The Workshop on Signature of Man-Made Isotope Production (WOSMIP)

CURIUM BRIEFING ON Mo-99 & Xe-133 PRODUCTION

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BACKGROUND ON CURIUM

About Curium

Curium is the world's largest nuclear medicine company. We develop, manufacture and distribute world-class radiopharmaceutical products to help patients around the globe. Our proven heritage combined with a pioneering approach are the hallmarks to deliver innovation, excellence and unparalleled service.

With manufacturing facilities across Europe and the United States, Curium delivers SPECT, PET and therapeutic radiopharmaceutical solutions for life-threatening diseases to over 14 million patients annually.

The name 'Curium' honors the legacy of pioneering radioactive materials researchers Marie and Pierre Curie, after whom the radioactive element curium was named and emphasizes our focus on nuclear medicine.

The tagline 'Life Forward' represents our commitment to securing a brighter future for all those we serve: An enhanced quality of care for our patients. A trusted partner to our customers. A supportive employer to our valued team.

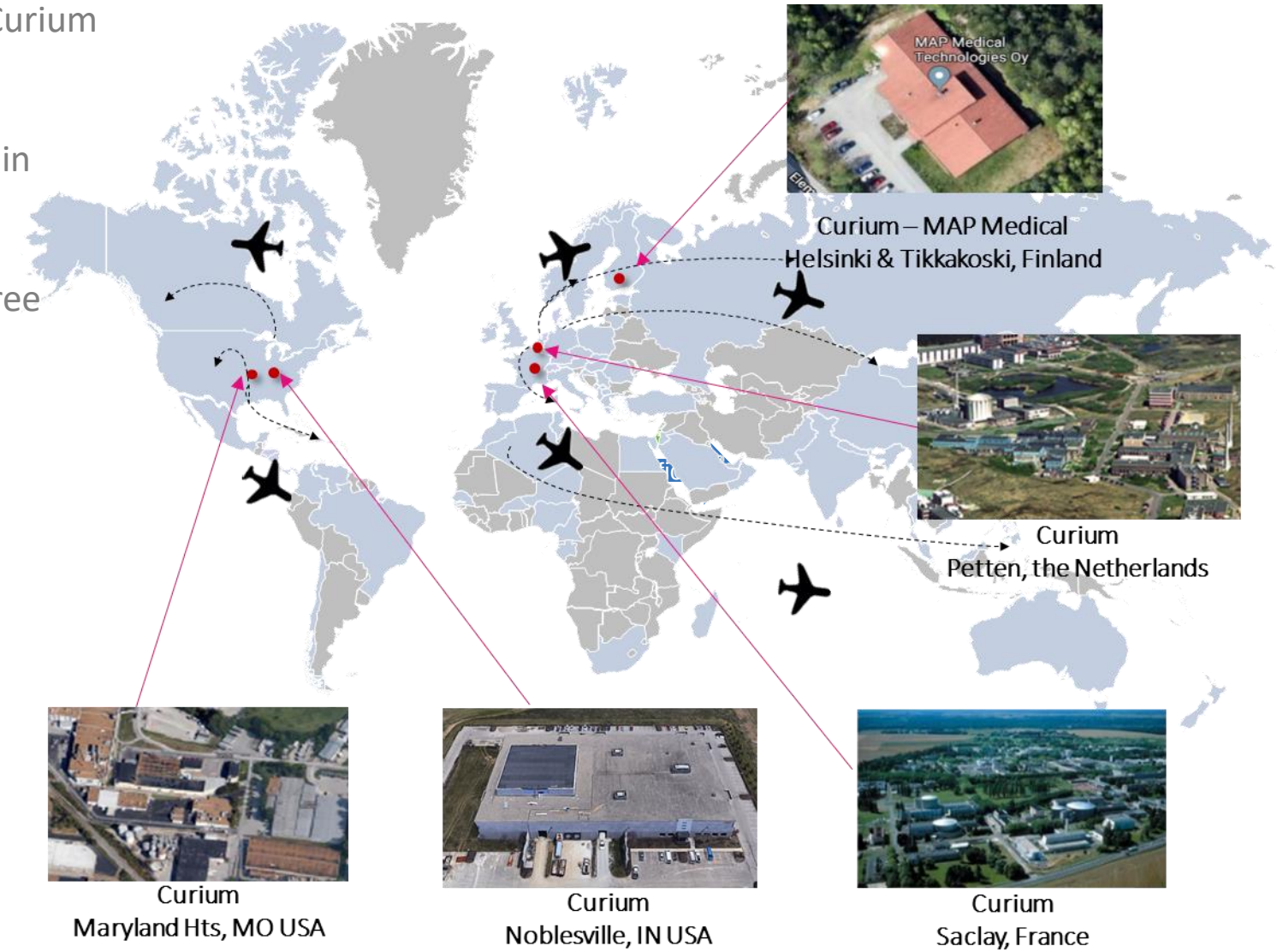
To learn more, visit **www.curiumpharma.com**

