Incentivizing Domestic Production of Molybdenum-99 for Diagnostic Medicine

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Executive Summary

With about thirty-eight million procedures performed worldwide each year, nuclear medicine has become one of the most frequently utilized diagnostic scanning procedures. This powerful technique enables physicians to gather images within the body and scan for various medical ailments in a non-invasive manner. With a relatively low radiation exposure to the patient, the application of radionuclides within medicine is growing in the medical practice worldwide.

The most common radionuclide used in nuclear scanning procedures is technetium-99m. Used in about eighty percent of all nuclear diagnostic procedures, technetium-99m (Tc-99m), a metastable isomer of technetium-99, is a medical radionuclide tracer that dissipates excess energy through the electromagnetic emission of photons. Its parent isotope, molybdenum-99 (Mo-99), is needed for transport purposes because of the 66 hour half-life of Tc-99m and is currently commercially produced at only five utilization facilities worldwide: the National Research Universal reactor in Canada, the Belgian Reactor 2 (BR2) reactor in Belgium, the Open Pool Australian Light Water reactor (OPAL) in Australia, the Petten High Flux Reactor (HFR) in the Netherlands, and the SAFARI-1 reactor in South Africa. Most of these facilities were constructed in the 1970’s and, as the production facilities began to age, maintenance and facility improvements became inevitable, requiring systematic and temporary shutdowns for each utilization facilities. These shutdowns have resulted in major shortages in the supply of Mo-99 in late 2007 and from February 2009 to August 2010.

Efforts have been made to incentivize domestic production of Mo-99. Legislative efforts, including the American Medical Isotope Production Act of 2011, granted the Nuclear Regulatory Commission the authority to issue licenses to companies exploring technologies to produce Mo-99 only by means of Light Enriched Uranium (LEU) target sources. It also authorized $147,000,000 for such projects from 2011 to 2014 to fund licensing applications, facility development, and radionuclide production costs.

However, current reimbursements and incentives do not meet all of the needs to promote domestic production of Mo-99. Many efforts do not aid all portions of the production-supply chain, producing a disjunction between the producers and the consumers. This has produced apprehension from investors to enter the domestic production market. Thus, in order to insure a stable supply of Mo-99 for patients and a favorable market for producers, a combination of reformation of existing incentives and development of new incentives must take place to stop the foreign dependence on medical isotopes.

This study investigates reformation and extension of the current Centers for Medicare and Medicaid Services reimbursement to nuclear pharmacies for dosages of LEU target sourced Mo-99 produced, as well as the creation of an analogous reimbursement program to aid the production costs of LEU target sourced Mo-99 for domestic producers.
Foreword

About the Author

Logan Michael Scott is a rising senior at Oklahoma State University. He is currently scheduled to graduate with a Bachelors of Science degree in Chemical Engineering and a minor degree in Nuclear Engineering with a designation as an Undergraduate Research Scholar in May of 2014. During his time at Oklahoma State University, Scott has balanced his coursework, community service, and campus leadership in conjunction with multiple research projects. His projects, ranging from ethanol distillation from blue green algae to comparative analysis of the cultural geography of college towns, earned his election into the Oklahoma State University Halligan Hall of Undergraduate Scholars. His involvement within the community and on campus led to his election as the College of Engineering, Architecture and Technology Ambassador President, the Student Government Association’s Speakers Board Executive Director, and the 2014 National Association of Engineering Student Council’s National Conference Executive Director. Logan’s career goals include pursuit of both a graduate degree in Applied Physics and a Juris Doctorate degree with a specialization in Intellectual Property Law. The American Nuclear Society selected Scott for sponsorship in the 2013 WISE Program.

About the WISE Program

Founded in 1980 through the collaborative efforts of several professional engineering societies, the Washington Internships for Students of Engineering (WISE) has become one of the premier Washington internship programs. The WISE goal is to prepare future leaders of the engineering profession in the United States who are aware of, and who can contribute to, the increasingly important issues at the intersection of science, technology, and public policy.

Each year, the WISE societies select outstanding 3rd or 4th year engineering/computer science students, or students in engineering/computer science graduate programs, from a nation-wide pool of applicants. The students spend nine weeks in the summer in Washington, D.C. during which they learn how government officials make decisions on complex technological issues, and how engineers can contribute to legislative and regulatory public policy decisions.

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I would like to thank all of the members of the American Nuclear Society for sponsoring my involvement in the 2013 WISE program. This program has been an eye opening and inspiring experience that has truly impacted my career path and my academic approach in ways that are indescribable. I would like to especially thank the 2013 Faculty Member in Residence, Dr. Gail Marcus, and my society mentor, Dr. Alan Levin. Without their guidance and leadership, none of my research efforts could have even begun to take form. I would also like to thank all parties who assisted me in my research efforts, namely Dr. Parrish Staples, Dr. Tomoko Steen, Dr. Dan Fenstermacher, Dr. Orhan Suleiman, Dr. Marcus Voth, Miss Sue Bunning, Dr. Wendy Galbraith, and Miss Molly Wahl. This paper is nothing but my interpretation and analysis of the knowledge of others, and it would not have been possible without their guidance. Finally, I would like to thank all of my fellow inters during the course of the program. They made this experience truly special.
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Introduction

Medical applications of nuclear technology are vital for patient care and well being worldwide. For nearly sixty years, both diagnostic and therapeutic uses of radioisotopes have been a crucial part of treatment for a diverse range of medical conditions. Physicians utilize gamma radiation therapy and, more specifically, radionuclides, or radioactive chemical isotopes, to treat thyroid cancer and lymphoma [1]. Compared to chemotherapy, radiation therapy powerfully and preferentially targets cancerous cells at a higher rate than body tissue cells [2]. However, an even more common and less invasive aspect of nuclear medicine pertains to the various diagnostic scans and imaging techniques able to specifically target any area of the body through pharmaceutical compounding.

With about thirty-eight million procedures performed worldwide per year, nuclear medicine has become one of the most frequently utilized diagnostic scanning procedures. This powerful technique enables physicians to scan for various medical ailments in a non-invasive manner. With relatively low radiation exposure to the patient, the application of radionuclides within medicine is growing in medical practice worldwide [3].

The most common radionuclide used in nuclear scanning procedures is technetium-99m. Used in about eighty percent of all nuclear diagnostic procedures, technetium-99m (Tc-99m), a metastable isomer of technetium-992, is a medical radionuclide tracer that dissipates excess energy through the electromagnetic emission of photons. Because of Tc-99m’s relatively short half-life of about six hours, its parent isotope, molybdenum-99 (Mo-99), is commercially produced to allow for transport from the production facility to the test administration site. With a half-life of about sixty-six hours, the Mo-99 is typically taken from the production facility, typically a nuclear reactor or neutron accelerator, to a processing facility, where it is purified to the Food and Drug Administration (FDA) standards and packaged in a radionuclide generator. The packaged “Tc-99m kit” is then shipped to a nuclear pharmacy to be prepared for individual patient administration. This includes utilizing the generator to facilitate the decay process the Mo-99 to Tc-99m, extract the Tc-99m doses, and bind them to compounds specific for an individual patient’s test needs. The Tc-99m compounded drug is then injected into the patient for various diagnostic scanning purposes. The completed process usually takes place in approximately a six to nine day timeline [4].

