Is the Global Shortage of Mo-99 Over?

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The opinions I express today are my own, and do not necessarily reflect the policies of my former employer or companies for whom I have consulted.

We deal with disruptions routinely, do they translate into shortages, short or long term?

Tc99m is the major medical isotope in the world

- Discovered and developed in U.S. national labs
- Used in over 30 million patient doses annually worldwide, including 14-15 million in the U.S. (50,000 daily)
- Represents ~80% of all nuclear medicine exams
- Ideal radionuclide
  - Optimal imaging energy (140 keV γ)
  - Practical half-life of 6 hours
  - Good chemical state
  - Easy to manufacture

Primary Method for Manufacturing of Tc-99m

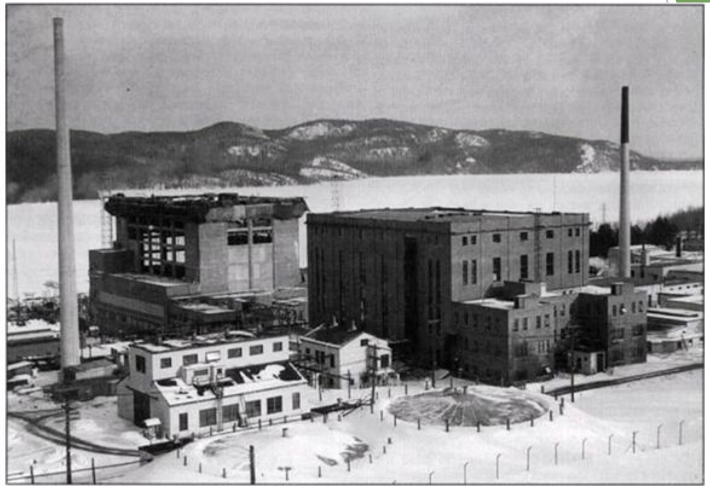
- Mo-99 produced by irradiating uranium in reactor (^{235}U + n -> fission products + ^{99}Mo)

- Mo-99 separated from fission products

- Tc-99m separated from Mo-99 via column (^{99}Mo -> ^{99m}Tc -> ^{99}Tc + 140 keV γ)

The Canadian Reactors

(Once largest producer of Mo99)



The National Research Universal (NRU) reactor had produced as much as 67% of global Mo99. It became operational in Chalk River in 1956, and was to cease operation in 2005.

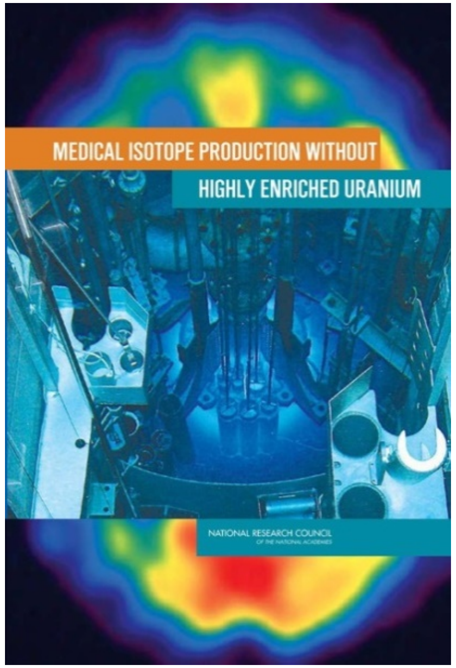
The NRU was to be replaced by the two Maple reactors, but due to design flaws these never became operational. Consequently, the NRU remained in service beyond its planned 2005 shutdown.

Shutdowns of the NRU in 2007 and 2009 precipitated several global Mo99 shortages and resulted in the establishment of the HLG-MR.

