OLD DOMINION UNIVERSITY
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July 28, 2021

Dr. Steve Binkley
Acting Director, Office of Science
U.S. Department of Energy
1000 Independence Ave.,
SW Washington, DC 20585

Dr. Sean Jones
Assistant Director
Directorate for Mathematical and Physical Sciences
National Science Foundation
2415 Eisenhower Avenue
Alexandria, Virginia 22314

Dear Drs. Binkley and Jones,

In the letter from your offices dated March 1, 2021, you charged NSAC to reconvene its standing subcommittee on Mo-99 to conduct a seventh annual assessment of the effectiveness of the National Nuclear Security Administration, Office of Material Management and Minimization (NNSA-MMM) Domestic Molybdenum-99 Program. Attached please find the report from the NSAC subcommittee, which was chaired by Professor Suzanne Lapi, from the University of Alabama at Birmingham. The subcommittee membership was composed of a small number of experts in nuclear medicine, nuclear and radio chemistry, radioisotope production, commercial isotope sales, radio pharmacy and clinical use, and project management.

Fact finding for this report was facilitated by an online subcommittee meeting held May 10, 2021, which featured briefings by NNSA and DOE-EM. The subcommittee invited input from all current cooperative agreement (CA) partners, all of whom submitted reports. The CA partners also had an opportunity to brief the subcommittee as part of the meeting on May 10. NNSA stated that their program objective is to bring online two U.S. producers, each capable of producing 3000 6-day Ci/week of ^{99}Mo. The subcommittee found that NNSA has continued to make progress toward the identified goals, despite the challenges presented by COVID-19. There is now U.S. produced ^{99}Mo in the market, but it has not reached 1000 6-day Ci/week yet. The transition to LEU from HEU by the international ^{99}Mo producers is now close to complete. The Uranium Lease and Take Back (ULTB) concept has been established with an anticipated first contract to be finalized in 2021.

The subcommittee made one recommendation. Given that the program has been underway since 2012 and that several CA partners are making good progress toward their production goals, the subcommittee recommends that NNSA should define the metrics for an exit strategy from this program. The metrics should be presented to the Mo-99 subcommittee at the next program assessment.

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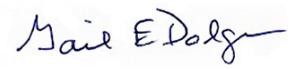
The subcommittee report was presented to NSAC during its July 19, 2021 meeting. Following discussion, the report was approved unanimously.

Sincerely yours,



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Denise Caldwell, NSF

Report to the Nuclear Science Advisory Committee

Annual Assessment of the NNSA-Material Management and Minimization (M^3) ^{99}Mo Program

July 5th, 2021
Report of the NSAC ^{99}Mo Subcommittee

Executive Summary

The Nuclear Science Advisory Committee (NSAC) Molybdenum-99 (^{99}Mo) Subcommittee met May 10, 2021, to address the charge to NSAC requesting that a seventh annual review of the National Nuclear Security Administration's (NNSA) ^{99}Mo program be performed. The Subcommittee found that NNSA has continued to make progress over the course of the year in the context of the specific requirements of the American Medical Isotopes Production Act of 2012 (AMIPA).

Since the last review, the landscape for ^{99}Mo availability has continued to evolve. The transition to LEU from HEU by the international ^{99}Mo producers is now close to complete with three of the four major global producers now producing ^{99}Mo using only LEU.

Despite the challenges presented by COVID-19, the program is continuing to make progress towards improving the reliability of the domestic ^{99}Mo supply. While there is now U.S. produced ^{99}Mo in the market, establishment of a large-scale domestic supply (1000 6-day Ci/week) has not yet occurred. A new FOA was issued with awards expected to be announced by the fall of 2021.

The Subcommittee found that the NNSA has partially addressed its concerns and recommendations from the previous review. The program has established a Uranium Lease and Take Back (ULTB) concept for those CA partners that might require it with an anticipated first contract to be finalized in 2021. However, while all the current partners have a path forward, the ULTB program is still incomplete as there is still no disposal path for greater than Class C waste.

The Subcommittee has one recommendation:

Recommendation

The NNSA Office of Material Management and Minimization's (M3) ^{99}Mo Program has been underway since 2012 with several FOAs and rounds of funding to develop a domestic source of ^{99}Mo. Several companies that have or have had cooperative agreements with the NNSA for funding are in various stages of completion. Accordingly, the NNSA should define the metrics for an exit strategy from this program. This should be presented to the NSAC ^{99}Mo Subcommittee at the next program assessment.

Introduction

The Nuclear Science Advisory Committee (NSAC) Molybdenum-99 (^{99}Mo) Subcommittee began its work in 2014. Additional members were added in 2015 and 2016 to address stakeholder input and additional meetings were held in 2017, 2018 and 2019. The creation of this subcommittee was motivated by the American Medical Isotopes Production Act (AMIPA) legislation contained in the National Defense Authorization Act for Fiscal Year 2013. This legislation required that the Secretary of Energy establish a technology-neutral program to provide assistance to commercial entities to accelerate the domestic production of ^{99}Mo, which is used to supply the diagnostic medical isotope ^{99m}Tc, without the use of highly enriched uranium (HEU) with the goal of ensuring a reliable domestic supply of ^{99}Mo. This Act also called for an annual review of the National Nuclear Security Administration (NNSA) ^{99}Mo program by the NSAC. In 2009, the NNSA was given responsibility for development of this program. Following an NNSA reorganization in 2014, the ^{99}Mo program is now within NNSA's Office of Material Management and Minimization (NNSA-M3).