Because of molybdenum-99’s production in nuclear facility and to technetium-99’s injection into the human patient, the production and supply of these radionuclides are strictly regulated by

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1 Iodine-131 Sodium Iodide is used in the treatment of thyroid tumors, Yttrium-90 (Zevalin) and Iodine-131 tositumomab (Bexxar) are used in non-Hodgkins lymphoma and Iodine-125 or Palladium-103 seeds are used to treat prostate tumors.
2 Technetium has no stable isotope or isomer.
government agencies. No domestic production facility currently exists; thus all the supply of Mo-99 is imported from one of five worldwide production reactors located in Canada, the Netherlands, Belgium, South Africa, and Australia. Because of the age of these reactors, there have been several shortages in the supply of Mo-99. One of these shortages, in 2010, was considered severe [5]. Recognizing the necessity of a stable supply of Mo-99 to insure the quality of patient well being, the United States government has passed several laws to encourage development of a domestic production facility. However, because of the lack of effective incentivization for private interests, the efforts have not been as effective as necessary to address the variability within the Mo-99 production and supply chain.

In this report, the existing incentives and reimbursement policies are discussed and analyzed in terms of economic viability. Two production facility models, nuclear reactor and particle accelerators, are compared in terms of their regulatory and policy standing in an effort to understand and maximize current federal incentives. In combining these efforts with information gathered from prospective participants in the production and supply chain, recommendations are proposed in an effort to best incentivize private interest in domestic Mo-99 production.

**Background**

*Production and Utilization of Molybdenum-99 and Technetium-99m*

The relationship between the parent isotope, molybdenum-99, and daughter isotope, technetium-99m, is a typical beta decay relationship. The beta decay isotope equation follows the model for all similar atomic decays:

\[
^{99}_{42}\text{Mo} \rightarrow ^{99m}_{43}\text{Tc} + ^{0}_{-1}\text{e} + ^{0}_{0}\nu_e.
\]

Due to the short half-life of Tc-99m, producers of the radioisotopes produce the much longer-lived parent isotope, Mo-99. Mo-99 can be produced as a fission product by the neutron irradiation of uranium-235 (U-235) targets within a nuclear reactor. Currently, over 95% of the Mo-99 produced for medical purposes is produced in reactors [5]. Much like power reactors, reactors designed for radionuclide production can utilize various levels of enriched U-235 targets. With less than one percent of uranium being composed of U-235, enrichment, the increase of concentration of U-235 isotopes to a reactor target, allows for the fraction of U-235 to be raised in an effort to increase the Mo-99 production efficiency. The categories of uranium are differentiated by the concentration of U-235 within the material, as shown in Table 1 [6].
Recently, the idea of commercially producing Mo-99 using accelerators, by means of proton transmutation of molybdenum-100, has gained attention as the regulation and oversight of HEU utilization and exportation becomes more stringent by the United States Nuclear Regulatory Commission (NRC). This production method, utilizing a photo-nuclear reaction, would produce Mo-99 from an electron beam impinging on a metal target to produce bremsstrahlung radiation, which in turn bombards an enriched Mo-100\(^3\) target to produce Mo-99 and an expelled neutron [7]. Through another accelerator production method, Mo-99 can also be created by the neutron bombardment of molybdenum-98 (Mo-98). While the use of accelerator-produced Mo-99 is relatively new by comparison to reactor produced Mo-99, the idea is currently gaining acceptance as new production facility designs are becoming available, and the viability of commercial production of Mo-99 has induced heavy research for this production method [8].

To insure the proper quality and purity of the Tc-99m administered to the patient, the production-supply chain has four main elements: Mo-99 production, Mo-99 processing, Tc-99m preparation, and Tc-99m patient administration. The process, shown visually in Figure 1, provides hospitals with a pure Mo-99 unit of a quality set by the Food and Drug Administration (FDA) in a standard Tc-99m generator kit, allowing nuclear pharmacies to harvest decayed Tc-99m from the Mo-99 unit and provide specific doses for each individual patient. The different aspects of the production-supply chain incorporate the nuclear physics of production, the chemical processing, and medical administration to the patient.

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\(^3\) Mo-100 has a half-life of \(1 \times 10^{19}\) years.
Figure 1: Global supply chain of Mo-99 and subsequent utilization[^9]

Once the Mo-99 is produced, a processing and manufacturing company receives the Mo-99 unit for the wholesale production price from the radionuclide producer[^4]. The processor purifies the Mo-99 by chemically washing the radionuclide of all other isotopes that could have been included in the unit sold by the producer. The processors then prepare an ionized solution of molybdate (MoO$_4^{2-}$) from the processed Mo-99, and the solution is then inspected and assured of the current FDA and other nation’s standards[^5], it is then sold (or transferred in some vertically integrated production chains) to the manufacturing companies. Manufacturing companies then place the purified Mo-99 solution in to the “Tc-99m generator” kit, with a typical unit size of one 6-day curie[^6]. In order to provide a 6-day curie unit size, manufacturing companies must place 9.4 micrograms of Mo-99 within the Tc-99m generator in the form of the molybdate solution. These generators, consisting of a column chromatograph, the molybdate solution adsorbed onto the surface of acid alumina metal, and an ionic saline solution pipette, are then sold as a package to the various nuclear pharmacies around the world.

Once the nuclear pharmacy receives the Tc-99m generator, it is able to immediately begin harvesting the technetium that has been generated by Mo-99 decay. Molybdate decays to pertechnetate (TcO$_4^-$), which binds more loosely to the acid alumina. This allows a normal ionic saline solution, drawn through the chromatograph holding the radionuclides, to pull the decayed pertechnetate further down the column than the molybdate, enabling the nuclear pharmacist to

[^4]: Production price will be referenced within the current policy procedures.
[^5]: Follows the same FDA policies that each other marketed drug for human use must follow.
[^6]: A 6-day curie is a unit of sale for Mo-99 that allows for one curie of Tc-99m to be harvested in a six-day period.
harvest the pertechnetate and prepare it for an individual patient through a process called compounding.

For such diagnostic purposes, compounding allows the pharmacist to bind the pertechnetate to another chemical agent that generally performs a specific purpose in the body. This allows physicians, who order specific compounded dosages for individual patients, to isolate specific regions and organs within the body and look for several different types of diseases in a non-invasive manner [3]. As is typical with transition metals, elemental technetium has multiple oxidation states; however, because of the intermolecular distribution of forces within the overlapping s and p orbitals, technetium has a great amount of electron shell instability. With a variance within the electron orbitals, multiple oxidation states allow for many different bonding mechanisms and stereoisomer orientations centered around the keystone compounding ligand, technetium. Nuclear pharmacies, through compounding, can use certain medical compounds absorbed by regions in the body to set the Tc-99m tracer on the desired diagnostic pathway within the patient’s bloodstream [10]. In this method, the radionuclide "tracer isotope" and its compounding agent can be administered to serve as an imaging radionuclide for a wide array of medical diagnostics.

After compounding, the compounded dose of Tc-99m can be administered to the patient for diagnostic scanning. Because Tc-99m’s nucleus is unstable, it decays to “normal” Tc-99 by emitting a gamma ray. The most common form of decay, known as a traditional gamma decay, is the emission of a gamma ray, or packet of electromagnetic energy with a short wavelength indicative of the gamma region within the electromagnetic spectrum [1]. The gamma decay radiation equation follows the model for all similar gamma nuclear decays:

\[
{}^{99m}_{43}Tc \rightarrow {}^{99}_{43}Tc + \gamma.
\]

The gamma energy of 140 thousand electron volts (keV) is relatively low compared to many other radionuclides, and, more important for the imaging aspect of the process, it is in the optimal range to excite sodium iodide crystals utilized by medical scintillation cameras. The emitted gamma ray excites the sodium iodide, allowing scintillation of the gamma camera to be interpreted by the imaging software as two-dimensional images. For the patient’s well being, the relatively short half-life of Tc-99m compared to other radionuclides limits the amount of time a patient is subjected to radioactivity. The patient will still be radioactive after the procedure; however, within twenty-four hours, a majority of the technetium in the patient will have decayed.