Security and Supply

- The Energy Policy Act of 1992.
- The Energy Policy Act of 2005
- The Department of Energy's National Nuclear Security Agency

Medical Isotope Production Without Highly Enriched Uranium- NAS 2009



95-98% of Mo-99 from HEU
DEMAND was 12,000 6-day Ci/week

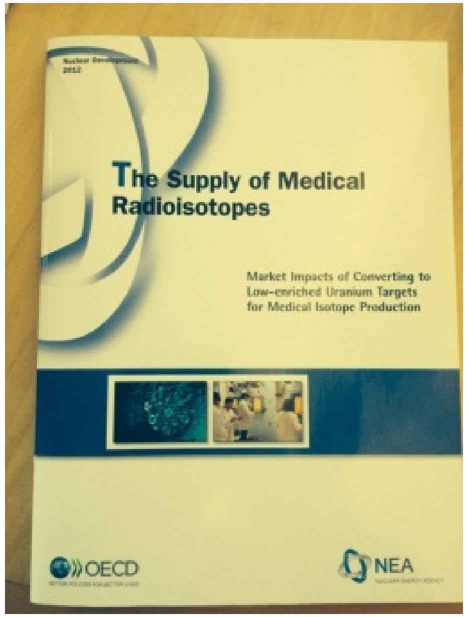
Operational Reactors Mo-99

NRU- Chalk River, Canada
HFR- Petten,Netherland
BR2- Belgium
OSIRIS- France
Safari- S Africa

High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR)

- In 2009 the Nuclear Energy Agency of the Organization of Economic Cooperation and Development (OECD-NEA) established the HLG-MR.

- Its purpose was to come up with a plan to ensure a (1) secure and (2) adequate supply of Mo-99 by working with 35 member governments.



Leadership and Partnerships to Forge a Solution

Canadian and United States Government

Organization of Economic Cooperation and Development's (OECD) Nuclear Energy Agency (NEA)

White House Office of Science and Technology Policy (OSTP)

Department of Energy's NNSA and the National Labs

Nuclear Regulatory Commission (NRC)

Department of Transportation (DoT)

Department of Health and Human Services' (DHHS)

Food and Drug Administration and the

Centers for Medicare and Medicaid Services (CMS)

Department of State

Office of the U.S. Trade representative

International Atomic Energy Agency (IAEA)

National Academies of Science, Engineering, and Medicine

Society of Nuclear Medicine and Molecular Imaging (SNMMI)

Council on Radionuclides and Radiopharmaceuticals (CORAR)

Association of Imaging Producers and Equipment Suppliers (AIPES)

Molybdenum-99 for Medical Imaging- NAS 2016

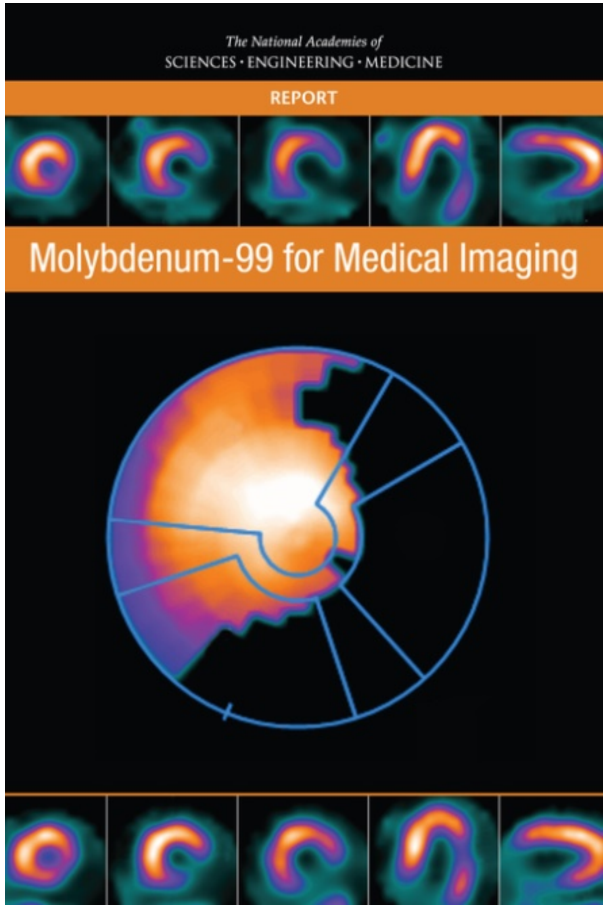
75% of Mo-99 from HEU
DEMAND reduced to 9,000 6-day Ci/week

~~NRU- Chalk River, Canada~~
HFR*- Petten,Netherland
BR2*- Belgium
~~OSIRIS- France~~
Safari- S Africa

