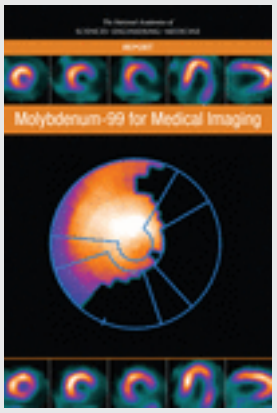

Molybdenum-99 for Medical Imaging

DETAILS

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Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium; Nuclear and Radiation Studies Board; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine

Molybdenum-99 for Medical Imaging

Committee on State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium

Nuclear and Radiation Studies Board

Division on Earth and Life Studies

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Cover: Technetium-99m, the decay product of molybdenum-99, is the most widely used radionuclide for medical imaging. The images on the cover were produced during a myocardial perfusion imaging (MPI) study using technetium-99m to assess blood flow to heart tissues (courtesy of Henry D. Royal, Washington University School of Medicine). The series of tomographic images at the top are produced during the stress portion (either exercise or pharmacological) of the test and the images at the bottom during the rest portion. The center image (referred to as a *bulls-eye image*) combines multiple images taken at stress or rest (in this case at rest) to assess myocardial perfusion defects. The black area of the bulls-eye image corresponds to areas of abnormal myocardial perfusion. The patient was diagnosed with a myocardial infarction (i.e., heart attack).

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COMMITTEE ON STATE OF MOLYBDENUM-99 PRODUCTION AND UTILIZATION AND PROGRESS TOWARD ELIMINATING USE OF HIGHLY ENRICHED URANIUM

S. JAMES ADELSTEIN, *Chair*, Harvard Medical School, Boston, Massachusetts
THOMAS J. RUTH, *Vice-Chair*, TRIUMF, Vancouver, British Columbia, Canada (emeritus)
LIN-WEN HU, Massachusetts Institute of Technology, Cambridge, Massachusetts
JOSEPH C. HUNG, Mayo Clinic, Rochester, Minnesota
ROBERT T. JUBIN, Oak Ridge National Laboratory, Oak Ridge, Tennessee
EMMETT B. KEELER, Pardee RAND Graduate School, Santa Monica, California
GERALD L. KULCINSKI, University of Wisconsin–Madison
JASON S. LEWIS, Memorial Sloan Kettering Cancer Center, New York, New York
KATHRYN A. MORTON, University of Utah, Salt Lake City
EUGENE J. PETERSON, Los Alamos National Laboratory, Los Alamos, New Mexico
TOR RAUBENHEIMER, SLAC National Accelerator Laboratory, Menlo Park, California
HENRY D. ROYAL, Washington University School of Medicine, St. Louis, Missouri
FELICIA L. TAW, Los Alamos National Laboratory, Los Alamos, New Mexico

Staff

KEVIN D. CROWLEY, Study Director
OURANIA KOSTI, Senior Program Officer
TONI GREENLEAF, Administrative and Financial Associate
DARLENE GROS, Senior Program Assistant

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and will ensure that this report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following individuals for their participation in the review of this report:

Carolyn J. Anderson, University of Pittsburgh
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Richard V. Coté, Atomic Energy of Canada Ltd. (retired)
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Michael M. Graham, University of Iowa Carver College of Medicine
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Julia M. Phillips, Sandia National Laboratory (retired)
Thomas Rockwell Mackie, University of Wisconsin–Madison
John P. Schiffer, Argonne National Laboratory
Orhan H. Suleiman, Food and Drug Administration (retired)

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions and recommendations of this report, nor did they see the final draft of the report before its release. The review of this report was overseen by Michael L. Corradini, University of Wisconsin–Madison, and Fred A. Mettler, Jr., University of New Mexico School of Medicine (professor emeritus). They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were considered carefully. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Contents

Executive Summary

This Academies study was mandated by the American Medical Isotopes Production Act of 2012. Key results[1] for each of the five study charges are summarized below; additional details are provided in the report summary and individual chapters.

Study charge 1: Provide a list of facilities that produce molybdenum-99 (Mo-99) for medical use including an indication of whether these facilities utilize highly enriched uranium (HEU). (Chapter 3) About 95 percent of the global supply of Mo-99 for medical use is produced in seven research reactors and supplied from five target processing facilities located in Australia, Canada, Europe, and South Africa. About 5 percent of the global supply is produced in other locations for regional use. About 75 percent of the global supply of Mo-99 for medical use is produced using HEU targets; the remaining 25 percent is produced with low enriched uranium targets. One of the reactors used to produce Mo-99 is fueled with HEU.

Study charge 2: Review international production of Mo-99 over the previous 5 years.[2] (Chapter 3) New Mo-99 suppliers have entered the global supply market since 2009 and further expansions are planned. An organization in Australia (Australian Nuclear Science and Technology Organisation) has become a global supplier and is currently expanding its available supply capacity; existing global suppliers in Europe (Mallinckrodt) and South Africa (NTP Radioisotopes) are also expanding their supply capacities; the

[1] Study results are based on information obtained through June 2016.

[2] These examinations are referenced to 2009, the year of publication of the previous Academies report on medical isotope production (NRC, 2009).

Russian Federation plans to become a global supplier at some point in the future; and entities in other countries have plans to produce Mo-99 for regional consumption. A reactor in France (OSIRIS) that produced Mo-99 shut down permanently in December 2015. The reactor in Canada (NRU) will stop the routine production of Mo-99 after October 2016 and permanently shut down at the end of March 2018.

Study charge 3: Assess progress made in the previous 5 years toward establishing domestic production of Mo-99 and associated medical isotopes iodine-131 (I-131) and xenon-133 (Xe-133). (Chapter 4) The American Medical Isotopes Production Act of 2012 and financial support from the Department of Energy's National Nuclear Security Administration (DOE-NNSA) have stimulated private-sector efforts to establish domestic production of Mo-99 and associated medical isotopes. Four NNSA-supported projects and several other private-sector efforts are under way to establish domestic capabilities to produce Mo-99; each project is intended to supply half or more of U.S. needs. Potential domestic Mo-99 suppliers face technical, financial, regulatory, and market penetration challenges; it is unlikely that substantial domestic supplies of Mo-99 will be available before 2018. Neither I-131 nor Xe-133 is currently produced in the United States, but one U.S. organization (University of Missouri Research Reactor Center) is developing the capability to supply I-131; some potential domestic Mo-99 suppliers also have plans to supply I-131 and/or Xe-133 in the future.

Study charge 4: Assess the adequacy of Mo-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond. (Chapters 6-7) The United States currently consumes about half of the global supply of Mo-99/technetium-99m (Tc-99m)[3] for medical use; global supplies of Mo-99 are adequate at present to meet domestic needs. Domestic demand for Mo-99/Tc-99m has been declining for at least a decade and has declined by about 25 percent between 2009-2010 and 2014-2015; domestic medical use of Mo-99/Tc-99m is unlikely to increase significantly over the next 5 years. The committee judges that there is a substantial (>50 percent) likelihood of severe Mo-99/Tc-99m supply shortages after October 2016, when Canada stops supplying Mo-99, lasting at least until current global Mo-99 suppliers complete their planned capacity expansions (planned for 2017) and substantial new domestic Mo-99 supplies enter the market (not likely until 2018 and beyond). The study recommends that the U.S. government continue to work with the Canadian government to ensure that there is an executable and well-communicated plan in place to restart production of Mo-99 in Canada should such shortages occur.

[3] Tc-99m, the decay product of Mo-99, is used for medical diagnostic imaging. Mo-99 is not used directly for this purpose. The letter "m" denotes that the isotope is metastable. See Chapter 2.

Study charge 5: Assess progress made by the DOE and others to eliminate worldwide use of HEU in reactor targets and medical isotope production facilities and identify key remaining obstacles for eliminating HEU use. (Chapter 5) The American Medical Isotopes Production Act of 2012 is accelerating the elimination of worldwide use of HEU for medical isotope production. Current global Mo-99 suppliers have committed to eliminating HEU use in reactor targets and medical isotope production facilities and are making uneven progress toward this goal. Progress is being facilitated by financial support from NNSA and technical support from U.S. national laboratories, but progress is also being impeded by the continued availability of Mo-99 produced with HEU targets. The study recommends that the U.S. government and others take additional actions to promote the wider utilization of Mo-99/Tc-99m produced without the use of HEU targets. Even after HEU is eliminated from Mo-99 production, large quantities of HEU-bearing wastes from past production will continue to exist at multiple locations throughout the world. The study recommends that the U.S. government continue to work with global Mo-99 suppliers and their regulators to reduce the proliferation hazard from wastes containing HEU.

Summary

Congress requested that the National Academies of Sciences, Engineering, and Medicine (the Academies) conduct a study on the production and utilization of the medical isotope molybdenum-99 (Mo-99). The congressional mandate for the study is provided in the American Medical Isotopes Production Act of 2012 (AMIPA; P.L. 112-239). This summary provides the findings and recommendations from the study, organized by the five study charges in the statement of task (see Sidebar S.1).

The decay product[1] of Mo-99, technetium-99m (Tc-99m), and associated[2] medical isotopes iodine-131 (I-131) and xenon-133 (Xe-133) are used worldwide for medical diagnostic imaging or therapy. The United States consumes about half of the world's supply of Mo-99, but there has been no domestic (i.e., U.S.-based) production of this isotope since the late 1980s. The United States imports Mo-99 for domestic use from Australia, Canada, Europe, and South Africa.

Mo-99 and Tc-99m cannot be stockpiled for use because of their short half-lives. Consequently, they must be routinely produced and delivered to medical imaging centers. Almost all Mo-99 for medical use is produced by irradiating highly enriched uranium (HEU) targets in research reactors, several of which are over 50 years old and are approaching the end of their operating lives. Unanticipated and extended shutdowns of some of these old reactors have resulted in severe Mo-99 supply shortages in the United

[1] Mo-99 and Tc-99m have about 66-hour and 6-hour half-lives, respectively. The letter "m" in Tc-99m denotes that the isotope is metastable. See Chapter 2.

[2] These isotopes are "associated" because they can be coproduced with Mo-99.

SIDEBAR S.1
Statement of Task

An ad hoc committee will conduct a study and provide a report with findings and recommendations on the status and utilization of molybdenum-99 for medical use. This study will provide

1. A list of facilities that produce molybdenum-99 for medical use, including an indication of whether these facilities utilize highly enriched uranium.
2. A review of international production of molybdenum-99 over the previous 5 years, including whether any new production was brought online; whether any facilities halted production unexpectedly; and whether any facilities used for production were decommissioned or otherwise permanently removed from service.
3. An assessment of progress made in the previous 5 years toward establishing domestic production of molybdenum-99 for medical use, including the extent to which other medical isotopes that have been produced with molybdenum-99, such as iodine-131 and xenon-133, are being used for medical purposes.
4. *The adequacy of molybdenum-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond.*
5. An assessment of the progress made by the Department of Energy and others to eliminate worldwide use of highly enriched uranium in reactor targets and medical isotope production facilities. *This assessment should identify key remaining obstacles for eliminating highly enriched uranium from reactor targets and medical isotope production facilities and recommend steps that could be taken to overcome the identified obstacles.*

Note about the statement of task: The language of the statement of task shown in italics was not part of the congressional mandate provided by AMIPA; it was added during the negotiations between the Academies and the sponsoring organization within DOE, the National Nuclear Security Administration (DOE-NNSA). DOE-NNSA and the Academies judged that these added tasks are in support of AMIPA and would assist DOE-NNSA with its nuclear non-proliferation mission.

States and other countries. Some of these shortages have disrupted the delivery of medical care.

The present study examines the production and utilization of Mo-99 and associated medical isotopes, including the elimination of HEU in the reactor targets used for such production. A second Academies study examined the use of HEU in research reactor fuel. This study was completed in early 2016 and published in the report titled *Reducing the Use of Highly Enriched Uranium in Civilian Research Reactors* (NASEM, 2016).

STUDY CHARGE 1

Provide a list of facilities that produce molybdenum-99 for medical use, including an indication of whether these facilities utilize highly enriched uranium.

The committee developed the following two findings to address this study charge (see Chapter 3):

FINDING 1A: As of June 2016, most (~95 percent) of the global supply of molybdenum-99 for medical use is produced in seven research reactors located in Australia, Canada, Europe, and South Africa and supplied from five target processing facilities in those same locations. The remainder (~5 percent) of the global supply is produced in other locations for regional use.

FINDING 1B: As of June 2016, about 75 percent of the global supply of molybdenum-99 for medical use is produced by irradiating highly enriched uranium targets in six research reactors; one of these reactors is also fueled with highly enriched uranium. The remaining 25 percent of global supply is produced by irradiating low enriched uranium targets in two research reactors.

One of the reactors used to produce Mo-99 (SAFARI-1 in South Africa) irradiates both HEU and low enriched uranium (LEU) targets. Information about these reactors and target processing facilities is provided in Tables 3.2 and 3.3 in Chapter 3.

STUDY CHARGE 2

Review international production of molybdenum-99 over the previous 5 years,[3] including whether any new production was brought online; whether any facilities halted production unexpectedly; and whether any facilities used for production were decommissioned or otherwise permanently removed from service.

[3] These examinations are referenced to 2009, the year of publication of the previous Academies report on medical isotope production (NRC, 2009).

The committee developed the following four findings to address this study charge (see Chapter 3):

FINDING 2A: New molybdenum-99 supplies have become available since 2009, and expansions in available supply capacity are planned by current and new suppliers: A supplier in Australia (Australian Nuclear Science and Technology Organisation) has entered the global supply market and plans to expand its available supply capacity; existing global suppliers in Europe (Mallinckrodt) and South Africa (NTP Radioisotopes) have initiated plans to expand their available supply capacities; and the Russian Federation plans to become a global supplier.

FINDING 2B: Reactors in France (OSIRIS) and Canada (NRU) have halted or announced plans to halt molybdenum-99 production since 2009. These shutdowns have reduced/will reduce available production capacity and reserve production capacity that could be used to cover supply shortages if they occur.

Implementation of the planned expansions by current global Mo-99 suppliers would add about 4,400 6-day Ci per week[4] of available supply capacity, almost offsetting the 4,680 6-day Ci per week of available supply capacity loss when the NRU reactor in Canada stops the routine production of Mo-99 after October 2016 and permanently shuts down at the end of March 2018. About 2,400 6-day Ci per week of available production capacity was lost after the OSIRIS reactor (France) shut down in December 2015.

Argentina, Brazil, and South Korea are building new reactors to provide regional supplies of Mo-99. Russia plans to become a global supplier of Mo-99 and capture about a 20 percent share of the global market using reactors at the Research Institute of Atomic Reactors in Dimitrovgrad (additional discussion of Russian plans is provided under study charge 5).

FINDING 2C: Molybdenum-99 production and supply were disrupted unexpectedly in 2009-2010 because of prolonged unplanned reactor and target processing facility shutdowns. These shutdowns caused protracted and severe molybdenum-99 supply shortages in the United States and some other countries. Shorter supply interruptions have

[4] Mo-99 is frequently priced and sold based on a quantity referred to as 6-day curie, which is the measurement of the remaining radioactivity of Mo-99 six days after the time of measurement. See Sidebar 2.3 in Chapter 2.

also occurred as a result of shorter planned and unplanned reactor and target processing facility shutdowns and transport disruptions.

FINDING 2D: Coordinated actions taken by governments, molybdenum-99 suppliers, technetium generator suppliers, technetium-99m suppliers, and others since the 2009-2010 supply shortages have improved the resilience of the global supply chain, minimized supply disruptions during unplanned reactor and processing facility shutdowns, and increased molybdenum-99/technetium-99m utilization efficiencies. Supply vulnerabilities remain, however, owing to the small number of participating organizations at some steps in the supply chain.

The 2009-2010 shortages occurred when Canada's NRU and Europe's HFR reactors were simultaneously shut down for extended periods. Supply interruptions also occurred in 2013 as a result of shorter planned and unplanned reactor and processing facility shutdowns. Mo-99 supply has also been interrupted frequently because of transportation denials and delays. However, these are typically resolved within hours or a few days.

Several actions have been taken since the 2009-2010 supply shortages to improve the resilience of the Mo-99/Tc-99m supply chain. These actions include the development of outage reserve capacity, coordination of reactor and target processing facility outages, enhanced communications among supply chain participants, and the creation of Mo-99 supplier alliances.

In spite of these actions, vulnerabilities still remain in some parts of the supply chain owing to the small number of participating organizations. This is particularly true for the front end of the supply chain, where one company (CERCA) provides the majority of the targets used to produce Mo-99.

STUDY CHARGE 3

Assess progress made in the previous 5 years toward establishing domestic production of molybdenum-99 for medical use, including the extent to which other medical isotopes that have been produced with molybdenum-99, such as iodine-131 and xenon-133, are being used for medical purposes.

The committee developed the following two findings to address this study charge (see Chapter 4):

FINDING 3A: The American Medical Isotopes Production Act of 2012 and financial support from the Department of Energy's National

Nuclear Security Administration have stimulated private-sector efforts to establish U.S. domestic production of molybdenum-99 for medical use. However, no domestic commercial production will be established before Canada stops producing molybdenum-99 after October 2016. Potential domestic molybdenum-99 suppliers face technical, financial, regulatory, and market penetration challenges. The market challenges will likely increase after current global suppliers expand production.

DOE-NNSA has entered into cooperative agreements with five U.S.-based companies to develop and demonstrate technologies for domestic production of Mo-99. Work by three companies (General Atomics,[5] NorthStar Medical Radioisotopes, and SHINE Medical Technologies) continues to progress toward commercial production. Each project is intended to supply half or more of U.S. needs. None of these companies will produce any Mo-99 for commercial sale before the end of October 2016 (when Canada halts production of Mo-99). It is unlikely that substantial domestic supplies of Mo-99 will become available until 2018 and beyond.

All but one of the existing global suppliers are expanding their Mo-99 production capacities to fill the supply gap that will be created when Canada stops producing Mo-99. The expanding supply of Mo-99 to the market will put further downward pressures on prices absent increased demand, likely making it difficult for new suppliers to gain a foothold in the market.

FINDING 3B: There is currently no domestic production of iodine-131 or xenon-133, but U.S. organizations are developing the capability to produce one or both of these isotopes.

Nordion (Canada) currently supplies most of the I-131 and Xe-133 used in the United States, and Institut National des Radioéléments (IRE, Belgium) recently began supplying Xe-133 to the United States. The University of Missouri Research Reactor Center has regulatory approval to produce I-131 by irradiating tellurium targets and is currently testing its process. Other potential domestic suppliers have plans to recover I-131 and Xe-133 as part of their Mo-99 production processes.

[5] General Atomics is cooperating with Nordion and the University of Missouri Research Reactor Center on this project.

STUDY CHARGE 4

The adequacy of molybdenum-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond.

Chapter 6 addresses future domestic medical needs, and Chapter 7 addresses supply adequacy. The committee interprets the term "beyond" in the study charge to mean the next 5 years (i.e., until about 2021). The committee judges that there are too many uncertainties in Mo-99 supply and demand (see Chapter 6) to look any further into the future.

The committee developed the following two findings and one recommendation to address this study charge:

FINDING 4A: Domestic demand for molybdenum-99/technetium-99m for medical use has been declining for at least a decade. The decline began well before the global molybdenum-99 supply shortages in 2009-2010 and is reflected in nuclear imaging procedures that utilize technetium-99m. The average decline in domestic molybdenum-99/technetium-99m utilization from 2009-2010 to 2014-2015 was about 25 percent, similar to the estimated decline in global molybdenum-99 demand for that same period. Some of the factors responsible for the decline in domestic demand will continue to operate into the future, making it unlikely that domestic demand will increase significantly over the next 5 years. International demand for molybdenum-99 for medical use may increase over the next 5 years primarily because of higher utilization in emerging Asian markets.

Domestic medical use of Mo-99/Tc-99m is unlikely to increase significantly over the next 5 years primarily because of changes in health care policies, reimbursement rules, and medical practices. Some of these changes will take several additional years to be fully implemented across the U.S. health care system and therefore will continue to put downward pressures on domestic demand; these pressures may not be offset by potential growth factors such as aging of the U.S. population.

FINDING 4B: Global supplies of molybdenum-99 are adequate at present to meet U.S. domestic needs. However, available supply capacity will be reduced substantially after October 2016 when the Canadian supplier shuts down, and supply capacity could be reduced further in 2017-2018 when European suppliers convert to low enriched uranium targets and the Australian supplier starts up a new target process-

ing facility, especially if these suppliers encounter conversion and/or start-up delays. The committee judges that there is a substantial (>50 percent) likelihood of severe molybdenum-99/technetium-99m supply shortages after October 2016, lasting at least until current global suppliers complete their planned capacity expansions.

RECOMMENDATION 4B: The U.S. government should continue to work with the Canadian government to ensure that there is an executable and well-communicated plan in place to restart Canadian supply of molybdenum-99 after October 2016.

The Canadian government announced that its NRU reactor at the Canadian Nuclear Laboratories (CNL) would cease the routine production of Mo-99 after October 2016. The NRU reactor and associated processing facilities at CNL would be kept on hot standby until the end of March 2018, after which time the reactor will be permanently shut down. Canada will be a "supplier of last resort" during this standby period.

The committee's finding that there is a substantial likelihood of severe Mo-99/Tc-99m supply shortages after October 2016 is based on several factors:

- The number of irradiation services suppliers will be reduced from seven to six after NRU stops producing Mo-99. Four of the remaining suppliers use reactors that are over 50 years old (BR-2, HFR, LVR-15, and SAFARI-1), and one supplier uses a reactor that is over 40 years old (Maria). Several of the reactors used to produce Mo-99 have already had unplanned and extended outages for major repairs. There is no reason to believe that such outages will not occur in the future.
- The number of global Mo-99 suppliers will be reduced from five to four after Canada halts production. Three of these suppliers (Australian Nuclear Science and Technology Organisation [ANSTO], IRE, and Mallinckrodt) are currently making substantial modifications to their facilities or processes. The potential for unexpected supply disruptions increases any time a supplier moves to a new facility or implements a new process.
- NTP and ANSTO also rely on one reactor each (SAFARI-1 and OPAL, respectively) for all of their target irradiations. They have backup-supply agreements but no backup irradiation services suppliers. Unplanned outages of one or both of these reactors could result in supply shortages, especially if the outages extend over multiple weeks.

Recommendation 4B is intended to ensure that production capacity is available after October 2016 and before April 2018 (when NRU is on hot standby) to address severe supply shortages of Mo-99 arising from unplanned shutdowns of reactors or target processing facilities.

STUDY CHARGE 5

An assessment of the progress made by the Department of Energy and others to eliminate worldwide use of highly enriched uranium in reactor targets and medical isotope production facilities. This assessment should identify key remaining obstacles for eliminating highly enriched uranium from reactor targets and medical isotope production facilities and recommend steps that could be taken to overcome the identified obstacles.

Chapter 5 provides the committee's assessment of the progress made by the DOE and others to eliminate worldwide use of highly enriched uranium in reactor targets and medical isotope production facilities. The committee developed the following four findings and three recommendations to address this study charge:

FINDING 5A: The American Medical Isotopes Production Act of 2012 is accelerating the elimination of worldwide use of U.S.-origin highly enriched uranium in targets and medical isotope production facilities. There are no insurmountable obstacles to the elimination of highly enriched uranium from medical isotope production. The four global molybdenum-99 suppliers that use highly enriched uranium have committed to eliminating its use in reactor targets and medical isotope production facilities and are making uneven progress toward this goal. This progress is being facilitated by financial support from the U.S. government and technical support from U.S. national laboratories.

NTP demonstrated early global leadership by being the first global supplier to demonstrate that it is technically and economically feasible to convert its facilities to produce Mo-99 using LEU targets. NTP was following in the footsteps of ANSTO, which has always produced Mo-99 with LEU targets. IRE and Mallinckrodt plan to use the same types of LEU targets and aqueous chemical processes that are currently being used by ANSTO and NTP.

Nordion plans to begin producing Mo-99 using a new technology.

However, Nordion's first-half 2018 schedule for initial commercial production is optimistic given the unexpected technical obstacles that frequently arise with these first-of-a-kind projects as well as the long regulatory lead times normally associated with the establishment of new Mo-99 production.

FINDING 5B: Several organizations have taken leadership roles in promoting the wider utilization of molybdenum-99 produced without the use of highly enriched uranium. However, progress is being impeded by several factors, including the continued availability of molybdenum-99 produced with highly enriched uranium targets.

RECOMMENDATION 5B: The U.S. government and others should take additional actions to promote the wider utilization of molybdenum-99 and technetium-99m produced without the use of highly enriched uranium targets.

Global Mo-99 suppliers are undergoing a protracted and difficult transition away from the use of mostly HEU targets to the exclusive use of LEU targets. Companies that are now producing Mo-99 with LEU targets (ANSTO and NTP Radioisotopes) find themselves at a competitive disadvantage in the market, a situation they describe as "unsustainable."

Market uptake of Mo-99/Tc-99m produced from LEU targets is lagging in spite of the commendable efforts being taken by many organizations to increase utilization. At present, the global demand for Mo-99 produced with LEU targets is lower than global supply capacity. Additional steps to promote the wider utilization of Mo-99/Tc-99m produced without the use of HEU targets and hasten the elimination of HEU from the global supply chain could include the following:

- Centers for Medicare & Medicaid Services: Continue to offer the $10 add-on reimbursement for Tc-99m from non-HEU sources until Mo-99 from HEU sources is no longer available for commercial sale in the United States; accelerate the retrospective analysis of medical procedure costs that utilize Tc-99m from non-HEU sources.
- NNSA: Examine options to eliminate the availability of HEU targets for Mo-99 production to shorten the transition period, for example, by buying back U.S.-origin HEU in raw or target form from global Mo-99 suppliers once Mo-99 production with LEU targets is firmly established.
- Technetium generator manufacturers and nuclear pharmacies: Continue to work with the medical community, their purchasing orga-

nizations, and private insurance companies to further increase the utilization of Mo-99 from non-HEU sources.
- U.S. Congress: Restrict or place financial penalties on the import of Mo-99 produced with HEU targets after Mo-99 from non-HEU sources becomes widely available for commercial sale in the United States.

FINDING 5C: Even after highly enriched uranium is eliminated from molybdenum-99 production, large quantities of processing wastes containing highly enriched uranium will continue to exist at multiple global locations. This weapons-grade material is a proliferation hazard. The Department of Energy's National Nuclear Security Administration is working with global suppliers and their governments to examine options for downblending or returning this material to the United States.

RECOMMENDATION 5C: The U.S. government should continue to work with global molybdenum suppliers and their regulators to reduce the proliferation hazard from processing waste from medical isotope production containing U.S.-origin highly enriched uranium. The U.S. government should also develop a global inventory of this waste if one does not already exist.

DOE-NNSA has taken several actions to implement the 2009 Academies' recommendation to manage the HEU wastes from Mo-99 production from U.S.-origin HEU. These actions are described in Section 5.5 of Chapter 5. Of particular note is NNSA's work with the Canadian government to return to the United States the HEU waste that is being stored in liquid form at CNL, as well as its work with Argentina and Indonesia to downblend their HEU wastes. The HEU waste from Mo-99 production in Pakistan, South Africa, and the Russian Federation is not of U.S. origin. Nevertheless, this waste is still a proliferation hazard.

FINDING 5D: The government of the Russian Federation has not announced a commitment or schedule for converting molybdenum-99 production from highly enriched uranium to low enriched uranium targets. The continued sale of molybdenum-99 produced with highly enriched uranium targets to international markets could disrupt progress toward full market adoption of molybdenum-99 from non-highly enriched uranium sources.

RECOMMENDATION 5D: The U.S. government—through the U.S. Department of State, the U.S. Department of Energy's National Nuclear

Security Administration, and the U.S. scientific and technical communities—should engage with the Russian government to clarify its schedule for converting molybdenum-99 production from highly enriched uranium to low enriched uranium targets. The U.S. government should pursue opportunities for engagements between U.S. and Russian scientific and technical organizations to facilitate conversion.

The continued sale of Mo-99 produced with HEU targets to international markets from the Russian Federation or any other country could delay the full transition to non-HEU supply, continue the current market distortions in Mo-99 prices, and impact the sustainability of Mo-99 supplies over the long term.

Several steps could be taken by the U.S. government to address Recommendation 5D. The U.S. government could work through the Organisation for Economic Co-operation and Development/Nuclear Energy Agency to obtain a better understanding of Russian plans and schedules for eliminating HEU from the targets used to produce Mo-99 for sale on international markets and examine options for discouraging such sales. The U.S. government could also encourage engagements on medical isotope production between the U.S. and Russian technical communities. Such engagements could also provide opportunities for unofficial exchanges of information and views between the U.S. and Russian governments.

1

Background and Study Task

This study was mandated by the U.S. Congress in the American Medical Isotopes Production Act of 2012[1] (AMIPA) (see Appendix A):

> The Secretary [of Energy] shall enter into an arrangement with the National Academy of Sciences[2] to conduct a study of the state of molybdenum-99 production and utilization, to be provided to Congress not later than 5 years after the date of enactment of this Act.

The decay product[3] of molybdenum-99 (Mo-99), technetium-99m[4] (Tc-99m), and associated[5] medical isotopes iodine-131 (I-131) and xenon-133 (Xe-133) are used worldwide for medical diagnostic imaging or therapy (see Sidebar 1.1). The United States consumes almost half of the world's supply of Mo-99, but there has been no domestic (i.e., U.S.-based) production of this isotope since the late 1980s.[6] The United States imports Mo-99 for domestic use from Australia, Canada, Europe, and South Africa.

Mo-99 and Tc-99m cannot be stockpiled for use because of their short

[1] Public Law 112-239.

[2] Now the National Academies of Sciences, Engineering, and Medicine, referred to as the "Academies" in this report.

[3] Mo-99 decays to Tc-99m with a 66-hour half-life. See Chapter 2.

[4] The letter "m" denotes that the isotope is metastable. See Chapter 2.

[5] These isotopes are "associated" because they can be coproduced with Mo-99. See Chapter 2.

[6] Cintichem, Inc., produced Mo-99 in Tuxedo, New York, until 1989.

