Report to the Nuclear Science Advisory Committee

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

October 20, 2016
Report of the NSAC ^{99}Mo Subcommittee

Executive Summary

The Nuclear Science Advisory Committee (NSAC) ^{99}Molybdenum (^{99}Mo) Subcommittee met September 29-30, 2016 to address the charge to NSAC requesting that a third annual review of the National Nuclear Security Administration (NNSA) ^{99}Mo program be performed. The Subcommittee found that the NNSA has continued to work diligently and proactively over the course of the year based on the specific American Medical Isotopes Production Act of 2012 (AMIPA) requirements, especially considering the many complex factors outside their direct control. They had previously conducted peer reviews of initial proposals based on well-defined criteria flowing from AMIPA and continue to review the progress of the cooperative agreement (CA) partners; they have made good use of the national laboratories to support their cooperative agreement partners; and they have been responsive in managing the projects they funded. They acted on previous recommendations from this Subcommittee, notably with regard to the partnering with other parts of the Department of Energy (DOE) to initiate operation of the Uranium Lease and Take Back (ULTB) Program and in supporting the efforts of the Canadian government to prepare to supply ^{99}Mo in the event of a critical shortage during the period of October 2016 through 2018. Still, the program faces challenges.

The international context for ^{99}Mo availability has changed since the last review. The Organization for Economic Cooperation and Development's Nuclear Energy Agency (OECD-NEA) has updated [1] its assessment of the ^{99}Mo production capacity and demand curves and the National Academies of Sciences, Engineering, and Medicine (NAS) has issued its report [2] on Molybdenum-99 for Medical Imaging. The Canadian government has issued [3] a contingency plan for providing ^{99}Mo during the period 2016-2018 should a worldwide shortage develop.

The Subcommittee found that NNSA had considered the previous

recommendations of the Subcommittee and acted on a number of them. A new CA project has begun since the last NSAC review. The other CA projects have incurred additional delays of about a year in the projected dates for first ^{99}Mo commercial production over the same period. It is probable that one or more of the NNSA supported projects will enter the market eventually, though likely not with sufficient capacity initially to mitigate potential shortages in the period 2016-2018. There are positive developments with respect to the ability of the Canadian National Research Universal (NRU) reactor in Canada to act to mitigate shortages during this critical period.

The recent report of the NAS indicates there is a "substantial likelihood of severe Mo-99/Tc-99m supply shortages after October 2016" whereas the most recent OECD-NEA study concludes the supply should be sufficient to deal with an unplanned outage of a reactor or processor. The Subcommittee finds that these somewhat differing estimates of risk indicate the difficulty and uncertainty inherent in these assessments. Therefore, the possibility of shortages cannot be ignored and continued diligence by the NNSA in promoting the entry of new U.S. producers into the market remains important.

The Subcommittee has one recommendation:

Recommendation: The costs associated with the take-back portion of the ULTB program must be defined in a way that potential customers have predictable costs. The Subcommittee considers it extremely urgent that DOE identify a way to cap the liability associated with spent nuclear fuel (SNF) and radioactive waste disposition in the ULTB program for potential U.S. ^{99}Mo producers.

Introduction

The NSAC ^{99}Molybdenum (^{99}Mo) Subcommittee began its work in 2016 in response to a charge letter dated June 13, 2016 (Appendix 1). This letter was motivated by the AMIPA legislation, which was contained in the National Defense Authorization Act for Fiscal Year 2013. This act requires the Secretary of Energy to establish a technology-neutral program to provide assistance to commercial entities to accelerate production of ^{99}Mo (aimed at ensuring a reliable domestic supply of the isotope ^{99}Mo) used to supply the medical diagnostic isotope ^{99m}Tc in the United States, without the use of Highly Enriched Uranium (HEU). The NNSA Global Threat Reduction Initiative (GTRI) was given the responsibility for development of this program in 2009. This act also called for an annual review of the NNSA GTRI ^{99}Mo program by the NSAC. Following a NNSA reorganization, the ^{99}Mo program is now within the NNSA Material Management and Minimization (NNSA-M^3) program.