Curium Combined Mallinckrodt Nuclear Medicine and IBA Molecular

> 100 yrs History	▪ Combination of two well-respected names in the industry ▪ 100% focus on Nuclear Medicine
> 50 Sites	▪ Producing more than 30% of Moly needs worldwide ▪ Producing more than 120,000 Tc-99m Generators p.a. (+ cold kits, hot products) ▪ Producing more than 320,000 doses of FDG p.a.
> 50 Products	▪ Broad product portfolio across SPECT (generators, cold kits, hot products) and PET
14 mil patients p.a.	▪ Serving +6,000 hospitals and Centers Of Excellence around the world
> 60 Countries	▪ Main markets are USA, France, Germany, Spain, Italy and Benelux
> 2500 Employees	▪ Engineers, Radiopharmacists, Radiochemists, …

Overview of Curium's Operations

- Molybdenum (Mo-99) facility in Petten makes Curium the only global vertically integrated SPECT manufacturer.
  - Very high reliability for the key isotope used in approximately 85% of all nuclear medicine procedures.
- Leading SPECT manufacturing footprint with three Tc-99m generator facilities, 2 in Europe and 1 in the U.S.
- 10 High Energy Cyclotrons across the network enabling a broad offering of complex medical isotopes.
- Delivering SPECT products to >60 countries worldwide.
- 40+ SPECT and PET radiopharmacies across Europe dispensing unit doses.
- 50+ products in portfolio for a wide diversity of medical applications (e.g. cardiovascular, oncology, bone).