The ^{99}Mo Subcommittee began its work for the current review in response to a charge letter dated March 1, 2021, (Appendix 1). The current Subcommittee membership and relevant experience are given in Appendix *2*. The full text of previous reports can be found at http://science.energy.gov/np/nsac/reports/.

The Subcommittee met virtually on May 10, 2021 and built on the extensive work of the previous six reviews. At this meeting, the Subcommittee was briefed by NNSA on details of their program. The Subcommittee invited input from all current CA partners, all of which submitted reports. Appendix 3 contains the agenda of the Subcommittee meeting.

Considerable information on ^{99}Mo production and the events leading to the AMIPA legislation was presented in the 2014 NSAC report. The reader is directed to Appendix 4 for a summary of this information.

Changes in the International Landscape since the Prior Report

The most dramatic change in the international landscape since the prior report was the impact of the COVID-19 pandemic. Fortunately, the pandemic caused minimal disruption of ^{99}Mo production and processing capacity. This was in large part due to the fact that both the producers and processers were proactive in developing plans to protect their workforces from COVID-19 and thereby ensure continuity of both production and processing capacity. The pandemic did, however, have an impact on international transportation of processed ^{99}Mo, primarily because of the large decrease in the number of international flights available to carry the processed ^{99}Mo. Fortunately, this disruption was resolved relatively quickly and only modestly impacted ^{99}Mo availability in the US.

The OECD-NEA did not issue an update to the 2019 report "The Supply of Medical Radioisotopes: *2019 Medical Isotope Demand and Capacity Projection for the 2019-2024 Period"* [1] in 2020. As can be seen in the 2019 report [1], the projected global demand growth is expected to be maintained through 2024; except of course, for the global disruption in demand caused by COVID-19 in 2020. At this point, however, patient volume at most US institutions has returned to, or even exceeds, 2019 volume. US demand for ^{99}Mo is, therefore, similar to that predicted by the 2019 report. Likewise, the conclusion on supply is similar to the previous report: "When existing facilities are well maintained and well scheduled, and when unplanned outages are avoided, total irradiator capacity should be sufficient. That said, the supply chain must fully implement the recommended levels of paid Outage Reserve Capacity (ORC) in order to be able to manage unplanned processor outages. However, when no additional processing capacity is added above the present level, the capability to manage adverse events will remain low and will be further reduced with time."

All ^{99}Mo production and processing projects, including those using conventional technologies and those supported by NNSA, were to some extent delayed by the COVID-19 pandemic, but none of the projects reported technical delays that will impact the current and future ^{99}Mo supply.

The 2019 OECD report stated that progress toward full cost recovery (FCR) continued to be slow and the market continues to be economically unsustainable. The variable adherence to FCR by the various foreign producers is an additional financial challenge for U.S. producers. This situation is unchanged since the previous report.

Longer-term OECD projections point to the possibility of a significant overcapacity internationally as additional facilities come on-line, both in the US and internationally. Such an overcapacity could threaten the sustained economic viability of the fledgling domestic projects. However, because the ^{99}Mo supply chain is complex, the capacity to produce larger amounts of ^{99}Mo does not directly correlate with ^{99}Mo availability in the marketplace if all of the contracts and validations are not in place.

Developments in the NNSA Program

The organization and goals of the NNSA-M3 program with respect to ^{99}Mo remain unchanged since the previous review: to achieve HEU minimization and to assist in establishing reliable domestic supplies of ^{99}Mo produced without the use of HEU. The NNSA-M3 program seeks to achieve these objectives through assisting global ^{99}Mo production facilities to convert to the use of low-enriched uranium (LEU) targets and by accelerating the establishment of commercial non-HEU-based ^{99}Mo production in the United States. As in previous reviews, it is the latter of these issues that was the main concern of this review. With respect to the former objective, it does appear that all of the major global ^{99}Mo producers will be using LEU targets by the end of 2022.

Sections 3173 (c) and (e) of the FY13 National Defense Authorization Act directed DOE to establish a Uranium Lease and Take Back (ULTB) program by January, 2016, to make LEU available, through lease contracts, for irradiation to enable the production of ^{99}Mo for medical uses. The Act requires DOE to take title to and be responsible for the final disposition of radioactive waste that is created by the irradiation, processing, or purification of the leased uranium for which the Secretary determines the producer does not have access to a disposal path. The Act also requires DOE to recover the costs associated with the ULTB Program. The ULTB Program is coordinated between different organizations within DOE; the NNSA Production Office (NPO) provides the leasing of LEU required for domestic fission-based ^{99}Mo production, while the DOE Office of Environmental Management (DOE-EM) manages the disposition radioactive waste that does not have an existing disposal path, both of which may be generated by ^{99}Mo production. The program has established a ULTB concept for those commercial entities that might require it with an anticipated first contract to be finalized in 2021. This is a major achievement for the program.

The movement of ^{99}Mo produced by NorthStar into the market and the resulting ^{99m}Tc into some patient procedures is an important step forward, especially in that it involves acceptance of a new generator technology. That said, no CA partner (past or present) projects meeting the original 3000 6-day Ci/week goal for at least several years.

In the next sub-sections, the Subcommittee addresses the specific questions presented in the NSAC charge.

What is the current status of implementing the goals of the NNSA-MMM ^{99}Mo Program? What progress has been made since the 2020 assessment?

Findings

Despite challenges presented by COVID-19, the program is continuing to make progress towards improving the reliability of domestic ^{99}Mo supply. While there is now U.S. produced ^{99}Mo in the market, establishment of a large-scale domestic supply (1000 6-day Ci/week) has not yet occurred.