SIDEBAR 1.1
Medical Isotope Production and Utilization

Technetium-99m (Tc-99m), the decay product of Mo-99, is used for medical diagnostic imaging to evaluate physiologic and metabolic processes in tissues and organs with the ultimate goal to diagnose disease. Most of the Tc-99m used for medical imaging is produced through a multistep process: Targets containing uranium-235 (see Sidebar 1.2) are irradiated with neutrons in research reactors. Irradiation causes the uranium-235 to fission, which produces a number of different fission products, including those of medical interest: Mo-99, I-131, and Xe-133. After irradiation, the targets are chemically processed to recover Mo-99 and, if desired, these other medical isotopes.

The recovered Mo-99 (in purified liquid form) is incorporated into *technetium generators* (see Chapter 2) for shipment to nuclear pharmacies, hospitals, and medical clinics. Tc-99m builds up in the generators over time as the Mo-99 decays (with a 66-hour half-life). Generators are typically *eluted* (see Chapter 2) once or twice per day for 1-2 weeks to obtain Tc-99m for medical use.

Tc-99m is usually chemically incorporated into small molecule ligands and proteins. When administered, these molecules concentrate in specific tissues or organs of interest. The Tc-99m contained in the labeled molecules decays with about a 6-hour half-life and emits 140 kiloelectron volt (keV) photons. These photons can be detected with gamma cameras and computer-processed to obtain functional images.

Mo-99 and Tc-99m cannot be stockpiled for medical use because of their short half-lives. An international supply chain has been developed to produce and ship these isotopes around the world on a routine basis.

half-lives.[7] Consequently, they must be routinely produced and delivered to medical imaging centers. At present, almost all Mo-99 for medical use is produced by irradiating targets containing weapons-grade highly enriched uranium (HEU) (see Sidebar 1.2) in research and test reactors,[8] some of which are over 50 years old (see Table 3.1 in Chapter 3). Unanticipated and extended shutdowns of some of these reactors have resulted in severe Mo-99 supply shortages in the United States and other countries. Some of these shortages have disrupted the delivery of medical care.

About 40-45 kilograms (kg) of weapons-grade HEU, mostly supplied

[7] Half-life (denoted as $t_{1/2}$) is defined as the time required for half of the atoms of a given radioisotope to decay to another radioisotope.

[8] Research and test reactors are used for scientific research, materials testing, and education/training. This report refers to these reactors as *research reactors* to be consistent with the usage in NASEM (2016). Sidebar 2.2 in Chapter 2 provides additional information about these reactors.

SIDEBAR 1.2
Uranium Enrichment and Use

Most uranium found in nature contains about 99.3 percent by weight of uranium-238 and about 0.7 percent by weight of uranium-235 along with minor amounts of other uranium isotopes. *Enrichment* refers to processes used to increase the weight percentage of uranium-235 relative to uranium-238. Uranium that is enriched to less than 20 percent uranium-235 by weight is referred to as *low enriched uranium* (LEU). *Highly enriched uranium* (HEU) contains 20 percent or greater weight percent of uranium-235. HEU enriched to 90 percent or above is referred to as *weapons-grade HEU*.

The processes used to enrich uranium exploit the small (three-neutron) mass difference between uranium-235 and uranium-238. Two enrichment processes, gaseous diffusion and gas centrifuge, have been used to produce HEU in the United States and several other countries for defense and civilian applications.

As noted in the text, the primary concern with civilian utilization of HEU is its potential diversion by terrorists to make nuclear explosive devices. The International Atomic Energy Agency (IAEA) defines a *significant quantity* of HEU to be the approximate quantity of HEU from which the possibility of manufacturing a nuclear explosive device cannot be excluded (see https://www.iaea.org/sites/default/files/iaea_safeguards_glossary.pdf). The IAEA significant quantity for HEU is 25 kilograms (kg). HEU from unirradiated targets or target processing waste could potentially be used to make a nuclear explosive device if sufficient quantities could be stolen by terrorists.

by the U.S. government,[9] are used annually to produce these targets. Civilian use of HEU is a proliferation hazard because of the potential for its diversion by terrorists to make nuclear explosive devices (see Sidebar 1.2).

In enacting AMIPA, Congress was attempting to balance two national interests:

1. Ensure a reliable U.S. supply of Mo-99 and associated medical isotopes.

[9] The U.S. government supplies HEU to Canada and Europe for production of medical isotopes. South Africa produces medical isotopes using indigenous HEU (and also using LEU that is currently supplied by Russia). See Chapter 5.

2. Eliminate the use of HEU in medical isotope production, especially in the targets used to produce medical isotopes.[10]

Congress recognized that these two interests were potentially in conflict; that is, elimination of HEU from medical isotope production without an alternate production method could affect the supply of Mo-99 to the United States. Congress provided additional provisions in AMIPA to promote the development of reliable domestic supplies of Mo-99 while also eliminating the use of HEU targets for its production. These include

- Technical and financial support to private-sector organizations for development of domestic production of Mo-99 without the use of HEU (see Chapter 5 of the present report for additional information);
- Leasing of low enriched uranium (LEU; see Sidebar 1.2) for domestic production of Mo-99 and take-back of radioactive waste from such production if alternate disposal pathways are not available (see Sidebar 4.1 in Chapter 4); and
- Phase-out of U.S. government exports of HEU for medical isotope production by 2020, with provision for extending this phase-out date if supplies of Mo-99 produced without HEU are not sufficient to meet U.S. needs (see Chapter 5).

The first and third provisions were suggested to Congress in the 2009 Academies report *Medical Isotope Production Without Highly Enriched Uranium* (NRC, 2009). The study that produced that report, which was mandated by the U.S. Congress in the Energy Policy Act of 2005, examined the technical and economic feasibility of producing medical isotopes without HEU. That study was motivated by a conflict between the objectives of the Energy Policy Act of 1992, which created increasing pressures to phase out HEU exports from the United States for medical isotope production, and the Energy Policy Act of 2005, which sought to increase the reliability of medical isotope supplies by permitting the export of HEU for medical isotope production, thus bypassing the requirements of the 1992 Act for HEU exports to Canada and Europe. That Academies' study (NRC, 2009) concluded that production of medical isotopes without HEU was economically and technically feasible.

The Department of Energy's National Nuclear Security Administra-

[10] Some reactors used to irradiate targets for medical isotope production are fueled with HEU. The U.S. government has been supporting programs to eliminate the use of HEU in research reactor fuel since the late 1970s (see NASEM, 2016). Elimination of HEU in research reactor fuel is not addressed in the present report.

tion (DOE-NNSA) is the lead agency within the U.S. government for implementing AMIPA. The agency is well positioned to implement the non-proliferation provisions of AMIPA given its interest and expertise in non-proliferation. NNSA has teamed up with other parts of the U.S. government—for example, the Office of Science and Technology Policy within the White House, and the Centers for Medicare & Medicaid Services and the U.S. Food and Drug Administration within the Department of Health and Human Services—to promote domestic production of Mo-99 without HEU and to improve the reliability and sustainability of Mo-99/Tc-99m supplies. NNSA is also working with other national governments, primarily through the Organisation for Economic Co-operation and Development, to eliminate HEU from Mo-99 production and improve supply reliability and sustainability.

1.1 STATEMENT OF TASK FOR PRESENT STUDY

The Academies have carried out the AMIPA-mandated examination in two parallel studies:

- The present study examines the production and utilization of Mo-99 and associated medical isotopes, including the elimination of HEU in the reactor targets used for such production.
- A second Academies study examined the use of HEU research reactor fuel. This study was completed in early 2016 and published in the report titled *Reducing the Use of Highly Enriched Uranium in Civilian Research Reactors* (NASEM, 2016).

The complete statement of task for the present study is shown in Sidebar 1.3. Study charges 1, 2, 3, and the first part of study charge 5 explicitly address the AMIPA mandate. Study charge 4 and the last part of 5 (shown in italics in Sidebar 1.3) were added in consultation with the study sponsor, DOE-NNSA, to assist NNSA with its nuclear non-proliferation mission and to provide important additional information to the U.S. Congress and the medical isotope production and utilization communities.

Study charge 5 (Sidebar 1.3) calls for an assessment of progress made in eliminating HEU from *reactor targets* and *medical isotope production facilities*. It is important to recognize that medical isotopes can be produced in reactors fueled with HEU (see Chapter 3). The present study does not address the elimination of HEU from reactor fuel; that issue was addressed in NASEM (2016) as noted above.

SIDEBAR 1.3
Statement of Task for This Study

An ad hoc committee will conduct a study and provide a report with findings and recommendations on the status and utilization of molybdenum-99 for medical use. This study will provide

1. A list of facilities that produce molybdenum-99 for medical use, including an indication of whether these facilities utilize highly enriched uranium.
2. A review of international production of molybdenum-99 over the previous 5 years, including whether any new production was brought online; whether any facilities halted production unexpectedly; and whether any facilities used for production were decommissioned or otherwise permanently removed from service.
3. An assessment of progress made in the previous 5 years toward establishing domestic production of molybdenum-99 for medical use, including the extent to which other medical isotopes that have been produced with molybdenum-99, such as iodine-131 and xenon-133, are being used for medical purposes.
4. *The adequacy of molybdenum-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond.*
5. An assessment of the progress made by the Department of Energy and others to eliminate worldwide use of highly enriched uranium in reactor targets and medical isotope production facilities. *This assessment should identify key remaining obstacles for eliminating highly enriched uranium from reactor targets and medical isotope production facilities and recommend steps that could be taken to overcome the identified obstacles.*

Note: The text in italics was not part of the congressional mandate in AMIPA; it was added in consultation with the study sponsor, the NNSA.

1.2 STRATEGY TO ADDRESS THE STUDY TASK

The present study was carried out by a committee of 13 experts with collective expertise in accelerator design and operation, chemistry and radiopharmaceutical chemistry, medical economics, medical isotope production, nuclear engineering, nuclear medicine, nuclear pharmacy operations, and radioactive waste processing and management. In selecting the membership of this committee, the Academies sought to obtain a balance between members with experience in the production and isotope utilization in nuclear medicine, and members with relevant technical expertise but little-to-no direct experience with medical isotope production or utiliza-

tion. Two members of the committee, including its vice chair, also served on the committee that authored the Academies' 2009 medical isotopes study (NRC, 2009). Biographical sketches of the committee members are provided in Appendix B.

The committee held six face-to-face meetings and additional teleconferences to gather the information it needed to complete this report. Information was gathered from the following organizations:

- The study sponsor (NNSA) and other federal agencies with responsibilities related to medical isotope production and utilization.
- Companies involved in the production, supply, and utilization of Mo-99/Tc-99m.
- Potential future U.S. suppliers of Mo-99.
- Potential future Canadian suppliers of Mo-99/Tc-99m.
- National laboratory experts who are providing technical support to current and potential future suppliers of Mo-99.
- International organizations with missions relevant to the reliability and sustainability of the medical isotope supply chain.
- Professional societies, including medical societies, as well as other nongovernmental organizations interested in the reliability and sustainability of medical isotope supply chains.

Subgroups of the committee also visited medical isotope production and supply facilities in Australia, Canada, Europe, Russia, and South Africa to learn about their operations and future plans. These information-gathering meetings and site visits are described in Appendix C.

The committee asked several organizations to perform accuracy checks on factual portions of this report during the Academies report review process.[11] These organizations included the study sponsor (NNSA) as well as current and potential future participants in the Mo-99/Tc-99m supply chain. The committee did not share the analytical portions of this report or the findings and recommendations with any outside persons or organizations.

1.3 REPORT ROAD MAP

This report is organized into seven chapters that address the statement of task (Sidebar 1.3) in its entirety:

- Chapter 1 (this chapter) provides background on the congressional mandate and describes the study task.

[11] These fact checks took place during July-August 2016.

- Chapter 2 provides technical information about Mo-99/Tc-99m production and utilization.
- Chapter 3 reviews the international production of Mo-99 for medical use since NRC (2009) was completed, and it examines future production prospects.
- Chapter 4 assesses progress toward establishing domestic production of Mo-99 for medical use.
- Chapter 5 reviews efforts to eliminate HEU from targets used for Mo-99 production.
- Chapter 6 reviews current and projected demand for Mo-99 for medical use.
- Chapter 7 describes the adequacy of current and projected Mo-99 supplies for medical use.

The appendixes provide the text from AMIPA (Appendix A), short biographies of the committee and staff (Appendix B), descriptions of the information-gathering activities for the study (Appendix C), a list of radiopharmaceuticals used to support the committee's analysis of domestic Mo-99/Tc-99m demand in Chapter 6 (Appendix D), and a list of acronyms (Appendix E).

2

Medical Isotope Production and Utilization

This chapter provides a primer on the production of molybdenum-99 (Mo-99), technetium-99m (Tc-99m), iodine-131 (I-131), and xenon-133 (Xe-133), and it also describes the Mo-99/Tc-99m supply chain and economics. It is intended for nonexpert readers.

Nuclear medicine is a medical specialty that utilizes radioactive isotopes, referred to as *radionuclides,* to diagnose and treat disease. These radionuclides are incorporated into *radiopharmaceuticals*[1] and introduced into the body by injection, swallowing, or inhalation. Physiologic/metabolic processes in the body concentrate the tracers in specific tissues and organs; the radioactive emissions from the tracers can be used to noninvasively image these processes (see Sidebar 2.1) or kill cells in regions where radionuclides have concentrated.

Other types of noninvasive diagnostic procedures—for example, computed tomography (CT) and magnetic resonance imaging (MRI)—can detect anatomical changes in tissues and organs as the result of disease. Nuclear medicine procedures can often detect the physiological and metabolic changes associated with disease before any anatomical changes occur. Such procedures can be used to identify disease at early stages and evaluate patients' early responses to therapeutic interventions.

The radionuclide of primary interest in this report is Tc-99m, the radioactive decay product of Mo-99 (see Section 2.1 in this chapter). Other

[1] Radiopharmaceuticals typically consist of radionuclides bound chemically to organic molecules that are part of biological pathways. The molecules are selected based on their affinities for organs or tissues of concern for a particular medical procedure.

SIDEBAR 2.1
Nuclear Medicine Imaging

This sidebar describes the nuclear medicine imaging methods (modalities) that are in common use today in the United States and many other countries.

Single Photon Emission Computed Tomography (SPECT) generates three-dimensional (3D) images of tissues and organs using radionuclides that emit gamma rays; the most commonly used radionuclide is Tc-99m. Individual gamma rays emitted from the decay of these radionuclides (i.e., *single photon emissions*) are detected using a gamma camera. This camera technology is used to obtain two-dimensional (2D) images; 3D SPECT images are computer generated from a large number of 2D images recorded at different angles.

Positron Emission Tomography (PET) generates 3D images of tissues and organs using tracers that emit positrons (i.e., positive electrons): for example, fluorine-18 (F-18). Annihilation reactions between the positrons from these radionuclides and electrons present in tissues and organs produce photons. (Two photons are emitted simultaneously for each annihilation reaction and essentially travel in opposite directions.) The photon pairs are detected with a camera having a ring of very fast detectors and electronics.

PET images generally have a higher contrast and spatial resolution than do SPECT images. However, PET equipment is more expensive and therefore not as widely available as SPECT equipment. Additionally, most PET tracers have short half-lives (e.g., nitrogen-13 (N-13): 10 minutes, carbon-11 (C-11): 20 minutes, and F-18: 110 minutes), so they have to be produced close to their point of use.

Both SPECT and PET cameras have been paired with CT to provide functional and anatomic imaging (SPECT/CT or PET/CT; see Figure S2.1). PET cameras have also been combined with MRI (PET/MRI). These hybrid images improve diagnostic accuracy.

radionuclides of interest are I-131 and Xe-133. Their production and use are described in the following sections.

2.1 Tc-99m

Tc-99m is used in approximately 80 percent of all nuclear medicine procedures performed worldwide each year. Historically, about half of these procedures have been performed in the United States (Verbeek, 2008); that proportion likely remains about the same today.

Tc-99m is a particularly useful imaging radionuclide because it

- Can be chemically incorporated into radiopharmaceuticals that have affinities for different tissue and organ systems.

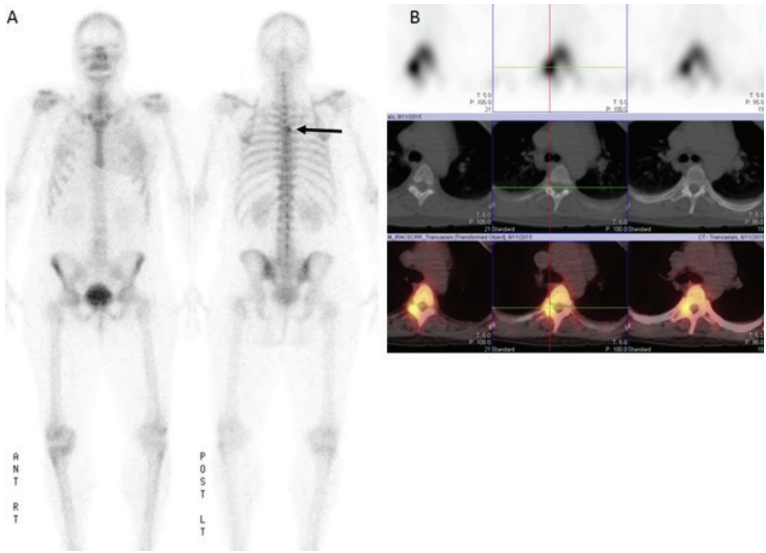


FIGURE S2.1 (A) planar (2D) whole body Tc-99m MDP bone scan taken from the front (ant) and back (post) combined with (B) SPECT/CT images used for disease diagnosis.

- Has a sufficiently long half-life (~6 hours) to be usable in nuclear medicine procedures.
- Emits energetic gamma rays (140 kiloelectron volts [keV]) that can be detected efficiently with widely available camera technologies (see Sidebar 2.1).
- Can be supplied efficiently to hospitals and clinics using *technetium generators*[2] (see Section 2.5.4 of this chapter).
- Provides low patient doses for some procedures because of its short half-life and lack of alpha or beta radiations.

[2] The official Food and Drug Administration (FDA) name of the device is *technetium Tc-99m generator*.

Tc-99m-based radiopharmaceuticals are used to diagnose disease in a large number of tissue and organ systems, including bone, brain, heart, kidneys, liver, and lungs. About 50 percent of Tc-99m utilization in the United States is in nuclear cardiology, predominantly for myocardial perfusion imaging[3] which images blood flow through heart muscle. Table 2.1 shows some commonly used Tc-99m-based radiopharmaceuticals. The list is not intended to be exhaustive; rather, it illustrates the wide application range of Tc-99m radiopharmaceuticals.

2.2 I-131 AND Xe-133

I-131 and Xe-133 also have important nuclear medicine applications. Xe-133 is used to image the distribution and rate of exchange of air in the lungs. It decays with a half-life of ~5.2 days and emits 81 keV gamma rays, which can be detected using existing camera technologies (see Sidebar 2.1). Xe-133 is the only approved tracer for this application in the United States. Many other countries use Technegas™, a radiopharmaceutical containing a dispersion of Tc-99m-labeled carbon, for lung imaging.

I-131 is used as a therapeutic agent to treat several types of disease. Its ~8-day half-life and emission of high-energy beta particles (mean energy ~190 keV) make it effective for killing cancer cells. The most commonly used I-131 therapeutic agents are

- I-131-labeled sodium iodide, used in the treatment of hyperthyroid disorders and thyroid cancer. Iodine-based therapies are effective for treating these diseases because iodine is naturally taken up by the thyroid (Van Nostrand and Wartofsky, 2007).
- I-131-labeled metaiodobenzylguanidin, used in the treatment of neuroblastomas[4] and some cancers of the adrenal glands—for example, pheochromocytoma.

2.3 PRODUCTION OF Mo-99

Almost all of the Tc-99m used in nuclear medicine today is produced by radioactive decay of Mo-99.[5] Mo-99 decays with about a 66-hour half-life by emitting a beta particle. About 88 percent of the decays produce Tc-99m via the pathway depicted in Figure 2.1.

[3] Nuclear cardiology is not as highly utilized in other countries. For example, in Europe, nuclear cardiology represents only about 14 percent of the nuclear medicine procedures performed. See Delbeke and Segall (2011).

[4] Cancer of the nerve tissue that occurs in children.

[5] Tc-99m can also be produced directly using cyclotrons; see Section 2.3.2 in this chapter.

Mo-99 can be produced by a number of processes using research reactors or accelerators (see Sidebar 2.2). The primary production method is fission of uranium-235 (U-235) in research reactors. Other production processes are in small-scale use today, and others are under development. A comprehensive list of potential Mo-99/Tc-99m production processes is shown in Figure 2.2. These processes can be subdivided into two groups:

1. Reactor-based production processes
2. Accelerator-based production processes

Some key production processes are described in the following sections.

2.3.1 Reactor-Based Production

Mo-99 has been produced for medical use for decades by irradiating targets containing uranium or molybdenum with neutrons produced by research reactors (see Sidebar 2.2). Mo-99 is produced through the following two reactions (see Figure 2.2):

Fission of uranium-235 (U-235): $^{235}U(n,f)^{99}Mo$ (1)
Activation of molybdenum-98 (Mo-98): $^{98}Mo(n,\gamma)^{99}Mo$ (2)

In reaction (1), fission (f) of U-235 by irradiation with neutrons (n) produces the double-hump distribution of fission products shown in Figure 2.3. About 6.1 percent of the fissions result in the production of Mo-99. I-131 and Xe-133 are also uranium fission products; their abundances are also shown in Figure 2.3. Uranium fission is considered to be the "gold standard" process for producing Mo-99 because (1) the production process is highly efficient, especially when highly enriched uranium (HEU; see Sidebar 1.2 in Chapter 1) is used; and (2) the Mo-99 produced has a high specific activity[6] (>1,000 curies per gram [Ci/g]), making it suitable for use in conventional technetium generators (see Section 2.5.4 in this chapter).

In reaction (2), Mo-98 captures a neutron (n) and transmutes to Mo-99 after emitting a gamma ray (γ). Neutron capture is a less efficient process for producing Mo-99 than is fission because the neutron capture cross section for Mo-98 is over three orders of magnitude smaller than the fission cross section for U-235.[7] Moreover, Mo-99 produced by neutron capture

[6] Specific activity is defined as radioactivity per unit mass, usually expressed as becquerel (Bq) per gram or curies (Ci) per gram. 1 Bq = 3.7×10^{10} Ci.

[7] Cross section is a measure of the probability of a neutron reaction, expressed as an area. The fission cross section for U-235 is about 580×10^{-24} cm^2; the neutron capture cross section for Mo-98 is 0.13×10^{-24} cm^2. Both cross sections are for thermal neutrons (i.e., neutrons in thermal equilibrium at about room temperature).

TABLE 2.1 Commonly Used Tc-99m-Based Radiopharmaceuticals in the United States

Radiopharmaceutical	Imaging	Manufacturer	Trade Name	FDA Approval Date
Tc-99m-Bicisate	Brain Perfusion	Lantheus Medical Imaging ("Lantheus")	Neurolite®	1994
Tc-99m-Exametazine	Brain Perfusion	GE Healthcare	Ceretec™	1988
Tc-99m-Macroaggregated albumin (MAA)	Pulmonary Perfusion	DraxImage	Technetium Tc-99m Albumin Aggregated Kit	1987
Tc-99m-Mebrofenin	Hepatobiliary Imaging	Bracco Diagnostics	Choletec®	1987
Tc-99m-Medronate	Bone Imaging	Jubilant DraxImage	DraxImage MDP-25	2004
		Pharmalucence	CIS-MDP	1982
		Bracco	MDP-Bracco	Approved prior to 1982
Tc-99m-Mertiadide	Kidney Imaging	Mallinckrodt Nuclear Medicine LLC ("Mallinckrodt")	Technescan MAG3™	1990
Tc-99m-Oxidronate	Skeletal Imaging	Mallinckrodt	Technescan HDP	1981
Tc-99m-Pentetate (DTPA)	Brain and Kidney Imaging	DraxImage	DTPA	1989
Tc-99m-Sodium Pertechnetate	Brain, Thyroid, Salivary Gland, Blood Pool, and Urinary Bladder Imaging	GE Healthcare	Technetium Tc-99m Generator	2013
		Lantheus	Technelite®	1976
		Mallinckrodt	Ultra-Technekow™ DTE	1973
Tc-99m-Pyrophosphate	Cardiac, Bone, and Blood Pool Imaging	Mallinckrodt	Technescan™ PYP™	1974
		Pharmalucence	CIS-PYRO	1987

Tc-99m-Red Blood Cells	Red Blood Cell Imaging[a]	Mallinckrodt	UltraTag RBC	1991
Tc-99m-Sestamibi	Cardiac Perfusion	Cardinal Health	Technetium Tc-99m Sestamibi	2009
		DraxImage	Technetium Tc-99m Sestamibi	2009
		Lantheus	Cardiolite	1990
		Mallinckrodt	Technetium Tc-99m Sestamibi Injection	2008
		Pharmalucence	Technetium Tc-99m Sestamibi	2009
Tc-99m-Sulfur Colloid	Liver, Spleen, and Bone Marrow Imaging	Pharmalucence	An-Sulfur Colloid	Approved prior to 1982
Tc-99m-Tetrofosmin	Cardiac Perfusion	GE Healthcare	Myoview™	1995
Tc-99m-Tilmanocept	Lymphatic Mapping and Guiding Sentinel Lymph Node Biopsy	Navidea Biopharmaceuticals, Inc.	Lymphoseek®	2013

NOTE: FDA = Food and Drug Administration.

[a] For example, to detect gastrointestinal bleeding and evaluate left ventricle function.

SOURCE: Adopted from http://www.cardinalhealth.com/content/dam/corp/web/documents/fact-sheet/CardinalHealth-FDAApprovedRadiopharmaceuticalsandApprovedUses.pdf with additional information from some current technetium generator suppliers. Information on FDA approval dates was generated by the committee.

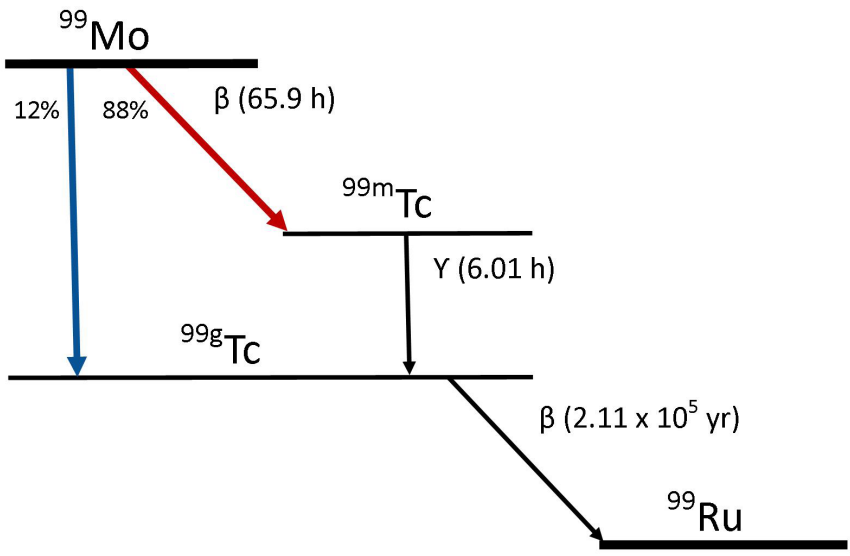


FIGURE 2.1 Graphical depiction of the Mo-99 decay chain. Mo-99 decays by emitting a beta particle (an electron). About 88 percent of the decays (red line) produce Tc-99m, which subsequently decays to the ground state, Tc-99g, by emitting a gamma ray. About 12 percent of the decays (blue line) produce Tc-99g directly. Tc-99g decays to stable (i.e., nonradioactive) ruthenium-99 (Ru-99) after emitting a beta particle. The half-lives for these decay processes are shown on the diagram.

has a lower specific activity (typically 0.1-1 Ci/g), too low for use in conventional technetium generators.

2.3.2 Accelerator-Based Production

Mo-99 and Tc-99m can be produced by irradiating uranium or molybdenum with neutrons, protons, or photons from accelerators (Sidebar 2.2). Several reaction pathways have been suggested and/or investigated, although none are used at present to produce Mo-99 or Tc-99m for medical use. Some key pathways include the following:

Fission of U-235: $^{235}U(n,f)^{99}Mo$ (3)

Photon-induced transmutation of molybdenum-100 (Mo-100): $^{100}Mo(\gamma,n)^{99}Mo$ (4)

Direct production of Tc-99m: $^{100}Mo(p,2n)^{99m}Tc$ (5)

SIDEBAR 2.2
Reactor and Accelerator Production of Mo-99/Tc-99m

Research reactors and accelerators produce neutrons, protons, and photons for medical isotope production (see Figure 2.2). This sidebar describes the operation and use of these technologies.

Research reactors generate neutrons primarily by fission of U-235 contained in the reactor fuel. These reactors are specifically designed to produce high neutron fluxes, typically on the order of 10^{14} neutrons/cm^2/s for scientific research, technology development, or production. They have compact cores (typically less than a cubic meter in volume) that are surrounded by graphite, beryllium, or heavy water (deuterium oxide [D_2O]) to moderate (slow down) and reflect neutrons. The core and reflector typically contain numerous empty channels for material irradiations. Uranium or molybdenum targets can be inserted into these channels to produce Mo-99 through the reactions shown in Section 2.3.1.

Accelerators generate ion beams and accelerate them to high energies with oscillating electromagnetic fields. The accelerated particle beams can be used to irradiate various types of targets to produce Tc-99m or Mo-99. For example, Tc-99m can be produced by irradiating a target containing Mo-100 with protons (reaction (5) in Section 2.3.2). Alternatively, an electron beam can be used to irradiate a tungsten target to produce high-energy photons, which in turn can be used to irradiate a target containing Mo-100 to produce Mo-99 (reaction (4) in Section 2.3.2). A deuterium beam can be used to irradiate deuterium or tritium targets to produce neutrons, which in turn can be used to produce Mo-99 via reaction (3) in Section 2.3.2.

Research reactors are ideally suited for producing Mo-99 because of their large irradiation capacities. However, they are expensive to construct, license, and operate, and they produce radioactive waste. Accelerators are less expensive to construct and operate (typically one to two orders of magnitude less expensive than reactors, depending on size and supporting infrastructure) and produce little radioactive waste. However, accelerators cannot match the Mo-99 production capacity of reactors.