NSAC established a Subcommittee to perform this review in 2014. Additional members were added in 2015 and 2016 to address stakeholder input. The 2016 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 September 29-30, 2016 in Bethesda, MD and built on the extensive work of the first and second reviews. At this meeting the Subcommittee was briefed by NNSA on details of the program and received input from representatives of the OECD-NEA High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) and the NAS Committee on the State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium. The Subcommittee invited input from all three current CA partners; they all presented briefings. Finally, the Subcommittee solicited feedback from a broad set of ^{99}Mo stakeholders, devoting a session to stakeholder input. 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 2015 Report

The OECD-NEA HLG-MR issued a new report "2016 Medical Isotope Supply Review: ^{99}Mo/^{99m}Tc Market Demand and Production Capacity Projection 2016-2021" [1]. This report summarizes global supply and demand for ^{99}Mo. The report concluded that "…the current irradiator and processor supply chain capacity should be sufficient and if well maintained, planned, and scheduled, be able to manage an unplanned outage of a reactor or a processor throughout the whole period to 2021". The Subcommittee was informed that a number of producers have increased their supply capacities since the report was issued.

The NAS issued a report [2] entitled "Molybdenum-99 for Medical Imaging". This report concludes that there is a "…substantial likelihood of severe ^{99}Mo/^{99m}Tc supply shortages after October 2016." The report points out that after the exit of the NRU the absence of supply from a single major source could bring supplies below the global demand, and further that there have been multiple unplanned supplier outages in the period 2012-2015. The report also noted that NRU could provide extra capacity that could be utilized in the event of an unplanned outage after it stops routine production of ^{99}Mo in October 2016.

The Canadian government continues to have a firm October 2016 deadline to stop routine production of ^{99}Mo. They previously announced [3] that the NRU will run through March 2018 (pending extension of license) but will not produce ^{99}Mo except on an emergency basis in the case of an extreme shortage. It is noted that the NAS report did not have details of Canadian plans for producing ^{99}Mo on a contingency basis when assessing the risk of a severe shortage. Since last year's review the Canadian government has issued a contingency plan (Appendix 5) and NNSA reported that a license application has been submitted (http://fissilematerials.org/blog/2016/09/united_states_to_prepare_.html) to allow the necessary HEU to be shipped to Canada.

The Subcommittee finds that the differing estimates of risk in the OECD-NEA and NAS reports indicate the difficulty and uncertainty inherent in these assessments. Therefore, the possibility of shortages cannot be ignored and continued diligence by the NNSA in promoting the entry of new U.S. producers into the market is important.

Developments in the NNSA Program

The organization and goals of the NNSA-M^3 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 HEU. The NNSA-M^3 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 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.

Sections 3173 (c) and (e) of the FY13 National Defense Authorization Act direct DOE to establish a 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 also requires DOE to retain responsibility for the final disposition of SNF and 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.

This ULTB Program is coordinated between different organizations within DOE: the NNSA Production Office (NNSA-PO) provides the management and leasing of LEU required for domestic fission-based ^{99}Mo production while the DOE Office of Environmental Management (DOE-EM) manages the disposition of SNF and radioactive waste that does not have an existing disposal path, both of which may be generated by ^{99}Mo production. The cost recovery models DOE will utilize for the ULTB Program are of particular interest to potential ULTB users (including two CA partners of the ^{99}Mo program) because they need estimated program costs to assess and incorporate into their business case planning. NNSA has established an intra-agency working group to coordinate the completion of various activities in order to establish the ULTB program; a positive development in the last year has been the official establishment of the ULTB program. In spite of this, challenges remain in defining the cost of the take-back portion of the program, particularly for greater-than-Class-C low-level radioactive waste (GTCC LLW).

As required by AMIPA, the NNSA-M^3 program has continued to provide assistance to commercial entities to pursue several technologies to accelerate production of ^{99}Mo in the United States without the use of HEU. This program involves creating cooperative agreements with a set of commercial entities based on a 50/50 cost share between the government and the commercial entity. NNSA continues to operate using a total funding limitation of $25M to each commercial project it supports; this is in accordance with the OECD-NEA guidelines on full cost recovery (FCR) principles.

