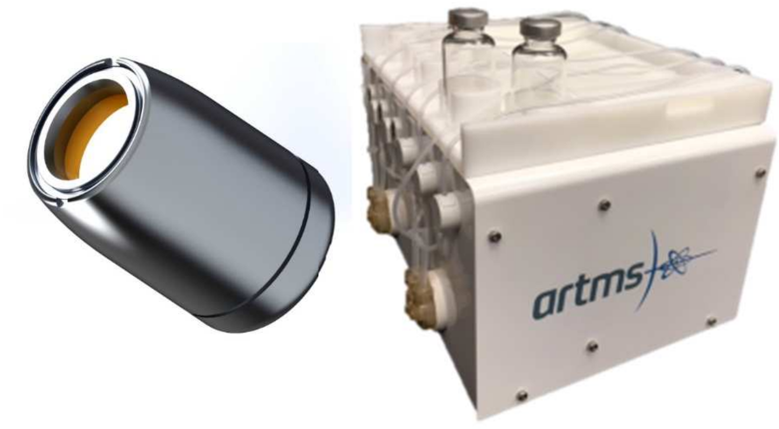
Tc99m Production capacity:

- ✓ 4 Ci in 3h run
- ✓ 7 Ci in 6h run

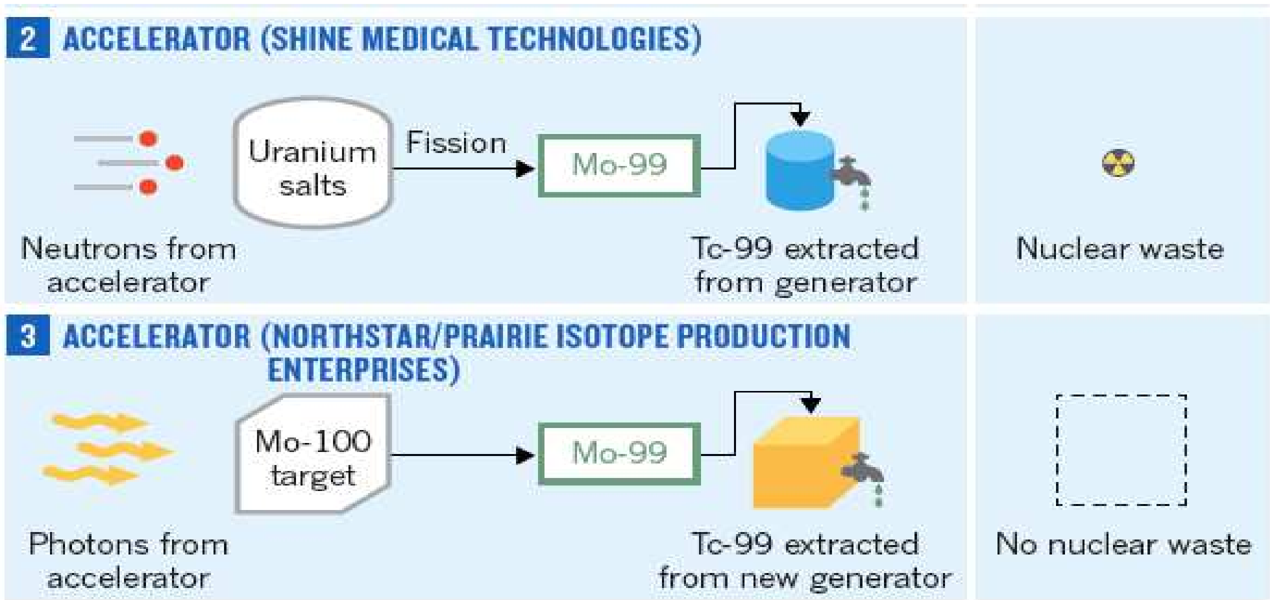


- ✓ Strong control required on Mo100 & Tc99m
- ✓ SPECIFIC equipment & lab

- ✓ **Need beam TIME**
- ✓ **Retrofit NOT always possible**

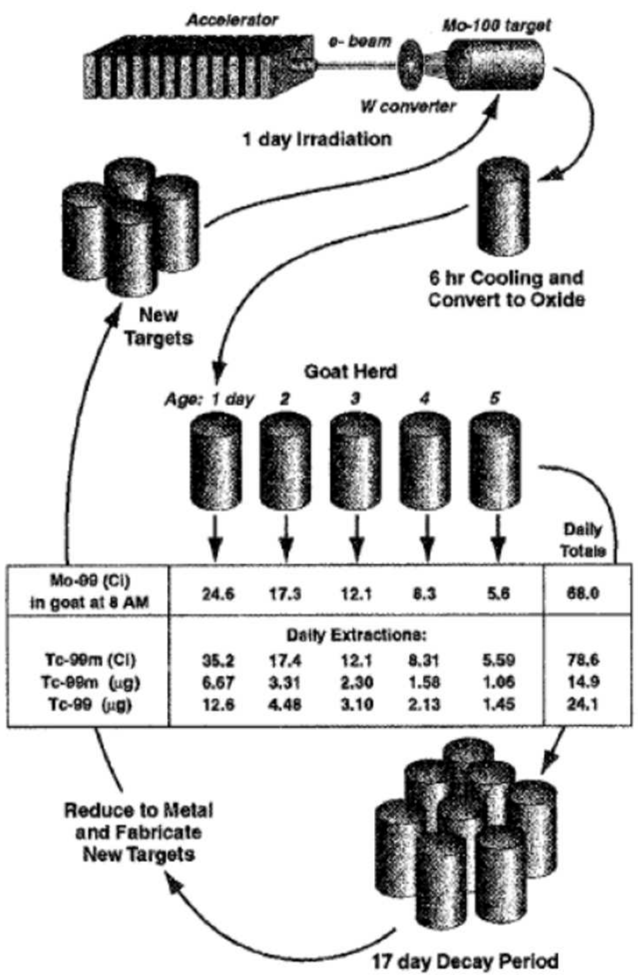


PRODUCTION OF MO^{99} WITH ACCELERATORS

