

## Can the SPECT nuclear imaging modality be sustained?

The impact of new technology, government and international regulations, egregious price increases, and collapsing reimbursement structures on the nuclear imaging space



This paper examines the impact on the cost of radiopharmaceutical procurement after the conversion of medical isotopes from highly-enriched uranium to other alternatives, the effect of proprietary product price increases, possible new regulatory changes, and the issues that health care organizations face regarding the bundling and declining reimbursements in the nuclear medicine space.

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## Executive summary

Radiopharmaceuticals used in molecular and nuclear imaging serve a vital purpose in patient care. Such imaging provides a unique functional and therapeutic resource for the physician whose patients face cardiovascular, neurologic, and oncologic disease challenges. The applications in which radiopharmaceuticals can be used continue to expand into new arenas, including the use of genetic screenings to identify patients with a propensity for certain medical conditions and for follow up after therapy using single-photon emission computed tomography (SPECT) and planar diagnostic imaging.

Molybdenum ( $\text{Mo}^{99}$ ) is a radionuclide whose decay (daughter) product, technetium ( $\text{Tc}^{99\text{m}}$ ), is an isotope that is frequently used in nuclear diagnostic imaging. More than 80% of prescription orders in the United States are performed using  $\text{Tc}^{99\text{m}}$ ; typically, it is radiolabeled to chemical ligands for injection to visualize the heart, lungs, brain, bone, and other organs, thus revealing physiological and functional capabilities or alterations in normal function. Currently,  $\text{Mo}^{99}$  is produced by 7 foreign nuclear research reactors, whose main target material—highly enriched uranium (HEU)—can also be used to create nuclear or “dirty” bombs. Because of this potentially deadly security concern, the US government established several initiatives that support the elimination of HEU from medical isotope production, such as the National Nuclear Security Administration’s  $\text{Mo}^{99}$  Program and the American Medical Isotope Production Act of 2013 (AMIPA). These initiatives also include the development of domestic  $\text{Mo}^{99}$  and  $\text{Tc}^{99\text{m}}$  production, as well as provisions for  $\text{Mo}^{99}$  manufacturers and processors to use full cost recovery (FCR) and outage reserve capacity (ORC) to recoup the costs that are necessary to make the conversion to non-HEU sources to meet consumer demand. To recover these costs, health care organizations’ expenses may increase significantly. Compounding the situation is the need to establish a domestic, sustainable supply, which will also add to the overall cost of the radiopharmaceuticals. Ultimately, these costs will inevitably be passed through the supply chain directly to health care organizations such as hospitals, nuclear cardiology clinics, and imaging centers.

Manufacturing the nonradioactive portion (ligand) of the final  $\text{Tc}^{99\text{m}}$  radiopharmaceutical is also costly. During the past 20 years, manufacturers have divested away many generic pharmaceuticals (known as “cold kits”) that are chemical or protein links to the  $\text{Tc}^{99\text{m}}$  moiety, and consolidation within the industry has seen the emergence of sole-source, proprietary producers. As a result,  $\text{Tc}^{99\text{m}}$ -labelled radiopharmaceuticals, which are composed of 2 distinct components, are subject to large price increase percentages that can range from single digits to thousands. For example, in 2014, a sole-source manufacturer announced an extraordinary one-time cold kit price increase of nearly 2,000%; that same year, one of its product lines also increased by more than 525%. Such increases not only lead to unprecedented product availability issues, but also markedly impact the budgets of health care provider organizations and their cost containment strategies.

In the near future, Food and Drug Administration (FDA) regulations regarding radiopharmaceutical preparation and compounding will mandate that nuclear pharmacies remain compliant with United States Pharmacopeia (USP) chapter <797> and the forthcoming chapter <825>. In response, many nuclear pharmacy organizations have already made substantial investments toward improving their facilities, meeting and surpassing regulatory compliance and educational program requirements, and adjusting the processes used to prepare and dispense radiopharmaceuticals, all of which cost thousands of extra dollars and add significant cost increases to the supply chain. Ultimately, unpredictable

radiopharmaceutical price increases and a potentially unreliable supply mean that health care organizations will have to pay more for their radiopharmaceuticals.

Although a bundled payment system is presently widely believed to be the most effective reimbursement method for controlling costs, in the future it could present health care organizations with a significant challenge: the cost of a prepared radiopharmaceutical could become the dominant part of the total procedure cost, potentially turning the bundled reimbursement into a loss leader and forcing health care organizations to either bear the full burden of market price increases from their own budgets or choose to perform less efficacious diagnostic tests, which could potentially lead to unfavorable patient outcomes. Clearly, appropriately managing the costs associated with the acquisition of radiopharmaceuticals, their component ligands, and the preparation of the final drug used in patient diagnostic imaging; radiotherapeutics applications; and the growing field of “theranostics,” which tailors diagnostic and therapy treatments for individual patients, may be highly dependent on a reimbursement reform strategy.

Appropriate and timely reimbursement models should be evaluated to assess the continued delivery of the SPECT imaging modality and keep overall health care costs as low as possible. In addition, government and commercial payer markets must be made aware of the impact that costs have on nuclear diagnostic procedures. We must work together to find a solution that continues to inspire industry to invest in new and innovative tests and therapies while helping to relieve health care organizations from some of these cost pressures and allowing them to make sound patient care decisions that are not based solely on cost mitigation strategies, but rather on providing the best, most effective care for patients. Obtaining appropriate reimbursement for these products may be the primary driver in ensuring that SPECT imaging continues to be an economically viable imaging modality.

# Understanding the molybdenum supply chain

## The history behind biomedical research

In June 1946, The Manhattan Project—created to produce the first nuclear weapons—announced its program for distributing isotopes to medical researchers. Research was to be unclassified and shared by all, and while initially the premise was that basic research would precede any medical applications, “clinical investigations” with humans were always planned from the very beginning.<sup>1</sup> Human use studies came under the control of the Atomic Energy Commission (AEC) on January 1, 1947.<sup>2</sup> Early radioisotopes of gold, mercury, iron, chromium, and iodine were used to image the physiological aspects of body organs; however, with the advent of the Anger Gamma Camera, radioisotope use for imaging migrated to  $\text{Mo}^{99}$ —produced  $\text{Tc}^{99\text{m}}$  for its ability to tag many chemical moieties and for its superior imaging characteristics based on its gamma emission energy and high photon flux. Today, the supply of  $\text{Tc}^{99\text{m}}$  and its cold reagent kits are regulated by the USP and the FDA as approved radiopharmaceuticals.

## Molybdenum production

$\text{Mo}^{99}$  is a radionuclide whose decay (daughter) product,  $\text{Tc}^{99\text{m}}$ , is the isotope of choice used in SPECT diagnostic imaging. In the United States, approximately 50,000 patients are imaged daily using SPECT;  $\text{Tc}^{99\text{m}}$  is the most widely used radioisotope in diagnostic nuclear medicine, and it is estimated that more than 80% of the nearly 25 million diagnostic nuclear medicine studies conducted annually are performed with this single isotope (Appendix A).<sup>3</sup>

Although  $\text{Tc}^{99\text{m}}$  yields high-quality, efficacious images using a lower radiation dose compared with other radionuclides, it has a short half-life and gamma energy profile. Thus,  $\text{Tc}^{99\text{m}}$  doses must be continuously produced by eluting  $\text{Mo}^{99}$  generators.  $\text{Mo}^{99}/\text{Tc}^{99\text{m}}$  generators use a challenging manufacturing process that includes the irradiation of uranium-235 ( $\text{U}^{235}$ ) with neutrons, resulting in the heavier nucleus splitting into lighter atoms by fission; one byproduct includes  $\text{Mo}^{99}$  (Figure 1). The  $\text{Mo}^{99}$  is transported to a processor where it is separated and purified, and from there it is sent in bulk to manufacturers that dispense it into generators and ship it to nuclear pharmacies for “milking.” (In the literature, the generators are often referred to as “cows,” because the daughter isotope  $\text{Tc}^{99\text{m}}$  is “milked” from its parent  $\text{Mo}^{99}$ .<sup>4</sup>) Because there are several time-sensitive steps that must be followed to label  $\text{Tc}^{99\text{m}}$  for patient use, an interruption or delay at any point in the supply chain could have a detrimental impact on patient care. For example, if  $\text{Mo}^{99}$  becomes unavailable, other diagnostic procedures may have to be used instead; these might not provide the most accurate physiologic results, could contribute to a higher patient radiation dose, or may require a more expensive test to be performed.<sup>5</sup>

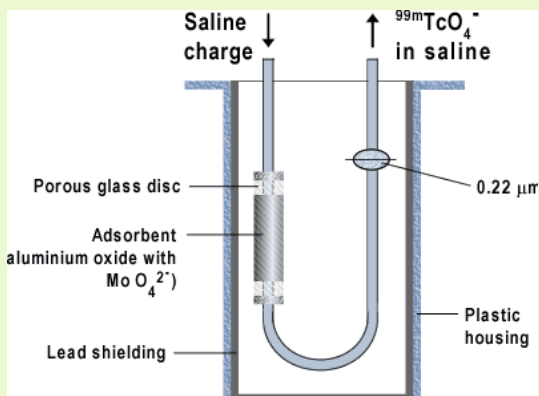
Figure 1. An induced fission reaction



A neutron is absorbed by a  $U^{235}$  nucleus, briefly turning it into an excited uranium-236 ( $U^{236}$ ) nucleus, with the excitation energy provided by the kinetic energy of the neutron plus the forces that bind the neutron. The resulting unstable  $U^{236}$ , in turn, splits into fast-moving lighter elements (fission products) and the process releases 3 free neutrons, leading to a chain reaction.

Currently, more than 95% of the  $Mo^{99}$  required for  $Tc^{99m}$  generators is produced by the fission of  $U^{235}$  targets ( $U^{235}$  fission yields 6.1%  $Mo^{99}$ ) in nuclear research reactors. The irradiated targets are then processed and the resulting purified  $Mo^{99}$  solution is subsequently distributed for use in the production of  $Mo^{99}/Tc^{99m}$  generators.

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Reprinted with permission from IAEA Human HealthCampus Radiopharmacy.<sup>7</sup>

In 1958, the first  $Mo^{99}/Tc^{99m}$  radionuclide generator using  $Mo^{99}$  was produced by Brookhaven National Laboratory.

The generator consisted of a support column containing  $Mo^{99}$  that was eluted with a solution to separate  $Tc^{99m}$ , the daughter product, for diagnostic imaging. The extracted  $Tc^{99m}$  was labeled to chemical ligands (cold reagent kits) for diagnostic nuclear imaging.

In 2009, unexpected research reactor shutdowns reduced the world's supply of  $Mo^{99}$  to less than one-half of the world demand<sup>8</sup> and negatively affected the entire diagnostic imaging community. The shortage raised serious questions about an aging research reactor fleet (Table 1) and the dependence on international reactors to produce  $Mo^{99}$ . In addition, the growing threat of international terrorist groups attempting to acquire HEU to build nuclear or "dirty" bombs was identified as a security risk. In response, the United States and the international community took several steps to ensure a long-term reliable  $Mo^{99}$  supply, including transitioning the industry to an FCR economic model, while also working to eliminate the use of HEU in  $Mo^{99}$  production.



There are other factors that contribute to the impact of domestic consumption and cost of Mo<sup>99</sup> generators, which are then translated to the patient-ready Tc<sup>99m</sup> radiopharmaceuticals.

First, the nuclear reactor-produced medical isotopes consumed in the United States are 100% reliant—now and in the foreseeable future—on production of the fission radionuclides in foreign reactors and processors, some of which continue to be partially subsidized by their host governments. Second, a large majority of foreign reactors are approaching their operational lifespan of 30 to 50 years (some, in fact, have recently closed). The aging reactor fleet faces ongoing challenges, such as routine maintenance that takes a unit offline, unscheduled shutdowns, or delays in returning to service. The third issue, and the most concerning to the US government, is that some foreign reactors continue to produce Mo<sup>99</sup> from HEU, which can be repurposed to produce nuclear bombs.

A "dirty bomb" is one type of a radiological dispersal device (RDD) that combines conventional explosives, such as dynamite, with radioactive material. Most RDDs would not release enough radiation to kill people or cause severe illness—the conventional explosive itself would probably be more harmful to individuals than the radioactive material. However, HEU can also be used to create a nuclear bomb; thus, depending on the situation, the HEU security risk could range from an RDD explosion that would just create fear and panic to the threat of a massive nuclear bomb attack. The removal of HEU in the production of medical isotopes will help to mitigate the potential threat of a nuclear weapon in the hands of a terrorist.<sup>9</sup>

**Table 1. Foreign medical reactors' age, fuel rod type, and target type<sup>a</sup>**

Nuclear reactor/country	Age/life/fuel type (comments)	Medical isotope production targetry: HEU/LEU (comments)
Br-2 <sup>a</sup> /Belgium	1961/2026/HEU <sup>10,b</sup> (Br-2 plans to convert to LEU fuel in 2026 and is expected to seek license extension and continue operation to an unknown date.)	HEU <sup>17</sup> (Institut de Radioelement; planned conversion to LEU targets is 2018.)
HFR/Netherlands	1961/2024/LEU <sup>11</sup> (License expires in 2024, but it may continue to operate; life expectancy is unknown.)	LEU in 2017/2018 <sup>18</sup> (Curium; planned conversion in 2017.)
OPAL/Australia	2007/2055/LEU <sup>12</sup>	LEU <sup>18</sup>
MARIA/Poland	1974/2030/LEU <sup>13</sup> (License expires in 2030, but will likely continue operations.)	LEU <sup>19</sup> (MARIA targets are HEU; a number of processing companies use them for irradiation.)
NRU/Canada	1957/2016/LEU <sup>14</sup> (closed Oct 2016)	HEU <sup>13</sup> (closed Oct 2016)
SAFARI-1/South Africa	1965/2020s/LEU <sup>15</sup> (License expires in 2030 but could be extended.)	LEU <sup>15</sup> (Nuclear Technology Products Radioisotopes; planned conversion in 2017.)
LVR-15/Czech Republic	1989/2018/LEU <sup>16</sup> (License expires in 2028 but will likely be extended.)	LEU <sup>16</sup> (LVR targets are HEU; a number of processing companies use them for irradiation.)

<sup>a</sup> Data adapted from National Research Council, Khlopkov et al, and National Academies of Sciences, Engineering, and Medicine.<sup>20-22</sup>

<sup>b</sup> 2016 reactor matrix replaced.

Abbreviations: HEU, highly-enriched uranium; HFR, High Flux Reactor; LEU, low-enriched uranium; NRU, National Research Universal; OPAL, Open Pool Australian Lightwater.

## The High-level Group on the Security of Supply of Medical Radioisotopes

In April 2009, the Nuclear Energy Agency (NEA), whose membership is currently composed of 31 countries in Europe, North America, and the Asia-Pacific region,<sup>23</sup> established the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) to investigate and understand the key issues in medical isotope production with HEU, examine the shortage created by the unexpected and extended shutdowns of 2 major reactors, and recommend policies and/or other tactical actions to help ensure a reliable global supply of Mo<sup>99</sup> and Tc<sup>99m</sup>. The HLG-MR also investigates other relevant issues surrounding the radionuclide supply chain and anticipates future issues. To achieve these objectives, the HLG-MR investigated the Mo<sup>99</sup>/Tc<sup>99m</sup> supply chain and identified key areas of vulnerability, issues that needed to be addressed, and mechanisms that could be used to address those problems. The HLG-MR agreed on a 6-point policy approach (Appendix B) to ensure the availability of a long-term economically sustainable reliable supply while being cognizant of the fact that governments are responsible for establishing an economic environment conducive to investment and regulation related to the Mo<sup>99</sup>/Tc<sup>99m</sup> supply chain.<sup>24</sup> The primary mission of these principles is to alleviate the chances of another worldwide Mo<sup>99</sup> shortage by

outlining the steps needed to ensure the economically sustainable production of medical isotopes used in nuclear medicine procedures. An emergency response protocol was then developed using the HLG-MR's principles; when the BR-2 reactor in Belgium had an unexpected shutdown in May and June of 2017, the protocol was implemented to alleviate a potential shortage issue through use of the ORC.