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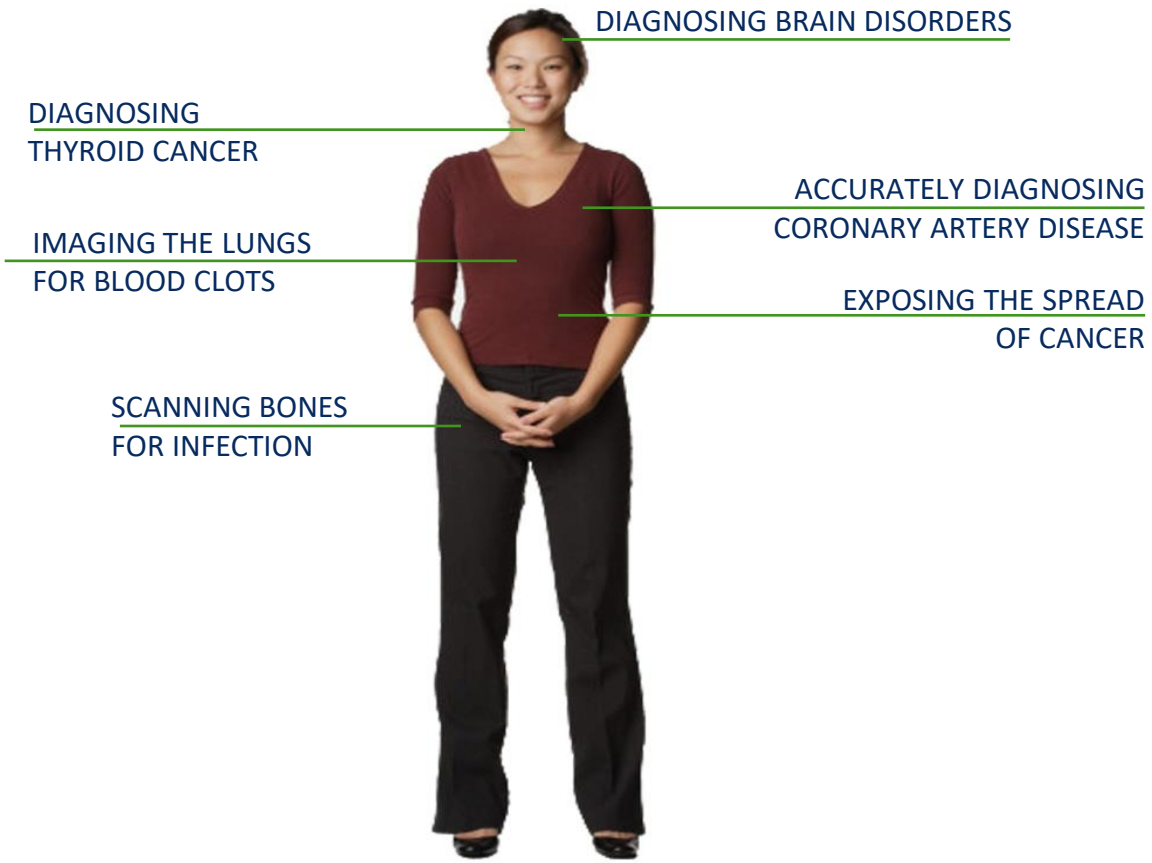
THE IMPORTANCE OF Mo-99

The Importance of Tc-99m

- Today, over 100 different nuclear medicine applications exist, such as diagnosing heart disease, brain disorders, infections and treating cancer.
- More than 85% of these use Tc-99m from Mo-99/Tc-99m generators.
- 40 million patients benefit from these procedures each year, more than half being in the U.S.
- These procedures are one of the most accurate methods of combating cardiovascular disease.
- This technique makes early diagnosis possible, thereby saving patients and the health industry millions of dollars every year.



Tc-99m Generators

- A generator provides a supply of Tc-99m that effectively decays with the half-life of the Mo-99 (~3 days) rather than the half–life of the Tc-99m (6 hours).
- Generators are typically used for two weeks, but can be used longer.
- Generators use Mo-99 produced from the fission of U-235 in research reactors

Curium‘s V4
Tc 99m Generator

CURIUM'S Mo-99 PRODUCTION

Curium's History of Producing Mo-99

- We have operated two Mo-99 production lines in Petten four days a week since the 1990's.
- We continue to produce the majority of our Mo-99 needs utilizing the HFR in the Netherlands, the BR2 in Belgium and Maria reactor in Poland.
- We maintain the ability to purchase Mo-99 from all four of the major global Mo-99 producers as part of our routine supply, and backup if needed.
- We are always looking for new partners to increase reliability or reduce costs.

One of Curium's Mo-99 Production lines in Petten

The Six Main Mo-99 Reactors

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Image used with permission.

SAFARI-1 Reactor
South Africa

Image used with permission.

Maria Research Reactor
Poland

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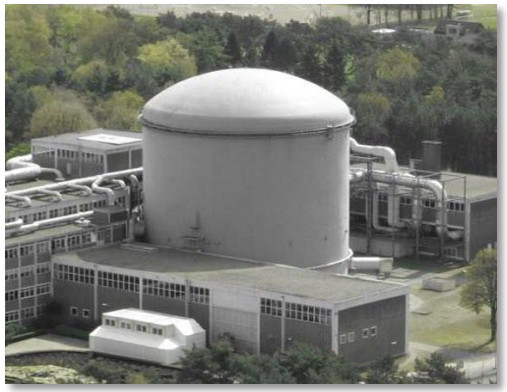
LVR-15 Reactor
Czech Republic

Credit Photo: NRG.

High Flux Reactor (HFR)
The Netherlands - The HFR is property of the European Commission and is operated by the Nuclear Research and Consultancy Group (NRG).