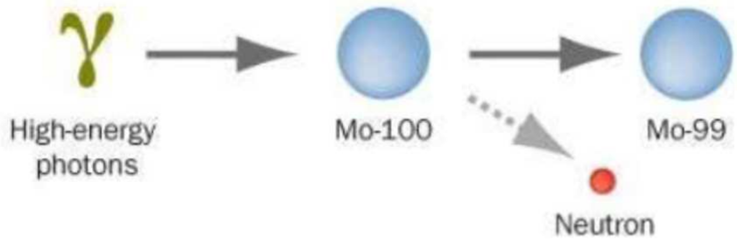


Photonuclear reaction (g,n) to Mo^{99}

Work at Idaho National Laboratory:

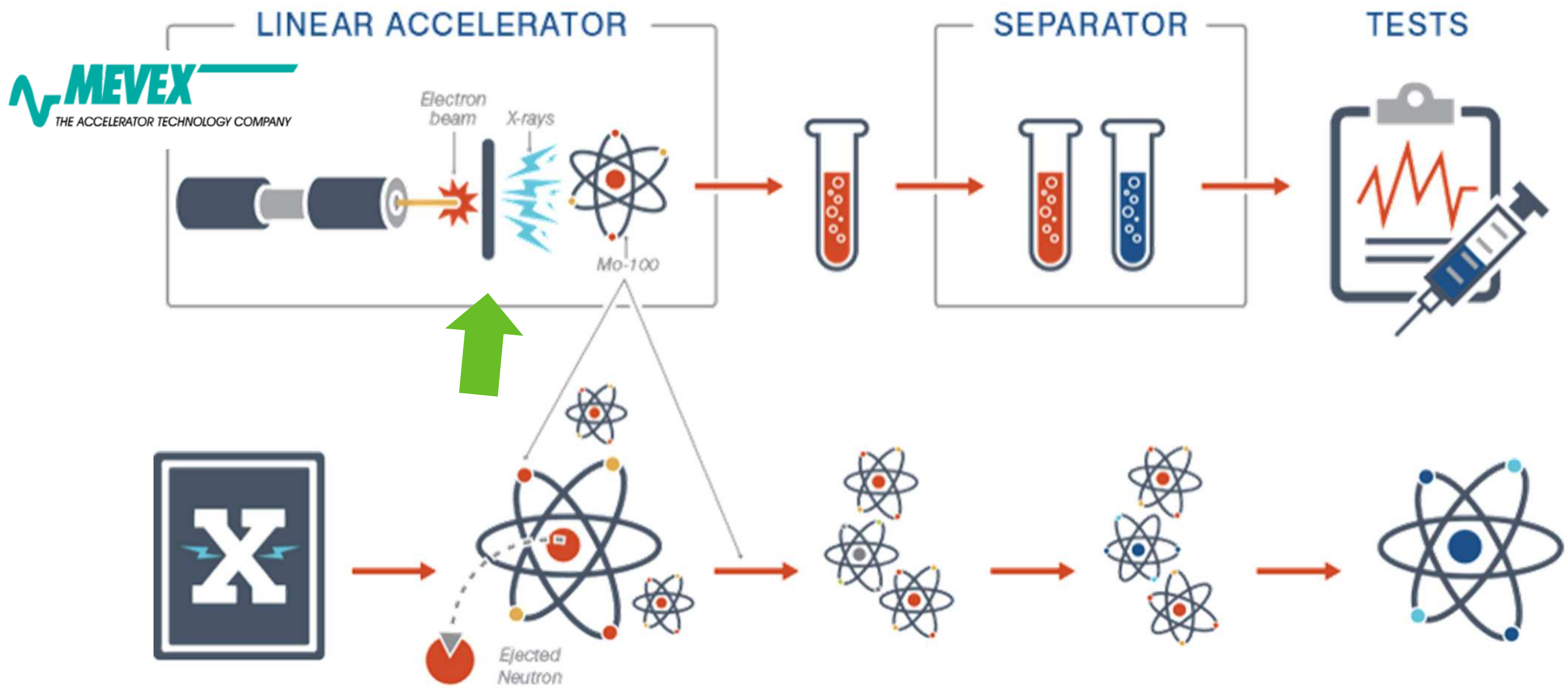


- Late 1990's
- Worked through technical, economic details
- Suggested single 15 kW accelerator for Florida
- Each target about 15 g (1 cm by 2 cm)
- Mo-100 consumption measured in µg
    - ✓ Less constraints on Mo100 quality