Photo-fission of uranium-238 (U-238): $^{238}U(\gamma,f)^{99}Mo$ (6)
Proton spallation of U-238: $^{238}U(p,f)^{99}Mo$ (7)

Reaction (3) is identical to reaction (1) except that neutrons are produced by accelerators instead of research reactors. Neutrons are produced by accelerating protons (p) or deuterons (a proton-neutron pair, denoted D) into high-atomic-mass materials (i.e., high-Z material)—for example, tungsten.[8] The Mo-99 produced by accelerator fission has a high specific

[8] Bombardment of high-Z materials with protons or deuterons strips neutrons from the nuclei of the target material, a process known as *spallation*.

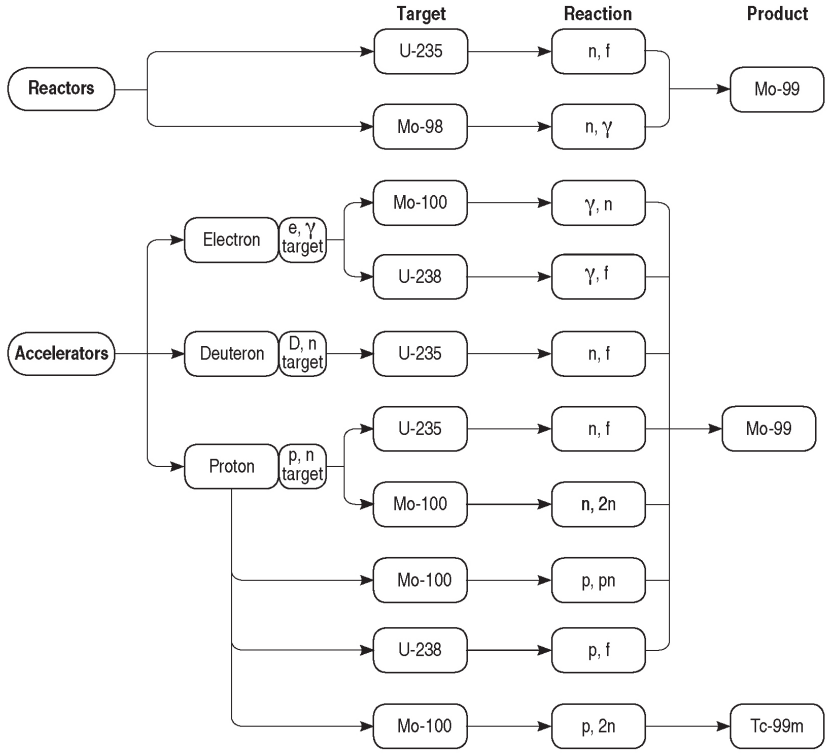


FIGURE 2.2 Methods for producing Mo-99 and Tc-99m using reactors and accelerators. The production methods are described in the text. Accelerators can be used to produce photons (γ) and neutrons (n) by accelerating electrons (e), deuterons (D), and protons (p) into solid targets. Irradiation of U-235, U-238, Mo-98, and Mo-100 target materials with these radiations produces Mo-99. Additionally, proton irradiation of Mo-100 produces Tc-99m directly.

activity (>1,000 Ci/g); however, neutron fluxes and corresponding Mo-99 production rates are typically one or two orders of magnitude lower in accelerators compared to reactors. Production of Mo-99 by accelerator fission is currently under active development in the United States (see Chapter 4).

Reaction (4) produces Mo-99 by spalling neutrons from Mo-100 nuclei with high-energy (14 MeV) photons. These photons are produced by accel-

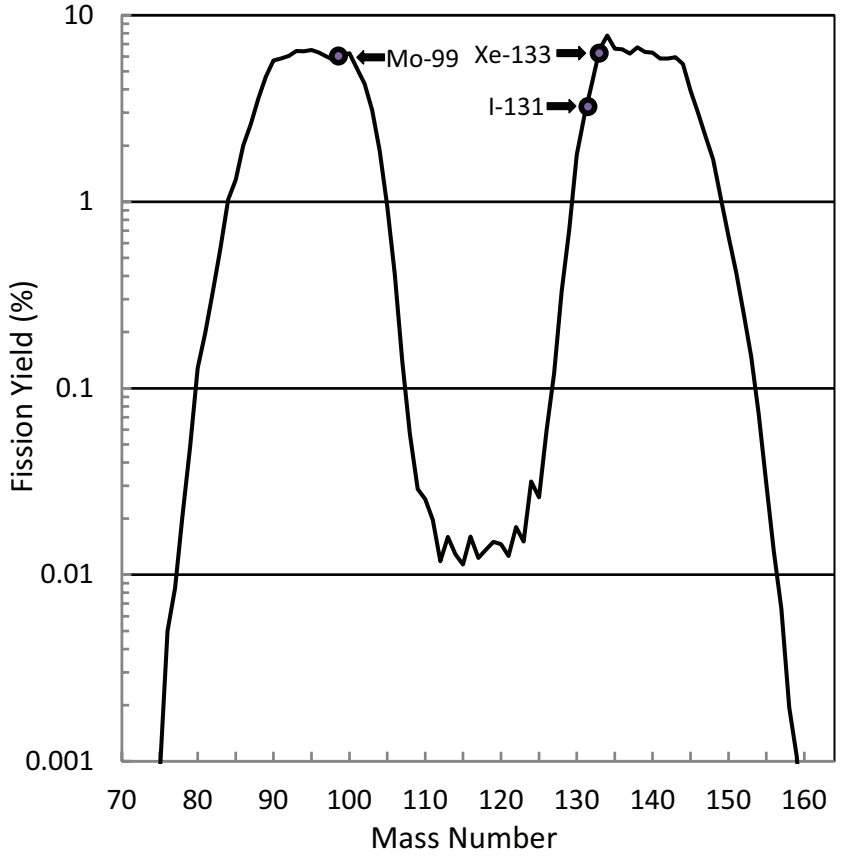


FIGURE 2.3 Fission yield for thermal neutron fission of U-235. The fission of U-235 produces a spectrum of fission products, including Mo-99, I-131, and Xe-133. SOURCE: Fission yield data from https://www-nds.iaea.org/sgnucdat/c1.htm#92-U-235.

erating high-intensity (35-50 MeV) electron beams into high-Z materials.[9] The Mo-99 produced using this reaction has a low specific activity (1-10 Ci/g), slightly higher than that produced from neutron activation of Mo-98, namely reaction (2).

Reaction (5) produces Tc-99m directly using protons (p) to remove

[9] Photons are produced by the slowing down of electrons in high-Z material; these photons are referred to as *Bremsstrahlung radiation*.

neutrons (n) from the nuclei of Mo-100 atoms. The Tc-99m produced by this reaction can be used directly in radiopharmaceuticals without further purification or packaging into a generator. The cyclotron[10] production of Tc-99m is under active development in Canada (see Chapter 4).

Reactions (6) and (7) are similar to reaction (1) except that high-energy photons (reaction (6)) or protons (reaction (7)) are used to fission U-238 instead of U-235. U-238 is more abundant in natural uranium than is U-235 (see Sidebar 1.2 in Chapter 1); however, the reaction cross sections are orders of magnitude lower than are those for reaction (1).

2.4 PRODUCTION OF I-131 AND Xe-133

I-131 and Xe-133 are products of U-235 fission and are coproduced with Mo-99 when U-235 is irradiated with neutrons (Figure 2.3):

$$^{235}\mathrm{U(n,f)}^{131}\mathrm{I} \quad (8)$$

$$^{235}\mathrm{U(n,f)}^{133}\mathrm{Xe} \quad (9)$$

Some current Mo-99 suppliers (see Section 2.5.3 in this chapter) co-recover Mo-99 and Xe-133 from irradiated uranium. There is currently no other production method for Xe-133.

I-131 can also be co-recovered with Mo-99, but no current suppliers of I-131 do so at present. Instead, they make I-131 by irradiating tellurium-130 (Te-130) with neutrons (El Bakkari et al., 2015; IAEA, 2003):

$$^{130}\mathrm{Te(n,\gamma)}^{131}\mathrm{Te} \xrightarrow{\beta^-} {}^{131}\mathrm{I} \quad (10)$$

Irradiation of Te-130 with neutrons produces Te-131 or Te-131m, which have half-lives of 25 minutes and 30 hours, respectively. Te-131 subsequently decays to I-131 by beta (β^-) emission.

2.5 OVERVIEW OF Mo-99/Tc-99m SUPPLY CHAIN

As noted previously, almost all Mo-99 for medical use is produced by irradiating targets containing U-235 in research reactors (reaction (1) in Section 2.3.1). The supply chain for this production process is illustrated graphically in Figure 2.4 and described below. This description is organized around the organizations that participate in the supply chain and the services they provide:

[10] A cyclotron accelerates charged particles such as protons along spiral paths. Cyclotrons having energy ranges between 14 and 24 megaelectron volts (MeV) can be used to produce Tc-99m.

1. *Target suppliers:* Organizations that fabricate U-235 targets for Mo-99 production.
2. *Irradiation services suppliers:* Organizations that irradiate U-235 targets to produce Mo-99.
3. *Mo-99 suppliers:* Organizations that process irradiated targets to recover and purify Mo-99 for commercial sale.
4. *Technetium generator suppliers:* Organizations that manufacture *technetium generators* for commercial sale.
5. *Tc-99m suppliers:* Organizations that sell Tc-99m sodium pertechnetate ($NaTcO_4$) and/or Tc-99m-labeled radiopharmaceuticals to end users.
6. *Tc-99m end users:* Hospitals and clinics that purchase Tc-99m sodium pertechnetate and/or Tc-99m-labeled radiopharmaceuticals for use in medical procedures.

This supply chain is designed to deliver Mo-99/Tc-99m on a weekly or more frequent basis. Such "just-in-time" delivery is essential to the successful operation of the supply chain because Mo-99 and Tc-99m have short half-lives (~66 and 6 hours, respectively) and therefore cannot be stockpiled. The activity of Mo-99 declines by about 1 percent per hour because of radioactive decay. It must be moved through the supply chain quickly to minimize decay losses. The elapsed time from production of Mo-99 in a reactor to the delivery of a Tc-99m dose to a hospital or clinic can be as short as 4-5 days.

The quantity of Mo-99 in the supply chain is time-dependent because of radioactive decay. The quantity of supply is conventionally measured in *6-day curies*,[11] that is, the amount of Mo-99 available 6 days after the point of measurement (see Sidebar 2.3). The point of measurement is not fixed in the supply chain but is instead determined by supply chain participants to suit their particular needs. This metric is used throughout this report to specify Mo-99 quantities.

2.5.1 Target Suppliers

A *target* contains U-235 (HEU or low enriched uranium [LEU]) in a form that is suitable for irradiation in research reactors. Most of the targets

[11] The 6-day curie is not an SI (the International System of Units) unit and therefore does not conform to international standards. The becquerel (Bq) is the SI equivalent to the curie for reporting the activity of a radionuclide. 1 curie equals 37 gigabecquerals (GBq). The Mo-99 supply chain and regulators report exclusively in 6-day curies and for this reason the committee uses this quantity instead of the SI equivalent in this report.

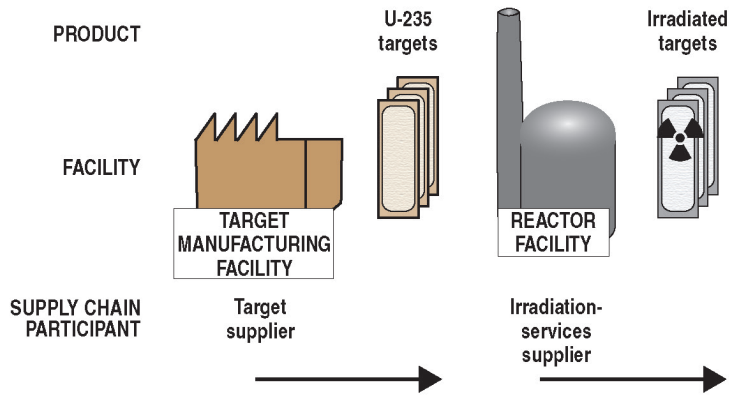
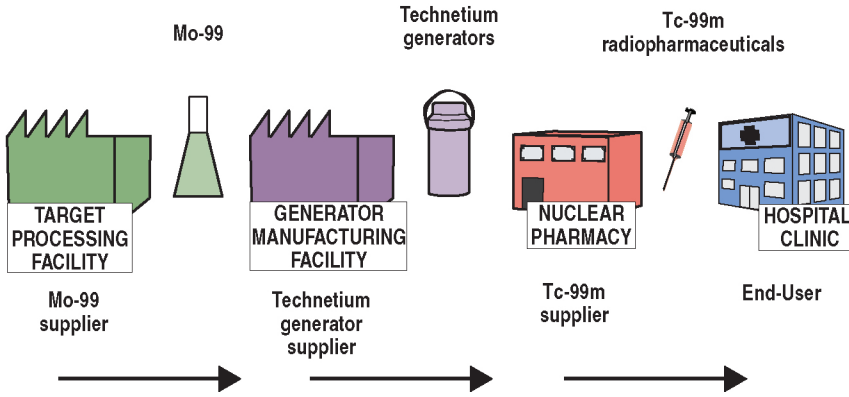


FIGURE 2.4 Graphical depiction of the existing Mo-99/Tc-99m supply chain for fission of U-235 in research reactors. SOURCE: Modifed from Ponsard (2010).

used to produce Mo-99 for medical use today have a sandwich design[12] (see Figure 2.5). The *meat* of the sandwich contains uranium-aluminum alloy particles dispersed in aluminum alloy matrices. The meat is encapsulated in an aluminum alloy cladding that provides a barrier to the release of fission products and transfers heat to the reactor coolant. Targets are typically 3-5 cm in width, 10-15 cm in length, and about 1-2 mm in thickness.

A small number of supplier companies manufacture targets essentially by hand (see Chapter 5). These companies work under contract to Mo-99 suppliers (see Section 2.5.3 in this chapter) to produce targets in accord to those suppliers' specifications using HEU or LEU purchased by those suppliers from national governments. (At present, most uranium used in target manufacture is purchased from the United States; see Chapter 5.) Targets are not interchangeable among Mo-99 suppliers because of their unique designs. It can take a year or more to obtain the uranium, manufacture it into the appropriate alloy form, and fabricate it into targets. Because of these long lead times, most Mo-99 suppliers stockpile targets at target irradiation facilities (see next section).

[12] One current Mo-99 supplier (Nordion) uses pin (i.e., rod-shaped) targets containing uranium oxide.



2.5.2 Irradiation Services Suppliers

Research reactors are designed to produce large neutron fluxes (typically around 10^{14} neutrons/cm^2-s) in a compact core (see Sidebar 2.2). These fluxes, which are higher than those produced in commercial power reactors, make research reactors suitable for a wide range of scientific, engineering, and industrial missions, including Mo-99 production. These reactors are owned by governments or universities but may be operated by private companies.

Research reactors sell irradiation services to multiple customers on a contract basis. Mo-99 production is an important revenue source for many of these reactors (see Section 2.7 in this chapter). Mo-99 suppliers (see next section) have long-term contracts with research reactors to irradiate and in some cases ship irradiated targets to suppliers' facilities for processing.

Targets are typically irradiated in reactors for about 5-7 days to allow Mo-99 to build up to between about 70 and 80 percent of saturation concentration[13] (see Sidebar 2.3, Figure S2.3). Only about 3 percent of the U-235 in the target is consumed during irradiation. After irradiation, the targets are removed from the reactor and set aside for a day or less to allow for decay of short-half-life fission products. The targets are then

[13] At saturation concentration, the production of Mo-99 in the target is balanced exactly by the loss of Mo-99 from radioactive decay.

SIDEBAR 2.3
6-day Curie

Mo-99 is frequently priced and sold based on a quantity referred to as *6-day curie,* typically defined as the remaining radioactivity of Mo-99 6 days after the end of target processing (EOP). The concept is illustrated graphically in Figure S2.3. This 6-day calibration time was originally intended to account for the time needed to move Mo-99 through the supply chain to end users. The amount of Mo-99 priced and sold as 6-day curies (end of the falling curve on the right side of the figure) is only a fraction of the amount present in the uranium targets at the end of bombardment (EOB) by neutrons in the reactor (end of the rising curve on the left side of the figure). In fact, decay over 6 days reduces Mo-99 to about 22 percent of its initial activity.

Paterson et al. (2015) noted that supply chain participants inconsistently define 6-day curie calibration times. The calibration time is variously stated as time since EOP, time since leaving the Mo-99 supplier's facility, or time since arrival at the technetium generator manufacturer.

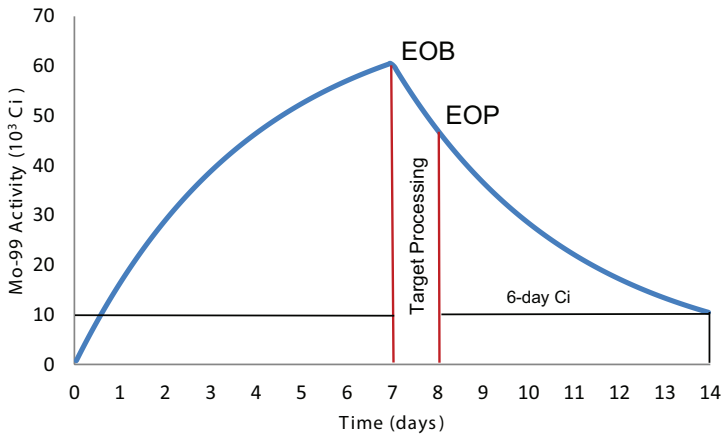


FIGURE S2.3 Schematic illustration of the buildup of Mo-99 in a uranium target during irradiation (rising curve on left) and the decay of Mo-99 after target processing (falling curve on right). NOTES: EOB = end of bombardment (i.e., end of target irradiation); EOP = end of target processing. Six-day curies are measured 6 days after EOP, expressed here in terms of the activity of Mo-99. For this simplified example target processing is assumed to take 1 day and Mo-99 recovery efficiency from the targets is assumed to be 100 percent.

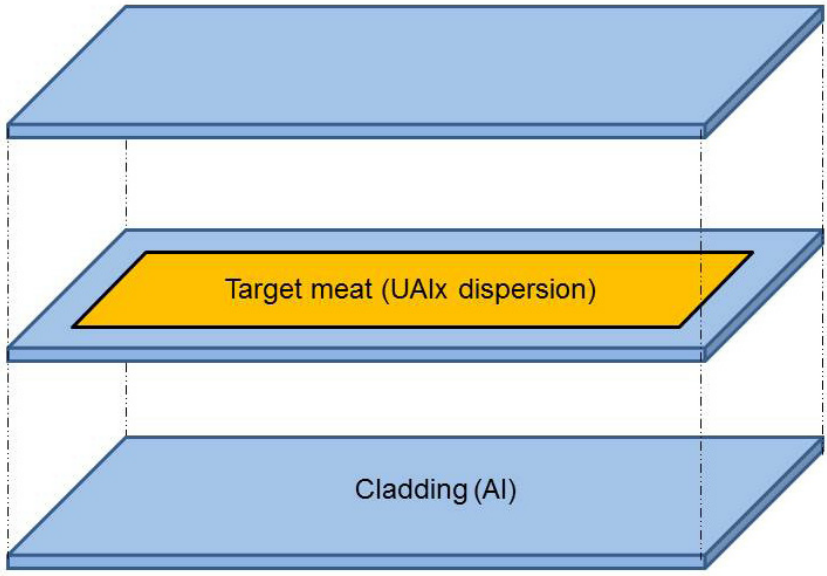


FIGURE 2.5 Exploded view of a target used for Mo-99 production. The target has a sandwich design. The meat of the sandwich (orange material) contains uranium-aluminum alloy (UAlx) particles dispersed in aluminum alloy matrices. The meat is encapsulated in an aluminum alloy cladding (blue material) that provides a barrier to the release of fission products and transfers heat from the meat to the reactor coolant. Targets are manufactured to meet suppliers' particular size specifications but are typically 3-5 cm in width, 10-15 cm in length, and about 1-2 mm in thickness.

packaged and shipped by truck to Mo-99 suppliers' facilities.[14] Shipping time can vary from less than an hour to about a day depending on distance and transport logistics.

2.5.3 Mo-99 Suppliers

Mo-99 suppliers chemically process irradiated targets to recover Mo-99 for commercial sale. Target processing takes place in heavily shielded,

[14] Transportation is constrained to land-based methods because of the size and weight of the shipping containers and transport regulations.

remote-controlled containment compartments, referred to as *hot cells*,[15] which are located in suppliers' facilities. Most current Mo-99 suppliers use an alkaline dissolution process[16] for processing irradiated targets. This process is well suited to target materials that contain aluminum, and it allows for the coproduction of I-131 if desired.

The process is described as *alkaline dissolution* because the targets are dissolved in sodium hydroxide. The uranium precipitates out as oxides, hydrated oxides, and/or hydroxides; the aluminum and some of the fission products, including Mo-99, remain in solution. The solutions are processed to separate and purify Mo-99 and package it for shipment. Further details about this process are provided in Chapter 5. Target processing typically takes 12-24 hours.

The separated Mo-99, which is contained in solution as molybdate (MoO_4^{2-}), is shipped to technetium generator suppliers (see next section) in specialized transport containers. These containers can be shipped by road or by air. Shipment can take from a few hours to 1-2 days depending on distance and transport logistics.

2.5.4 Technetium Generator Suppliers

Technetium generators are systems that store Mo-99 and allow its decay product, Tc-99m, to be recovered for use. Most technetium generators are designed to be used with high-specific-activity Mo-99 (>1,000 Ci/g) produced by U-235 fission. The generator consists of an alumina (Al_2O_3) column having the diameter of a large pencil along with associated filters and tubing for obtaining Tc-99m (see Figure 2.6). This apparatus is installed into radiation-shielded packages for shipment to Tc-99m suppliers (see next section). The generator includes both the package (the plastic container shown in Figure 2.6) and its contained apparatus. Technetium generators contain from 1 to 19 Ci of Mo-99, matched to address the needs and workloads of Tc-99m suppliers (see next section).

It takes 18-24 hours to prepare technetium generators for shipment. Preparation involves loading the molybdate solution onto the columns and sterilizing them; installing the columns, tubing, and filters into the shielded generator package; and packaging the generators for shipment. Tc-99m generators are typically shipped to Tc-99m suppliers within a day of their manufacture. Generators are shipped in regulatory-compliant boxes. The delivery methods can be air, ground, or a combination of both depending on customer location and contracted transportation network.

[15] The term "hot" in hot cell refers to radioactivity, not temperature.

[16] One Mo-99 supplier (Nordion) uses an acidic process to produce Mo-99. All of the remaining global producers use an alkaline process.

FIGURE 2.6 Internal structure and external view of a TechneLite® Tc-99m generator used for obtaining Tc-99m from high-specific-activity Mo-99. The generator (including shielding) is 25 cm in height, 13.2 cm in diameter (14.2 cm at generator top), and weighs 11 kg and 15 kg for a 37-74 GBq and 111-666 GBq activity generator, respectively. A typical generator column (vertical cylinder in center of container) is about 6-8 cm long and about 1.5-2 cm in diameter. The column is enclosed in a radiation-shielded plastic container. SOURCE: Image courtesy of Lantheus Medical Imaging, Inc.

2.5.5 Tc-99m Suppliers

Technetium generators are delivered primarily to two types of Tc-99m suppliers: regional nuclear pharmacies and hospital nuclear pharmacies. A small number of generators are also delivered directly to hospital nuclear medicine departments for on-site emergency (on-call) situations during afterhours, weekends, and holidays.

Tc-99m is obtained from technetium generators through a process referred to as *elution*. Tc-99m pertechnetate (TcO_4^-) is produced on the alumina column as Mo-99 decays. A saline solution (0.9% NaCl) is used to

wash the pertechnetate from the column.[17] The recovered sodium pertechnetate ($NaTcO_4$ as noted previously) is mixed with cold kits[18] to produce radiopharmaceuticals. A typical elution of a technetium generator takes about 5 minutes.

The Tc-99m eluted from the generator should ideally contain no radionuclide impurities.[19] However, Mo-99 is sometimes co-eluted from the generator. This process is referred to as *Mo-99 breakthrough*. The contamination of Tc-99m with Mo-99 can interfere with radiopharmaceutical production, reduce image quality (Mo-99 emits high-energy [740 and 780 keV] gamma rays), and expose patients to unnecessary radiation.

The accepted activity limit of Mo-99 in the eluate is 0.15 microcuries (μCi) per millicurie (mCi) of Tc-99m in all generators.[20] Package inserts that accompany the generators recommend that customers test each elution for Mo-99 breakthrough. However, the U.S. Nuclear Regulatory Commission only requires the measurement of Mo-99 concentration in the first eluate recovered after receipt of a Mo-99/Tc-99m generator.

Technetium generators are typically eluted once or twice per day for 1 to 2 weeks. Maximum buildup of Tc-99m occurs approximately 24 hours after each elution (see Figure 2.7). More frequent generator elutions prior to maximum Tc-99m buildup can increase the amount of Tc-99m available for the day. For example, 50 percent of maximum Tc-99m buildup is reached in about 4.5 hours and 75 percent of maximum buildup is reached in about 8 hours.

The amount of Tc-99m in a generator decreases by approximately 20 percent each day. Consequently, Tc-99m suppliers must manage their generators to maximize use of Tc-99m. The most efficient distribution of Tc-99m radiopharmaceuticals happens in centralized nuclear pharmacies because they can most efficiently match the timing of generator delivery to radiopharmaceutical demand. Centralized nuclear pharmacies typically receive a number of generator deliveries staggered throughout the week, and they have the staff needed to produce and distribute radiopharmaceuticals either in multi-dose vials or as single doses to multiple imaging centers and hospitals.

[17] The pertechnetate ion is less tightly bound to the alumina because it has only a single negative charge, versus the double negative charge for molybdate.

[18] These kits provide prepackaged chemicals to simplify incorporation of Tc-99m into molecules and preparation of Tc-99m radiopharmaceuticals for specific imaging tests. These kits are characterized as "cold" because they do not contain radioactivity.

[19] Possible impurities include Mo-99, I-131, ruthenium-103, strontium-89, and strontium-90.

[20] Title 10 of the Code of Federal Regulations, Part 35, Section 35.204 (10 CFR 35.204), "Permissible molybdenum-99, strontium-82, and strontium-85 concentrations."

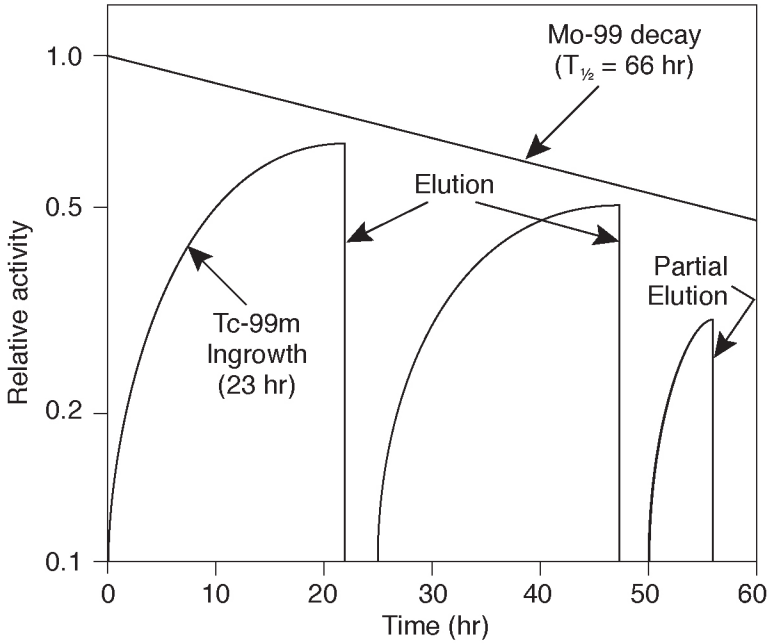


FIGURE 2.7 Tc-99m in-growth and elution in a technetium generator. The relative activity of Tc-99m in the generator (shown by the logarithmic scale on the vertical axis) decreases each time the generator is eluted. The relative activity of Tc-99m subsequently grows back in as the Mo-99 in the generator decays. The sloped curve at the top of the figure shows relative Mo-99 activity in the generator. SOURCE: Modified from Ziessman et al. (2014). Copyright 2014, with permission from Elsevier.

2.5.6 Tc-99m End Users

Tc-99m is supplied to hospitals and clinics for use in medical isotope procedures. Tc-99m may be supplied as bulk sodium pertechnetate or as single doses of Tc-99m-labeled radiopharmaceuticals for administration to specific patients. End users can receive Tc-99m one or more times per day depending on their patient loads.

2.6 WASTE MANAGEMENT

The production of Mo-99 from irradiated uranium targets produces four waste streams:

- Solids containing uranium.

- Processing off-gases, primarily the noble gases xenon (Xe-131m, Xe-133, Xe-133m, and Xe-135) and krypton (Kr-85).
- Process liquids from target dissolution.
- Other solid wastes produced during target processing: for example, radioactively contaminated processing equipment.

All of these waste streams are generated in Mo-99 supplier facilities. The management of these wastes is described in Chapter 5.

Xenon plays an important role in monitoring international compliance with the Comprehensive Nuclear-Test-Ban Treaty (CTBT), which prohibits nuclear weapons testing (see, for example, Matthews et al., 2010). This noble gas is mostly nonreactive and has a high yield from uranium fission (see Figure 2.3). Several short-lived isotopes of xenon are produced when a nuclear weapon is detonated, notably Xe-133 (~5.2-day half-life) and Xe-135 (~9.1-hour half-life). A global network of sensitive monitors has been established to measure atmospheric levels of these isotopes. This network can be used to detect illicit nuclear weapons tests, even when they occur underground.[21]

Radioxenon isotopes are also produced when uranium targets are irradiated to make Mo-99. Xenon and other radioactive off-gases are captured during target processing, temporarily stored to allow for radioactive decay, and subsequently released to the atmosphere. Mo-99 suppliers release sufficient Xe-133 from their target processing facilities to be detected by the CTBT monitoring network. The background radioxenon signals from these facilities can potentially interfere with CTBT compliance monitoring (Matthews et al., 2010).

Technetium generator suppliers also have to manage smaller amounts of Mo-99/Tc-99m waste produced during the manufacture of generators. This waste is typically stored for decay (about 60 hours for Tc-99m and 1 month for Mo-99) and then disposed of as regular trash. Spent technetium generators are usually returned to the generator suppliers for dismantlement (IAEA, 1998). The shielding is reused but the internal apparatus is replaced.