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7 A typical dosage of compounded Tc-99m ranges from 15 to 30 curies.
8 140 keV gamma ray has a wavelength of 8.856 x 10^{-12} m.
9 Sodium iodide for nuclear medicine scintillation is activated with thallium, NaI(Tl).
to technetium-99, with a half-life of 211,000 years\(^\text{10}\) [11]. From the prospective of the diagnostic test administration, Tc-99m has all the characteristics to optimize utilization ease and patient safety [12].

**Molybdenum-99 and Technetium-99m History and Supply Shortages**

Beginning with the discovery of Tc-99m isotope by Emilio Segré and Glenn Seaborg in 1938, the relationship between the Mo-99 and Tc-99m was clearly evident. As an observable fission product of uranium-235 in one of Segré’s later experiments, Mo-99, having a half-life of about sixty-six hours, was observed emitting beta particles in its progression to a more stable state [13]. In 1958, two scientists under the direction of Powell Richards at the Brookhaven National Laboratory, Walter Tucker and Margaret Green, hypothesized, based on their work with iodine-132 and tellurium-132, that a “generator” could be developed using Mo-99 to produce Tc-99m. Richards later became the first to suggest the notion of utilizing Tc-99m as a medical radionuclide tracer in 1960 [14].

Benefitting from advancements in gamma camera technology, the production and medical utilization of Tc-99m grew rapidly in the 1960s. Private companies Nuclear Consultants, Inc. and Union Carbide Nuclear Corporation began to manufacture commercial Tc-99m generators. Mallinckrodt Nuclear Company first undertook the production of the parent isotope Mo-99 using the research reactor at the University of Missouri; however, the size and flux capacity of the reactor at the University of Missouri was insufficient to sustain a constant supply and production of the isotope was stopped in the early 1980’s [15]. From 1968 to 1972, Union Carbide has successfully developed a process at its Cintichem facility utilizing highly enriched uranium (HEU) targets, which permitted easy separation of the products of the fission process, and it began domestic production of commercial Mo-99 in 1980. Separating from Union Carbide, Cintichem Inc. became the sole producer of domestic Mo-99 during the 1980’s [9].

International production began in the same time frame, with Canada and Australia building production facilities in the early 1970s. A balance within the production-supply chain soon existed between the United States, Canada, the Netherlands, Belgium, and the Australian production facilities, each having its share in the market and working collaboratively to help fill shortages created by any of a number of varying effects, including maintenance, inspection, and plant modifications.

However, in 1989, Cintichem detected an underground leak of radioactive products from its Mo-99 production facility. There was an immense amount of pressure from the community and the

\(^{10}\) Over a 24-hour period, about 93.7% of the Tc-99m, signifying the biological half-life of one day.

\(^{11}\) Work detailed eluted daughter production process with Iodine-132 and Tellurium-132.
New York state government for Cintichem to cease domestic production of Mo-99 entirely and shut down the facility entirely. In May of 1990, Cintichem closed and filed for decommissioning of its production facility, essentially shifting all production to Canada and Europe [16].

During the same time frame, the utilization of Tc-99m in diagnostic scanning continued to grow. In compliance with national regulatory agencies and the International Atomic Energy Agency (IAEA) recommendations, five reactor facilities sustained the production supply: the National Research Universal reactor in Canada, the Belgian Reactor 2 (BR2) reactor in Belgium, the Open Pool Australian Light Water reactor (OPAL) in Australia\textsuperscript{12}, the Petten High Flux Reactor (HFR) in the Netherlands, and the SAFARI-1 in South Africa\textsuperscript{13} [9]. With a relatively constant supply and demand, the industry, utilizing all of the production facilities, was able to produce the quantity of Mo-99 needed to fill generator orders from nuclear pharmacies all over the world. However, as the production facilities began to age, additional maintenance and facility improvements became inevitable, requiring temporary shutdowns for individual production facilities.

The first main worldwide shortage came in November 2007, when the Canadian NRU shut down for about month because of routine maintenance. While the reactor was offline for repairs, the managing agency, Atomic Energy of Canada Limited (AECL), decided to install an additional seismically-qualified emergency power system for the two cooling pumps in the reactor, as required by the Canadian Nuclear Safety Commission (CNSC) operating license, as amended in 2006. However, as opposed to allowing for full inspections and testing of the new pumps, the Canadian House of Commons, acting on alleged expert advice, passed emergency legislation to restart the NRU for commercial production with only one of the two seismic connections complete without the consent of the CNSC [17]. With a 120-day grace period of operation issued by the Canadian House of Commons, the NRU had its second seismic connection completed in February of 2008, and the quoted risk of failure by the CNSC’s chairman at the time was very low [18].

However, the most significant shutdown began in 2009 when the Canadian NRU shut down and reached its peak in for six months in 2010 with coincidental shutdown of the Dutch HFR. In May 2009, in the Canadian production facilities, accounting for nearly forty percent of the world’s supply of Mo-99, a small heavy water leak was detected in the NRU reactor. While originally seen as a routine production stoppage, because of new regulations passed in the January 2009, all operating reactors had to undergo intensive design reviews for to comply with new safety standards in order to obtain a renewal of license from the CNSC for commercial isotope production [19]. Originally seen as a ninety-day renovation, compliance with new regulations consequently evolved into a 17 month complete restructuring and redesign of the reactor and

\textsuperscript{12} The Osiris reactor facility in France also produced Mo-99; however, export was limited.
\textsuperscript{13} SAFARI-1 began commercial production of Mo-99 in 1993.
facility. With two-fifths of the world’s molybdenum-99 supply rendered inoperative for that period, production shifted mainly to the South African and Netherlands production sites [5]. The situation is illustrated in Figure 2.

![Commercial Mo-99 Production (% Production)](image)

**Figure 2:** Commercial Production Percentage of Mo-99 for 2009

As with the Canadian plant, the plant in the Netherlands faced renewal of its license in May of 2010. With the supply of Mo-99 already depleted, the closing of the Dutch plant placed a heavy strain on the worldwide production of the radioactive isotope. Nearly two-thirds of the production supply of Mo-99 for medical applications went offline for about six months. While the market did cope with the severe shortages by shifting production to other facilities and finding new ways to produce Tc-99m through other isotope decay, the worldwide shortage exposed the large variability and fragility within the production process\(^{14}\).

### Current and Future Reactor and Accelerator Production and Operations

**Current Conversion Efforts from HEU to LEU Source Molybdenum-99 Production**

As of 2005, 95% of all commercial radioisotopes were produced using highly enriched uranium sources within reactor production facilities. Most reactors utilized highly enriched sources both for the efficiency and cost of production of the commercial radioisotopes. Specifically for Mo-99 production, some of the reactors would use uranium targets enriched as high as 90%\(^{15}\) [8].

\(^{14}\) Tc-99m generators using Nobelium-99 as the parent isotope were developed, but the time needed to undergo two beta decay mechanisms was too great to sustain in a large scale.

\(^{15}\) Enriched uranium above 90% is sometimes referred to as weapons grade uranium.
With such several tons of enriched target material, there is an obvious amount of oversight by national regulatory agencies because of the security risk associated with nuclear weapons. While large quantities of HEU were used to produce Mo-99, the same centrifuges used to produce these isotopes could also be used to enrich uranium to a level that would be considered weapons grade, i.e., useable within a nuclear weapon. Although the United States has strict regulations on the export of HEU, unstable regions could receive fuel and target HEU from either China or Russia. Because of the technologies used to produce radionuclides, and specifically Mo-99, could be utilized to facilitate the manufacturing of nuclear weapons, international discussions regarding proliferation efforts began in the early 2000’s [20]

Proliferation discussions also began to gain momentum with the worldwide radioisotope shortages during this timeframe. Concerns about politically unstable, developing countries looking to develop nuclear arms capabilities under the façade of producing radioisotopes grew immensely. Most notably, Iran concentrated efforts to construct a 40 MW heavy water reactor. Amidst internal political discourse and extremist activism, Iranian nuclear operators were able to acquire installation licensing from the IAEA and development materials from allies within the region [19]. The reactor, named IR-40, gained international attention as a threat for producing weapons grade plutonium, despite the Iranian stated intended uses for the reactor limiting it to research and nuclear medical isotope production [21].

