

ENSURING A STABLE SUPPLY OF MO-99 IN THE UNITED STATES WITHOUT THE USE OF HEU

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Abstract

Technetium-99m (Tc-99m) is a radioisotope used in approximately 85% of all medical imaging procedures across the globe. With a half-life of approximately six hours, this important medical radioisotope cannot be stockpiled and must be either used immediately upon direct production or repeatedly milked from generators bearing the parent isotope, molybdenum-99 (Mo-99), which has a half-life of approximately 66 hours. Historically, Mo-99 has been produced in research reactors by the irradiation of high enriched uranium (HEU) targets. In order to minimize the proliferation risks posed by HEU-based medical isotope production, the U.S. Department of Energy's National Nuclear Security Administration (DOE/NNSA) has funded a program to accelerate the deployment of technologies to produce Mo-99 without the use of HEU. Internationally, this work has supported large-scale Mo-99 producers with the conversion of their existing Mo-99 production processes from the use of HEU targets to low enriched uranium targets. Within the United States, operating under a full cost-recovery paradigm, DOE/NNSA has directly funded the development of diverse technologies via cost-sharing cooperative agreements with potential domestic commercial producers. In addition to the cooperative agreement partners, U.S. National Laboratory assistance has been provided to both international producers and potential U.S. producers, beyond those receiving direct financial assistance from DOE/NNSA. This paper will provide an overview of the Mo-99 production technologies funded under the cooperative agreements, as well as the technologies developed at the U.S. national laboratories in support of the production of Mo-99 without the use of HEU.

1. INTRODUCTION

Technetium-99m (Tc-99m) is a radioisotope used in approximately 85% of all medical imaging procedures around the world [1]. Within the United States, approximately 40,000 medical imaging procedures are performed every day using Tc-99m labeled radiopharmaceuticals, representing about half of the worldwide demand for the isotope [2]. With a half-life of approximately six hours, this important medical radioisotope cannot be stockpiled and must be either used immediately upon direct production or repeatedly milked from generators bearing the parent isotope, molybdenum-99 (Mo-99), which has a half-life of approximately 66 hours. Historically, Mo-99 has been produced in research reactors by the irradiation of high enriched uranium (HEU) targets.

2. THE SIGNIFICANCE OF MEDICAL ISOTOPE PRODUCTION IN NUCLEAR NONPROLIFERATION

Historically, the United States has not had the capability to produce Mo-99 domestically and, until 2018, imported 100 percent of its supply from international producers. Some of this Mo-99 was produced using targets fabricated with proliferation sensitive HEU. The use of HEU required for Mo-99 production created an interesting challenge at the nexus between health care and nuclear non-proliferation given that medical isotope production using HEU has the potential for material diversion.

The current estimated weekly demand for Mo-99 is approximately 333 6-day TBq (9,000 6-day Ci)[3]. Assuming a 24-hour processing time following a 6-day target irradiation at a reactor thermal neutron flux of $10^{14} \text{ n cm}^{-2} \text{ s}^{-1}$, the annual demand for uranium-235 (U-235) to support Mo-99 production is approximately 16 to 50 kg per year. If supplied solely by HEU targets with a nominal enrichment of 93 wt% U-235 and 80% fabrication yield, the demand for HEU would range from 20 to 67 kg per year.

3. THE DOE/NNSA OFFICE OF MATERIAL MANAGEMENT AND MINIMIZATION'S ROLE IN NUCLEAR NONPROLIFERATION

In order to minimize the proliferation risks posed by medical isotope production, the U.S. Department of Energy-National Nuclear Security Administration's (NNSA) Office of Material Management and Minimization (M³) has funded a program to accelerate the deployment of technologies to produce Mo-99 without the use of HEU. Internationally, this work has supported large-scale Mo-99 producers with the conversion of their existing Mo-99 production processes from the use of HEU targets to low enriched uranium (LEU) equivalents. Within the United States, operating under a full cost-recovery paradigm, DOE/NNSA has directly funded the development of diverse technologies via cost-sharing cooperative agreements (CAs) with potential domestic commercial producers.