2.7 SUPPLY CHAIN ECONOMICS

The supply chain for Tc-99m and associated medical isotopes is a public-private partnership involving national and state governments, government-owned entities, and private companies. These partners have diverse and sometimes conflicting interests, but their collective success requires mutual cooperation and coordination.

[21] Gaseous xenon can escape to the atmosphere by migrating through pore spaces and fractures created by an underground detonation.

Mo-99 intended for medical use is produced mostly in multipurpose research reactors constructed with government funding. These reactors were built primarily for research and materials testing; target irradiation for Mo-99 production was a secondary activity. However, this activity has become a progressively larger part of reactors' workloads as demand for Mo-99 has increased, beginning in the late 1970s. Some reactors now obtain most of their revenues from irradiation of targets for Mo-99 production.

Historically, reactor facilities have charged suppliers of Mo-99 only for the marginal operating costs associated with target irradiation. Suppliers were not charged for the life-cycle costs of operating the reactor facilities, which include depreciation of capital costs for facility construction, general operations, maintenance, and decommissioning (OECD-NEA, 2010). These costs were absorbed by the governments that own the reactors.

Reactor facilities—and by extension, their government owners—have also absorbed the costs for maintaining extra irradiation capacity beyond that needed for the routine production of Mo-99. This extra capacity, referred to as *outage reserve capacity,* allows the reactor to rapidly scale up Mo-99 production to meet demand when other irradiation facilities shut down for scheduled or unscheduled maintenance. The facilities that process irradiated targets also have reserve processing capacity.

Outage reserve capacity helps to ensure that adequate supplies of Mo-99 are available during planned and unplanned outages of target irradiation and/or processing facilities. Mo-99 suppliers traditionally paid for this reserve capacity only when they used it. This created an incentive for irradiation services suppliers to use this reserve capacity for other customers to gain revenue, further driving down prices for irradiation services (OECD-NEA, 2010). In recent years, Mo-99 suppliers have started to pay for the costs for maintaining the outage reserve capacity. However, there is no direct way of measuring the amount of paid outage reserve capacity that is maintained throughout the supply chain (OECD-NEA, 2016).

Governments also subsidize—to various extents—the purchase of Tc-99m for medical procedures. Many governments, including the U.S. government, provide health care to all or a portion of their citizens[22] and set reimbursement rates for medical procedures, including those that utilize Tc-99m. Many private insurance companies use government reimbursement rates as guides for setting their own reimbursement rates. Costs for Tc-99m are frequently bundled with the medical procedure rather than being reimbursed separately.

The other supply chain participants—Mo-99 suppliers, technetium

[22] For example, the U.S. government provides health care to individuals who are over 65 years of age and disabled (through Medicare) and to families and individuals with low income and limited resources (through Medicaid).

generator suppliers, and Tc-99m suppliers—are mostly private companies and can set their own prices for the products they sell. These entities have limited pricing power for their products, however, because

1. The products they sell (i.e., Mo-99, technetium generators, and Tc-99m) are commodities that are available from several companies;
2. These commodities are usually sold through multiyear contracts that limit sellers' abilities to raise prices; and
3. Governments and private insurance companies set reimbursement rates for the nuclear medicine procedures.

Some of the cold kits used to produce Tc-99m radiopharmaceuticals are proprietary items and may be available from only one technetium generator supplier. These companies can make a profit by bundling these kits and a technetium generator in purchase agreements, even if they only break even or incur a small loss for selling generators. This profit does not flow back up the supply chain to Mo-99 suppliers (OECD-NEA, 2010).

2.7.1 Full-Cost Recovery

The High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) was established in 2009 by the Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA) to examine the underlying causes of global Mo-99/Tc-99m shortages and recommend actions to ensure adequate supplies in the future. The HLG-MR is comprised of approximately 40 experts representing the governments of 17 countries as well as from the European Commission and the International Atomic Energy Agency. The HLG-MR has been working to achieve several goals, including reducing government subsidies for reactors that produce Mo-99.

The HLG-MR has developed six principles to promote *full-cost recovery* of medical isotope production (see Sidebar 2.4) and the availability of outage reserve capacity to be paid for by higher prices in the supply chain rather than through continued government subsidies. The governments of the HLG-MR member countries agreed to implement the policy approach within 3 years of its adoption (by 2014). This deadline was not met, and progress to implement full-cost recovery is slower than desired (OECD-NEA, 2014a).

The HLG-MR recognizes that existing long-term contracts between irradiation services suppliers and Mo-99 suppliers and/or ongoing government support prevents implementation of full-cost recovery. In addition, some supply chain participants are resisting the price increases necessary for full-cost recovery to occur.

SIDEBAR 2.4
Full-Cost Recovery

The HLG-MR released its policy approach to move the Mo-99/Tc-99m supply chain to a sustainable economic basis and to ensure the reliability of supply. The policy approach seeks to address the fundamental problems that threaten reliable global supply of Mo-99/Tc-99m and is comprised of six policy principles (OECD-NEA, 2011a). The first principle addresses full-cost recovery:

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

Full-cost recovery would eliminate government subsidies for production of Mo-99 in research reactors by increasing prices for reactor irradiation services to cover the costs of reactor capital, general overhead, general operating, depreciation of capital costs, and decommissioning as well as the costs associated with provision of outage reserve capacity. According to OECD's HLG-MR, full-cost recovery would have additional benefits beyond reducing government expenditures on reactors by

- Encouraging new infrastructure investment by making production of unprocessed Mo-99 economically sustainable;
- Facilitating the development of non-HEU-based Mo-99/Tc-99m production sources; and
- Promoting more efficient use of Mo-99/Tc-99m and therefore reducing excess production and the associated radioactive waste.

The HLG-MR estimates that moving to full-cost recovery for irradiation services would have a small impact on the costs of patient procedures because Tc-99m is a small component of the total procedure costs. However, HLG-MR noted that the costs of technetium generators would increase somewhere between 50 and 140 percent and the costs of Tc-99m radiopharmaceuticals would increase between about 10 and 30 percent.

The OECD has asked Mo-99/Tc-99m supply chain participants to self-assess progress toward implementing full-cost recovery. The latest (second) of these self-assessments was published in 2014 (OECD-NEA, 2014a) and a third self-assessment report was in preparation when the present report was being finalized.

Moreover, it is unclear whether full-cost recovery can ever be implemented across the supply chain in a free market. Some Mo-99 suppliers are in a strong bargaining position relative to the irradiation services suppliers. Two of the five current global Mo-99 suppliers (IRE and Mallinckrodt; see Chapter 3) use multiple irradiation suppliers.[23] This gives these Mo-99

[23] All of the other global producers are tied to single reactors: ANSTO (OPAL), Nordion (NRU), and NTP (SAFARI-1).

suppliers bargaining power over irradiation costs. If these Mo-99 suppliers offer to purchase irradiation services at prices above marginal costs but below full-cost recovery, it is better for the irradiation services suppliers to accept those prices to generate revenues to cover reactor operating costs, even if those revenues are insufficient to cover general operating costs and depreciation. These prices may not be sustainable in the long run, but irradiation services suppliers would lose less in the short run by accepting lower prices.

Additional discussion of full-cost recovery is provided in Section 4.5 in Chapter 4.

3

Global Production of Molybdenum-99 and Future Prospects

This chapter addresses the first and second charges of the statement of task (see Sidebar 1.3 in Chapter 1), which direct the Academies to provide

1. A list of facilities that produce molybdenum-99 for medical use, including an indication of whether these facilities utilize highly enriched uranium.
2. A review of international production of molybdenum-99 over the previous 5 years, including whether any new production was brought online; whether any facilities halted production unexpectedly; and whether any facilities used for production were decommissioned or otherwise permanently removed from service.

This chapter provides information on the molybdenum-99 (Mo-99) supply chain as of June 2016 and Mo-99 production for the period January 2009[1] to June 2016. Although not explicitly requested by Congress, the chapter also describes plans by current global Mo-99 suppliers to expand their capacities to supply Mo-99 to the market. Plans to develop domestic (U.S.) supplies of Mo-99 are described in Chapter 4.

This chapter also provides current and potential future estimates of

[1] The previous Academies report on Mo-99 production was completed in late 2008 and published in 2009 (NRC, 2009). The present report examines Mo-99 production trends from January 2009 to the present and Mo-99 supply disruptions from 2007 to the present.

SIDEBAR 3.1
Mo-99 Production and Supply Concepts

This sidebar defines the terms that are used in this report to describe the production and supply of Mo-99.

Irradiation services suppliers irradiate uranium targets in research reactors to *produce* Mo-99. Mo-99 suppliers process the irradiated targets to recover and *supply* Mo-99 (see Figure 2.4 in Chapter 2). Mo-99 production and supply are quantified in this report using two measures:

- *Available capacity*—the maximum amount of Mo-99 that can be produced or supplied on a routine basis. *Available production capacity* is determined by the capacity of a reactor to irradiate targets on a routine basis. *Available supply capacity* is determined by capacity of a target processing facility to process irradiated targets on a routine basis.
- *Supply*—the actual amount of Mo-99 being produced or supplied. Supply is less than or equal to available capacity.

The difference between available capacity and supply is the *reserve capacity*. This capacity can be utilized—depending on the irradiation services suppliers' missions—to produce more Mo-99 to increase their market shares and for irradiations for other customers. Some reserve capacity is also used to cover Mo-99 supply shortfalls resulting from planned or unplanned reactor or target processing facility outages. The Organisation for Economic Co-operation and Development-Nuclear Energy Agency (OECD-NEA) refers to this reserve capacity as *outage reserve capacity* (OECD-NEA, 2013). Outage reserve capacity is available all of the time and may or may not be used depending on whether there are Mo-99 supply shortfalls.

Irradiation services suppliers and Mo-99 suppliers may be able to increase production and supply above their available capacities. However, this additional capacity requires extraordinary measures and cannot be obtained on a routine basis.

Mo-99 production and supply. Sidebar 3.1 defines the quantities used to characterize production and supply.

3.1 Mo-99 SUPPLY CHAIN PARTICIPANTS

Companies in Australia, Canada, Europe, South Africa, and the United States currently participate in the global supply chain for Mo-99/technetium-99m (Tc-99m) (see Figure 3.1). These include

- Four target suppliers (see Table 3.1),
- Seven irradiation services suppliers (see Table 3.2),

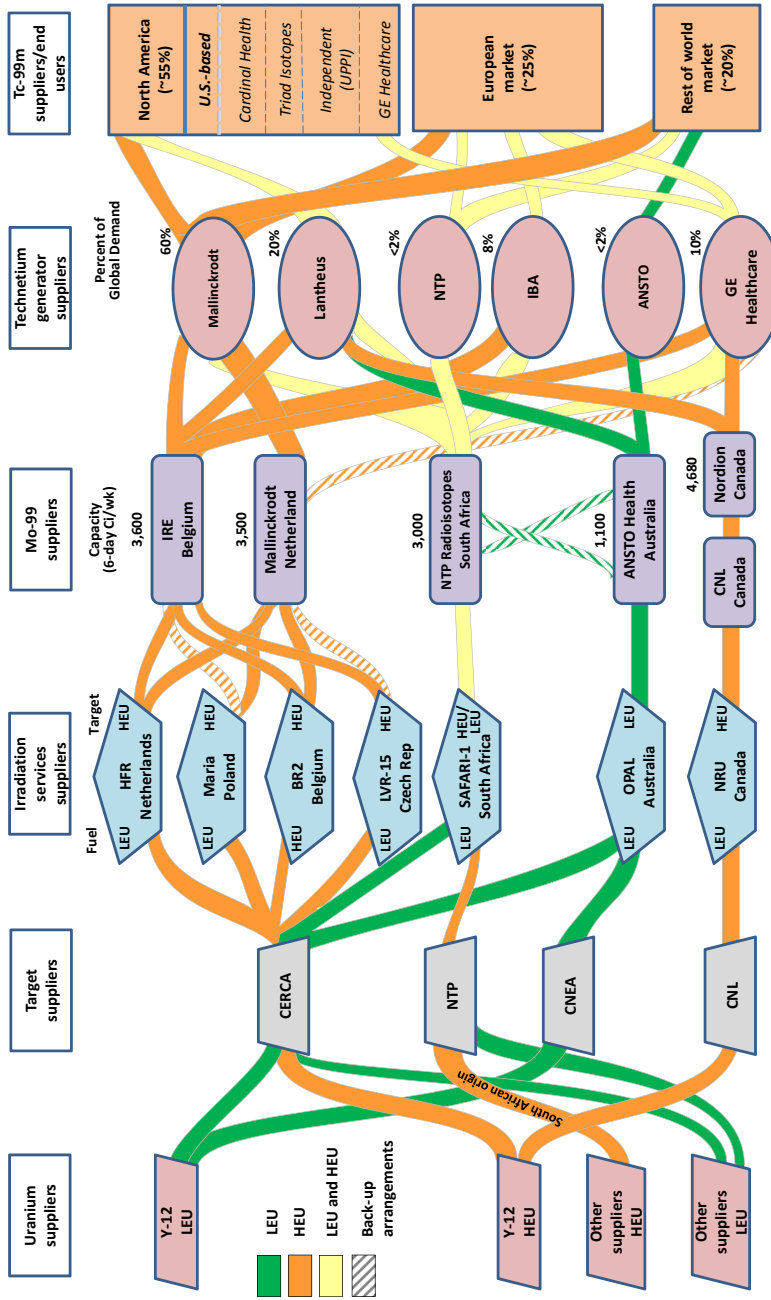


FIGURE 3.1 Mo-99/Tc-99m "global" supply chain. This diagram illustrates the supply chain for about 95 percent of the Mo-99 produced and supplied globally. The remaining 5 percent of Mo-99/Tc-99m supply is produced and supplied regionally.

TABLE 3.1 Target Suppliers for Global Mo-99 Production as of June 2016

Target Supplier	Mo-99 Supplier	Target Type
CERCA (France)	IRE (Belgium)	HEU, LEU
CERCA	Mallinckrodt (Netherlands)	HEU, LEU
CERCA	ANSTO (Australia)	LEU
CERCA	NTP (South Africa)	LEU
NTP	NTP	HEU
CNEA	ANSTO	LEU
CNL (Canada)	Nordion (Canada)[a]	HEU

NOTES: CERCA = Compagnie pour l'Etude et la Réalisation de Combustibles Atomiques; HEU = highly enriched uranium; LEU = low enriched uranium; NTP = Nuclear Technology Products Radioisotopes.

[a] Nordion purifies, packages, and ships Mo-99 produced at CNL. It does not process targets.

- Five Mo-99 suppliers (see Table 3.3),
- Six technetium generator suppliers (see Table 3.4), and
- Several Tc-99m-labeled radiopharmaceutical suppliers.

The portion of the supply chain that provides Mo-99 and associated medical isotopes to the United States is also illustrated in Figure 3.1.

3.1.1 Target Suppliers

Between approximately 9,000 and 10,000 targets are used annually to produce Mo-99 for medical use; about 80 percent of these targets contain highly enriched uranium (HEU) and 20 percent contain low enriched uranium (LEU).[2] Four companies currently supply these targets (see Table 3.1):

- Compagnie pour l'Etude et la Réalisation de Combustibles Atomiques[3] (CERCA), France;
- Comision Nacional de Ernergia Atomica[4] (CNEA), Argentina;
- Canadian Nuclear Laboratories (CNL), Canada; and
- Nuclear Technology Products (NTP) Radioisotopes ("NTP"), South Africa.

[2] ANSTO and NTP collectively consume about 2,000 LEU targets per year.

[3] The English translation is "Company for the Study and Production of Atomic Fuels."

[4] The English translation is "Atomic Energy Commission of Argentina."

Brief descriptions of these suppliers are provided in the following subsections.

BWX Technologies, Inc., in Lynchburg, Virginia, previously supplied HEU targets for the MAPLE reactors at CNL. These reactors were constructed to produce Mo-99 for Nordion but were never put into commercial operation (see NRC, 2009, pp. 115-120, and Section 3.1.2.5 in this chapter).

3.1.1.1 CERCA

CERCA is part of AREVA-NP (Nuclear Parts Center), a subsidiary of AREVA, a private company that is 80 percent owned by the French government.[5] Its target manufacturing facilities are located in Romans, France. The company currently produces 93 percent uranium-235 (U-235) HEU and 19.75 percent U-235 LEU targets. Based on the company's customer projections the company expects to discontinue HEU target production by the end of 2016 (see Chapter 5).

CERCA produces HEU and LEU targets for Institut National des Radioéléments (IRE) and Mallinckrodt Pharmaceuticals ("Mallinckrodt") (these companies are described in Section 3.1.3); the United States supplies the HEU used in these targets;[6] the LEU used in these targets is provided by various suppliers. CERCA also produces LEU targets for the Australian Nuclear Science and Technology Organisation (ANSTO) and NTP Radioisotopes. The LEU used in these targets is supplied by the United States (for ANSTO's targets) and the Russian Federation (for NTP's targets).

CERCA estimates that it currently supplies the majority of the targets used to produce Mo-99 for medical use. CERCA also estimates that it has the manufacturing capacity to supply all of the targets used globally for Mo-99 production.[7]

The committee estimates that CERCA currently supplies at least 60 percent of the targets used by global Mo-99 suppliers; the company's proportion of target supply probably varies from year to year depending on the timing of target purchases by Mo-99 suppliers. The committee also estimates that CERCA's share of the global market for target supply could increase to almost 100 percent once Nordion stops producing Mo-99 (after October 2016) and global Mo-99 suppliers convert to LEU targets (2019). Some global Mo-99 suppliers are seeking alternate sources of target supplies, which could reduce CERCA's market share in the future.

Other target suppliers (described below) provide the remainder global

[5] In 2017 the majority of AREVA-NP's reactor business will be sold to Électricité de France; see http://www.world-nuclear-news.org/C-Areva-outlines-restructuring-plan-1506164.html.

[6] CERCA receives HEU through a 1960 U.S./Euratom supply agreement.

[7] Berndt Stepnik, CERCA, verbal communication, October 19, 2015.

TABLE 3.2 Reactors That Irradiate Targets for Global Mo-99 Suppliers as of June 2016

Reactor	Country	Power (MWt)	Fuel Type	Target Type	Start of Operation (year)
BR-2	Belgium	100	HEU	HEU	1961
HFR[e]	Netherlands	45	LEU	HEU	1961
LVR-15	Czech Republic	10	LEU	HEU	1957
Maria	Poland	30	LEU	HEU	1974
NRU	Canada	135	LEU	HEU	1957
OPAL	Australia	20	LEU	LEU	2006
SAFARI-1	South Africa	20	LEU	HEU/ LEU[c]	1965

NOTES: BR-2 = Belgian Reactor 2; HEU = highly enriched uranium; LEU = low enriched uranium; HFR = High Flux Reactor; NRU = National Research Universal; OPAL = Open Pool Australian Lightwater; SAFARI-1 = South African Fundamental Atomic Research Installation 1.

[a] Most reactors do not have the capability to produce Mo-99 all of the days they operate.

[b] Production weeks per year is typically derived by dividing normal operating days per year by 7. However, this is not always the case. For example Maria runs short irradiation cycles that typically last less than a week, after which the reactor is stopped to remove the HEU targets for Mo-99 production. Therefore, the number of anticipated Mo-99 production weeks for Maria is 36 and not 29 (or else 200/7) (Kevin Charlton, OECD-NEA, written communication, September 15, 2015).

supply of targets used for Mo-99 production. The committee was unable to obtain reliable estimates of the percentages of targets supplied by each of these companies because this information is proprietary.

3.1.1.2 CNEA

CNEA supplies 19.75 percent LEU targets to Argentina, Australia, and Egypt from its Constituyentes Atomic Centre in Buenos Aires. The LEU used in the targets is supplied by the United States.

Reactor Operation License Expiration (year)	Normal Operating Days (days/year)[a]	Mo-99 Production (weeks/year)[b]	Available Production Capacity per week (6-day Ci Mo-99/week)[c]	Available Production Capacity per year (6-day Ci Mo-99/year)	Percent Global Available Production Capacity[d]
2026	190	27	7,800	210,600	21
2024	266	38	5,400	228,000	23
2028	210	30	2,400	72,000	7
2030	200	36	2,700	95,000	9
2018	280	40	4,680	187,200	19
2055[f]	300	43	1,750	75,250	8
2030	305	44	3,000	130,700	13
		Totals:	27,730	998,750	100

[c] Available production capacity is the theoretical maximum capacity that can be normally produced. It is a measure of actual capacity and target usage levels.

[d] A reactor's percent global available production capacity is calculated by dividing the available production capacity per year for that reactor by the total available capacity per year for the seven reactors (i.e., 998,750 6-day Ci of Mo-99/year) and multiplying the result by 100.

[e] OECD-NEA (2016) reports HFR's available capacity after the 2017 scheduled expansion.

[f] For OPAL this is the estimated end of operation and not the reactor's operation license expiration date.

SOURCE: Modified from OECD-NEA (2016).

3.1.1.3 Canadian Nuclear Laboratories

CNL is the private-sector entity that manages and operates Atomic Energy of Canada Limited's (AECL's) Chalk River Laboratories[8] under a government-owned, contractor-operated arrangement. It produces 93 percent HEU targets for production of medical isotopes in the National Research Universal (NRU) reactor; these targets are processed by CNL and Nordion. The HEU used in these targets is supplied by the United States.

[8] CNL is located near Chalk River, Ontario, Canada.

TABLE 3.3 Global Mo-99 Suppliers as of June 2016

Supplier	Country	Target Type	Expected Conversion to Using LEU Targets[a] (year)	Mo-99 Supply (weeks/year	Available Supply Capacity (6-day Ci Mo-99/week)	Available Supply Capacity (6-day Ci Mo-99/year)	Global Supply Capacity (%)
ANSTO	Australia	LEU	N/A[b]	43	1,100[c]	47,300[c]	6
IRE	Belgium	HEU	2016	52	3,600[e]	187,200	24
Mallinckrodt	Netherlands	HEU	2017	52	3,500[f]	182,000	24
Nordion	Canada	HEU	2018[d]	48	4,680	224,640	29
NTP	South Africa	HEU/LEU	2010	44	3,000	132,000	17
				Totals:	15,880	773,140	100

NOTES: ANSTO = Australian Nuclear Science and Technology Organisation; HEU = highly enriched uranium; LEU = low enriched uranium; IRE= Institut National des Radioéléments; NTP= Nuclear Technology Products Radioisotopes.

[a] The reactor used to irradiate these targets may be fueled with LEU or HEU.

[b] ANSTO has always produced Mo-99 with LEU targets; see Chapter 5.

[c] Information gathered by the committee during site visit to ANSTO.

[d] Nordion is developing a new process for producing Mo-99 that will utilize LEU targets; see Chapter 5.

[e] Information gathered by the committee during site visit to IRE.

[f] OECD-NEA (2016) reports Mallinckrodt's supply capacity after the scheduled expansion.

SOURCE: Modified from OECD-NEA (2016).

TABLE 3.4 Major Technetium Generator Suppliers as of June 2016

Country	Generator Supplier	Generator Name	Target Type for Mo-99 Contained in Generator	Global Generator Market in 2015 (%)
Australia	ANSTO Health	Gentech®	LEU	<2
United Kingdom	GE Healthcare	Drytec™	HEU	10
France	IBA Molecular	TEKCIS®	HEU	8
United States	Lantheus Medical Imaging	TechneLite®	LEU and HEU	20
Netherlands and United States	Mallinckrodt Pharmaceuticals	Ultra-Technekow™ DTE Generator	HEU	60
South Africa	NTP Radioisotopes	NovaTec-PTM	LEU	<2

NOTES: ANSTO = Australian Nuclear Science and Technology Organisation; HEU = highly enriched uranium; LEU = low enriched uranium; IBA = Ion Beam Applications.
SOURCE: Global generator market in 2015 (right-most column) from Brown (2015).

3.1.1.4 NTP

NTP is located at the South African nuclear complex at Pelindaba. It supplies its own HEU targets (45 percent enriched) and purchases LEU targets (19.75 percent) from CERCA. The HEU is of South African origin and the LEU is currently of Russian origin.

3.1.2 Irradiation Services Suppliers

Almost all of the Mo-99 for medical use is currently produced by irradiating uranium targets in seven research reactors:

- Belgian Reactor-2 (BR-2), Belgium
- High Flux Reactor (HFR), the Netherlands
- LVR-15, Czech Republic
- Maria, Poland
- NRU, Canada
- Open Pool Australian Lightwater (OPAL), Australia
- South Africa Fundamental Atomic Research Installation 1 (SAFARI-1), South Africa

An additional research reactor, OSIRIS in France, produced Mo-99 for medical use until it was shut down in December 2015. The seven currently operating reactors listed above produce over 95 percent of Mo-99 used globally for medical use, and they produce all of the Mo-99 for medical use in the United States. The remaining (~5 percent) supply of Mo-99 for medical use is produced primarily for regional use in research reactors in other countries, for example Argentina, Egypt, Indonesia, and Russia.

Table 3.2 provides information about the seven currently operating reactors and their Mo-99 production capacities. Note particularly:

- Six reactors (BR-2, HFR, LVR-15, Maria, NRU, and SAFARI-1) irradiate HEU targets to produce Mo-99 for medical use; one of these reactors (BR-2) is fueled with HEU. About 75 percent of the global supply of Mo-99 is produced with HEU targets.
- Two reactors (OPAL and SAFARI-1) irradiate LEU targets to produce Mo-99 for medical use. About 25 percent of the global supply of Mo-99 is produced with LEU targets.
- All but one of these reactors (OPAL) were constructed in the 1970s or earlier. Their average age is 53 years. The OPAL reactor became operational in 2006.
- On average, each of these seven reactors operates about 240 days (~67 percent) per year. These reactors do not produce Mo-99 on all of the days they operate.
- The combined available production capacity (see Sidebar 3.1) for these seven reactors is almost 28,000 6-day curies (Ci) of Mo-99 per week when they are operating. This is about three times the current weekly demand for Mo-99, which is estimated to be about 9,000 6-day Ci per week (OECD-NEA, 2016; see Chapter 6).

Additional information about these seven reactors is provided in the following sections.

3.1.2.1 BR-2

BR-2 is a 100 megawatt-thermal[9] (MWt), tank-type,[10] HEU-fueled, light-water-cooled research reactor located at Mol, Belgium. It is operated by the Belgian Nuclear Research Center (SCK•CEN)[11] and is used primarily

[9] MWt is the thermal (heat) output of a reactor. Research reactors are not used to generate electricity.

[10] The reactor core is contained in a tank of water, and water is actively circulated through the core to remove heat.

[11] Dutch: Studiecentrum voor Kernenergie; French: Centre d'Étude de l'Energie Nucléair; English: Belgian Nuclear Research Centre.

for the testing of reactor fuels and materials. BR-2 currently accounts for about 21 percent of global available production capacity.[12] Mo-99 produced in this reactor is purified and distributed through IRE and Mallinckrodt. BR-2 also produces I-131 and Xe-133 for distribution by IRE. (These Mo-99 suppliers are described in Section 3.1.3 in this chapter.)

BR-2 started operation in 1961 and its current operating license expires in 2026. It was shut down in March 2015 for an 18-month refurbishment; the refurbishment work included replacement of the beryllium reflector, a critical component of the reactor.[13] The work was completed in July 2016 and the reactor has resumed irradiating targets for Mo-99 production.[14]

BR-2 produces Mo-99 about 140 days per year. SCK•CEN is considering expanding the reactor's capacity for producing Mo-99 by increasing its irradiation schedule to 190 days per year (Ponsard, 2015). This expansion, which could increase BR-2's available production capacity from 7,800 to 10,530 6-day Ci per week, is expected to occur gradually.[15]

SCK•CEN is developing MYRRHA (Multi-purpose hYbrid Research Reactor for High-tech Applications), a multifunctional experimental irradiation facility, to replace BR-2. MYRRHA would be the world's first liquid-metal-cooled nuclear reactor driven by a particle accelerator. Construction of MYRRHA is planned for the period 2017-2021 and full commissioning of the facility is scheduled for 2022-2024.[16] MYRRHA would start producing Mo-99 after 2026.[17]

3.1.2.2 HFR

HFR is a 45 MWt, tank-type, LEU-fueled, light-water-cooled research reactor located in Petten, the Netherlands. It is owned by the Institute for Energy of the Joint Research Centre of the European Commission and is operated by the Nuclear Research and Consultancy Group (NRG). NRG also holds the reactor's operating license. The reactor supports nuclear research and development, radioisotope production, and industry irradiation services.

HFR started operation in 1961 and was converted from HEU to LEU fuel in 2006. The reactor currently accounts for about 23 percent of global

[12] Production capacity is the maximum capacity of the reactor to produce Mo-99 on a routine basis. Most reactors produce Mo-99 below their production capacity. The percentage of global available production capacity for each reactor describes the reactor's share of total annual available production capacity (see Table 3.2).

[13] See https://www.sckcen.be/en/News/20150325_BR2.

[14] Bernard Ponsard, SCK•CEN, written communication, August 2, 2016.

[15] Bernard Ponsard, SCK•CEN, written communication, August 2, 2016.

[16] See http://myrrha.sckcen.be.

[17] Bernard Ponsard, SCK•CEN, written communication, August 2, 2016.

available production capacity, but its capacity will increase from 5,400 to 6,200 6-day Ci per week starting in 2017 (OECD-NEA, 2016). Mo-99 produced in HFR is distributed through IRE and Mallinckrodt. HFR also produces I-131 and Xe-133 for distrubtion by IRE.

HFR will probably be shut down when its current operating license expires in 2024. A privately funded replacement reactor, PALLAS, is planned to be built at Petten. PALLAS will likely be a 55 MWt, tank-type reactor. A licensable design is expected to be completed by 2017 and construction by 2023 (WNN, 2014). The funding sources for PALLAS have not yet been identified.

3.1.2.3 LVR-15

LVR-15 is a 10 MWt, tank-type, LEU-fueled, light-water-cooled research reactor situated at Research Centre Řež near Prague, Czech Republic. It is owned and operated by the Nuclear Research Institute Řež, plc. Its main missions are in materials testing, industry irradiation services, and radioisotope production. LVR-15 currently accounts for about 7 percent of global available production capacity. LVR-15 produces Mo-99, I-131, and Xe-133 for distribution by IRE. Mallinckrodt has an agreement with IRE to share access to this reactor in exchange for IRE's access to the Maria reactor.