At the start, NNSA-GTRI took an aggressive approach to accelerate reliable ^{99}Mo production in the US by funding four CA partners. In 2009 and 2010 the goal was to achieve domestic production as soon as possible, a time scale estimated as 3-4 years. Therefore, the CA goal for each of the partners was to demonstrate a capability to produce 3,000 6-day Curies per week by the end of calendar 2013. The first two CAs were put in place through a non-competitive process based on an initial NNSA survey of extant capabilities. The next three were

selected based on responses to a public Funding Opportunity Announcement (FOA).

The CA projects active in 2015 covered complementary technical approaches to ^{99}Mo production. One technical approach (NorthStar) is to reestablish production of ^{99}Mo by neutron capture at the Missouri University Research Reactor (MURR). MURR uses HEU as reactor fuel because there is as of yet no LEU fuel developed for MURR, but MURR plans to transition to a LEU fuel when such fuel is available. The ^{99}Mo material generated with this technology will require a ^{99m}Tc isotope generator (which Northstar has developed) that differs from existing generators for fission-produced material because of its low specific activity. Production at MURR will begin using natural molybdenum targets, but enriched-isotope ^{98}Mo targets will be required to achieve 3,000 6-day Ci/week. NorthStar's second project uses electron accelerators to produce ^{99}Mo through photo-neutron reactions on ^{100}Mo; it can use the same Northstar generator for the low specific activity ^{99}Mo that is produced. Achieving 3,000 6-day Ci/week would require multiple electron accelerators and irradiation target stations. The technical approach of the third CA project active last year (SHINE) is to produce ^{99}Mo by fission using neutrons produced by an accelerator driven D-T neutron source. The target is a sub-critical LEU aqueous solution surrounding a tritium gas cylinder that is irradiated with low energy deuterons. The high specific activity ^{99}Mo material generated in this technology can use current generators, but an FDA submission will be required by SHINE's customers to qualify SHINE as a new raw material supplier. All three of these projects are still active.

The NorthStar neutron capture project has been provided an additional $8.9 million. With this award NNSA has provided the full $25 million NNSA cost share to this project. NorthStar is in the process of obtaining U.S. Food and Drug Administration (FDA) approval for their RadioGenix ^{99m}Tc generating system (RGX). They have previously made an initial New Drug Application (NDA) to the FDA and are in the end stages of preparing an amendment addressing the latest requests from the FDA. In the last year NorthStar has reported progress in preparation for ^{99}Mo production. Their reported accomplishments since May 2015 include:

- Completion of more than 30 ^{99}Mo production runs of 100 6-day Ci each
- Prepared more than 12,000 Ci of ^{99}Mo
- Filled about 300 generator Source Vessels (SV)
- Tested and validated their shipping logistics
- Mounted and ran ^{99}Mo produced at MURR using the RGX system, eluted ^{99m}Tc and performed multiple labeling runs
- Initiated clean room SV production operations at Beloit
- Initiated expansion of the MURR fill line operations to four times current production rate
- Ordered six MIDUS Type B shipping containers for enriched targets for ^{99}Mo production

- Pre-Approval Inspection readiness audits were performed by outside experts

NorthStar expects to complete submission of responses to the FDA in 4QTR16. They state that when approval is granted they will be ready to provide ^{99}Mo to the U.S. market.

NorthStar reports that they are now increasing the emphasis on their second project. NNSA has provided an additional $1.6 million to this project. The estimated completion on this project has been delayed by almost 2 years since March of 2015.

The Subcommittee notes that NorthStar's ^{99}Mo neutron capture and accelerator production technologies require enriched ^{98}Mo and ^{100}Mo, respectively. The supply of the enriched molybdenum is a long-term question that will need to be addressed by NorthStar. NorthStar has communicated that they have secured sufficient inventory of enriched molybdenum from overseas producers for production of ^{99}Mo via both methods and that they are currently working with two potential future suppliers. There is currently no U.S. production of these isotopes. The DOE Isotope Program, managed by the Office of Science for Nuclear Physics, is also working to reestablish U.S. enrichment capability that would address this issue.