DOE/NNSA supported the successful conversion of NTP radioisotopes (South Africa) and curium (the Netherlands) to LEU targets in 2017 and 2018, respectively. ANSTO (Australia) has always used LEU targets for Mo-99 production. DOE/NNSA continues to work with Belgium's Institute of Radioelements (IRE), the last major global supplier of Mo-99 to the United States, on their conversion from HEU to LEU targets.

In 2019, the U.S. Government competitively awarded four CAs to U.S. commercial entities based on the technical merits of each applicant's non-HEU based Mo-99 production technology and their ability to bring that technology to the marketplace. This cost-sharing vehicle allows the CA partnering organization to be reimbursed by the Federal government for 50% of allowable expenses under the contractually agreed to scope of work during the period of performance. The cost-sharing provided by DOE/NNSA allows the CA partners to accelerate the maturation and deployment of their technologies.

4. OVERVIEW OF THE DOE/NNSA COOPERATIVE AGREEMENT PARTNER TECHNOLOGIES

Each of the CA partners is developing a unique non-HEU based method to supply the United States with a significant percentage of the domestic weekly demand for Mo-99. The four CA partners are NorthStar Medical Radioisotopes, SHINE Medical Technologies, Niowave, Inc. and Northwest Medical Isotopes. Two of these companies, NorthStar Medical Radioisotopes and SHINE Medical Technologies, were funded under a previous CA award issued in 2010. This section will give a brief overview of each CA partner's technology for the production of Mo-99 without the use of HEU.

4.1. NorthStar Medical Radioisotopes

NorthStar Medical Radioisotopes¹ (NorthStar) is based in Beloit, Wisconsin, United States, and is pursuing two diverse Mo-99 production pathways: neutron capture and accelerator. Since November 2018, NorthStar has been producing non-HEU Mo-99 via the neutron capture technology and distributing it to U.S. radiopharmacies – the first production of Mo-99 in the United States since the closure of Cintichem, Inc. in 1989 [3].

NorthStar produces Mo-99 by irradiating natural molybdenum disks in the University of Missouri Research Reactor (MURR) located in Columbia, Missouri, United States [4]. Mo-99 production in natural molybdenum disks results from neutron capture by the $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$ reaction. Molybdenum-98 (Mo-98) is present in natural molybdenum as a 24.1 atom% isotopic constituent [5]. NorthStar plans to upgrade to enriched (>95 wt%) Mo-98 targets in the future, which will result in a four-fold increase in production capacity.

In addition to the production of Mo-99 at MURR, NorthStar is also building the capability to produce Mo-99 in their Beloit facility by electron-beam irradiation of enriched (>95 wt%) molybdenum-100 (Mo-100) targets undergoing a $^{100}\text{Mo}(\gamma,n)^{99}\text{Mo}$ reaction via the induced Bremsstrahlung radiation.

¹ <https://www.northstarm.com/>

NorthStar relies on a proprietary method to extract high-specific activity Tc-99m from low-specific activity Mo-99. This extraction is achieved via NorthStar's RadioGenix® System, an alternative to the traditional Tc-99m generator used by radiopharmacies [4]. With an installed RadioGenix® System, a radiopharmacy (1) receives Mo-99 solution vessels from NorthStar; (2) elutes the Tc-99m sodium pertechnetate used for diagnostic procedures; and (3) ships used source and waste vessels from the RadioGenix® System back to NorthStar.

The U.S. Food and Drug Administration (FDA) has approved Tc-99m from Mo-99 produced at MURR by the irradiation of natural molybdenum targets for use in patients. The first Mo-99 shipment from MURR that resulted in Tc-99m doses dispensed by the RadioGenix® System and used in patients occurred on 19 November, 2018 [6]. Since this date, NorthStar has been producing a weekly uninterrupted supply of Mo-99 to radiopharmacies in the United States.