LVR-15 started operation in 1957 and its current operating license expires in 2028. The reactor converted from HEU to LEU fuel in 2010.

3.1.2.4 Maria

The Maria reactor is a 30 MWt, pool-type,[18] LEU-fueled, light-water-cooled research reactor located at Świerk-Otwock, near Warsaw, Poland. It is operated by Poland's National Center for Nuclear Research (NCBJ) (POLATOM) Radioisotope Center. Maria began irradiating Mo-99 targets in 2010 to help ease the isotope shortages due to unplanned shutdowns of the NRU and HFR reactors (WNN, 2010; see Section 3.3.1 in this chapter). It currently accounts for about 9 percent of global available production capacity. Mo-99 produced in Maria is distributed by Mallinckrodt. IRE plans to irradiate targets for Mo-99 production in Maria in the near future under the aforementioned access agreement with Mallinckrodt.

Maria started operation in 1974 and its current operating license expires in 2030. It was taken offline in 1985 for a complete redesign and resumed normal operations in 1993. It completed conversion to LEU fuel in 2012.

[18] The reactor core is contained in an open pool of water and water is actively circulated through the core to remove heat.

3.1.2.5 NRU

The NRU reactor is a 135 MWt, tank-type, LEU-fueled, heavy-water-cooled and moderated research reactor located at CNL near Chalk River, Ontario, Canada. It is owned by the Canadian government and operated by CNL. The reactor is used for industrial and medical radioisotope production, neutron beam research, and materials research and development for CANDU power reactors.[19]

The NRU reactor started operation in 1957 and was converted from HEU to LEU fuel in 1991. It produces Mo-99 and Xe-133 from HEU targets and I-131 from tellurium targets. All of these isotopes are distributed through Nordion. NRU accounted for 40 to 60 percent of global available production capacity for several decades. It currently accounts for about 19 percent of available annual production capacity (Brady and Pruneau, 2015).

Two dedicated isotope production reactors, Multipurpose Applied Physics Lattice Experiment (MAPLE) 1 and 2, and a new dedicated target processing facility were constructed to replace the NRU reactor. These new facilities were scheduled to produce Mo-99 starting in 2000. The Mo-99 production capacity of these new facilities was to exceed the then-current global demand for Mo-99 (see OECD-NEA, 2010). However, the MAPLE reactors were never used to produce Mo-99 because of technical and regulatory problems that were deemed too expensive to address (IAEA, 2009). In 2008, AECL terminated the MAPLE project. In 2011, the operating license for the Chalk River Site, including the NRU, was renewed to October 31, 2016.

The Canadian government announced in 2015 that it would extend NRU's operations through March 2018 "to help support global medical isotope demand between 2016 and 2018 in the unexpected circumstances of shortages" (NRCan, 2015). The Canadian Nuclear Safety Commission (CNSC) has approved the extension of the license to March 31, 2018. NRU will continue to operate between the end of October 2016 and the end of March 2018 but will not be used for routine production of Mo-99. CNL's facility for processing irradiated targets will be kept in hot standby during this period as well.

The Canadian government is currently investing in four projects to produce Mo-99/Tc-99m for Canadian domestic consumption:

- Canadian Isotope Innovations (CII), a for-profit spinoff from Canadian Light Source, to produce Mo-99 via the $^{100}Mo(\gamma,n)^{99}Mo$ reaction (see Chapter 2) using linear accelerators. The company plans to start Mo-99 production in 2019 (De Jong, 2015).

[19] CANDU (CANada Deuterium Uranium) power reactors are pressurized heavy water reactors developed by Canada and used commercially to generate electricity.

- Prairie Isotope Production Enterprise, a not-for-profit organization formed in 2009 to develop Tc-99m supply for the Canadian health care sector, and also to produce Mo-99 via the $^{100}Mo(\gamma,n)^{99}Mo$ reaction using linear accelerators. The company plans to start Mo-99 production in 2016 (Saunders, 2015).
- A consortium between Advanced Cyclotron Systems, Inc., CRCHUS (the research center of the Centre Hospitalier Universitaire de Sherbrooke), and the University of Alberta to produce Tc-99m via the $^{100}Mo(p,2n)^{99m}Tc$ reaction (see Chapter 2) using cyclotrons. The consortium partners plan to start Tc-99m production in 2017-2018 (Guérin, 2015).
- TRIUMF, Canada's national laboratory for particle and nuclear physics and accelerator-based science, also to produce Tc-99m via the $^{100}Mo(p,2n)^{99m}Tc$ reaction using cyclotrons. TRIUMF plans to start production in 2017 (Buckley, 2015).

Tc-99m production by these companies would have to take place close to end users because of the short (~6 hour) half-life for this radionuclide. At least two of these potential Canadian suppliers (Canadian Isotope Innovations and Advanced Cyclotron Systems) intend to provide Tc-99m to the U.S. market provided they can meet U.S. regulatory requirements.

3.1.2.6 OPAL

OPAL is a 20 MWt, pool-type, LEU-fueled, light-water-cooled research reactor located in Lucas Heights, a suburb of Sydney, Australia. OPAL is owned and operated by ANSTO. The reactor is used for isotope production, silicon doping, neutron activation analysis, and neutron beam research. All of the reactor's activities are scheduled around medical isotope production. ANSTO increased its available production capacity in 2016 from 1,000 to 1,750 6-day Ci per week and currently accounts for about 8 percent of global available production capacity. It also produces I-131 using tellurium targets and other isotopes used in nuclear medicine. These isotopes are produced and distributed by ANSTO.

OPAL replaced the High Flux Australian Reactor (HIFAR), which produced medical isotopes from 1958 to 2007. OPAL started operations in 2007 and production of Mo-99 in 2009. The reactor's estimated end of operation is 2055. OPAL is the first research reactor in the world to be built to use LEU fuel and LEU targets for production of Mo-99. It is also the youngest reactor in the world that is used to produce Mo-99 on a commercial scale.

3.1.2.7 SAFARI-1

SAFARI-1 is a 20 MWt, pool-type, LEU-fueled, light-water-cooled research reactor located at Pelindaba, South Africa. The reactor is owned and operated by South African Nuclear Energy Corporation (NECSA). It was initially used for nuclear physics research programs, but its primary purpose today is production of radioisotopes, mostly Mo-99. It currently accounts for about 13 percent of global available production capacity. Targets are irradiated in SAFARI-1 and Mo-99 is produced and distributed by NTP Radioisotopes, a subsidiary of NECSA.

SAFARI-1 was commissioned in 1965 and was built in cooperation with the Atoms for Peace program run by the U.S. Atomic Energy Commission.[20] The reactor was initially fueled with HEU supplied by the United States. South Africa developed its own 45 percent HEU fuel for the reactor after the United States cut off HEU fuel exports in 1975. SAFARI-1 converted to LEU fuel in 2009 (NECSA, 2009) and started using LEU targets for medical isotope production in 2010. The first ever supply of commercial-scale, LEU-derived Mo-99 to the United States was made that same year from NTP (WWN, 2011). The reactor currently irradiates Mo-99 targets with 45 percent HEU and 19.75 percent LEU. About 48 percent of Mo-99 production was from LEU targets in 2015; 80 percent of Mo-99 production was from LEU targets in the first quarter of 2016.

3.1.2.8 OSIRIS

OSIRIS is a 70 MWt, pool-type, LEU-fueled, light-water-cooled research reactor located at Saclay Centre, France. It started operation in 1966 and was shut down in December 2015 after a safety and performance assessment showed that the reactor would not be a reliable irradiation facility even after a major refurbishment (ASN, 2014). OSIRIS was operated by France's Atomic Energy Commission (CEA) and was used for irradiation tests of nuclear reactor fuels and structural materials and irradiation of targets for Mo-99 production. OSIRIS accounted for about 5 percent of available production capacity (2,400 6-day Ci per week) at the time it was shut down. Mo-99 produced in OSIRIS was distributed by IRE.

The Jules Horowitz Reactor (JHR), currently under construction at the CEA Cadarache Centre in France, will replace OSIRIS. The reactor is expected to start operation in 2020. It will have a weekly Mo-99 production capacity of 4,800 6-day Ci and produce Mo-99 32 weeks per year (OECD-NEA, 2016). JHR will provide irradiation capacity for materials,

[20] The U.S. Atomic Energy Commission was the predecessor of the U.S. Department of Energy and the U.S. Nuclear Regulatory Commission.

fuel, and other engineering testing to support nuclear reactor development and for Mo-99 and other radioisotope production.

3.1.3 Mo-99 Suppliers

There are five global suppliers of Mo-99 at present (see Figure 3.1):

- ANSTO, Australia
- IRE, Belgium
- Mallinckrodt, Netherlands
- Nordion, Canada
- NTP, South Africa

All of these suppliers provide Mo-99 to the United States (see Figure 3.1). Their combined available supply capacity (see Sidebar 3.1) is 15,880 6-day Ci per week (see Table 3.3) when all of the suppliers are operating, somewhat less than twice the current global demand for Mo-99, estimated to be about 9,000 6-day Ci per week (OECD-NEA, 2016; see Chapter 6). Their annual available supply capacity is about 773,000 6-day Ci per year. This quantity accounts for the number of operating weeks per year for each supplier.

Mo-99 is also produced for regional use by other suppliers. Some of these suppliers are described in Section 3.2.2 in this chapter.

3.1.3.1 ANSTO

ANSTO's target processing facility is located at the company's Lucas Heights facility, which is also the location of the OPAL reactor. It currently accounts for about 6 percent of available annual supply capacity (1,100 6-day Ci per week) from processing LEU targets irradiated in OPAL. ANSTO currently exports Mo-99 to several countries, including the United States, China, Japan, and South Korea.

3.1.3.2 IRE

IRE's target processing facility is located in Fleurus, Belgium. It currently accounts for about 24 percent of available supply capacity (3,600 6-day Ci per week) from processing HEU targets irradiated in BR-2, HFR, and LVR-15.[21] It plans to obtain irradiated targets from Maria, JHR, and Forschungsreaktors München II (FRM-II) reactor (Germany) in the future. FRM-II has been operating since 2005 and is currently undergoing modifi-

[21] IRE also irradiated targets in OSIRIS until 2015.

cations to allow for the irradiation of LEU targets starting in 2018. IRE also supplies I-131 to Mallinckrodt and unprocessed bulk radiochemical Xe-133 to Lantheus Medical Imaging ("Lantheus") for processing and sale.[22]

3.1.3.3 Mallinckrodt

Mallinckrodt[23] processes irradiated targets at the Petten site in the Netherlands in a joint venture with NRG, the operator of HFR. It currently accounts for about 24 percent of available annual supply capacity (3,500 6-day Ci per week) by processing targets irradiated in BR-2, HFR, LVR-15, and Maria. It may obtain irradiated targets from FRM-II and JHR in the future. Mallinckrodt purchases I-131 from IRE and Nordion for sale in the United States and other countries. The company plans to purchase Xe-133 from Nordion once its new Mo-99 production process is implemented (see Chapter 4).

As the committee was finalizing this report for publication, Mallinckrodt announced that it had entered into an agreement with Ion Beam Applications (IBA) Molecular, a technetium generator supplier in Europe (see Section 3.1.4 in this chapter), to sell its nuclear imaging business.[24]

3.1.3.4 Nordion

Nordion has the largest Mo-99 supply capacity of the current global suppliers. It obtains bulk Mo-99 from CNL and purifies and distributes it at its Kanata, Ontario, Canada, facility. It currently accounts for about 29 percent of available annual supply capacity (4,680 6-day Ci per week), down from 40 to 60 percent prior to 2010.

Nordion will stop supplying Mo-99 once the NRU reactor stops production after October 31, 2016. The company is developing a new Mo-99 production process in cooperation with General Atomics and the University of Missouri Research Reactor Center. This process is described in Chapter 4.

3.1.3.5 NTP

NTP, a subsidiary of NECSA, produces Mo-99 from HEU (45 percent enriched) and LEU (19.75 percent enriched) targets, which are irradiated in the SAFARI-1 reactor and processed in an adjacent facility. It currently

[22] Lantheus received Food and Drug Administration approval for Xe-133 sourced from IRE on June 10, 2016, and made the first commercial shipment on June 30, 2016.

[23] Mallinckrodt was spun off from Covidien in 2013.

[24] See http://www.mallinckrodt.com/about/news-and-media/2197068.

accounts for about 17 percent of available annual supply capacity (3,000 6-day Ci per week), about half of which was produced with LEU targets. The company also produces and sells I-131 to the global market.

3.1.4 Technetium Generator Suppliers

There are six major suppliers of technetium generators at present (see Table 3.4):

- ANSTO, Australia
- General Electric (GE) Healthcare, United Kingdom (UK)
- IBA Molecular, France
- Lantheus Medical Imaging, United States
- Mallinckrodt, the Netherlands and United States
- NTP, South Africa

These are not the only technetium generator suppliers in the world. For example, there are also suppliers in India, Japan, Poland, Russia, and Turkey.

Mallinckrodt and Lantheus supply about 80 percent of the technetium generators used globally (see Table 3.4) and most of the generators used in the United States. (GE Healthcare also provides technetium generators manufactured in the UK to their commercial nuclear pharmacies in the United States [Business Wire, 2014]). Both companies have generator manufacturing facilities in the United States; Mallinckrodt also manufactures generators in Europe. As noted earlier in this chapter, Mallinckrodt announced that the company has entered into an agreement with IBA Molecular to sell its nuclear imaging business. If this agreement is carried out, the number of major suppliers of technetium generators will be reduced by one.

Mallinckrodt supplies most of the Mo-99 used in its technetium generators but has backup supply arrangements with other global Mo-99 suppliers. Lantheus purchases Mo-99 in roughly equal proportions from ANSTO, IRE, Nordion, and NTP.[25]

The other technetium generator suppliers shown in Table 3.4 supply generators locally and regionally. For example, ANSTO supplies generators to China, Hong Kong, Indonesia, Myanmar, New Zealand, the Philippines, Singapore, Taiwan, Thailand, and Vietnam. GE Healthcare primarily distributes generators in Europe.

[25] Ira Goldman, Lantheus Medical Imaging, written communication, June 3, 2016.

3.1.5 Tc-99m Suppliers

Tc-99m-labeled radiopharmaceuticals are supplied to hospitals and clinics from a large number of nuclear pharmacies. Supply is a local business. In the United States, there are four commercial nuclear pharmacies with national chain store operations: Cardinal Health™, GE Healthcare, Triad Isotopes, and United Pharmacy Partners (UPPI, LLC) (see Figure 3.1). The latter is a network of locally owned nuclear pharmacies and independent nuclear pharmacies.

3.2 PROSPECTS FOR NEW Mo-99 SUPPLIES

Several Mo-99 suppliers have initiated or announced plans to increase their Mo-99 available supply capacities in the near future. Plans by existing suppliers are described in Section 3.2.1; plans by potential new suppliers are described in Section 3.2.2.

3.2.1 Existing Global Suppliers

Three existing global Mo-99 suppliers (ANSTO, Mallinckrodt, and NTP) have announced plans to expand their available supply capacities. If all of these plans are realized, available supply capacities would be increased by about 4,400 6-day Ci per week by the end of 2017 (see Figure 3.2). This added capacity would almost offset the loss of available supply capacity (4,680 6-day Ci per week) when Canada (NRU/Nordion) stops producing and supplying Mo-99 after October 31, 2016. Additional details are provided in the following subsections.

3.2.1.1 ANSTO

ANSTO plans to increase its available supply capacity from 1,100 to 3,500 6-day Ci per week by mid-2017. This increase in capacity will be accomplished by making additional irradiations and processing runs. Most of the increased supply is targeted for the United States. The Australian government has loaned the necessary funding to ANSTO to construct a new target processing facility and a new radioactive waste treatment plant to enable this increased supply capacity. Construction of these facilities is under way.

3.2.1.2 Mallinckrodt

Mallinckrodt plans to increase its available supply capacity from 3,500 to 5,000 6-day Ci per week by the end of 2017. This will be accomplished

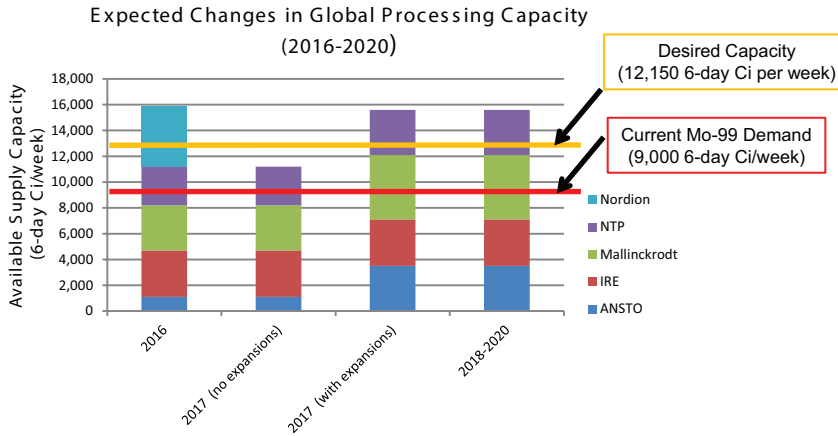


FIGURE 3.2 Expected changes in available supply capacity for existing Mo-99 suppliers for the period 2016-2020. If all expansion plans are realized, added capacity would almost offset the loss of available production capacity from NRU/Nordion. However, if expansions are not realized on time, available production capacity would fall below desired capacity. Plans by existing global suppliers to expand their available supply capacities are described in the text. Notes: ANSTO = Australian Nuclear Science and Technology Organisation; IRE = Institut National des Radioéléments; NTP = Nuclear Technology Products Radioisotopes.

by increasing target processing runs from four to six times per week. The company is also considering irradiating additional targets. These could be irradiated in the FRM II reactor in Germany and/or the reactor currently under construction (JHR) in France.

3.2.1.3 NTP

NTP plans to increase its available supply capacity from 3,000 to 3,500 6-day curies per week by September 2017.[26] The company may use a number of strategies to increase capacity, including irradiating additional targets and improving target processing efficiencies.

3.2.2 Potential New Global and Regional Suppliers

Additional new global or regional supplies of Mo-99 may become available from other countries in the future. Plans by Argentina, Brazil,

[26] Tina Eboka, NTP, written communication, May 31, 2016.

South Korea, and Russia are described in the following subsections. Other countries may also have plans to enter the Mo-99 supply market, but these plans have not been publicized and are therefore not well enough known to be discussed here.

3.2.2.1 Argentina

Argentina currently supplies about 400 6-day Ci per week by irradiating LEU targets at the RA-3 reactor, which is operated by CNEA. This reactor is scheduled to be shut down in 2027; a 30 MWt replacement reactor, RA-10, is expected to be operational in 2020 (OECD-NEA, 2016). This new reactor will support increased radioisotope production to cover future demands; provide fuel and materials testing irradiation facilities to support national technology development; and offer modern neutron applications in science and technology (Sánchez et al., 2014).

The RA-10 reactor is designed by INVAP (Investigación Aplicada), the Argentina nuclear technology company that designed and built the OPAL reactor (WNN, 2013). RA-10 is expected to start commercial production of Mo-99 with an available supply capacity at 2,500 6-day Ci per week to cover domestic and regional needs (OECD-NEA, 2015). This is an increase of 1,900 6-day Ci per week compared to existing capacity levels.

3.2.2.2 Brazil

The Brazilian government has formalized the decision to build RMB, a 30 MWt, open-pool reactor that will be part of a new nuclear research center near the city of São Paulo (Perrotta and Soare, 2015). The project is part of a joint declaration with Argentina to develop multipurpose reactors and to demonstrate their common interest in promoting peaceful use of nuclear energy (Merco Press, 2013).

RMB will serve three purposes: neutron activation analysis; materials and fuels testing; and radioisotope production, including production of Mo-99. (Brazil currently imports all of the Mo-99 needed for medical use.) The reactor is expected to start commercial production of Mo-99 with an available supply capacity of 1,000 6-day Ci per week (OECD-NEA, 2016).

The RMB project is still at the design phase and further progress depends on funding. It is not expected to produce any Mo-99 before at least 2021.

3.2.2.3 South Korea

South Korea has been producing I-131 and Ir-192 on a commercial scale at HANARO (High-flux Advanced Neutron Application ReactOr)

since 1995 but has been importing Mo-99 from other countries (Wu et al., 2013). The country produces technetium generators for domestic use and export, and it also imports generators for domestic use.[27]

The Korean government began an effort in 2012 to build the Kijang Research Reactor (KJRR) to supply Mo-99, I-131, I-125, and Ir-192 (Wu et al., 2013). This 15 MWt, pool-type, LEU-fueled, light-water-cooled reactor will be constructed near Busan City by the Korea Atomic Energy Research Institute. Several facilities are being constructed: the reactor, a radioisotope production facility, an LEU Mo-99 target production facility, a neutron transmutation doping facility, and a radioactive waste treatment facility (Lim et al., 2011).

A construction permit for the reactor was in review by the regulatory body in December 2015. Production of Mo-99 is expected to start in 2020 (OECD-NEA, 2016). The available supply capacity for Mo-99 is expected to be 2,000 6-day Ci per week, with initial supply of 400 6-day Ci per week. The Mo-99 produced at KJRR will be supplied domestically and regionally.[28]

3.2.2.4 Russia

Russia has been producing Mo-99 for decades in two reactors: the WWR-TS reactor at the Karpov Institute in Obninsk and, starting from 2013, the RBT-10/2 and RBT-6 reactors at the Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad. These reactors and associated Mo-99 processing facilities are owned and operated by the Russian government agency ROSATOM. All three reactors use HEU fuel and targets. Currently, the three reactors supply hundreds 6-day Ci per week of Mo-99 for domestic consumption (demand in Russia is about 100 6-day Ci per week; Zhuikov, 2014); regular export to Iran; and export on a trial basis to Canada, India, the Philippines, Poland, and Saudi Arabia (Khlopkov et al., 2014). Recently, Russia signed a contract with the National Nuclear Energy Commission in Brazil to supply Mo-99.[29]

The Russian government plans to become a global supplier of Mo-99 and to capture about a 20 percent share of the global market but has not announced a schedule for doing so. The government plans to increase Mo-99 supplies by irradiating targets at the RBT-10/2 and RBT-6 reactors at RIAR in Dimitrovgrad. There are two facilities at RIAR for processing

[27] Jun S. Lee, Director, RI Research Division, KAERI, written communication, March 8, 2016.

[28] Jun S. Lee, Director, RI Research Division, KAERI, written communication, August 20, 2015.

[29] See http://www.rosatom.ru/en/presscentre/news/f1eefa804784b5d98bdbfb6578d50f5d.

irradiated targets from RBT-10/2 and RBT-6 with a combined available supply capacity of 900 to 1,000 6-day Ci per week. In addition to the RIAR reactors, other reactors in Russia are being assessed for feasibility to supply Mo-99 on a commercial basis.

3.2.2.5 Other Potential Suppliers

Several other countries produce Mo-99 for domestic use and could potentially expand production in the future[30]:

- China
- Egypt
- India
- Indonesia

Consumption of Mo-99 in these countries typically ranges from a few tens to about 200 6-day Ci per week. This demand is met by a combination of local production and imports. Other countries may produce Mo-99/Tc-99m exclusively for local use.

3.3 RECENT SUPPLY INTERRUPTIONS

The global Mo-99 supply chain is *inherently* fragile. The fragility stems from three factors:

1. Mo-99 and its daughter isotope Tc-99m have short half-lives (66 and 6 hours, respectively) and therefore cannot be stockpiled. These radioisotopes need to be produced and delivered to the supply chain on a weekly or more frequent basis.
2. Global supply of Mo-99 relies on a small number of reactors (seven currently; Table 3.2) and a small number of suppliers (five currently; Table 3.3), as noted previously.
3. With the exception of the OPAL reactor, which is only 10 years old, the remaining six reactors that are used to irradiate targets for Mo-99 production are on average 53 years old.

Mo-99 production has been interrupted unexpectedly on numerous occasions since 2009 because of unplanned shutdowns of these aging reactors. These interruptions have caused Mo-99 supply shortages and in some cases, severe shortages. Table 3.5 lists some of the notable interruptions

[30] Information for this section was obtained from the IAEA (2010) and discussions with current global suppliers.

in Mo-99 supply due to planned and unplanned shutdowns of reactors and Mo-99 suppliers from 2009 to present. Some of interruptions were discussed in the previous Academies' report on medical isotope production (NRC, 2009); see especially Chapter 3 in that report. Additional discussion is provided in the following subsections.

The committee is not aware of any interruptions of Mo-99 supply due to target supplier shutdowns (see, e.g., European Observatory on the Supply of Medical Radioisotopes [2014]). However, there was a several-month interruption of technetium generator supplies from Covidien (now Mallinckrodt) in 2005 due to routine sterility assurance process revalidation. There was another interruption of Mo-99 supply in 2007 due to the shutdown of the Covidien technetium generator manufacturing facility for 1 month. The cause of the shutdown was a Mo-99 breakthrough in the company's technetium generators and subsequent recall of these generators.

3.3.1 Reactor Shutdowns

Supplies of Mo-99 were repeatedly and severely affected in 2007 because of planned and unplanned shutdowns of two major reactors: NRU in Canada and HFR in the Netherlands. NRU shut down in November 2007 for a planned 5-day maintenance outage, which was then voluntarily extended by the reactor owner/operator (AECL) to install seismically qualified emergency power systems for two of the reactor's cooling pumps. These upgrades were required for compliance with AECL's (now CNL's) 2006 operating license issued by the CNSC. The shutdown, which lasted for about 2 months, occurred without any coordination with other reactors and interrupted supplies of Mo-99 to North America. NRU resumed operations after the Canadian parliament passed emergency legislation authorizing restart before the seismic updates were complete, countermanding the CNSC (Ljunggren et al., 2007).

The NRU shut down again for 14 months starting in May 2009 because of a vessel leak and subsequent repair. HFR shut down at about that same time because of cooling system leaks. The HFR shutdowns occurred from August 2008 to February 2009, an additional month in 2009, and 6 more months in 2010. NRU and HFR provided about 40 percent and 30 percent, respectively, of global Mo-99 supplies at the time of these shutdowns. Their overlapping shutdowns caused major disruptions in global supplies in 2009-2010 and led to the cancellation or postponement of diagnostic imaging procedures in some countries, including the United States. Increased Mo-99 supplies from Europe could not offset these supply losses because there was insufficient target processing capacity.

The United States was among the countries most seriously impacted by the 2009-2010 supply shortages, likely due to the country's heavy reliance

on NRU and Nordion for Mo-99 supplies (see Collier, 2008). Canada, Japan, and Korea were also severely affected.

Unplanned Mo-99 supply interruptions occurred on at least five occasions since 2009-2010 (see Table 3.5). In 2013-2014, for example, interruptions occurred because of the simultaneous shutdowns of two major reactors (HFR and SAFARI-1).

In March 2015, BR-2 started an 18-month refurbishment that was completed in July 2016. The refurbishment work included the replacement of the beryllium reflector (NEI, 2014). The shutdown of the BR-2 reactor was planned and did not cause any major interruptions in Mo-99 supplies. However, an unplanned outage in HFR in October 2015 resulted in some minor supply disruptions because BR-2 was not operating.

3.3.2 Target Processing Facility Shutdowns

Target processing facilities shutdowns are potentially more serious than reactor shutdowns because they can temporarily remove a larger share of global Mo-99 supply. This is particularly true for IRE and Mallinckrodt, the two global Mo-99 suppliers that obtain target irradiation services from multiple reactors in Europe.

There have been two major shutdowns of target processing facilities since 2009:

- In 2013, positive pressure in a hot cell caused a leak of radioactive noble gases at NTP's target processing facility. No workers were injured, but the facility was shut down for 2 months while the problem was diagnosed and fixed.
- Mallinckrodt was shut down in 2013-2014 due to an unplanned outage at HFR.

IRE was also shut down for about 3 months in 2008 because of an unplanned release of I-131 to the environment. The leak went undetected for several days and resulted in cumulative release of about 45 gigabecquerels (GBq) of I-131, which exceeded the authorized annual release of I-131 from this facility (Federaal Agentschap voor Nucleaire Controle, 2008).

3.3.3 Transportation Denials and Delays

Mo-99 supply is interrupted frequently because of transportation denials and delays. These interruptions are typically resolved within hours or a few days and do not lead to severe interruptions in Mo-99 supply.

According to an IAEA analysis (Esarey, 2015), common reasons for transportation denials or delays include transit logistics problems involving

customs declarations; airlines being concerned about radiation or lacking information about how to handle radioactive substances; and confusing regulations on transportation of radioactive material. Additional reasons for refusing air transport of Mo-99 include the pilots denying the added freight weight.

Two other transportation-related events have caused Mo-99 supply shortages since 2009:

- The eruption of the Eyjafjallajökull volcano in Iceland in April 2010 grounded transatlantic air travel and air travel within Europe for a week. Mo-99 suppliers explored alternative transportation options to deliver Mo-99 (Triad Isotopes, 2010).
- The terrorist attacks in Belgium in March 2016 led the Belgian government to close all public transport in the country's capital, Brussels, including the airport. The Belgian government prohibited transport of all radioactive material in the country for a couple of days, causing IRE to halt production for one day.

3.4 ACTIONS TO MITIGATE SUPPLY DISRUPTIONS

Since the 2009-2010 Mo-99 supply shortages, organizations participating in the global supply chain for Mo-99/Tc-99m have worked together to improve the stability of supply through the following four initiatives:

1. Development of outage reserve capacity (see Sidebar 3.1) at several levels in the Mo-99/Tc-99m supply chain.
2. Coordination of reactor and processing facility outages.
3. Enhanced communications among supply chain participants.
4. Creation of Mo-99 supplier alliances.

These initiatives are described in the following subsections.

3.4.1 Development of Outage Reserve Capacity

On average, research reactors operate 67 percent of the time annually (see Table 3.2). Under normal circumstances (i.e., when there are no unexpected or prolonged reactor shutdowns), these reactors have the capacity to irradiate sufficient targets to supply the 9,000 6-day Ci per week global demand for Mo-99.

