LESSONS LEARNED DURING CONVERSION FROM HEU TO LEU

Roy W. Brown
September 24, 2018
INTRODUCING CURIUM

CURIUM – UNITING IBA MOLECULAR AND MALLINCKRODT NUCLEAR MEDICINE LLC

• January 27, 2017 – Mallinckrodt Pharmaceuticals completed the sale of its Global Nuclear Imaging business to IBA Molecular.

• 100 years of combined experience in the nuclear medicine industry.

• Singular focus – to develop, manufacture and supply SPECT, PET and therapeutic radiopharmaceuticals.

• More than 1,600 dedicated employees work to provide nuclear medicine products for over 14 million patients worldwide each year through 6,000 customers in 70 countries.

• Largest vertically integrated radiopharmaceutical manufacturing network with one global Mo-99 production facility, three large SPECT manufacturing facilities, and more than 40 SPECT and PET radiopharmacies.
LEU TARGET COMPOSITION

- The new LEU target was designed so it would meet the needs for Mo-99 production, reactor compatibility and fabrication.
- The Al alloy cladding chosen for metallurgy principles contained a metallic impurity which created a new chemistry removal challenge in the process development.
- The target manufacturing process at CERCA (Framatome) introduced another metallic impurity into the LEU targets, which created a new chemistry removal challenge.
- Similar issues were also faced by Mo-99 processors NTP and IRE in their conversion efforts, leading to longer development time.
RESOLVED METALLIC IMPURITY ISSUE IN ALLOY

• We confirmed the metallic impurity in the LEU targets formed oxides and clogged the uranium filter, slowing the filtration process.
• We did not want to change the AG3 alloy in the new LEU target because it would have added at least 12-18 months to the conversion.
• We designed/tested/validated a new uranium filter which could handle the metallic impurity load and still optimize waste disposal.
RESOLVED METALLIC IMPURITY ISSUE IN TARGET

- Metallic contamination from target manufacturing process caused problems in the radiochemistry process.
- Although Y-12 (Oak Ridge National Lab – U.S.) can control the level of metallic impurity in the bulk LEU, that same metal was being added as part of the target manufacturing process.
- Any of this metallic impurity contained in the target as a contaminant, is activated to a radionuclide of concern during the target irradiation process.
- Any of this radionuclide of concern present in the finished Mo-99 presents a problem.
- We added an additional sorbent column to remove this metallic contaminant, and to ensure the absence of any of this metal in the finished product.
OTHER CHALLENGES OVERCOME

• Unexpected shutdowns of the HFR and MARIA and the Be matrix replacement in the BR2 during time scheduled for validation runs caused delays in the irradiation schedules.

• Previously drug regulatory agencies had a final material specification check for gross alphas, whereas new requirements specified development of methods for sampling and measuring Pu-239, Am-241 and U-235 individually.

• Updated approval by the French transport competent authority (ASN/IRSN) was needed for the Type B container we use to transport irradiated LEU targets from the reactors to our Petten site.
## REGULATORY APPROVALS

<table>
<thead>
<tr>
<th>Key Country/Region</th>
<th>RA Submissions to Health Authority (Master File + Variation / Supplement)</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>16-January-17</td>
<td>25-April-17</td>
</tr>
<tr>
<td>Switzerland</td>
<td>16-January-17</td>
<td>31-October-17</td>
</tr>
<tr>
<td>US</td>
<td>31-January-17</td>
<td>27-April-17</td>
</tr>
<tr>
<td>Canada</td>
<td>21-March-17</td>
<td>31-May-17</td>
</tr>
<tr>
<td>Asia</td>
<td>31-May-17</td>
<td>21-June-17</td>
</tr>
</tbody>
</table>

**Experiences from previous drug regulatory submissions**

EU - Work sharing with National MA. Grouped submissions. ASMF and Type IB Variation as prospectively agreed by Reference Authority.

US – DMF and Prior Approval Supplement

Canada – DMF and Notifiable Change

**The commitment and collaboration between Global Drug and Nuclear governing bodies was outstanding and served as a solid foundation for LEU regulatory success**
CURIUM IS NOW FULLY CONVERTED

- After all the regulatory approvals were received, Curium burned the last of our HEU targets late last year.
- As of early January 100% of the Mo-99 produced by Curium is from LEU targets.
- We have already seen the lower yield and higher cost associated with producing LEU Mo-99.
- We appreciate the technical and financial assistance provided by the U.S. Department of Energy during our conversion effort.
CURIUM HAS BEGUN LEU Xe-133 GAS PRODUCTION

• Curium (Mallinckrodt) previously manufactured Xe-133 gas from an HEU process.
• During the Mo-99 HEU conversion project Curium also developed a method for separating LEU produced Xe-133 from our process in Petten.
• Curium has now re-entered the Xe-133 market utilizing LEU produced Xe-133, used for pulmonary function, lung imaging, and cerebral blood flow scans.
• Curium’s Xe-133 provides customers with the only 100% Low Enriched Uranium (LEU) offering.
CURRENT Mo-99 SUPPLY OUTLOOK

- Curium has increased the number of Mo-99 production runs in Petten from four days per week to five. We have the ability to add a sixth production.
- Those extra production days coupled with the increased Outage Reserve Capacity creates even more reliability for Curium.
- We increased Mo-99 production during the recent NTP operational challenges in S. Africa, enabling Curium to provide additional coverage to patients.
CURIUM Mo-99 SUPPLY METRICS

- Curium Mo-99 production began in the Netherlands in the late 1990s.
- Production capacity has steadily increased since then.
- Additional capacity has been recently added.
- Capacity added to account for loss of the OSIRIS and NRU reactors.
- Capacity has been added to account for loss of efficiency due to LEU conversion.
PRODUCTION OF LEU Mo-99 DURING MARKET TRANSITION

• Production of Mo-99 with LEU versus HEU is less efficient and generates significantly more radioactive waste.

• Another Mo-99 producer reported at the EU Observatory meeting in April they may not be fully converted to LEU until late 2020.

• This higher cost of LEU production of Mo-99 impacts Curium in making Tc-99m generators at its plants in Petten, the Netherlands, Maryland Heights, MO and Saclay, France.

• Curium is now at a competitive disadvantage because we are producing LEU-based Mo-99, while our principle competitor in Mo-99 production continues to produce HEU-based Mo-99 at lower cost.

Mo-99 PRODUCERS WHO HAVE ALREADY CONVERTED TO LEU ARE AT A COMPETITIVE DISADVANTAGE
SUMMARY

- Curium began its LEU conversion project in 2010.
- During that time we have resolved several technical development challenges in the radiochemistry and analytical testing.
- Regulatory approvals from drug agencies and transport authorities were needed for the new LEU targets.
- We have established arrangements with a diverse network of reactors to irradiate targets for our Mo-99 production process.
- Curium has taken steps to steadily increase reliability and capacity of Mo-99 production to account for loss of older reactors and for the loss of efficiency due to LEU conversion.
- LEU conversion for Mo-99 was fully achieved in early January of 2018, and Xe-133 in May of 2018.
- Mo-99 producers who have already converted to LEU are at a competitive disadvantage until all are converted.