## Domestic involvement

In response to the 2009 shortage and as part of its mission to minimize the use of HEU in civilian applications, the US Department of Energy's (DOE's) National Nuclear Security Administration (NNSA) established an Mo<sup>99</sup> program. Since that time the program, which is overseen by the NNSA's Office of Material Management and Minimization (M<sup>3</sup>), has worked to eliminate the use of HEU in Mo<sup>99</sup> production worldwide while ensuring a reliable Mo<sup>99</sup> supply for patient use. This is accomplished by supporting major global Mo<sup>99</sup> producers in converting their production processes from HEU to LEU, and by supporting the establishment of commercial, non-HEU-based Mo<sup>99</sup> production in the United States.

Since 2009, the DOE/NNSA has partnered with US commercial entities to accelerate the development of a diverse set of non-HEU technologies to produce Mo<sup>99</sup> in the United States (Table 2). The DOE/NNSA's current commercial partners include:

- NorthStar Medical Radioisotopes,<sup>25</sup> which is developing both neutron capture and accelerator-based technologies. Both will use NorthStar's RadioGenix™ Tc<sup>99m</sup> Generating System.
- SHINE Medical Technologies,<sup>25</sup> which is developing an accelerator technology with LEU fission.
- General Atomics (GA), which in collaboration with the University of Missouri Research Reactor (MURR) and Nordion, is developing an LEU fission-based selective gaseous extraction technology.<sup>26</sup>

NNSA's Mo<sup>99</sup> program supports these commercial partners via cooperative agreements that are implemented under a 50/50 cost-share arrangement, with an NNSA cost share of up to \$25 million, consistent with AMIPA and Section 988 of the Energy Policy Act of 2005. The DOE/NNSA also shares technical expertise, on a nonproprietary basis, with existing and potential Mo<sup>99</sup> producers to help them develop new non-HEU-based Mo<sup>99</sup> production technologies.

Other commercial entities in the United States are also working to develop the ability to produce non-HEU-based Mo<sup>99</sup>. Although these efforts are not related to the DOE/NNSA's Mo<sup>99</sup> program, they are complementary to domestic and international efforts to ensure a reliable supply of Mo<sup>99</sup> produced without HEU; if desired, they may use NNSA's Uranium Lease and Take-Back (ULTB) program, which was created as part of AMIPA.

**Table 2. Current domestic Mo<sup>99</sup> program partners<sup>a</sup>**

	Neutron capture technology	Accelerator technology	Accelerator with LEU fission technology	LEU target technology
Company	NorthStar Medical Radioisotopes	NorthStar Medical Radioisotopes	Morgridge Institute for Research and SHINE Technologies	General Atomics/MURR/Nordion
Awarded	\$25 million	\$25 million	\$25 million	\$25 million
Funding received to date	\$25 million	\$11 million	\$17 million	\$13 million
Anticipated market entry <sup>b</sup>	Sep 2017	Jul 2019	Jun 2020	Sep 2019

<sup>a</sup> Reprinted with permission from the National Nuclear Security Administration.<sup>25</sup>

<sup>b</sup> Date provided by the supplier and defined as beginning production (approximately 100 6-day curies [Ci] per week and increasing to 3000 6-day Ci per week).

Abbreviations: FDA, Food and Drug Administration; LEU, low-enriched uranium; NRC, Nuclear Regulatory Commission; SGE, selective gaseous exchange.

## American Medical Isotope Production Act

In 2013, AMIPA was signed into law and incorporated into the National Defense Authorization Act (NDAA) for fiscal year 2013. AMIPA provides legislative authorization for NNSA’s Mo<sup>99</sup> program and directs the Secretary of Energy to establish a technology-neutral program to support and accelerate domestic Mo<sup>99</sup> production; use the National Science Advisory Committee (NSAC) to conduct annual reviews of M<sup>3</sup>; report on progress made toward improving the reliability of the domestic medical isotope supply; make recommendations to improve effectiveness; and establish a ULTB program to support domestic Mo<sup>99</sup> production.

## Uranium Lease and Take-Back program

Consistent with AMIPA, the DOE/NNSA established a ULTB program in January 2016. Under this program, the DOE/NNSA makes LEU available—through lease contracts—for the irradiation and production of Mo<sup>99</sup> for medical uses. The DOE/NNSA oversees the final disposition of spent nuclear fuel created by the irradiation, processing, or purification of the leased uranium, and will accept responsibility for the final disposition of radioactive waste created by the irradiation, processing, or purification of uranium leased when the Secretary of Energy determines the producer does not have access to a disposal path. Per AMIPA, producers that choose to use the ULTB program must reimburse the DOE/NNSA for the cost of the LEU consumed as well as the cost for final disposition of spent nuclear fuel or radioactive waste. Thus, consistent with OECD policy principles and the global consensus that the Mo<sup>99</sup> industry must move to an FCR economic model, the ULTB program might add another potential cost increase to domestic Mo<sup>99</sup> production.<sup>27</sup> Operating under the FCR model, a company that is part of the

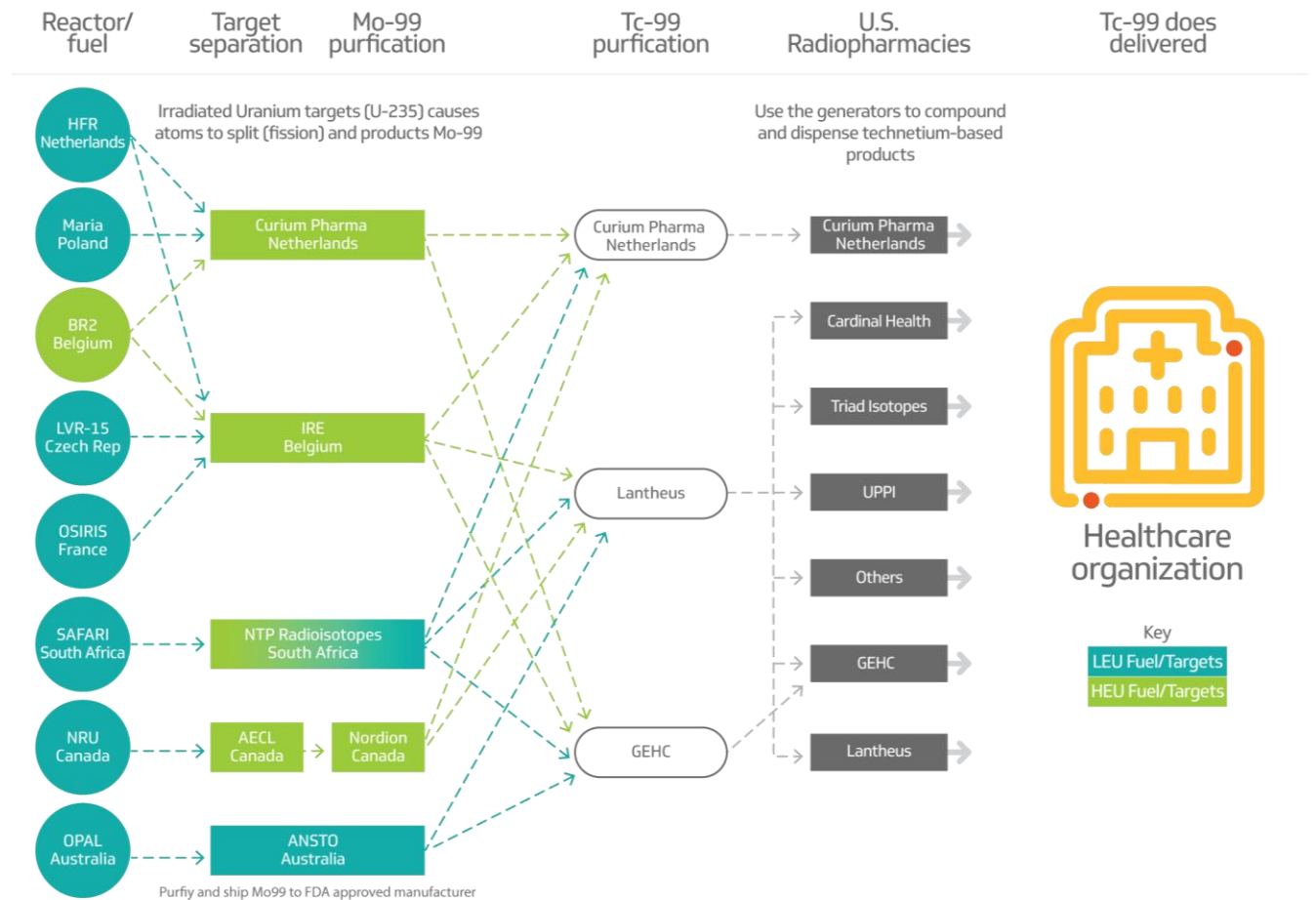
ULTB program will pass the costs of production, the LEU lease, and waste on to the nuclear imaging market space.<sup>27</sup>

## Bringing Tc<sup>99m</sup> radiopharmaceuticals to the market

Bringing Tc<sup>99m</sup> radiopharmaceuticals to the market currently requires several steps (Figure 2):

- Mo<sup>99</sup> must be manufactured in medical until non-fission-based technologies are developed and deployed to market.
- The HEU–LEU targets are processed to recover and purify the Mo<sup>99</sup>.
- The purified medical isotope is placed into a column supported in a shielded generator unit.
- The generator units are received by nuclear pharmacies or nuclear medicine departments, which elute the Mo<sup>99</sup> column and combine the resultant daughter product, Tc<sup>99m</sup>, with the cold kit or ligand.
- The individual Tc<sup>99m</sup> radiopharmaceuticals are calibrated and dispensed to the imaging department for patient use.

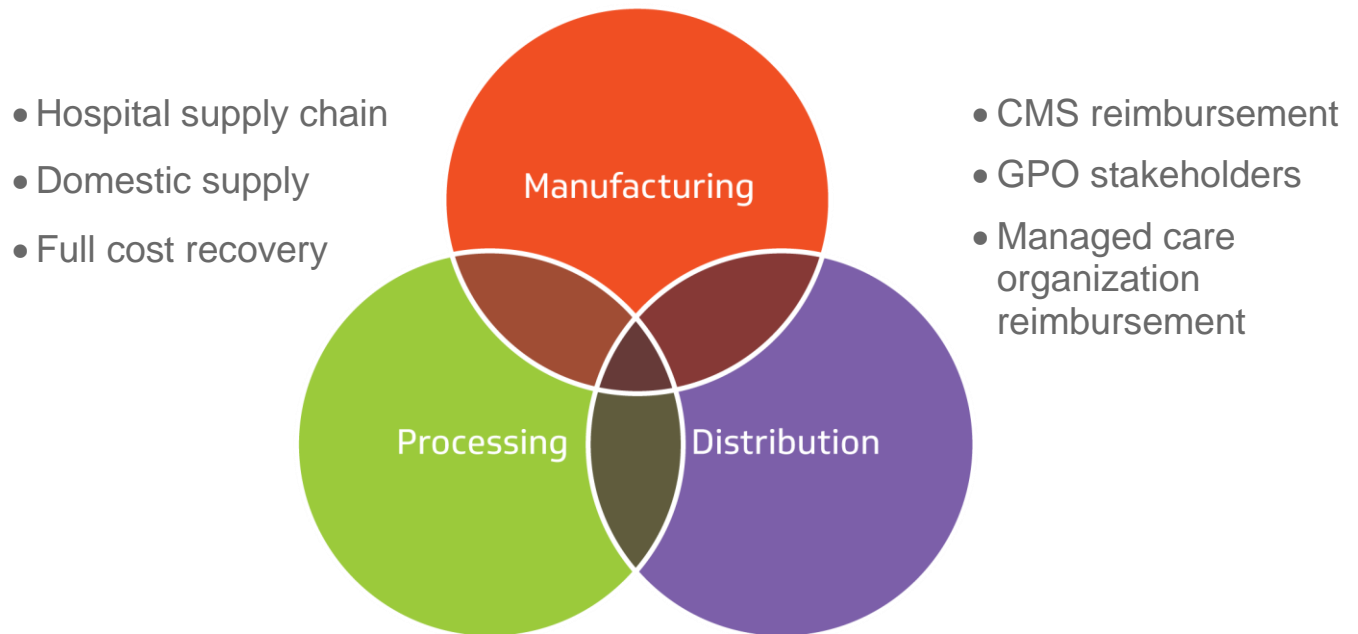
Figure 2. Current US Mo<sup>99</sup> supply matrix<sup>a</sup>



<sup>a</sup>Reprinted with permission from the National Nuclear Security Administration.<sup>28</sup>

The manufacturing/processing/distribution model has become more complicated, and transitioning to the production of non-HEU medical isotopes involves many diverse stakeholders (Figure 3). For example, the FDA and NRC are critical in the approval process of domestic Mo<sup>99</sup> production and the validation of new foreign LEU Mo<sup>99</sup> sources. Since the domestic manufacture of Mo<sup>99</sup>/Tc<sup>99m</sup> will be fully engaged in the FCR, ORC, and ULTB recovery processes, reimbursement will be instrumental in accommodating the nontraditional increase in Mo<sup>99</sup> acquisition costs.

**Figure 3. Successfully transitioning to an HEU-free medical isotope supply involves many stakeholders<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.

Abbreviations: CMS, Centers for Medicare & Medicaid Services; GPO, group purchasing organization; HEU, highly-enriched uranium.

### The FDA/Center for Drug Evaluation and Research (CDER) radiopharmaceutical approval requirements

To approve a new non-HEU Mo<sup>99</sup> generator or a non-HEU production method, such as cyclotron-produced Tc<sup>99m</sup>, the FDA/CDER provides specific advice on the FDA regulatory pathway to approval.

The FDA/CDER requires:

- A drug master file (DMF) on the production method, which is used during the approval review
- An new drug application (NDA) that identifies sources of Mo<sup>99</sup>
  - Considers uses in human engineering, microbiology, and postmarketing surveillance
- A manufacturing site inspection prior to approval

## Nuclear Regulatory Commission requirements

To obtain NRC licensing for a new non-HEU  $\text{Mo}^{99}$  generator or a non-HEU production method, such as cyclotron produced  $\text{Tc}^{99\text{m}}$ , the licensee must satisfy specific requirements:

- 10 CFR Part 50: domestic licensing of production and utilization facilities
  - Target irradiation
  - Fission product separation
- 10 CFR Part 70: domestic licensing of special nuclear material or 10 CFR 30: domestic licensing of byproduct material
- Environmental impact study
- Preliminary and final safety analysis
- Two-part construction permit
- Operating license application

Contributing to the future nontraditional cost increase of reactor-produced medical isotopes are FCR and ORC. These factors' importance in terms of economically sustainable supply became evident when the nuclear imaging market faced a severe worldwide shortage of  $\text{Mo}^{99}$ , which began in May 2009 with the unexpected outage of the National Research Universal (NRU) reactor in Chalk River, Canada. It is estimated that the NRU supplied 40%<sup>12</sup> of the world's demand for  $\text{Mo}^{99}$  and the unanticipated shutdown that occurred was primarily due to a loss of power as well as reactor vessel failure when an attempt was made to restart the system. Upon restart, a release of radiation in the facility led to the reactor being taken off-line completely. The closure remained in effect until August 2010, a total of 15 months. In early 2010, the High Flux Reactor (HFR) in Petten, Netherlands went off-line unexpectedly due to a leak in a coolant water pipe located beneath the reactor vessel. The HFR provided 30%<sup>12</sup> of the US demand for  $\text{Mo}^{99}$ , and was unable to produce medical isotopes for almost a year.