Reactors can utilize their outage reserve capacity (ORC; see Sidebar 3.1) to produce additional Mo-99 to fill supply gaps created by outages in other reactors. This ORC has become especially important since 2009-2010 because extended reactor shutdowns have become more frequent (see

Table 3.5). ORC needs to be available on short notice—typically within about 48 hours—to fill supply gaps (OECD-NEA, 2013). There are a number of ways to create reserve capacity: for example, by dedicating additional days in a reactor's schedule for irradiation of targets, or increasing the number of available positions in the reactor to irradiate targets.

Provision for reserve capacity is a key principle for ensuring a long-term secure supply of Mo-99/Tc-99m (OECD-NEA, 2011a). The OECD-NEA has proposed that Mo-99 suppliers should hold sufficient paid target irradiation reserve capacity at reactors to replace the largest irradiation services supplier in their supply chain. Organizations further down the supply chain should also hold a similar level of reserve capacity. This is described in the OECD-NEA report as the (n–1) criterion, which sets the desired capacity to meet Mo-99 demand at

Current demand + 35% Outage reserve capacity = Desired capacity

The desired capacity for Mo-99 suppliers is

9,000 6-day Ci per week + 0.35 (9,000) = 12,150 6-day Ci per week

A 35 percent ORC would not have been sufficient to prevent Mo-99 shortages in 2013, when two irradiation services suppliers (HFR and SAFARI-1) were in outage at the same time. The reserve capacity necessary to cover an (n–2) scenario (i.e., replacing the two largest irradiation services suppliers) has not been determined by OECD-NEA.[31] According to supply chain participants surveyed by OECD-NEA, however, a 50 percent ORC would give an acceptable probability of a reliable supply of irradiated targets to the processor.

Reserve capacity levels based on the (n–1) or (n–2) criteria change with time as reactors are removed from service, new reactors offer irradiation services, and existing reactors expand target irradiation capacities. Reserve capacity levels can also differ between irradiation services suppliers and Mo-99 suppliers. In 2015, for example, technetium generator suppliers and Mo-99 suppliers had access to reserve capacities that were estimated to be on average about 14,800 6-day Ci per week with a large week-to-week variation (see Figure 3.3).

[31] OECD-NEA (2014b) estimated this reserve capacity to be 62 percent, but OECD-NEA (2015) recognized that the percentage was lower.

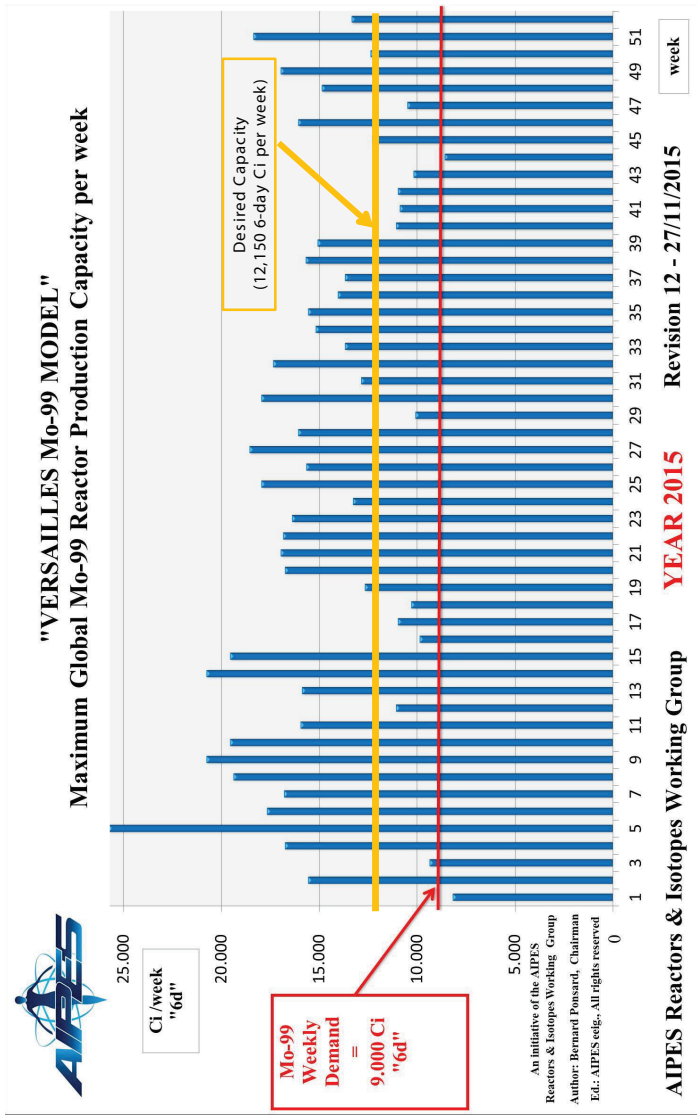


FIGURE 3.3 AIPES VERSAILLES Mo-99 MODEL, 2015. The average maximum global Mo-99 reactor production capacity in 2015 was 14,800 6-day Ci per week with a large week-to-week variation. (The standard deviation was ±3,600 6-day Ci per week.) The weekly Mo-99 demand in 2015 was 9,000 6-day Ci (red line) and the desired capacity was 12,150 6-day Ci (yellow line). SOURCE: Adapted and modified from Bernard Ponsard, SCK•CEN, written communication, February 11, 2016, by authorization of AIPES. See http://www.aipes-eeig.org.

3.4.2 Coordination of Facility Outages

The Association of Imaging Producers and Equipment Suppliers (AIPES)[32] works with irradiation services suppliers and Mo-99 suppliers to minimize Mo-99 supply disruptions by coordinating research reactor outage schedules. Schedule coordination began during the 2009-2010 reactor outages (see Section 3.3 in this chapter) and reduced the impacts of Mo-99 shortages in Europe. For example, the OSIRIS reactor in France was originally scheduled for a 5-month maintenance shutdown starting April 2010. The shutdown was postponed until mid-June 2010, however, because two other reactors (NRU and HFR) were shut down in early 2010 (see Table 3.5).

Following the 2009-2010 Mo-99 supply shortages, the coordination of reactor scheduling through AIPES has become more *future looking* (see Figure 3.4). AIPES periodically reviews reactor operating schedules and identifies periods with high potentials for multiple outages. Irradiation services suppliers and AIPES work together to minimize supply disruptions during these periods, either by modifying reactor outage schedules or utilizing reactor reserve capacities to fill Mo-99 production gaps. Communication of operating schedules is restricted to relevant stakeholders only.

AIPES also developed the *VERSAILLES Mo-99 MODEL*, an analysis tool to improve reactor operation scheduling and to assess the impacts of schedules on Mo-99 production. The model was validated using 2013 and 2014 data and is now being used to assess maximum global Mo-99 production capacity on a week-by-week basis (see Figure 3.3). The model helps to identify periods of increased potential for Mo-99 supply shortages by taking into account current and planned future reactor outage schedules. The model has been especially useful in planning reactor operating schedules to accommodate the extended scheduled shutdown of the BR-2 reactor for beryllium reflector replacement (February 2015-July 2016); the permanent shutdown of the OSIRIS reactor (December 2015); the planned cessation of Mo-99 production in the NRU reactor (after October 2016); and the expected 2016-2017 transition period to production of Mo-99 from LEU targets in Europe.[33]

3.4.3 Enhanced Communications

The 2009-2010 Mo-99 supply shortages demonstrated that frequent communications among supply chain participants can help to mitigate

[32] AIPES provides a forum for addressing specific radiopharmaceutical issues, similar to CORAR (*Council on Radionuclides and Radiopharmaceuticals*) in the United States. It also lobbies the European Commission on issues related to diagnostic imaging.

[33] Bernard Ponsard, SCK•CEN, written communication, February 11, 2016.

TABLE 3.5 Interruptions of Mo-99 Supply (2009-2016)

Year(s)	Reactor or Processing Facility	Duration of Facility Shutdown	Planned or Unplanned Shutdown	Reason for Shutdown
2008-2009	HFR (Netherlands)	6 months	unplanned	Gas bubbles detected in the main cooling system
2009-2010	NRU (Canada)	14 months	unplanned	Reactor vessel welding repairs
2010	HFR	6 months	unplanned	Repair of a primary cooling pipework
2012-2013	HFR	8 months	unplanned	Repair of a primary cooling pipework
2013-2014	HFR	6 months	unplanned	Issue with control rod
2013-2014	NTP (South Africa)	2 months	unplanned	Positive pressure in a hot cell caused a leak of noble gases
2013-2014	SAFARI-1 (South Africa)	2 months	unplanned	NTP processing facilities shutdown
2013-2014	Mallinckrodt (Netherlands)	6 months	unplanned	HFR unplanned outage
2015	HFR	1 reactor cycle	unplanned	Maintenance
2015-June 2016	BR-2 (Belgium)	16 months	planned	Major refurbishment

NOTES: BR-2 = Belgian Reactor 2; HFR= High Flux Reactor; NRU = National Research Universal; NTP = Nuclear Technology Products; SAFARI-1 = South African Fundamental Atomic Research Installation 1.

the consequences of supply disruptions. Technetium generator suppliers, for example, issued regular press releases during the 2009-2010 shortages to keep their customers (Tc-99m suppliers and the medical community) informed about actions being taken to address the Mo-99 supply shortages. The actions communicated included the following (Puthenedam, 2010; Triad Isotopes, 2009a,b):

- Entering into new Mo-99 supply agreements to maximize access to Mo-99.
- Providing projection calendars for technetium generator deliveries to assist with planning of medical procedures.
- Adjusting generator production and distribution schedules to meet customer needs.
- Providing advice to nuclear pharmacy operators and the medical community on how to maximize the availability of Tc-99m.
- Increasing production of alternate radiopharmaceuticals that could be used in place of Tc-99m radiopharmaceuticals.[34]

Nuclear pharmacy operators have created dedicated web pages explaining the events that led to the shortages as well as actions taken to address these issues. Actions included the following (Cardinal Health, 2009):

- Diversifying purchases of technetium generators across suppliers.
- Improving efficiencies of technetium generator elutions.

Professional societies such as the Society of Nuclear Medicine and Molecular Imaging[35] provided recommendations for dealing with the Mo-99 shortages (SNMMI, 2010). The recommendations focused on maximizing existing Tc-99m supplies by scheduling patients around Tc-99m availability, use of low-dose imaging protocols, and utilization of alternate radiopharmaceuticals or procedures to replace Tc-99m-based procedures.

The communication enhancements that were initiated during the 2009-2010 Mo-99 shortages continue today.

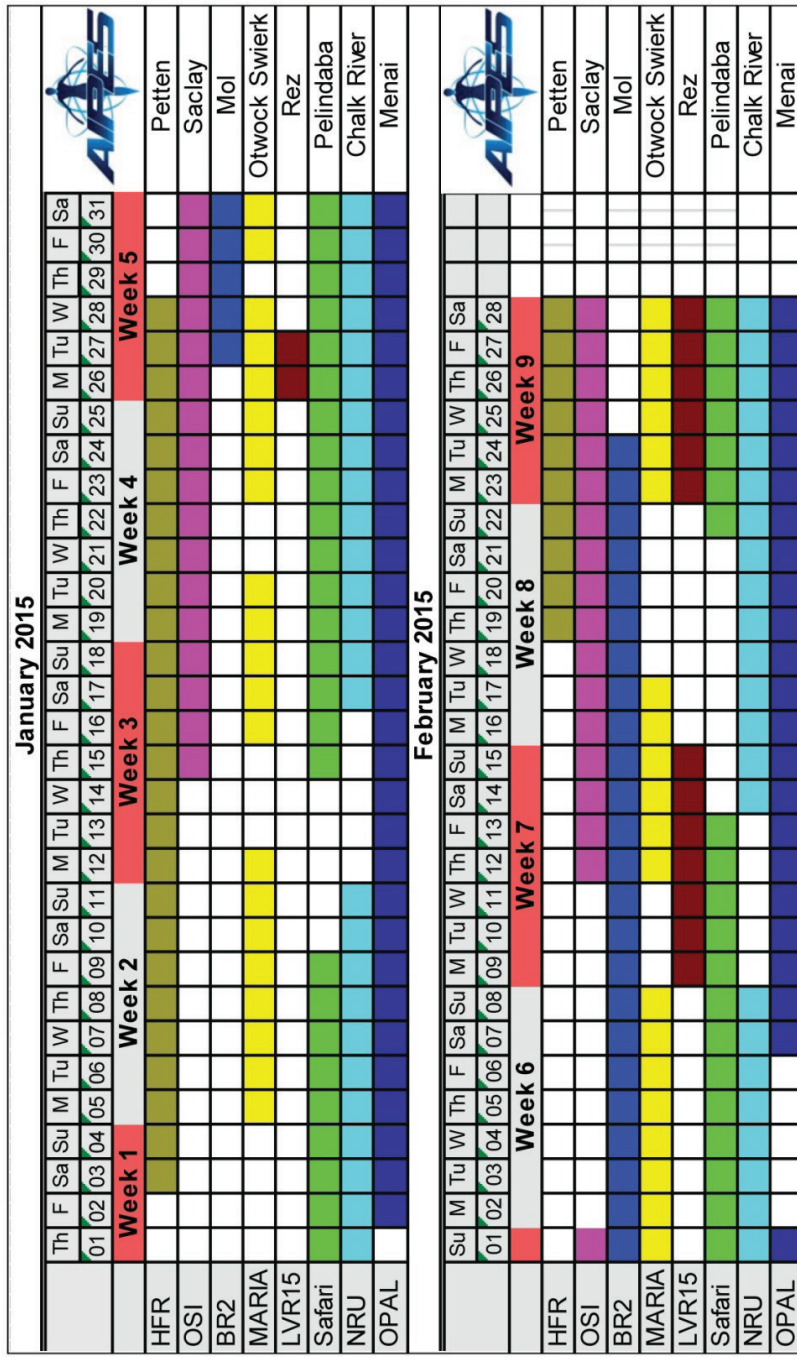
3.4.4 Creation of Mo-99 Supplier Alliances

At present, ANSTO, IRE, and NTP support each other through backup-supply arrangements. Additionally, ANSTO and NTP are forming the Southern Radioisotopes Alliance Inc. (SRA) as a marketing and sales alliance for the supply of Mo-99.[36] The alliance aims to help optimize supply routes and reduce decay losses. It also allows ANSTO and NTP to coordinate their reactor schedules and provide mutual backup capability. ANSTO and NTP will sell Mo-99 to the alliance, which in turn will supply it to customers. ANSTO and NTP also have an agreement to sell Mo-99 to

[34] For example, Lantheus increased thallium production by almost 300 percent during the times of significant Mo-99 shortages to meet cardiac imaging needs.

[35] Formerly the Society of Nuclear Medicine.

[36] See http://southernradioisotopes.com/. NTP informed the committee that this alliance has not yet been formally established.



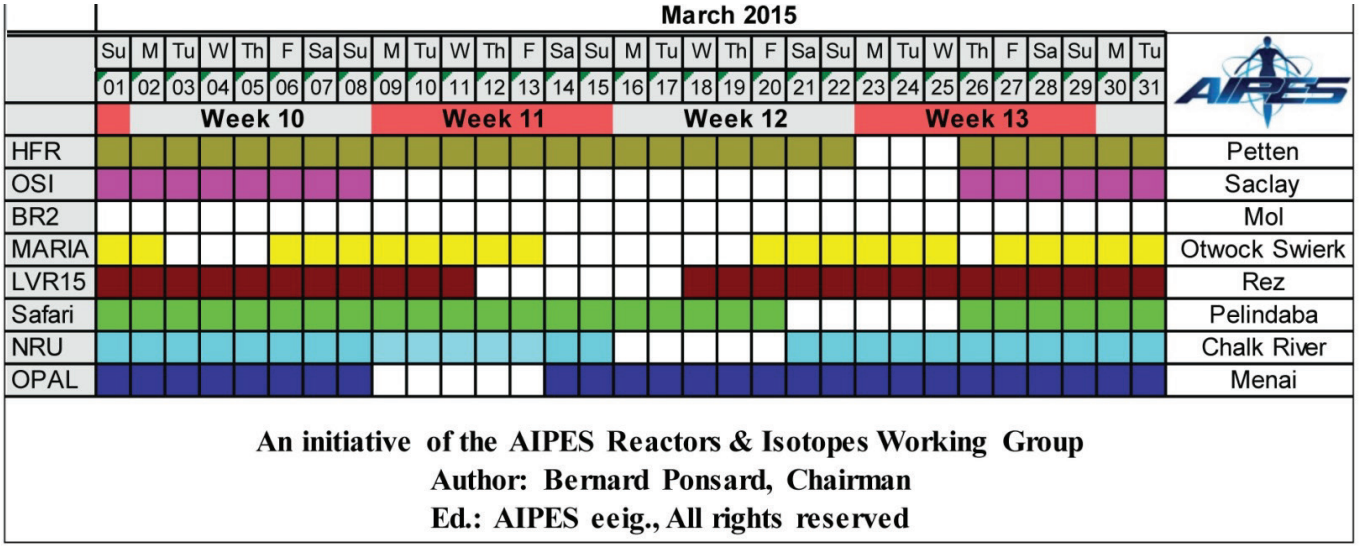


FIGURE 3.4 AIPES Reactor Schedule, first trimester, 2015. NOTES: BR-2 = Belgian Reactor 2; HFR = High Flux Reactor; NRU = National Research Universal; OPAL = Open Pool Australian Lightwater reactor; SAFARI-1 = South African Fundamental Atomic Research Installation 1. SOURCE: Bernard Ponsard, SCK•CEN, written communication, February 11, 2016.

each other to meet supply needs during facility outages. NTP and IRE also have a separate Mo-99 supply arrangement, but IRE is not part of SRA.

3.5 FINDINGS

The committee developed four findings to address the first two charges of the statement of task (see Sidebar 1.3 in Chapter 1). These findings are presented below.

FINDING 1A: As of June 2016, most (~95 percent) of the global supply of molybdenum-99 for medical use is produced in seven research reactors located in Australia, Canada, Europe, and South Africa and supplied from five target processing facilities in those same locations. The remainder (~5 percent) of the global supply is produced in other locations for regional use.

Information about the seven reactors that produce most of the Mo-99 for medical use, including their average Mo-99 production levels in 6-day Ci per week, is provided in Table 3.2. The global supply of Mo-99 is schematically illustrated in Figure 3.1.

FINDING 1B: As of June 2016, about 75 percent of the global supply of molybdenum-99 for medical use is produced by irradiating highly enriched uranium targets in six research reactors; one of these reactors is also fueled with highly enriched uranium. The remaining 25 percent of the global supply is produced by irradiating low enriched uranium targets in two research reactors.[37]

Table 3.2 provides information on HEU and LEU use in targets used to produce Mo-99 and in the fuel used in the reactors that irradiate these targets. Five reactors produce Mo-99 exclusively with HEU targets; one reactor produces Mo-99 exclusively with LEU targets; and one reactor produces Mo-99 using both HEU and LEU targets. One of the reactors used to produce Mo-99 with HEU targets is also fueled with HEU.

FINDING 2A: New molybdenum-99 supplies have become available since 2009, and expansions in available supply capacity are planned by current and new suppliers: A supplier in Australia (Australian Nuclear Science and Technology Organisation) has entered the global supply market and plans to expand its available supply capacity; existing global suppliers in Europe (Mallinckrodt) and South Africa (NTP Radioiso-

[37] One research reactor irradiates both HEU and LEU targets.

topes) have initiated plans to expand their available supply capacities; and the Russian Federation plans to become a global supplier.

FINDING 2B: Reactors in France (OSIRIS) and Canada (NRU) have halted or announced plans to halt molybdenum-99 production since 2009. These shutdowns have reduced/will reduce available production capacity and reserve production capacity that could be used to cover supply shortages if they occur.

There have been several changes in global supply of Mo-99 since the 2009 Academies report on medical isotope production (NRC, 2009). ANSTO became a global Mo-99 supplier in 2009 and now accounts for about 6 percent of available supply capacity (1,100 6-day Ci per week). The company plans to further expand Mo-99 supply in 2017, which would increase its available supply capacity by over a factor of three (to 3,500 6-day Ci per week). Mallinckrodt and NTP also plan to expand their available supply capacities by 1,500 6-day Ci per week and 500 6-day Ci per week, respectively, in 2017. If all of these plans are realized, available supply capacity would be increased by 4,400 6-day Ci per week by the end of 2017 (see Figure 3.2). This added capacity would almost offset the loss of available production capacity from NRU/Nordion (4,680 6-day Ci per week). However, if expansions are not realized on time, available supply capacity would fall below the desired capacity.

Other organizations have plans to expand or initiate supply of Mo-99. Argentina, Brazil, and South Korea are building new reactors to provide regional supplies of Mo-99. Russia plans to become a global supplier of Mo-99 and capture about a 20 percent share of the global market but has not published a schedule for doing so.

The OSIRIS reactor, which was permanently shut down in December 2015, and the NRU reactor, which will stop producing Mo-99 at the end of October 2016, have a combined available production capacity of over 7,000 6-day Ci per week. This is a little less than half of the current available production capacity for Mo-99 globally. The Canadian reactor also produces Xe-133 and I-131.

FINDING 2C: Molybdenum-99 production and supply were disrupted unexpectedly in 2009-2010 because of prolonged unplanned reactor and target processing facility shutdowns. These shutdowns caused protracted and severe molybdenum-99 supply shortages in the United States and some other countries. Shorter supply interruptions have also occurred as a result of shorter planned and unplanned reactor and target processing facility shutdowns and transport disruptions.

FINDING 2D: Coordinated actions taken by governments, molybdenum-99 suppliers, technetium generator suppliers, technetium-99m suppliers, and others since the 2009-2010 supply shortages have improved the resilience of the global supply chain, minimized supply disruptions during unplanned reactor and processing facility shutdowns, and increased molybdenum-99/technetium-99m utilization efficiencies. Supply vulnerabilities remain, however, owing to the small number of participating organizations at some steps in the supply chain.

Mo-99 production has been disrupted unexpectedly on numerous occasions since 2009. Some of these disruptions resulted in severe supply shortages in the United States and other countries. Disruptions in 2009-2010 occurred when Canada's NRU and Europe's HFR reactors were simultaneously shut down for extended periods. These shutdowns caused major disruptions in Mo-99 supplies and in diagnostic imaging procedures in some countries, including Canada and the United States. Supply interruptions have also occurred as a result of transportation denials and delays. However, these are typically resolved within hours or a few days.

Several actions have been taken since the 2009-2010 supply shortages to improve the resilience of the Mo-99 supply chain. These actions, which are described in Section 3.4, involve the development of ORC, coordination of reactor and target processing facility outages, enhanced communications among supply chain participants, and the creation of Mo-99 supplier alliances.

In spite of these actions, however, vulnerabilities remain in some parts of the supply chain owing to the small number of participating organizations. This is particularly true for the front end of the supply chain, where one company (CERCA) provides the majority of the targets used to produce Mo-99. This large market share also gives this manufacturer strong pricing power. The relatively small number of global Mo-99 suppliers is another potential point of vulnerability, particularly after one of them (Nordion) ceases supplying Mo-99 after October 2016. See Chapter 7 for additional discussion.

4

Progress Toward Establishing Domestic Production of Molybdenum-99 and Associated Medical Isotopes

This chapter addresses the third charge of the statement of task for this study (see Sidebar 1.3 in Chapter 1):

> An assessment of progress made in the previous 5 years toward establishing domestic production of molybdenum-99 for medical use, including the extent to which other medical isotopes that have been produced with molybdenum-99, such as iodine-131 and xenon-133, are being used for medical purposes.

As noted in Chapter 1, the committee interprets "the previous 5 years" to encompass the time since completion of the 2009 Academies report on medical isotope production (NRC, 2009), that, is since January 2009.

Since 2009, the Department of Energy's National Nuclear Security Administration (DOE-NNSA) has signed cooperative agreements with five private-sector companies to assist their efforts to develop domestic (i.e., U.S.-based) capabilities to supply molybdenum-99 (Mo-99) without the use of highly enriched uranium (HEU) targets. Section 4.1 describes the progress by these partners in establishing domestic production as of June 2016.[1]

Several U.S. national laboratories are also being funded by NNSA to support the development of domestic production of Mo-99 without HEU. The involved national laboratories include Argonne National Laboratory (ANL), Oak Ridge National Laboratory (ORNL), Los Alamos National Laboratory (LANL), Pacific Northwest National Laboratory (PNNL), and

[1] When the present report was being finalized for publication.

Savannah River National Laboratory (SRNL). The Y-12 National Security Complex, an NNSA facility located in Oak Ridge, Tennessee, is also providing technical support. These development activities, which are public domain and nonproprietary, are summarized in Table 4.1.

In addition to the activities funded directly by NNSA, some national laboratories have also established *cooperative research and development agreements* or *strategic partnership projects* (formerly known as *work for others agreements*) directly with companies seeking to develop Mo-99 production technologies. These agreements constitute contracts between companies and national laboratories to carry out company-specified research and development (R&D) work. The companies pay the labs directly for this work, and the results of this work are provided directly to the companies and are not made public.

At least seven other private-sector companies are working independently of NNSA to develop domestic Mo-99 production or related capabilities. These efforts are described in Section 4.2. Efforts to develop capabilities for domestic production of iodine-131 (I-131) and xenon-133 (Xe-133) are described in Section 4.3. The committee's analysis of progress toward establishing domestic production of Mo-99 and other medical isotopes is provided in Section 4.4.

4.1 DOE-NNSA COOPERATIVE AGREEMENT PROJECTS

DOE-NNSA supports the establishment of U.S. domestic production of Mo-99 under its HEU minimization mission. As noted previously, NNSA has signed cooperative agreements with five companies to assist their efforts to develop domestic capabilities to produce Mo-99:

- Babcock & Wilcox (B&W) (now BWX Technologies)
- General Atomics (GA)
- General Electric-Hitachi (GEH)
- NorthStar Medical Radioisotopes
- SHINE Medical Technologies

These cooperative agreements provide for 50-50 cost sharing between NNSA and these companies; NNSA provides up to $25M in cost sharing per project for work that contributes directly to the establishment of a domestic Mo-99 production capability.

The first NNSA cooperative agreements were awarded to B&W and GEH in 2009 through a noncompetitive process. The companies suspended their projects in 2012 and 2011, respectively, after completing their planned first phases of work but before developing any commercial Mo-99 produc-

TABLE 4.1 National Laboratory Support to Non-HEU Mo-99 Production Technologies

Laboratory	Partner	Technology Area	Specific Support Objective
ANL	SHINE	Separations	• Separation process development o Sorbent-based recovery of Mo o Mo purification o Cleanup of uranyl sulfate target solution • Demonstration of Mo separation efficiency o >97% recovery from uranyl sulfate solution o High uranium recovery • Production of demo product o Demo runs have produced curie-quantities of Mo-99 o Product purity specification met for I-131, Ru-103, Te-132, and Sr-89/90 in 3 of 4 runs
ANL	SHINE	Irradiation physics	• Radiation stability and radiolysis effects • Thermal hydraulic effects of radiolytic gas formation
ANL/PNNL	SHINE		Sample off-gas for volatile fission products (Xe, Kr, I)
ANL/ORNL	NorthStar	Target design	Optimization of sintered Mo disks for density and dissolution kinetics
ANL	NorthStar	Irradiation	• Demonstrate accelerator-based production of Mo-99 o $^{100}Mo(\gamma,n)^{99}Mo$ reaction o Radionuclide inventory o Production modeling
ANL	NorthStar	Chemical processing	• Chemical processing of irradiated targets • Front-end purification of irradiated Mo • Recycle process to recover enriched Mo • Large-scale dissolution process demonstration • Support to development and the FDA review of RadioGenix Mo-99 dispensing unit

continued

TABLE 4.1 Continued

Laboratory	Partner	Technology Area	Specific Support Objective
LANL/ANL	NorthStar	Target design	• Target design and irradiation testing o Target thermal performance • Subsystem development and testing o Beam diagnostics o Beam position monitor o Target He cooling system o Control systems • Licensing of IP
LANL	NorthStar	Target design	• Production facility design support o Local target shielding o Beam line design o Target removal and conveyance • Support to production and thermal tests at ANL • Licensing of IP
LANL	SHINE	Analysis of nuclear system transient response Irradiation support Separations chemistry	• Simulation and modeling of accelerator-driven subcritical solution reactor Irradiations and separations chemistry • Uranium measurement and accounting methods • Modeling of reaction vessel cooling systems
ORNL	GE Hitachi Nuclear Energy	Neutron capture technology	• Irradiation of Mo targets in HFIR • Assess impurities in Mo samples • Explore methods to mitigate Mo target oxidation and sublimation. This included silicon coating using chemical vapor deposition.
ORNL	NorthStar Medical Radioisotopes	Accelerator target and production process	• Understand the requirements for and fabrication of Mo target disks • Develop a powder metallurgy process for fabricating accelerator target disks with a density of ≥90% • Identify parameters that affect dissolution rate of the target disks • Assist in developing recycle process for isotopically enriched Mo.

ORNL	Morgridge Institute for Research and SHINE	Accelerator technology with LEU fission	Evaluation of candidate materials for the solution vessel • Irradiation testing • Corrosion testing • Stress-corrosion testing • Flow-induced corrosion testing • Gamma-induced corrosion testing
ORNL (Y-12/ANL)		High-density LEU target technology	Testing of various target designs: • Acid and electrochemical dissolution concepts Planning was completed for HFIR irradiations but targets were not qualified for irradiation at the time the project ended.
SRNL		Tritium	• Thermal Cycling Absorption Process (TCAP) • Tritium purification system (TPS)
SRNL	SHINE	Tritium systems	• Design and fabrication of prototype cold-test TCAP unit • Design of TPS for transfer to architectural and engineering firm • TPS automation studies
Y-12		High-density LEU target technology	Testing of various target designs: • LEU-Foil Target Fabrication o Nickel capsule with uranium foil and annular target and uranium foil
Y-12	SHINE	Technical consultation	
Y-12		Uranium Lease and Take-Back Program	Support to the implementation of the supply portion of the Uranium Lease and Take-Back Program

SOURCE: Presentations to committee at Meeting #2 (see Appendix C).

tion capabilities. NNSA awarded $9.1M to B&W[2] and $2.25M to GEH in cost-shared funding before the companies suspended work.