Credit photo: ANSTO

OPAL Reactor
Australia

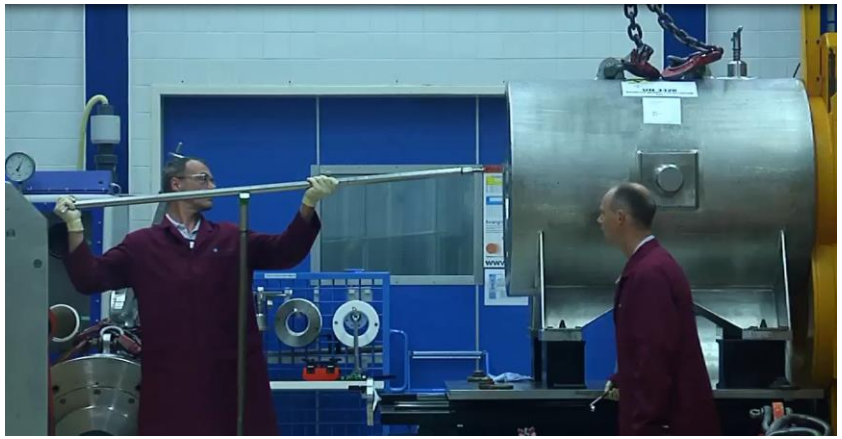


Nuclear Research Centre's Belgian Reactor 2 (BR2)
Belgium

Transport of Irradiated Targets

One of Curium's Type B(U)F Target Transport Containers

- Irradiated targets are transferred from the reactor to Petten in a dedicated Type B(U)F container.
- The targets are then transferred into the hotcells for processing.



