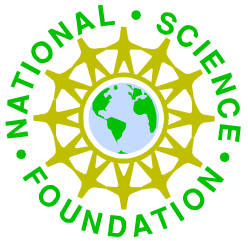
Mo-99 Presentation to NSAC

April 25, 2014

Susan J. Seestrom



Outline

- Charge and Subcommittee process
- Background – the ^{99}Mo issue
- Overview of the NNSA Global Threat Reduction Initiative ^{99}Mo program
- Findings
- Recommendations

Charge to NSAC

Accordingly, we request that NSAC form a Subcommittee to provide an initial assessment of the following charge elements:

- Are NNSA GTRI programmatic goals for establishing a domestic supply of Mo-99 well defined?
- Have the risks in implementing those goals been fully identified?
- What is the current status of implementing these goals?
- Is the strategy for implementing the NNSA goals complete and feasible, within an international context?
- What steps should be taken to improve NNSA program effectiveness in establishing a domestic supply of Mo-99?

Subcommittee Members

Carolyn Anderson, University of Pittsburgh
Jeff Binder, University of Illinois
Ronald Crone, Oak Ridge National Laboratory
Jack Faught, LINDE
Mitch Ferren, Oak Ridge National Laboratory
Donald Geesaman, Argonne National Laboratory
Suzanne Lapi, Washington University Saint Louis
Leonard Mausner, Brookhaven National Laboratory
Meiring Nortier, Los Alamos National Laboratory
Berndt Mueller, Brookhaven National Laboratory
Ken Nash, Washington State University
Joseph Natowitz, Texas A&M University
Thomas Ruth, TRIUMF
Susan Seestrom, Chair, Los Alamos National Laboratory

Subcommittee Process

- The Subcommittee met in the Washington area in January and in February 2014.
- We were briefed by NNSA as well as representations for the OECD, The NAS study group, the FDA, and the NRS.
- We invited all cooperative agreement partners to talk to us; 3 attended.
- We devoted a session to input from the broad stakeholder community.

The Subcommittee was briefed by a number of individuals

- Rod Cameron (by phone) – OECD
- Tom Ruth – representing NAS study group
- Orhan Suleiman – FDA
- Al Adams – NRC
- Erin Grady, *Society of Nuclear Medicine and Medical Imaging*
- Carmen Bigles, *Coquí Radio Pharmaceuticals Corp.*
- Roy Brown, *Mallinckrodt Pharmaceuticals*
- Ira Goldman, *Lantheus Medical Imaging*
- *Presentation from National Association of Nuclear Pharmacies*
- *Representatives of 3 of 4 CA partners*

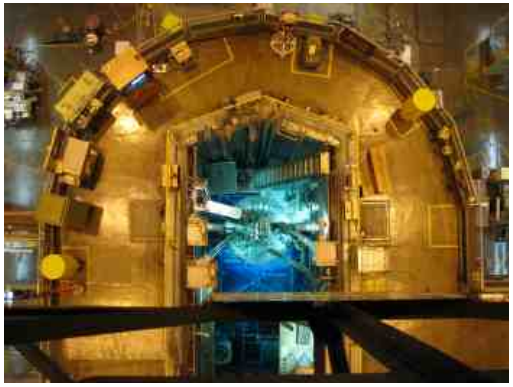
Background

- There is widespread use of ^{99m}Tc for nuclear medicine diagnostic imaging, which is the daughter of ^{99}Mo.
- Today,^{99}Mo is produced by fission of ^{235}U.
- There is U.S. government interest in reducing the use of Highly Enriched Uranium (HEU)
- There was concern in the medical community that this could lead to shortages or a significant increase in price.
- This issue was addressed in the 2009 National Academy study.
- Supply Chain disruptions have occurred 2005-2014
- There is currently no U.S. producer of ^{99}Mo

What is Mo-99?

- Molybdenum-99 (Mo-99) is the parent product of Tc-99m, a radioisotope used in approximately 50,000 medical diagnostic tests per day in the U.S. (over 18 million per year in the U.S.)
- Primary uses include detection of heart disease, cancer, study of organ structure and function, and other applications.
- Mo-99 has a short half life (66 hours) and cannot be stockpiled
- U.S. demand is approximately 50% of the world market
  - The historic global demand is ~12,000 6-day curies per week.
  - Since the 2009-2010 shortages, global demand has been ~10,000 6-day curies per week.
- Mo-99 is produced at only 5 processing facilities worldwide, in cooperation with 8 research reactor facilities
  - Processing facilities located in Canada (HEU), The Netherlands (HEU), Belgium (HEU), South Africa (HEU and LEU), and Australia (LEU)
  - Research reactors used for irradiation located in Canada, The Netherlands, Belgium, France, Poland, Czech Republic, South Africa, and Australia

Tc-99m generator and labeling kits



SAFARI-1 Reactor (South Africa)

Image from the National Academy Study:
Medical Isotope Production Without Highly Enriched Uranium

