# Diversification in the Supply Chain of $^{99}$Mo Ensures a Future for $^{99m}$Tc

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The uncertain availability of $^{99m}$Tc has become a concern for nuclear medicine departments across the globe. An issue for the United States is that currently it is dependent on a supply of $^{99m}$Tc (from $^{99}$Mo) that is derived solely by production outside the United States. Since the United States uses half the world's $^{99}$Mo production, the U.S. $^{99}$Mo supply chain would be greatly enhanced if a producer were located within the United States. The fragility of the old $^{99}$Mo supply chain is being addressed as new facilities are constructed and new processes are developed to produce $^{99}$Mo without highly enriched uranium. The conversion to low-enriched uranium is necessary to minimize the potential misuse of highly enriched uranium in the world for nonpeaceful means. New production facilities, new methods for the production of $^{99}$Mo, and a new generator elution system for the supply of $^{99m}$Tc are currently being pursued. The progress made in all these areas will be discussed, as they all highlight the need to embrace diversity to ensure that we have a robust and reliable supply of $^{99m}$Tc in the future.

**Key Words:** novel $^{99}$Mo production; HEU; LEU; CMS reimbursement; $^{99m}$Tc generator

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Each day, $^{99m}$Tc produced from the β decay of $^{99}$Mo is used in approximately 50,000 procedures in the United States (*1*). $^{99m}$Tc has been referred to as the workhorse of nuclear medicine because it allows for noninvasive imaging of function at the cellular level without perturbing or otherwise modifying the system. This imaging capability allows physicians to diagnose abnormalities early in a disease process when the disease is much easier and less expensive to treat than after it has progressed to the level that can be visualized using anatomic imaging. In recent history, the precursor $^{99}$Mo has been produced at reactors by fission production using highly enriched uranium (HEU). These facilities have been government-operated and subsidized in both the production and handling of the waste produced by these methods. There are several complex issues regarding $^{99}$Mo production, such as aging nuclear reactors and the limited number of processing sites of the irradiated $^{99}$Mo targets. In addition, industry efforts are further complicated by the U.S. National Nuclear Security Administration's (NNSA) efforts to convert all $^{99}$Mo production from HEU to low-enriched uranium (LEU). This effort by the NNSA is part of its Global Threat Reduction Initiative to prevent terrorists from accessing nuclear and radiologic materials. Since the $^{99}$Mo shortages in 2009, the industry has made significant progress to stabilize and improve the supply of $^{99}$Mo. Part of this shortage was due to the shutdown of the National Research Universal (NRU) reactor in Canada, which typically produces one third of the world's $^{99}$Mo. Yet another challenge for the industry is the planned permanent shutdown of the NRU reactor in 2016. The aim of this article is to review the current state of $^{99}$Mo production since the release of the article by Pillai et al. (*2*) and progress on innovative solutions that may reduce or eliminate many of the issues currently threatening a robust $^{99}$Mo supply. Additionally, the article will provide added focus on the regulatory issues.

The uranium isotope used for fission is $^{235}$U and occurs naturally at an isotopic abundance of 0.7%. HEU is defined as being at least 20% $^{235}$U, and LEU is defined as being less than 20% $^{235}$U.

## HISTORICAL $^{99}$MO PRODUCTION

Currently, most HEU used in isotope production is enriched to greater than 90% (*3*). The United States produces 93% of the HEU that is used in the world for the production of $^{99}$Mo. Since the early 1980s, most commercially produced $^{99}$Mo has been created using an HEU fission process through a limited number of nuclear reactors and has not been produced in the United States. In the United States, the source has mainly been the NRU reactor at the Chalk River Laboratories in Canada and the High Flux Reactor (HFR) in Petten, The Netherlands, with additional production from 3 other reactors. All 5 of the reactors are over 45 y old. Both NRU and the HFR reactors are approaching the end of their life cycle, with NRU scheduled to close in 2016 and HFR shortly thereafter. These nuclear reactors are at risk of experiencing unscheduled shutdowns or increased shutdowns due to their age and have contributed to the fragility of the $^{99}$Mo supply in the recent past. To increase and strengthen the supply of $^{99}$Mo, additional nuclear reactors have been brought online into the supply chain. The nuclear reactors in the $^{99}$Mo supply chain are government-supported and in the past have subsidized the true cost of the $^{99}$Mo produced. The size of this government support is wavering because it is based on the local political climate to maintain those subsidies. The Organization for Economic Cooperation and Development (OECD), which includes all the current countries involved in $^{99}$Mo production, has recommended that all subsidies be phased out by June 2014 (*4*). The OECD has suggested that subsidization

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of $^{99}$Mo production costs has prevented commercial firms from entering the market, because they would be at a cost disadvantage. The OECD recommends that the only way to develop a robust and reliable supply of $^{99}$Mo is to cultivate a system that establishes full cost recovery.