The NorthStar neutron-capture project for ^{99}Mo production continues to make good progress. NorthStar has received FDA approval for new larger sizes of ^{99}Mo source vials to be used in their RadioGenix system. This allows them to be competitive in terms of generator activity compared with other ^{99}Mo/^{99m}Tc generators currently on the market. NorthStar has also received FDA approval to implement enriched ^{98}Mo targets at MURR for ^{99}Mo production. These enriched ^{98}Mo targets increase the production capacity of ^{99}Mo up to four times that of the previous targets. They have installed a new hot cell line and fill line onsite at MURR, and these are undergoing commissioning with anticipated FDA approval in 2022. They plan to have the capability to produce up to 1,500 6-day Ci/week by the end of 2022 and up to 3,000 6-day Ci/week by the end of 2023 by neutron capture.

Since the last update, NorthStar has completed construction of the electron accelerator production building and the concrete bunker for the beam line and target station. They have completed the design and ordered several production sub-systems such as the beamlines, helium cooling systems, target shield and target manipulation hot cell. They have also begun installation of the first two 40 MeV, 125 kW electron accelerators.

Activities scheduled in 2021 include the installation of the beamlines, target shield and target manipulation hot cell. They plan to have a fully integrated electron accelerator production system ready to initiate commissioning by October of 2021. Commissioning activities, qualification production runs of ^{99}Mo and submissions to the FDA are scheduled in 2022 with planned production beginning in January 2023.

SHINE continues to make good progress. The two-year NRC review of the Operating License Application for the ^{99}Mo production facility continues on schedule. Final determination by the NRC should be completed by October 2021. Construction of the production facility's safety-related concrete structures is nearly complete. The design of the major production process equipment has been completed and the equipment was under contract for fabrication by the end of 2020. The completion of the first neutron driver assembly system (NDAS) progressed in 2020. It will be used as a demonstration unit and allow for reliability testing, training and operational experience, and operating in different configurations while the NDAS units for the main production facility are built. SHINE expects to be able to produce 1,500 6-day Ci/week of ^{99}Mo with the first two NDAS by the end of 2022. When the additional NDAS units come on line in 2023, they expect to be able to produce 3,000 6-day Ci/week of ^{99}Mo.

Niowave plans to produce ^{99}Mo and other isotopes via photonuclear fission of uranium targets and has made progress in scaling up the ^{99}Mo process at their R&D facility. This progress includes optimization of all aspects of their closed-loop fuel cycle, including automating the UREX process, scaling up the uranium recovery and pellet pressing, improving the ^{99}Mo purification, and extraction of other beta-emitting isotopes. They continue to make progress with their NRC license amendment to possess LEU for their Pilot Facility and expect approval this summer. They have added a new GMP Quality system that will allow them to provide active pharmaceutical ingredients (radioisotopes) to the pharmaceutical community in 2021. This same system will also allow them to provide ^{99}Mo under GMP conditions once they have scaled up their production capabilities.

Over the past year, Northwest Medical Isotopes (NWMI) had changes in management as well as to their original plan/process. Given these changes, NWMI and NNSA are working together to determine the best path forward for the cooperative agreement. NWMI did not submit a report for this time period.

NNSA issued a new Funding Opportunity Announcement (DE-FOA-0002303) in July 2020, to solicit applications to competitively award new cooperative agreements in order to accelerate the establishment of domestic supplies of ^{99}Mo. The FOA was open to both new and existing cooperative agreement partners, This FOA is supported by Congressional funding in FY 2020 ($35,000,000) and FY 2021 ($50,000,000) to fund the new cooperative agreements. The FOA's merit review has three criteria, all with the goal of 1,500 6-day Ci/week of ^{99}Mo without the use of HEU to the U.S. market on or before December 31, 2023. The applicant must also demonstrate the ability and plans to increase the production of ^{99}Mo to 3,000 6-day Ci/week in the future.

- Criterion 1 – Commercial Deployment (weighted 50%): The applicant's proposal will be evaluated to measure the degree to which the applicant's approach will enable the project to produce and sell above quantities.
- Criterion 2 – Technology Maturity (Weighted 30%): The applicant's proposal will be evaluated to measure the degree to which the applicant's technical approach is able to produce and deliver above quantities.
- Criterion 3 – Business Strategy and Management Capabilities (Weighted 20%): The applicant's proposal will be evaluated to measure the degree to which the company's business strategy and management capabilities will enable the project to achieve commercially approved ^{99}Mo in the above quantities.

This FOA process is underway, and awards are expected to be announced by the fall of 2021.

In addition to its support of CA partners, the NNSA-M3 continues to provide non-proprietary technical support at the DOE National Laboratories that benefits both the CA and non-CA projects. The CA partners acknowledged the importance of the assistance from the national labs.

Comments

SHINE and Niowave will produce high-specific-activity ^{99}Mo, a product that will fit seamlessly into the current ^{99}Mo/^{99m}Tc generator supply chain. This is the same supply chain that dominates the market today.

While the production capacity will meet a portion of U.S. market demand, all of the NorthStar methods produce low-specific-activity ^{99}Mo that require the use of their novel RadioGenix system. This system is different than the standard ^{99}Mo/^{99m}Tc generator that uses high-specific-activity ^{99}Mo.

NorthStar's two processes do not use uranium, nor do they generate any greater than Class-C radioactive waste, hence they do not need the ULTB program. SHINE will produce a small amount of greater than Class-C radioactive waste. They are in negotiations with the DOE and expect to have a contract finalized in 2021. Niowave will also produce greater than Class-C radioactive waste but will not be using the ULTB program.

