Report to the Nuclear Science Advisory Committee

Review of the NNSA GTRI Mo-99 Program

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Report of the NSAC ^{99}Mo Sub-Committee

Introduction

The Nuclear Science Advisory Committee (NSAC) ^{99}Molybdenum (^{99}Mo) subcommittee was formed in response to a charge letter (see *Appendix 1*) from Dr. Patricia Dehmer, Acting Director of the Department of Energy (DOE) Office of Science and Dr. F. Fleming Crim, Assistant Director for Mathematical and Physical Sciences of the National Science Foundation (NSF), dated December 5, 2013. This letter was motivated by the legislation "American Medical Isotopes Production Act of 2012" that 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 on the isotope ^{99}Mo) used to supply the medical diagnostic ^{99m}Tc in the United States, without the use of Highly Enriched Uranium (HEU). The entity responsible for development of this program is the National Nuclear Security Administration (NNSA) Global Threat Reduction Initiative (GTRI). This act also called for an annual review of the NNSA GTRI program by the NSAC.

NSAC set up a Subcommittee to perform this review. The Subcommittee membership is given in *Appendix 2*.

The Subcommittee started its work by collecting background information and identifying a set of materials about the GTRI program that it then requested from NNSA. The Subcommittee had two meetings – January 9-10, 2014 and February 26-27, 2014 in Washington DC. At these meetings the Subcommittee was briefed by NNSA on details of the program, and had input from representatives of the Organization for Economic Co-operation and Development (OECD), the National Academy of Science (NAS) Study Group, Food and Drug Administration (FDA), and Nuclear Regulatory Commission (NRC). (See Appendix 3 for the agendas of these meetings) The Subcommittee invited input from all cooperative agreement partners and three agreed to present briefings. In addition, we solicited feedback from a broad set of ^{99}Mo stakeholders, devoting a session to all stakeholders who requested time to make a presentation in person. A number of other stakeholders submitted written input to the committee.

Background on ^{99}Mo

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.

The present review only applies to the activities in support of domestic production, not the development assistance, uranium lease and take-back program or the export issues.

The ^{99}Mo program does not appear as a line item within the NNSA appropriation but is included within the GTRI appropriation, currently under the HEU Reactor

Conversion program. Budget language in the 2015 President's request identifies " the major milestone in FY2015 of the development of a new domestic, non HEU-based supply of the critical medical isotope molybdenum-99 (Mo-99), which is being executed under multi-year contracts funded in previous fiscal years, is nearing completion." The reduction of requested funding in FY2015 reflects the anticipated establishment of the first domestic source of non-HEU produced ^{99}Mo. Guidance has also been included in appropriations subcommittee report language; for example, in the Senate report language of 2014, "supporting NNSA's efforts in developing a capacity which does not currently exist in the U.S. to produce Moly-99 … with low enriched uranium by 2016."

NNSA Program

The National Nuclear Security Administration is responsible for the Global Threat Reduction Initiative (NNSA-GTRI). The overall mission of the GTRI is to reduce and protect vulnerable nuclear and radiological materials located at civilian sites worldwide.

The dual objectives of the GTRI ^{99}Mo program are to achieve HEU minimization and to establish reliable domestic supplies of ^{99}Mo produced without HEU. The GTRI seeks to achieve these objectives through assisting global ^{99}Mo production facilities to convert to the use of LEU targets and accelerating the establishment of commercial non-HEU-based ^{99}Mo production in the United States. It is the latter of these that was the main concern of this review.

The problem of improving the reliability of the domestic isotope supply is an extremely complex one and many of the factors lie outside the direct control of the NNSA, or of the U.S. government. NNSA has identified several strategies to address weaknesses in the current ^{99}Mo supply chain (Figure 1 reproduces a slide from NNSA illustrating the overall supply chain).