(CNS Workshop Dec-09)

Photonuclear system CII – Light source

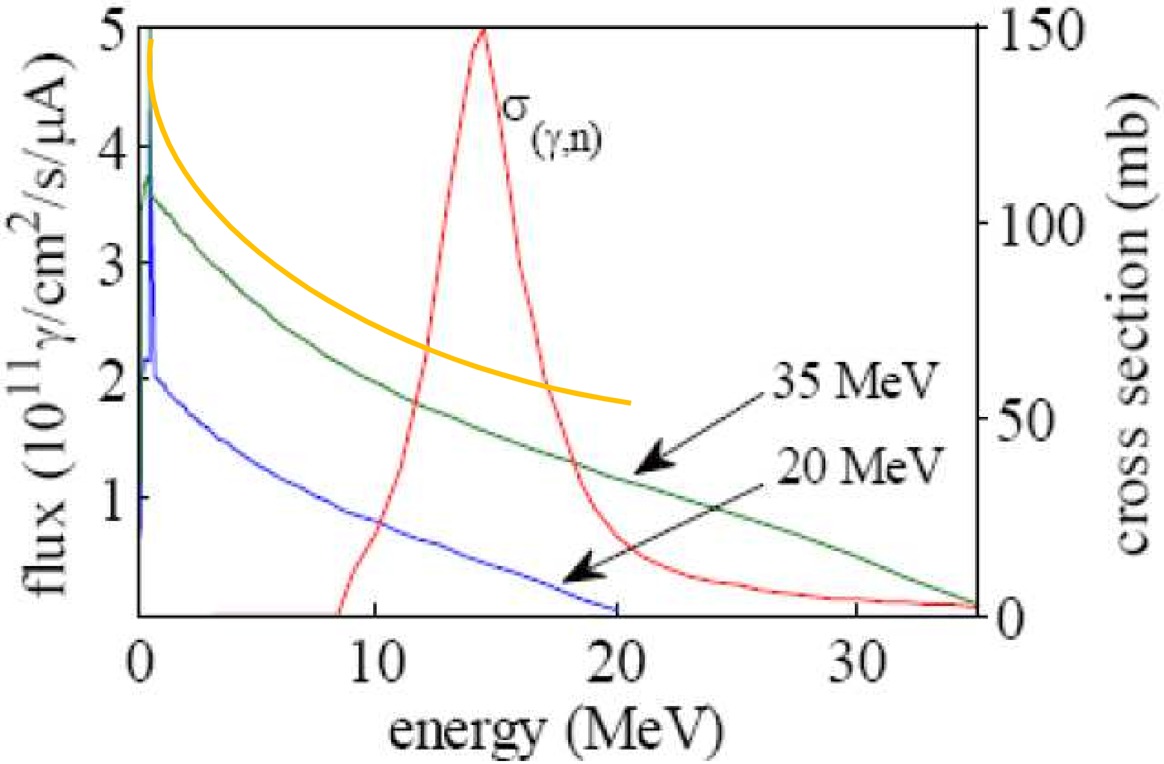


35 MeV, 40 kW linac operational since **2014**
~4 TBq per week calibrated EOP +24h

40 MeV, 120 kW linac (48 months)
Cost of facility is approximately **$50M CDN**

Photonuclear reaction (g,n) in Mo100 target

Accessible with electron- photon conversion



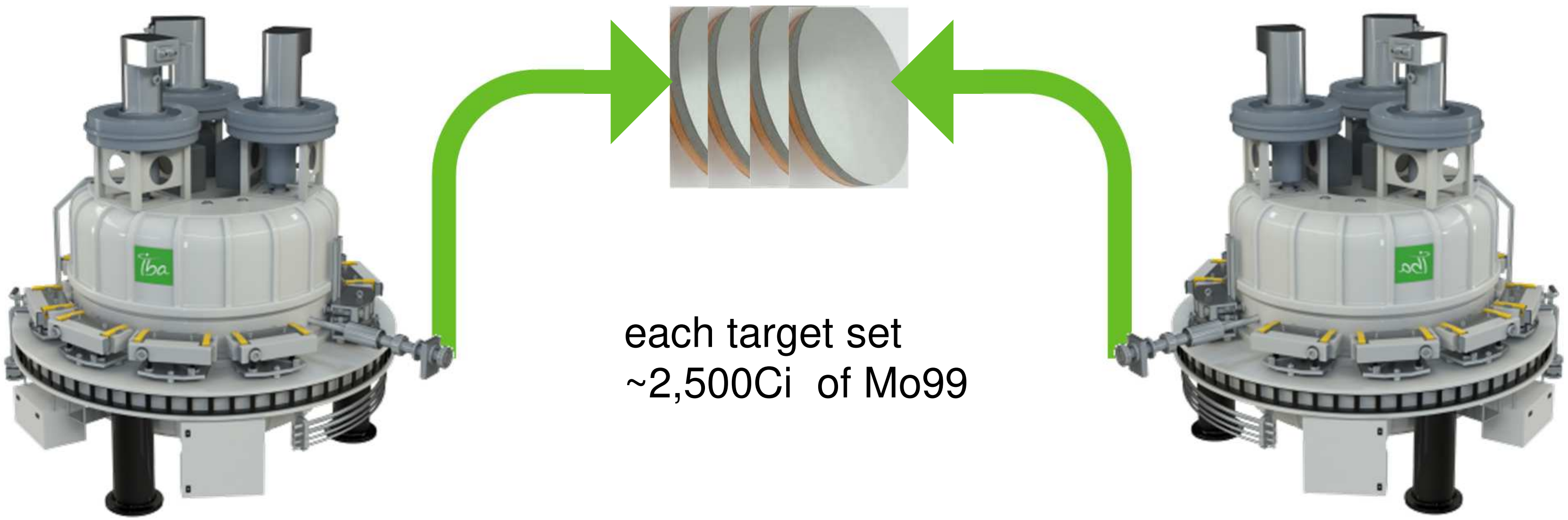
N_m – atom density of material m
E_{th} – threshold energy in m
$\Phi_{E0}(E)$ – photon fluence spectrum
$\sigma(\gamma,n)$ – cross section

Average bremsstrahlung photon spectra produced with 20- and 35-MeV electron beams in a Mo target compared to the photonuclear cross section of ^{100}Mo.

NorthStar MEDICAL RADIOISOTOPES, LLC Argonne NATIONAL LABORATORY