NorthStar has strong investor support that has allowed them to progress faster than the other CA partners. NorthStar has stated that beyond the current FOA, they will no longer need any additional support via a CA. However, the generator is more complex to operate and considerably larger than a standard generator and thus widespread acceptance in the marketplace is still an open question.

Recommendations

None

Is the strategy for continuing to implement the NNSA goals complete and feasible, within an international context?

Findings

The transition to LEU from HEU by the international ^{99}Mo producers is close to complete with three of the four major producers now producing ^{99}Mo using LEU. The Belgium Institute for Radioelements (IRE) is in the process of conversion to LEU, with a target date of 2022 for 100% LEU production. The conversion of world producers to LEU targets has been very successful.

The program has invested over $150 M since 2012 in the national laboratories who are engaged in direct, non-proprietary efforts with cooperative partner prioritized strategic R&D.

The program has established a Uranium Lease and Take Back (ULTB) concept for those commercial entities that might require it. In accordance with the USEC Privatization Act, the Secretary of Energy signed a determination to allow the sale, lease or transfer of up to 500 kg of high assay LEU per calendar year in support of this program. No ULTB contracts were signed in 2020; however, one company (SHINE) has agreed, in principle, to the terms for disposition. It is anticipated that the company will sign a contract in 2021.

As noted in last year's report, one U.S. producer – NorthStar – has a product in the U.S. market. Their business model is based on neutron capture of natural Mo, with a plan to use enriched ^{98}Mo in the near future. Their process creates ^{99}Mo with a lower specific activity than other methods, which requires use of a proprietary generator system by the radiopharmacy. NorthStar has begun installation of two electron accelerators at their Beloit, Wisconsin facility as well as beamlines and target stations. This is the first step towards producing ^{99}Mo via the ^{100}Mo(γ,n) reaction. The plan is to produce 800 6-day Ci/week by 2023 and 3000 6-day Ci/week by 2025. The higher production level will require 6 accelerators.

Comments

The Subcommittee finds the dual goals of the NNSA program to be on track to realize both a significant domestic ^{99}Mo supply and a global conversion to non-HEU sources. Notably, the CA partners have developed novel production methods that will produce low-level waste or minimal greater than Class-C waste volume.

The national laboratory program has been very effective and should be continued with a focus on R&D specific to advancing ^{99}Mo production. During the life of the program this support has been given to all producers, including the CA partners. CA partners who are engaged with the laboratories strongly reinforced this assertion, giving numerous technical examples of successful projects. NNSA has also been successful in aiding the conversion to LEU targets for international producers.

The ULTB program has made progress in resolving the major outstanding issue related to the disposition of the returned uranium/waste and the costs associated with this transfer. At this point only one of the CA partners is pursuing this approach (SHINE). NorthStar does not use uranium in its process and Niowave has opted for purchasing its LEU directly and not utilizing the ULTB.

Some international producers appear to have defined pathways for greater than type-C waste that the US producers cannot access. The demise of the OECD HLG (in 2019) hampers any attempt to establish FCR by foreign producers. While the NNSA hopes to reconvene the HLG, FCR remains a significant challenge to establish and to enforce. This puts any US producer that uses the ULTB program at a disadvantage given its full cost recovery requirements, which are not clearly defined.

The U.S. production of ^{99}Mo and entrance of NorthStar into the U.S. market – even with their unique generator system – does establish that the NNSA program of CA partner support can work. There is also evidence that other CA partners are close to market, suggesting that the strategy appears to be successful.

Recommendations

None

Are the risks identified in implementing those goals being appropriately managed?

Findings

NNSA has identified a comprehensive set of risks; these were discussed in previous reports and no new risks have been identified.

Comments

Some of these risks are beyond the direct control of the NNSA. All risks within the scope of their program are now being well managed.

Recommendations

None

Has the NNSA-MMM Program addressed concerns and/or recommendations articulated in the 2019/2020 NSAC assessment of the ^{99}Mo Program appropriately and adequately?

Findings

Prior Recommendation 1

The limitations of the ULTB program continues to be one of the biggest risks to the program's success. The ULTB contract templates should be reviewed and revised as necessary; in particular, with respect to reducing the continuing significant uncertainties in the take-back aspects of the DOE-EM program. The results of this review should be presented to the NSAC ^{99}Mo Subcommittee at the next program assessment.

Response:

The lease contract between NNSA and SHINE and the take-back contract between EM and SHINE are expected to be signed following issuance of the Operating License by the U.S. Nuclear Regulatory Commission (NRC). Because SHINE will only be producing minimal amounts of greater than type C waste, their ULTB contract negotiations with DOE-EM was somewhat simplified.

In developing the contract, DOE/EM used existing model contract language as the starting point for a specific contractual agreement between SHINE and DOE/EM. Portions of the model contract were updated, including appendices dealing with radioactive waste in the take-back contract. DOE/EM updated the cost estimate for inflation, pricing, and technical information provided by SHINE, as well as financial assurance costs. SHINE'S NRC Operating License will ensure that financial assurance is apportioned for decommissioning and waste takeback, pursuant to 10 CFR 50.75. Contract terms allow for annual reviews and adjustment, particularly following financial assurance reviews by NRC.

One CA partner, Niowave, purchased 18 kg of LEU from Y-12 for their pilot facility and agreed to terms for additional LEU for their commercial facility. They believe that purchasing the LEU was a better option than utilizing the ULTB.