The SHINE project reports progress in the last year. Their reported accomplishments include:

- Construction Permit was issued by the U.S. Nuclear Regulatory Commission (NRC); this is the first Construction Permit issued for a non-power facility since 1985
- Ran an accelerator demonstration for 132 consecutive hours of operation with 97% uptime
- Produced ^{99}Mo at Argonne National Laboratory using the SHINE process and shipping the product to General Electric Health Care (GE). GE then tested the ^{99}Mo in their DryTec generator and found that both the ^{99}Mo and the resulting ^{99m}Tc met all specifications
- Executed a supply agreement with HTA Co., Ltd., the largest distributor of radiopharmaceuticals in China

First production from this project is delayed about one year since the 2015 review (now expected in 2019). Although SHINE reports that it has raised enough funds to complete design, the progress of this project has been hindered by the limited availability of investment funds. The company reports they are now raising the funds to start building the facility in 2017.

Since the last review, NNSA has added a new CA project with General Atomics (GA). This project uses selective gas extraction (SGE) to extract ^{99}Mo produced by fissioning of LEU targets in the MURR reactor. This project has been provided

$9.7M. GA was a selected awardee of the 2010 FOA, but declined at the time following their own business evaluation. NNSA and GA agreed to re-engage on the project if GA's position changed. GA's position did change and they formally submitted a revised proposal to NNSA.

General Atomics reports progress since the CA project was begun in the last year. Progress includes:

- Performance and accident analyses have been completed for target assembly
- Design reviews of target assembly, cooling, and collection systems were completed
- 1/10 scale experiments on ^{99}Mo-doped pellets have measured yields higher than required
- Curie quantities have been extracted by SGE from irradiated pellets
- A LEU lease agreement between MURR and NNSA was signed; delivery of 20 kg LEU is imminent
- Hot cell equipment was defined and a vendor selected

Findings

The Subcommittee found that the NNSA has moved the NNSA-M^3 program forward consistent with the specific AMIPA requirements. They conducted peer reviews of all proposals based on well-defined criteria flowing from AMIPA and continue to review awarded projects annually through the use of Independent Technical Reviewers; they have made good use of the national laboratories to support their cooperative agreement partners; and they have been responsive in managing the projects they awarded. In addition, they have effectively partnered with other parts of DOE where it is needed to advance the ^{99}Mo program, e.g. working with DOE-EM on the establishment of a ULTB Program. NNSA has continued their efforts to coordinate with the other organizations within DOE.

In the Subcommittee discussions, the NNSA expanded on their high level goal, stating that the program will be successful when there is U.S. production of ^{99}Mo that has achieved FDA approval for use in the U.S. market. The Subcommittee concludes, based on progress reported by CA partner NorthStar, that there is a significant chance that NNSA will succeed in meeting that goal during 2017. The dates projected for the other CA partners to provide ^{99}Mo to the U.S. market are in 2018 and later. These projects face issues related to cost and/or funds availability that could possibly result in one or both failing to produce any ^{99}Mo for the commercial market.

There are issues related to the long-term financial viability of any producers that *do* succeed in entering the market. The ^{99}Mo program itself has concluded that commercial viability of domestic production depends, in large part, on the global move toward FCR. NNSA stated that the slowness [4] of the global move toward FCR could impact the level of U.S. production in the long term.

The NNSA-M^3 program is a mature program that is expected to reach its goals in the near future. Given the maturity of the program and the advanced state of technical progress of CA projects focused on demonstrating feasibility for domestic ^{99}Mo production, it is unlikely that future NSAC reviews would identify new recommendations that could impact the program's success.

In the next sub-sections, the Subcommittee addresses the specific questions laid out 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 2015 assessment?*

The projected dates of production from the CA projects that were active in 2014 have incurred delays ranging from 1-2 years since last year. Those CA partners have nonetheless all made progress during the last year. An agreement has been established with an additional CA partner who previously declined an

agreement. This is a positive development. In another very positive development, NNSA has shown initiative in working to help in the establishment of the ULTB program, and that program has started. The Canadian government has issued a contingency plan for emergency production of ^{99}Mo at the NRU. NNSA has transmitted an HEU export license application to NRC for 3 kg HEU, consistent with the Government of Canada's 'NRU Contingency' Plan.