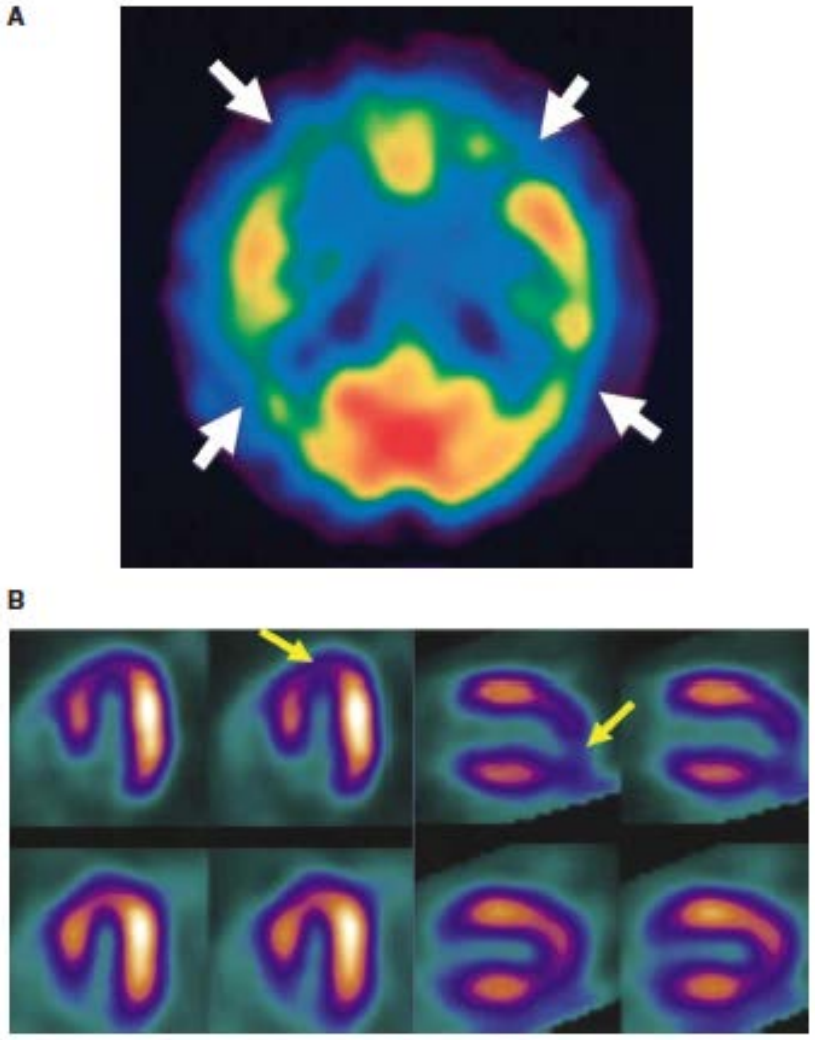
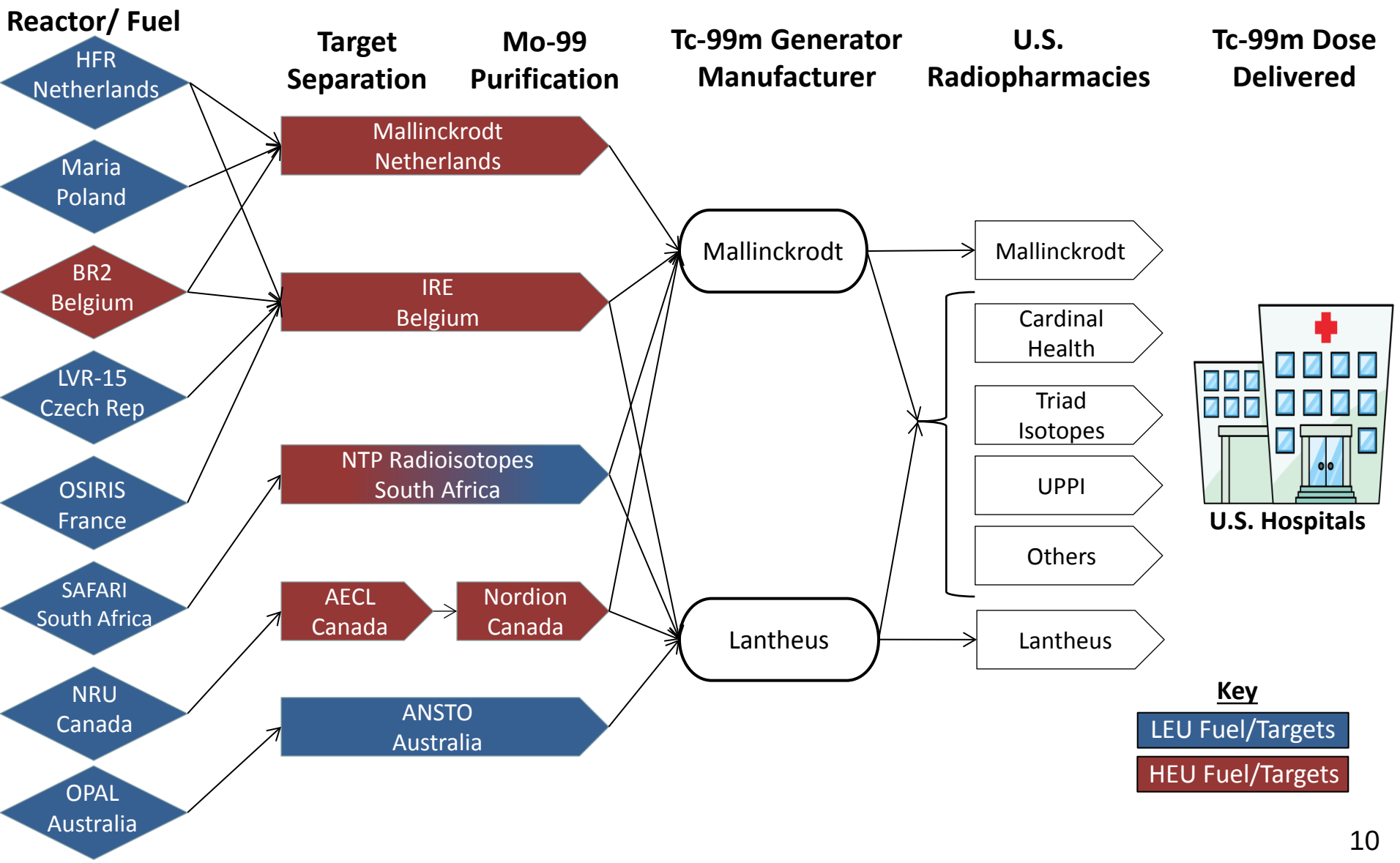


FIGURE 2.3 (a) Image acquired from a Tc-99m cerebral blood flow brain scan of a person with Alzheimer's disease. The arrows indicate areas of diminished blood flow due to the disease. SOURCE: Courtesy of Satoshi Minoshima, University of Washington. (b) Images acquired from a cardiac perfusion SPECT study at stress and rest using a Tc-99m radiotracer. The images on the top row are taken during stress, and the images at rest are shown on the bottom. The arrows indicate areas of decreased perfusion, visualized by the darker colors in the image. SOURCE: Reprinted with permission from Elsevier from Rispler et al., 2007.