Transferring the Targets into the Petten Hotcell

Molybdenum Facility Hotcells

Front Side of Petten Mo-99 Hotcells

Back Side of Petten Mo-99 Hotcells

Inside the Mo-99 Hot Cells

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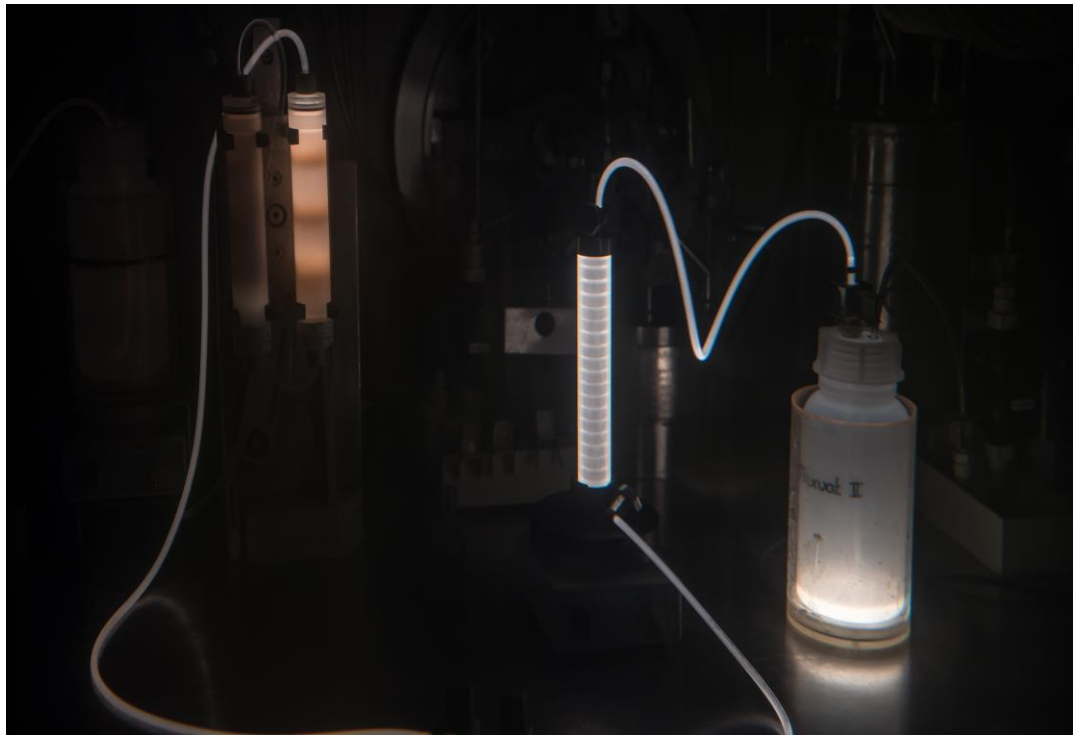
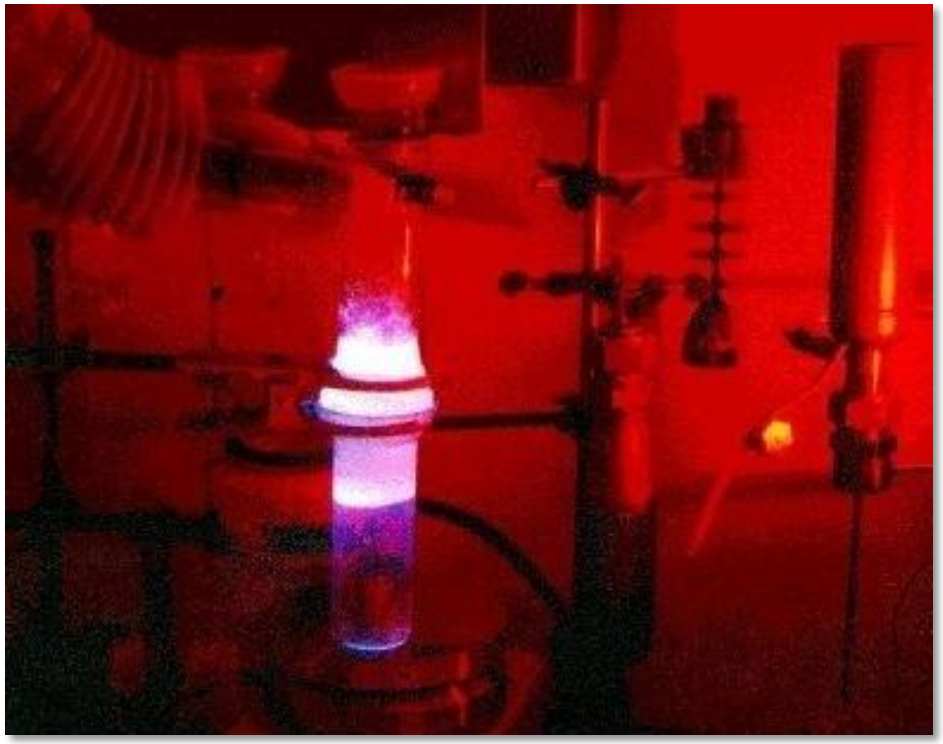
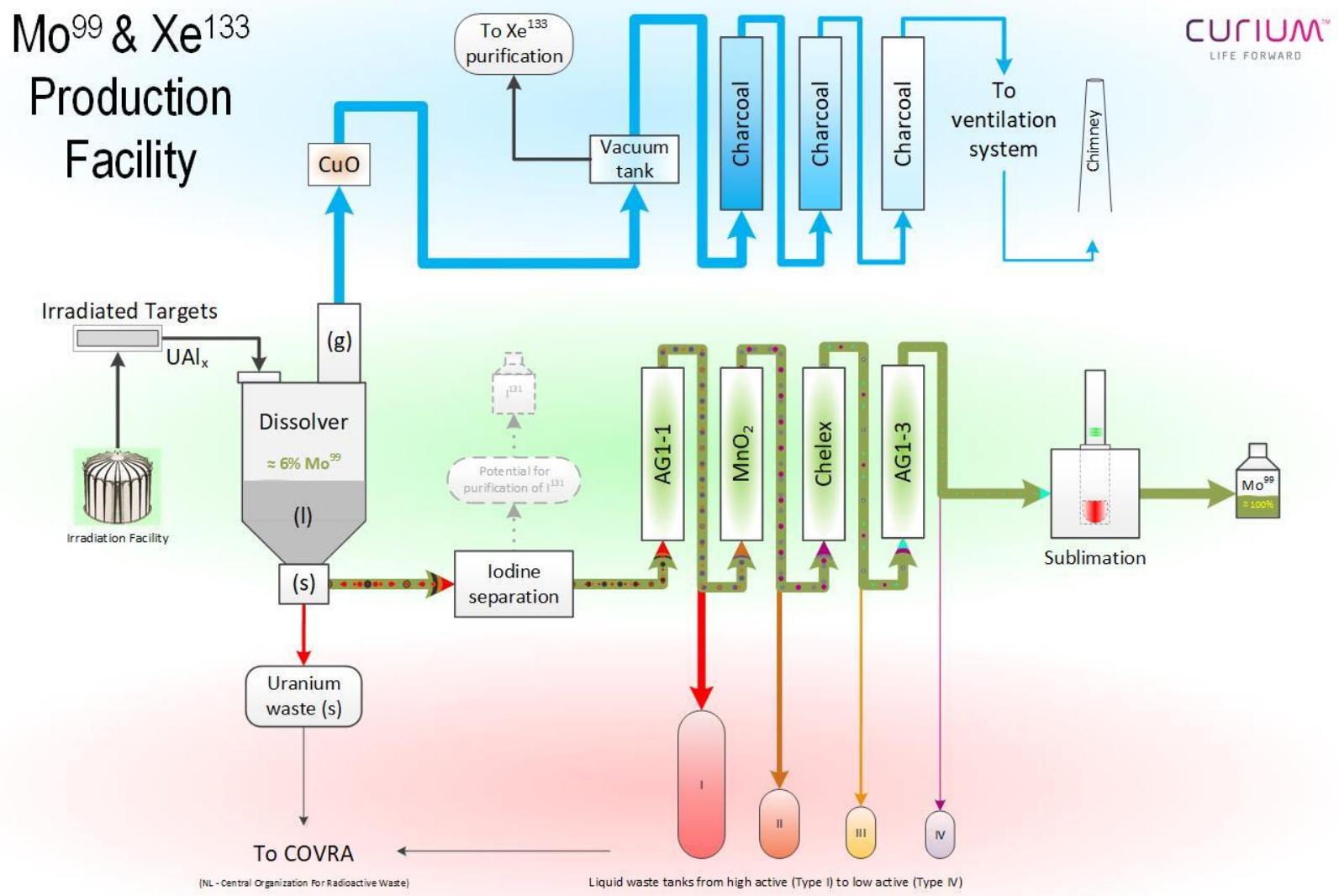