4.2. SHINE Medical Technologies

SHINE Medical Technologies² (SHINE) is based in Janesville, Wisconsin, United States. SHINE intends to produce Mo-99 from the fission of LEU liquid targets by the $^{235}\text{U}(\text{n},\text{f})^{99}\text{Mo}$ reaction [7]. SHINE will use a compact ion beam linear accelerator to drive the fission reaction in a subcritical liquid target. The ion beam accelerator drives a steady-state beam of deuterium ions into a tritium gas target to produce the population of 14 MeV neutrons by the $^3\text{H}(^2\text{H},\text{n})^4\text{He}$ fusion reaction, driving LEU fission in the liquid target [3]. The ion beam accelerator technology to be used for the production of Mo-99 at SHINE has been demonstrated at over 5.5 days of continuous run time (>99% uptime) and an output of $4.6 \times 10^{13} \text{ n s}^{-1}$ [8][9].

The liquid target used for Mo-99 production will consist of a water-cooled and moderated LEU uranyl sulfate salt dissolved in sulfuric acid. The SHINE isotope production facility will have the capacity to operate up to eight irradiation units, consisting of a paired accelerator and LEU liquid target. At the end of irradiation, Mo-99 is extracted from the liquid target, the uranium and acid concentrations are adjusted and the liquid target is reused in a future irradiation cycle. The Mo-99 produced at SHINE will be shipped to Tc-99m generator manufacturers utilizing the existing supply chain.

4.3. Niowave, Inc.

Niowave, Inc.³ (Niowave) is based in Lansing, Michigan, United States. Niowave intends to produce Mo-99 from the fission of LEU solid targets by the $^{238}\text{U}(\gamma,\text{f})^{99}\text{Mo}$ and $^{235}\text{U}(\text{n},\text{f})^{99}\text{Mo}$ reactions [10]. Niowave will use a two-pass 20 MeV superconducting electron linear accelerator to drive an electron beam at nearly 40 MeV into a liquid metal target. The Bremsstrahlung radiation (x-rays) from the electrons impinging on the liquid metal target drives the photo-fission reaction, $^{238}\text{U}(\gamma,\text{f})^{99}\text{Mo}$, with the neutrons produced from this reaction driving the U-235 fission reaction, $^{235}\text{U}(\text{n},\text{f})^{99}\text{Mo}$.

The LEU targets used by Niowave will consist of a water-cooled and moderated array of pressed uranium oxide pellets in a subcritical configuration. At the end of irradiation, the LEU pellets are dissolved, forming a solution of LEU uranyl nitrate salt in nitric acid. Mo-99 is extracted from the uranyl nitrate solution, the raffinate is purified, the purified uranyl nitrate is calcined and the resulting uranium oxide is pressed into pellets for use in future irradiation cycles. The Mo-99 produced at Niowave will be shipped to Tc-99m generator manufacturers utilizing the existing supply chain.

4.4. Northwest Medical Isotopes

Northwest Medical Isotopes⁴ (NWMI) is based in Corvallis, Oregon, United States. NWMI intends to produce Mo-99 from the fission of LEU solid targets by the $^{235}\text{U}(\text{n},\text{f})^{99}\text{Mo}$ reaction [11]. NWMI has developed a process to produce LEU microspheres, which are used in the fabrication of irradiation targets in a fleet of U.S. based university research reactors. The flagship reactor in this fleet is MURR, which will provide the first irradiation services to NWMI.

² <https://shinemed.com/>

³ <https://www.niowaveinc.com/>

⁴ <https://www.nwmedicalisotopes.com/>

NWMI is constructing a target fabrication and Mo-99 radioisotope production facility (RPF) in Columbia, Missouri, United States, in close proximity to MURR. At the end of irradiation, the targets will be retrieved from MURR or another reactor in the fleet and shipped to the RPF. Once received at the RPF, the targets will be disassembled and the microspheres dissolved. Mo-99 will be extracted, the raffinate from the extraction will have the fission products removed and the purified LEU solution will be converted back into microspheres for use in targets for a future irradiation cycle. The Mo-99 produced at NWMI will be shipped to Tc-99m generator manufacturers utilizing the existing supply chain.