These sudden closures and the subsequent worldwide shortage, when analyzed for root causes, determined that  $\text{Mo}^{99}$  production could only become predictable, reliable, and sustainable by removing foreign government subsidies of research reactors (i.e., obtaining FCR by turning manufacturing and processing facilities into cost centers, and pushing out the true cost of  $\text{Mo}^{99}$  and other reactor-produced medical isotopes, such as Xenon-133 [ $\text{Xe}^{133}$ ], Iodine-131 [ $\text{I}^{131}$ ], Yttrium-90 [ $\text{Y}^{90}$ ], and Lutetium-177 [ $\text{Lu}^{177}$ ], to the market). In addition, to provide ORC, extra target spaces were reserved in the research reactors; these would then be readily available to irradiate the additional targets needed to produce medical isotopes in the event of supply shortfall.

## Current supply chain of non-HEU technologies

While the United States continues on a path toward domestic solutions for  $\text{Mo}^{99}$  production, some LEU providers currently exist in the market. For example, both Curium Pharma and Lantheus Medical Imaging use irradiated products from various international processors as of June 2017. Lantheus plans to convert



to LEU manufacturing late in 2017, after its Institute for Radioelements (IRE) processor is approved by the FDA, while Curium Pharma announced its intention to complete LEU conversion in late 2017 or early 2018.<sup>29</sup>

In early 2012, at the request of the DOE, the Centers for Medicare & Medicaid Services (CMS) began assisting hospitals with their transition to non-HEU medical isotopes. CMS provided an added-on reimbursement code (Q9969) for the Hospital Outpatient Prospective Payment System (HOPPS) setting to offset the added cost for LEU doses with > 95% LEU-derived Tc<sup>99m</sup>. The Veterans Administration also recognized the need to eliminate HEU from medical isotopes and issued a memorandum for the preferential procurement of non-HEU medical isotopes in 2013, with a reissuance in March 2016.<sup>22</sup>

Group purchasing organizations (GPOs) and the health care supply chain need to understand both the causes and the increased cost complexities of the transition to non-HEU medical isotopes, as well as the need to support the prevention of proliferation of HEU.

## Supporting the transition to non-HEU technologies

United Pharmacy Partners, LLC (UPPI), established in 1998, is a cooperative of 77 low-energy nuclear pharmacies and 11 cyclotron member nuclear pharmacies that represents independently owned and university-based facilities. UPPI has played a significant role in implementing non-HEU medical isotope distribution into the diagnostic nuclear imaging segment. In 2013, UPPI, in partnership with Vizient, recognized that the pipeline of LEU Mo<sup>99</sup> generators was limited and created the “UPPI LEU Walk” campaign. The program began when 3 independently-owned nuclear pharmacies decided—during a time in which demand for LEU Tc<sup>99m</sup> unit doses was virtually nonexistent—to be innovators of the new non-HEU radiopharmaceutical by investing revenues and establishing a reliable LEU Mo<sup>99</sup> supply chain. The number of innovators has grown, and currently 39 locations across the country are early adopters of non-HEU technology (Figure 4).

When UPPI members began using LEU Mo<sup>99</sup>, there were few early adopters in the medical imaging community that used non-HEU medical isotopes in their patients. UPPI responded by developing new users at each of its locations. This growth continues, and has evolved into a collaboration between imaging centers, where information regarding topics such as product availability and additional reimbursement opportunities can be exchanged.

In response to some of the reimbursement challenges, UPPI has also initiated a private-payer C-suite reimbursement initiative, which continues to enhance the commercial payer segment by providing better reimbursement coverage. However, the intent is to endorse and continue to lobby for the continuation of the currently reimbursed Q9969 LEU code for all covered lives, even after the LEU/non-HEU pipeline conversion.

Figure 4. UPPI “LEU Walk” facilities<sup>a</sup>



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
 Abbreviations: DOD, US Department of Defense; FBOP, Federal Bureau of Prisons;  
 LEU, low-enriched uranium; UPPI, United Pharmacy Partners, LLC;  
 VA, Veterans Administration.

### The UPPI/Vizient collaboration

UPPI works closely with Vizient, the largest member-driven health care company in the United States, to transition non-HEU Tc<sup>99m</sup> into the product portfolio for its imaging facilities. Vizient is an active Mo<sup>99</sup> stakeholder, along with the NNSA, NRC, CMS, FDA, global Mo<sup>99</sup> manufacturers, other government agencies, and business entities. Its involvement has expanded to the Organization for Economic Co-operation and Development (OECD) HLG-MR and the White House Office of Science and Technology Policy Mo<sup>99</sup> Stakeholders (OSTP) due to its large US market role in the purchase of non-HEU medical isotopes. Vizient represents the early majority ready to transition to non-HEU medical isotopes; to that end, it works with health care providers and nuclear pharmacies so that members and shareholders are aware of not only the complex and fragile supply chain issues associated with the transition to non-HEU medical isotopes, but also the potential FCR, ORC, and ULTB cost ramifications.<sup>30</sup>

## Cost implications of implementing a domestic supply

The business issues related to establishing a domestic source for non-HEU medical isotope production are intertwined in the complexity of the FDA and/or NRC regulatory reviews needed to bring a new non-HEU  $\text{Mo}^{99}$  generator system, approved under a new drug application (NDA), to the market, or to build non-HEU  $\text{Mo}^{99}$  manufacturing and processing facilities. Cyclotron production of  $\text{Tc}^{99m}$ , another non-HEU alternative, also requires an NDA, as well as FDA approval. (UPPI briefly considered whether several of its cyclotrons could be used to manufacture  $\text{Tc}^{99m}$ , but decided against it due to very expensive cyclotron build-out, targetry development costs, the age of the cyclotrons, submittal costs of an NDA, and the costs associated with making revisions to submittals to obtain approval. It was determined the geographical reach and cost to market were too great to recoup expenses.)

Because of other diverse costs associated with the licensing process, drug or license submittals, environmental impact studies for manufacturing and processing facilities, and the construction outlay, only one new domestic source may be approved in 2017-2018, but others are not expected to enter the market until 2019-2020. By the time this new privately financed source—with its requirement of capital funding, and some projects necessitating as much as \$200 million to become licensed and operational—reaches the marketplace, the cost per milliCurie (mCi) of  $\text{Mo}^{99}/\text{Tc}^{99m}$  will likely rival or surpass the cost of mCi produced by foreign entities employing FCR and ORC recovery.

Whether the source of non-HEU medical isotopes is foreign or domestic, the cost of the  $\text{Mo}^{99}$  product will follow nontraditional price increases. This is due to the substantial investment needed to either convert a research reactor to LEU, or to otherwise manufacture non-HEU  $\text{Mo}^{99}$ , especially when facilities need to be built, commissioned, and receive regulatory approvals. Thus, the marketplace will have to embrace a new economic picture for molecular imaging studies. The acquisition cost of  $\text{Mo}^{99}$  generators and/or unit doses of  $\text{Tc}^{99m}$  radiolabeled products will increase; its effects will be felt in the cost of new oncological treatments and in the development of new pharmaceuticals.

With the investment in new non-HEU technologies; the continued movement toward conversion to LEU targets, which produce around 20% less material than equivalent HEU targets while generating 7 or more times the quantity of waste product; and FCR, ORC, and perhaps ULTB costs, the financial impact to health care providers over the next 3 to 7 years should be substantial. Coupled with a diagnostic imaging reimbursement system that characterizes physician injectable radiopharmaceuticals as “supplies”—determined by a review of invoices for the previous 2 years of contemporaneous studies—the recovery of such cost increases will be difficult. Unfortunately, health care organizations facing significantly higher prices for non-HEU medical isotopes are in need of a fundamental change in radiopharmaceutical reimbursement, such as the average selling price (ASP) model that is currently used for pharmaceutical drugs.

# The global pharmaceutical market: impact and challenges

## Generic/proprietary pharmaceuticals

There has been considerable focus on the extraordinary, nontraditional price hikes related to generic pharmaceuticals, also known in the radiopharmaceutical industry as “cold reagent kits” or “cold kits.” A nontraditional single price increase can range from several hundred to several thousand percent. This trend costs end users hundreds of thousands of dollars, and is unfortunately becoming more commonplace.<sup>31</sup> As a result, the global pharmaceutical industry—and by default, drugs that are considered to be in short supply and those that have been subjected to significant price increases—has faced major scrutiny by Congress over the past 2 years. According to the *Wall Street Journal*, more than 75% of Americans now say their top health concern is the rising price of prescription drugs<sup>32</sup>; its analysis of government data found that expensive medicines are increasingly raising costs for older adults and other beneficiaries of Medicare Part D, despite drugmakers' increasing discounts and federal legislation meant to reduce out-of-pocket costs. In 2015, the median out-of-pocket cost for a drug purchased through Part D was \$117, up nearly one-half from \$79 in 2011 (in inflation-adjusted dollars).<sup>33</sup>

## Drug shortages

One main factor driving pharmaceutical price increases is drug shortages. According to the FDA, one of the most common reasons drug shortages occur is due to quality/manufacturing issues with the final product.<sup>34</sup> However, there are several other reasons that pharmaceutical companies experience drug shortages, including:

- Production delays.
- Delays experienced in the delivery of raw materials, active pharmaceutical ingredients (API), or qualifying new sources of API.
- Contract manufacturing and technology transfer.
- Discontinuations within the product portfolio or changing pharmaceutical life cycle management strategies. The FDA cannot compel or require a firm to continue to manufacture a drug it wants to discontinue, especially if newer, more profitable drugs can be produced instead.<sup>35</sup>

Fewer firms are making older/generic sterile injectable drugs, due to the prevalence of less expensive imaging modalities that can provide information more quickly as well as a historical margin reduction for some of these types of drugs. As a result, there are a limited number of production lines that can meet demand. The production dilemma is compounded when the API suppliers—which the pharmaceutical firms rely on—can only produce a limited amount of drugs due to their manufacturing capacity (the number of vials that can be produced in a production run) and delays associated with the delivery of finished raw materials. A small number of manufacturers, limited production capacity, long lead times on raw materials acceptable for Current Good Manufacturing Practices (cGMPs), and the complexity of the injectable drug manufacturing process all result in supply vulnerability. The expensive barriers to entry of generics have led to shortages and/or extraordinary price hikes. When one company experiences production problems or discontinues a pharmaceutical for any of the above-mentioned reasons, it is

difficult for other firms manufacturing a similar drug to quickly increase production and thus prevent a drug shortage.<sup>35</sup>

These problems are compounded when multiple manufacturers exit the market. If only one manufacturer remains and no other manufacturer enters with a generic product, then that manufacturer has little to no competition, which leads to unusual price escalation. Thus, the general pharmaceutical industry has seen price increases of anywhere from 500% to 5000%<sup>36</sup>; these types of increase continue to occur rapidly when there are no replacements or competition exists with the same type or class of drug.

## Reentering the market

It can be very costly for manufacturers to reenter the market. Some manufacturers reenter to ensure sustainability of a supply for products that already existed, but it is difficult to relaunch when manufacturing lines and processes have already been dismantled. It requires a significant investment to not only begin providing and supporting a reintroduced drug again, but also to develop and organize a sales, marketing, and operations team dedicated to the sourcing of new/reintroduced product lines. Such investments translate to increasing costs to the end user.

In addition, it can be difficult for a manufacturer to “dust off” an abbreviated new drug application (ANDA) and reenter the market when prices begin to move upward again. (A registration must be maintained for a discontinued drug; otherwise the FDA requires that an NDA be submitted, as noted in the box on page 14, which is cost prohibitive and causes delays). All the supporting information associated with an ANDA—the reference list drug, drug master file (DMF), supplements, and all protocols—has to be submitted to the FDA for review before it can be approved. Often, the FDA requires manufacturers to submit to rigorous protocols to obtain cGMP certification, which also adds significant time and investment to a discontinued product’s return. The many costs associated with moving a product through the FDA, including operational and technology transfer costs and filing fees, are shown in Table 3.

### Approved drug products

The publication *Approved Drug Products With Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, identifies drug products approved on the basis of their safety and effectiveness by the FDA.<sup>37</sup> Generally, an approved drug product appears in the “Prescription Drug Product List” or the “Over-the-Counter Drug Product List”; these sections are commonly referred to as the *active sections*. When an approved drug product is not marketed, the drug product is moved to the “Discontinued Drug Product List,” which is commonly referred to as the *discontinued section*. A listed drug is usually moved to the discontinued section when the applicant notifies the FDA that it is withdrawing the listed drug from sale or the FDA determines that the listed drug has been withdrawn from sale. A listed drug also may be moved to the discontinued section if the applicant requests that approval of the NDA or ANDA be withdrawn because the drug product is no longer being marketed.<sup>38</sup>

**Table 3. Fee rates for FY 2017<sup>a</sup>**

Fee category	Fee rates
NDA	\$2,038,100
ANDA	\$70,480
PAS to an ANDA	\$35,240
DMF	\$51,140
Facilities (inspection and approval)	Cost not specified
API—domestic	\$44,234
API—foreign	\$59,234
FDF—domestic	\$258,646
FDF—foreign	\$273,646

<sup>a</sup> Data from the Food and Drug Administration.<sup>39</sup>

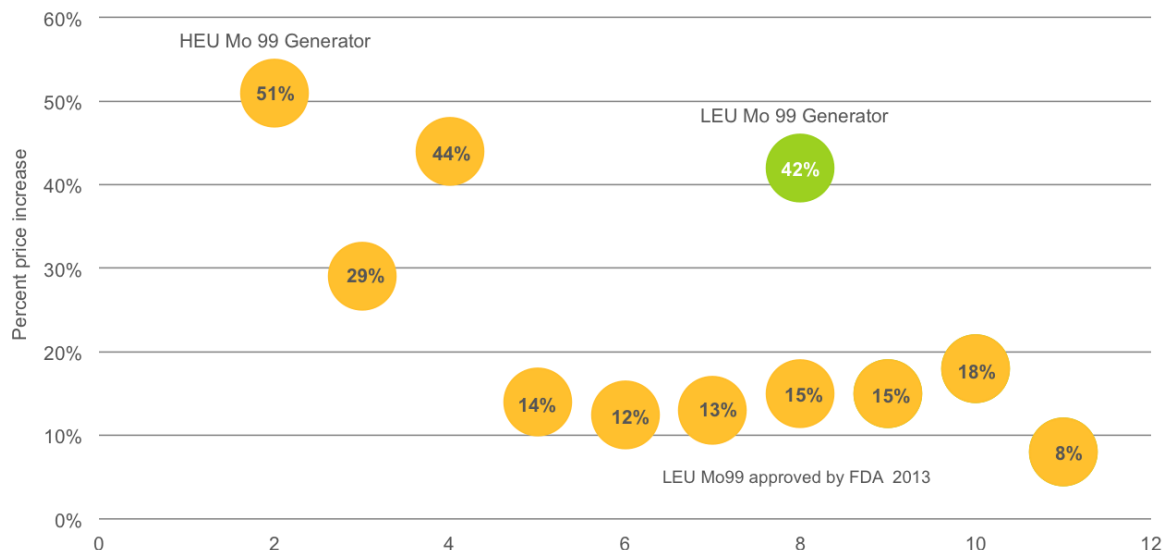
Abbreviations: ANDA, abbreviated new drug application; API, active pharmaceutical ingredient; DMF, drug master file; FDF, finished dosage form; FY, fiscal year; NDA, new drug application; PAS, prior approval supplement.