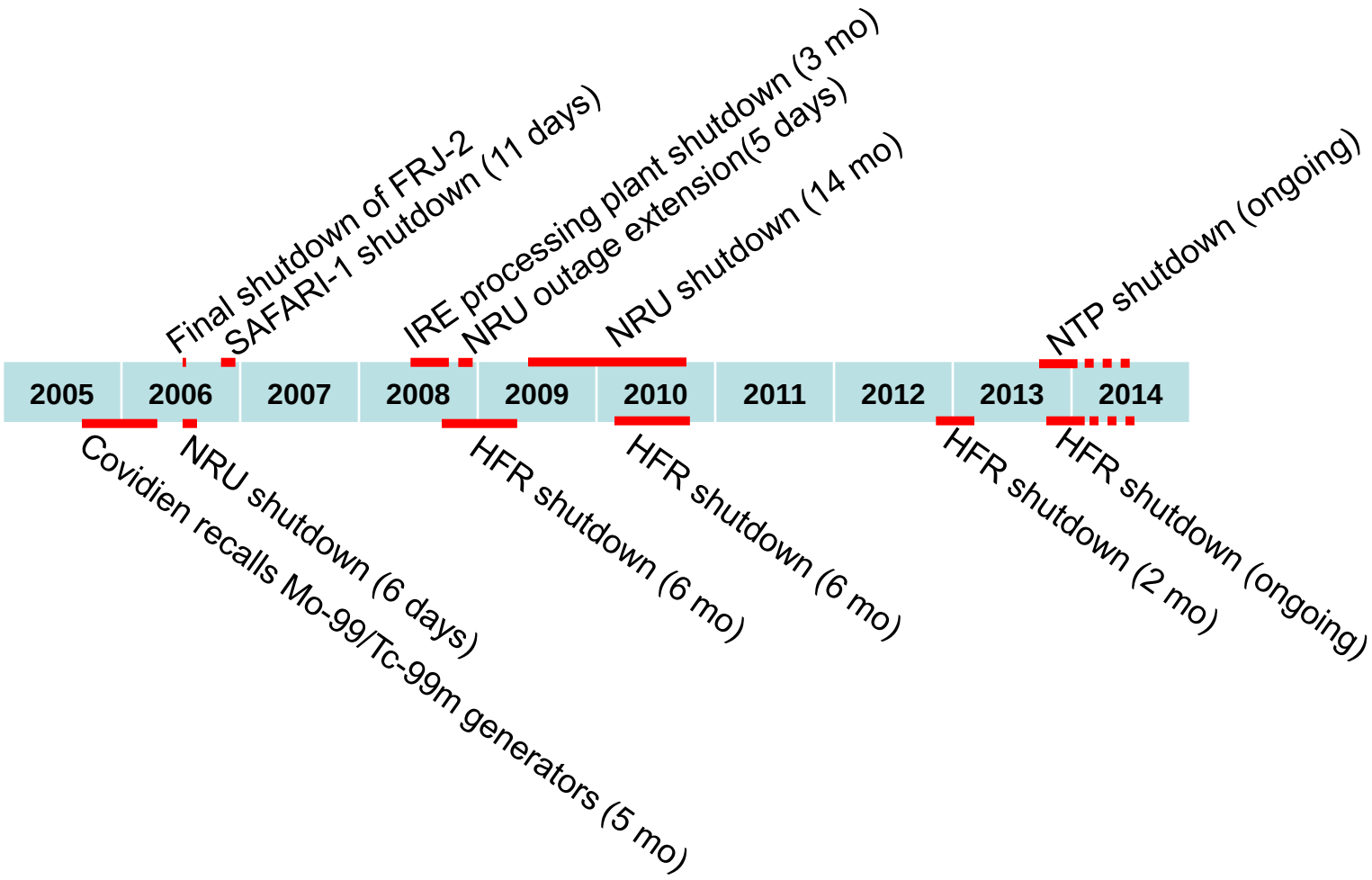
Current U.S. Mo-99 Supply Matrix



U.S. DEPARTMENT OF ENERGY

Major Mo-99 Supply Disruptions 2005-2014

National Nuclear Security Administration
Defense Nuclear Nonproliferation



Economics of the Mo-99 Supply Chain

"All the major producers irradiate targets using multipurpose research reactors, which were originally constructed and operated with 100% government funding, mainly for research and materials-testing purposes. When Mo-99 production started, the reactors' original capital costs had been paid or fully justified for other purposes. As a result, Mo-99 was seen as a by-product that provided another mission for the reactor that could generate extra revenue to support research."

The Supply of Medical Radioisotopes, The Path to Reliability
OECD-NEA, 2011

"This lack of economic sustainability and the related lack of new investment have resulted in a system that has had reliability concerns over the last decade. The shortage seen in 2009 and 2010 is a symptom of this economic problem. Once the short-term supply becomes stable again, it is important to stress that although the symptom has been addressed, the underlying problem – the unsustainable economic structure – has not."

"Overall, it is clear that there is a market failure in the Mo-99 supply chain. This market failure has contributed to a supply chain that is economically unsustainable. This pricing structure has resulted in a lack of investment in current and new infrastructure to reliably supply Mo-99."

The Supply of Medical Radioisotopes,
An Economic Study of the Mo-99 Supply Chain
OECD-NEA, 2010

GTRI Mission & Program Goals

Mission

reduce and protect vulnerable nuclear and radiological material located at civilian sites worldwide.

Goals

1. Convert
2. Remove
3. Protect

Convert

Convert research reactors and isotope production facilities from the use of highly enriched uranium (HEU) to low enriched uranium (LEU)

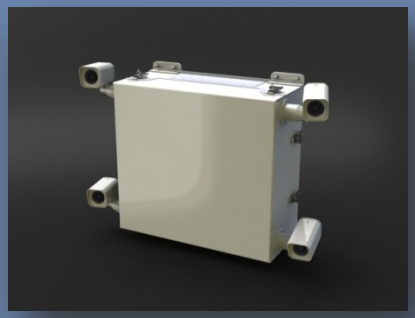
These efforts result in permanent threat reduction by minimizing and, to the extent possible, eliminating the need for HEU in civilian applications – each reactor converted or shut down eliminates a source of bomb material.