## $^{99}$MO PRODUCTION: PAST AND PRESENT

Root cause analysis of the $^{99}$Mo supply chain shortage has identified the current primary production route, using HEU target irradiation at national facilities, as the main problem (*4*). The current $^{235}$U irradiation and processing is routinely performed at 5 aging facilities: NRU, HFR, Orisis in France, Belgian Reactor 2 (BR2), and the Safari reactor in South Africa (*5*). In addition, the Maria reactor in Poland and the Light Water Reactor 15 (LVR-15) in the Czech Republic have recently been engaged to irradiate targets. Overall, only 10%–15% of the $^{99}$Mo produced today is from LEU targets (*4*). Two facilities that now provide $^{99}$Mo produced from LEU are the Open Pool Australian Lightwater (OPAL) reactor in Australia and the Safari reactor in South Africa, though Safari is not 100% converted to LEU at this time. These targets are then processed at a limited number of sites, in most cases at facilities close to the irradiation site. The OPAL facility is currently doubling the size of its target processing facility. Hence, in the future it will be able to double its $^{99}$Mo production using LEU targets. The $^{99}$Mo is extracted and provided to commercial entities that produce and supply the $^{99}$Mo/$^{99m}$Tc generators.

## U.S. GOVERNMENT DEVELOPMENT PLANS

The Department of Energy (DOE) and NNSA have been working since 2008 to minimize the use of HEU. The NNSA, which is part of the DOE, started its Global Threat Reduction Initiative (GTRI) in 2004 to convert the use of HEU to LEU in the production of medical isotopes (*6*) and to develop alternative sources of $^{99}$Mo production, particularly in the United States, which has not produced $^{99}$Mo for patient studies since the early 1980s. The NNSA has facilitated this effort by also offering funding to producers outside the United States to aid in the conversion from HEU to LEU production. U.S. national laboratories are also assisting in conversion of HEU to LEU for target design and processing after irradiation. The latest progress is described in the chairman's summary from the $^{99}$Mo Topical Meeting held April 1–4, 2013 (*7*). Additionally, the International Atomic Energy Association is working in conjunction with the NNSA to convert the use of HEU to LEU for medical isotope production (*8*).

On June 8, 2012, the White House issued a press release in which it outlined the steps the government was planning to take to ensure a viable U.S. market for domestic manufacturers (*9*). The sections of this announcement that are critical to the nuclear medicine community include procurement of $^{99}$Mo produced without the use of HEU, in a manner consistent with U.S. international trade agreements; establishment of unique product codes for radiopharmaceuticals produced without the use of HEU; a further reduction in exports of HEU for medical isotope production when sufficient non-HEU $^{99}$Mo is available globally; encouragement of domestic commercial entities in their efforts to produce $^{99}$Mo without HEU during the transition of the $^{99}$Mo industry to full cost-recovery; direction of those resources to the projects with the greatest demonstrated progress; and continued support of international producers to assist in the conversion of $^{99}$Mo production facilities from HEU to LEU.

In October 2012, Parrish Staples, the NNSA GTRI director, stated in an oral communication to one of the authors that "The NNSA's GTRI is working to accelerate the establishment of a reliable supply of the medical isotope $^{99}$Mo produced without HEU. To achieve this objective, GTRI works with existing large-scale isotope producers to assist in the conversion of global isotope production facilities from HEU targets to LEU targets. In addition, GTRI has partnered with 4 U.S. commercial entities to develop a diverse set of non-HEU–based technologies to produce $^{99}$Mo in the United States. In both cases GTRI makes the expertise of the U.S. national laboratories available to support these technical developments. The demonstration of multiple technical pathways for $^{99}$Mo production will ensure that a reliable $^{99}$Mo production industry is established for patients both in the United States as well as internationally."