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

The Subcommittee concludes that the NNSA strategy is complete and feasible based on the actions listed below:

- The NNSA strategy has been adjusted based on the delays incurred by the CA partners.
- A three-pronged approach was presented and the Subcommittee agrees that it should achieve the goals stated by the program. The elements of this approach are 1 - Support international conversion efforts, 2 - Support domestic cooperative agreement projects and 3 - Work with international and U.S. interagency stakeholders.
- GA has been brought in as a fourth CA project and they have made progress.
- The ULTB Program has been established in coordination with DOE-EM.
- The Canadian government has created a contingency start-up plan for NRU production of ^{99}Mo, and NNSA has transmitted an HEU export license application for 3 kg HEU to the NRC.
- NNSA made a thorough evaluation considering whether to raise the cap on CA project funding above $25M as recommended by the NSAC review in 2015; NNSA considered raising the cost share in the context of AMIPA and elected to maintain the cap at $25M and the 50/50 cost share. The Subcommittee found this evaluation to be a reasonable and acceptable response.

Are the risks identified in implementation being appropriately managed?

Several risks remain to achieving the goals of the program. Some of these are specific to each CA partner and some are associated with the program as a whole. The risks over which NNSA-M^3 has some control include working with DOE-EM in executing the ULTB program and working with the Canadian government to lessen the impact of the NRU ceasing regular ^{99}Mo production. In both instances, NNSA-M^3 has made significant efforts to reduce these particular risks. The ULTB program has been implemented and potential users of this provision have begun discussions with NNSA on leasing LEU and with DOE-EM on the take-back of SNF and certain authorized radioactive waste without an established disposal path. DOE-EM has provided the ^{99}Mo producers with take-back contracts that include good faith cost range estimates.

A remaining challenge is that under the "take back" portion of the ULTB Program there is not a disposal pathway for GTCC LLW and SNF at this time. Therefore, costs in the take-back contract are estimated ranges based on information known to-date. The costs associated with the final disposition of the used uranium requires an understanding of both the disposal path and the composition of the waste. If a ^{99}Mo producer wants to lease LEU from the NNSA-PO, then they must also sign a take-back contract since the LEU is owned by NNSA-PO. If the ^{99}Mo producer purchases the LEU from NNSA-PO then they do not have to sign a take-back contract. At least one CA partner has stated that there must be a resolution in the coming months that provides a limitation on the final liability they might have for waste disposal costs if they are to proceed on schedule in pursuing new technology based on the fissioning of LEU.

The NAS 2016 Report indicated that there was a substantial risk of a shortage of ^{99}Mo, especially during the period between when the NRU stops irradiating targets and when the NRU license expires (1 Nov 2016 and 31 March 2018, respectively). One of the NAS recommendations was to request the NNSA to continue to pursue cooperation between the US and Canadian governments in developing a workable plan for using the NRU during such shortages. Based on information provided by NNSA, it appears the mechanism(s) for the Government of Canada to have the NRU restart in a severe shortage are in place. With these events the risks associated with a major outage are lessened. That said, there could be a shortage of short duration due to the time required to determine that a shortage is of sufficient severity to warrant restarting the NRU irradiations and the time to commence irradiations after that decision. The Subcommittee is not privy to the details on targets because of security issues. It is therefore unclear how long the NRU could operate before needing additional HEU targets (the Canadian Nuclear Laboratories (CNL) manufacture their own targets from the HEU received from the United States). Thus there is a near term risk for a secure domestic supply of ^{99}Mo due to the time required by the NRC to process a license application and the subsequent time required to fabricate targets. NNSA has transmitted an HEU export license application to NRC for 3 kg HEU, consistent with the Government of Canada's 'NRU Contingency' Plan. The subcommittee concludes that the NNSA has done everything in their control to reduce this risk.

The NNSA is continuing to take reasonable actions to reduce risks that are not within their direct control. These risks and actions include:

- CA partners requiring new generators still have risks associated with FDA approval. One CA partner has filed with the FDA and is in the process of addressing the request for information from the FDA.
- A shortage of private investment remains a risk for at least one CA partner.
- NNSA-M^3 continues to reduce risk by working with interagency partners such as NRC and FDA to help as needed on approvals required by the projects.

- The slow progress toward FCR in the global ^{99}Mo supply chain threatens the longer term financial viability of any U.S. producers that succeed in entering the market. NNSA continues to work with the OECD HLG-MR on this issue.

Overall, the Subcommittee finds that NNSA is appropriately managing the risks identified in implementation of the ^{99}Mo program.