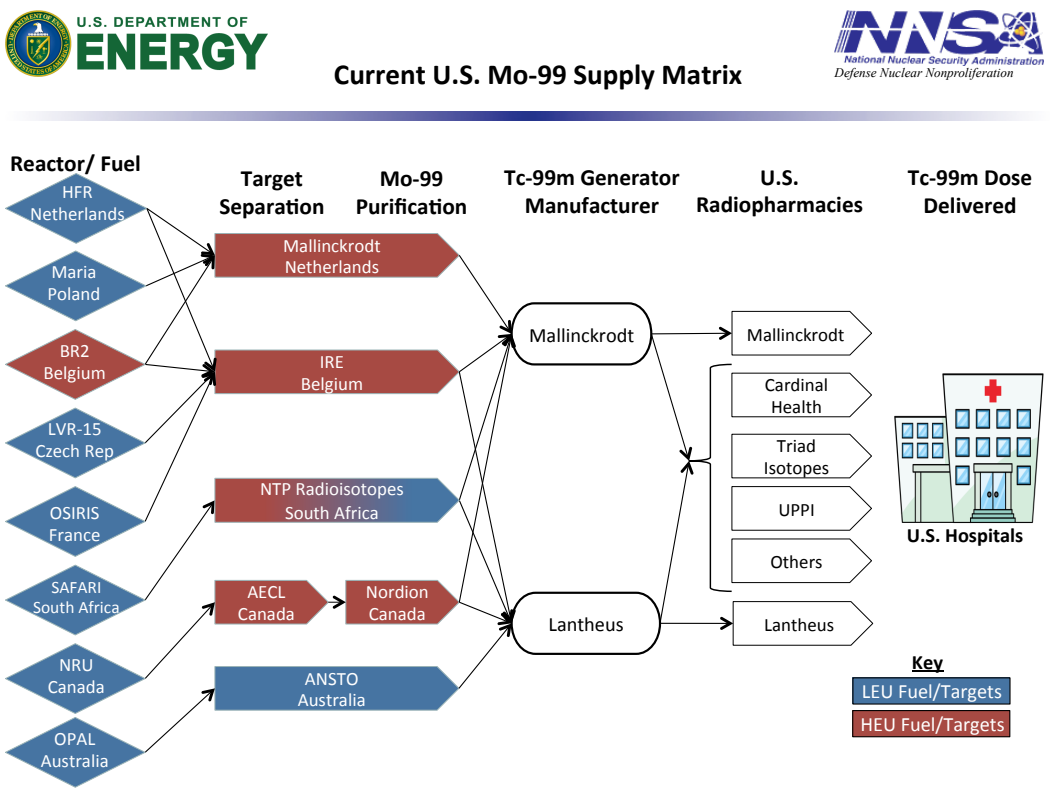

Figure 1: NNSA illustration on U.S. ^{99}Mo supply matrix.

The supply chain weaknesses identified by NNSA include:

- The current supply chain uses HEU to produce ^{99}Mo.
- Foreign governments subsidize most ^{99}Mo production in today's marketplace through their investment in the reactor facilities that are being used.
- The current supply chain does not always have enough reserve capacity to ensure a reliable supply when one or more producers are out of operation.
- The current supply chain is primarily dependent on aging facilities.
- The current supply chain relies on one technology to produce ^{99}Mo.

NNSA is working with the international community towards establishing a level playing field for competition in the ^{99}Mo market through implementation of full cost recovery. They are developing fuels, production targets and processes for ^{99}Mo production that does not use HEU. They are working with regulatory agencies through the interagency working group and the HHS to have reimbursement for medical procedures provide additional funding for procedures that do not use HEU-produced material. Beginning in 2013 a $10 per procedure supplement is available from the Centers for Medicare and Medicaid Services for

procedures using non-HEU produced ^{99m}Tc. The Veterans Administration has instituted preferential procurement for non-HEU produced ^{99m}Tc. NNSA also participates in various domestic and international working groups in an attempt to ensure the implementation of OECD-NEA policy recommendations in the United States and abroad.

In parallel, as required by AMIPA, NNSA GTRI has pursued a technology-neutral program to provide assistance to commercial entities 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 (*as required by AMIPA*). The OECD guidelines for full cost recovery production follow the World Trade Organization standard on subsidies; the GTRI program follows this guidance that government support be less than 15% of total project cost to initiate production. NNSA sees this as consistent with a policy of not subsidizing production. Therefore, NNSA has set a total funding limitation of $25M to each commercial project it supports; this is less than 15% of the estimated project cost of about $200M.

At the start, NNSA-GTRI took an aggressive approach to accelerate reliable ^{99}Mo production in the US by funding four Cooperative Agreement (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 clearly defined to be 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). Technical experts subjected all proposals in both processes to peer review and funded proposals were selected by an NNSA internal panel based on the results of this peer review. NNSA was provided information on business case as part of the initial evaluation of the potential CA partners. This information was used by NNSA in determining the final selection of CA partners. One additional entity was offered a cooperative agreement, but to date has not accepted it. No proposal based on the proven technology currently in use was selected for funding.

The funded CAs covered diverse and complementary technical approaches to ^{99}Mo production consistent with the technology neutral direction of the AMIPA. One approach involves producing ^{99}Mo by fission in an aqueous solution reactor. This could potentially use existing ^{99m}Tc generator designs. A second seeks to use a commercial power reactor to perform neutron capture on ^{98}Mo. This approach produces ^{99}Mo from irradiation of either natural or isotopically enriched molybdenum and produces ^{99}Mo with low specific activity that is not compatible with current generator technology in the U.S. These first two CA partners, started through the non-competitive process, have paused their efforts. Both cited concerns on the long-term business model as reasons for halting their efforts.