5. OVERVIEW OF U.S. NATIONAL LABORATORY SUPPORT FOR MO-99 TECHNOLOGY DEVELOPMENT

In addition to the cooperative agreement partners, U.S. national laboratory assistance has been provided to both international producers and U.S. potential producers beyond those receiving direct financial assistance from DOE/NNSA. The intent of national laboratory support is to help producers – including the CA partners – overcome technical challenges and accelerate technology development for the production of Mo-99 without the use of HEU [12]. National laboratory resources – scientific staff, engineering staff, experimental equipment, laboratories and support staff – are made available to producers through the M³ Office of Conversion. Work packages are developed cooperatively by the participating national laboratory and producer. These work package proposals are submitted by the national laboratory on behalf of the producer and are then reviewed and approved, if appropriate, by the Office of Conversion. The data and reports generated by these activities are in the public domain unless restricted by U.S. export control law.

Currently six U.S. national laboratories actively participate in the DOE/NNSA M³ Mo-99 technology development program: Argonne, Los Alamos, Oak Ridge, Pacific Northwest, Savannah River and the Y-12 National Security Complex. Each laboratory brings a particular expertise to the program, but when capabilities at national laboratories overlap it supports substantial cross-laboratory collaboration. The following sections provide a brief overview of each laboratory's contribution to the development of Mo-99 production without the use of HEU.

5.1. Argonne National Laboratory

Argonne National Laboratory (ANL) provides a robust range of support for Mo-99 technology development [13]. ANL is home to a Low-Energy Accelerator Facility⁵ (LEAF) and radiochemistry laboratories. LEAF houses a 50 MeV electron linear accelerator and a 3 MeV Van de Graaff electron accelerator. Argonne engages in two main research areas for the Mo-99 Program:

5.1.1. Enabling a reliable supply of Mo-99

- ANL supports DOE/NNSA's domestic CA partners by working to
 - Demonstrate fission and photo-nuclear production of Mo-99;
 - Conduct radiation stability testing of equipment and process chemistry;
 - Evaluate Mo-99 targetry through MCNPX and heat deposition modelling;
 - Conduct thermal-hydraulic analysis of the target system;
 - Design beamline and facility shielding; and
 - Conduct target and accelerator protection during production runs.
- ANL also assists international Mo-99 producers with chemical processes relevant to conversion from HEU to LEU targets.

5.1.2. Process development and scale-up for Mo-99 producers

- Support the development of processes for Mo-99 recovery and purification:
 - Optimize, scale-up and automate processes for hot cell operations;
 - Develop analytical tests for trace-metal detection in complex matrices;

⁵ <https://www.ne.anl.gov/facilities/leaf/>

- Meet European Pharmacopeia purity specs; and
- Characterize waste disposition pathways.
- Develop and demonstrate processing equipment produced by advanced manufacturing methods:
 - Metal and non-metal 3D printed annular centrifugal contactors
 - Evaluate equipment performance and materials corrosion

5.2. Los Alamos National Laboratory

Los Alamos National Laboratory (LANL) provides the Mo-99 program with expertise in multiphysics systems modeling, accelerator component research and development and facility radiation shielding design [14]. LANL supports NorthStar and SHINE in the following areas:

5.2.1. LANL Support to NorthStar Mo-99 Production

- Target design and testing, both in and out of beam;
- Cooling system design using helium;
- Target insertion scheme; and
- Facility and shielding layouts.

5.2.2. LANL Support to SHINE Mo-99 Production

- 2D and 3D computational fluid dynamics (CFD) validation modeling of LANL's historic uranyl nitrate solution reactor, SUPO; and
- Experiment design and modeling of a radiolytic gas bubble experiment to be conducted at ANL using the electron LINAC.