Remove

Remove and dispose of excess nuclear and radiological materials.

These efforts result in permanent threat reduction by eliminating bomb material at civilian sites – each kilogram or curie of this dangerous material that is removed reduces the risk of a terrorist bomb.

Protect



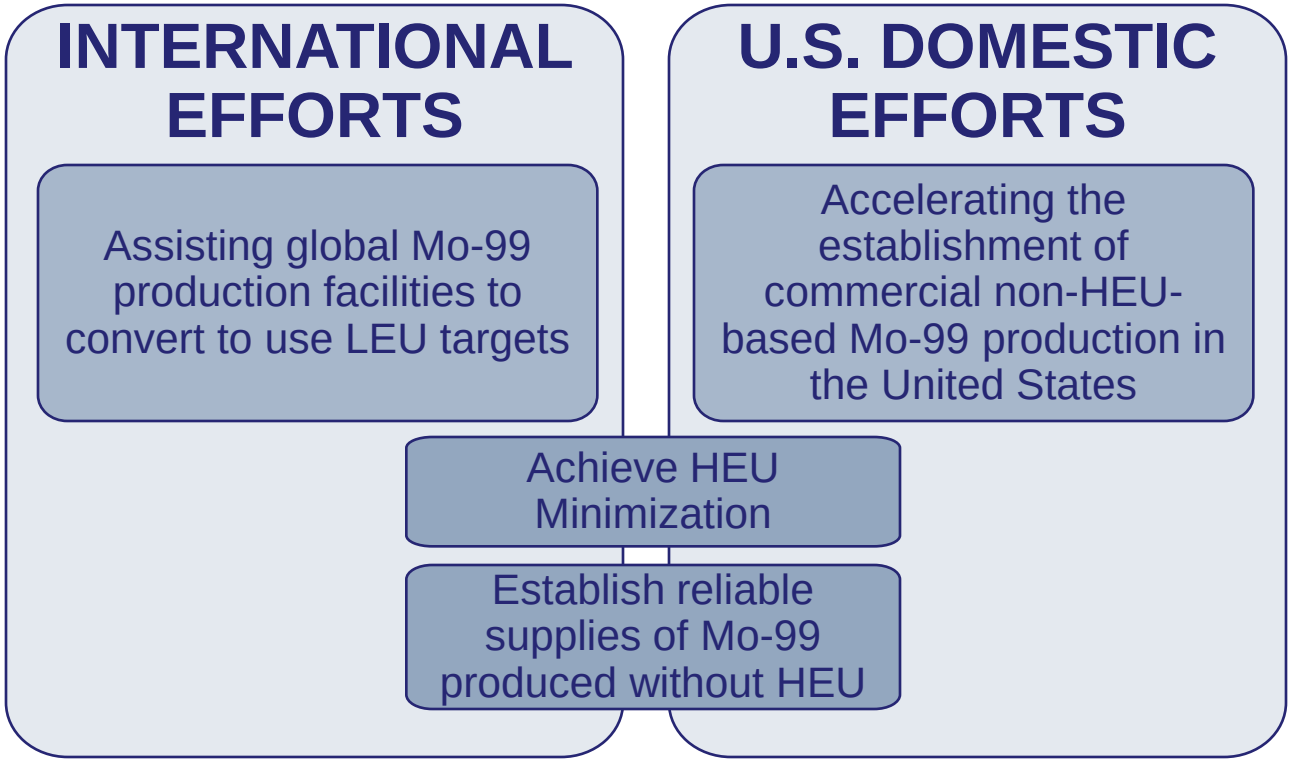
Protect high priority nuclear and radiological materials from theft and sabotage

These efforts result in threat reduction by improving security on the bomb material remaining at civilian sites – each vulnerable building that is protected reduces the risk until a permanent threat reduction solution can be implemented.

GTRI's Mo-99 Objective and Strategy

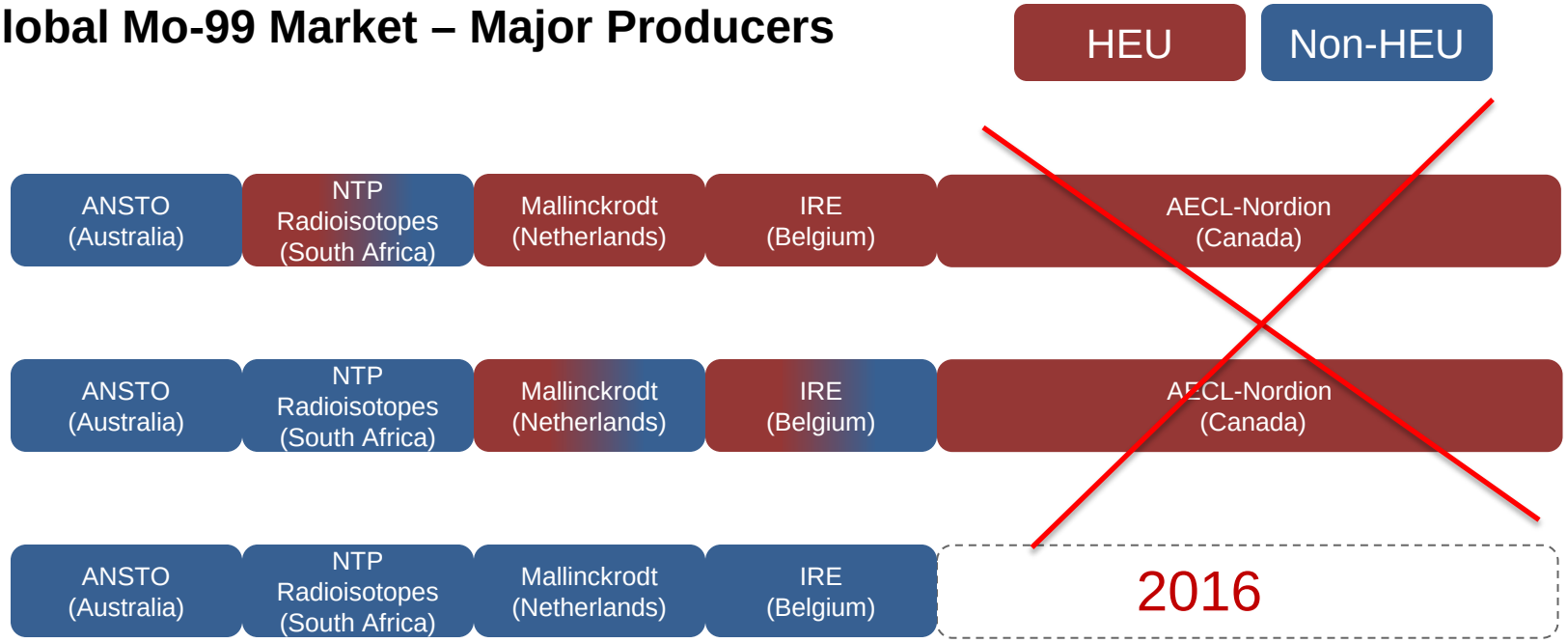
International & U.S. Domestic Approaches