A third initiative has two thrusts with the same commercial entity, each leading to a separate technology. One thrust has the goal to reestablish a program of neutron-capture production of ^{99}Mo at the Missouri University Research Reactor MURR, which uses HEU as reactor fuel. In this case also generator technology that differs from the existing generator technology in the U.S. would be required. The partner is in the process of obtaining FDA approval for a new generator system that will be used with this low specific activity material. Once approval is obtained, production is expected to begin in 2014 using natural Mo targets. In the future, production could be ramped up to achieve 3,000 6-day Ci/week using separated isotope ^{98}Mo targets.

The same cooperative partner's second thrust is based on using electron accelerator technology to produce ^{99}Mo through photo-neutron reactions on ^{100}Mo and to use the same new generator for low specific activity ^{99}Mo. Achieving 3,000 6-day Ci/week would require multiple electron accelerators and irradiation target stations, and this project will require significant funds to move forward.

A fourth CA partner is pursuing a technology similar to reactor fission production of ^{99}Mo, however the neutrons originate from a D-T neutron generator, instead of a reactor. The target is a sub-critical LEU aqueous solution. It surrounds a tritium gas cylinder irradiated with low energy deuterons. The material generated in this technology will likely not require new FDA approval if it meets the specifications of the reactor generated product and current generators can be used. However, NRC approval is needed both to begin construction and to operate the resulting facility of accelerators and sub-critical assemblies.

NNSA uses a number of processes to manage this program. GTRI's ^{99}Mo program is managed in accordance with GTRI's Program Management Plan (PMP) and fits under GTRI's existing architecture to manage all GTRI projects. The program tracks each commercial partner's project to ensure that progress is being made on time and within budget. The cooperative agreement partners are responsible for managing the development of each commercial project, and subsequent ongoing operations. GTRI uses a program management system (G2) to track summary level scope, and a software tool to track detailed scope. In 2010 GTRI received the Project Management Institute's Distinguished Project Award for the G2 Project Management System.

Molybdenum-99 program performance reporting consists of comparing cost, schedule, and scope performance against the program baseline to provide GTRI with a means of assessing program progress, forecasting potential problems, and taking corrective action when necessary. They utilize a number of project level reports that were identified by NNSA:

- CA Partners Monthly Progress Report

- An independent technical review team assesses and validates progress on a semi-annual basis
- Laboratory Monthly/Weekly Programmatic Highlights Report
- Monthly GTRI ^{99}Mo Executive Report
- Schedule Performance and Cost Reports for CAs and Laboratory work (G2)

To date, a total of $34M federal funds have been committed in CAs. Congressional Budget Office estimates of the direct funding impact in earlier proposed authorization legislation were on the order of $150M. Since they are not line-item entries in the budget, it is not possible for the subcommittee to track actual appropriated funds for this purpose.

Findings

The NNSA GTRI program is complex and success is impacted by many factors outside their direct control. *The program is to be lauded for their attempts to deal with this complexity and to work with and provide leadership to various federal and international entities to try to achieve a situation that results in a stable United States supply of ^{99}Mo***.*** To track the progress of the projects they have initiated, the NNSA GTRI program uses a formal project management system. In spite of this, the projects have undergone delays and baseline changes that may negatively impact the Program's ability to reach the ultimate goal.

Shifts in the commercial marketplace now make it plausible that there will continue to be a reliable supply of ^{99}Mo in the U.S. up until the period when the NRU reactor stops production at the end of 2016. The present supply, however, is based entirely on international reactors presently subsidized by foreign governments. All but two of these reactors are quite old. These two factors represent a direct risk to the United States supply of ^{99}Mo.

The NNSA strategy to both work with the international community to move toward a model of total cost recovery and to support development of a U.S. production capability is well founded and the Agency should be given credit for attacking the problem on such a broad front. Yet none of the CA partners achieved the original goal of 3,000 6-day Ci/week by the end of 2013. Given possible technical and regulatory delays and difficulties in entering the marketplace while current supplies are being met there is substantial risk that none will achieve more than 1,000 Ci/week by 2016. Whether U.S. producers will be ready to take up the slack at the end of 2016 or whether other new foreign producers will satisfy the market demand is not clear. The likelihood of a significant U.S. production capability might be significantly increased if NNSA were able to increase their cost share (either percentage or total amount) or if some sort of government loan guarantee could be obtained for the most successful projects to move them to the phase of facility construction. Even in

this case, it is not obvious to the Subcommittee whether the potential domestic producers would be commercially viable long term.

In the next sub-sections we address the specific questions laid out in the NSAC charge.

Are NNSA GTRI programmatic goals for establishing a domestic supply of ^{99}Mo-well defined?