Prior Recommendation 2

The NNSA stated during this review that a program objective was to have at least two US producers, each capable of producing 3000 6-day Ci/week of ^{99}Mo. The third FOA for this program is anticipated in 2020. After 10 years of significant investment in this program, the NNSA should focus their strategy on prioritizing future awards such that time-to-market, consistent with the stated objective, is considered as the most important review criteria. This strategy should be reflected in the approach to allocation of CA funding and national laboratory resources.

The review committee considers this recommendation addressed. The NNSA FOA issued on July 30, 2020, included 3 separate merit review criteria: Commercial Deployment (Weighted 50%), Technology Maturity (Weighted 30%), Business Strategy and Management Capabilities (Weighted 20%). In addition, the FOA clearly stated that it was not intended to support Research and Development (R&D) projects.

Comments

With respect to recommendation 1.
The Subcommittee found that the NNSA has partially addressed its concerns and recommendations from the previous review. The program has established a Uranium Lease and Take Back (ULTB) concept for those CA partners that might require it with an anticipated first contract to be finalized in 2021. However, while all the current partners have a path forward, the ULTB program is still incomplete as there is still no disposal path for greater than Class C waste.

With respect to recommendation 2.
The combined criteria developed by NNSA and the subsequent sub-criteria provided in the FOA satisfied the committee's recommendation to prioritize time to market as the most important review criteria.

Recommendations

None

What steps should be taken to further improve the NNSA program effectiveness in establishing the domestic supply of ^{99}Mo?

Findings

One CA partner, NorthStar, has brought the RadioGenix generator to market, with a number of systems currently installed. They estimate that they will have the capacity to supply a significant fraction of the U.S. market. NorthStar encourages continued effective program oversight by NNSA management and continued public interaction. NorthStar recommends that funding continue for the national laboratories in support of domestic production. No further CA funds will be sought by NorthStar past 2023. One factor that has delayed deployment of NorthStar's generator technology has been delays in issuing licenses for use of RadioGenix generator in agreement states.

A second CA partner, SHINE, has submitted their NRC operating license application (Q2 of 2019) and had a successful NRC construction site inspection. They have conducted a successful test of their production process at Argonne National Laboratory. They have also successfully tested the accelerator at their facility and aim to have ^{99}Mo in the U.S. market end of 2022 and will have the capability to produce 3,000 6-day Ci/week by 2023. Significant progress has been made towards finalizing an agreement for execution of the ULTB option by the end of 2021.

A third CA partner, Niowave, has their production facility underway and a superconducting electron LINAC in place at their research facility. They have verified their gamma and neutron production methods. LEU needed for ^{99}Mo pilot production has been purchased from Y-12, and they aim to have ^{99}Mo in the US market in the 2024/2025 timeframe.

Comments

NorthStar plans to utilize enriched ^{98}Mo targets, which would allow them to make higher activity generators (~19 Ci loading, based on their assessment) upon FDA approval. Their accelerator method to produce ^{99}Mo would allow them to further increase ^{99}Mo capacity while still using the same RadioGenix generator. Thus, the implementation of the photonuclear production route is likely to be faster than the time-to-market of the neutron-capture ^{99}Mo. Initial domestic ^{99}Mo production via electron accelerators is expected to begin January 2023. NorthStar recommends that no further funding be allocated by Congress beyond those allocated in FY 2020/2021. As stated before, due to the large footprint and complexity of the RadioGenix system relative to the current ^{99}Mo/^{99m}Tc generators, the committee still has concerns about market acceptance of the RadioGenix generator systems.

SHINE's recycling process allows them to minimize radioactive waste production. Their production method builds on two existing, well-established methods and is innovative. This technology produces high-specific-activity ^{99}Mo that can be used in current generators. Take-back of the LEU waste constituents is not expected to be required until the decommissioning of the facility.

Niowave's process builds on their expertise in superconducting electron LINACs. Their process is relatively simple and straightforward and produces high-specific-activity ^{99}Mo, which can be used in existing generators. However, they aim to produce ^{99}Mo in addition to a number of other isotopes, and it is not clear that ^{99}Mo is the top priority.

Two CA partners, NorthStar and SHINE are projected to be capable of producing 3,000 6-day curies/week during 2023. This is on track with NNSA's focus on commercial development rather than technology development.

The NNSA should consider the methodology for ending the FOA process beyond what is already approved to align with two successful producers in the market in 2023.

The laboratory technical support could be extended beyond termination of the FOA process to assist with ongoing technical issues.

The NNSA should emphasize to the NRC the importance of their role in this program and the need for expedited review of the CA partners license applications. Additionally, the charging for financial assurances (FA) for their greater than Class-C waste should only occur once (i.e., through the ULTB or NRC operating license).

The pathways for disposal of greater than Class-C nuclear waste remain an issue and should continue to be investigated along with refinements to the disposal cost model.

Recommendation

The NNSA-Material Management and Minimization (M^3) ^{99}Mo Program has been underway since 2009 with several FOAs and rounds of funding to develop a domestic source of ^{99}Mo. Several companies that have or have had cooperative agreements with the NNSA for funding are in various stages of completion. The NNSA should define the metrics for an exit strategy from this program. This should be presented to the NSAC ^{99}Mo Subcommittee at the next program assessment.

References

[1] OECD/NEA (2019), The Supply of Medical Radioisotopes: *2019 Medical Isotope Demand and Capacity Projection for the 2019-2024 Period,* NEA/SEN/HLGMR (2019) OECD Publishing, Paris, France.