- Under its long-standing HEU minimization mission, GTRI provides assistance to research reactors and isotope production facilities to convert from the use of HEU to LEU.
- GTRI's mission includes accelerating the establishment of a reliable U.S. domestic supply of Mo-99 produced without the use of HEU.



GTRI's Strategy for Reliable Non-HEU-Based Mo-99 Supply

Global Mo-99 Market – Major Producers

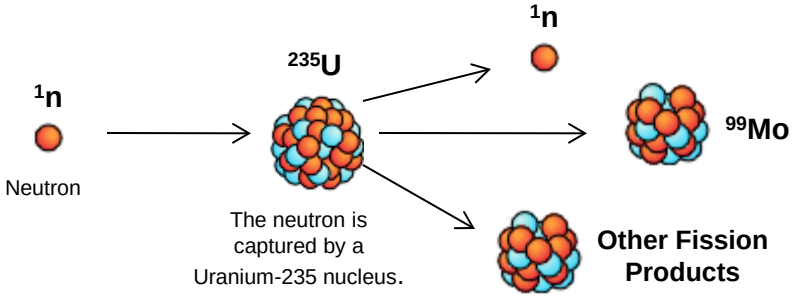


U.S. Domestic Mo-99 Projects

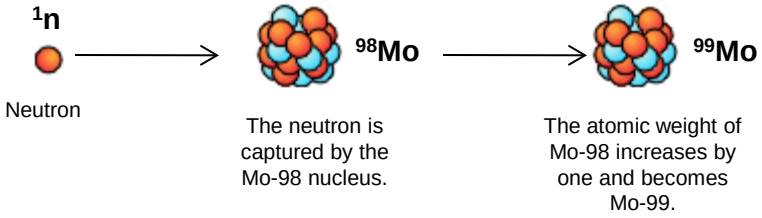
GTRI and U.S. Domestic Mo-99

Implementing a Technology-Neutral Program

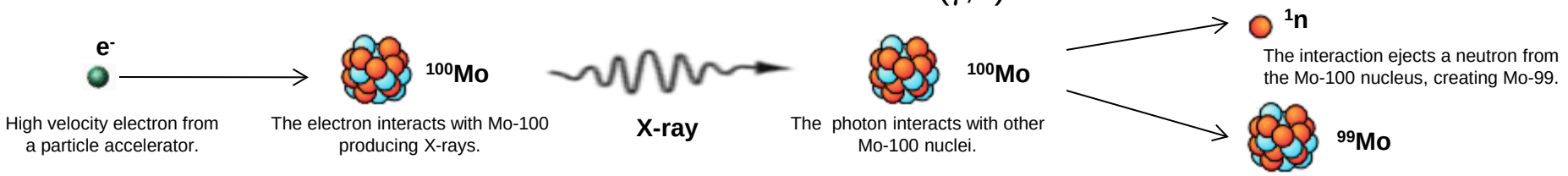
LEU Fission Based: ^{235}U (n,f)



Neutron Capture:(n,γ)



Accelerator Based: (γ,n)



GTRI and U.S. Domestic Mo-99
Cooperative Agreement Partners

Objective: To accelerate existing commercial projects to meet at least 100% of the U.S. demand of Mo-99 produced without HEU.

NorthStar Medical Radioisotopes, LLC

- NNSA has partnered with NorthStar Medical Radioisotopes to pursue accelerator and neutron capture technologies.

Morgridge Institute for Research/SHINE Medical Technologies

- NNSA has partnered with Morgridge Institute for Research to pursue accelerator with LEU fission technology in cooperation with SHINE Medical Technologies.

Babcock and Wilcox (B&W):

- NNSA has partnered with Babcock and Wilcox (B&W) to pursue LEU solution reactor technology.

General Electric-Hitachi (GEH):

- NNSA has partnered with General Electric-Hitachi to pursue neutron capture technology.

Each cooperative agreement is awarded under a 50% - 50% cost-share arrangement, consistent with the American Medical Isotopes Production Act and Section 988 of the Energy Policy Act of 2005. The cooperative agreements are currently limited to $25M each.

Cooperative Agreement Awards

- B&W and GEH were awarded cooperative agreements through the NNSA Albuquerque Complex under a Determination of Non-Competitive Financial Assistance in September 2009, following an evaluation by a merit review board of independent technical experts.

- In March 2010, GTRI issued a Funding Opportunity Announcement to select partners to develop LEU target technology and accelerator technology to produce Mo-99. NNSA received eight proposals and following their evaluation by a merit review board of independent technical experts, GTRI offered awards to three entities in September 2010. These included:

    - LEU Target technology:
        1. General Atomics

    - Accelerator technology:
        2. Morgridge
        3. NorthStar

Funding through Cooperative Agreement Awards

For each of GTRI's domestic Mo-99 projects, NNSA must be compliant with the National Environmental Policy Act (NEPA). GTRI provides support to the cooperative agreement partners in two phases in accordance with NEPA obligations:

- **Phase 1:** GTRI supports activities that are "categorically excluded" from NEPA, or already covered under an existing NEPA document.
  e.g. conceptual and preliminary design, project management, engaging with regulator, etc.