The American Medical Isotope Production Act (also known as the $^{99}$Mo Bill) passed in December 2012. This bill outlines the DOE's efforts to implement programs to support the U.S. production of $^{99}$Mo without the use of HEU. After 7 y, it will prohibit the Nuclear Regulatory Commission from issuing a license for the export of HEU from the United States. It requires the DOE to retain responsibility for the final disposition of spent nuclear fuel and radioactive waste from production and processing of uranium (*10*). Before this bill, there was no place for the waste to be transferred. A recent e-newsletter from the European Nuclear Medicine Association addressed the global situation regarding $^{99}$Mo supply. This association has reviewed the report from the Nuclear Energy Agency/OECD High-Level Group on the Security of Supply of Medical Isotopes (*11*). The key recommendation made, in order to create a reliable and sustainable future for nuclear medicine, lies in a new policy for the $^{99}$Mo/$^{99m}$Tc generator that is similar to U.S. policy. This includes implementation of the agreed Nuclear Energy Agency/OECD policy of full cost recovery, security, and safety for nuclear operations, including implementation of nuclear nonproliferation measures, development of new production processes, new radioactive waste management facilities, and a financial model without subsidies from government. Globally, these improvements in the $^{99}$Mo supply chain will help to reduce the use of HEU worldwide.

An added issue concerning the production of $^{99}$Mo and other fission-derived radionuclides for medical imaging is the radioactive releases that accompany their production. In particular, the fission gases of radioxenon are produced and released into the environment, causing detection in monitoring networks. Because radioxenon is a key indicator of nuclear testing (*12,13*), these emissions are interfering with treaty monitoring operations connected with the Comprehensive Nuclear-Test-Ban Treaty, the Non-Proliferation Treaty, and considerations of a future Fissile Material Cutoff Treaty (*14*). Reductions in radioxenon emissions are being sought to minimize or eliminate their impact on nuclear monitoring systems (*12*). Pacific Northwest National Laboratories through the Comprehensive Nuclear Test Ban Treaty Organization has been asking producers to sign a pledge that they will work toward minimizing xenon emissions. Currently, there are 4 companies that have signed the pledge: the Institute of Radioelements, Korea, the Australian Nuclear Science and Technology Organisation (ANSTO), and Batan.

## DOE/NNSA COOPERATIVE AGREEMENTS: NEW SOURCES OF $^{99}$MO

In 2009, DOE/NNSA put out a call for cooperative agreements to establish production facilities in the United States without the

use of HEU. These cooperative agreements were required to cover 50% of the cost and to ensure that certain guidelines would be met to ensure the production lines were environmentally viable. Four cooperative agreements have been funded.

First, GE Hitachi at the Clinton Power Station in Illinois will use commercial power reactors for neutron irradiation of $^{99}$Mo. This project is currently on hold. Pillai has described the various reactor separation techniques that could potentially be used in the power reactor production and the drawbacks causing the process to be economically unfeasible (*2*).

Second, Babcock and Wilcox Technical Services Co. proposed using the Medical Isotope Production System Aqueous LEU Homogenous Reactor, or "solution reactor." This project has now been suspended after the discovery that the time and cost involved with the project would be greater than anticipated (*15*).

Third, Shine Medical Technologies, LLC, has been working in partnership with the Morgridge Institute for Research (jointly known as Shine) on an accelerator-driven LEU solution fission process. This process was also described in the Pillai article in 2013 (*2*). Shine uses LEU in the production of $^{99}$Mo through new technologies being developed as part of their cooperative agreements. One major benefit of this process is that the $^{99}$Mo is of high specific activity and fits into the current supply chain for existing $^{99m}$Tc generators. An additional consideration is the cost of managing the radioactive waste. Shine will be using a "target solution vessel" that will reduce the anticipated waste stream to less than what is encountered with typical solid targets. The company has made progress in dealing with its proposed waste stream, as it filed a construction permit with the Nuclear Regulatory Commission in June 2014. This permit application also includes the company's environmental analysis program (*16*).

Fourth, NorthStar Medical Technologies, LLC (formerly NorthStar), has proposed 2 paths forward—one using accelerator irradiation of $^{100}$Mo ($\gamma$,n) $^{99}$Mo production, that received funding from the NNSA, and the other using reactor irradiation of $^{98}$Mo (n,$\gamma$) $^{99}$Mo production, using the reactor at the Missouri University Research Reactor in Columbia—both methods producing a low-specific-activity $^{99}$Mo that could be loaded onto a novel generator/separator. This process appears to be the most viable of these 4 options.