NNSA states that their overarching programmatic objective is to accelerate the establishment of reliable supplies of the medical isotope ^{99}Mo molybdenum produced without highly enriched uranium. They further define this programmatic objective with specific goals related to the elimination of HEU by assisting conversion or verified shutdown of existing international ^{99}Mo facilities in Belgium, Netherlands, South Africa, and Canada; and accelerating development of new reliable ^{99}Mo supplies by supporting four projects in the United States to develop new domestic production capability. The present CA targets were modified in response to the planned cessation of ^{99}Mo production in Canada in 2016.

The top-level objective, to accelerate the establishment of reliable supplies of the medical isotope ^{99}Mo without highly enriched uranium, is not specific as to timelines or what constitutes "acceleration." However, within the projects implemented by the program, there are more specific goals delineated for the commercial partners in the NNSA funded activities. For each of the four cooperative agreements the goal was to provide 3,000 6-day curies of ^{99}Mo per week by 2016 (re-baselined from the original December 31, 2013) without the use of HEU. These latter goals are quite specific and well defined.

Have the risks in implementing those goals been fully identified?

A comprehensive list of risks to the success of the Program has been compiled by NNSA. The full risk register is labeled *Official Use Only* and therefore the Subcommittee's summary of risks is presented in Appendix 5. It is evident that many of the risks in this program are outside the control of NNSA. It is also recognized that at a high level the risks have been identified and are understood by NNSA. There is concern by the Subcommittee, however, that in some cases the risks are more complex than indicated in documentation provided by NNSA. We would like to point to two of these:

- Potential market saturation that could negatively impact potential new suppliers is a risk that has been identified. We would like to point out that in addition to suspicion among potential suppliers that NRU might not shut down in 2016 there are additional market risks.
    - The ANSTO OPAL reactor is coming online with a new LEU based production capability.
    - Other potential foreign sources have been proposed.

    - Foreign entities could ignore the international protocols and market with less expensive HEU produced ^{99}Mo.
    - If all of the NNSA initiatives were successful, the market would be oversaturated.
- Having *only* a foreign source of a reliable, cost effective supply of stable Mo isotopes needed for production of ^{99}Mo by neutron capture (^{98}Mo) or photo-nuclear (^{100}Mo) reactions is a potential risk.

Efforts to mitigate most of risks have been presented. For example, NNSA has worked very effectively with the relevant regulatory authorities (NRC and FDA) in the interagency working group and at stakeholders meetings in an effort to ensure streamlining the sometimes lengthy licensing processes associated with new domestic production capabilities in order to proceed in a timely fashion. NNSA also facilitates the engagement of relevant expertise at the National Laboratories to help mitigate the risks associated with the commercialization of novel technologies. While the NNSA has developed significant strategies to mitigate risks that are within their control, there still remain substantial risks that are outside of their control.

What is the current status of implementing these goals?

NNSA-GTRI has taken an aggressive approach to accelerate reliable ^{99}Mo production in the US by funding four Cooperative Agreement partners. Each CA goal was initially clearly defined to be that the commercial partner was to show capability to produce 3,000 6-day Curies per week by the end of calendar 2013. None of the CA partners met this goal, and only one is likely to produce ANY ^{99}Mo in 2014.

The specific status of the projects is detailed in the bullets below.

- The approach of one CA partner funded in the competitive FOA process is based on using neutron-capture on natural molybdenum to make ^{99}Mo at an existing research reactor. This project is scheduled to produce ^{99}Mo during 2014. Contingent on the approval of a generator system by the FDA, this CA is on track for completion on this schedule. Subsequent expansion to a 3,000 six-day Curie capacity could follow with the use of enriched ^{98}Mo. The success of this approach takes advantage of the use of existing facilities. Commercial acceptance of the new generator system remains to be determined since it is based on low specific activity ^{99}Mo using a new generator concept. (1-10 Ci/g versus the >5,000 Ci/g for fission ^{99}Mo). Presentations by U.S. generator producers (who would be competing with the new system) to this committee did not help to clarify this issue. Return and recycling of the expensive ^{98}Mo will be necessary.