- **Phase 2:** Once GTRI's NEPA obligations are fulfilled, GTRI has the ability to fully fund the cooperative agreement partner for all activities, up to the current total funding limit of $25M.

Each cooperative agreement is awarded under a 50% - 50% cost-share arrangement, consistent with the American Medical Isotopes Production Act and Section 988 of the Energy Policy Act of 2005.

The cooperative agreements function as a reimbursement system, where the partner submits expenses accrued and NNSA pays 50% of those expenses up to the award amount.

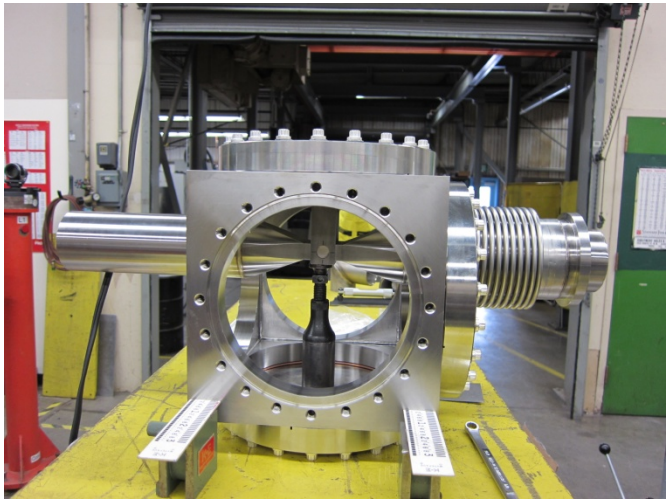
The cooperative agreements are currently limited to $25M each. Beyond the Government funding provided under the cost-sharing arrangement, all costs incurred will be the responsibility of the commercial entity.

U.S. National Laboratories Support to Mo-99 Production

GTRI makes the expertise of the U.S. National Laboratories available to:

- Support technical development of each of the Mo-99 technical pathways
- Ensure the expertise at the national laboratories is available to support the acceleration of commercial projects using non-HEU technologies

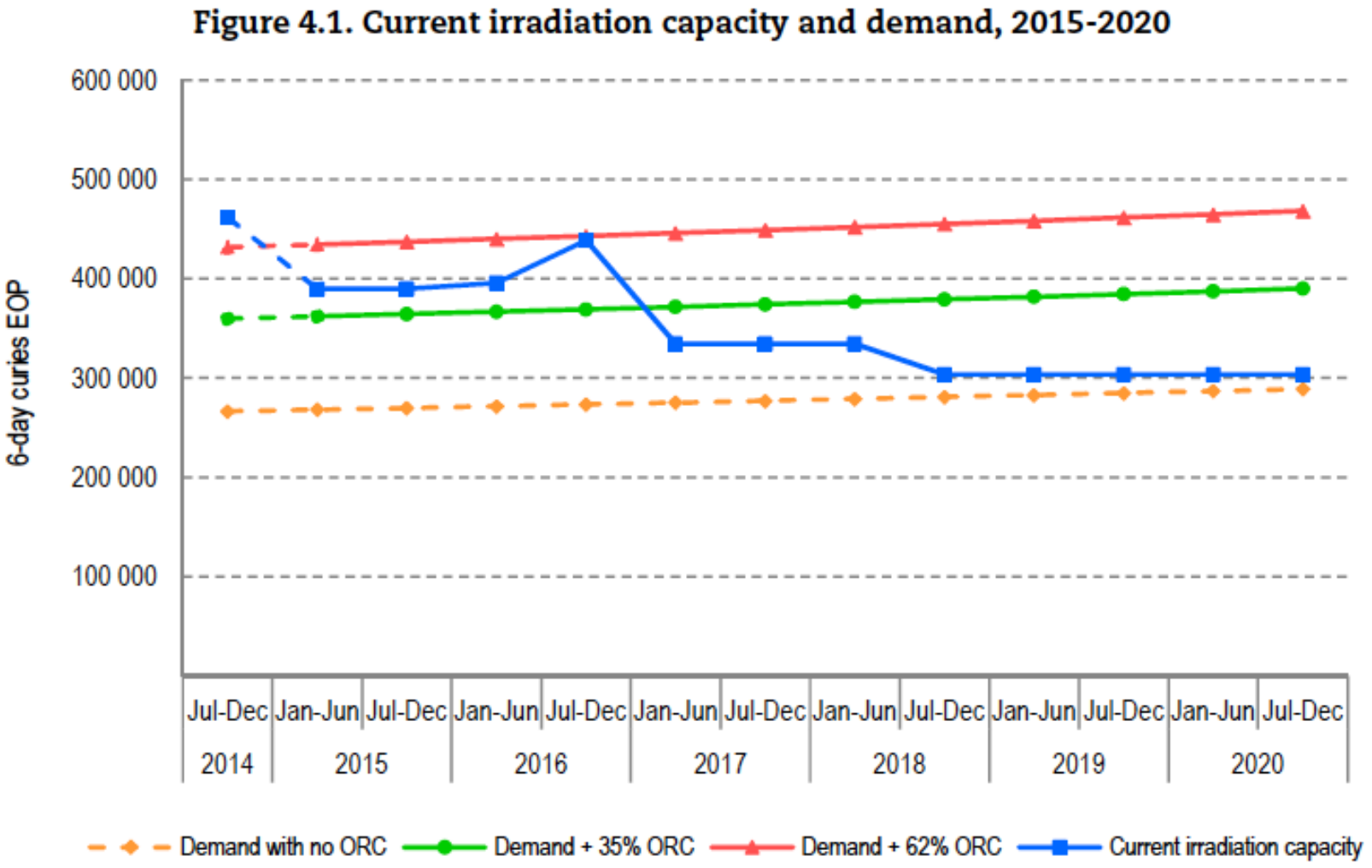
All work packages funded by NNSA outside the cooperative agreement are open-sourced, non-proprietary, non-critical-path activities.



General Conclusions

- There is a complex international situation, with many factors outside the direct control of NNSA
- It is *plausible* there will be a reliable U.S. supply of ^{99}MO >2016.
  - Risk associated with aging facilities
- NNSA is working with the international community to achieve full cost recovery and thus a level playing field for new U.S. producers.
- NNSA is trying to accelerate development of new domestic suppliers – funding seems to be an issue.