Photonuclear system NorthStar : work in pairs

March 29th, 2019 / NorthStar Medical Radioisotopes, LLC Signs Contract with IBA for Eight Rhodotron® Electron Beam Accelerators to Expand U.S. Production of Non-uranium Based Radioisotope Mo-99



40 MeV – 120 kW electron

40 MeV – 120 kW electron

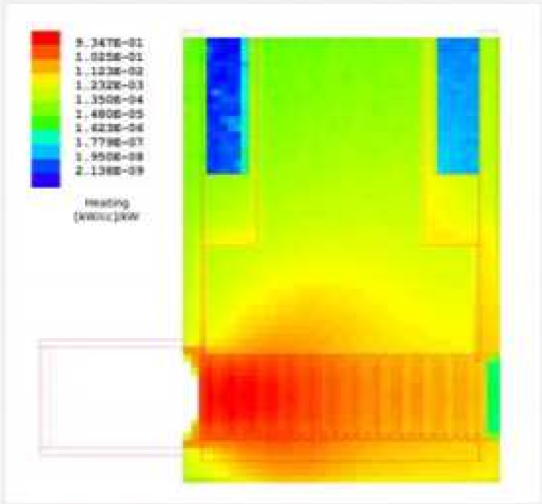
40 MeV electron ‘Rhodotron’ accelerator: 120 kW (3mA)

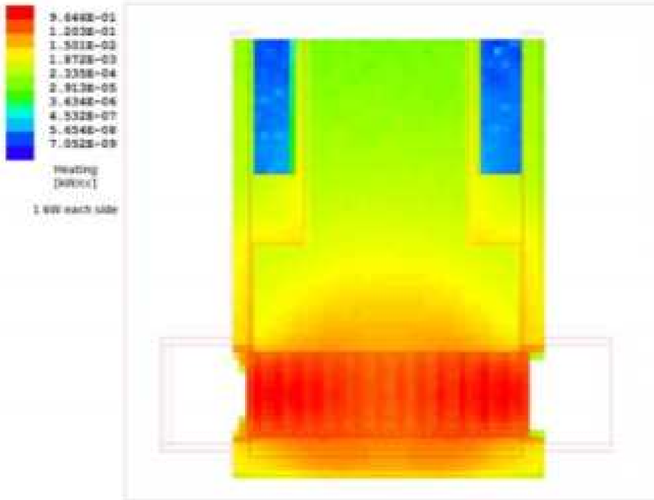
- **Reliable: based on 10 MeV Rhodotron**
  - More than 3MW of beam power installed all over the world **running 24-7 with >99% availability**
  - Exit window crash proof
  - low activation (>99.9% transmission at high energy)
  - Simple RF system 108 MHz (broadcast band)