5.3. Oak Ridge National Laboratory

Oak Ridge National Laboratory (ORNL) supports Mo-99 production research and development in the area of fundamental materials science on both unirradiated and irradiated materials [15]. ORNL also has expertise in hot cell chemistry and testing, neutronics modeling and simulation, radioactive material shipping and additive manufacturing. ORNL is home to the High Flux Isotope Reactor (HFIR), which has experimental capacity with high-intensity neutron fluxes and cold neutron science⁶. In support of Mo-99 research and development, ORNL has engaged in the following activities:

- Optimizing accelerator target design and fabrication using powder metallurgy and additive manufacturing for NorthStar;
- Materials selection and neutron irradiation testing for the SHINE production system;
- Test irradiation target design and qualification in support of Coquí RadioPharmaceuticals reactor qualification; and
- Test irradiation target design, qualification, irradiation and shipment to support BWX Technologies, Inc.

5.4. Pacific Northwest National Laboratory

Pacific Northwest National Laboratory (PNNL) supports the Mo-99 program with research and development activities in the areas of radioxenon transport and emissions abatement, process modeling, non-destructive and destructive post-irradiation examination (PIE) and hot cell radiochemistry [16]. PNNL has performed work to assist multiple producers in the following areas:

- Develop a PNNL multiphysics model for producers' xenon abatement adsorbent beds:
 - Develop a universal adsorption bed model that can answer questions about xenon abatement trap designs and adsorbent effectiveness;
 - Incorporate heat of decay from high activity radioxenon gas emissions trapped on abatement beds; and
 - Evaluate ambient temperature bed designs and cooled bed designs.

⁶ <https://neutrons.ornl.gov/hfir>

- Adsorption process modeling:
 - COMSOL Multiphysics enables modelling adsorption processes coupled to heat transfer.
- Hidden gravimetric adsorption analyzer development:
 - Can output the rate of uptake, as well as the final amount adsorbed, at a given pressure and temperature.
- Adsorption breakthrough instrument development:
 - Can perform breakthrough experiments for gas mixtures.

5.5. Savannah River National Laboratory

Savannah River National Laboratory (SRNL) supports the Mo-99 program in the areas of tritium processing systems development, optimization of uranium dissolution flowsheets and Mo-99 processing chemistry residue management [17]. They have conducted work scope in the following areas:

- Development of tritium handling and purification systems such as the Thermal Cycling Adsorption Column (TCAP) and Micro-TCAP;
- Optimization of uranium dissolution using a parametric analysis of dissolution conditions and constraints;
- Development of actinide processing flowsheets and analytical techniques;
- Development of radiological material disposition strategies;
- Development of Mo-99 extraction and purification residue management strategies; and
- Development of tritium handling and component detritiation strategies.

5.6. The Y-12 National Security Complex

The Y-12 National Security Complex (Y-12) supports the Mo-99 program with uranium component engineering research and development as well as LEU inventory management [18]. Y-12 has conducted work scope in support of three Mo-99 producers:

5.6.1. Niowave

- Analysis of pellets that make up the uranium target assembly manufactured at Niowave along with the U_3O_8 oxide from the pellets;
- Optimizing the conversion process from metal to oxide;
- Aiding in pellet pressing optimization; and
- Optimizing and scaling up uranium recovery from irradiated pellets.

5.6.2. Coquí RadioPharmaceuticals

- Design, develop and fabricate dispersion target plates that utilize a uranium core in an aluminum frame that is encased in aluminum cladding.

5.6.3. Eden Radioisotopes

- Design, develop and fabricate high-density annular targets that utilize a rolled foil uranium core encased between inner and outer aluminum tubing.

6. CONCLUSION

The CA financial vehicle and supplementary support from the U.S. national laboratories have been instrumental in accelerating the deployment of a non-HEU based Mo-99 production capability in the United States. NorthStar Medical Radioisotopes' entrance into the domestic Mo-99 market in 2018 is a significant success, having achieved the first domestic production in almost 30 years. This, combined with the conversion of large-scale global Mo-99 producers and the continued progress of the companies funded under the CAs, demonstrates the significant progress the community is making in eliminating the use of HEU in medical isotope production around the world.

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