Understanding the Radiopharmaceutical Drug Supply Problem: Session 1

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The Council on Radionuclides and Radiopharmaceuticals, Inc. (CORAR) is an association comprised of companies in the United States and Canada who manufacture and distribute radiopharmaceuticals, sealed sources, radionuclides, and contrast agents primarily used in medicine and life science research. CORAR is tasked with advocating for regulations and legislation that facilitate the growth and viability of its member companies.
CORAR Member Companies

- Bayer Healthcare Pharmaceuticals
- Cardinal Health Nuclear Pharmacy Services
- Eckert & Ziegler Radiopharma
- International Isotopes Inc.
- Jazz Pharmaceuticals, Inc.
- Jubilant DraxImage Inc.
- Lantheus Medical Imaging
- Mallinckrodt Pharmaceuticals
- Northwest Medical Isotopes, Inc.
- Nordion, Inc.
- Northstar Medical Technologies, LLC
- Pharmalucence
- SHINE Medical Technologies
- Spectrum Pharmaceuticals, Inc.

- Mo-99/Tc-99m generator manufacturers
- Mo-99 processors
- Radiopharmaceutical manufacturers
- PET manufacturers
- Nuclear pharmacies
- Sealed sources and isotope based products
- DOE Cooperative Agreement Partners
Anti-Trust Guidance

• The federal and state antitrust laws are intended to ensure that there be free and open competition to the maximum extent possible. The antitrust laws prohibit most business behavior that unreasonably restrains competition.

• CORAR complies with US anti-trust laws and we are prohibited from discussing:
  – Current or future selling prices
  – Contract terms and conditions
  – Discounts
  – Specific product costs
  – Market plans relative to entering or exiting markets or product categories
Learning Objectives

- Describe current government programs working to improve the supply of medical radioisotopes.
- Discuss the Department of Energy/National Nuclear Security Administration efforts to make medical radioisotopes available for commercial and research applications.
- Discuss the current and projected production and availability of molybdenum-99 (Mo-99).
- Discuss possible constraints to Mo-99 supply in 2016 and beyond.
- Describe the trigger (think process) for enacting the emergency use clause for National Research Universal to produce Mo-99.
- Recognize U.S. obligations under international trade agreements to sustain non–highly enriched uranium production.
What is Mean Age of Current Mo-99 Producing Reactors?

- A. 27 years
- B. 33 years
- C. 47 years
- D. 54 years
Mo-99 Background

- Mo-99 is the parent isotope of Tc-99m
  - Used in ~80% of the nuclear medicine procedures worldwide
  - 30 to 40 MM Tc-99m procedures worldwide annually
- Mo-99 provided through international supply chain
  - Current Mo-99 facilities and infrastructure are aging
- Severe Mo-99 shortages in 2009 and 2010
  - Unexpected and extended shutdowns of key research reactors producing Mo-99
  - Substitute isotopes were used
  - Shift to other modalities occurred
- Nuclear pharmacies have increased Tc-99 efficiencies since 2009 and 2010
- Currently, no producer of Mo-99 in United States
  - Significant number of potential domestic Mo-99 producers
Mo-99 Background

- Worldwide Mo-99 demand has decreased since 2009
  - Reported in recent OECD HLG-MR supply demand report
- Reduction and elimination of Highly Enriched Uranium (HEU) based Mo-99 production
  - US Government GTRI mission to reduce and eliminate the use of HEU for medical isotope production
  - Current fission technology has relied on HEU
  - Fission based producers are converting to Low Enriched Uranium (LEU)
  - Some new technology doesn’t rely on U^{235}
- American Medical Isotope Production Act (AMIPA) 2013
  - Non-HEU domestic Mo-99/Tc-99m production
  - Uranium lease and waste take-back
  - Phase-out HEU exports over seven years
Mo-99 Targets:

- **LEU**: ANSTO/OPAL, NTP/SAFARI
- **HEU**: Mallinckrodt w/HFR, MARIA, Nordion/NRU, IRE w/BR2, HFR, LVR-15, OSIRIS