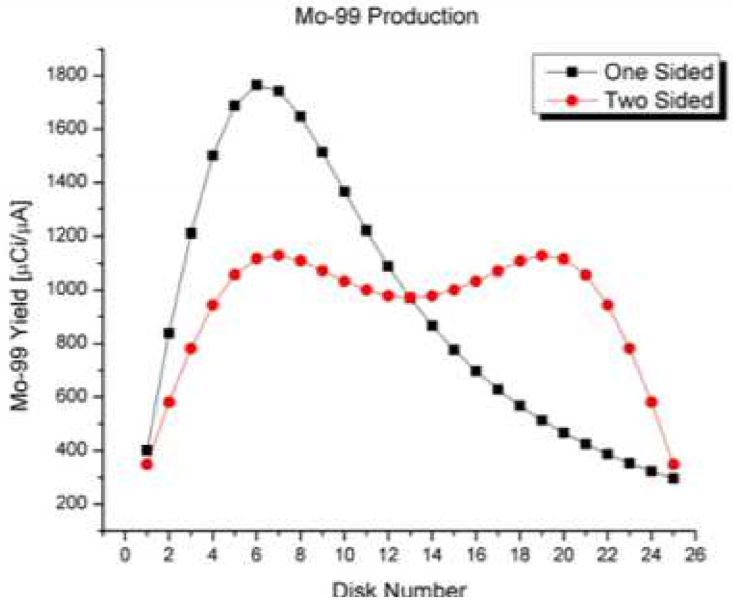
- **Economical** alternative to 25-35 MeV Linac
  - Half the consumption of a Linac
  - Smaller footprint
  - Lower maintenance cost

3.5m dia.

Rhodotrons & two sided irradiation



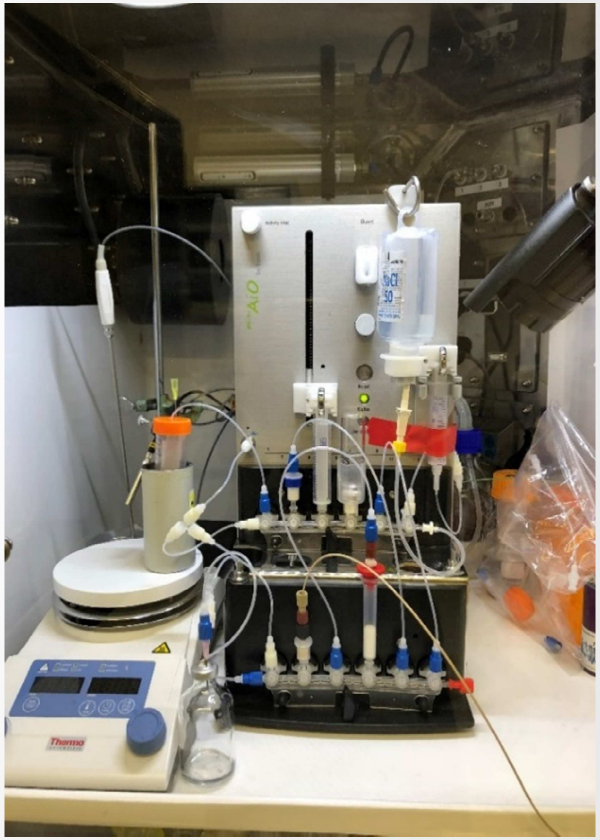




P. Tkac *et al,* Mo-99 topical meeting, Santa Fe, Dec. 2011

Development of Generator

- Solvent extraction with <u>MEK</u>
- Chromatographic purification



Results:

- Very high radionuclidic purity **100% Tc-99**, no other nuclides detectable
- Radiochemical purity >**97%**

Clinical Trial Application (~~if necessary~~) - 2020 March
Target - Health Canada market authorization in 2021

RadioGenix® System

NorthStar
MEDICAL RADIOISOTOPES, LLC

- RadioGenix® is a radioisotope separation platform for separation of technetium-99m (Tc-99m) from non-uranium produced molybdenum-99 (Mo-99)
- *Using simple columns - NO'difficult' solvents*
- potentially applicable to as Ac-225/Bi-213, W-188/Re-188, Ge-68/Ga-68, etc.

Approved by the U.S. Food and Drug Administration in **February 2018**

NorthStar
MEDICAL RADIOISOTOPES, LLC

NorthStar's Non-uranium Based Manufacturing Process

Our non-uranium Mo-99 processing involves three distinct development phases

Neutron Capture Production of Mo-99 using nMo	Neutron Capture Production of Mo-99 using eMo-98	Accelerator (Neutron Knock-Out) Production of Mo-99 using eMo-100

Regulatory approval of new Mo-99 manufacturing processes is simplified when compared to the initial New Drug Application (NDA). Supplements to the initial NDA can be used, and reviews are often completed in months or less.