## Radiopharmaceuticals

The same production issues described above plague the radiopharmaceutical cold kit manufacturers, whose branded and generic ligands are presently offered in the marketplace. In the past, generic radioligands were available from numerous manufacturers, and the lyophilized kits declined in both cost as well as profitability to the manufacturer and became unsustainable. As a result, a significant number of manufacturers of generically equivalent products exited the market, leaving only proprietary or sole-source manufacturers that could produce the cold kit that is used in combination with Tc<sup>99m</sup> for the final labelled radiopharmaceutical dose.<sup>40</sup>

The radiopharmaceutical industry is not immune to substantial price increases for proprietary, sole-source products. For example, it is no longer uncommon for price increases for sole-source radioligands to range from 200% to as much as 2,000%.<sup>41</sup> FCR, ORC, and UTLB all contribute to nontraditional price increases for Mo<sup>99</sup>; when combined with cold kits, it is expected that extraordinary price increases for these components will continue to occur in the foreseeable future. Figure 5 identifies several significant price increases that have occurred in the radiopharmaceutical market during the last 7 years.

**Figure 5. Mo<sup>99</sup>/Tc<sup>99m</sup> generator, sole-source ligand and reactor/accelerator radiopharmaceutical price increases (2007-2017)<sup>a</sup>**



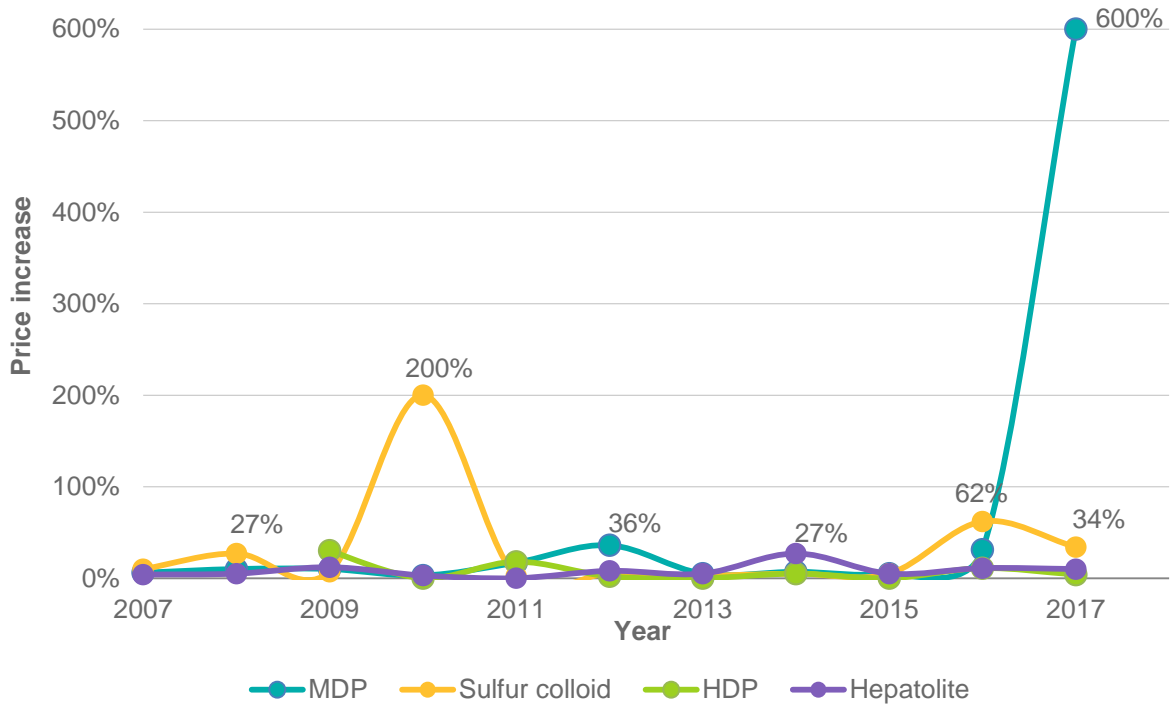
<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.

Abbreviations: FDA, Food and Drug Administration; HEU, highly enriched uranium; LEU, low enriched uranium; Mo<sup>99</sup>, molybdenum-99; Tc<sup>99m</sup>, technetium-<sup>99m</sup>.

As outlined in Figure 5, there have been declining increases in percentages over the years, due to the fact that FCR and ORC costs have not yet been pushed into the market by the supply chain of irradiator, processor, and generator. ULTB costs incurred by domestic producers and pushed out onto the supply chain have not yet occurred either. LEU Mo<sup>99</sup> generators entered the market in 2013 and the pipeline has been building each year. As a result, HEU Mo<sup>99</sup> generators will cease production around 2019 to 2020, as the Mo<sup>99</sup> manufacturers convert to LEU sources for irradiation. With the complete push out of FCR, ORC, ULTB, and special nuclear and other radioactive waste disposal, costs are estimated to increase annually by 25% or more when fully realized.

Figure 6 shows manufacturers' price increases for nuclear oncology cold kits for the years 2007 to 2017. This figure indicates that costs for most nuclear oncology drugs have increased, but one manufacturer's egregious price increases negate some of the other large increases that have impacted several of the other agents; these increases range from 3% to more than 600%.

**Figure 6. Nuclear oncology imaging product price increases (2007-2017)<sup>a</sup>**

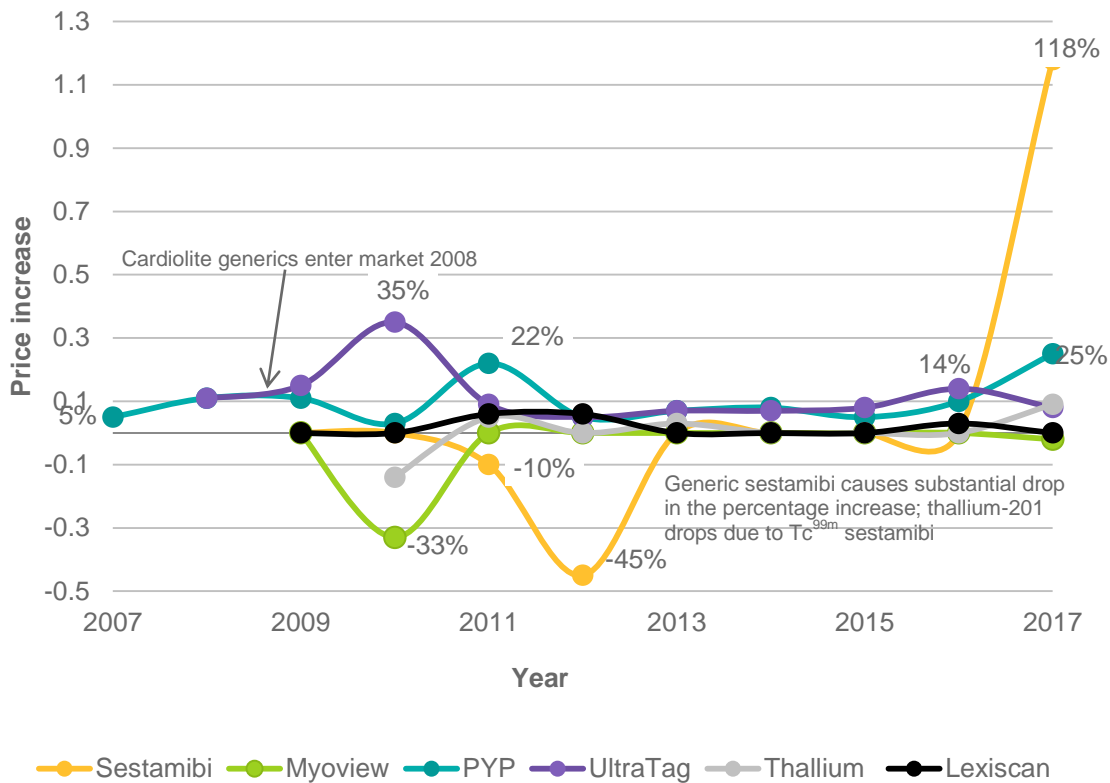


<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
 Abbreviations: HDP, hydroxymethylene diphosphonate; MDP, methylene diphosphonate.



Figure 7 details manufacturers' price increases for nuclear cardiology imaging cold reagent kits and Thallium-201 for the years 2007 to 2017. After 2008, large price declines were seen with the sestamibi and myoview cold reagent kits due to multiple manufacturers entering the Tc<sup>99m</sup> nuclear cardiology market space. Pricing declined for thallium-201 because of sestamibi's market penetration, and in 2017 one manufacturer had a price increase of more than 100% for its generic sestamibi kit.

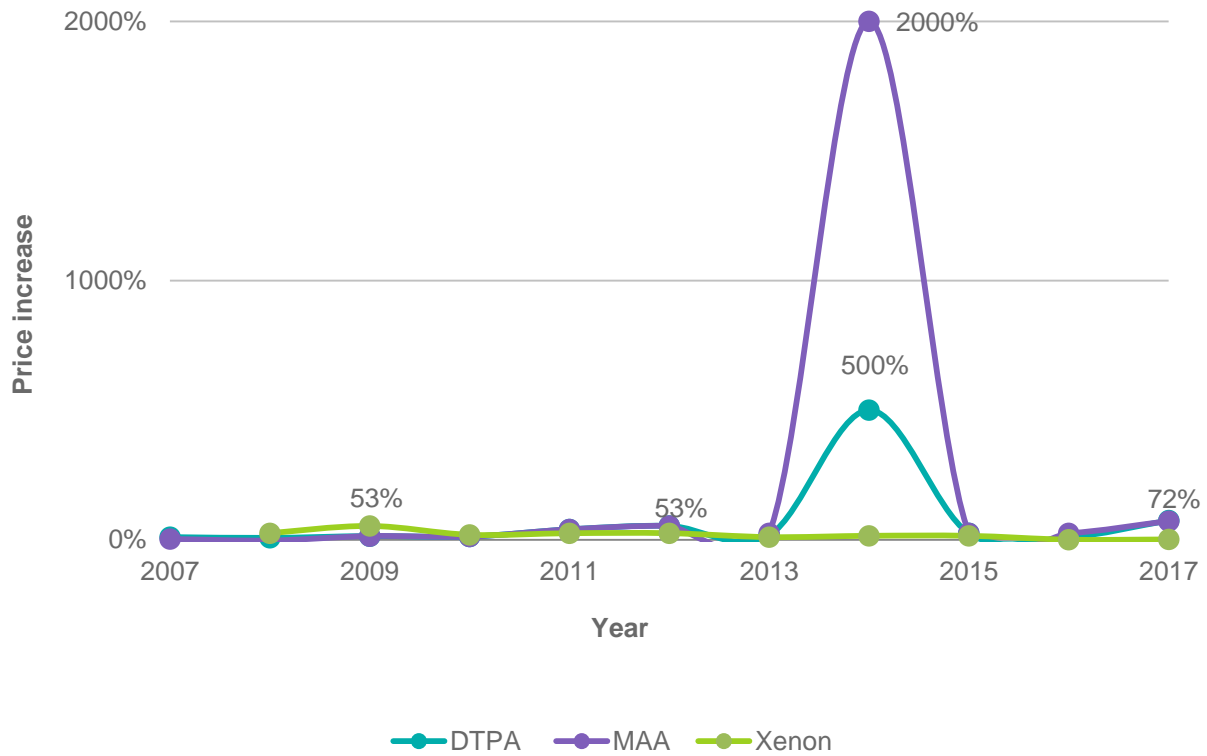
**Figure 7. Nuclear cardiology product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
 Abbreviations: PYP, pyrophosphate; Tc<sup>99m</sup>, technetium-99m.

Figure 8 shows manufacturers' price increases for nuclear pulmonary imaging cold reagent kits and Xenon-133 (all sole-source pulmonary imaging products) for the years 2007 to 2017. Worth noting is that one manufacturer had a 500% increase in 2014 for its diethylene-triamine-pentaacetate (DTPA) (aerosol) cold reagent kit as well as a 2000% increase for its macroaggregated albumin (MAA) cold reagent kit.

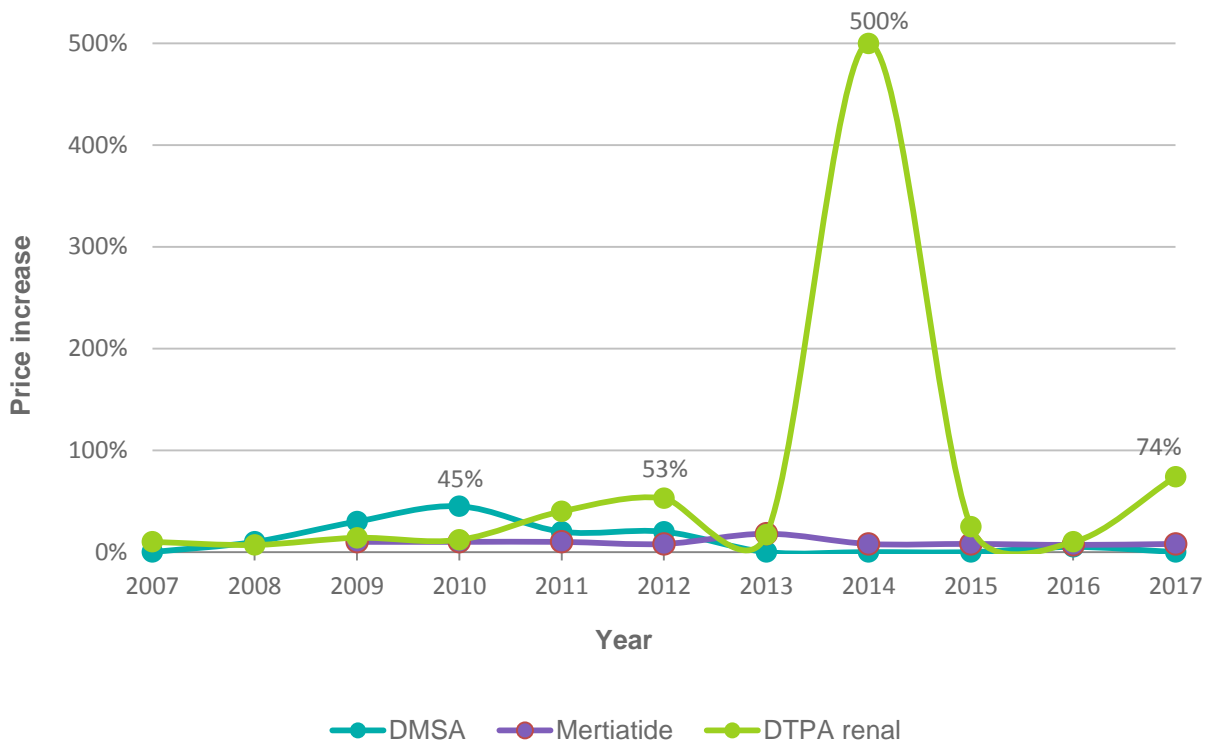
**Figure 8. Nuclear pulmonary imaging product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
 Abbreviations: DTPA, diethylene-triamine-pentaacetate; MAA, macroaggregated albumin.

Figure 9 outlines the manufacturers' price increases for nuclear renal imaging cold reagent kits (all sole-source products) for the years 2007 to 2017. One manufacturer had a 500% increase in 2014 for its DTPA (renal) cold reagent kit and a 74% increase for the same kit in 2017. There has been a shortage of dimercaptosuccinic acid (DMSA) for the past 3 years; an FDA shortage notice issued in June 2017 predicts that it will return to the market in 2020.