With growing concern about possible nuclear threats, a partnership between the IAEA, the Organization for Economic Cooperation and Development’s Nuclear Energy Agency (NEA), and the U.S. Department of Energy’s National Nuclear Security Administration (NNSA) began in 2004 with a goal to reduce the worldwide nuclear threat and protect civilians while insuring the positive effects of nuclear technology for societal benefits. The effort, labeled the Global Threat Reduction Initiative, was led by the NNSA and endorsed by the NEA and IAEA [22].

Specifically with regard to radioisotope production sites around the world, the NNSA sought to convert all commercial radioisotope production sites at research reactors from HEU sources to LEU sources for both fuel and targets. Seen as a process to greatly reduce the threat of enrichment of uranium by converting the production source, the goal of the effort was to permanently minimize the extent of a worldwide threat and eliminate the need for HEU in civilian nuclear applications. With cooperation from all of the current commercial producers of radioisotopes, the NNSA began aggressively pursuing complete conversion of medical isotope production sourcing in 2009, setting the goal for total conversion from HEU source to LEU source production by 2016 [23].
Future Reactor and Accelerator Production Methods

The shifting of the worldwide production sourcing material from HEU to LEU has caused discussions about future technologies. The current production sites and the proposed timeline for conversion are shown in Figure 3.

As Figure 3 indicates, conversion is projected to be well underway as of 2014. However, the Canadian AECL, after the abandonment of the Multipurpose Applied Physics Lattice Experiment (MAPLE) reactor project in 2008, has decided to exit the medical isotope market in 2016, stating the cost of maintenance and conversion to an LEU production facility would not be worth remaining in the market\textsuperscript{16}. With forty percent of the worldwide supply chain currently dependent upon the Canadian production facility, a large portion of the market will be available for potential private investors. After Cintichem’s shutdown in 1990, regulations and restrictions have discouraged private interest in domestic production of medical isotopes, yet, with a growing worldwide and domestic dependence on radioisotopes and a large gap in the market scheduled to be created in 2016, there is growing interest in the United States in restarting domestic production and commercialization of medical radioisotopes, given that production using LEU has become a point of critical importance.

Several domestic production conceptual designs have been developed since Canada announced its exit from the market in 2011. One company, Coqui Pharmaceuticals Corp., has begun the

\textsuperscript{16} MAPLE laboratories, completed in 2000, could have supplied 100% of the world’s demand, but the project was abandoned because of recurring design and operational problems.
formal process to seek NRC licensing for a research reactor, in conjunction with the University of Florida School of Engineering. With a 40-acre facility outside the University of Florida, in Alachua, Coqui has completed preliminary designs for its utilization facility, as well as an environmental impact survey on the ecosystem of the proposed production site. In compliance with current legislation\textsuperscript{17}, the production facility ensures its production methods are dependent upon utilization of LEU to produce Mo-99 \textsuperscript{24}.

However, as of June 2013, no formal licensing application from Coqui has been filed with the NRC. The authorizing regulations of the NRC, detailing every aspect of a nuclear facility, require complete review by the appropriate reviewing party within the NRC. Committed to insuring the safety of the country and the nuclear industry, the NRC thoroughly reviews all parts of each application, a process that can take upwards of four years \textsuperscript{34}. For many of the new investing parties for domestic production, this can discourage private investment because of the time and cost of the application period.

Compared to the reactor designs, two domestic companies, NorthStar Nuclear Medicine and SHINE Medical Technologies, have conceptualized designs for domestic radioisotope production facilities utilizing accelerators. Accelerators do have nuclear materials present within their utilization facilities; however, under the NRC regulatory authority outlined in the Atomic Energy Act of 1954 (AEA), the NRC can provide assistance to states expressing interest in establishing nuclear technologies\textsuperscript{18}. By relinquishing authority to the states to license and regulate nuclear byproduct material, in this case radioisotopes, states can set licensing and inspection regulations for non-power nuclear facilities, including small scale research reactors and accelerators \textsuperscript{25}. While there is oversight by the NRC through communication and educational efforts, agreement states would have most of the regulatory authority over any accelerators seeking commercial production of radioisotopes \textsuperscript{26}. This drastically decreases the amount of time within the license-seeking phase of nuclear facility development.

Both companies with projected domestic radioisotope production accelerators are planning to develop their facilities in the state of Wisconsin, which is an Agreement State. NorthStar Nuclear Medicine’s facility, which is currently in the design development stage, will not utilize uranium at all; instead, it will utilize a gamma-N reaction \textsuperscript{27}\textsuperscript{19}. Alternatively, the SHINE Medical Technology design, in coordination with the University of Wisconsin in Madison, will utilize a deuteron beam to bombard enriched Mo-100 targets, producing Mo-99. The SHINE facility would utilize LEU as a fuel source \textsuperscript{28}. Both companies are currently seeking permit from the

\textsuperscript{17} American Medical Isotopes Production Act of 2011, detailed later in this paper.

\textsuperscript{18} There are currently 37 agreement states, one of which is Wisconsin (2003).

\textsuperscript{19} Described previously as the photo-nuclear method.
NRC to begin construction, a portion of oversight retained by the NRC\textsuperscript{20} [25]. According to company representatives, both facilities are on schedule to receive permission to commence on construction in early 2014; projected production is scheduled for both facilities in early 2016 [28].

\textit{Regulatory Standards and Legislative Action}

With shortages resulting from expiring international licenses for production facilities and proliferation concerns leading to more stringent restrictions on the use of HEU, the U.S. Congress began efforts to authorize research and development for domestic production of medical isotopes in late 2004. The following pieces of legislation directly impacted the efforts to domestically produce medical radioisotopes.

\textit{Energy Policy Act of 2005}

The Energy Policy Act of 2005 effectively allowed for research and development to begin in an effort to domestically produce medical radioisotopes, while strengthening the oversight of uranium enrichment and export. Allowing the NRC to issue licenses on conditional terms for companies looking to domestically produce pharmaceutical radionuclides, the U.S. began to impose more pressure on the international community to begin to shift worldwide production of medical isotopes from HEU targets to LEU targets\textsuperscript{21}. Additionally, the Act restricted the use and export of US-produced HEU as a reactor fuel and limited export of target HEU to only the currently operating radioisotope production facilities in Canada, Belgium, France, Germany, and the Netherlands on the compliance of their conversion to LEU as outlined by the GTRI [29].

Within the framework of the bill deadlines, Congress also required the Secretary of Energy to provide funding to the National Academy of Sciences to produce a detailed report on the “feasibility of procuring supplies of medical isotopes from sources that do not use highly enriched uranium [30].” The report\textsuperscript{22}, compiled and published in 2009, provides sufficient evidence that Mo-99 could be produced by methods utilizing LEU, including both reactor and accelerator production facilities, while still presenting a process that is economically viable to private companies looking to enter the market. Making use of advancements in reactor technology and irradiation techniques, medical isotopes could be produced without HEU targets in already existing production facilities by converting the reactor to a LEU target-based

\textsuperscript{20} This includes environmental analysis reports and preliminary safety analysis reviews, customary with any domestic nuclear facility.
\textsuperscript{21} 2005 Energy Policy Act, Title IV, Subtitle B, Section 630.
\textsuperscript{22} Medical Isotope Production without Highly Enriched Uranium, National Research Council of the National Academies (2009)
Incentivizing Domestic Production of Molybdenum-99 for Diagnostic Medicine

American Medical Isotopes Production Act of 2011

The U.S. Government also saw the opportunity for domestic supply to enter the market. In 2012, Congress passed “American Medical Isotopes Production Act of 2011”, effectively authorizing the domestic production and commercialization of medical radioisotopes. By establishing a program independent of production process bias within the authorization of the Secretary of Energy, the bill allowed for the evaluation and support for “the production in the United States, without the use of highly enriched uranium, of significant quantities of molybdenum-99 for medical uses... [31].” The projects were to be evaluated by the length of time required to initiate production of Mo-99, the capability to produce a supply sufficient to meet US demand, either as one project or a combination of projects, and the relative cost of the project. It also permits the Secretary of Energy provide assistance for the development of the domestic Mo-99 production as well as commercial operating costs, with an appropriation of $143 million to from fiscal years 2011 to 2014.