A competitive process was put into place by NNSA in 2010 to select the remaining three cooperative agreement partners.[3] The criteria for evaluation of projects by NNSA included project significance, technical feasibility, ability to demonstrate the capability to produce 3,000 6-day curies (Ci) per week by the end of calendar year 2013, and business-case viability. NNSA informed the committee that it established this production demonstration goal for three reasons[4]:

1. To provide the team of independent technical experts (which was assembled by NNSA to review the proposed projects) with an objective criterion by which to judge the viability of the proposed projects.
2. To give the commercial partners, selected under the NNSA's Funding Opportunity Announcement (FOA), an aggressive schedule goal to work toward in executing their projects.
3. To encourage commercial entities in the United States to secure a domestic supply of Mo-99 before Canada stops production of Mo-99 after October 2016 (see Chapters 3 and 7).

The 3,000 6-day Ci per week production demonstration goal proved to be overly optimistic: None of the cooperative agreement partners met this goal by the end of 2013; in fact, this goal still had not been met when the present report was being finalized for publication.

NNSA currently evaluates proposals for additional funding from current cooperative agreement partners using 2016 as the evaluation criterion for schedule. NNSA uses other criteria in addition to schedule for evaluating these proposals.

The cooperative agreement projects are depicted graphically in Figure 4.1 and described in the following subsections. These descriptions are based on information provided to the committee by representatives of the companies that are involved in these projects and from the committee's independent research. The schedule information provided below is current as of the end of July 2016.

[2] The B&W Phase 1 cooperative agreement was awarded for a total NNSA contribution of $9.1M. Due to a reduction in B&W's scope, the resulting total of the NNSA contribution to the Phase 1 cooperative agreement was $6.1M.

[3] NNSA published a Funding Opportunity Announcement (FOA) in March 2010 to solicit proposals from private-sector companies. It was implemented under 10 CFR 600 Subpart H, Assistance Regulations. The FOA closed in June 2010.

[4] Rilla Hamilton, DOE-NNSA, written communication, June 8, 2016.

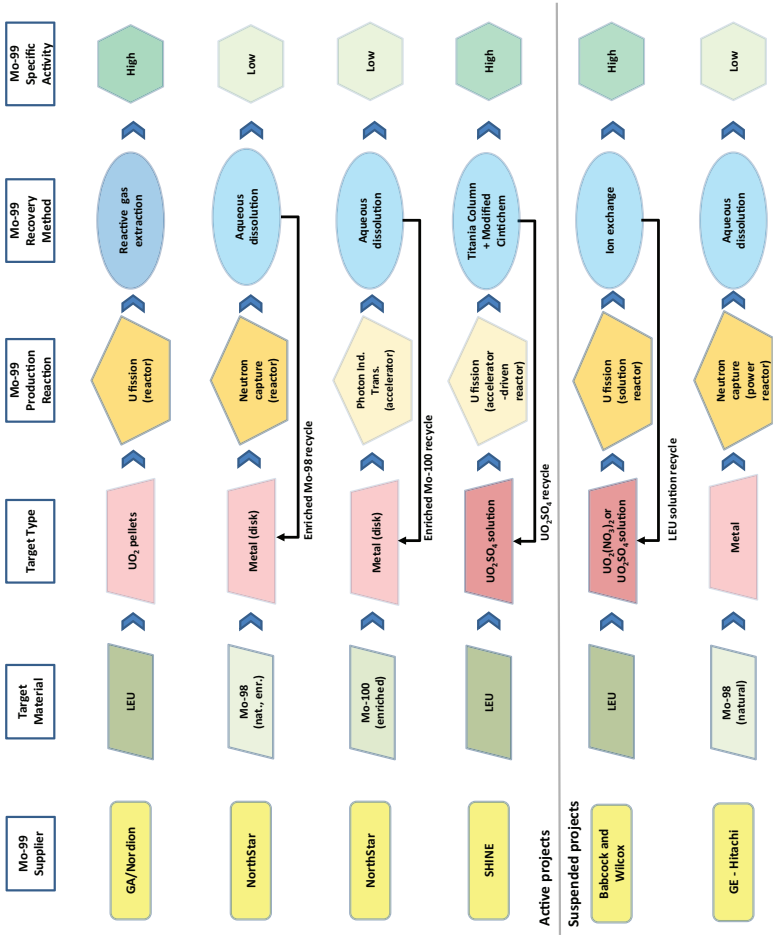


FIGURE 4.1 Domestic Mo-99 production projects supported by NNSA cooperative agreements.

4.1.1 NorthStar Medical Radioisotopes

NorthStar Medical Radioisotopes LLC[5] (NorthStar) has entered into cooperative agreements with NNSA to develop domestic Mo-99 production using two different processes:

1. Photon-induced transmutation of molybdenum-100 ($^{100}Mo(\gamma,n)^{99}Mo$) using photons produced with linear accelerators. The cooperative agreement for this project was awarded in September 2010 (Staples, 2011).
2. Neutron capture of molybdenum-98 ($^{98}Mo(n,\gamma)^{99}Mo$) using neutrons produced in a research reactor. The cooperative agreement for this project was awarded in November 2013 (NNSA, 2013).

These production processes are described in Section 2.3.2 in Chapter 2. To date, NNSA has given NorthStar roughly $6M for its photon-induced transmutation project and $25M for its neutron capture project.

The Mo-99 produced by these two processes has a low specific activity (1-10 curies (Ci)/gram), too low to be used in the conventional technetium generators described in Chapter 2. NorthStar has developed a new technetium generator system, the RadioGenix Tc-99m Generating System, to utilize low-specific-activity Mo-99. This system is described in Section 4.1.1.3 in this chapter.

4.1.1.1 Photon-Induced Transmutation

NorthStar plans to establish the capacity to produce >3,000 6-day Ci of Mo-99 per week at its Beloit, Wisconsin, facility by irradiating Mo-100 targets with electrons produced by linear accelerators. This approach heavily leveraged work at the Idaho National Laboratory in the mid-1990s (Bennett et al., 1999) and the late 2000s (Nelson et al., 2007; TRIUMF, 2008). Several accelerators and target stations will be used, each capable of producing roughly 500 6-day Ci per week of low-specific-activity Mo-99 (see Figure 4.2). The target stations will contain many separated disks of Mo-100 that will be cooled with high-pressure gaseous helium (He) during irradiation. The targets will be irradiated with a total of 240 kilowatts (kW) of 40 megaelectron volt (MeV) electrons (120 kW would be directed at each end of the target assembly). Two different types of electron accelerators are being considered to generate the electron beams.

NorthStar is working with ANL and LANL to develop their technical approach for Mo-99 production using photon-induced transmutation

[5] NorthStar was founded in 2006 and is based in Madison, Wisconsin.

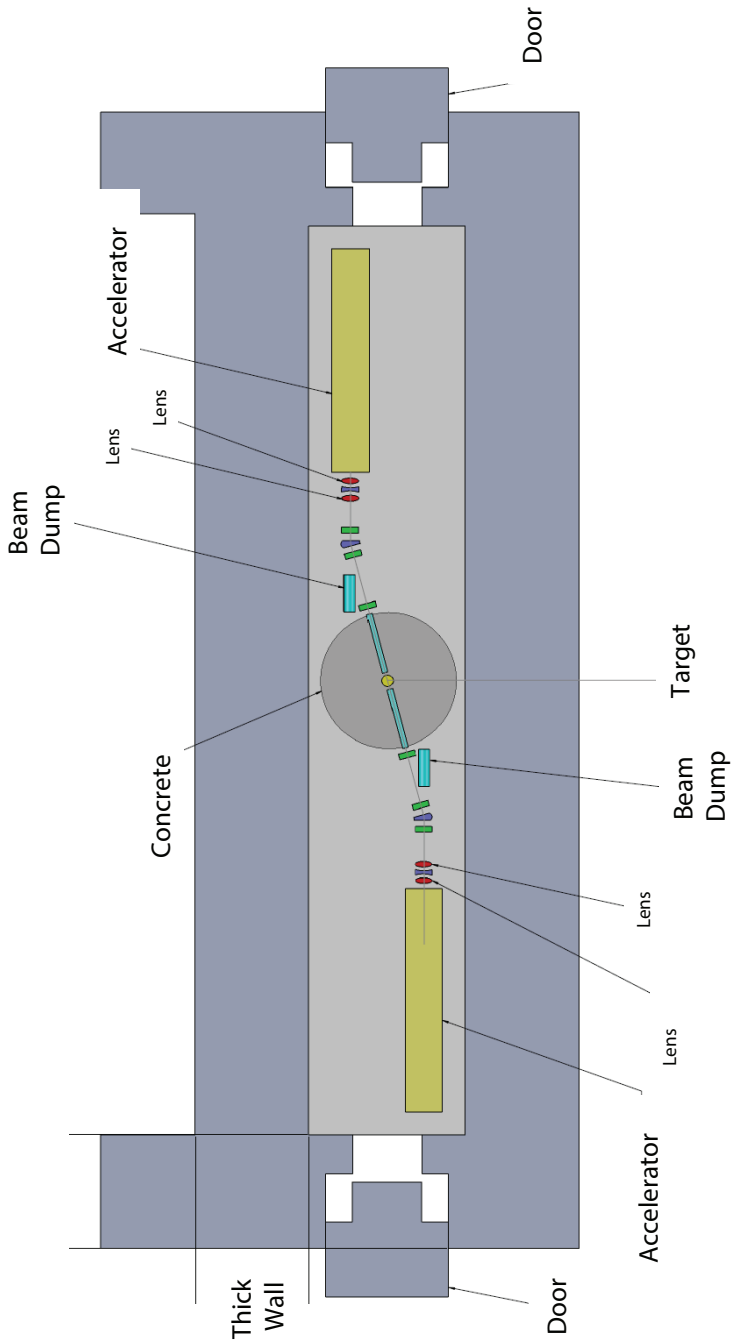


FIGURE 4.2 Schematic layout of an accelerator vault for NorthStar's photon-induced transmutation production project. The vault accommodates two linear accelerators and two target irradiation stations. SOURCE: Gregory E. Dale, Los Alamos National Laboratory.

(see Table 4.1). Four critical subsystems have been tested at ANL using an electron linear accelerator having 10-20 kW power: (1) the target, (2) He cooling, (3) accelerator diagnostics, and (4) Mo-100 recovery. In addition, ANL is helping to design the production facility beamline and shielding. LANL is designing the production target and remote handling assembly.

The targets tested at ANL consist of up to 25 molybdenum disks, each 12 mm in diameter, 1-mm thick, and separated by 1 mm for He cooling. The target being designed for NorthStar would consist of 82 molybdenum disks, 29 mm in diameter, 0.5-mm thick and separated by 0.25 mm for He cooling. The ANL tests have also studied the He-cooling system and accelerator diagnostics (diagnostics are challenging because of high radiation in the target region). Full-power tests of these systems have not been completed.

One of the challenges with this production method is the availability and cost of Mo-100 target material. Enriched targets are required for this production method to be effective (natural molybdenum contains only about 10 percent Mo-100). The cost of the targets will be significant.[6] Only a small fraction of the Mo-100 is converted into Mo-99 during irradiation; consequently, cost-effective recycling schemes will be needed to recover unused Mo-100. Approximately 95 percent efficiency of recycling of Mo-100 has been demonstrated at ANL (Tkac, 2015).

NorthStar plans to install and start up the accelerators at its Beloit, Wisconsin, facility in 2018 and to establish the capability to produce 3,000 6-day Ci of Mo-99 by the end of 2019. The feasibility of Mo-100 production using accelerators has been demonstrated at low power, but tests of high-power systems have not yet been completed.

4.1.1.2 Neutron Capture Production

NorthStar will use the University of Missouri Research Reactor Center[7] (MURR) reactor to irradiate Mo-98 targets to produce Mo-99 by neutron capture. The targets will contain either natural (24 percent Mo-98) or enriched (>90 percent Mo-98) molybdenum. The company expects to be able to produce 750 6-day Ci of Mo-99 per week using natural molybdenum targets and at least 3,000 6-day Ci of Mo-99 per week using enriched Mo-98 targets.

A few kilograms of enriched Mo-98 will be required each year to

[6] At present, the cost of enriched Mo-100 is a few hundred to a thousand U.S. dollars per gram in kilogram quantities. The primary supplier is Isoflex, a U.S-owned and operated company that sole-sources Russian-separated isotopes.

[7] The reactor at MURR is a 10 megawatt (MW), HEU-fueled, pool-type, light-water-cooled reactor. The reactor is described in NRC (2009). NorthStar has an agreement to use the MURR reactor through 2019.

produce these quantities of Mo-99,[8] assuming that Mo-98 from irradiated targets is recovered and reused. Recycling of enriched targets has been demonstrated at ANL with about a 95 percent recovery rate (Tkac and Vandegrift, 2015).

A proprietary system has been constructed at MURR to dissolve natural and enriched molybdenum targets and extract Mo-99; two of the hot cells used for Mo-99 extraction are illustrated in Figure 4.3. Additionally, the first of two fill lines has been installed at MURR to prepare Mo-99 for shipment to nuclear pharmacies that will be equipped with NorthStar's RadioGenix Tc-99m Generating System. A second fill line is planned for installation at MURR in fall 2016. Spent generator solutions will be returned to NorthStar, where they will be held to decay before recycling or disposal. Recycling of enriched targets and spent solutions will take place in the company's Beloit facility.

NorthStar has completed its first Mo-99 production-scale test run[9] and has received approval from MURR[10] to begin routine production of 200 6-day Ci of Mo-99 per week. The next significant step in the regulatory approval process will be Food and Drug Administration (FDA) approval of a final amendment to NorthStar's New Drug Application (NDA) (see Appendix 4A). NorthStar expects to have the capacity to produce up to 3,000 6-day Ci of Mo-99 per week on a routine basis in 2017.

4.1.1.3 RadioGenix Tc-99m Generating System

The RadioGenix Generator System utilizes a Tc-99m-selective resin column (ABEC-2000) to recover sodium pertechnetate ($NaTcO_4$) containing Tc-99m from an alkaline solution of Mo-99 (see Figure 4.4).[11] The generator can utilize either high- or low-specific-activity Mo-99 but was designed specifically for use with the low-specific-activity Mo-99 produced by NorthStar. The column is charged with a solution of low-specific-activity Mo-99 in 5 molar (M) KOH. The column is sequentially washed with a 5 M KOH solution to remove any Mo-99 that was adsorbed onto the column and then with a pH 8 buffer solution.

Tc-99m is eluted from the generator as sodium pertechnetate using 0.9

[8] NorthStar is purchasing enriched Mo-98 from the chemical plant at Krasnoyarsk, Russian Federation, and is in discussion with two additional potential suppliers.

[9] The operating license for the reactor at MURR already allows for the irradiation of Mo-98 targets to produce Mo-99.

[10] NorthStar works under MURR's U.S. Nuclear Regulatory Commission (NRC) license.

[11] The ABEC resin was developed in the 1990s and became the basis for the Automated Radionuclide Separation (ARS) system developed in the early 2000s. NorthStar bought the technology in 2005 and has continued to develop the system based on feedback from regulators and focus groups. See Le (2014).

FIGURE 4.3 *Top*: Hot cells at MURR for processing of Mo-98 targets for NorthStar's neutron capture production process. *Bottom*: Dissolution apparatus in the hot cell. SOURCE: Courtesy of University of Missouri Research Reactor Center.

FIGURE 4.4 NorthStar's RadioGenix Tc-99m Generating System. The system is 54″ (1.4 m) wide × 28″ (0.7 m) deep × 75″ (1.9 m) tall, including the monitor. SOURCE: Jim Harvey, NorthStar Medical Radioisotopes.

percent NaCl solution. The eluate is passed through an alumina (Al_2O_3) guard column to remove residual Mo-99 impurities. The Tc-99m eluate is also passed through a 0.22-μm membrane filter (located inside the system) for microbe removal prior to preparation of radiopharmaceuticals or direct administration to patients.

The RadioGenix system is largely automated. After 40 minutes of initial setup, the system will generate an elution of sodium pertechnetate in a few tens of minutes without further operator intervention (the total cycle time is 60-70 minutes). The system includes shielded waste containers and an ozonation system to control bio-contamination. The generator can be eluted multiple times a day just like conventional technetium generators. Tc-99m separation efficiencies of >90 percent have been obtained for several consecutive days of elution with no detectable Mo-99 breakthrough.

The RadioGenix system is currently undergoing FDA review. An NDA (see Appendix 4A) was submitted in 2013 and modifications were made in response to a Complete Response Letter. The current (fifth generation) version of the RadioGenix system is being used to generate data to support a resubmission of the NDA for FDA review. NorthStar plans to introduce the generator system to the market once this NDA is approved by the FDA.

NorthStar has signed a letter of intent with GE Healthcare to supply Mo-99 to produce Tc-99m for compounding and distribution (NorthStar, 2014a) once its generator system has been approved by the FDA and is commercially available. NorthStar also recently signed a similar agreement with the nuclear pharmacy chain Triad Isotopes, Inc. (NorthStar, 2014b).

4.1.2 SHINE Medical Technologies

Morgridge Institute for Research,[12] in cooperation with SHINE Medical Technologies,[13] entered into a cooperative agreement with NNSA in September 2010 (Sereno, 2012) and has so far received $15M in funding from NNSA (NNSA, 2015a). The company is developing an accelerator-driven subcritical low enriched uranium (LEU) assembly to produce Mo-99 by neutron fission ($^{235}U(n,f)^{99}Mo$). The general concept is illustrated in Figure 4.5. SHINE plans to build multiple accelerator–LEU target assemblies to produce 4,000 6-day Ci per week of Mo-99 for domestic and overseas sale.

A linear accelerator is used to inject a 300 kV, 60 mA beam of deuterium ions (see Figure 4.6) into a tritium gas target. The deuterium fuses with tritium to produce helium and approximately 5×10^{13} free 14 MeV neutrons per second over a 100 cm length. The neutrons are multiplied as they pass through a natural uranium layer. These neutrons are used to irradiate an aqueous solution of LEU uranyl sulfate to produce Mo-99, I-131, Xe-133, and other fission products. The LEU solution is passed through

[12] The original cooperative agreement holder for this project was Morgridge Institute for Research. SHINE is now the primary cooperative agreement holder.

[13] The company was founded in 2010 and is based in Monona, Wisconsin, a suburb of Madison.

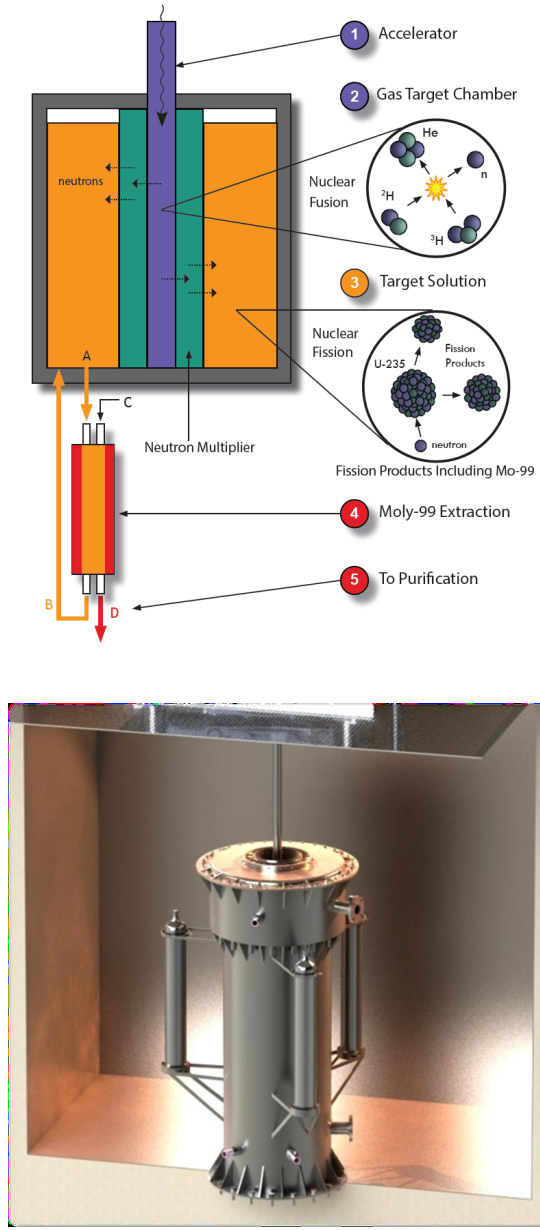


FIGURE 4.5 *Top*: Schematic depiction of SHINE's deuterium-tritium fusion-driven subcritical reactor concept. *Bottom*: Image of the system. SOURCE: Courtesy of SHINE Medical Technologies, Inc.

FIGURE 4.6 Photo of a beam of deuterium ions after acceleration in the neutron driver produced for SHINE by Phoenix Nuclear Labs. SOURCE: Courtesy of Phoenix Nuclear Labs.

a titanium dioxide column after about 5.5 days of irradiation to extract Mo-99.

ANL has performed the first several in a series of "mini-SHINE" experiments (ANL/CSE-14/2; see Table 4.1) in which they demonstrated the overall integrated process, which includes target solution preparation from uranium metal, target solution irradiation, extraction, and purification. The main difference between these experiments and the planned SHINE facility is that an electron accelerator was used in the experiments to generate neutrons. ANL has conducted the first two of these irradiations, successfully producing Mo-99 to British Pharmacopeia[14]–level specifications at curie levels. ANL plans to scale up production to tens of curies in fiscal year 2017. Additionally, LANL has demonstrated that the target solution can be recycled, allowing for multiple irradiations of a target solution preparation without affecting molybdenum extraction.

The electrostatic accelerator-based neutron driver is produced for SHINE by Phoenix Nuclear Labs (PNL). The accelerator generates deuterium ions, accelerates them, and focuses them into the gaseous tritium target chamber. PNL has built three generations of this neutron generator, and the lab has demonstrated stable operation with 99 percent uptime at 50 percent of the planned beam output for the facility version. PNL has also successfully demonstrated the required ion extraction and focusing behavior, target gas operation and pumping, and the expected fusion reaction yields in the target chamber. PNL has delivered a fully functioning, high-reliability accelerator to Picatinny Arsenal for the U.S. Army, a system that shares many design aspects with the accelerator design for the SHINE facility. PNL has also delivered a high-output neutron generator to Ultra Electronics in the United Kingdom.

[14] See https://www.pharmacopoeia.com/.

The tritium inventory in the accelerator and pumping systems is <100 mg (<1,000 Ci). The tritium recovery and purification system used by SHINE is based on a process from the SRNL known as the Thermal Cycling Absorption Process (TCAP). This process has been used at SRNL for decades on a significantly larger scale than is required for SHINE. SRNL has built a smaller prototype TCAP system that can handle recovery demands from three operating accelerators. The TCAP prototype acceptance testing was conducted at SRNL in December 2013.

The SHINE assembly does not reach criticality[15] like an aqueous reactor does; however, the nuclear physics principles governing the operations of subcritical assemblies and reactors are similar. These principles have been validated through a number of national laboratory experiments, including in KEWB-Core A, KEWB-Core B, LOPO, HYPO, SUPO, and SILENE aqueous reactors. These reactors have been shown to operate in a predictable and stable manner. Working in support of SHINE, LANL has shown excellent agreement between the modeling codes and the measurements from these reactors for steady-state and transient behavior. SHINE has also validated its computer models against benchmark data to ensure that the predictions of the codes are accurate.

Irradiation of the uranyl sulfate target solution produces hydrogen and oxygen through radiolysis. These gases bubble out of the target solution and accumulate in the target solution vessel (TSV) headspace. Without proper mitigation, the hydrogen in this headspace would quickly reach potentially explosive concentrations. SHINE uses a gas recirculation and treatment system called the TSV Off-Gas System (TOGS) to mitigate this risk and maintain hydrogen concentrations well below lower flammability limits. TOGS is designed to remove hydrogen from the TSV atmosphere using catalytic recombination, a recognized and proven technology. Reduced-scale demonstration systems have been built at LANL and ANL, and a full-scale test system has been built at SHINE. Testing and experimentation on these systems has demonstrated that the established technologies implemented in TOGS are capable of safely and reliably mitigating hydrogen accumulation risk in the TSV. Additionally, hydrogen recombination using catalytic recombiners is a common process used at nuclear power facilities throughout the United States.

After irradiation and cool-down, the LEU target solution is transferred to a processing hot cell and loaded onto a proprietary titanium oxide chromatography column for separation of molybdenum from uranium and most other fission products. This process has been demonstrated a number of times at both LANL (May et al., 2013, 2014) and ANL (Stepinski et al., 2013; Youker et al., 2014). Additionally, multiple irradiations have

[15] That is, uranium-fission reactions in the assembly do not become self-sustaining.

been performed on target solutions without affecting the ability to extract molybdenum, allowing for multiple recycles of the target solution.[16] The recycling of target material allows for higher uranium-235 utilization compared to conventional reactor-based Mo-99 production.

After separation, the molybdenum is further purified for medical use. This purification consists of several well-established chemical processing steps that have been demonstrated multiple times at ANL.[17] A similar purification process was in commercial use at Cintichem (formerly Union Carbide in Tuxedo, New York) and is currently in commercial use in Indonesia at Badan Tenaga Atom Nasional, where LEU is used to produce Mo-99. GE Healthcare announced in November 2015 that it had successfully obtained pharmaceutical-grade Tc-99m from their Drytec generators using Mo-99 made from the SHINE process.

The licensing process for the SHINE project is in progress. An Environmental Impact Statement and Safety Evaluation Report were published in October 2015, and the Construction Permit for the facility in Janesville, Wisconsin, was issued in February 2016.

SHINE has signed agreements to supply Mo-99 to GE Healthcare,[18] Lantheus,[19] and China's HTA Co., Ltd.[20] SHINE plans to begin commercial sales of Mo-99 in 2019.

4.1.3 Babcock & Wilcox

B&W, now known as BWX Technologies, was awarded a cooperative agreement by NNSA on September 30, 2009, to develop a 200-kW homogeneous solution reactor, referred to as the Medical Isotope Production System (MIPS), to produce Mo-99 (Reynolds, 2008). B&W suspended work on this project in 2012 after determining that the time and cost involved with the project would be greater than anticipated (SNMMI, 2012).

The MIPS is a compact cylindrical solution reactor that is surrounded by a neutron reflector and contains control rods and cooling coils. The reactor fuel is a solution containing an LEU salt, such as uranyl nitrate [$UO_2(NO_3)_2$], dissolved in water and acid. This fuel is also the target material for Mo-99 production. The reactor is designed to operate at about 80°C and ambient atmospheric pressure. The reactor would be operated

[16] Information about the quantities and concentrations of target solutions is proprietary.

[17] See Proceedings of the 22nd International Meeting on Reduced Enrichment for Research and Test Reactors, Budapest, Hungary, October 3–8, 1999.

[18] See http://shinemed.com/news/it-takes-two-ge-healthcare-and-shine-team-up-to-solve-longstanding-radiopharmaceutical-supply-concerns-in-medical-imaging/.

[19] See http://shinemed.com/news/shine-signs-second-mo-99-supply-agreement/.

[20] See http://archive.jsonline.com/business/shine-medical-inks-supply-agreement-with-hta-co-ltd-of-beijing-b99748237z1-383810761.html.

for approximately 5 days, during which time Mo-99 builds up in the fuel solution as a result of uranium fission reactions. The reactor would then be shut down for two days, during which time the Mo-99 will be recovered and purified (DOE, 2014; IAEA, 2013). A three-reactor system could supply about 50 percent (~2,500 6-day Ci) of U.S. demand for Mo-99.

B&W has also investigated uranyl sulfate fuel solutions. The main advantage of this fuel is that its radiolytic decomposition products are H_2 and O_2 only. Radiolytic decomposition of a uranyl nitrate solution is far more complex, because nitrate is reduced to form nitrite, nitrogen, and nitrogen oxide (NO_x) gases. Ammonium ions are also generated (IAEA, 2013). The difficulty of using the uranyl nitrate solution was a major contributor to the discontinuation of this project.

The MIPS reactor is conceptually similar in design to the Argus Reactor at the Kurchatov Institute in Russia. This reactor has already been used to demonstrate the production of Mo-99 from uranyl sulfate (Ball, 1999).

R&D was under way to address several technical issues when the project was suspended (e.g., Chemerisov et al., 2008; Gelis et al., 2008; Vandegrift et al., 2008; Ziegler et al., 2008). The Argentine company INVAP was performing R&D under a contract with B&W on reactor design and Mo-99 sorbent efficiency. ANL was carrying out analyses of the chemistry of salt solutions in operating solution reactors and the recovery of Mo-99. The laboratory was researching the potential for formation of uranium precipitates in the nitrate salt solution, radiation effects on oxidation of molybdenum, and the effects of nitrate decomposition on the treatment of gases produced by radiolysis in the reactor. Argonne researchers reported that there was a "high potential for the successful implementation of this technology" (Vandegrift et al., 2008).

B&W had hoped to construct MIPS facilities to supply Mo-99 to U.S. and international markets. The company estimated that their facilities would be operating by 2014-2015 provided that they had identified a radiopharmaceutical partner and had obtained full funding for the project. This schedule assumed the successful completion of the R&D programs and the resolution of several legal and regulatory issues, including MIPS licensing, waste disposal, and LEU availability.

4.1.4 General Electric-Hitachi

GEH was awarded a cooperative agreement by NNSA on September 30, 2009, to pursue the use of power reactors as the source of neutrons to produce Mo-99 via neutron capture ($^{98}Mo(n,\gamma)^{99}Mo$), the same process being used in one of the NorthStar projects (see Section 4.1.1). GEH and Exelon announced in September 2011 that they were jointly studying the feasibility of producing Mo-99 at the Clinton Power Station, a boiling

water reactor located in central Illinois. Clinton is already being used to produce cobalt-60 for medical use. GEH also signed memoranda of understanding with NuView Life Sciences (see Section 4.2.6 in this chapter) and NorthStar Medical Radioisotopes to process irradiated targets and sell the recovered Mo-99 (GEH, 2011). GEH suspended the project in February 2012 because of an adverse market outlook (Forrest, 2012).

4.1.5 General Atomics

NNSA selected a project proposed by GA[21] for cooperative agreement funding through the 2010 FOA. However, GA did not sign the agreement with NNSA until October 2015. The project has received $9.7M in NNSA funding to date (NNSA, 2015b).

GA is partnering[22] with Nordion and MURR to develop, demonstrate, and commercialize a GA-patented technology, selective gaseous extraction (SGE), for production of Mo-99 with LEU targets. GA is developing the LEU targets and gas extraction systems; MURR will install these systems in its reactor and operate them to produce Mo-99 for Nordion; and Nordion is providing the necessary capital to develop and implement the technology and has exclusively licensed it to MURR for a 20-year period.