- A separate thrust with the same commercial partner has the goal to develop the capacity to produce 3,000 six-day curies of ^{99}Mo via an electron linac. The surrounding technology requires further development of a high power accelerator, high power conversion system and targetry in order to be effective. It utilizes the ^{100}Mo(γ,n)^{99}Mo reaction. To achieve full-scale production levels requires multiple linacs to meet capacity and reliability needs. The specific activity of material produced with this approach is also low. Recovery and recycling of the expensive ^{100}Mo will be necessary. This task could be completed by early 2017 contingent on adequate commercial funding, which is over three years beyond the original baseline completion date of Q4 2013. This phase has been slowed to concentrate on the technology described in the first bullet. Further delays jeopardize the economic sweet spot of entering the market with significant production capacity by the end of 2016.
- A CA was also competitively awarded based on fission of uranium in solution by neutrons from a D-T neutron generator, instead of a reactor. The target is a sub-critical LEU aqueous solution surrounding a tritium gas cylinder irradiated with low energy deuterons. This approach will likely not require new FDA approval of a new generator. There are, however, technical and regulatory issues left to address. NRC recognizes that this is new technology requiring substantial resources and time to review. NRC approval for a construction permit is typically 18-24 months, and a similar period to approve an operating license. This earliest start up would be 2017-2018, which is years beyond the original baseline date of Q4 2013 to provide a capacity of 3,000 six-day curies. The projected completion may also miss the commercially desirable schedule of providing production capacity as the NRU reactor supply turns off by the end of 2016.
- A CA was awarded to investigate a homogenous liquid reactor approach. This partner has suspended their CA efforts because they suffered withdrawal of a needed commercial partner due to perceived unfavorable market conditions. This effort is therefore unsuccessful in meeting the NNSA goals.
- A CA was awarded to use neutron capture on ^{98}Mo in a commercial electric power reactor. This effort has also been suspended, with market conditions cited as the reason. Thus this effort has been unsuccessful in meeting the goals of 3,000 six-day curies per week by Q4 2013.
- A fifth potential commercial partner proposed an effort using fission of LEU in small research reactors. They were offered cost sharing under a CA, but declined to participate.
- Part of the NNSA strategy has also been to help accelerate these commercial efforts by directly funding national laboratory non-proprietary R&D relevant to the CA participants. These areas include target design, radiation damage and corrosion impacts on materials, process chemistry development, and safety analysis. The CA partners who spoke to us said that this R&D has been helpful.

It should be noted that each of the CA participants were asked to develop technologies and then apply these technologies at a large scale on an accelerated schedule to meet a specific portion of a commercial market. Although specific deadlines for technology applications are not being met, one of the efforts is making substantial progress, but less so with the other active CA. The other two projects have ceased work and therefore cannot be considered successful. In Canada, an alternative technology of direct ^{99m}Tc production via low energy cyclotrons is being explored. This regional production capability may not be appropriate for the U.S., but the exploration of this model as it progresses in Canada could be valuable to determine if it should become part of the U.S. path going forward.

Is the strategy for implementing the NNSA goals complete and feasible, within an International context?

As previously stated, the overall vision of the NNSA/GTRI ^{99}Mo program is to ensure a reliable domestic supply of the isotope ^{99}Mo without the use of HEU. The strategy to achieve this vision is two-fold: 1) to help international suppliers transition to the use of non-HEU targets and 2) to establish commercial non-HEU based production capability in the U. S. The second part of the strategy seeks to address weaknesses in the global supply chain and to assist commercial entities seeking to enter the market with new technologies.

The NNSA has been working with the producers of ^{99}Mo to convert from HEU target materials to LEU targets. Up until about 2010 the four primary producers were all using HEU targets for ^{99}Mo production. In the intervening years major strides have been made towards this conversion with three of the producers now having conversion schedules and one (NRU in Canada) is planning on ceasing production in 2016. In addition, a new supplier based on LEU fuel and targets has come on line with plans to expand production. Thus the strategy of increasing availability of ^{99}Mo produced from LEU targets has resulted in commitments from the major producers of ^{99}Mo. However, the time lines for this conversion vary greatly among the producers and are highly dependent upon the internal efforts of each manufacturer.

The approach to removing weaknesses in the supply chain has been multi-faceted. The NNSA has worked with the OECD and the international community to achieve agreement to the HLG-MR Policy principles (Appendix 4). There have been a number of positive outcomes from these efforts**.** The White House released a Fact Sheet announcing possible options to support the establishment of a reliable supply of ^{99}Mo produced without HEU. Nuclear Security Summits in 2010 and 2012 issued strong statements of support. Belgium, the Netherlands, and France, in cooperation with the United States, reaffirmed "*their determination to support conversion of European production industries to non-HEU-based processes by 2015, subject to regulatory approvals, to reach a sustainable medical isotope production for the benefit of patients in Europe, the United States*

*and elsewhere. As a result, in the longer term, the use of HEU will be completely eliminated for medical isotopes that are produced in Belgium, France, and The Netherlands and used in those countries and in the United States.***"** The NNSA has also worked with the CMS to implement appropriate reimbursements to remove cost barriers to the use of non-HEU produced ^{99}Mo/^{99m}Tc in medical procedures.

The approach to development of a domestic supply of ^{99}Mo has been to establish cooperative agreements with commercial entities that proposed approaching the supply problem using a variety of technologies. A primary metric in choosing these partners was the ability to demonstrate the capability to produce of 3,000 six-day curies of ^{99}Mo/week by 2014. To assist with these efforts NNSA also supported research at the DOE National Labs. In addition, NNSA worked with regulatory bodies (NRC and FDA) to allow the CA partners to receive high priority for the review of the pertinent aspects of the respective projects.