Additionally, the American Medical Isotopes Production Act of 2011 amended the AEA, banning export of medical isotopes produced by HEU means after seven years from the signing of the bill. To limit the usage of HEU as a source in all commercial domestic development of Mo-99, an exclusionary clause was added in stating: “…highly enriched uranium as a target for medical isotope production in a nuclear reactor [may be used], only if, in addition to any other requirements of this Act- the [Nuclear Regulatory] Commission determines that- there is no alternative medical isotope production target, enriched in the isotope U-235 to less than 20 percent, that can be used in that reactor... [31].” This effectively gives reactors the ability to use HEU sources if, and only if, LEU is in no way available or viable as a supply source for the production. However, with the conversion of the worldwide supply of commercially produced Mo-99 set to LEU source production by 2020, it effectively sets a timeline for HEU source Mo-99 production and consumption in the United States. This bill allowed for a means for private companies to begin to explore production options for medical isotopes by strengthening export restrictions on HEU in addition to providing avenues for government subsidies to companies willing to invest in new domestic production Mo-99 technologies.

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23 Internal goal for NNSA is complete conversion by 2016.
24 In an effort to reduce fuel cost, it also establishes a uranium lease program for LEU, with the responsibility for disposition lying with the Secretary of Energy.
25 The designation of the HEU restriction on export is the main purpose of the amendment to the Atomic Energy Act of 1954.
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The National Defense Authorization Act for Fiscal Year 2013 effectively opened doors to make the production by private companies as sustainable as possible with long term proliferation and patient safety goals in mind. By establishing a renewed appropriations for programs such as 50/50 match program under the DOE for developments in LEU production technology and the NNSA’s 50/50 grant partnership specifically for LEU source production of Mo-99 facilities, the United States government solidified its position in support of the conversion goal outlined by the GTRI of complete source conversion to LEU by 2016.

Current Policy Incentives and Reimbursements

Although the legislative barriers restricting the domestic production of Mo-99 have been gradually lifted, there seems to be a rather prominent disjunction between the production industry and the drug’s administration in hospitals and nuclear pharmacies. Both sides of the production-supply chain currently have some sort of financial incentive or reimbursement meant to help facilitate the entirety of the production process. However, with the various steps in the process line from production to administration, no one incentive or reimbursement policy truly accommodates all of the parties involved to the magnitude as originally intended by the various policy framers. Different federal agencies offer financial and logistical support to help provide incentives companies, and the efforts are working to spur innovative business ideas. Yet, no incentive seems to bridge the gap between the radioisotope supplier and the drug administration. Because of this, private companies, and especially investors, are hesitant about moving forward with a risky business endeavor.

The following are the three main reimbursements and incentives currently in place to help promote domestic radioisotope production.

National Nuclear Security Administration 50/50 Match Grant

The NNSA has also created a 50/50 match program for any LEU production facility geared towards molybdenum-99 production within the United States. This program, authorized by the American Medical Isotope Production Act of 2011, is valued up to 25 million dollars annually and shares analogous intentions with the original DOE program; however, it looks to help develop the non-energy research reactor and accelerator design aspects characterized by the production of radionuclides. Aiding the production of mo-99 from non-HEU sources, the NNSA hopes to incentivize the LEU supply of radioisotopes, coinciding with its GTRI goals of reducing threat from HEU production sources. With the goal of the DOE residing in the complete

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26 Authorized appropriation value from FY 2011 to FY 2014 totals $143 million.
worldwide conversion to non-HEU sources by 2016, the incentive helps to stabilize the LEU source Mo-99 supply chain by the entrance of a domestic supplier into the market vacancy created by Canada’s exit. While the facility costs are much greater than these small grants, both support programs from both governmental and private entities have shown the appeal within the marketplace for domestic Mo-99 production.

Currently, two companies, SHINE Medical, Inc. and NorthStar Nuclear Medicine, LLC, have filed applications with Letters of Intent with the NRC to explore production methods and applied for recognition with the respective states of projected production by means of accelerators. SHINE Medical, in coordination with the University of Wisconsin, has also filed a Construction Permit in its entirety with the NRC. As for reactor designs, Babcock and Wilcox is pursuing an LEU solution reactor design that would be able to produce Mo-99 at a relatively low cost; however, the project is still in the research and design stage. Coqui, in coordination with the University of Florida, is researching the efforts for constructing a research reactor that would be able to produce LEU source Mo-99. However, much like B&W, their designs are still in the research and development stage.

With the exception of Coqui, all of the other previously mentioned projects have received NNSA grant match funding for the 2012 Fiscal Year. The applications and appropriations for the 2013 Fiscal Year are still in the application process, but it is likely that the budget will increase slightly. The grant amounts are shown in Table 2 [23].

<table>
<thead>
<tr>
<th>Company</th>
<th>Facility Type</th>
<th>2012 Grant Amount</th>
<th>Estimated Completion Date (approx.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NorthStar Medical Radioisotopes, LLC</td>
<td>Accelerator Technology (Photo-nuclear)</td>
<td>$25,000,000</td>
<td>Completion late 2015. Production by early 2016.</td>
</tr>
<tr>
<td>Babcock and Wilcox</td>
<td>LEU Solution Reactor</td>
<td>$9,100,000</td>
<td>Design Stage, no Licensing Application filed. Estimated production by late 2018.</td>
</tr>
<tr>
<td>General Electric-Hitachi</td>
<td>Neutron Capture Technology</td>
<td>$2,3000,000</td>
<td>Current Project Suspended Indefinitely</td>
</tr>
</tbody>
</table>

Table 2: Current NNSA 50/50 Match Grants and Projects. All dates from respective industry timelines.
Based on current benchmarks within the licensing review process for SHINE Inc., the timeline for licensing of accelerator-based production is projected to be shorter than that of reactor produced molybdenum-99. Whereas private investors and companies looking to enter the production market with reactor-produced radionuclides must gain licensing approval from the NRC under its current formal licensing application and review, the jurisdiction for agreement states lying in conjunction to the NRC allows the proposing party to only look to file letters of intent to produce and submit applications for Construction Permits in two parts [32]27. Thus, because of the state regulation of an accelerator facility proposed within an agreement state, the period between the initial applications and the beginning of construction or production for accelerators could take less time than a typical reactor licensing application through the NRC, making the timeline for investment return more immediately lucrative for investors. However, until SHINE’s application, no company had attempted this route in seeking a domestic operation license.

Centers for Medicare and Medicaid Services Dosage Reimbursement

Nuclear pharmacies, while supporting the conversion ethically and professionally, are having trouble justifying the cost increase to the pharmacy and, indirectly, to the patient. In an attempt to solve this problem, the Centers for Medicare and Medicaid (CMS), the agency responsible for setting Medicare and Medicaid policies and reimbursements, passed a reimbursement policy currently issuing an addition $10 reimbursement to the nuclear pharmacy on top of the cost assessed by the hospital for the testing procedure for each dosage of LEU Mo-99 it administered to the patient. The CMS claims its economic analysis demonstrated the reimbursement is beneficial to the producers of the isotopes with respect to trickle down economic model while still being sufficient for nuclear pharmacies to induce the purchase of LEU doses as opposed to HEU doses. As an agency that deals primarily with Medicare and Medicaid oversight as medical care providers, the CMS believes its support for the conversion of Mo-99 production is at the upper bounds of its ability as a federal agency; however, as an insuring agency for medical procedures, it can issue coverage for medically associated costs. With efforts to help industry by aiding the purchase in the process, the efforts aim to aid both sides of the production and supply chain in the conversion to LEU production [33].