Natural Molybdenum (nMo) Neutron Capture Production

- 10% USmkt-2019

Enriched Molybdenum-98 (eMo-98) Neutron Capture Production

- 40% USmkt-2021

Enriched Molybdenum-100 (eMo-100) Accelerator Production

- 850 Ci 6D- mid 2022
- 50% USmkt with 3 pairs

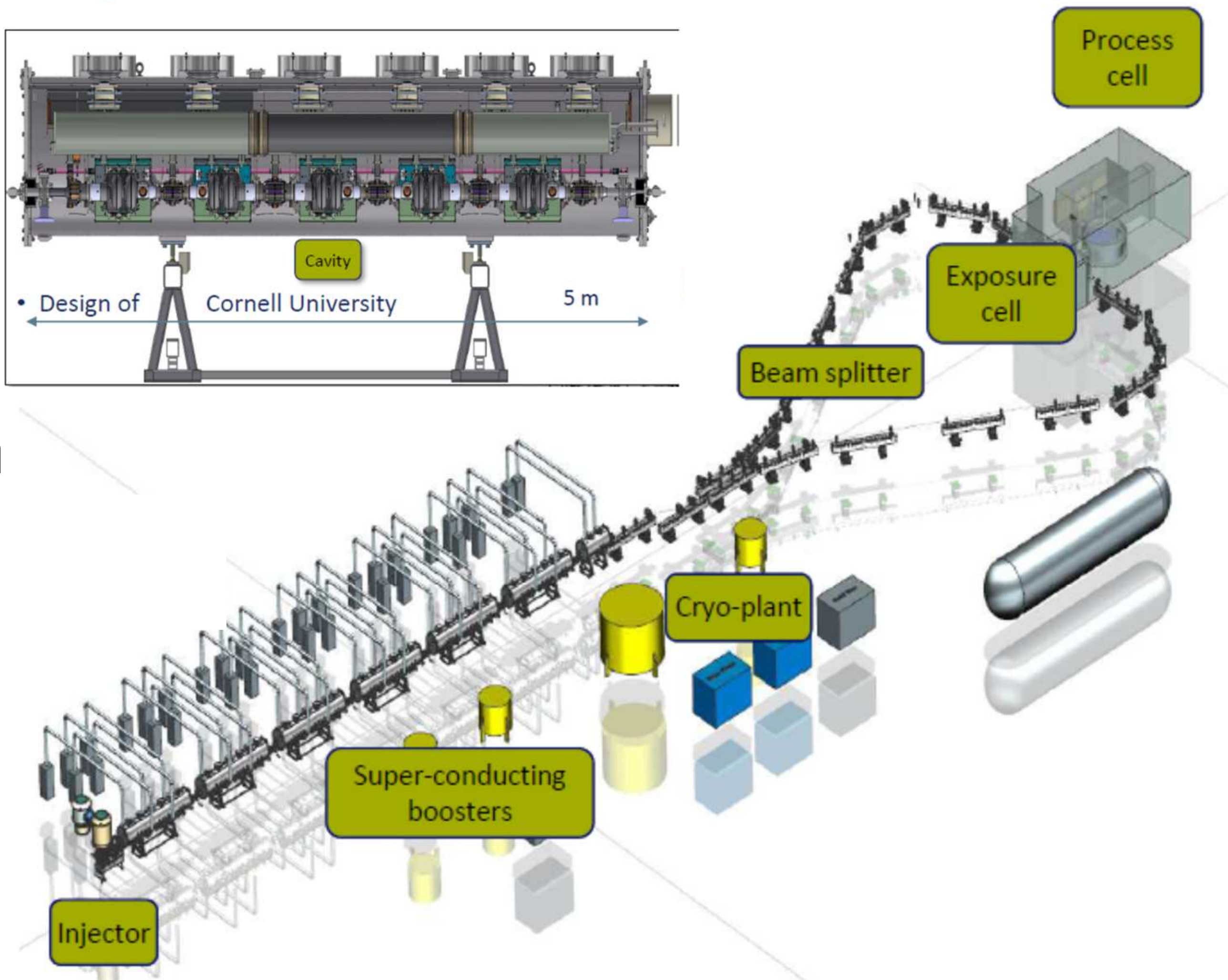
Elligible to Medicare Hospital Outpatient Prospective Payment System **$10 add on** payment (non HEU source)

Another Electron project

Excellence dedicated to nuclear medicine, healthcare and environment

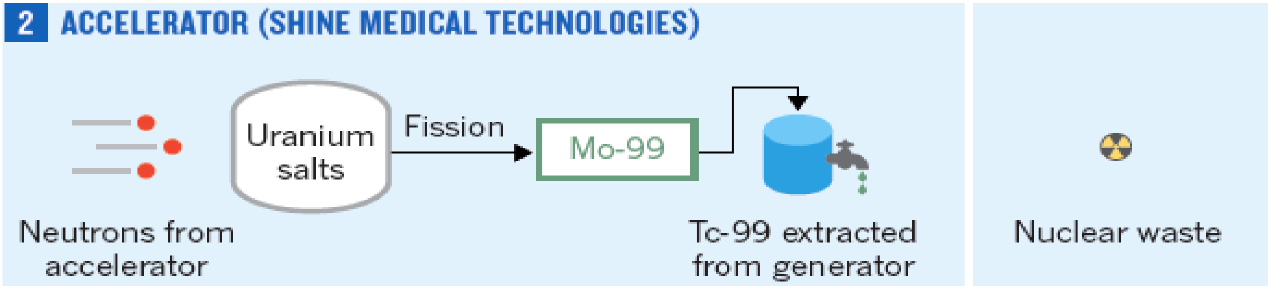
- 75 MeV
- High current 40mA
- SC linac & GHz RF
- Splitter