Has the NNSA-MMM Program addressed concerns and/or recommendations articulated in the 2015 NSAC assessment of the ^{99}Mo Program appropriately and adequately?

The NNSA-M^3 program has been responsive to the 2015 NSAC assessment. The Subcommittee finds that the actions of NNSA have been appropriate and adequate based on the responses summarized below.

The Subcommittee recommended in 2015 that DOE should increase funds available to individual CA projects sufficient to significantly accelerate their ability to rapidly establish domestic production. NNSA described their consideration of raising the cap on CA project funding above $25M as recommended by the NSAC review in 2015; NNSA considered raising the cost share in the context of AMIPA and elected to maintain the cap at $25M and the 50/50 cost share. The Subcommittee found this evaluation to be a reasonable and acceptable response.

The Subcommittee recommended in 2015 that DOE must support NNSA in their continued efforts to advocate for the timely establishment of the ULTB Program. This program was established in January of 2016.

The Subcommittee recommended in 2015 that NNSA should document a contingency plan to ensure a supply of ^{99}Mo from Canada within a few months if a significant shortage of ^{99}Mo appears imminent during the period 2016-2018. The Canadian government has issued such a plan. NNSA has transmitted an HEU export license application to NRC for 3 kg HEU, consistent with the Government of Canada's 'NRU Contingency' Plan.

The subcommittee recommended in 2015 that NNSA should develop a contingency plan to adapt the program should OECD-NEA continue to determine that the global community is not making adequate progress toward FCR in order for domestic production to be economically feasible. NNSA has not acted on this recommendation.

Recommendations

The NNSA-M^3 program is working toward their high-level goal to accelerate domestic production of ^{99}Mo. It is possible that one of the CA partners will enter the market with U.S. produced ^{99}Mo in 2017. A new CA project based on fission production of ^{99}Mo has been initiated this year. The success of some projects based on fissioning of LEU may depend critically on the costs associated with waste disposal through the ULTB.

The Subcommittee has one recommendation:

Recommendation: The costs associated with the take-back portion of the ULTB program must be defined in a way that potential customers have predictable costs. The Subcommittee considers it extremely urgent that DOE identify a way to cap the liability associated with spent nuclear fuel (SNF) and radioactive waste in the ULTB program for potential U. S. ^{99}Mo producers.

References

[1] OECD/NEA (2016), *2016 Medical Isotope Supply Review: 99Mo/99mTc Market Demand and Production Capacity Projection 2016-2021,* NEA/SEN/HLGMR(2016)2, Paris, France.

[2] National Academies of Sciences, Engineering, and Medicine. 2016. *Molybdenum-99 for Medical Imaging*. Washington, DC: The National Academies (http://www.nap.edu/23563).

[3] Contingency plan supplied to subcommittee by the NNSA and previous press release by the Canadian government, February 6, 2015 http://www.newswire.ca/news-releases/government-of-canada-announces-extension-of-national-research-universal-nru-reactor-516954021.html

[4] OECD/NEA (2014), *The Supply of Medical Radioisotopes: Results from the Second Self Assessment of the Global ^{99}Mo/^{99m}Tc Supply Chain*, OECD, Paris, France.

Appendix 1 – Charge Letter

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

June 13, 2016

Professor David Hertzog
Chair, DOE/NSF Nuclear Science Advisory Committee
Department of Physics
University of Washington
Seattle, Washington 98195

Dear Professor Hertzog:

This letter is to request that, in accordance with direction given to the DOE in the National Defense Authorization Act (NDAA) for FY2013, 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 National Defense Authorization Act (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 Department of Energy (DOE) and National Science Foundation (NSF) very much appreciate NSAC's previous assessments as described in reports transmitted to the agencies on May 8, 2014, and July 10, 2015.

Subsequently, we request that NSAC reconvene the Subcommittee to provide a third 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 2nd NSAC assessment?
- Is the strategy for continuing to implement the NNSA goals complete and feasible, within an international context?
- Are risks identified in implementing those goals being appropriately managed?
- Has the NNSA-MMM Program addressed concerns and/or recommendations articulated in the 2015 NSAC assessment of the Mo-99 Program appropriately and adequately?