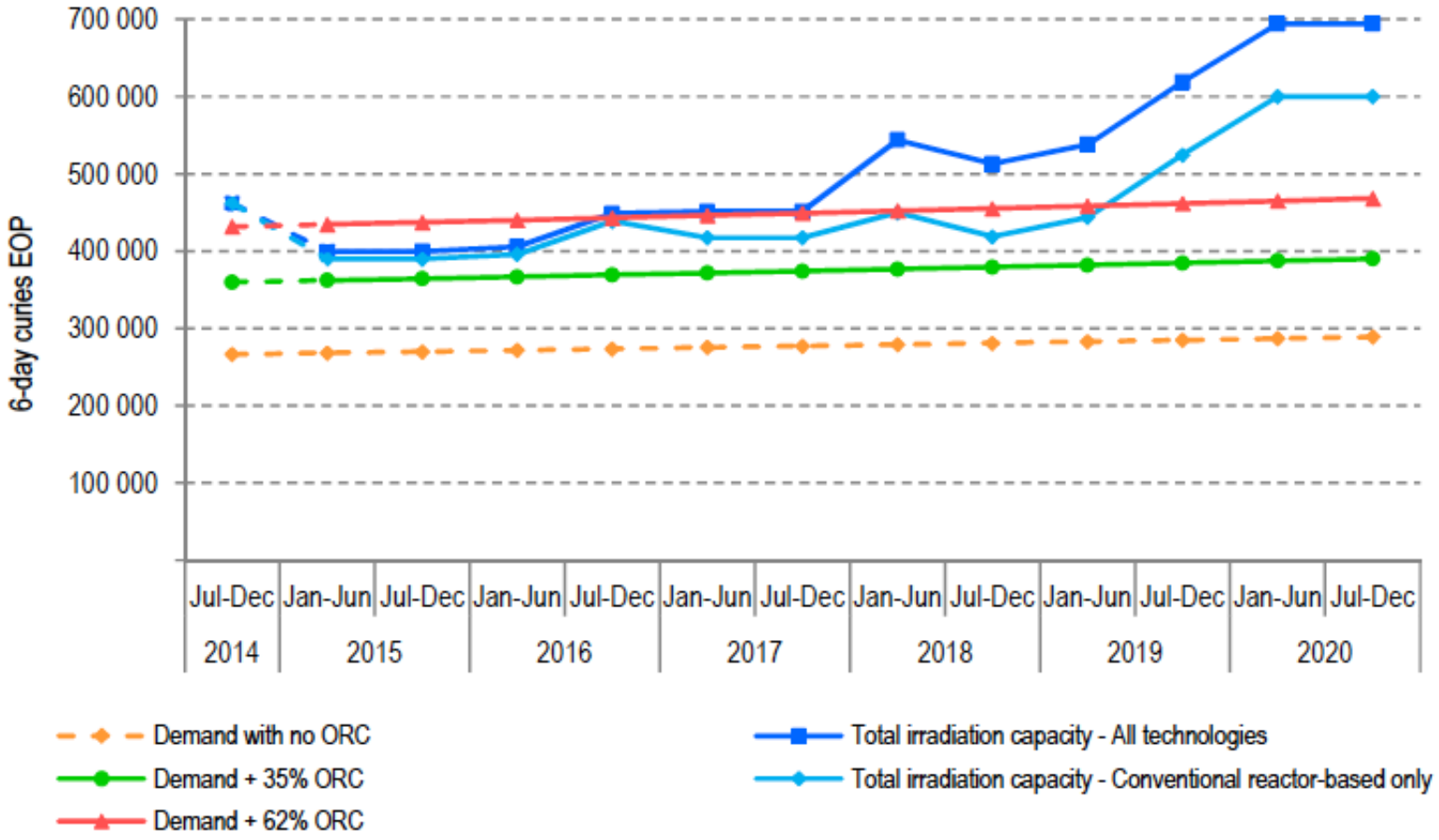
OECD* Estimates of Supply/Demand



April 2014: Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the 99Mo/99mTc Market, 2015-2020

OECD* Estimates of Supply/Demand with projected new capability

Figure 5.1. Current and selected new irradiation capacity and demand, 2015-2020



April 2014: Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the 99Mo/99mTc Market, 2015-2020

Are the NNSA GTRI goals for establishing a domestic supply of ^{99}Mo well defined?

- The NNSA overarching programmatic objective is to accelerate the establishment of reliable supplies of the medical isotope ^{99}Mo molybdenum produced without highly enriched uranium.
- This goal is not specific as to timelines or what constitutes “acceleration.”
- There are specific and well defined goals for the commercial partners.
  - For each of the four cooperative agreements the goal was to provide 3,000 6-day curies of ^{99}Mo per week by 2016 (re-baselined from the original December 31, 2013).

What is the current status of implementing these goals?

- None of the CA partners met the original goal to produce 3,000 6-day Curies by 2014
- Only one of has a high probability of producing any ^{99}Mo in 2014
- Two partners have paused their efforts

Have the risks in implementing those goals been fully identified?

- NNSA has compiled a comprehensive list of risks
- In some cases the risks are more complex than indicated by NNSA:
  - Potential market saturation that could negatively impact potential new suppliers is a risk that has been identified.
    - There is suspicion among potential suppliers that NRU might not shut down in 2016 there are additional market risks.
    - The ANSTO OPAL reactor is coming online with a new LEU based production capability.
    - Other potential foreign sources have been proposed.
    - Foreign entities could ignore the international protocols and market with less expensive HEU produced ^{99}Mo.
    - If all of the NNSA initiatives were successful, the market would be oversaturated.
  - Having only a foreign source of a reliable, cost effective supply of stable Mo isotopes needed for production of ^{99}Mo by neutron capture (^{98}Mo, ^{100}Mo), without a domestic supply, is a potential risk.
- NNSA is working to mitigate risks, but there are many that are outside their control

Is the strategy complete and feasible, within an international context?