Mo-99 Supply Chain
Reactors & Processors
## Current Global Mo-99 Sources

<table>
<thead>
<tr>
<th>Reactor</th>
<th>Location</th>
<th>Commissioning Date</th>
<th>Fuel Type</th>
<th>Target Type</th>
<th>Global Mo-99 Processor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRU</td>
<td>Chalk River, Canada</td>
<td>1957</td>
<td>LEU</td>
<td>HEU</td>
<td>Nordion</td>
</tr>
<tr>
<td>HFR</td>
<td>Petten, Netherlands</td>
<td>1961</td>
<td>LEU</td>
<td>HEU*</td>
<td>Mallinckrodt/IRE</td>
</tr>
<tr>
<td>BR2</td>
<td>Mol, Belgium</td>
<td>1961</td>
<td>HEU</td>
<td>HEU*</td>
<td>Mallinckrodt/IRE</td>
</tr>
<tr>
<td>SAFARI</td>
<td>Pelindaba, South Africa</td>
<td>1965</td>
<td>LEU</td>
<td>HEU/LEU**</td>
<td>NTP</td>
</tr>
<tr>
<td>MARIA</td>
<td>Otwock-Swierk, Poland</td>
<td>1974</td>
<td>LEU</td>
<td>HEU*</td>
<td>Mallinckrodt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1993 (rebuilt)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVR-15</td>
<td>Rez, Czech Republic</td>
<td>Mid 1950’s</td>
<td>LEU</td>
<td>HEU*</td>
<td>IRE</td>
</tr>
<tr>
<td>OPAL</td>
<td>Lucas Heights, Australia</td>
<td>2007</td>
<td>LEU</td>
<td>LEU</td>
<td>ANSTO</td>
</tr>
</tbody>
</table>

*In the process of converting to LEU targets
** Phase HEU out in 2016
LEU - Low Enriched Uranium
HEU - Highly Enriched Uranium

Mean age ~ 47 years
Exclude Opal – Mean Age of Remaining Reactors ~ 54 years
Delivering Reliable Supply

• Current Mo-99 Production
  – Extra targets added at current reactors
  – Additional reactors were added to the fleet (Maria and LVR-15)
  – Increasing Outage Reserve Capacity (ORC)
  – Use of higher neutron flux positions in reactors

• Mo-99 Generator Manufacturers
  – Supply chain diversification; multi-sourcing Mo-99 (requiring mutual back-up arrangements)
  – Advance planning for scheduled outages

• Nuclear Pharmacies
  – Improving Tc-99m efficiency (e.g. reduce bulk Tc-99m, optimize delivery, new information technology)

• Hospitals and Physician Offices
  – Coordinate patient scheduling with Tc-99m availability
Delivering Reliable Future Supply

- New North American Mo-99 Production Options – CORAR Members:
  - Northwest Medical Isotopes, LLC:
    - Traditional fission (reactor) based approach irradiating LEU targets
    - Process irradiates targets/recover Mo-99 and recycle Uranium
  - Nordion, Inc.:
    - In conjunction with General Atomics and MURR research reactor using LEU targets with Selective Gaseous Extraction Technology
  - NorthStar Medical Technologies, LLC:
    - Traditional reactor irradiation of stable molybdenum targets; either natural Mo-98 or enriched Mo-98 and
    - Accelerator irradiation utilizing stable enriched Mo-100 targets
  - SHINE Medical Technologies
    - Accelerator based technology utilizing LEU solution

- Ongoing Efforts:
  - Mallinckrodt Pharmaceuticals
    - Enhancing Mo-99 production capacity
    - Converting to LEU targets
    - LEU Generators
  - Lantheus Medical Imaging
    - Diversifying Mo-99 and Xe-133 supply chain
    - LEU Generators
Reliable Supply - NRU Post 2016

• Natural Resources Canada Announcement (Feb. 6, 2015)
  – NRU operations extended to March 31, 2018; thereafter will be decommissioned
  – Support global Mo-99 demand between 2016 and 2018 in the unexpected circumstances of severe shortage
  – Other medical isotopes will continue to be produced (not Mo-99 or Xe-133)
  – Reactor will have a routine operating schedule

• CORAR Appreciates Canadian Government decision to support continuing operations of NRU reactor as a back-up Mo-99 producer from November 2016 - March 2018
  – Ensure that patients have continued access to important nuclear medicine products and procedures
Additional Domestic Mo-99 Projects

• Coqui Radiopharmaceuticals
  – Twin research-level small nuclear reactors using LEU targets
  – Radiochemical processing plant for Mo-99

• Niowave, Inc.
  – Superconducting electron linear accelerator using LEU ($\gamma,n$)
  – Radiochemical processing plant for Mo-99

• PermaFix
  – Neutron capture of Mo-98
  – Mo-99 loaded on a column containing proprietary ion-exchange material

• This is not an all inclusive list
Key Points

• Increased Mo-99 efficiencies have been realized in the supply chain
• Worldwide Mo-99 demand has decreased since 2009 – as reported by the OECD
• Fission production of Mo-99 will convert to LEU
• Current Mo-99 manufacturers have publicly reported increases in Mo-99 production capacity by current producers
• Canadian government plans for NRU - supplier of last resort through March 31, 2018
• Potential domestic Mo-99 producers are working on several technology tracks – none require HEU
  – Augment international Mo-99 production activities
  – Domestic Mo-99 supply for patients in the United States
• Reduced risk for short and mid-term global Mo-99 shortages
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