- Mo^{99} SA compatible with existing generators



- One line 100 000 Ci Capacity
- First line : operational 2024
- Second line : operational 2028

MO^{99} USING URANIUM FISSION WITH ACCELERATORS



SHINE ‘accelerator driven liquid reactor’

>4,000 6-day Ci/wk

Xe-133, I-131, Lu-177, Sr-89, others

8 independent units

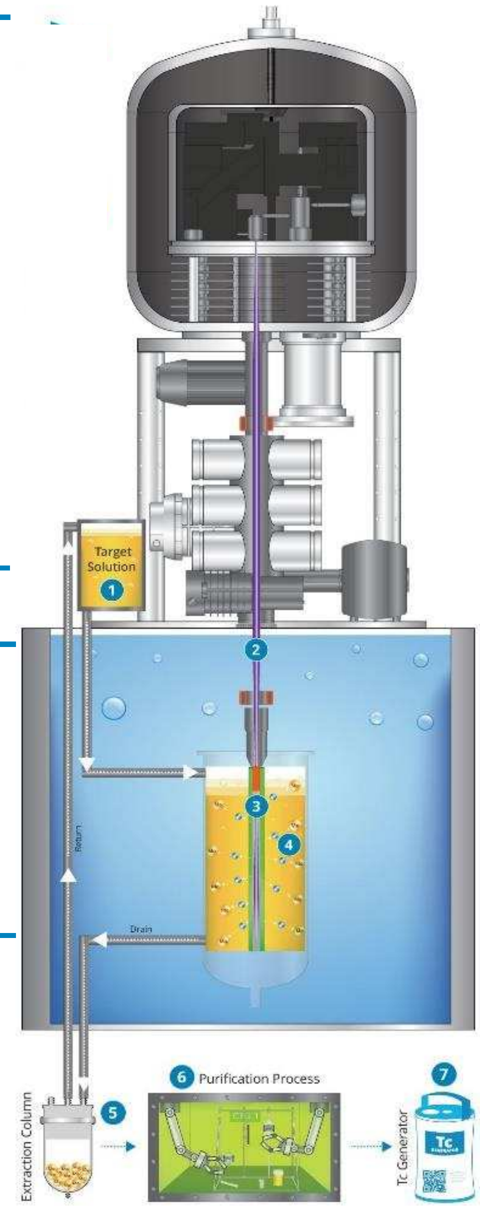
ACCELERATOR (D+T)