However, the nuclear pharmacies disagree with the degree of aid to the pharmacies, believing the incentive is not great enough to accomplish any cost saving to the pharmacy or the patient, and they state the conversion to LEU will result in the closing of many nuclear pharmacies across the United States. Because of the production cost increases for LEU units of Mo-99, nuclear pharmacists assert a reimbursement of $10 is not enough to cover the cost of purchasing LEU dosages at this time, compromising the intent of the policy. This cost increase could force the pharmacies to lose money on each test and compromise the economic sustainability of the

27 As congruent with 10 CFR 2.101[(a)(5)], 10 CFR 2.390, and 10 CFR 50.30.
pharmacies. Believing the lack of extension of the cost to the physician hinders the reimbursement program, the Society of Nuclear Medicine and Molecular Imaging opposes the limiting aspects of this reimbursement [34]. The limitation of CMS to provide reimbursements only for procedures for patients covered by Medicare and Medicaid, which only accounts for 6.7% of all procedures performed, makes the scale of the reimbursements rather small comparative to the total cost for the pharmacy for source conversion.

Nuclear pharmacies also claim the process to claim reimbursement is rather difficult and time intensive compared to the value. Many production and processing facilities are currently blending HEU and LEU sourced Mo-99, which creates confusion about the validity of the reimbursement, which requires that the dosage is derived from a unit consisting of at least 95% LEU sourced Mo-99. While the different generators are marked with the sourcing of the Mo-99, in terms of filing for reimbursement, this adds to the amount of administrative cost on the part of the pharmacy. Also, each reimbursement requires a paper form that must be faxed to and processed by CMS. This task, usually completed by staff of the nuclear pharmacy, can take upwards of 20 minutes to complete in some instances [35]. From that point, the reimbursement can take weeks to be processed and cleared by CMS, requiring an upfront cost for the pharmacy. Thus, the gap between industry and the patient is growing as the stress is placed on the market to convert from HEU production to LEU production.

Policy Recommendations and Legislative Action

A major problem remains the production cost of LEU radionuclides in comparison to HEU radionuclides. Because of the conversion cost and the extra time and energy needed to irradiate or bombard targets, companies in the process of shifting from HEU to LEU sources are charging a greater amount for the LEU radioisotopes to offset capital and operating costs. A total profit margin for each 6-day Ci of Mo-99/Tc-99m produced can be established because of the process-supply chain and the markup at each intervening step. Thus, the nuclear pharmacists, while supporting the conversion ethically and professionally, cannot justify financial loses by the pharmacy because of the cost increase to the pharmacy and, indirectly, to the patient.

Thus, the future production of Mo-99 faces several challenges in the upcoming years if the NNSA goal of complete LEU Mo-99 production by 2016, and, without efforts by industry by 2015, the legislative deadline of 2020 will also be in jeopardy [36]. With no domestic production site since 1990, there had been very little research and development on production technology until 2008. While several incentives exist to help the production efforts domestically, the fact remains that none provides sufficient financial incentives for the private investment necessary to make domestic production viable within the timeline outlined by the American Medical Isotope Production Act of 2011 and the GTRI.
Many possible methods by which to provide incentives for domestic production of molybdenum-99 have been proposed; however, none of the ideas promote the desired effect on the market. One such idea includes “unpackaging” the Tc-99m generator kit, which includes the radionuclide and the generator. The effect of this would essentially separate the cost of the radionuclide from the cost of the generator. While the radionuclide and the generator would be shipped as a single unit from the processing facility, the payment would be sent individually to the utilization facility and the manufacturing facility\(^{28}\). While the nuclear medicine community endorses this proposal, allowing easier tracking and reimbursement of the LEU sourced Mo-99, the production sites feel this will affect the effectiveness of the CMS reimbursement because of the division of the production costs from the manufacturing costs in the product-supply chain. Generator manufacturers, who now act as the main supplier of Mo-99 to nuclear pharmacies, would then become only a generator distributor and essentially lose the stake within market as supplier of Mo-99 within a linear supply chain.

Another proposed solution is to have higher federal incentives for the producers. In theory, by providing incentives to the utilization facility for each unit of Mo-99 produced by LEU sources, the concept provides incentive directly to the supplier. The goal would be for the cost benefit to trickle down to the cost of each Tc-99m dosage produced and administered to the patient. The nuclear pharmacies believe, while decreasing the initial price, the transfer of direct supply duties to the processing and generator parties will not produce the amount of saving necessary to incentivize the purchasing of tests by physicians, thus promoting the desired effect on the market. Regardless of economic theory, this incentive would require more federal funding than what is currently appropriated by Congress.

Regardless of the programs to help the market and incentivize domestic production of molybdenum-99, the difference in opinions from various portions of the industry will cause one side of the production-supply chain to be dissatisfied with the efforts because of the financial flow of funding. However, there are ways of combining the various reimbursements and incentives, paired with an increase in efficiency in collection and administration, to possibly entice private interest and investment in the necessary domestic production of molybdenum-99. The following policy and legislative recommendations look to satisfy each party in the production-supply chain and stabilize the international and domestic market for LEU source Mo-99, while not increasing the necessary budget for any agency receiving appropriations from Congress.

\(^{28}\) In the event of a vertically integrated supplier (Mallinckrodt), the payment would be sent in two separate portions.
Restructure and Extension of CMS Reimbursement

Much of the disagreement about the CMS reimbursement for each LEU dosage of Tc-99m administered to a patient stems from whether or not it actually covers the cost of source conversion. Much like many other economic metrics for insurance companies, CMS withholds its mathematical reasoning supporting only a $10 reimbursement; however, it has been stated that the $10 is a round number for reimbursement and is much greater than the metric suggests for a dosage cost for LEU sourced Tc-99m [33]. Pharmacies are claiming an average dosage price between $12-13, which would in fact be greater than the $10 reimbursement and would also be about twice the current price per dose. With such a large variance in cost approximation, questions are raised about how these estimates are generated and where additional costs are incurred.

The most likely source of ineffectiveness is in administrative costs on the part of the pharmacy. As a business, nuclear pharmacies have a similar structure to all businesses, with technical professionals and supporting staff. However, in terms of the reimbursement from CMS, a staff person, usually paid hourly, must file paperwork and reimbursement forms to allow the pharmacy to claim the CMS reimbursement. When this cost is deducted from the $10 reimbursement, it does reduce the effective benefits for the reimbursement.

With many industries, and specifically the medical field, benefiting from automated administrative services, nuclear pharmacies and testing facilities would most likely benefit the reimbursement process. Figure 4 below shows the economic model of the CMS reimbursement.

**Figure 4**: Economic Pyramid for CMS Reimbursement. Orange line is theoretical impact.
Most of the economic theory relies on the assumption that cost reimbursement will incentivize a greater purchase of LEU sourced Mo-99, therefore providing a market for LEU producers. However, because of differing opinions on the effectiveness of the reimbursement for that purpose, the CMS reimbursement does not accomplish its purpose.

If an automated service were utilized to track LEU sourced units and file reimbursement requests from pharmacies, it would drastically cut the administrative costs and increase the efficiency of the reimbursement. Currently, when a pharmacy receives a Tc-99m generator, it must immediately document its reception. Upon delivery, this is usually done in a similar fashion to receiving a package from any parcel company. A delivery service already utilizes a digital signature system to document reception of the Tc-99m generator, complete with the information by the receiving party as required by the Nuclear Regulatory Commission (NRC).