Moly processing facility "hot cells"

Overview of Curium Mo-99 Process

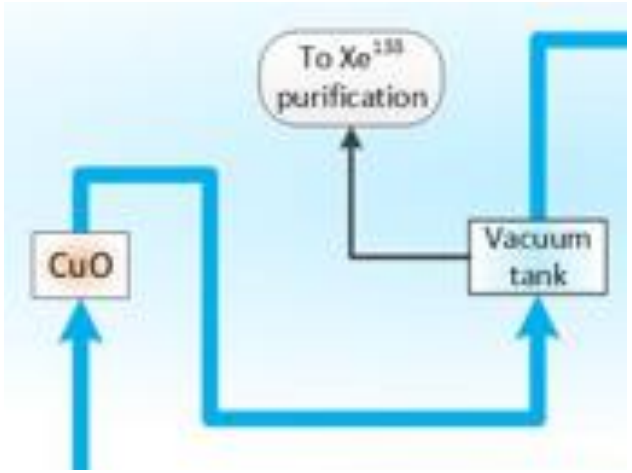


CURIUM'S Xe-133 PRODUCTION

Co-Production of Xe-133

- During the fission of U-235 for Mo-99 production, Xe-133 and many other radionuclides are co-produced.
- Although most of these fission radionuclides are discarded as radioactive waste, Xe-133 is recovered for use in nuclear medicine.
- Extensive decay beds are utilized to capture and decay the Xe-133, minimizing the release into the environment.
- This effective capture and release of Xe-133 prevents impact on the CTBTO collection program and can easily be accounted for in the environmental sampling program.
- The Xe-133 for medical use is diverted to a dedicated hotcell for capture and dispensing into coils for transfer.
- This Xe-133 is shipped to the U.S. where it is packaged into unit dose vials for use by nuclear medicine physicians.