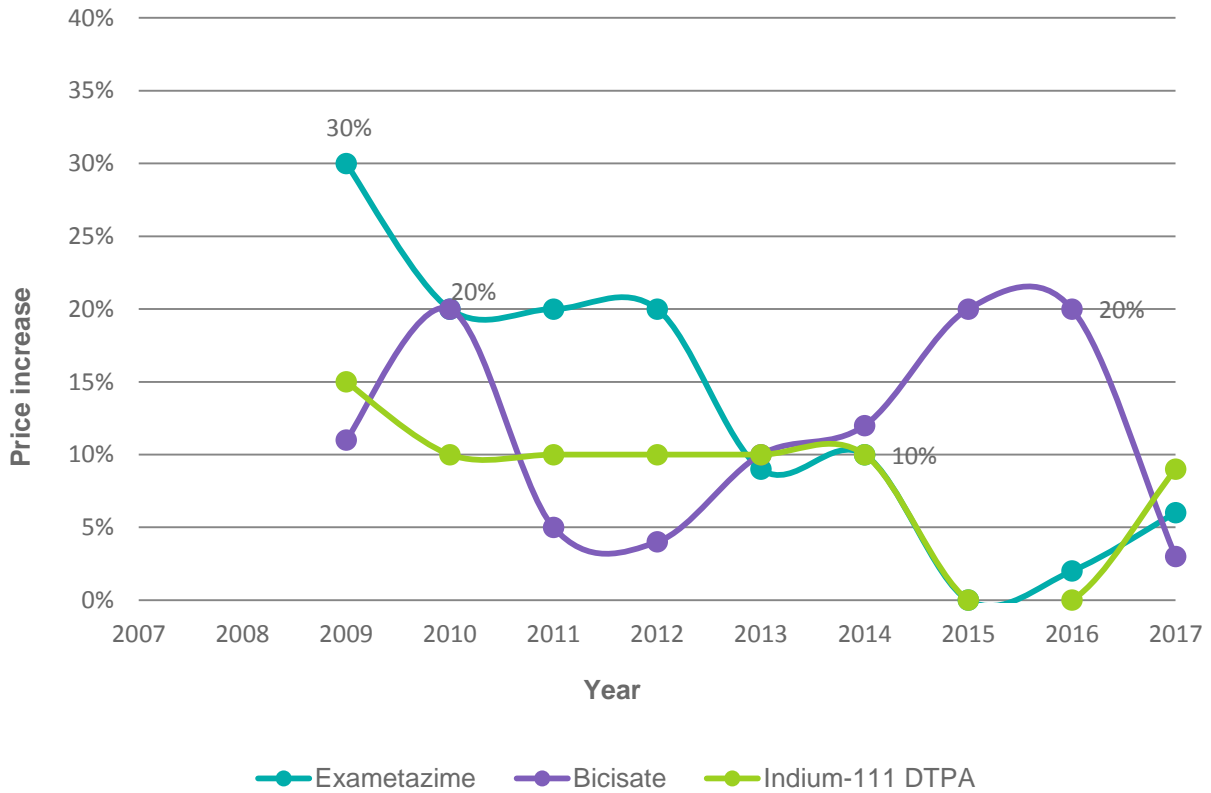
**Figure 9. Nuclear renal imaging product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
 Abbreviations: DMSA, dimercaptosuccinic acid; DTPA, diethylene-triamine-pentaacetate.

Figure 10 details the manufacturers' price increases for nuclear neuroimaging cold reagent kits and Indium-111 DTPA (all sole-source products) for the years 2007 to 2017.

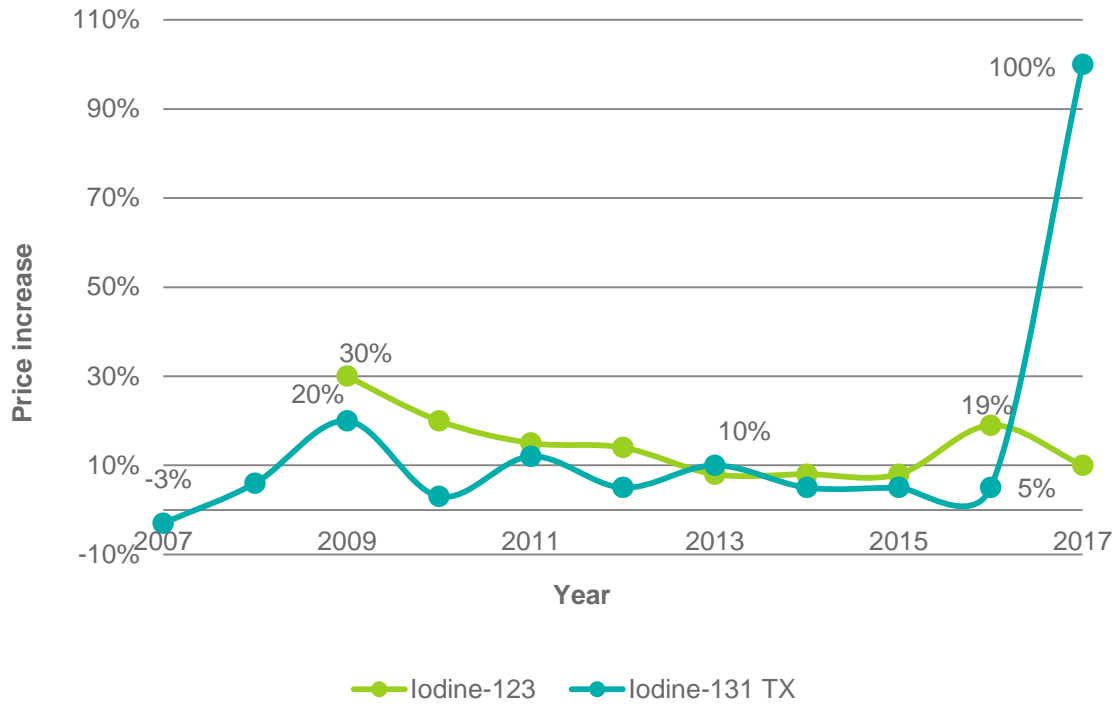
**Figure 10. Nuclear neuroimaging product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
Abbreviation: DTPA, diethylene-triamine-pentaacetate.

Figure 11 shows the manufacturers' price increases for nuclear thyroid imaging capsules and Iodine-131 therapy for the years 2007 to 2017. Similar to the other imaging modalities, one manufacturer had a 100% increase in 2017 for its Iodine-131 therapy.

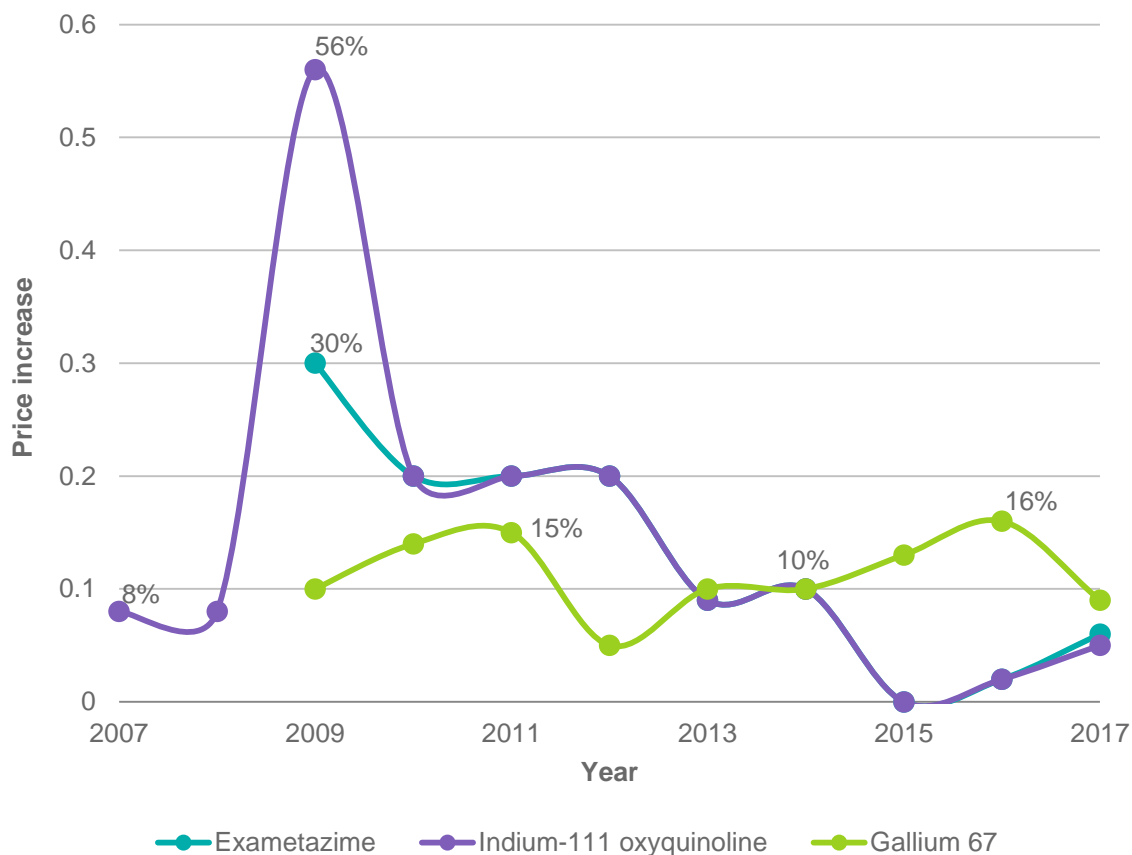
**Figure 11. Nuclear thyroid imaging and thyroid therapy product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.  
Abbreviation: TX, therapy

Figure 12 shows the manufacturers' price increases for nuclear infection imaging for the years 2007 to 2017. Exametazime and Indium-111 oxyquinoline are sole-source products.

**Figure 12. Nuclear infection imaging product price increases (2007-2017)<sup>a</sup>**



<sup>a</sup> Reprinted with permission from United Pharmacy Partners, LLC.

As indicated in Figures 5-12, many cold kits are no longer being manufactured, mainly because of declining revenues. To better outline some of the challenges that this market currently faces, Table 4 lists the cold reagent kit products that were discontinued in the United States from 2002 to 2015. Because a number of manufacturers make the same product (eg, Mallinckrodt Technecoll's sulfur colloid kit), multisource generic kits are slowly evolving into sole-source manufacturer products; in these cases extraordinary and/or nontraditional price increases are typically attributable to sourcing and API acquisition costs.

**Table 4. Discontinued Tc<sup>99m</sup> cold reagent kits (United States, 2002-2015)<sup>a</sup>**

Year	Market name	Compounded radiopharmaceutical	Area imaged	Manufacturer
2015	MDP-Bracco	Tc <sup>99m</sup> medronate	Bone	Bracco
2009	Technetope II Generator	Tc <sup>99m</sup> sodium pertechnetate sterile generator	Preparation of Tc <sup>99m</sup> kits	Bracco
2009	Tesuloid	Tc <sup>99m</sup> sulfur colloid kit	Liver	Bracco
2009	Renotec	Tc <sup>99m</sup> ferpenetate kit	Renal	Bracco
2009	TechneColl	Tc <sup>99m</sup> sulfur colloid kit	Liver	Mallinckrodt
2009	TechneSca Pyrophosphate	Tc <sup>99m</sup> pyrophosphate kit	Bone	Mallinckrodt
2009	Technescan Gluceptate	Tc <sup>99m</sup> gluceptate kit	Brain and renal	Mallinckrodt
2008	Gluceptate Kit	Tc <sup>99m</sup> gluceptate injection	Brain and renal	DraxImage
2008	NeuroSpec	Tc <sup>99m</sup> fanolesomab kit	Infection	Mallinckrodt
2007	Sodium Pertechnetate	Sodium pertechnetate Tc <sup>99m</sup> solution	Thyroid and brain	Mallinckrodt
2007	Glucoscan	Tc <sup>99m</sup> gluceptate kit	Brain and renal	Bristol Meyers Squibb
2007	Lung Aggregate Kit	Tc <sup>99m</sup> macroaggregates of albumin kit	Lung perfusion	GE Healthcare
2007	Technescan HIDA	Tc <sup>99m</sup> HIDA kit for preparation of lidofenin injection	Hepatobiliary	DraxImage
2007	AcuTect	Tc <sup>99m</sup> apticide kit	Deep vein thrombosis	CIS-US
2007	NeoTect	Tc <sup>99m</sup> depreotide kit	Pulmonary lesions—known malignancy	CIS-US
2005	Sodium Pertechnetate	Sodium pertechnetate Tc <sup>99m</sup> solution	Thyroid and brain	Amersham
2005	Tc <sup>99m</sup> MAA Kit	Tc <sup>99m</sup> macroaggregates of albumin kit	Lung perfusion	Amersham
2005	Tc <sup>99m</sup> Medronate Kit	Tc <sup>99m</sup> medronate MDP kit	Bone	Amersham
2003	HEDSPA Multidose Kit	Tc <sup>99m</sup> etidronate kit	Bone	Amersham
2003	HSA Kit	Tc <sup>99m</sup> human serum albumin kit	Blood pool	Amersham
2003	TSC Kit	Tc <sup>99m</sup> sulfur colloid kit	Liver	Amersham
2003	RBC Kit	Tc <sup>99m</sup> red blood cell kit	Blood pool	Cadema
2002	Sulfur Colloid	Tc <sup>99m</sup> sulfur colloid kit	Liver	E. I. DuPont de Nemours
2002	Osteoscan	Tc <sup>99m</sup> etidronate kit	Bone	Mallinckrodt
2002	Pyrophosphate Kit	Tc <sup>99m</sup> pyrophosphate kit	Bone	Syncor International Group

<sup>a</sup> Data derived from Food and Drug Administration discontinued drug reports from 2002 onward.<sup>42</sup> Abbreviations: HIDA, hepatobiliary iminodiacetic acid; MDP, methylene diphosphonate; Tc<sup>99m</sup>, technetium 99m.

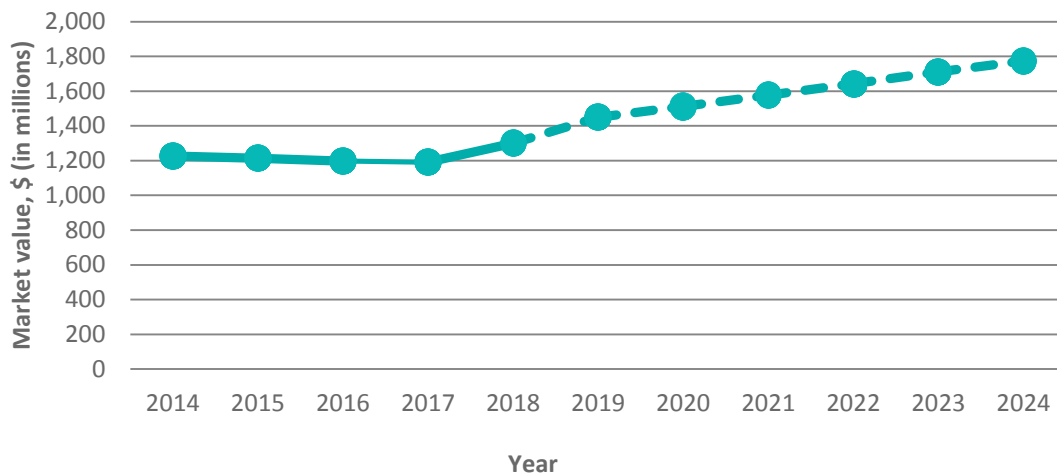
## The effect of price increases on nuclear medicine procedures

When the cost of radiopharmaceuticals increases, there is a corresponding increase in the cost of the procedures that use those radiopharmaceuticals. As a result, the health of the US SPECT imaging

modality has declined,<sup>18</sup> and other, less expensive and sometimes less efficacious imaging modalities are being used in its place.