An automated reimbursement would work much like any other option within a digital user form template. A simple check box could be implemented within the user form software to initiate a reimbursement claim, followed by a text box indicating the number of dosages to be utilized by the pharmacy. Each generator is currently marked with a suggested number of dosages, as required by the NRC, thus, asking the party receiving the generator to read the readily available label on the generator and input the dosage limit would not require much effort. In the event a pharmacy is able to obtain more dosages than suggested by the generator company, an amendment for reimbursement would be available and require similar effort to the current filing procedure. This would induce dosage compliance on the part of the pharmacy, a problem frequently expressed by the producer and generator parties. A 6-day curie Tc-99m generator can generally supply about 60 dosages for the pharmacy, with variance in the distance from the pharmacy to the manufacturing facility. Upon confirmation of the generator and input of dosage by the pharmacy, the reimbursement claim would be routed through a network into an automated processor within the CMS claim service, to be processed in the fashion in which it is currently preformed. This digital confirmation and reimbursement would greatly reduce the administrative costs of the reimbursement and improve the efficiency of the reimbursement cost process.

The other problem existing within the current reimbursement practices pertains to the lack of recognition by third party insurers. With only 6.7% of dosages administered covered by CMS, this reimbursement process could have a much greater impact if matched by the private health insurers. However, there is currently no legislative or industry standard that would make this recommended or required.

Looking ahead to 2014, the Affordable Care Act will require almost all citizens to be covered by health insurance, either by their employer or purchased from the government or a third party provider.

29 Only one parcel carrier, Federal Express, is licensed to carry radionuclides. Because there is only one carrier, this works as a fixed cost in the economic model analysis.
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The ACA will emphasize preventative and diagnostic medicine as opposed to the traditional approach of treating existing conditions [37]. With the current government insurance provider piloting the reimbursement system to one of the most frequent diagnostic scanning procedures, it would not be unreasonable to expect any other government insurance provider to match the reimbursement process or procedure. With a larger number of citizens receiving government insurance coverage after 2014, there would be pressure for the third party insurers to adopt the reimbursement procedure while still keeping their own premium and co-pay costs separate. While third party extensions cannot be forced or guaranteed, the pressure placed on third party insurers would act as an inventive to provide a similar reimbursement to nuclear pharmacies.

The increases administrative efficiency of the existing CMS LEU dosage reimbursement and an analogous program provided by third party insurers would provide incentives for the purchase of LEU source Mo-99 by nuclear pharmacies, thus establishing a steady domestic consumption within the market.

Reimbursement Model for Production Units

In an analogous model to the CMS reimbursement for LEU source Mo-99, a reimbursement to the producer for units of Mo-99 produced by means of LEU sourcing could provide a large economic incentive for companies looking to enter the LEU radioisotope market. Figure 5 displays the theoretical impact of such a reimbursement.

*2009 HEU Mo-99 production cost: $225
*Projected 2016 LEU Mo-99 production cost: $344.26

Figure 5: Economic Pyramid for analogous production reimbursement for LEU source Mo-99. Orange line is theoretical impact.
Currently, the higher production cost of Mo-99 using LEU, compared to that produced using HEU, is the largest barrier for investment in commercial production in the United States. Investors for such production facilities are hesitant to commit to an economic model that will potentially return less than the economic model similar to existing companies within the LEU market. However, similar to the CMS reimbursement currently in place to attempt to offset the cost for the nuclear pharmacies, a similar reimbursement policy could benefit the cost of production, in theory meeting the desired goal of increased production by LEU means and eventually decreasing the cost for the entire supply chain.

For the sake of analysis, many values had to either be inferred or obtained in a piecewise fashion from several sources that lack congruency. The values and necessary metrics to evaluate the possible effectiveness of a production reimbursement are included within Appendix A. Also, all values are approximated using reactor irradiation method for production for Mo-99.

In theory, reimbursing a producer to cover the cost increase from HEU to LEU source could effectively keep the producer’s profit margin constant while decreasing the overall cost for each step of the supply chain. For this metric, the reimbursement given for each unit of LEU source Mo-99 produced would be the current cost of a HEU unit of 1 6-day Ci Mo-99: $225 [28]. The general projection of cost for LEU vs. HEU is an increase of about thirty percent [38]. Assuming this, and utilizing an overall inflation as provided by the Bureau of Labor Statistics (BLS), the approximate cost of production for LEU sources in 2016 will be assumed to be $344.26.

Applying the assumed cost of the generator, capital cost, and transportation, the approximate cost per 6-day curie without the reimbursement is $741.10, equating to a Tc-99m dosage cost of about $12.35 for an average 20 mCi dose [8]. However, applying the reimbursement to the initial stage of production and decreasing the cost passed to the processor by $250, the cost per 6-day Ci, using similar metric approximations as Updergraff and Hoedl, the price per 20 mCi decreases to $8.60.

More important, the approximate cost in 2016 includes the assumption that two production facilities will exist domestically, contributing to worldwide production. Thus, the existing NNSA grant program, designed to incentivize domestic production facilities, would have accomplished its purpose. However, because it is budgeted currently and within the scope of appropriations from Congress within the American Medical Isotope Production Act of 2011, the budgeted amount could be diverted to cover the cost of LEU source production in the form of reimbursement. If a producer is reimbursed $250 for each 6-day Ci, the total cost for the projected domestic production in 2016 of 200,000 6-day Ci would be $45 million. This is $3.1 million less than the $48.1 million budgeted for the total amount given through the NNSA grants in 2012. This would accrue a budgetary savings of $3.1 million for the NNSA, assuming the budget in 2012 for the match grant does not increase. However, the NNSA budget is anticipated
to rise in the coming years, thus, in evaluating upon the aforementioned metric, allowing maintenance of profit margins for each aspect of the supply chain, could result in an essentially equitable dose cost for the nuclear pharmacy. Additionally, applying the CMS reimbursement of $10 to the 6.7% of applicable dosages, pharmacies would make just over $1.1 million from the reimbursement as opposed to the current claim of losing revenue because of the LEU sourced Mo-99.

**Legislation to Insulate Domestic Market from HEU Source Molybdenum-99**

Because domestic production of radioisotopes must be done by LEU sources, legislative action must insure the market will be based solely on commercial LEU sources after 2016. Currently, the conversion efforts are focusing on all commercial sources globally; however, this does not prohibit other countries from starting HEU production and commercialization. Because of the lower production price of HEU radioisotopes, there is growing concern that the market could be influenced by an HEU source of production after 2016. In order to insure a stable domestic market for only LEU source radioisotopes, legislative efforts must be made to protect the LEU source market from potential actions by others that would undercut the economic viability of this transition to LEU. While the legislations could be time-limited, it is essential to assure potential investors and producers of legislative commitment and to protect development of LEU sources.

Current efforts within the “Energy Policy Act of 2005” and “American Medical Isotope Production Act of 2011” have placed restrictions on the export of HEU for commercial radioisotope production. Limiting the export of HEU for medical isotope production promotes the conversion to LEU sources; however, it does not actually place explicit limitations on the import of HEU source Mo-99. While all imports with nuclear technologies are highly regulated, there is currently no legislation in place to insulate the domestic market from being contaminated by international supplies of HEU sourced Mo-99.

While it would be beneficial to simply ban the import of HEU sourced Mo-99 after 2016, doing so would compromise the free market economic system. While HEU production poses a risk for civilian security, the import of such sourced Mo-99 does not pose any additional risk to civilian security aside from the diversion of HEU for purposes other than isotope production. With no breach to national security and in an effort to promote the free market economic system within a growing worldwide economy, a complete ban would not be realistic.