Overview of Curium's Xe-133 Process



- The Xe-133 for production is redirected from the Copper Oxide oven to a processing glovebox.

- There it prepared as an Active Pharmaceutical Ingredient (API).

- The Xe-133 is shipped to the U.S. for use in the FDA approved product.

Xe-133 Ventilation Studies in Nuclear Medicine

- Xe-133 ventilation study allows for dynamic imaging over time
  - Anterior and posterior images obtained most frequently
- Three phases of imaging:
  1. Breathing in Xe-133 and air through a closed system
  2. While Xe-133 equilibrates (wash-in)
  3. During Xe-133 exhalation (wash-out)
- Both wash-in and wash-out phases can identify ventilatory deficiencies

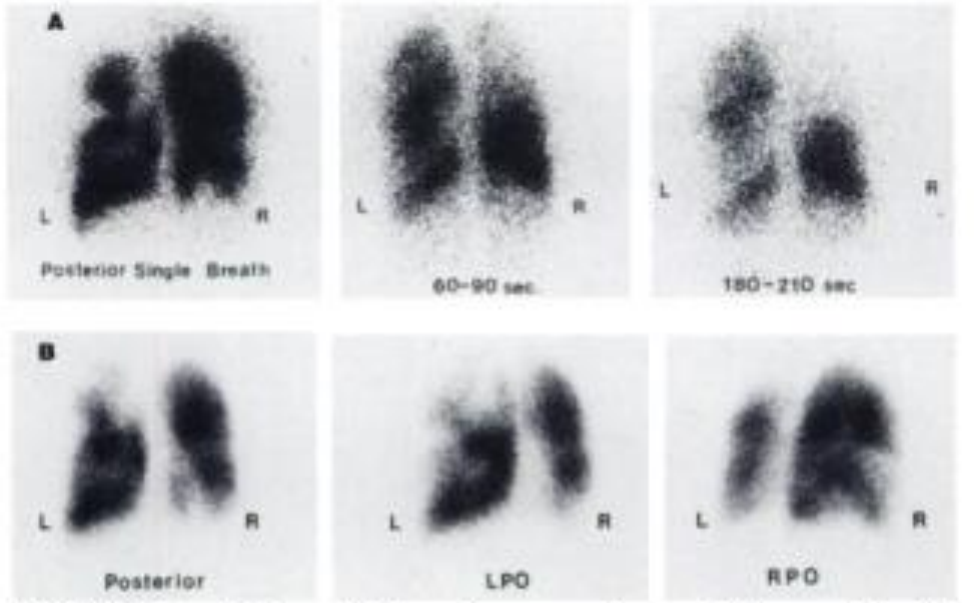


FIGURE 1. A 23-yr-old female nonsmoker on birth control pills, was referred for ventilation and perfusion scans because of sudden onset of shortness of breath. The chest x-ray showed no infiltrates. The washout images (A) reveal significant retention involving more than 50% of the lung fields. The washin ^{133}Xe image (A) shows defects matching the perfusion abnormalities seen on the posterior view (B). Pulmonary angiogram was negative for pulmonary emboli.

Elgazzar AH, et al. J Nucl Med. 1995;36:64-67

ANOTHER Xe-133 ISSUE

The Potential Increase in Demand for Xe-133 from Limited Availability of Kr-85

- Kr-85 users are reporting increased difficulty getting it from Russia.
- Several companies and users are examining the use of Xe-133 to replace Kr-85 in well logging and inspection operations.
- The huge half-life difference of Kr-85 ($t_{1/2}$= 10.76 yr.) versus Xe-133 ($t_{1/2}$= 5.25 days) could have an impact on the annual usage.
- WOSMIP should be aware of this to limit any major change in usage on the global environmental sampling program.