[2] OECD Joint Declaration on the Security of Supply of Medical Radioisotopes online at https://www.oecd-nea.org/med-radio/jointdeclaration.html

Appendix 1 – Subcommittee Charge

U.S. Department of Energy
and the
National Science Foundation

March 1, 2021

Professor Gail Dodge
Chair, DOE/NSF Nuclear Science Advisory Committee
College of Sciences
Old Dominion University
4600 Elkhorn Avenue
Norfolk, Virginia 23529

Dear Professor Dodge:

This letter is to request that, in accordance with direction given to the Department of Energy (DOE) in the National Defense Authorization Act (NDAA) for FY 2013, the Nuclear Science Advisory Committee (NSAC) standing Subcommittee on Mo-99 conduct its annual assessment of the effectiveness of the National Nuclear Security Administration, Office of Material Management and Minimization (NNSA-MMM) Domestic Molybdenum-99 (Mo-99) Program (formerly known as the Global Threat Reduction Initiative).

The American Medical Isotopes Production Act of 2012 (Act), formerly known as S. 99 and H.R. 3276, was incorporated into the NDAA for FY 2013. On January 2, 2013, President Obama signed the NDAA into law, enacting this legislation. A stipulation of the NDAA under section 3173 – *IMPROVING THE RELIABILITY OF DOMESTIC MEDICAL ISOTOPE SUPPLY* is that:

"... the Secretary [of Energy] shall...use the Nuclear Science Advisory Committee to conduct annual reviews of the progress made in achieving the [NNSA-MMM] program goals and make recommendations to improve effectiveness."

The DOE and the National Science Foundation very much appreciate NSAC's six previous assessments as described in reports transmitted to the agencies on May 8, 2014, July 30, 2015, November 3, 2016, March 19, 2018, April 17, 2019, and March 16, 2020.

We request that NSAC provide a seventh annual assessment addressing the following charge elements:

- What is the current status of implementing the goals of the NNSA-MMM Mo-99 Program? What progress has been made since the 6th NSAC assessment?
- Is the strategy for continuing to implement the NNSA goals complete and feasible, within an international context?
- Are the risks identified in implementing those goals being appropriately managed?
- Has the NNSA-MMM Program addressed concerns and/or recommendations articulated in the 2019/2020 NSAC assessment of the Mo-99 Program appropriately and adequately?

- What steps should be taken to further improve NNSA program effectiveness in establishing a domestic supply of Mo-99?

It is requested that this assessment be submitted by spring of 2021.

We are aware that this charge represents an additional burden on your time. However, the involvement of NSAC is essential to inform the Agency regarding the effectiveness of efforts to steward Mo-99, and isotope essential for the health and well-being of the Nation.

Sincerely,

JOHN BINKLEY

Digitally signed by JOHN BINKLEY
Date: 2021.03.01 11:27:27 -05'00'

J. Stephen Binkley
Acting Director
Office of Science

Sean L. Jones

Digitally signed by Sean L. Jones
Date: 2021.03.01 13:19:51 -05'00'

Sean Jones
Assistant Director
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Appendix 2 – Membership of the NSAC Molybdenum-99 Subcommittee

Ronald Crone, Idaho National Laboratory
Mitch Ferren, Oak Ridge National Laboratory
Silvia Jurisson, University of Missouri - Columbia
Gail Dodge, Old Dominion University
Suzanne Lapi, Chair, University of Alabama at Birmingham
Steve Mattmuller, Kettering Medical Center
Alan Packard, Boston Children's Hospital
Thomas Ruth, TRIUMF

Committee Expertise		
Nuclear Medicine	**Radioisotope Production**	**Radiopharmacy and Clinical Use**
Alan Packard Suzanne Lapi Silvia Jurisson	Mitch Ferren Suzanne Lapi Thomas J. Ruth	Steve Mattmuller Alan Packard
Nuclear and Radio Chemistry	**Commercial Isotope Sales**	**Project Management**
Silvia Jurisson Suzanne Lapi Thomas J. Ruth	Mitch Ferren Suzanne Lapi	Gail Dodge Ron Crone

Appendix 3 – Meeting Agenda

Meeting Agenda
2021 DOE/NSF Nuclear Science Advisory Committee Mo-99 Program Review

May 10, 2021

(Designated Times are ET)

OPEN SESSION

10:00 – 10:15 Discussion of Charge and Introductions (NSF and DOE/NP)

10:15 – 10:30 Review of 2019 Recommendations (Lapi)

10:30 – 10:45 NNSA Response to 2019 NSAC recommendations (NNSA)

10:45 – 11:45 Review of Progress in the NNSA Mo99 Program
- Current status of cooperative agreement projects
- National lab support for CA partners and others
- ULTB status (NNSA and DOE/EM)

11:45 – 12:15 Break

CLOSED SESSION (Committee, NSF and DOE/NP)

12:15 – 1:00 **WORKING LUNCH (Committee, NSF, DOE/NP only)**

CLOSED SESSION (Committee, NSF, DOE/NP, and DOE/NNSA)

1:00 – 1:45 Closed-session updates from NNSA and DOE-EM

1:45 – 2:45 Updates from NNSA Cooperative Agreement Partners
- 1:45– 2:15 NorthStar Medical Radioisotopes
- 2:15 – 2:45 SHINE Medical Technologies

2:45 – 3:00 **Break**

OPEN SESSION

3:00 – 3:30 Mo-99 Stakeholder Input and Public Comment Session

CLOSED SESSION (Committee, NSF and DOE/NP)