As indicated elsewhere in this document, the lack of success in achieving the production quantity and deadlines is mainly due to issues beyond the direct control of the NNSA. Many factors have impacted the ability of these commercial entities to secure the private sector investment required to move forward to implementation.

The NNSA strategy appears to be effective in so far as introducing non- HEU produced ^{99}Mo into the US market and *assisting* the introduction of a US producer of ^{99}Mo. However, market forces, especially from the international suppliers, will influence the acceptance of any new source of ^{99}Mo and these are not under NNSA's control. Also the funding available for supporting the CAs may not be adequate to assure success of any of the partners. A significant risk appears to be the ability of the commercial partners to attract the private investment for production facility construction without a guarantee of full cost recovery by all international competitors. Where the NNSA has foreseen technical risks they have made credible attempts to mitigate these risks. For example, National Laboratory efforts have been supported in furthering the development of electron accelerators and conversion targets for the γ-ray induced reaction on ^{100}Mo. In a similar fashion, development of high powered, low energy accelerators for neutron generation have been advanced through the National Labs involvement.

Creation of a market driven system without subsidies that incorporates full cost recovery for the production of ^{99}Mo is a laudable goal that if achieved could result in a balance between supply and demand in the market for ^{99}Mo and hence a more stable supply for the U.S. market. A U.S. producer could emerge and succeed in such a market. The present suppliers have benefited greatly from past (foreign) government investments, and the path to a truly level playing field will be long.

In conclusion, the NNSA's strategy to accelerate the development of domestic production of ^{99}Mo is feasible in that if all the risks work out in the best way, it can result in a stable U.S. supply of ^{99}Mo that has at least one U.S. producer. There are significant risks to success on the time lines indicated, and consequently it is not complete. While the NNSA also considers that achieving a stable U.S. supply without any domestic production of ^{99}Mo to be an acceptable outcome, the Subcommittee has identified this as a risk to achieving a stable supply. One improvement may be to increase the $25M cap (on cost-sharing by the government) for a single CA, which would increase the likelihood of a successful domestic producer.

Recommendations

NNSA is working toward a high level goal to accelerate domestic production of ^{99}Mo, and each of the CA partners have very specific and measurable goals and delivery dates. It is appropriate that NNSA continue to invest in the most successful projects. This may require concentrating its resources, and perhaps rethinking the limits on total investment in any project. Further, even the successful CA partners may not be able to secure sufficient resources to bring their projects to the point at which they produce significant quantities of ^{99}Mo. Based on these facts, we have two recommendations:

Recommendation #1: NNSA should look carefully across the domestic production part of the ^{99}Mo program in view of present facts (such as progress on CA projects, economic environment for capital and projected operating costs) in order to focus resources on the most promising CA agreements.

Recommendation #2: Based on the slowness of progress toward implementation of full cost recovery internationally, NNSA should consider relaxing their present $25M cap on investment in any project. This change could increase the likelihood of generating a successful domestic producer of ^{99}Mo as the international market continues to move toward full cost recovery. This would address one of the major risks in the present program. We are not suggesting modifying the Congressionally mandated 50/50 cost sharing.

References

[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 1 – Charge Letter

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

December 5, 2013

Dr. Donald Geesaman
Chair, DOE/NSF Nuclear Science Advisory Committee
Argonne National Laboratory
9800 South Cass Avenue
Argonne, Illinois 60439

Dear Dr. Geesaman:

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) form a Subcommittee to assess the effectiveness of the National Nuclear Security Administration-Global Threat Reduction Initiative's (NNSA-GTRI) Domestic Molybdenum-99 (Mo-99) Program.

As you may know, the primary mission of the GTRI Convert Program is to reduce and eliminate the use of highly enriched uranium (HEU)-235 in civilian applications, including in the production of medical isotopes. Technetium-99m (Tc-99m) is the decay product of the radioisotope Mo-99 and is used in diagnosing heart disease, cancer treatment, and studying organ structure and function. Present day technology for producing Mo-99 relies heavily on recovering Mo-99 from HEU targets irradiated at research reactors and processed at isotope production facilities located outside the United States. For this reason, the NNSA GTRI Convert program works with international producers to convert isotope production from the use of HEU targets to low enriched uranium targets, without negatively impacting the Mo-99 supply. In recent years, planned and unplanned outages at facilities producing Mo-99 outside the United States have greatly increased the urgency of NNSA GTRI supported efforts to also accelerate the establishment of a domestic supply of Mo-99 produced without the use of HEU.

As a part of the GTRI stewardship of establishing a domestic supply of Mo-99, NNSA entered into cooperative agreements in FY2009 and FY2010 with four commercial entities, each pursuing unique, non-HEU-based technologies to develop the capacity to produce 3,000 six-day curies of Mo-99 per week.

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 FY2013. On January 2, 2013, President Obama signed the NDAA into law, enacting this legislation. A stipulation of the NNDA 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 GTRI] program goals and make recommendations to improve program effectiveness."