$^{99}$Mo production via neutron irradiation of $^{98}$Mo (n,$\gamma$ reaction) is the same method as was used for the first generation of $^{99m}$Tc generators. Neutron irradiation of $^{98}$Mo has a waste stream that appears to be simpler and less expensive to dispose of than LEU/HEU fission process waste (*2*). This advantage may allow production of $^{99}$Mo at a price competitive with both HEU- and LEU-produced $^{99}$Mo. One technical hurdle is the limited supply of enriched target material that is required for some of these new processes. Currently, enriched $^{98}$Mo and $^{100}$Mo are available in only limited supply from 2 sources: Trace Life Sciences, which is supplied by Urenco, and Isoflex, which is supplied by Electrochemical Plant in Russia. In addition, recycling methods have been developed for these target materials in support of NorthStar's initiatives.

## GENERATOR SYSTEM FOR $^{99}$MO WITH LOW SPECIFIC ACTIVITY

NorthStar's inclusion of a novel generator system, TechneGen, is a breakthrough that opens up the $^{99}$Mo supply chain. The concept for the generator dates back to the mid 1990s from privately funded contract research beginning at the University of Chicago (*17*). The current design uses a combination of 2 cartridges to first extract the $^{99m}$Tc and then purify it. The generator is able to concentrate high-specific-activity $^{99m}$Tc from low-specific-activity $^{99}$Mo. The eluent has been tested and meets the U.S. Pharmacopeial Convention requirements for $^{99m}$Tc-pertechnetate. NorthStar currently has a new drug application under review by the Food and Drug Administration (FDA) for the $^{99m}$Tc-pertechnetate. The application includes test results for the formulation of $^{99m}$Tc-labeled sestamibi, exametazime, and mercaptoacetyltriglycine that met U.S. Pharmacopeial Convention requirements. In addition, NorthStar has demonstrated that its product meets all the microbiology and sterility requirements of the FDA.

During the last 3 months of 2012, Iso-Tex Diagnostics Inc. of Texas performed over 100 TechneGen elutions. They prepared sestamibi, exametazime, and mercaptoacetyltriglycine radiopharmaceuticals with the $^{99m}$Tc eluent. These kit formulations met all of the package insert requirements, including radiochemical purity and stability.

The TechneGen generator is more complicated to use than a traditional $^{99m}$Tc generator. The steps necessary to prepare the generator for an elution are in some ways similar to those for an $^{18}$F-FDG automated synthesis module but are much simpler. Once the generator is set up for an elution, a computerized program operates the generator to complete the elution automatically. The first noticeable difference from a traditional $^{99m}$Tc generator is that the nuclear pharmacy will receive the $^{99}$Mo as a solution in the source vial to be connected to the TechneGen; it will not be preloaded onto an alumina column within the generator. The $^{99}$Mo passes through the separation cartridge and is returned to the original source vial. The recycled $^{99}$Mo is held in the source vial to allow for the regrowth of $^{99m}$Tc for the next elution. The regrowth of $^{99m}$Tc occurs at the same physical decay rate as with a traditional generator; it is independent of its physical state, that is, on an alumina column or in solution. In the next step, the $^{99m}$Tc is eluted off the separation column and is passed through an alumina column as a purification step to scavenge any breakthrough $^{99}$Mo. The final step is passage through a 0.22-$\mu$m sterilizing filter. NorthStar submitted the new drug application for the TechneGen generator in January 2013.

## SUPPORT OF U.S. NATIONAL LABORATORIES

The GTRI-conversion program supports the conversion of domestic and international civilian research reactors and isotope production facilities from HEU to LEU; this conversion includes working with $^{99}$Mo producers to convert their operations to the use of LEU targets. In addition to the 4 funded projects discussed previously, the GTRI is also supporting work at many of the DOE national laboratories to address some of the technical hurdles in converting from $^{99}$Mo derived from HEU to $^{99}$Mo derived from non-HEU sources. Including the development of non-HEU technologies for $^{99}$Mo production, Los Alamos National Laboratory has demonstrated the viability of extracting $^{99}$Mo from aqueous uranium sulfate using a chemical process favored by Shine Medical Technologies. A process flow sheet developed by Argonne National Laboratory (ANL) was used to develop a small-scale process that demonstrates the technical viability of extracting $^{99}$Mo in high yield with recovery of the uranium sulfate target. Los Alamos National Laboratory has also performed 5 accelerator tests using the electron accelerator on natural molybdenum targets evaluating production and heating in support of NorthStar Medical Technologies accelerator production of $^{99}$Mo via the photonuclear reaction on $^{100}$Mo (*18,19*).