3:30 – 5:00 Committee Discussion/Q&A/NNSA

Appendix 4 – Background on ^{99}Mo from the NSAC 2014 Report

The technetium-99m isomeric state (^{99m}Tc) is the most common radioisotope used in nuclear medicine procedures in the U.S. It is employed in about 14 million procedures per year. The isomeric decay produces a 140 keV gamma-ray that is well suited for gamma camera imaging and the half-life, 6.0 hours, allows sufficient time for preparing radiopharmaceuticals while being short enough to assure relatively rapid physical decay following the procedure. There are a variety of radiopharmaceuticals containing ^{99m}Tc for planar gamma scintigraphy and single photon emission computed tomography (SPECT) imaging in patients having multiple types of diseases. Technetium-99m has found extensive use in nuclear cardiology (50% of procedures), nuclear oncology (25%) and in other imaging of the brain, endocrine system, lungs, gastro-intestinal (GI) and genito-urinary (GU) and bones. Technetium-99m can be produced directly on a cyclotron or other type of particle accelerator, but is most conveniently obtained from the beta-decay of ^{99}Mo with a half-life of 66 hours.

The development of the ^{99}Mo generator for producing ^{99m}Tc is a success story of the DOE National Laboratories. In the late 1950's scientists at Brookhaven National Laboratory were working on improving a separation process for materials produced in the Brookhaven Graphite Research Reactor. They detected a trace contaminant of ^{99m}Tc, which was coming from contaminant ^{99}Mo. Based on the similarities with the chemistry of the tellurium-iodine parent-daughter pair, they developed the first ^{99m}Tc generator in 1958 [1]. At this time the head of the radioisotope production effort, Powell Richards, realized the potential of ^{99m}Tc as a medical radiotracer and promoted its use among the medical community. Dr. Paul Harper of the Argonne Cancer Research Hospital ordered and used the first ^{99m}Tc generator in 1961, and the boom began.

The ^{99m}Tc generators allow a quick and convenient chemical separation of ^{99m}Tc daughter nuclei from the ^{99}Mo parent material. The longer half-life of the ^{99}Mo makes it possible for ^{99}Mo to be produced at central large capacity locations and then transported to centralized radiopharmacies, which produce ^{99m}Tc radiopharmaceuticals and distribute them to hospitals and other imaging facilities. ^{99}Mo production is traditionally measured in "6-day Curies" based on the activity of the material six days after it is shipped (22% of the activity at the time of shipping). The historical worldwide demand has been about 12,000 6-day Ci per week with the U.S. demand at 6,000 6-day Ci per week; recent estimates show reduced demand of 10,000 6-day Ci per week worldwide (5,000 U.S.).

Molybdenum-99 is a fission fragment that is abundantly produced in the neutron-induced fission of ^{235}U (6% of all fissions). The last commercial production of ^{99}Mo in the U.S. ended in 1989. Since that time U.S. supply has relied on international producers who took advantage of the high efficiency of irradiating highly enriched uranium (HEU) targets, using material often exported from the U.S., at eight existing multi-purpose research reactors, with six of these sites being over 45-55 years old. Approximately half of the U.S. supply of ^{99}Mo has typically come from the National Research Universal (NRU) reactor in Canada. As part of its nuclear non-proliferation efforts, the U.S. plans to minimize the export of HEU, which is used both for targets for isotope production and for fuel for reactors. This has been a primary mission of the NNSA Global Threat

Reduction Initiative. When concern arose that this reduction in HEU exports would negatively affect the supply of radioisotopes in the U.S., Congress asked the National Research Council in the Energy Policy Act of 2005 to deliver a report on the feasibility and likely cost of non-HEU production of ^{99}Mo. This report, "Production of Medical Isotopes without Highly Enriched Uranium"[2] concluded that production with low enriched uranium (LEU) targets was feasible and estimated the additional cost for each procedure if LEU was used.

Around the same time, the ^{99}Mo supply underwent a series of shocks. In 2005, a U.S. based technetium generator producer shut down production for 5 months for a product recall. The NRU reactor shut down for one month in 2007. In August 2008 the High Flux Reactor at Petten (Netherlands) was shut down for six months. The NRU reactor was unexpectedly shut down in May 2009 as a result of a leak in the reactor vessel and only returned to service in August 2010. Simultaneously the HFR reactor in Petten was again shut down for more than 6 months. The global supply of ^{99}Mo could not meet the demand during these periods and some hospitals and clinics were forced to postpone or cancel imaging procedures. In some cases alternative-imaging procedures could be used and some even gave better results (e.g. ^{82}Rb for cardio-perfusion imaging). However, many of these alternatives involve higher radiation dose rates and often give lower quality results to the patient, e.g. ^{201}Tl cardiac scans. Additionally, most of these alternative-imaging agents were more expensive than ^{99m}Tc radiopharmaceuticals. Under this pressure, pharmacies did learn to use the ^{99}Mo they had more efficiently. As a result of the adaptation to these issues, and with the growth of alternative procedures, while the number of ^{99m}Tc procedures has continued to increase, ^{99}Mo demand in the U.S. is now calculated by OECD Nuclear Energy Agency (OECD-NEA) to be reduced to about 5,000 6-day Ci/week. [3]

To coordinate the international efforts to address these shortages, the OECD-NEA set up an international group to look at issues concerning the supply of medical isotopes, the High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR), in April 2009. This group performed detailed economic analyses of the ^{99}Mo supply [4] and concluded that the fundamental issue in the market was an unsustainable pricing structure based on government subsidization. The HLG-MR developed six principles and supporting recommendations to improve the reliability of the supply [5] (See *Appendix 4*). The first principle proposed is the implementation of full cost recovery pricing, including costs related to capital replacement. At the time of this review, Parrish Staples of NNSA was serving as the chairman of this group.