Accordingly, we request that NSAC form a Subcommittee to provide an initial assessment of the following charge elements:

- Are NNSA GTRI programmatic goals for establishing a domestic supply of Mo-99 well defined?
- Have the risks in implementing those goals been fully identified?
- What is the current status of implementing these goals?
- Is the strategy for implementing the NNSA goals complete and feasible, within an international context?
- What steps should be taken to improve NNSA program effectiveness in establishing a domestic supply of Mo-99?

This Subcommittee will be constituted as a standing subcommittee of NSAC for three years. It is requested that an initial assessment be submitted to the Office of Science by April 30, 2014. Subsequent assessments are to be provided annually.

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, an isotope essential for the health and well being of the Nation.

Sincerely,

Patricia M. Dehmer
Acting Director
Office of Science

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

Appendix 2 – Molybdenum-99 Sub-committee membership

Susan Seestrom, Chair, Los Alamos National Laboratory
Carolyn Anderson, University of Pittsburgh
Jeff Binder, University of Illinois
Ronald Crone, Oak Ridge National Laboratory
Jack Faught, LINDE
Mitch Ferren, Oak Ridge National Laboratory
Donald Geesaman, Argonne National Laboratory
Suzanne Lapi, Washington University Saint Louis
Leonard Mausner, Brookhaven National Laboratory
Meiring Nortier, Los Alamos National Laboratory
Berndt Mueller, Brookhaven National Laboratory
Ken Nash, Washington State University
Joseph Natowitz, Texas A&M University
Thomas Ruth, TRIUMF

Appendix 3 – Meeting Agendas

Agenda Items - NSAC Mo-99 Program Review
January 9-10, 2014
Hilton Washington DC/Rockville Hotel & Executive Meeting Center
1750 Rockville Pike, Rockville, Maryland 20852

January 9

08:30 Discussion of Charge (DOE NP) (30 minutes)

09:00 What is Mo-99, how is it used (NNSA- Staples) (45 minutes)
- What is Mo-99
- Mo-99 Supply Chain
- Policy history – what, why, how

10:00 Economic Challenges (Cameron from OECD by phone) (30 minutes)
- OECD Economic Study Overview

10:30 Break

10:45 Technical Challenges (Thomas Ruth) (60 minutes)
- NAS Study Overview

11:45-1:00 Working Lunch

1:00 Overview of the NNSA Program (NNSA – Staples) (60 minutes)
- GTRI Mission & Program Goals (including Risks)
- International and Domestic Approaches
- Mo-99/Tc99m Supply and Demand
- Program Organization & Structure
- Program Reviews and stakeholder communication

2:00 Discussion (45minutes)

2:45 Break

3:00 Review of Program Sub-elements (NNSA) (60 minutes)
- Mo-99 Cooperative Agreement Evaluation Process
- GTRI Domestic Support
  - NorthStar Medical Isotopes
    - Technical Approach
    - Cooperative Agreement Status
    - National Laboratory Technical Support
    - Anticipated Production Dates
  - Morgridge/SHINE
  - GE-Hitachi
  - Babcock and Wilcox
- Other Potential Producers

4:00 Discussion

5:00 Committee Closed Session

January 10
(Closed session)

Questions for Partners to address:

- Are the GTRI goals sufficiently well defined for you to execute your part in the program?
- What is your assessment of the risk involved?
- Do you receive clear communication on NNSA expectations?
- What improvements do you suggest in the management of this program?

08:00 NorthStar Representative (60 minutes presentation, 30 discussion**)**

09:30 Morgridge Representative (30 minutes presentation, 30 discussion**)**

10:30 GE-Hitachi Representative – by phone (30 minutes presentation, 30 discussion**)**

11:30 Committee Discussion on Path Forward

12:30 Adjourn

Agenda Items - NSAC Mo-99 Program Review
February 26-27, 2014
Hilton Washington DC/Rockville Hotel & Executive Meeting Center
1750 Rockville Pike, Rockville, Maryland 20852

Wednesday, February 26

08:30 Executive Session (Sub-committee)

09:30 Discussions with NNSA Closed Session

10:30 Break

11:00 Regulatory Challenges (Orhan Suleiman – FDA) (60 minutes) Closed Session

12:00-1:00 Working Lunch (Al Adams – NRC**)** Closed Session

1:00 Stake Holder Input Session – Open session
(15 minute presentations)
Erin Grady, *Society of Nuclear Medicine and Medical Imaging*
Carmen Bigles, *Coquí Radio Pharmaceuticals Corp.*
Roy Brown, *Mallinckrodt Pharmaceuticals*
Ira Goldman, *Lantheus Medical Imaging*
Michael Gill, *National Association of Nuclear Pharmacies*

3:30 Public Comments – Open session

4:30 Executive Session – Closed Session

5:30 Adjourn

Thursday, February 27

(ALL Day Closed session)

08:30 Executive Session

10:00 Writing Session

12:00 – 1:00 Working Lunch

1:00 Executive Session
- **NNSA call back if needed**

2:00 Writing Session

3:00 Outbrief from Sub-teams

5:00 Adjourn

Appendix 4 - HLG-MR Policy Principles

Principle 1: All ^{99m}Tc supply chain participants should implement full-cost recovery, including costs related to capital replacement.