Savannah River National Laboratory is testing a 2-MW open-pool reactor using less than 20% uranium oxide fuel to produce $^{99}$Mo in a cost-effective manner. This reactor is low-power, similar to research reactors. Testing will aid in supporting future licensing of a dedicated facility for medical isotope production (*20*). Additionally, Savannah River National Laboratory is working on a preconceptual design for a tritium purification system for the Shine $^{99}$Mo production. The process includes tritium evacuation, cleanup, and removal of impurities in the process (*21*).

ANL has several projects ongoing to support the production of non-HEU–derived $^{99}$Mo. The work in support of the Molecular Isotope Production System and the Shine program has 3 aims: first, to study the radiolytic gas generation; second, to develop an understanding of the solution chemistry under operating conditions; and third, to develop a $^{99}$Mo recovery and purification system (*22*). The work is being performed in phases going from low- to high-power densities and from less to more complex experiments. Argonne is additionally assisting Shine by performing plant-scale column tests for low-scale $^{99}$Mo recovery via column recovery and concentration to reduce the volume before entering the LEU-modified CentiChem purification process (*23*). These studies are aiding in evaluating how the different metal impurities will behave in the process and how the high radiation doses expected from $^{99}$Mo will affect the absorption and recovery from the sorbents. ANL further performed dissolution studies of $^{99}$Mo-sintered disks to determine how the physical properties of the disks affect dissolution rates. Tests evaluated the effect of sintering on dissolution rates and packing densities (*24*).

Oak Ridge National Laboratories evaluated compaction and sintering of a variety of molybdenum powders including enriched $^{99}$Mo. Natural powders could be cold-pressed to reach densities of more than 90%, but enriched $^{99}$Mo required both compression and sintering to reach a density of more than 90% (*25*).

Y-12, a National Security Complex in Oak Ridge, is producing and supplying LEU to support nonproliferation objectives. Additionally, Y-12 is developing and testing a manufacturing method of high-density LEU foils for the production of $^{99}$Mo. The goal is to develop a cost-effective method to manufacture a safe LEU foil that is relatively inexpensive to offset the inherent economic disadvantage of using LEU in place of HEU (*20*). Y-12 is working with Oak Ridge National Laboratories, ANL, and the Missouri University Research Reactor to develop target quality-control specifications, develop chemical dissolution equipment, and evaluate irradiated targets (*26*).

ANL has developed and tested 2 front-end methods for dissolving the LEU targets, resulting in a solution that can then enter into the currently used separation processes by $^{99}$Mo producers. One dissolution process involves the use of nitric acid and ambient pressure and the second an electrochemical dissolution in an aqueous bicarbonate solution; both have demonstrated technical feasibility (*27*).

## ACCELERATOR PRODUCTION OF $^{99}$MO AND $^{99m}$TC

In addition to these 4 DOE/NNSA–funded projects, several groups have been pursuing the production of $^{99m}$Tc on small cyclotrons. Although the amounts of $^{99}$Mo made by this route will not make up for the huge quantities produced via fission, the amounts could be enough for local supply of low populated areas. This work has been largely advanced in Canada and is backed by significant effort due to government funding and regional collaborations. National Resources of Canada funded 4 projects under the Non-Reactor Based Isotope Supply Contribution Program (*28*). The first of 2 projects moving forward involves several midsize cyclotrons across the country for the direct production of $^{99m}$Tc on a solid target. The second project involves using linear accelerators in the same manner as NorthStar's plans to produce $^{99}$Mo—that is, via the ($\gamma$,n) reaction on $^{100}$Mo targets (*28,29*). $^{99}$Mo production via an accelerator is also being pursued by Canadian Light Source in Saskatoon, Saskatchewan; Prairie Isotope Production Enterprise in Winnipeg, Manitoba; CERN (Conseil Européen pour la Recherche Nucléaire [European Council for Nuclear Research]) in Geneva, Switzerland; and Japan (*30,31*). To date, these groups have demonstrated the feasibility. The Medical Isotope and Cyclotron Facility at the University of Alberta has shown it can recycle the target, $^{100}$Mo, use a resin to purify the $^{99m}$Tc, and formulate $^{99m}$Tc-radiopharmaceuticals using commercial kits. It has also demonstrated that regulatory specifications can be met (*32*). Preliminary discussions with regulatory authorities are occurring, with no significant hurdles in obtaining approval for the material anticipated. It is unclear what the final cost will be, because of the long cyclotron run times and processing time, as well as the expense of the limited target material.