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- 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 October 31, 2016.

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,

C. A. Murray
Director
Office of Science

F. Fleming Crim
Assistant Director
Directorate for Mathematical
And Physical Sciences

Appendix 2 – Membership of the NSAC Molybdenum-99 Subcommittee

Susan Seestrom, Chair, Los Alamos National Laboratory
Carolyn Anderson, University of Pittsburgh
Jeff Binder, University of Illinois
Ronald Crone, Idaho National Laboratory
Frederic Fahey, Boston Children's Hospital
Jack Faught, LINDE
Mitch Ferren, Oak Ridge National Laboratory
David Hertzog, University of Washington
Suzanne Lapi, University of Alabama at Birmingham
Meiring Nortier, Los Alamos National Laboratory
Steve Mattmuller, Kettering Medical Center
Berndt Mueller, Brookhaven National Laboratory
Ken Nash, Washington State University
Joseph Natowitz, Texas A&M University
Thomas Ruth, TRIUMF

Committee Expertise		
Reactor Design and Operation	**Radioisotope Production**	**Radiopharmaceutical Chemistry**
Ron Crone Jeff Binder	Mitch Ferren Jeff Binder Suzanne Lapi Meiring Nortier Thomas J. Ruth	Carolyn Anderson Suzanne Lapi Thomas J. Ruth
Nuclear and Radio Chemistry	**Commercial Isotope Sales**	**Project Management**
Carolyn Anderson Suzanne Lapi Ken Nash Joe Natowitz Meiring Nortier Thomas J. Ruth	Jack Faught Mitch Ferren	Berndt Mueller David Hertzog Susan Seestrom Ron Crone
Nuclear Physics	**Nuclear Engineering**	**Radiopharmacy and Clinical Use**
David Hertzog Berndt Mueller Joe Natowitz Susan Seestrom	Ron Crone Jeff Binder Meiring Nortier	Steve Mattmuller Frederic Fahey

Appendix 3 – Meeting Agenda

2016 Nuclear Science Advisory Committee Mo-99 Program Review

September 29-30, 2016

Hyatt Regency Bethesda Hotel, Susquehanna/Sever Conference Room,
One Bethesda Metro Center, Bethesda, Maryland

SEPTEMBER 29, 2016

OPEN SESSION

08:15 – 08:30 Discussion of Charge and Introductions (DOE NP)

08:30 – 09:00 Review of 2015 Recommendations (Seestrom)

09:00 – 10:15 Developments in the Mo-99 Program since 2015 review (NNSA)

- Current status of cooperative agreement projects
- NNSA response to 2015 NSAC recommendations

10:15 – 10:30 Break

10:30 – 11:30 Status of the Uranium Lease and Take-Back Program (Peter Karcz, DOE-EM)

11:30 – 12:30 Review of NAS 2016 Report (Thomas Ruth, TRIUMF)

CLOSED SESSION (Committee, NSF and DOE NP)

12:30 – 1:30 WORKING LUNCH

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

1:30– 2:00 Closed-session updates from NNSA

2:00 – 5:00 Updates from NNSA Cooperative Agreement Partners

- 2:00-3:00 General Atomics (MURR and Nordion)
- 3:00-4:00 NorthStar Medical Radioisotopes
- 4:00-5:00 SHINE Medical Technologies

5:00 – 5:30 Committee Discussion (Committee, NSF, and DOE NP)

2016 Nuclear Science Advisory Committee Mo-99 Program Review
September 29-30, 2016
Hyatt Regency Bethesda Hotel, Susquehanna/Sever Conference Room,
One Bethesda Metro Center, Bethesda, Maryland

SEPTEMBER 30, 2016

OPEN SESSION

08:30 – 9:30	Presentation OECD projections of supply and demand (Kevin Charlton, OECD-NEA) (*web link*)
9:30 – 11:00	Mo-99 Stakeholder Input and Public Comment Session
11:00 – 12:00	Committee Discussion / Q&A for Open Session Participants

CLOSED SESSION

12:00 – 1:00	Working lunch (Committee, NSF, DOE NP, and NNSA)
1:00 – 5:00	Committee Working Session (Committee, NSF, and DOE NP only)
5:00	Adjourn

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 AMPIA 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 – NRU Contingency Plan