OPAL*- ANSTO
MARIA- Poland
LVR-15 Czech Republic

Renewed interest:
By other countries, and
In Alternative Technologies

- Refurbished and increased capacity since 2009
- New sources of Mo-99
- Expressed interest



Status of Reactors Past, Present, Future (Excludes Potential Future Players)

~~NRU- Chalk River, Canada~~	~~(4680 6-day Ci/wk)~~		
HFR*- Petten, Netherland	5400/	5400	6,200
BR2*- Belgium	7800/	7800	10,530
~~OSIRIS- France~~	~~(2400)~~		
Safari-S Africa	3000/	3000	
OPAL*- ANSTO	**0/**	**1750/3500**	
MARIA- Poland		**2700**	
LVR-15 Czech Republic		**2400**	
TOTAL	**23,280/**	**24,800/**	**28,330**

- **2009** DEMAND 12,000 6-day Ci/wk
- **2016** DEMAND 9,000 6-day Ci/wk
- **Future** DEMAND ≥9,000 6-day Ci/wk

Potential New non-US Producers

Argentina	RA-10 2020	2,500 6-day Ci/week
Brazil	RMB 2021	1000 6-day Ci/week
France	Jules Horowitz Reactor	
Russia	Intent to sell 20% of global supply	1000 plus 6-day Ci/week
S Korea	KJRR 2020	2,000 6-day Ci/week

DOMESTIC PRODUCERS (10 -200 6-day Ci/week)

Kazakhstan	?
China	?
Egypt	?
India	?
Indonesia	?
Canada	Four Accelerator Projects: CII, Prairie, Consortium, TRIUMF

Alternative Manufacturing of Tc99m

- Mo99 can also be produced by irradiating Mo98 or Mo100 using an accelerator based process:

  ^{98}Mo (n,γ) ^{99}Mo

  ^{100}Mo (γ,n) ^{99}Mo

- Mo99 then incorporated into Generator System

(^{99}Mo -> ^{99m}Tc -> ^{99}Tc + 140 keV γ)

Potential New Domestic Producers

NEW TECHNOLOGIES (NNSA Cooperative Agreements)

NorthStar - acccelerator

SHINE - accelerator

General Atomics – reactor based gaseous extraction

Coqui Pharmaceuticals – New reactor based producer

Northwest Medical Isotopes- Reactor based network

Eden Radioisotopes- Novel Reactor Design may provide total global demand

Flibe Energy – Liquid Fluoride Thorium Reactor (LFTR)

Niowave- accelerator based producer

reactor based

accelerator based producer

Lessons Learned and Actions that have ensured availability and stability of supply

- Planning and coordinating production schedules single most critical action
- Multi sourcing versus Single Sourcing
- Alliances to improve bargaining Power
- Smarter Contracts to guard against price increases

Knowledge of Reactor Production and Downtime Schedules was Critical Step in Minimizing Risk of Multiple Outages (NAS 2016)