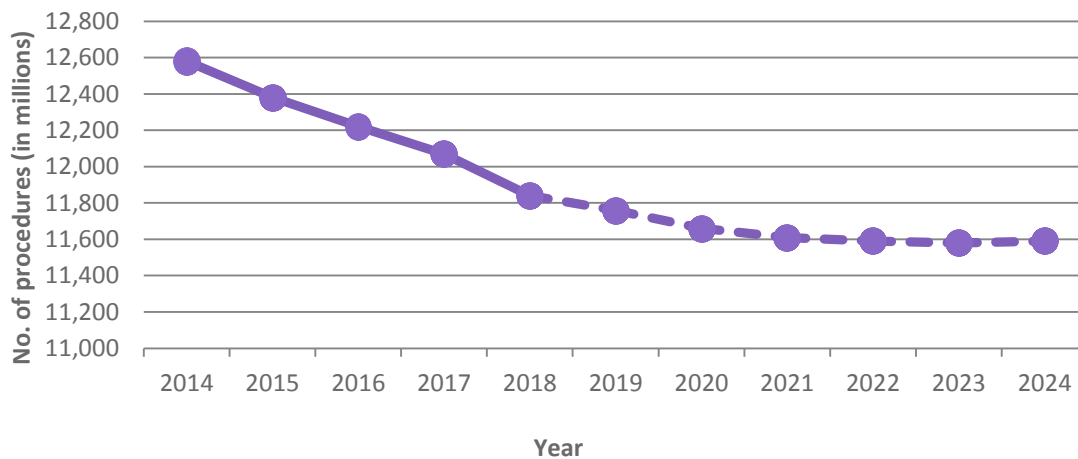
The figures below clearly demonstrate the impact that radiopharmaceutical price increases will have on procedure shifting to other imaging modalities. Figure 13 shows the potential market value increases based on ASP per procedure; it is estimated that costs will increase annually by approximately 4% or more. Figure 14 references the potential reduction in the number of procedures performed, likely due to the corresponding increase in procedure costs or reductions in reimbursement.

**Figure 13. US radiopharmaceutical market volume (USD, 2014-2024)<sup>a</sup>**



<sup>a</sup> Data were derived from Millennium Research Group, Inc. (based on data from Arlington Medical Resources).<sup>43</sup>

**Figure 14. US radiopharmaceutical procedure volume (2014-2024 [predicted])<sup>a</sup>**



<sup>a</sup> Data were derived from Millennium Research Group, Inc. (based on data from Arlington Medical Resources).<sup>43</sup> Numbers reflect rounding.



## Remaining compliant with the USP chapter <797> while anticipating chapter <825>: cost to nuclear pharmacies

### The purpose of the United States Pharmacopeia

The USP is a nonprofit organization whose mission is to improve global health through the issuance of public standards for drug quality, strength, packaging, storage, and other requirements.<sup>46-48</sup> Founded in 1820, the USP has been instrumental in helping protect public health worldwide by disseminating information about medicines, pharmacy, patient care, and health care technologies.<sup>47</sup> To that end, the USP has developed a collaborative relationship with the FDA. USP standards are recognized in federal law and oversight activities; for example, USP standards are cited in the FDA 2013 Drug Quality and Security Act, also known as DQSA. Many states also accept the USP drug standards and have adopted them into law.

### USP <797>

The USP publishes the USP-NF, which is a combination of 2 compendia: the USP and the National Formulary. This book is composed of drug monographs, which not only focus on drug strength, quality, and purity, but also assays, tests, analytical methods, and procedures.<sup>46</sup> USP <797> refers to a chapter in the USP-NF that describes requirements for the preparation of sterile drugs, including radiopharmaceuticals.<sup>46</sup> Entitled Pharmaceutical Compounding—Sterile Preparations, the chapter sets out a framework of practice standards to help ensure that compounded sterile preparations are of the highest quality. When these standards are properly implemented, they help pharmacists, physicians, nurses, technicians, and other health care personnel provide patient preparations that are stable and sterile based on current scientific and best practices as determined by its experts.

Although the June 2008 version of USP <797> is current and enforceable, revisions to this chapter are currently being considered. In 2011, a scientific review of USP <797> began, followed by the selection of an expert panel in 2012. In September 2015, the USP provided notice that its Compounding Expert Committee intended to propose several revisions to the chapter, mainly due to changing practices in preparing labelled doses. The FDA submitted draft guidances in 2016, and suggested that radiopharmaceuticals be discussed in a separate chapter, a recommendation that industry participants are considering. In February 2017, USP roundtable discussions with invited experts from the radiopharmacy industry began to look at strategies and other considerations to gain a broader understanding of current best practices; further discussions occurred in June 2017, with a new FDA listening session regarding further changes and adaptations to the draft guidance on radiopharmacy preparation and compounding. A draft of the recommendations from the roundtable discussions and/or listening sessions will be submitted to the Compounding Expert Committee shortly thereafter.<sup>49</sup>

## USP <825>

USP <797> hasn't always met the needs of radiopharmacies, and in February 2017 the USP announced the formation of a new chapter, USP <825>, to specifically address the radiopharmacy practice:

On February 1, 2017, the USP hosted a roundtable discussion on compounding standards for radiopharmaceuticals. The roundtable was attended by stakeholders from the nuclear medicine community, regulatory agencies, and USP staff. During this day-long session, participants discussed potential approaches to address the challenges associated with this class of products. Based on this discussion, the stakeholders from the nuclear medicine community strongly favored the development of a new general chapter for radiopharmaceutical compounding. After considering these stakeholder inputs, the USP staff and Compounding Expert Committee agreed with the development of a separate chapter to effectively address these needs.

The objective of the new General Chapter <825> *Compounding—Radiopharmaceuticals* is to provide clear and effective USP public standards that meet patient and practitioner needs for compounded sterile radiopharmaceuticals today and in the future. The proposed new general chapter will delineate compounding activities for radiopharmaceuticals and provide standards associated with these activities. When complete, General Chapter <825> will contain standards for this class of products.<sup>50</sup>

## The Food and Drug Administration's involvement in radiopharmacy compliance with USP <797> and <825>

Perhaps surprisingly, the federal courts do not support the unilateral encroachment of the FDA into the practice of pharmacy.<sup>51</sup> The FDA can investigate public safety issues regarding certain compounded prescriptions (those in which a physician combines, mixes, or alters a drug's ingredients to create a medication that is tailored to the needs of an individual patient) that pose a hazard, and it can also use its discretion to confront pharmacies whose preparation of items meets the FDA's definition of manufacturing and registration as 503A or 503B compounders. 503A compounders are traditional compounding pharmacies that comply with USP <797> standards and focus on customized, patient-specific compounding that can only be dispensed with a prescription. Conversely, 503B outsourced compounding pharmacies provide batch compounding while remaining compliant with federal cGMP regulations for pharmaceuticals; this includes Test, Hold, and Release, a new cGMP level standard for anticipatory compounding that applies to quality assurance.<sup>52</sup>

An FDA exemption was granted to nuclear pharmacies in 1984; that exemption stated that if certain requirements were met, a nuclear pharmacy could prepare a radioactive drug without being required to register with the FDA. Additionally, on December 29, 2016, the FDA issued a long-awaited draft guidance entitled *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies*, which specifically addresses situations in which the FDA will not take action against 503A state-licensed nuclear pharmacies that compound or repackage radiopharmaceuticals for human use that result in violations of 505, 502(f)(1), and 501(a)(2)(B) of the Food, Drug and Cosmetic Act (FDCA).<sup>53</sup>

The draft guidance recognizes that radiopharmaceutical preparation is unique, especially when one considers that nuclear pharmacies must comply with existing ALARA (as low as reasonably achievable) requirements under the Occupational Radiation Protection Program (10 CFR 835); ALARA principles involve shielding, distance, and time requirements in nuclear pharmacy practices.<sup>54</sup>

## The high cost of compliance

Nuclear pharmacies must meet radiopharmaceutical compounding compliance standards issued by the State Boards of Pharmacy, which enforce adherence to USP <797> standards.<sup>55</sup> In addition, regulatory compliance by nuclear pharmacies is monitored by the NRC and state bodies involved in radiological health and safety; the US Department of Transportation and the Federal Aviation Administration, both of which ensure the safe transportation of radioactive materials; and the Occupational Safety and Health Administration. A maze of radiopharmaceutical preparation and compounding regulations and guidelines issued by federal, state, and standard-setting organizations, such as The Joint Commission, has also affected the nuclear pharmacy practice.

In an effort to remain compliant with the current USP <797> and future <825> regulations for sterile preparation, nuclear pharmacies have made significant site improvements, including clean room separation from other semi-sterile work areas, pass-through boxes, improved air filtration systems, laminar flow hoods, and changes to workflow and operational procedures, all of which have pushed the spend from tens of thousands of dollars to more than \$100,000.<sup>56</sup>

USP <797> and <825> regulations are (and will be) in place to protect health care organizations; however, complying with them has significant cost implications for nuclear pharmacies. If other significant industry changes and new requirements are implemented, the costs to remain compliant with USP requirements will be even higher, especially when the extraordinary, nontraditional, and frequent price increases seen with Mo<sup>99</sup> and sole-source cold kits are taken into account. Ultimately, the net effect of tightening regulations means yet another element of cost will be introduced into the radiopharmaceutical supply chain, which will increase the price of the prepared unit doses—a cost that will inevitably funnel directly to the health care organization.

## Current reimbursement systems: challenges and solutions

Industry thought leaders and various trade associations, such as the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the Council on Radionuclides and Radiopharmaceuticals (CORAR), and the National Association of Nuclear Pharmacies (NANP), recognize that appropriate radiopharmaceutical reimbursement has been an issue in the health care arena for some time. Although organizations such as the SNMMI and the OECD-NEA HLG-MR have indicated that they favor a separate payment structure for radiopharmaceuticals through implementation of an unbundled reimbursement system, CMS and other private payers continue to implement a bundled payment initiative.

### Reimbursement reform

In 2008, the SNMMI published a paper entitled *Radiopharmaceutical Reimbursement Under Medicare: Recommendations for Reform*, which stated that under the current reimbursement system, CMS classifies all diagnostic radiopharmaceuticals as "supplies" instead of "drugs."<sup>57</sup> In a practice known as *bundling*, procedures and related drugs/biologicals are coded and billed separately, although both are reimbursed in the procedure payment. The paper stressed that radiopharmaceuticals should be classified as drugs, not supplies, and that an appropriate payment policy should be established that accurately reflects radiopharmaceutical acquisition costs.<sup>57</sup> To achieve this aim, the SNMMI took the position that radiopharmaceuticals should be unbundled (in which each component is billed separately) and appropriately reimbursed, as with other pharmaceuticals.

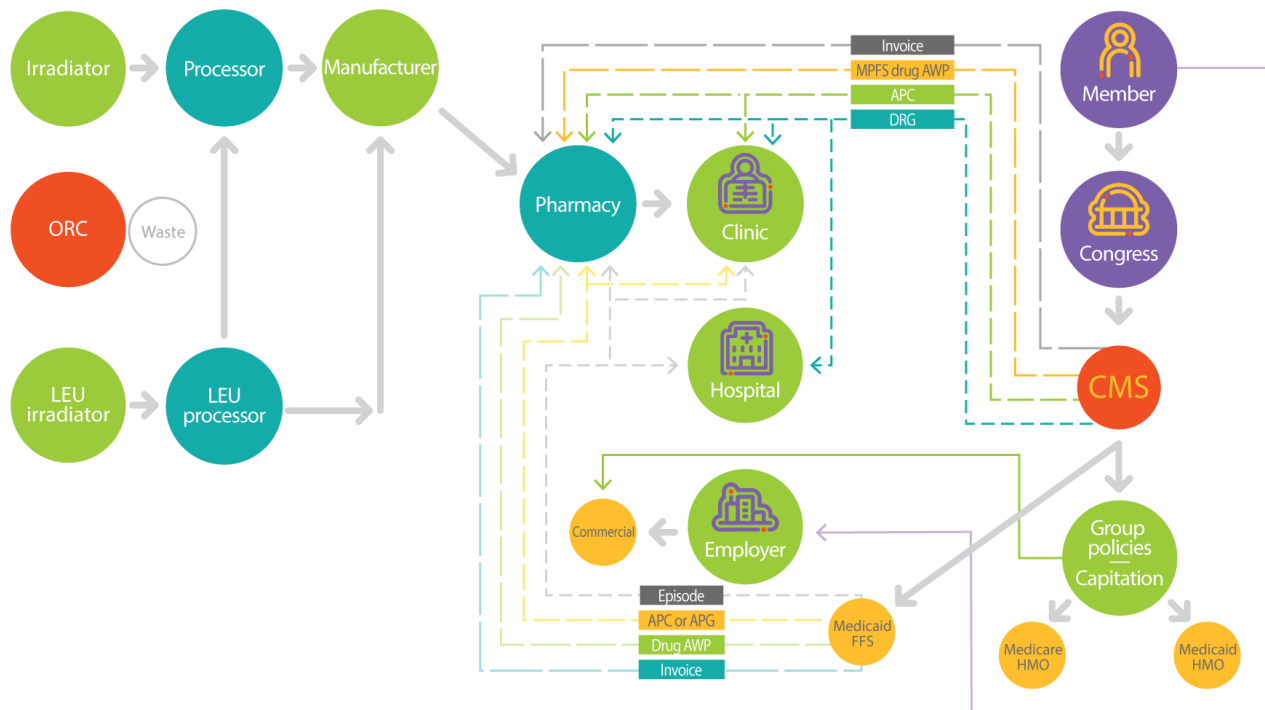
Similarly, in 2012, the OECD HLG-MR wrote a guidance document entitled *Full-cost Recovery for Molybdenum-99 Irradiation Services: Methodology and Implementation*. The report stated that price increases expected to impact the manufacturing and processing of non-HEU medical isotopes "should flow through the supply chain and should be reflected in costs of the final medical procedure, to be reimbursed appropriately by the health care system."<sup>58</sup> Similar to other high cost branded pharmaceuticals, billed and paid for separately because of the cost structure that is applied when caring for a patient (ie, the hospital/imaging center acquisition cost for the radiopharmaceutical, the time and labor needed to perform the procedure, and the physician's/radiologist's interpretation of the final study), the OECD HLG-MR suggests that separate and sufficient reimbursement rates (or payments) could be used by public and private health insurance organizations to support the industry move to FCR for irradiation services. Thus, FCR and ORC costs would ultimately be passed through the supply chain and paid for by the health care facility.<sup>59</sup>

However, neither paper addressed the proprietary, sole-source kit products labeled to Tc<sup>99m</sup> whose costs are increased annually and, in some cases, are well beyond traditional increases seen in years past. In addition, the nuclear pharmacies will incur costs to meet planned changes to USP <797> as well as new proposed <825> standards. Currently, the new regulatory requirements aimed at the radiopharmacy industry and the relative cost increases to the total isotope preparation are not considered in a bundled payment system. Coupled with the FCR, ORC, and ULTB costs to bring non-HEU/LEU Mo<sup>99</sup> to market, the result is a perfect storm that could cause radiology departments to abandon SPECT imaging procedures in search of alternative, less expensive diagnostics and/or therapeutics.

## APC collapsing could mean lower reimbursements

In late 2015, CMS announced that it would compress the number of Ambulatory Payment Classifications from 23 to the current 5.<sup>60</sup> However, as more procedures are bundled into fewer groups, overall payment amounts could be reduced and reimbursements may become smaller. Because of AMIPA, agencies such as the NRC, FDA, and the DOE's NNSA (as well as medical reactor operators, processors, and generator manufacturers) will be required to transition to non-HEU medical isotopes; thus, manufacturing and processing costs will likely cause the price of radiopharmaceuticals to rise to unprecedented levels. If reimbursement is not adapted to current market conditions, it may disrupt the kind of diagnostic imaging support that the industry needs to stay viable. Figure 15 illustrates the challenges facing all of the current radiopharmaceutical supply chains and the cluster of issues that health care organizations must deal with when submitting for reimbursement for their nuclear procedures.

**Figure 15. Radiopharmaceuticals: from production to payment<sup>62</sup>**



Abbreviations: APC, ambulatory payment classification; APG, ambulatory payment grouping; AWP, average wholesale price; CMS, Centers for Medicare & Medicaid Services; DRG, diagnosis-related group; FFS, fee for service; LEU, low-enriched uranium; MPFS, Medicare Physician Fee Schedule; ORC, outage reserve capacity.