+

RE-USABLE
Uranium LIQUID TARGET

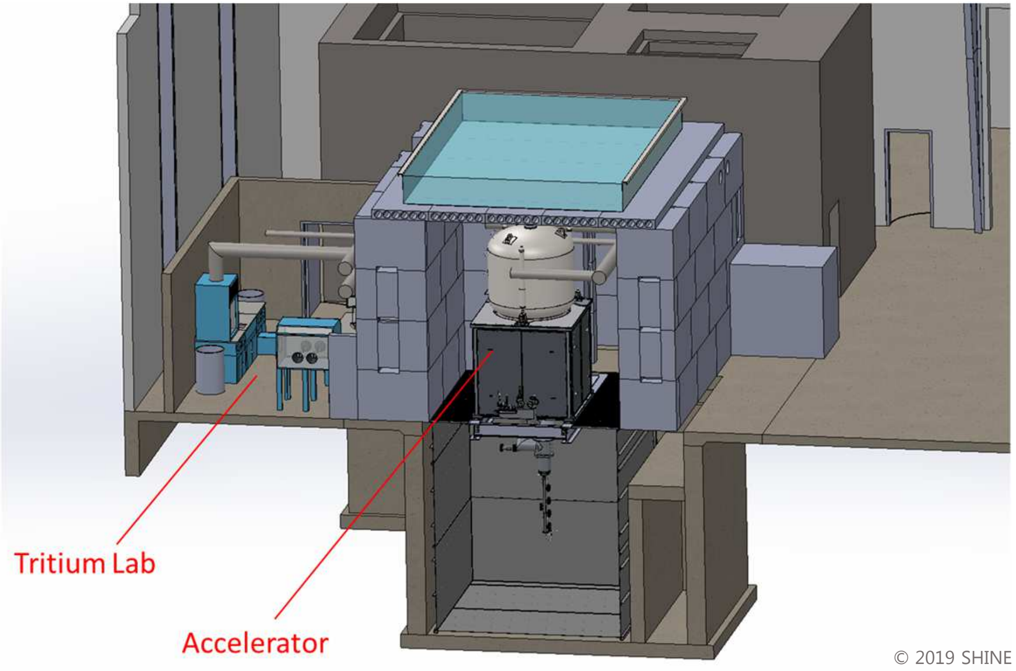
=

SAFER
70-80% LOWER COSTS
1/100th WASTE



Full-Scale Accelerator Production Demonstration 2019

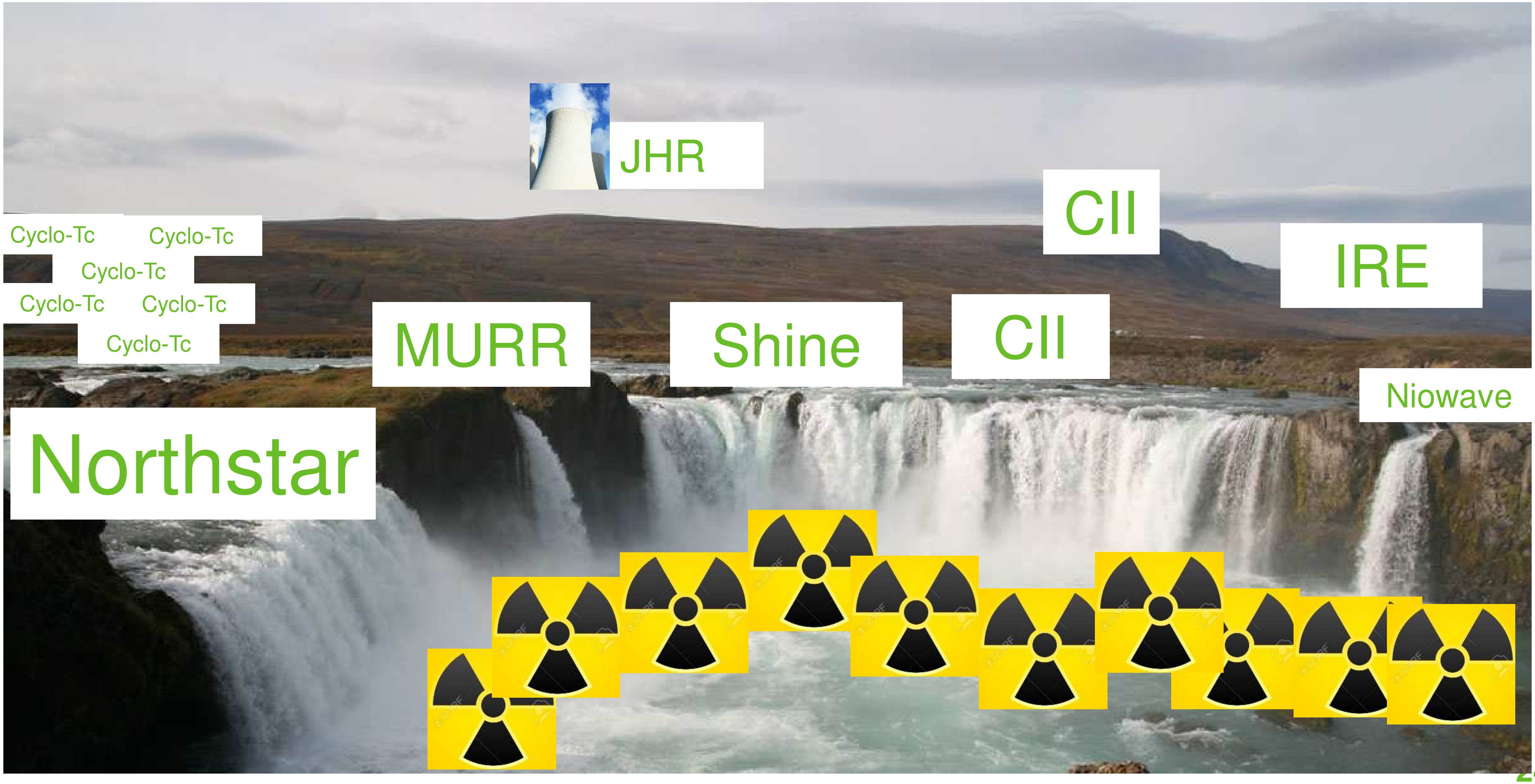
Milestone	Timing
Groundbreaking and start construction	**Q2 2019**
Operating license approval and first isotope production	H2 2021
Phase I commercial operations: Mo-99 sales	**2022**
Largest global producer; Start construction on 2nd plant	2023



SHINE
Health. Illuminated.

Mo^{99} Future : Around 2022- 2024 ?

Mo^{99} Future : Around 2022- 2024 ?



Thank you

Bernard Ponsard	SCK-CEN
Veerle Van de steen	IRE
Katrina Pitas	SHINE
Dave Wilson	NorthStar
Mark de Jong	CII

RADIO
PHARMA
SOLUTIONS