In the U.S., growing concern over supply of medical isotopes led to the introduction of the American Medical Isotopes Production Act (AMIPA). A bill, H.R. 3276, which passed the House of Representatives in November 2009, directed the Secretary of Energy to establish a program to evaluate and support projects for the production of significant quantities of ^{99}Mo in the U.S. for medical use, without the use of highly enriched uranium. It also directed the creation of a lease and take-back program to make low enrichment uranium available for the production of medical isotopes and proposed to end the export of highly enriched uranium for medical isotope production in the future. The bill died without action in the Senate. On November 17, 2011 the Senate passed S. 99, The American Medical Isotopes Production Act of 2011 which contained similar language. Neither of the proposed actions carried the force of law.

The NNSA GTRI took on the mission to address the ^{99}Mo production issue even before the AMIPA legislation was finally passed. There is strong overlap with their on-going work of minimizing the use of HEU. Senate report 112-17 provided a cost framework for the scope of the work, but was not an appropriation. Since the problem involved non-proliferation, health, international issues and nuclear and medical regulation issues, an inter-agency working group led by the White House Office of Science and Technology Policy (OSTP) (involving NNSA GTRI, Department of Energy (DOE)/ Office of Science, DOE/Nuclear Energy, FDA, Department of Health and Human Services (HHS)/Centers for Medicare & Medicaid Services (CMS), Department of State, Department of Homeland Security, NRC, Department of Transportation, National Institutes of Health/National Cancer Institute, and the Office of Management and Budget) was formed to coordinate activities, again even before the AMIPA legislation was passed. A stakeholders group was also formed to ensure input from and communication with the suppliers and end users.

The final version of the AMIPA was included in the Defense Authorization Act for 2013 and signed into law in January 2013. It requires the Secretary of Energy to *"establish a technology-neutral program . . . to evaluate and support projects for the production in the United States, without the use of highly enriched uranium, of significant quantities of molybdenum-99 for medical uses."* It also required "*the costs of which shall be shared in accordance with section 988 of the Energy Policy Act of 2005*." This latter act requires no less than a 50% cost sharing for non-R&D activities and no less than a 20% cost sharing for R&D activities, as determined by the Secretary. The act also directed the Secretary to "*use the Nuclear Science Advisory Committee to conduct annual reviews of the progress made in achieving the program goals and make recommendations to improve program effectiveness*". The final language of the law requires the Secretary of Energy to "*establish a program to make low enriched uranium available, through lease contracts, for irradiation for the production of molybdenum-99 for medical uses and to (i) to retain responsibility for the final disposition of spent nuclear fuel created by the irradiation, processing, or purification of uranium leased under this section for the production of medical isotopes."* However, the Secretary is only required to be responsible for final disposition of radioactive waste for which the Secretary determines that the producer does not have access to a disposal path.

References to Appendix 4

[1] Tucker, W.D., Greene, M.W., Weiss, A.J., and Murenhoff, A.P. *Methods of preparation of some carrier-free radioisotopes involving sorption on alumina*. BNL 3746. American Nuclear Society Annual Meeting, Los Angeles, CA, June 1958. Trans. Am. Nucl. Soc. 1,1958,160.

[2] National Research Council. *Medical Isotope Production Without Highly Enriched Uranium*. Washington, DC: The National Academies Press, 2009. http://www.nap.edu/catalog.php?record_id=12569

[3] OECD/NEA (2014), *The Supply of Medical Radioisotopes: Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the 99Mo/99mTc Market, 2015-2020,* OECD, Paris, France.

[4] OECD/NEA (2010), *The Supply of Medical Radioisotopes: An Economic Study of the Molybdenum-99 Supply Chain*, OECD, Paris, France.

[5] OECD/NEA (2011), *The Supply of Medical Radioisotopes: The Path to Reliability*, OECD, Paris, France.

Appendix 5 – Acronym List

AMIPA - American Medical Isotopes Production Act of 2012

CA - Cooperative Agreement

CNL - Canadian Nuclear Laboratories

DOE - U.S. Department of Energy

DOE-EM - U.S. Department of Energy Office of Environmental Management

FCR - full cost recovery

FDA - U.S. Food and Drug Administration

FOA – funding opportunity announcement

GA - General Atomics

GE - General Electric

GTCC LLW - greater than Class C low-level radioactive waste

GTRI - the NNSA Global Threat Reduction Initiative

HEU - Highly Enriched Uranium

HLG-MR - High Level Group on the Security of Supply of Medical Radioisotopes of the OECD-NEA

LEU - Low-Enriched Uranium

MURR - Missouri University Research Reactor

NAS - National Academies of Sciences, Engineering, and Medicine

NDA - New Drug Application

NNSA - National Nuclear Security Administration

NNSA-M^3 - the NNSA Material Management and Minimization Program

NNSA-PO - the NNSA Production Office

NRC - U.S. Nuclear Regulatory Commission

NRU - National Research Universal reactor

NTP – NTP Radioisotopes SOC Limited, South Africa

NSAC - Nuclear Science Advisory Committee

OECD-NEA - Organization for Economic Cooperation and Development's Nuclear Energy Agency

OSU – Oregon State University

PMDA - Plutonium Management Disposition Agreement

RGX - NorthStar RadioGenix ^{99m}Tc generating system

SGE - selective gas extraction

SNF - spent nuclear fuel

SV - source vessel

TRIGA - Training, Research and Isotopes, General Atomic reactor

ULTB - Uranium Lease and Take Back