## Q9969 reimbursement initiative

CMS launched an initiative in 2012 to pay an additional \$10 per non-HEU derived Tc<sup>99m</sup> patient dose (known as Healthcare Common Procedure Coding System [HCPCS] Q9969).<sup>63</sup> Since 2013, more than 38 commercial and government payers have active Q9969 reimbursement for all covered lives. (In some cases, more than \$10 is reimbursed according to the private payers' plans.) In July 2016, CMS recommended the following within its payment adjustment policy:

We stated in the CY 2013 OPPI/ASC final rule with comment period (77 FR 68321) that our expectation is that this additional payment will be needed for the duration of the industry's conversion to alternative methods to producing Tc-<sup>99m</sup> without HEU. We also stated that we would reassess, and propose if necessary, on an annual basis whether such an adjustment continued to be necessary and whether any changes to the adjustment were warranted (77 FR 68316). We have reassessed this payment for CY 2017 and did not identify any new information that would cause us to modify payment. Therefore, for CY 2017, we are proposing to continue to provide an additional \$10 payment for radioisotopes produced by non-HEU sources.<sup>64,65</sup>

This reimbursement continues to assist health care facilities in the transition to non-HEU medical isotopes, and is often (but not always) applied to Medicare's HOPPS to help with the cost of overhead to source a non-HEU product.

In reality, the Q9969 code should have been established as a reimbursement policy with all commercial payers since its inception in 2013. To monitor US progress in adopting non-HEU medical isotopes, Mo<sup>99</sup> and industry stakeholders are tracking how many patients currently receive the LEU Tc<sup>99m</sup> dose and a reimbursement. It is crucial that more hospitals make the non-HEU transition to show progress, to access and demand the additional reimbursement, and to stop the proliferation of HEU in medical isotope manufacture. At the very least, the Q9969 code must continue until 2020 since the cost wave from FCR and ORC medical reactors have not been pushed out in the supply chain. If Q9969 is discontinued before 2020, the loss of reimbursement will further increase the total nuclear imaging acquisition costs, potentially causing clinicians to look for other imaging modalities that will be more profitable.

## The impact of radiology benefit managers

Currently, an accountable care organization model—in which groups of doctors, hospitals, and health care providers work together to provide high-quality care while avoiding the duplication of services and medical errors<sup>66</sup>—is the first choice for most health care organizations in terms of radiopharmaceutical reimbursement.

As stated by Bernardy et al, "Imaging represents a substantial and growing portion of the costs of American health care. When performed correctly and for the right reasons, medical imaging facilitates quality medical care that brings value to both patients and payers. When used incorrectly because of inappropriate economic incentives, unnecessary patient demands, or provider concerns for medical-legal risk, imaging costs can increase without increasing diagnostic yields."<sup>67</sup> With that in mind, radiology benefit managers (RBMs) and/or private payers often attempt to create "protocols" to reduce the number

of expensive imaging procedures that are ordered within hospitals and freestanding imaging centers. American Imaging Management (AMI), a medical management company that oversees the utilization and quality of diagnostic imaging services,<sup>68</sup> is key to the creation of these guidelines, although many RBMs develop their own criteria. Typically, protocols focus on the most expensive procedures that are prescribed and/or referred and recommend that a less expensive procedure be performed first (eg, an echocardiogram is required before an RBM will even consider sending a patient for a cardiac stress test).

There are several issues that undermine the success rate of these protocols. First, RBMs often receive preauthorization from a referring physician, who might not be aware of more diagnostically accurate tests. The RBMs may suggest a different procedure (eg, computed tomography [CT] with contrast instead of a requested positron emission tomography/PET/CT scan); however, quality is not always the key decision factor. Cost reduction is always considered first, which means the best test is not always the one that is administered. Second, alternative procedures often prove more time consuming and costly, as they may not adequately define a patient’s physiological or functional problem. As a result, multiple further tests may be needed to obtain the same outcome that a single test could have provided.

## Benefits of an average selling price model

The ASP model, in which manufacturers’ sales data is used to establish the Medicare payment amount for a particular drug, would help health care organizations achieve equitable acquisition cost recovery (especially in a time of extraordinary and nontraditional price increases for Mo<sup>99</sup>/Tc<sup>99m</sup>). The model would also include cost increases associated with the various cold kit components, thereby treating the unit dose radiopharmaceutical as a physician-injected drug (Table 5). An ASP model would permit the quarterly adjustment of acquisition costs, which in turn allows contemporaneous reimbursement to the hospital. Under the current system of retroactive invoice review, there is an 18- to 24-month lag in establishing reimbursement for the current year, which has caused gross underpayment for lung perfusion studies and other procedures that experience extraordinary or nontraditional price increases during the lag years. This is especially true if the manufacturer fails to change the average wholesale price, now more commonly referred to as the wholesale acquisition cost, of the cold reagent kit.

**Table 5. Average selling price of unit dose radiopharmaceutical cold reagent kits<sup>a</sup>**

Description	Unit of measure	Average selling price, US \$ (normalized to 100 in 2013)					Trendlines
		2013	2014	2015	2016	2017	
DTPA (pentetate) kit	1 vial	100	700	900	900	1,233	
Ga-67 (gallium citrate) UD	1 mCi	100	122	138	138	147	
I-123 (sodium iodide I-123 capsule)	100 uCi	100	116	122	140	160	
I-123 (sodium iodide I-123 capsule)	200 uCi	100	114	122	139	159	
I-131 diagnostic capsule	10-100 uCi	100	106	106	106	108	
I-131 NAI therapy capsule	1-6 mCi	100	103	110	118	131	
I-131 NAI therapy capsule	Each additional	100	111	111	122	133	

Description	Unit of measure	Average selling price, US \$ (normalized to 100 in 2013)					Trendlines
		2013	2014	2015	2016	2017	
	mCi						
I-131 NAI therapy solution	1-6 mCi	100	103	110	119	133	
I-131 NAI therapy solution	Each additional mCi	100	111	111	122	133	
In-111 DTPA (indium-111 pentetate)	1.5 mCi	100	120	120	120	136	
In-111 WBC labeling*	Study (dose and labeling)	100	119	119	120	136	
Indium-111 pentetreotide (OctreoScan)	6 mCi	100	127	136	152	180	
Indium-111 capromab pendetide (Prostascint)	6 mCi	100	100	102	114	120	
Indium-111 chloride (chloride) UD	5 mCi	100	100	105	118	134	
Iodine-123 iobenguane sulfate (AdreView) UD	Study	100	100	118	118	130	
Kinevac kit	1 vial	100	128	133	139	152	
Lexiscan	5 mL	100	100	100	100	110	
MAA kit	1 vial	100	1710	2050	2050	2832	
MDP (medronate) kit	1 vial	100	100	100	120	124	
Mebrofenin kit	1 vial	100	113	113	113	121	
Neurolite kit	1 vial	100	123	157	166	182	
PYP vials	1 vial	100	109	115	124	130	
Sulfur colloid kit	1 vial	100	105	111	166	228	
Tl-201 (thallous chloride) UD	1 mCi	100	100	100	100	100	
Tc <sup>99m</sup> Cardiolite UD	1-30 mCi	100	103	106	108	108	
Tc <sup>99m</sup> Ceretec (exametazime injection) UD	1-30 mCi	100	118	118	127	136	
Tc <sup>99m</sup> Ceretec (exametazime) WBC labeling	Per study	100	116	116	123	136	
Tc <sup>99m</sup> DTPA (pentetate) aerosol UD	26-40 mCi	100	364	431	437	491	
Tc <sup>99m</sup> DTPA (pentetate) renal UD	1-25 mCi	100	352	455	462	524	
Tc <sup>99m</sup> HDP (Oxidronate) UD	1-25 mCi	100	111	118	136	143	
Tc <sup>99m</sup> MAA UD	1-7 mCi	100	1421	1671	1679	1729	
Tc <sup>99m</sup> MAG-3 (mertiatide) UD	1-15 mCi	100	124	133	142	163	
Tc <sup>99m</sup> MDP (medronate) UD	1-25 mCi	100	108	121	142	154	
Tc <sup>99m</sup> mebrofenin UD	1-10 mCi	100	103	107	110	113	
Tc <sup>99m</sup> Myoview (tetrofosmin) UD	1-30 mCi	100	105	107	109	113	
Tc <sup>99m</sup> NaTcO4 (bulk)	1 mCi	100	100	100	100	100	



Description	Unit of measure	Average selling price, US \$ (normalized to 100 in 2013)					Trendlines
		2013	2014	2015	2016	2017	
Tc <sup>99m</sup> NaTcO4 UD	1–25 mCi	100	104	113	122	126	
Tc <sup>99m</sup> NaTcO4 UD	< 1 mCi	100	100	100	100	113	
Tc <sup>99m</sup> Neurolite UD	1-30 mCi	100	123	150	157	173	
Tc <sup>99m</sup> PYP UD	1-25 mCi	100	115	123	136	149	
Tc <sup>99m</sup> sestamibi UD	1-30 mCi	100	104	110	112	110	
Tc <sup>99m</sup> sulfur colloid UD, filtered	0.1-2 mCi	100	109	121	145	146	
Tc <sup>99m</sup> sulfur colloid UD	1-8 mCi	100	110	124	149	151	
UltraTag kit	1 vial	100	115	122	139	153	
Xe-133 (xenon) gas	10 mCi	100	126	145	145	145	
Xe-133 (xenon) gas	20 mCi	100	126	144	144	154	

Abbreviat<sup>9</sup> Reprinted with permission from United Pharmacy Partners, LLC; based on independent commercial radiopharmacy data. ions: DTPA, diethylenetriamine pentaacetate; HDP, hydroxymethylene diphosphonate; MAA, macroaggregated albumin; MDP, methylene diphosphonate; NaTcO4, sodium pertechnetate; PYP, pyrophosphate; Tc<sup>99m</sup>, technetium 99m; UD, unit dose; WBC, white blood cell.

## Other reimbursement challenges

The current reimbursement structure fails not only in terms of the Mo<sup>99</sup> supply chain, but also in cyclotron-produced products. Indium-111 is a cyclotron-produced radionuclide with scintigraphic applications that range from leukocyte imaging for infectious/inflammatory processes, to cerebrospinal fluid patency/leak studies, to neuroendocrine tumor (NET) detection. In the latter case, Indium-111 tagging of a somatostatin receptor analog can aid in the metabolic definition of uncharacterized tumors, which helps an appropriate treatment plan to be developed.<sup>69</sup> Iodine-123 meta-iodobenzylguanidine is another cyclotron-produced imaging agent used to diagnose certain NETs; it exhibits high diagnostic value in the case of primary neuroblastoma<sup>70</sup> and is thought to be essential in managing this disease.<sup>71</sup> It is an unfortunate reality that the utilization of such valuable diagnostic agents may decrease in the near future due to increasing radiopharmaceutical costs. Under the current reimbursement structure for radiopharmaceuticals, high overhead costs without adequate compensation may drive institutions away from diagnostically valuable imaging studies, thus limiting the diagnostic capabilities of the ordering physician. Foregoing diagnostic imaging due to radiopharmaceutical cost has the potential to delay diagnosis and lead to uncertainty on behalf of the patient and physician. Table 6 displays this unbalanced relationship in an east coast urban academic medical facility with a CMS reclassified wage index of 1.2804.

**Table 6. Cost of radiopharmaceutical versus revenues lost (East coast urban AMC derived data)<sup>a</sup>**

Study name	CPT code	Cost of radionuclide	CMS weighted reimbursement (does not include professional fees)	Total facility overhead (includes direct and indirect <sup>b</sup> technical costs)	Revenue
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Indium-111 octreotide planar and SPECT <sup>c</sup>	78804 78803	\$3995.00	\$1810.56	\$5768.00	-\$3957.44
Indium-111 Oxine WBC planar and SPECT <sup>c</sup>	78806 78807	\$1750.00	\$1810.56	\$2625.00	-\$814.44
Indium-111 DTPA for cisternogram <sup>c</sup>	78650	\$1950.00	\$1294.95	\$2125.00 plus Interventional fees	-\$830.05
123I mIBG planar and SPECT <sup>c</sup>	78804 78803	\$3200.00	\$1810.56	\$4725.00	-\$2914.44
Tc <sup>99m</sup> HMPAO WBC planar and SPECT <sup>d</sup>	78806 78807	\$1670.00	\$1810.56	\$2434.00	-\$623.44
Tc <sup>99m</sup> HMPAO brain <sup>d</sup>	78607	\$1475.00	\$1294.95	\$2015.00	-\$720.05
Tc <sup>99m</sup> MUGA <sup>d</sup>	78472	\$151.40 (with UltraTag Kit)	\$388.62	\$281.96	+\$106.66
Tc <sup>99m</sup> hemangioma <sup>d</sup>	78807	\$151.40 (with UltraTag Kit)	\$388.62	\$316.96	+\$71.66
Tc <sup>99m</sup> whole body bone scan <sup>d</sup>	78306	\$22.50	\$388.62	\$108.75	+\$279.87
Tc <sup>99m</sup> 3-phase bone scan <sup>d</sup>	78315	\$22.50	\$388.62	\$136.50	+\$252.12
Tc <sup>99m</sup> liver/spleen <sup>d</sup>	78215	\$83.00	\$388.62	\$186.20	+202.42
Tc <sup>99m</sup> V/Q scan <sup>d</sup>	78582	\$227.00	\$515.61	\$373.80	+\$141.81
Tc <sup>99m</sup> renal scan <sup>d</sup>	78708	\$300.00	\$515.61	\$490.00	+\$25.61
Tc <sup>99m</sup> parathyroid scan <sup>d</sup>	78070	\$32.25	\$388.62	\$220.15	+\$168.47
Tc <sup>99m</sup> gastric emptying 4-hour protocol <sup>d</sup>	78264	\$83.00	\$388.62	\$396.20	-\$7.58

<sup>a</sup> Reprinted with permission from University Medical Center.<sup>72</sup>

<sup>b</sup> Indirect costs are estimated to be 40% of the direct costs.

<sup>c</sup> Cyclotron produced.

<sup>d</sup> Molybdenum derived.

Abbreviations: CPT, Current Procedural Terminology; CMS, Centers for Medicare and Medicaid Services; DTPA, diethylenetriamine pentaacetate; HMPAO, hexamethylpropyleneamine oxime; mIBG, meta-iodobenzylguanidine; MUGA, multigated acquisition scan; SPECT, single-photon emission computed tomography ; Tc<sup>99m</sup>, technetium-99m; V/Q, ventilation-perfusion; WBC, white blood cell.

## Potential reimbursement solutions

In today's market, declining reimbursements and the increasing costs of radiopharmaceuticals are placing an incredible burden on health care organizations. It is only through reimbursement reform that the viability of nuclear imaging modalities can be sustained; based on current research, the ASP model described above, which allows for equitable and timely reimbursement, should provide the most effective and relevant solution.

### UPPI: supporting the transition to non-HEU medical isotope production

Over the past 3 years, each UPPI member with an LEU Mo99 generator dispensed  $\geq 95\%$  LEU Tc99m radiolabeled ligands for diagnostic imaging, which drove the utilization of the Q9969 add-on reimbursement for non-HEU medical isotopes within the diagnostic imaging centers. The reimbursement expanded to the private payer sector and UPPI worked with imaging centers to successfully receive payment for those that submitted the Q9969 code. UPPI expanded the role of private payers as stakeholders in support of nonproliferation of HEU in medical isotope production.

UPPI found private payers that provided reimbursement for  $\geq 95\%$  LEU Tc99m for all covered lives, in addition to the Medicare HOPPS patients. Tricare, for example, was the first private government payer to recognize the Q9969 add-on reimbursement in all 50 states.<sup>73</sup> Since commercial payers are the real drivers for reimbursement coverage of the add-on payment, UPPI has initiated a C-suite Nonproliferation Outreach and Education Program for the carriers' policy committees and medical directors. All commercial payers—from the largest, such as Cigna, Humana, and United Healthcare, to the narrow networks, such as Geisinger Health Plan, Providence Health Plan, and Sentara Healthcare—play a significant role in eliminating HEU from medical isotope production.