However, with the goal to insulate the more desirable LEU market from a cheaper product, the federal government could impose import limits, taxes, or tariffs on HEU source Mo-99. This would effectively level the market and set a price for Mo-99 as a standard, insulating the market for producers. With the conversion of the worldwide commercial supply to LEU, this would

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30 The largest concern stems from possible Russian HEU source production.
allow assurance to investors about legislative and administrative commitment to price margins of the market. Also, placing such cost fixations on the import as opposed to a legislative import ban allow for the possibility of HEU source supply should severe shortages in the current and expected LEU source supply arises. This protects the patient and the industry from complete insulation of the supply chain while allowing confident market evaluation for investors in domestic production facilities.

**Conclusions**

The utilization of radionuclides for diagnostic medicine is critical to insure the health and well being of patients around the world. Based on past supply shortages, a worldwide source conversion, and the exit of Canada from the supply market, the market is very favorable for domestic production of molybdenum-99. Whether by accelerator or reactor production methods, the entrance of United States producers into the Mo-99 production market would greatly stabilize the global supply and aid the non-proliferation efforts by encouraging the worldwide conversion from HEU to LEU sourced Mo-99. However, additional effort must be made to incentivize domestic production.

Efforts must be made to maximize the efficiency of current reimbursements and incentives for producers, suppliers, and patients. This will effectively act to satisfy all parties within the production-supply chain and insure cooperation with the conversation of Mo-99 sources. Balancing the needs of the production facilities to incentivize domestic production with the needs of the medical community for a stable supply of Mo-99 is essential to stabilizing the entire worldwide production-supply chain.

Additional reimbursement programs could help offset the increased cost of Mo-99 resulting from conversion for both the producer and the nuclear pharmacy, effectively incentivizing the utilization of LEU sources for Mo-99 production. Through approximated economic metrics for reducing the production cost of LEU Mo-99, the savings incurred by the producer could effectively limit the cost to the pharmacy and, in turn, the patient. However, the exact impact of such a reimbursement cannot be assessed precisely due to the large amount of variation and uncertainty in the current and projected market.

The market is very receptive for domestic production of Mo-99, and the federal government is showing its support by aiding such production. The commercial production of radioactive isotopes using LEU within the United States should occur by 2016 to insure the nuclear applications in medicine allow effective patient care for years.
Appendix A: Values and Calculations for Production Unit Reimbursement

For molybdenum-99 and technetium-99m, the production is measured in 6-day Ci, which equals the activity of Mo-99 scaled to source strength after six days of decay in transit. Because of the half-life of Mo-99, this suggests about 60 doses of Tc-99m can be acquired from a 6-day Ci.

Using this approximation, the price of a Mo-99 6-day curie can be approximated on future values based on the average costs outlined within the National Research Council’s publication, *Medical Isotope Production without Highly Enriched Uranium*. This report states the production cost of a 6-day Ci of Mo-99 in 2008 as $225 and the average cost of a 30 mCi dose of Tc-99m in 2005 as $11 [9]. The average generator cost per dose estimated in 2009 as $1.25 per dose [39]. For these approximations, an average dose will be evaluated as 20 mCi, and the dosage cost will be proportionately decreased from the average cost or a 30 mCi dose [39]. Accounting for United States currency inflation rates as published by the Bureau of Labor Statics (BLS), future values for the production and dosage cost can be approximated [40]. Combining these values with the dosages per 6-day Ci for acquired Tc-99m, the revenue costs can be isolated as to insulate the total profit margin of the production-supply chain. The yearly inflation values are shown in Table 3.

<table>
<thead>
<tr>
<th>Year</th>
<th>Inflation Rate (%)</th>
<th>Dosage Cost ($)</th>
<th>HEU Source Production Cost ($)</th>
<th>Generator Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>-</td>
<td>7.33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2006</td>
<td>3.2</td>
<td>7.57</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2007</td>
<td>2.8</td>
<td>7.78</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2008</td>
<td>3.8</td>
<td>8.08</td>
<td>225.00</td>
<td>-</td>
</tr>
<tr>
<td>2009</td>
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<td>8.17</td>
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<td>1.27</td>
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<td>2011</td>
<td>3.2</td>
<td>8.43</td>
<td>234.97</td>
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</tr>
<tr>
<td>2012</td>
<td>2.1</td>
<td>8.61</td>
<td>239.91</td>
<td>1.34</td>
</tr>
</tbody>
</table>

*Table 3.* Given values and derived future values based on currency inflation.

Based on the National Research Council’s report, the percentage of cost increase from LEU to HEU source Mo-99 as about a 30% increase as of 2012, which is also congruent with an approximation given by the IAEA report [38]. Using the 2012 inflated cost per dose and the assumption of 60 doses per 6-day Ci, the total cost for a 6-day Ci is approximated as $671.40. The approximated LEU production cost value $311.88 in 2012. Subtracting the production cost of the a 6-day Ci and the cumulative generator cost for 60 doses, the profit margin for the entire LEU production-supply chain is approximated as $279.12.
Approximating an average yearly inflation rate of 2.5% from 2012 to 2016, the future values of the profit margin, production cost, and total cost can be estimated to evaluate the impact of a dose reimbursement issued to production facilities for the dosage cost. These values are shown in Table 4.

<table>
<thead>
<tr>
<th>Year</th>
<th>Inflation Rate (%)</th>
<th>LEU Source Production Cost ($)</th>
<th>Generator and Processing Cost ($)</th>
<th>Profit Margin ($)</th>
<th>Total Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>2.5</td>
<td>311.88</td>
<td>80.40</td>
<td>279.12</td>
<td>671.40</td>
</tr>
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<td>2013</td>
<td>2.5</td>
<td>319.68</td>
<td>80.41</td>
<td>286.10</td>
<td>688.19</td>
</tr>
<tr>
<td>2014</td>
<td>2.5</td>
<td>327.67</td>
<td>80.47</td>
<td>293.25</td>
<td>705.39</td>
</tr>
<tr>
<td>2015</td>
<td>2.5</td>
<td>335.86</td>
<td>86.58</td>
<td>300.50</td>
<td>723.02</td>
</tr>
<tr>
<td>2016</td>
<td>2.5</td>
<td>344.26</td>
<td>86.74</td>
<td>308.10</td>
<td>741.10</td>
</tr>
</tbody>
</table>

Table 4. Future values based on inflation for LEU source 6-day Ci.

The goal for the production reimbursement program is to fix the profit margin while inducing a cost savings for the entire production-supply chain. In an effort to approximate a NNSA budget for the supposed initial production date of 2016, the 2012 NNSA match-grant budget of $48.1 million is assumed to stagnate by experiencing no increases, decreases, or inflation effects to produce. Also, to hypothetically minimize the reimbursement to the producer for each 6-day Ci produced, we will assume a maximum market share by the domestic producers in 2016 of 100%, or about 200,000 6-day Ci of Mo-99. In issuing a reimbursement of $225 to the producer for each 6-day Ci produced, a total amount of $45 million would be utilized from the existing $48.1, amassing a budget surplus of $3.1 million.

For the economic effect of reducing dose cost for LEU source Tc-99m, the reimbursement would decrease the production value of each 6-day Ci from $344.26 to $119.26, thus reducing the overall cost from $741.10 to $516.10. Assuming the same approximation for dosages extracted per 6-day Ci of 60, the reimbursement would reduce the overall LEU source dose cost from $12.35 to $8.60 for an assumed average dosage of 20 mCi. The reimbursement essentially equates the 2016 LEU dose cost to the 2012 HEU source Tc-99m dose cost. In assessing the $10 CMS reimbursement to the applicable of 6.7% of the total doses, a profit of $1.40 for each of the 804,000 doses included within the CMS reimbursement equates to a profit margin of $1,125,600 for nuclear pharmacies.
Works Cited


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