Principle 2: Reserve capacity should be sourced and paid for by the supply chain. A common approach should be used to determine the amount of reserve capacity required.

Principle 3: Recognising and encouraging the role of the market, governments should:

- establish the proper environment for infrastructure investment;
- set the rules and establish the regulatory environment for safe and efficient market operation;
- ensure that all market-ready technologies implement full-cost recovery methodology; and
- refrain from direct intervention in day-to-day market operations as such intervention may hinder long-term security of supply.

Governments should target a period of three years to fully implement this principle, allowing time for the market to adjust to the new pricing paradigm, while not delaying the move to a secure and reliable supply chain.

Principle 4: Given their political commitments to non-proliferation and nuclear security, governments should provide support, as appropriate, to reactors and processors to facilitate the conversion of their facilities to low-enriched uranium (LEU) or to transition away from the use of highly enriched uranium (HEU), wherever technically and economically feasible.

Principle 5: International collaboration should be continued through a policy and information-sharing forum, recognizing the importance of a globally consistent approach to addressing security of supply of ^{99}Mo/^{99m}Tc and the value of international consensus in encouraging domestic action.

Principle 6: There is a need for periodic review of the supply chain to verify whether ^{99}Mo/^{99m}Tc producers are implementing full-cost recovery and whether essential players are implementing the other approaches agreed to by the HLG-MR, and that the co-ordination of operating schedules or other operational activities have no negative effects on market operations.

Appendix 5 – Overall list of Programmatic Risks

1. **Market Risks: The US needs to be on a level playing field with foreign competitors. However this is threatened in several ways:**
    a. Continued foreign government subsidization of ^{99}Mo producers creates an unleveled playing field for private sector domestic investors. Full cost recovery for foreign producers cannot be guaranteed. Currently, foreign producers are being supported via existing infrastructure and new domestic suppliers may not have that benefit.
    b. Continued HEU-based ^{99}Mo domestic and international production will discourage potential new entrants. HEU exports must be reduced to prevent continued use of this route of production. As long as HEU is being exported, generator producers have less incentive to consider other sources. This program needs to consider that generator manufacturers may procure ^{99}Mo from other non-US HEU sources.
    c. New products may face additional difficulty to penetrate the market due to existing long-term contracts that lock generator manufacturers in to specific non-US suppliers.
    d. Unknown cost of GTCC/HLW disposal significantly impacts the business case of commercial partners. The parameters and costs for DOE “take back program” for uranium waste are not clear. Risks associated with this may be underestimated. There is a perception among some potential producers that this will be an inexpensive way of disposal. However, it appears the mandate is that this program will only be implemented for material that does not have a commercial disposal route.
    e. The CMS reimbursement supplement for LEU produced ^{99}Mo may not have a decisive impact.
    f. High capital costs and uncertainty due to unproven technology make private financing difficult and the lack of government loans or loan guarantees limits investor confidence.
    g. Loss of commercial partners due to poor market conditions or business models, i.e. supply and demand, are balanced with low cost product.
2. **Technical Risks**
    a. Novel technology challenges associated with production of ^{99}Mo as well as the new generator strategies could result in the loss of a commercial partner.

   b. Patent limitation could prevent or challenge further technology development. For example, one key patent technology may be held by a current CA partner or another group, which makes it unavailable for other potential partners.

3. **Timely Regulatory Approval Risk**
   a. Licensing from NRC, FDA, and NEPA created by a change in the process of record (POR) moving from HEU to LEU based production requires studies to evaluate potential differences in the ^{99}Mo assay for a new drug master file (DMF). Such licensing approval processes are lengthy and could significantly impact schedule.
   b. Getting approval for new technologies from the NRC, FDA and other regulatory agencies presents a financial barrier and can lead to substantial delays in projects. Both the FDA and the NRC are aware of the issue and will review applications upon receipt, however the time to review will depend heavily on the quality of the application.
   c. Other countries may be slow to receive regulatory approval for LEU -produced material patient use, which affects LEU-produced material supply in the U.S.
4. **Contractual Risks**
   a. The lack of contracts among supply chain participants (economic, technical, legal, etc.) or existing contracts present barriers to entry for new participants.
5. **Policy Risks**
   a. Possible future loss of high-level government support will slow down conversion from HEU to LEU globally and could endanger the program.