## ADDITIONAL REACTOR SOURCES

Lantheus and Mallinckrodt, current suppliers of $^{99m}$Tc generators in the United States, have approached the $^{99m}$Tc shortage by adding reactors to the supply chain such as the Maria reactor in Poland (*33*). Mallinckrodt is developing an LEU target for several reactors—that is, HFR, Maria, and BR2 (*24*). Although it has been demonstrated that the use of LEU targets will lower the production efficiency and increase the cost of $^{99}$Mo production, Mallinckrodt believes conversion to LEU targets will improve the long-term reliability of the supply of $^{99}$Mo (*34*). A bright spot on the horizon is the new Jules Horowitz Reactor that is currently under construction in France. It is projected to come online in 2016. Both replacement reactors for the HFR and BR2 will come later: the MYRRHA (Multipurpose Hybrid Research Reactor for High-Tech Applications) in Belgium and the Pallas reactor in The Netherlands are projected for 2022. Another promising area of progress, though still a few years away, is the OPAL reactor. The reactor's production capacity has not been the limiting factor for the production of $^{99}$Mo. ANSTO has been limited by its low processing capability for irradiated $^{99}$Mo targets. In early 2013, ANSTO plans were approved by the Australian Radiation Protection and Nuclear Safety Agency to construct an additional processing facility for $^{99}$Mo targets, in effect doubling the capacity for $^{99}$Mo.

Nordion had established an agreement with the Russians through JSC Isotope, a subsidiary of Rosatom, to supply $^{99}$Mo in anticipation of closure of the NRU reactor in 2016, but agreement has now been cancelled. Additional suppliers that are expected to be online in the future are South Korea, Brazil, Argentina, India, and China. All of these reactors will be using LEU or $^{98}$Mo to produce $^{99}$Mo. Although Lantheus and Mallinckrodt indicate they are monitoring and assessing all possible opportunities to further diversify and strengthen their supply chain, as of yet they are not in a position to sign a supply agreement with an entity that is not making $^{99}$Mo outside the fission process.

## MANUFACTURING PROCESS: $^{99m}$TC GENERATORS WITH LEU $^{99}$MO

As of August 2012, the U.S. Mallinckrodt plant had already received approval from the FDA and Health Canada to use

LEU-based $^{99}$Mo from the Safari reactor (*33*). Mallinckrodt is waiting for European Medicines Agency approval for use of Safari LEU-based $^{99}$Mo for the Mallinckrodt plant in The Netherlands. Mallinckrodt is in the process of evaluating the use of LEU-produced $^{99}$Mo from the OPAL reactor and is continuing to explore partnerships with other LEU-based $^{99}$Mo producers.

For Lantheus Medical Imaging, LEU currently comprises a double-digit percentage of the Lantheus supply on a monthly basis, but there was not sufficient LEU in 2013 to meet 100% of the Lantheus demand. NTP and ANSTO are the primary suppliers of LEU $^{99}$Mo for Lantheus. As these 2 suppliers increase their production, Lantheus plans to be 100% LEU $^{99}$Mo by the end of 2016.

Mallinckrodt is replacing $^{99}$Mo HEU targets with LEU targets and is evaluating the feasibility of sharing an LEU target design with the Institute of Radioelements in Belgium for a single European target (*33*). A unified LEU target would offer maximum flexibility for all European $^{99}$Mo production and processing sites. An LEU target design has been locked in for use at the HFR, Maria, and BR2 reactors. Target qualification is currently under way at those reactors. Trial target irradiation and radiochemical processing began in 2012 and will run into 2013. Regulatory filings will be made in 2013 and 2014 for LEU-based production of $^{99}$Mo, and total conversion is expected to be completed by the end of 2015 with significant company investment.