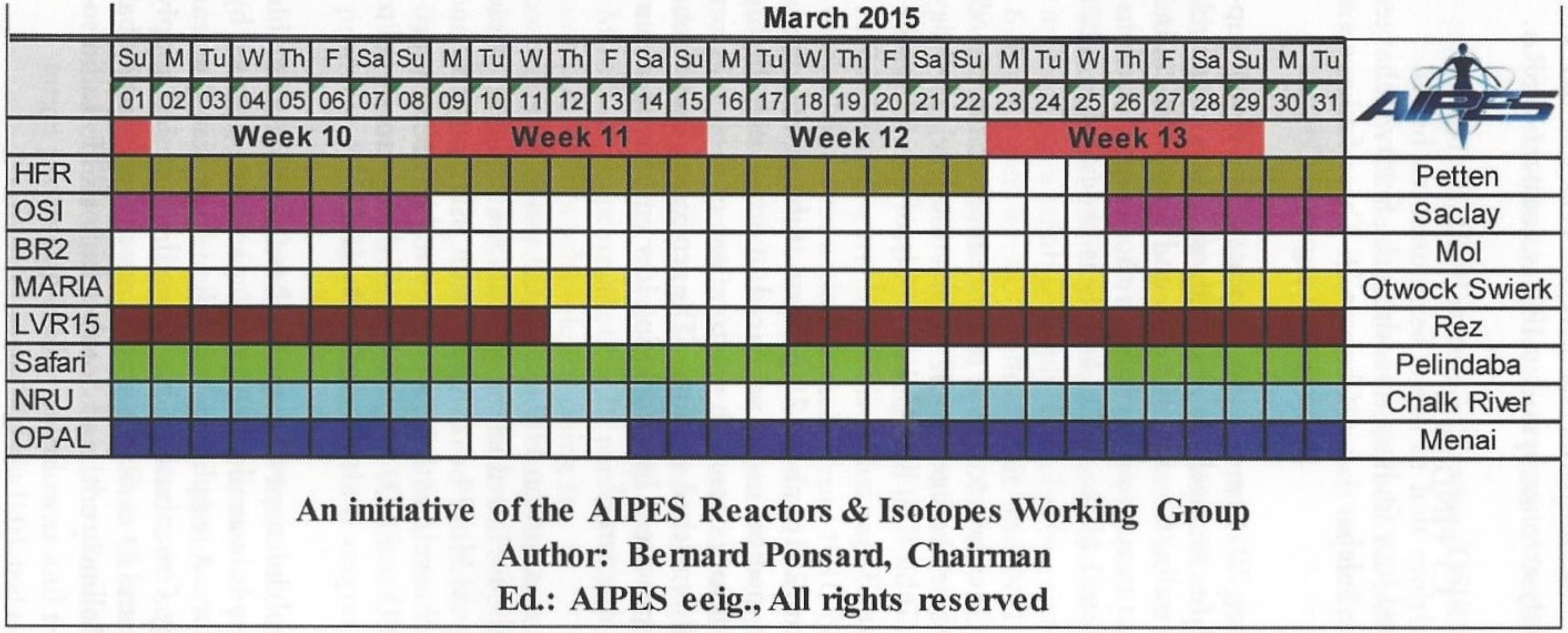


FIGURE 3.4 AIPES Reactor Schedule, first trimester, 2015. NOTES: BR-2 = Belgian Reactor 2; HFR = High Flux Reactor; NRU = National Research Universal; OPAL = Open Pool Australian Lightwater reactor; SAFARI-1 = South African Fundamental Atomic Research Installation 1. SOURCE: Bernard Ponsard, SCK•CEN, written communication, February 11, 2016.

THE REST OF THE SUPPLY CHAIN (NAS 2016)