## Summary and conclusions

### A new reimbursement reform strategy is needed

The nuclear medicine industry is experiencing financial challenges for a number of reasons, including (1) converting to non-HEU manufacturing, which includes additional cost elements such as investing in a domestic supply partner or realizing the full effect of FCR, ORC, or ULTB, (2) facing nontraditional sole-source price increases of cold reagent kits that are used to label and tag the Tc<sup>99m</sup> isotope, and (3) implementing site improvements at nuclear pharmacies in order to meet radiopharmaceutical compounding compliance standards issued by the State Boards of Pharmacy, which enforce adherence to USP <797> and future USP <825> standards. It is imperative that we understand and consider these challenges, and implement a strategy that will ultimately create long-term sustainability of the SPECT imaging modality and the radiopharmaceuticals used in nuclear medicine procedures.

Unfortunately, as costs increase for Tc<sup>99m</sup>-labeled products, reimbursements for many nuclear procedures are on the decline. Although bundling the cost of a supply may be an efficient way to manage overall costs for a procedure, the unpredictable costs associated with Tc<sup>99m</sup> radiopharmaceuticals highlight the need to look at reimbursement reform as a solution to the impending cost pressures health care organizations will face.

### The ASP model: one potential solution to the problematic radiopharmaceutical reimbursement issue

It is critical that a different reimbursement model be implemented in the nuclear imaging space. Despite acquisition cost increases for unit dose radiopharmaceuticals, it is highly unlikely that other anatomical imaging modalities or diagnostic studies will replace molecular imaging, due to its superior physiological and functional imaging and its positive contribution to patient outcomes. Thus, a new reimbursement reform strategy will ensure investments in new technology for both the SPECT and PET modalities, advance diagnostic and therapeutic applications in nuclear medicine while continuing to assist global threat reduction initiatives, and reduce the pressure on the industry in general as it grapples with continued increased costs for non-HEU medical isotopes and radiopharmaceutical cold kits.

An ASP model could help establish timelier reimbursement for the vast majority of nuclear diagnostic and radiotherapeutic procedures. On average, there is an 18- to 24-month lag time before the current average procedure cost (APC) for radiopharmaceuticals is modified by CMS; during that time, it is likely that at least 1, and possibly 2, significant radiopharmaceutical cost increases will have already occurred in the marketplace. An ASP model could help prevent and reduce the 18- to 24-month lag time by capturing contemporaneous cost increases that the current reporting/reimbursement models are unable to address in real time, especially in terms of recouping manufacturers' price increases, some of which, although they are essential in terms of product availability for patient imaging, have been described as "egregious." In addition, as new domestic suppliers and products continue to move into the market, it is entirely feasible that the acquisition cost of a radiopharmaceutical could be more than 50% of the APC. Thus, the

costs to perform a nuclear medicine procedure might not be fully reimbursed, which could be disastrous in terms of the procedures that health care organizations could offer patients.

## The time is now

It is necessary to educate our key opinion leaders in all health care arenas (Table 7) and work with these key stakeholders to achieve appropriate reimbursement for radiopharmaceuticals and adopt a new, more dynamic model for diagnostic imaging procedures. If we continue to wait to implement a new reimbursement reform strategy, it could have negative consequences on the health of the SPECT imaging modality and potentially affect future therapeutic technologies.

**Table 7. Key stakeholders positioned to assist with reimbursement reform of radiopharmaceuticals<sup>a</sup>**

Key stakeholders	Support needed from each stakeholder
OECD-NEA	<ul style="list-style-type: none"> <li>• Serve as spokesperson for all stakeholders with the objective of ensuring economically sustainable supply</li> <li>• Monitor the continued conversion to non-HEU production</li> </ul>
Trade associations such as SNMMI, HSCA, AHRA, RSNA, and RBMA	<ul style="list-style-type: none"> <li>• Inspire faster adoption of new technologies for reimbursement</li> <li>• Involve stakeholders that can intervene with the generic price model when increases are beyond a reasonable market price</li> <li>• Inform industry associations about the real costs associated with cold reagent kit (proprietary and generic) increases and the full cost recovery tsunami that will be passed through to the diagnostic imagers</li> </ul>
FDA and USP	<ul style="list-style-type: none"> <li>• Inspire faster approvals through FDA and vetting of new market entrants (international) for generically equivalent products</li> <li>• Inspire faster adoption of new technologies for reimbursement</li> <li>• Harmonization of the new USP chapter &lt;825&gt; radiopharmaceutical preparation and compounding with FDA guidances currently undergoing review</li> </ul>
GPO and HCO communities	<ul style="list-style-type: none"> <li>• Involve stakeholders that can intervene with the generic price model when increases are beyond a reasonable market price</li> <li>• Inspire faster adoption of new technologies for reimbursement</li> </ul>
CMS/private payers	<ul style="list-style-type: none"> <li>• Encourage managed care organizations to adopt an LEU/non-HEU reimbursement policy for all covered individuals' medical isotopes</li> <li>• Inspire faster adoption of new technologies for reimbursement</li> <li>• Refine clinical decision support to adequately reimburse radiopharmaceuticals by separating the isotopically labelled product from bundling with the procedure costs and professional fees</li> </ul>

<sup>a</sup> Reprinted with permission from Vizient and United Pharmacy Partners, LLC.

Abbreviations: AHRA, Association for Medical Imaging Management; CMS, Centers for Medicare and Medicaid Services; FDA, Food and Drug Administration; GPO, group purchasing organization; HCO, health care organization; HSCA, Healthcare Supply Chain Association; OECD-NEA, Organisation for Economic Co-operation and Development-Nuclear Energy Agency; RBMA, Radiology Business Management Association; RSNA, Radiological Society of North America; SNMMI, Society of Nuclear Medicine and Molecular Imaging.

It is imperative that the government and private payers understand the issues affecting the imaging community—such as treating radiopharmaceuticals as “physician injectable drugs” and through use of an appropriate reimbursement model such as the ASP model versus the current bundling of radiopharmaceuticals as “supplies”—as well as the impact that future costs will have on nuclear diagnostic procedures that are already being subjected to unprecedented price increases. In this ever-changing environment of higher and/or uncontrolled acquisition costs, key stakeholders in the radiopharmaceutical supply chain must band together to not only provide timely and relevant feedback to the industry regarding the cost pressures they are facing now and will experience in the future, but also stress the need to both commercial and private payers that reimbursement change is critical to preserving the overall health of the nuclear medicine industry. We must work together to ensure that nuclear imaging studies can continue to be performed in the health care setting. Only then will we be able to invest in the future of this modality and the therapeutic agents that aid in promoting overall patient health, improving patient outcomes, and reducing health care costs.

## Appendix A. Potential effect of Tc<sup>99m</sup> full cost recovery on the supply chain

A purchase/supply chain issue arises when the Tc<sup>99m</sup> per mCi costs accelerate under a wave of Mo<sup>99</sup> generator increases due to 3 components of cost center deployment: the FCR itself, ORC, and costs from the ULTB government programs for LEU uranium.

The table below shows the per-unit dose cost of the Tc<sup>99m</sup> component in the labelled radiopharmaceutical based upon a range of input costs per mCi Tc<sup>99m</sup>. Typically, Tc<sup>99m</sup> is used in combination with cold ligands such as macroaggregated albumin (MAA), DTPA, and mercaptoacetyltriglycine, which together help to determine the entire cost of the labelled drugs.

In recent years, ligands have undergone annual, nontraditional increases. Two products in particular—MAA and DTPA—experienced an “extraordinary one-time increase,” which compounded the final unit dose cost.

### Potential effect on the per mCi Tc<sup>99m</sup> unit dose acquisition cost: FCR, ORC, and ULTB<sup>a,b</sup>

Product	Tc <sup>99m</sup> dose activity	\$1.00/mCi	\$2.50/mCi	\$5.00/mCi	\$7.50/mCi
Tc <sup>99m</sup> Cardiolite UD	30 mCi	\$30.00	\$75.00	\$150.00	\$225.00
Tc <sup>99m</sup> Ceretec (exametazime injection) UD	30 mCi	\$30.00	\$75.00	\$150.00	\$225.00
Tc <sup>99m</sup> Ceretec (exametazime) WBC labeling	15 mCi	\$15.00	\$37.50	\$75.00	\$112.50
Tc <sup>99m</sup> DTPA (pentetate) aerosol UD	40 mCi	\$40.00	\$100.00	\$200.00	\$300.00
Tc <sup>99m</sup> DTPA (pentetate) renal UD	25 mCi	\$25.00	\$62.50	\$125.00	\$187.50
Tc <sup>99m</sup> HDP (oxidronate) UD	25 mCi	\$25.00	\$62.50	\$125.00	\$187.50
Tc <sup>99m</sup> MAA UD	7 mCi	\$7.00	\$17.50	\$35.00	\$52.50
Tc <sup>99m</sup> MAG-3 (mertiatide) UD	15 mCi	\$15.00	\$37.50	\$75.00	\$112.50
Tc <sup>99m</sup> MDP (medronate) UD	25 mCi	\$25.00	\$62.50	\$125.00	\$187.50
Tc <sup>99m</sup> mebrofenin UD	10 mCi	\$10.00	\$25.00	\$50.00	\$75.00
Tc <sup>99m</sup> Myoview (tetrofosmin) UD	30 mCi	\$30.00	\$75.00	\$150.00	\$225.00
Tc <sup>99m</sup> NaTcO <sub>4</sub> (bulk)	1 mCi	\$1.00	\$2.50	\$5.00	\$7.50

Product	Tc <sup>99m</sup> dose activity	\$1.00/mCi	\$2.50/mCi	\$5.00/mCi	\$7.50/mCi
Tc <sup>99m</sup> NaTcO <sub>4</sub> UD	25 mCi	\$25.00	\$62.50	\$125.00	\$187.50
Tc <sup>99m</sup> Neurolite UD	30 mCi	\$30.00	\$75.00	\$150.00	\$225.00
Tc <sup>99m</sup> PYP UD	25 mCi	\$25.00	\$62.50	\$125.00	\$187.50
Tc <sup>99m</sup> sestamibi UD	30 mCi	\$30.00	\$75.00	\$150.00	\$225.00
Tc <sup>99m</sup> sulfur colloid UD (filtered)	2 mCi	\$2.00	\$5.00	\$10.00	\$15.00
Tc <sup>99m</sup> sulfur colloid UD	8 mCi	\$8.00	\$20.00	\$40.00	\$60.00

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<sup>b</sup> Acquisition cost of the cold kit (ligand) is not included in the cost of the Tc<sup>99m</sup> component; Tc<sup>99m</sup> NaTcO<sub>4</sub> (bulk) is Tc<sup>99m</sup> only and does not employ a ligand.

Abbreviations: DTPA, diethylene-triamine-pentaacetate; FCR, full cost recovery; HDP, hydroxymethylene diphosphonate; MAA, macroaggregated albumin; MAG-3, mercaptoacetyltriglycine; MDP, methylene diphosphonate; NaTcO<sub>4</sub>, sodium pertechnetate; ORC, outage reserve capacity; PYP, pyrophosphate; Tc<sup>99m</sup>, technetium-99m; UD, unit dose; ULTB, uranium lease and take back; WBC, white blood cells.



## Appendix B. Overview of the 6 principles of the HLG-MR's policy approach<sup>a</sup>

Principle	Intent of principle
All Tc <sup>99m</sup> supply chain participants should implement full-cost recovery for irradiation services, including costs related to capital replacement.	Eliminate foreign subsidies and implement new cost structures related to capital costs, general overhead costs of the entire site, general operational costs of the reactor, decommissioning funding, and other specific Mo <sup>99</sup> irradiation costs.  Applying the full cost recovery methodology ensures that there are no hidden subsidies directed toward Mo <sup>99</sup> production, allowing for a level playing field between the world's producers.
Reserve capacity should be sourced and paid for by the supply chain. A common approach should be used to determine the amount of reserve capacity required.	ORC is the capacity that exists within the system to account for the fact that research reactors sometimes have unplanned or extended shutdowns.  Research reactors do not operate 100% of the time and, when there is an unexpected or extended shutdown, reserve capacity in another reactor or production source is required to counter the lost production capacity. This reserve capacity was traditionally not paid for by the supply chain, but the supply chain will now be responsible for ensuring adequate reserve capacity to cope with unexpected losses of supply and for any associated costs.
Recognizing and encouraging the role of the market. Governments should intervene accordingly (3-year target to implement this principle).	Work to establish the proper environment for infrastructure investment.  Set the rules and establish the regulatory environment for safe and efficient market operation.  Ensure that all market-ready technologies implement full cost recovery methodology.  Refrain from direct intervention in day-to-day market operations as such intervention may hinder long-term security of supply.
Given their political commitments to nonproliferation and nuclear security, governments should provide support, as appropriate, to reactors and processors to facilitate the conversion of their facilities to LEU or to transition away from the use of HEU, wherever technically and economically feasible.	Suggests that government intervention should support the shift from HEU to LEU and provide incentives to the private sector wherever possible.
International collaboration should be continued through a policy and information sharing forum, recognizing the importance of a globally consistent approach to addressing security of supply of Mo <sup>99</sup> /Tc <sup>99m</sup> and the value of international consensus in encouraging domestic action.	Regularly review progress toward creating a sustainable supply of Mo <sup>99</sup> and share successes and challenges across countries.
There is a need for periodic review of the supply chain to verify whether Mo <sup>99</sup> /Tc <sup>99m</sup> producers are implementing full cost recovery and whether essential players are implementing the other approaches agreed to by the HLG-MR, and that the coordination of operating schedules or other operational activities have no negative effects on market operations.	Engage key stakeholders annually to review progress and identify potential threats to the market that can be mitigated with implementation of the strategy presented by the HLG-MR.

<sup>a</sup> As extracted from a statement by the OECD-NEA steering committee for nuclear energy regarding policy actions necessary for the long-term security of supply of medical radioisotopes (2011). Reprinted with permission from the Nuclear Energy Agency.<sup>74</sup> Abbreviations: HEU, highly-enriched uranium; HLG-MR, High-level Group on the Security of Supply of Medical Radioisotopes; LEU, low-enriched uranium; Mo<sup>99</sup>, molybdenum-99; ORC, outage reserve capacity; Tc<sup>99m</sup>, technetium-99m.

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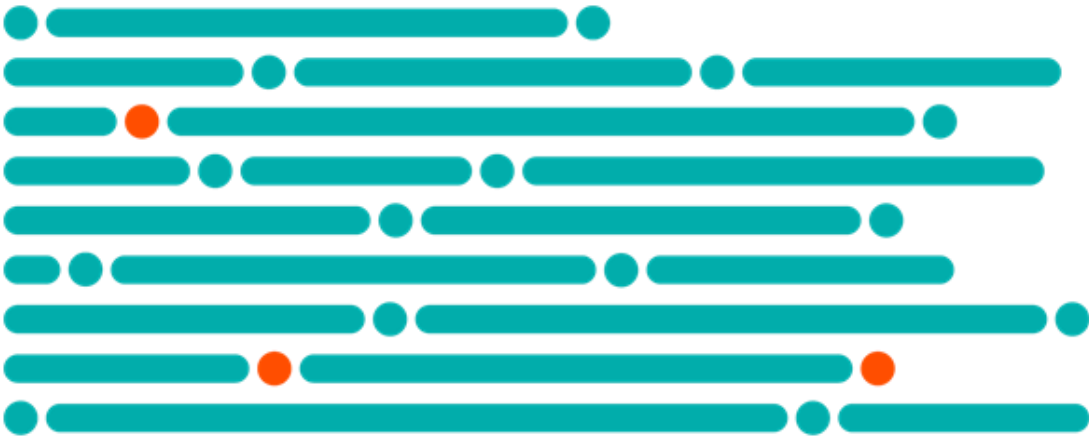
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