## COST, THE FINAL HURDLE OF LEU $^{99}$MO

Worldwide, the producers of $^{99}$Mo are making excellent progress toward compliance with the NNSA's GTRI. They are in the process of successfully converting the production of $^{99}$Mo to LEU. There are, however, multiple increased cost components to this conversion process. The biggest cost increase is due to the nearly 5-fold decrease in uranium density in the targets irradiated for $^{99}$Mo. The new LEU targets will now produce about one fifth the amount of $^{99}$Mo produced by an HEU target. Hence, it will take approximately 5 LEU targets to equal the production of a single old HEU target. The second biggest cost component is now the waste stream volume from processing the LEU targets, as it will be approximately 5 times greater than the old HEU waste stream. There are other increased cost components that are being incurred, such as those needed for design and testing of new LEU targets, facility modifications, and regulatory costs. The goal of the U.S. government and organizations such as the OECD is to reduce subsidization of the cost of producing $^{99}$Mo so as to level the production field for potential commercial vendors. According to these groups, this leveling is important for new vendors, to allow them a fair opportunity to enter the field and diversify the $^{99}$Mo supply chain.

To preserve nuclear medicine as a cost-effective clinical science, it is critical that current distributors embrace the novel technologies described above and include them in a diversified supply chain. It is anticipated that at least one new technology will become available in 2014: the partnered use of low specific $^{99}$Mo produced by the Missouri University Research Reactor with the NorthStar TechneGen generator. This option may prove to be more cost-effective and reliable and could eliminate the concerns about effectively using the limited production of LEU-produced $^{99}$Mo to realize the additional Centers for Medicare and Medicaid Services (CMS) reimbursement.

## REIMBURSEMENT

In the United States, the CMS recognizes that there are conversion costs as the industry moves away from HEU-produced $^{99}$Mo to full cost recovery and converts to the use of LEU targets or other non-HEU technologies to produce $^{99}$Mo. CMS has responded by including in the hospital outpatient prospective payment system an add-on $10 payment effective January 2013 for $^{99m}$Tc doses prepared from any non-HEU sources of $^{99}$Mo. The additional reimbursement is applicable only for $^{99}$Mo produced using non-HEU technologies (*35*).

Lantheus Medical Imaging announced that it would manufacture for the U.S. market $^{99m}$Tc generators that meet the CMS criteria for the $10 add-on payment. Lantheus reportedly produced such generators on an almost weekly basis through 2013.

However, several factors apparently limited the adoption of LEU generators in 2013, including availability, cost, and added administrative burden for the use of non-HEU–derived $^{99m}$Tc doses. In addition, to substantiate a CMS payment (as with all CMS payments), a department has to be able to provide a paper trail to document charges incurred. Each hospital needs to establish a process for tracking those patients who receive the non-HEU–derived $^{99m}$Tc dose, and hospitals that have implemented such tracking into their daily operations have reported that CMS is processing the claims for the $10 add-on payment.

The U.S. government, including CMS, has indicated a desire that this add-on payment be voluntarily adopted by private, third-party payers and thus not be limited only to Medicare-eligible patients. However, at the time of writing, there are no confirmed reports that third-party insurance companies have yet implemented this additional payment to nuclear medicine departments for non-Medicare outpatients.

It is anticipated that as availability improves and further experience with the management and reimbursement of LEU doses is gained, the transition to non-HEU–derived $^{99m}$Tc doses will accelerate in 2014 and 2015.

However, although the transition to non-HEU $^{99m}$Tc is moving forward, the $10 incentive payment will not continue in perpetuity. Hence, because of problems with availability, cost, and added administrative burden for the use of non-HEU $^{99m}$Tc doses, departments have been reluctant to purchase these doses. This low initial demand further complicates the transition of the industry to non-HEU–derived $^{99m}$Tc.

## CONCLUSION

Several years ago, the industry was faced with an aging infrastructure of old reactors, government mandates to convert to LEU production, and limited resources to pay for more expensive $^{99}$Mo. Since that time, significant progress has been made in new processes to produce $^{99}$Mo with LEU or even without using uranium. Some of these new processes use an accelerator instead of a nuclear reactor. In addition, a new generator system under review by the FDA uses low-specific-activity $^{99}$Mo. The ability to use low-specific-activity $^{99}$Mo allows other production methods to be added to the supply chain. A new $^{99}$Mo target processing center is under way that will double the OPAL reactor's production capacity, and the new Jules Horowitz Reactor will be operating by 2016. The significant gains from these various projects promise to deliver a diverse and robust $^{99}$Mo supply chain for nuclear medicine. Perhaps the most significant hurdle we have yet to conquer is to determine whether we can afford our new non-HEU–derived $^{99}$Mo.

## DISCLOSURE

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