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The Government of Canada's 'NRU Contingency' Plan

Overview

In 2015, the Government of Canada announced that Atomic Energy of Canada Limited's (AECL's) National Research Universal (NRU) reactor would continue to operate until March 31, 2018, subject to re-licensing approval by Canadian nuclear regulatory authorities. While the NRU will cease routine production of molybdenum-99 (Mo-99) as of October 31, 2016, the capability to produce Mo-99 at the NRU will be maintained between November 1, 2016 and March 31, 2018. This capability is known as the 'NRU Contingency'. After March 31, 2018, the NRU is scheduled to cease operations and be placed in a safe shutdown state, pending its decommissioning.

The NRU Contingency is not to be considered 'reserve outage capacity' that the market can expect to draw upon as a matter of normal course of business. Furthermore, it is not meant to hinder or prevent the market entry of alternative sources of supply of medical isotopes on a sound commercial basis, which Canada continues to support as the long-term solution to the security of supply of medical radioisotopes. In the event that the NRU Contingency is triggered due to a shortage, it is expected that market dynamics would likely place a premium on the pricing of isotopes at that time.

Decision-Making

The decision to enact the NRU Contingency will be made by the Government of Canada. In turn, Canada is committed to actively engaging those major stakeholders nationally and internationally with data relevant to potential and actual supply disruptions, including information related to supply and demand and potential risks. The Government of Canada will analyze the information received through this engagement and assess the need to call upon the NRU Contingency.

The Government of Canada understands that a decision regarding the NRU Contingency would need to be taken very swiftly, and is cognizant that resuming production from the NRU and getting the product to market may take some time and will depend on many factors (e.g. the planned outage schedule for the NRU, amongst other things). For this reason, and to ensure swift communications and decision-making in the event of a request to enact the NRU Contingency, the Government of Canada has:

- developed a series of communications protocols to structure engagement with international and domestic partners in the event of a global isotopes shortage;
- formulated an internal decision-making protocol to facilitate timely consideration of a request to draw upon the NRU; and
- committed to continue working with the United States to ensure an adequate and timely supply of additional HEU, should it be required.

Canada

June 2016

Conditions

The circumstances under which Canada may enact the NRU Contingency cannot be fully anticipated, and Canada has therefore established a number of considerations that will inform decision making – the most important of which will be whether the enactment is truly providing the 'isotope of last resort' to mitigate significant impact to patients. Other considerations will include the degree (e.g. volume, expected length) of the global shortage, and the availability of other potential mitigation measures (e.g. the availability of alternative sources of supply, and demand-side efforts to maximize use of available product).

The NRU Contingency would be used only:

- in the unexpected circumstance of a significant global shortage of extended duration; and
- if alternative technologies or other sources of supply are not available.

Furthermore, enactment of the NRU Contingency would be subject to several conditions. These include:

- Canadian Nuclear Laboratories (CNL, operator of the NRU) obtaining the necessary regulatory approvals;
- the availability of highly-enriched uranium (HEU) targets; and
- the availability of processing capability and capacity at CNL and Nordion Inc. (private company that processes the Mo-99 produced at the NRU).

Preparations

To ensure readiness throughout the NRU Contingency period, CNL is working with the Canadian regulator to extend relevant licenses, implementing retention strategies to address human resource needs, and planning preventative maintenance. As concerns HEU, Canadian and US government officials have had productive engagement, and will continue to work together, with respect to process to ensure the timely availability of HEU targets, should they be required. Finally, there have also been constructive discussions between the Government of Canada and Nordion regarding the availability of processing capability and capacity in the event of the operationalization of the NRU Contingency.

Questions on the Government of Canada's NRU Contingency Plan and/or use of this document can be directed to one of the following Canadian representatives to the High-Level Group on the Security of Supply of Medical Radioisotopes:

- Niall O'Dea, Natural Resources Canada – niall.odea@canada.ca, 1-343-292-6200
- Nicole Charron, Health Canada – nicole.charron2@canada.ca, 1-613-946-1821
- Shannon Quinn – Atomic Energy of Canada Limited, squinn@aecl.ca, 1-613-589-2085

Appendix 6 – 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

NSAC - Nuclear Science Advisory Committee

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

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 Program