- The NNSA strategy to achieve their vision is two-fold:
  - to help international suppliers transition to the use of non-HEU targets
  - to establish commercial non-HEU based production capability in the U. S.
    - address weaknesses in the global supply chain
    - assist commercial entities seeking to enter the market with new technologies.

Availability of ^{99}Mo from LEU targets

- Commitments from the major producers of ^{99}Mo to move to LEU targets are in place.
- The time lines for this conversion vary greatly among the producers.
- Results are highly dependent upon the internal efforts of each manufacturer.

Weakness in the supply chain

- The NNSA has worked with the OECD and the international community to achieve agreement to the HLG-MR Policy principles
- The White House released a Fact Sheet announcing possible options to support the establishment of a reliable supply of ^{99}Mo produced without HEU
- Belgium, the Netherlands, and France, in cooperation with the United States, reaffirmed "*their determination to support conversion of European production industries to non-HEU-based processes by 2015…*"

Development of a domestic supply of ^{99}Mo

- Establish cooperative agreements (CAs) based on new technologies.
- Support with non-proprietary research at national labs.
- Work with other government agencies to facilitate approval of new product.
- A significant risk appears to be the ability of the commercial partners to attract the private investment for production facility construction without a guarantee of full cost recovery by all international competitors.

Is the strategy complete and feasible, within an international context?

- The strategy is feasible.
- There are significant risks to success on the time lines indicated, and consequently it is not complete.
- While the NNSA also considers that achieving a stable U.S. supply without any domestic production of ^{99}Mo to be an acceptable outcome, the Subcommittee has identified this as a risk to achieving a stable supply.

Recommendations

1. NNSA should look carefully across the domestic production part of the ^{99}Mo program in view of present facts (such as progress on CA projects, economic environment for capital and projected operating costs) in order to focus resources on the most promising CA agreements.
2. Based on the slowness of progress toward implementation of full cost recovery internationally, NNSA should consider relaxing their present $25M cap on investment in any project. This change could increase the likelihood of generating a successful domestic producer of ^{99}Mo as the international market continues to move toward full cost recovery. This would address one of the major risks in the present program

BACKUPS

OECD Conclusions on Risk

Despite the risk of supply shortages in the first half of the forecast period, both alternative scenarios in this report that include new 99Mo production capacity indicate significant over-capacity in the market by 2020. Much of this new capacity may not be commercially based, which would present future challenges for producers who have or will have implemented full-cost recovery by then, and other new projects that are being planned to operate on full-cost recovery. In the limit, those producers could be forced to exit the market because of a lack of ability to compete on price. This emphasizes the need for all countries to implement the six HLG-MR policy principles in a timely and globally consistent manner.

The results from this 2015-2020 capacity forecast reinforce the need to establish an economically sustainable 99Mo/99mTc supply chain as quickly as possible. This would enable investment in new/replacement, non-HEU-based production capacity and its timely entry in operation, and provide sufficient amounts of funded ORC to the market. The ageing fleet of research reactors – the backbone of global 99Mo production at present and for the foreseeable future – and recent extended outages at major producers, underscore the importance of universally adopting full-cost recovery and funded ORC.

Other Potential Domestic Mo-99 Producers*

- Alpha Source, LLC
- American Medical Isotopes Company
- Coquí Radiopharmaceuticals
- Eden Radioisotopes, LLC
- FLiBe Energy
- General Atomics
- GreenTec99
- Northwest Medical Isotopes
- Nuclear Applications Company
- PermaFix
- Precision Engineering Consultants, Inc.
- U.S. Radiopharmaceuticals

* This list is not exhaustive, and GTRI does not have insight in to the details of the projects. GTRI keeps apprised of potential producers through interaction during the OSTP Stakeholders Meeting, the OECD-NEA's High Level Group on the Security of Supply of Medical Radioisotopes, and the Mo-99 Topical Meeting.

The American Medical Isotopes Production Act of 2012

- The Act was incorporated in the National Defense Authorization Act for Fiscal Year 2013 and enacted on January 2, 2013.

- Intended to help establish a reliable domestic supply of Mo-99 produced without the use of HEU and includes a number of short, medium, and long-term actions.

  - Requires the Secretary of Energy to establish a technology-neutral program to provide assistance to commercial entities to accelerate production of Mo-99 in the United States without the use of HEU

  - Requires annual public participation and review

  - Requires development assistance for fuels, targets, and processes

  - Establishes a Uranium Lease and Take Back program

  - Requires DOE and NRC to coordinate environmental reviews where practicable

  - Provides a cutoff in exports of HEU for isotope production in 7 years, with possibility for extension in the event of a supply shortage

  - Requires a number of reports to be submitted to Congress

GTRI's Mo-99 Objective and Strategy

Objective: Accelerate the establishment of reliable supplies of the medical isotope molybdenum-99 produced without highly enriched uranium

GTRI's strategy seeks to address weaknesses in the current Mo-99 supply chain:

- The current supply chain uses HEU to produce Mo-99
- Most Mo-99 production in today's marketplace is subsidized by foreign governments
- The current supply chain does not always have enough reserve capacity to ensure a reliable supply when one or more producers are out of operation
- The current supply chain is primarily dependent on aging facilities
- The current supply chain relies on one technology to produce Mo-99

A long-term, reliable supply of Mo-99 requires that global production of Mo-99 transition to a full-cost recovery, non-HEU-based industry

Other USG Initiatives

In addition to the American Medical Isotopes Production Act, there are other USG efforts to help achieve the objective to accelerate the establishment of reliable supplies of the medical isotope Mo-99 produced without HEU, including:

- White House Fact Sheet on Mo-99
- Participating in various domestic and international working groups
- Mo-99 stakeholder outreach
- Ensuring the implementation of OECD-NEA policy recommendations in the United States

GTRI and U.S. Domestic Mo-99
Cooperative Agreement Partners

Objective: To accelerate existing commercial projects to meet at least 100% of the U.S. demand of Mo-99 produced without HEU.

To achieve this objective, NNSA has partnered with four commercial entities:

- **NorthStar Medical Radioisotopes**
- **Morgridge Institute for Research - SHINE Medical Technologies**
- **Babcock and Wilcox (B&W)**
- **General Electric Hitachi (GEH)**