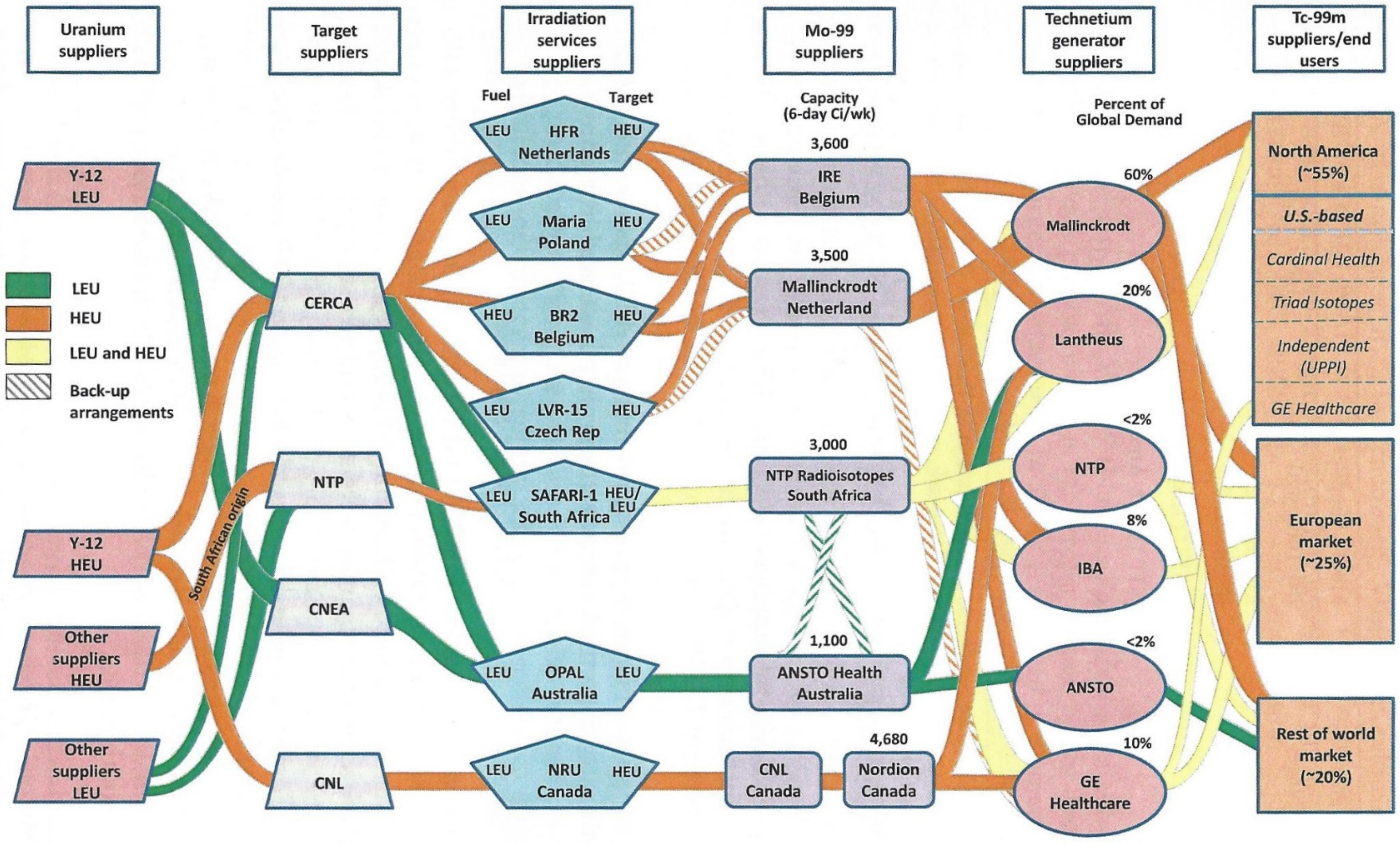


FIGURE 3.1 Mo-99/Tc-99m "global" supply chain. This diagram illustrates the supply chain for about 95 percent of the Mo-99 produced and supplied globally. The remaining 5 percent of Mo-99/Tc-99m supply is produced and supplied regionally.

If Supply cannot meet demand……

The Demand can be modified.

There is Significant Elasticity in the System

More efficient elution of generators for efficient generation of ^{99m}Tc.

More efficient scheduling of patients for optimal use of available Tc99m

Rescheduling of patients for non-critical imaging.

Use of alternative tests to Tc99m labeled drugs/medicines.

Alternative Tests for Tc99m.

NM procedures (Th-201, Rb-82, N-13 ammonia)

Fluoroscopic Angiography

Computed Tomography Angiography

Magnetic Resonance Angiography

Ultrasound

- Doppler
- Intravascular Ultrasound

Non-Imaging actions such as patient history, risk factors, and tests such as EKG or blood tests.

Observations

- **Global demand is down 25%, from 12,000 (2009) to 9,000 (2017) 6-day Curies/week.**
- **The loss of the Canadian NRU and French OSIRIS reactors, have been offset by the addition of OPAL, MARIA, & LVR-15.**
- **There is an additional 35% outage reserve capacity in the model projections.**
- **There is increased awareness and coordination of global Mo-99 production schedules to minimize downtime overlap (AIPES).**
- **There are many potential new entrants using conventional reactor technology.**
- **There are potential new producers, using non-HEU based new technologies.**

Conclusions

The Shortage is effectively over, but only because of the continued effort by many of the players.

"...supply chain capacity should be sufficient and if well maintained, planned and scheduled, be able to manage an unplanned outage of a reactor, or a processor throughout the period to 2022."- OECD 2017

There is concern that not all of the potential future suppliers will be able to successfully enter the market.

References

- Medical Isotope Production Without Highly Enriched Uranium NAS (The National Academy of Sciences) 2009, Washington, D.C.
- Molybdenum-99 for Medical Imaging. NASEM (The National Academy of Sciences, Engineering, and Medicine) 2016, Washington, DC.
- The Supply of Medical Isotopes 2017, Medical Isotope Review: ^{99}Mo/^{99m}Tc Market Demand and Production Capacity Projection 2017-2022, OECD NEA,

Thank you

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