The original concept for this project involved the in situ extraction of Mo-99 from two LEU targets installed in the graphite reflector in the MURR reactor (see Figure 4.7) to produce up to 4,200 6-day Ci of Mo-99 per week. The targets would be irradiated continuously while the reactor was operating. Mo-99 would be extracted periodically from each target by flowing a gas mixture containing chlorine and oxygen through the target material. (Molybdenum would be extracted as gaseous molybdenum oxychloride [MoO_2Cl_2]). The gas mixture containing extracted Mo-99 would be piped to a hot cell for subsequent processing.

This technical approach was modified after preliminary testing of some design components. Mo-99 will now be produced using single-use targets consisting of UO_2 pellets contained in zirconium rods.[23] The rods will be placed into two wedge-shaped housings (see Figure 4.8) installed in the graphite reflector in the MURR reactor. The targets will be irradiated continuously for 1-3 weeks depending on customer demand and then removed for processing during planned reactor shutdowns.

The rods will be transferred to a bank of hot cells at MURR and

[21] GA is located in San Diego, California. It has more than 50 years of experience in reactor and fuel target design.

[22] The partnership was announced in February 2015. See General Atomics (2015).

[23] The designs of the target rods and housings and supporting performance analyses are proprietary.

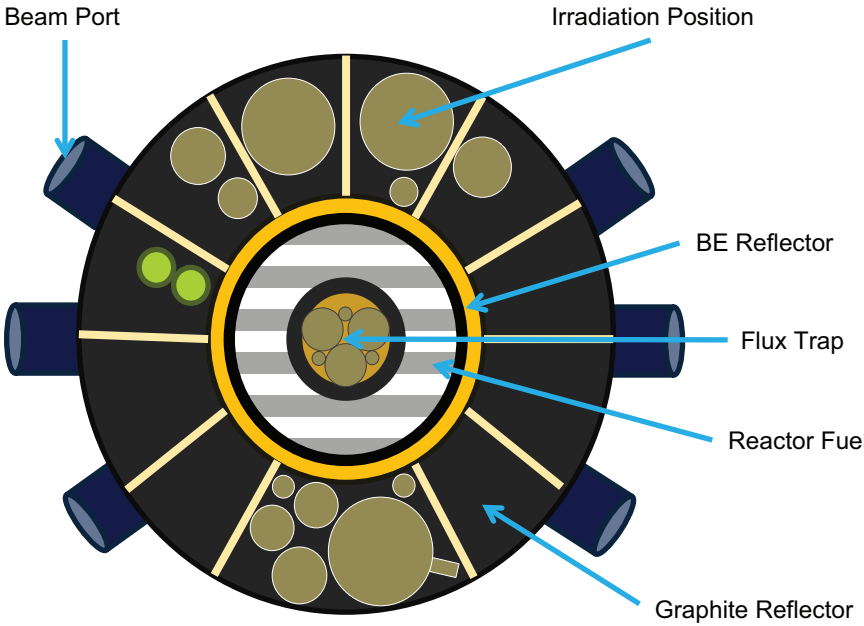


FIGURE 4.7 Schematic illustration of the major components of the reactor at MURR. The targets for selective gaseous extraction will be installed in the graphite reflector. SOURCE: Modified from a graphic provided by Ralph Butler, MURR.

processed using SGE to recover Mo-99. Noble gases will be co-extracted with Mo-99 and captured in a cryogenic trap. Some other fission products will also be separated.[24] The extraction waste will consist of UO_2 powder. The separated Mo-99 will be transported to Nordion for purification and packaging for commercial sale. Nordion estimates that up to 3,200 6-day Ci of Mo-99 per week can be produced using this modified SGE process.

SGE has been demonstrated in the laboratory with single-use targets doped with Mo-99 and with irradiated target pellets. According to Nordion, both tests demonstrated high Mo-99 yields.

Work is under way to obtain regulatory approvals for this modified process. MURR is proposing a license amendment to its regulator (NRC) to implement this technology. Once regulatory approval is received, prototype targets will be installed in the MURR reactor. (This action is planned for the summer of 2017.) The prototypes will be irradiated over a period of 3 months to gather the data needed for filing a Drug Master File (DMF; see

[24] Nordion did not reveal the intended use for these other fission products.

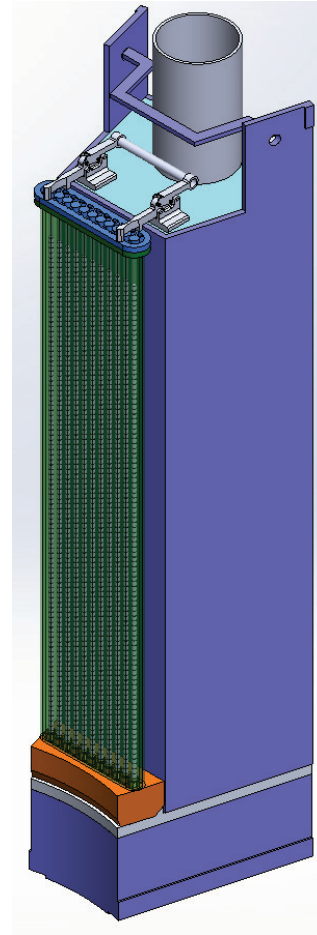


FIGURE 4.8 GA's target assembly for Mo-99 production. The target material is contained in the vertical tubes shown in green; the large tube shown in gray at the top of the target housing is for water cooling. SOURCE: Kathy Murray, General Atomics (GA).

Appendix 4A) with the FDA. Once the DMF is completed, Nordion will install additional targets in the MURR reactor for producing Mo-99 for commercial sale. Nordion expects to install these targets and begin producing Mo-99 in the first half of 2018.

4.2 OTHER PROJECTS FOR DOMESTIC PRODUCTION OF Mo-99

Several private companies are working toward establishing domestic production of Mo-99 or related processes without NNSA funding. The

committee obtained information on development efforts by seven companies[25] (NNSA, 2014):

- Coquí RadioPharmaceuticals
- Eden Radioisotopes
- Flibe Energy
- Niowave
- Northwest Medical Isotopes (NWMI)
- NuView Life Sciences
- PermaFix Medical

The first five of these projects are depicted graphically in Figure 4.9, and all seven of these projects are described briefly in the following subsections.

4.2.1 Coquí RadioPharmaceuticals

Coquí RadioPharmaceuticals, a Puerto Rico–based company, plans to produce up to 7,000 6-day Ci of Mo-99 per week for the U.S. and export markets by irradiating LEU targets in two 10 megawatt (MW) LEU-fueled research reactors (Coquí RadioPharmarmaceuticals, 2015a). The company plans to build these reactors and associated Mo-99 production facility on the 170 acre "Duct Island" site at Oak Ridge, Tennessee. The land was granted by DOE and the Community Reuse Organization of East Tennessee in June 2016.[26] Coquí has contracted with the Argentinian nuclear engineering firm INVAP to design and construct the facility, which will include two open-pool reactors similar in design to Australia's INVAP-designed OPAL reactor. The facility will also include a radioisotope processing plant, a waste conditioning plant, a radiopharmaceutical production plant, nuclear and medical support services, and administrative offices (Coquí RadioPharmaceuticals, 2015b).

A schematic and concept design for the facility was completed in April 2015 (Coquí RadioPharmaceuticals, 2015c), and the company has announced its intention to submit a license application to the NRC to construct the facility. The application had not been submitted when the present report was being finalized for publication.

[25] Additional companies may be developing capabilities to produce Mo-99 and associated medical isotopes with or without publicly announcing their plans.

[26] Coquí's original plan was to build one reactor at a 25-acre plot in Alachua, Florida. All announcements by the company made in 2015 referred to facilities at that location.

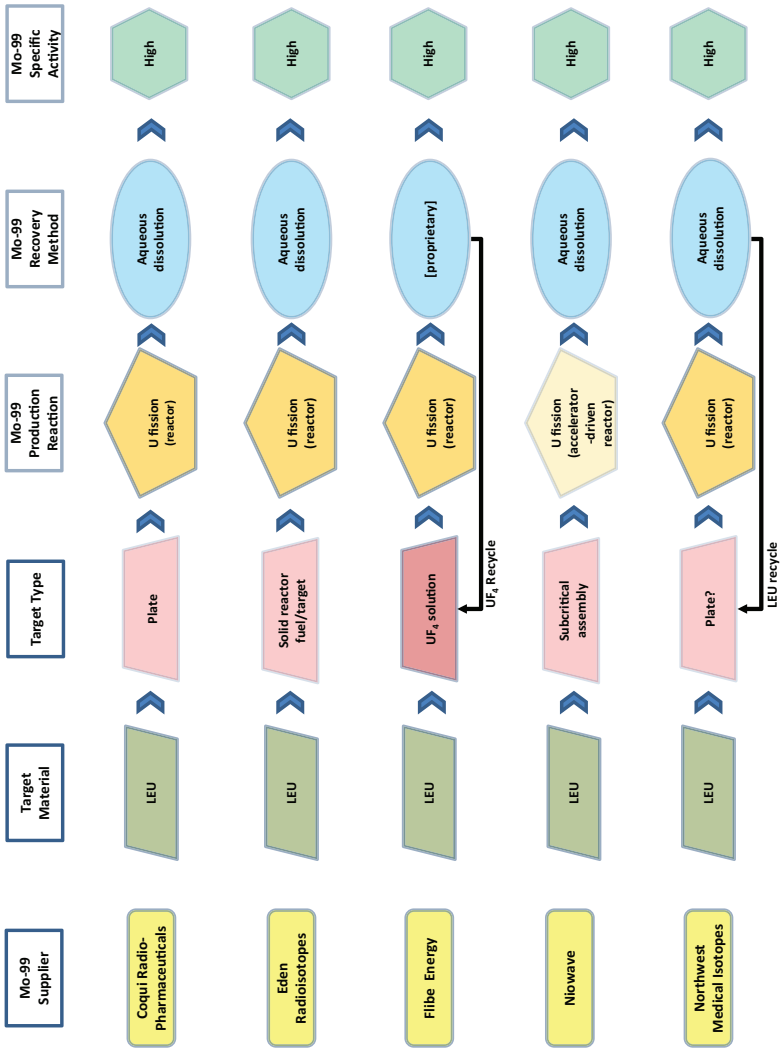


FIGURE 4.9 Five private-sector domestic Mo-99 production projects.

4.2.2 Eden Radioisotopes

Eden Radioisotopes, established in 2013, has licensed Sandia National Laboratories' design for a dedicated Mo-99 production reactor (Salem, 2014). This open-pool reactor has a compact (less than 0.5 m in diameter and height), low-power (<2 MW) core consisting of LEU fuel that also serves as targets for Mo-99 production. The individual fuel elements would be removed and chemically processed using a modified Cintichem process to recover Mo-99, I-131, and Xe-133. The company claims that it could supply U.S. needs for Mo-99 by operating the reactor at 670 kW and removing the fuel elements for chemical processing every 7 days. The company also claims that it could supply current world needs for Mo-99 by operating the reactor at 1.5 MW.[27] The company has notified the NRC that it intends to file a license application to construct a reactor and processing facility near Hobbs, New Mexico. The company is in the process of raising funds to complete and submit the license application. The company must also qualify the fuel and targets to be used in the reactor.

4.2.3 Flibe Energy

Flibe Energy, located in Huntsville, Alabama, but registered in Delaware, is a nuclear startup company that aims to develop a liquid fluoride thorium reactor (LFTR) for nuclear power production.[28] The company submitted a notice of intent (Flibe Energy, 2013) to the NRC in May 2013 to submit a license application for an LFTR and Mo-99 production facility. The site for the reactor and production facility has not been selected. The notice indicated that the reactor would have a thermal power of less than 2 MW and would be fueled with fluoride salt containing thorium.

During operation of the reactor, thorium in the reactor fuel captures a neutron and is transmuted to uranium-233 (U-233), which is fissile. The fission of U-233 with neutrons produces a spectrum of fission products including Mo-99. The Mo-99 produced in the reactor would be extracted on-line.

The notice of intent indicated that the company was raising private funding to support the conceptual design, construction, licensing, and operation of the reactor, and also that the company tentatively anticipated the submission of a research reactor license application in the fall of 2015. This application had not been submitted by the time the present report was being finalized for publication.

[27] A company representative characterized these estimates as "conservative and fully account[ing] for cooling, processing, and shipping times to deliver desired quantities of 6-day curies to the customer" (Richard Coats, Eden Radioisotopes LLC, written communication, July 30, 2016).

[28] See http://flibe-energy.com.

4.2.4 Niowave

Niowave, a Michigan-based company, plans to build a Mo-99 medical isotope production facility in Lansing, Michigan.[29] The facility would produce Mo-99 using a neutron source that drives a subcritical LEU assembly to create fission Mo-99, similar to the approach being developed by SHINE (see Section 4.1.2 in this chapter).

The Niowave accelerator could produce 1-2 × 10^{14} neutrons per second using a 100 kW, 40 MeV electron beam on a lead-bismuth eutectic target, or >10^{15} neutrons per second with a 400 kW, 80 MeV electron beam. The 100 kW electron beam is expected to be sufficient to create roughly 400 6-day Ci of Mo-99 per week with an upgrade path to a 400 kW electron beam that would produce roughly 1,500 6-day Ci of Mo-99 per week.[30]

The company produces a line of turnkey commercial superconducting electron linear accelerators that could be used to produce a 100 kW, 40 MeV electron beam. The company indicated that this accelerator could be upgraded to 400 kW electron beam power.

Niowave has constructed a facility adjacent to the Lansing airport that will house the superconducting accelerator and associated infrastructure, and it has installed the necessary cryogenics plant for a 100 kW accelerator. This accelerator facility is licensed by the State of Michigan. The liquid lead-bismuth target for neutron production has been demonstrated at 2 kW beam power and was used to irradiate a small sample of uranium. Niowave announced the production of small quantities of Mo-99 from a LEU sample in late 2015. Further testing is under way, but a schedule for completing the testing and commencing of Mo-99 production has not yet been announced.

4.2.5 Northwest Medical Isotopes

NWMI, an Oregon-based company, plans to produce 3,500 6-day Ci of Mo-99 per week by irradiating LEU targets in the MURR reactor and a research reactor at Oregon State University. The targets would be processed to recover Mo-99 in a radioisotope production facility to be constructed by the company in Columbia, Missouri.[31] The production facility would also be used to recover uranium from the dissolved LEU solution and recycle it back into new LEU target material. The LEU material production process would utilize a proprietary technology developed by Oregon State University.

A construction permit application for the processing facility was sub-

[29] See http://www.niowaveinc.com.

[30] A similar approach has been proposed by IBA and AMIC using lower energy electron beams. See Stevenson and Schenter (2010) and Stichelbaut and Jongen (2011).

[31] See http://nwmedicalisotopes.com/.

mitted to the NRC in 2014. The company expects to start construction of the facility in early 2017.

4.2.6 NuView Life Sciences

As noted in Section 4.1.4 of this chapter, NuView Life Sciences, located in Denton, Texas, signed a memorandum of understanding with GEH in 2011[32] to process irradiated targets from GEH's neuron capture project. GEH announced in February 2012 that it was suspending its Mo-99 production project (Forrest, 2012).

4.2.7 Perma-Fix Medical

Perma-Fix Medical, a subsidiary of Perma-Fix Environmental Services in Atlanta, Georgia, was formed to develop and commercialize a new class of radiation-resistant resin (Micro-Porous Composite Material) that allows for high loading of molybdenum and efficient elution of Tc-99m. This material could be especially useful in technetium generators containing low-specific-activity Mo-99.

In March 2014, Perma-Fix Medical announced the successful validation of the radiation resistance of this resin and its high elution efficiency for Tc-99m based on testing at POLATOM in Warsaw, Poland, and MURR (Perma-Fix Environmental Services, Inc, 2014). The company has filed patent applications for this resin and has signed a letter of intent to form a strategic partnership with Digirad Corporation, a major national provider of in-office nuclear cardiology imaging services (Digirad, 2015). Perma-Fix has no plans to produce Mo-99 or Tc-99m.

4.3 DOMESTIC PRODUCTION OF I-131 AND Xe-133

At present, there is no production of I-131 or Xe-133 in the United States. Nordion (Canada) currently supplies most of these isotopes. Institut National des Radioéléments (IRE) (Belgium) began supplying Xe-133 to the United States under an arrangement with Lantheus Medical Imaging (see Chapter 3).

A number of U.S.-based organizations may produce these isotopes domestically in the future:

- MURR has received a license amendment from the NRC to produce I-131 by irradiating tellurium targets (the production process is described in Chapter 2). MURR is performing qualification runs

[32] See http://www.reuters.com/article/idUS186817+12-Sep-2011+BW20110912.

to develop the information needed for a DMF, which is planned to be filed with the FDA in the second half of 2016. MURR has signed an I-131 supply agreement with one customer (the identity of this customer has not yet been made public) and is in negotiations with another potential customer.

- SHINE is planning to recover Xe-133 and/or I-131 and possibly other isotopes from its Mo-99 production process.[33] The decision on which isotopes to recover will be made at a later date and will likely depend on market conditions.
- The contract between Nordion and GA for the SGE technology to be implemented at MURR allows for the recovery of other fission isotopes besides Mo-99.[34] However, Nordion has not made any public statements regarding its plans to recover I-131 or Xe-133.
- Eden Radioisotopes has also indicated that it plans to recover both I-131 and Xe-133 as part of its Mo-99 production processes.

4.4 PROGRESS TOWARD ESTABLISHING DOMESTIC PRODUCTION OF Mo-99

This section provides the results of the committee's *readiness assessment* for each of the Mo-99 production projects described in Sections 4.1 and 4.2 of this chapter. This assessment provides the committee's collective technical judgment about the progress being made by each of these projects to demonstrate the establishment of a domestic capability to produce Mo-99.

The committee used the following criteria to assess project readiness (see Table 4.2):

- Has the Mo-99 production technology been demonstrated?
- Are production facilities available?
- Are the target materials needed for production available?
- Is the product (Mo-99 or Tc-99m) compatible in the existing supply chain?
- Have the necessary regulatory approvals for the facilities used for production been obtained?
- Have the necessary regulatory approvals for the production products (Mo-99, Tc-99m) been obtained?
- What is the estimated timescale for bringing these production products to the marketplace?

[33] Greg Piefer, SHINE, written communication, March 7, 2016.
[34] Phil Larabie, Nordion, written communication, March 14, 2016.

TABLE 4.2 Criteria Developed by the Committee to Assess Readiness of Domestic Mo-99 Production Projects

Criterion	Description
Has production technology been demonstrated?	
A: Commercial scale	The technologies used to produce Mo-99/Tc-99m have been demonstrated at commercial scale in this or other projects.
B: Pilot scale	The technologies used to produce Mo-99/Tc-99m have been demonstrated as a complete system at less than commercial scale in this or other projects.
C: Bench scale	All critical system components have been demonstrated at bench scale in this or other projects.
D: Under development	All or some critical system components are still under development.
Are production facilities available? • **Irradiation** • **Processing**	
A: All needed production facilities available	All of the facilities needed to produce the product for commercial sale are available to the project.
B: Some production facilities available	Some, but not all, of the facilities needed to produce the product for commercial sale are available or potentially available to the project.
C: Some pilot facilities available	Some pilot-scale production facilities needed for project development and testing are available or potentially available to the project.
D: No needed facilities available	None of the facilities needed to produce the product for commercial sale are available to the project.
Are target materials available?	
A: Available from multiple suppliers	Adequate commercially available quantities of the target materials needed to produce Mo-99/Tc-99m can be obtained from two or more suppliers.
B: Available from a single government supplier	Adequate commercially available quantities of the target materials needed to produce Mo-99/Tc-99m can be obtained from one government supplier.
C: Available from a single commercial supplier	Adequate commercially available quantities of the target materials needed to produce Mo-99/Tc-99m can be obtained from one commercial supplier.
D: Not readily available	Adequate commercially available quantities of the target materials needed to produce Mo-99/Tc-99m are not currently available from any government or commercial suppliers.
Is the product (Mo-99, Tc-99m) compatible in the existing supply chain?[a]	
A: Product compatible	The product is of high specific activity and can be used in conventional Tc-99m generators.

continued

TABLE 4.2 Continued

Criterion	Description
B: Product partially compatible	The product is of low specific activity and cannot be used in conventional Tc-99m generators.
D: Product incompatible	The product is not compatible with the existing supply chain.
Have regulatory approvals for facilities been obtained? • **Irradiation** • **Processing**	
A: Approval for operation	The facilities to produce Mo-99/Tc-99m exist or have been constructed and the project has received approvals from regulatory authorities to operate them.
B: Approval for construction	The project has received necessary approvals from regulatory authorities to construct the necessary facilities to produce Mo-99/Tc-99m.
C: Approvals for testing	The project has received approvals from regulatory authorities to conduct the testing activities necessary to develop a construction application.
D: No approvals	No approvals have been received.
Have regulatory approvals for products (Mo-99, Tc-99m) been obtained?	
A: ANDA/sANDA/NDA/ sNDA approved	The product has been approved for medical use by regulatory authorities.
B: ANDA/sANDA/NDA/ sNDA submitted, no additional FDA request	An application to use the product for medical use has been submitted with no additional requested information from FDA.
C: ANDA/sANDA/NDA/ sNDA submitted, additional FDA information request	An application to use the product for medical use has been submitted with additional requested information from FDA.
D: No ANDA/sANDA/NDA/ sNDA	No ANDA/sANDA/NDA/sNDA is being developed.
What is the timescale for bringing products (Mo-99, Tc-99m) to the marketplace?	
A: Before November 2016	Products will likely be available in the marketplace before the NRU reactor in Canada stops production of Mo-99 at the end of October 2016.
B: Between November 2016 and March 2018	Products will likely be available in the marketplace after the NRU reactor stops production of Mo-99 at the end of October 2016 but before the reactor shuts down permanently at the end of March 2018.
C: After March 2018	Products will likely be available in the marketplace after the NRU reactor shuts down permanently after March 2018.
D: Project suspended	Company is not currently developing the project.

NOTES: ANDA = abbreviated new drug application; NDA = new drug application; sANDA = supplemental ANDA; sNDA = supplemental NDA.

[a] There is no letter score "C" for this criterion.

The committee selected these criteria because (1) they address the wide range of technical and regulatory hurdles that will have to be overcome to demonstrate the establishment of a domestic capability to produce Mo-99; and (2) they can be assessed using publicly available information.

These committee-selected criteria are important for demonstrating the establishment of a domestic production capability, but they are by no means sufficient. Potential domestic suppliers also have to be able to successfully construct and operate Mo-99 production facilities and establish commercial relationships with customers. Their success in this regard will depend on a number of factors, including the availability of funding, previous experience in the medical isotope business, market timing, as well as the other economic considerations described in Section 4.5 of this chapter. These factors cannot be readily assessed with publicly available information.

For example, none of the projects described in Sections 4.1 or 4.2 of this chapter have previous experience in the medical isotope business. However, these projects can probably obtain the necessary experience through consulting or other types of contractual arrangements. The information needed to assess the efficacy of such arrangements is likely to be proprietary.

Project readiness for each of the projects described in Sections 4.1 and 4.2 is assessed by assigning a letter score (A-D) for each criterion, with higher scores indicating higher readiness levels. The scoring system is described in Table 4.2. A summary of the committee's readiness assessment for the NNSA-supported projects (see Section 4.1) is shown in Table 4.3; the assessment for the other projects (see Section 4.2) is shown in Table 4.4. Brief explanations for key readiness scores for these projects are provided below.

4.4.1 NorthStar Medical Radioisotopes

NorthStar's neutron capture project has the highest readiness level of all of the NNSA-supported projects. The technology has been demonstrated at commercial scale, production facilities are available, and regulatory approvals have been obtained or are in progress. The project can likely bring Mo-99 to market sometime after Canada stops production of Mo-99 at the end of October 2016 but before NRU shuts down permanently in March 2018. However, large-scale supply of Mo-99 to the market may not occur until after NRU shuts down permanently at the end of March 2018.

This project received lower readiness scores for the availability of enriched Mo-98 target material and the compatibility of the product in the supply chain because

TABLE 4.3 Project Readiness for NNSA-Supported Domestic Mo-99 Production Projects

	NNSA-Supported Domestic Mo-99 Production Projects						
Criterion	NorthStar (n, γ)	NorthStar (γ, n)	SHINE	GA	B&W	GE-Hitachi	Criterion Description
Has production technology been demonstrated?	A	C	B[a]	C	B	A	A: Yes, at commercial scale B: Yes, at pilot scale C: Yes, at bench scale D: No
Are production facilities available?							A: All needed facilities are available B: Some needed facilities are available
• Irradiation	A	D	C	A	D	A	C: Some pilot facilities are available
• Processing	B	D	C	A	D	B	D: No facilities are available
Are target materials available?	A (natural) C (enriched)	A (natural) C (enriched)	B	B	B	B	A: Available from multiple suppliers B: Available from a single government supplier C: Available from a single commercial supplier D: Not readily available
[Type of target]	[Mo-98]	[Mo-100]	[LEU]	[LEU]	[LEU]	[Mo-98]	
Is the product (Mo-99, Tc-99m) compatible in the supply chain?	B	B	A	A	A	B	A: Product compatible B: Product partially compatible D: Product incompatible

Have regulatory approvals for facilities been obtained?							A: Approval for operation B: Approval for construction C: Approval for testing D: No approvals
• Irradiation	A	D[b]	B	C	D	D	
• Processing	B	B	B	A[c]	D	D	
Have regulatory approvals for products (Mo-99, Tc-99m) been obtained?	B	D	D	D	D	D	A: ANDA/sANDA/NDA/sNDA approved B. ANDA/sANDA/NDA/sNDA submitted with additional information requested[d] C: ANDA/sANDA/NDA/sNDA submitted with no additional information requested D. No ANDA/sANDA/NDA/sNDA
What is the committee's estimated timescale for bringing products to the marketplace?	B	C	C	C	D	D	A: Before November 2016 B: Between November 2016 and March 2018 C: After March 2018 D: Project suspended

[a] Individual components for SHINE's production technology have been demonstrated at commercial scales, but the performance of the integrated system has not.

[b] NorthStar has received a "machines" license from state regulatory authorities to possess and install up to 16 accelerators at its Beloit facility. The company has not received a "materials" license from state regulators to produce isotopes with these accelerators.

[c] GA proposes two-step target processing. The first step will occur at MURR and the second at Nordion in Kanata, Canada.

[d] Information provided by the potential producer. FDA submission documents are not public information.

TABLE 4.4 Project Readiness for Privately Funded Domestic Mo-99 Production Projects

	Other Potential Domestic Mo-99 Production Projects							
Criterion	Coquí RP	Eden RI	Flibe Energy	PermaFix	Niowave	NuView	NWMI	Criterion Description
Has production technology been demonstrated?	A	A	D	B	C	A	A (reactor) D (targets)	A: Yes, at commercial scale B: Yes, at pilot scale C: Yes, at bench scale D: No
Are production facilities available?								A: All needed facilities are available
• Irradiation	D	D	D	N/A	B	A	B	B: Some needed facilities are available
• Processing	D	D	D	D	D	unknown	D	C: Some pilot facilities are available D: No facilities are available
Are target materials available?	B	B	B	N/A	B	B	B	A: Available from multiple suppliers B: Available from a single government supplier
[Type of target]	LEU	LEU	LFT[a]	N/A[b]	LEU	Mo-98	LEU	C: Available from a single commercial supplier D: Not readily available
Is the product (Mo-99, Tc-99m) compatible in the existing supply chain?	A	A	A	A	A	B	A	A: Product compatible B: Product partially compatible D: Product incompatible

Have regulatory approvals for facilities been obtained?								A: Approval for operation B: Approval for construction C: Approvals for testing D: No approvals
• Irradiation	D	D	D	N/A	A	D	A	
• Processing	D	D	?	D	D		D	
Have regulatory approvals for products (Mo-99, Tc-99m) been obtained?	D	D	D	D	D	D	D	A: ANDA/sANDA/NDA/sNDA approved B: ANDA/sANDA/NDA/sNDA in development with additional information requested C: ANDA/sANDA/NDA/sNDA submitted with no additional information requested D: No ANDA/sANDA/NDA/sNDA
What is the committee's estimated timescale for bringing products (Mo-99, Tc-99m) to the marketplace?	C	C	C	C	C	D	C	A: Before November 2016 B: Between November 2016 and March 2018 C: After March 2018 D: Project suspended

[a] Liquid fluoride thorium.
[b] The Perma-Fix project does not involve target development or use. It is focused on development of a resin for use in technetium generators.

- Enriched Mo-98 is available only from a single supplier in the Russian Federation, although two sources of supply may become available in the future.
- A special technetium generator system (RadioGenix Generating System) is required to use the low-specific-activity Mo-99 produced by neutron capture. The generator system occupies the same floor space as about four conventional Tc-99m generators. Most U.S. nuclear pharmacies have limited floor space, so they may have to reduce or eliminate their conventional generators to accommodate a RadioGenix system. Nuclear pharmacies might be reluctant to adopt a single new generator system that lacks an operational record. Additionally, the long elution time for the RadioGenix generator system (60-70 minute cycle time) compared to conventional technetium generators (about 5 minutes) may be a barrier to use by some nuclear pharmacies.

NorthStar's photon-induced transmutation project received lower readiness scores than the company's neutron capture project because the technology has not been demonstrated at commercial scales and production facilities are not yet available or licensed. NorthStar's photon-induced transmutation project is not likely to bring Mo-99 to market until after March 2018.

4.4.2 SHINE Medical Technologies

SHINE's accelerator-driven subcritical LEU assembly Mo-99 production project received lower readiness scores because the technology has not been demonstrated at commercial scales as an integrated system, production facilities are not yet available, and some, but not all, regulatory approvals have been obtained. This project is not likely to bring Mo-99 to market until 2019, long after NRU shutdown.

SHINE plans to purchase LEU from DOE and will have two options for doing so: (1) it can purchase LEU directly, or (2) it can lease LEU through DOE's Uranium Lease and Take-Back (ULTB) Program (see Sidebar 4.1). Leasing would allow SHINE to pay for the LEU as it is consumed, rather than paying for the entire cost of LEU up front. Additionally, DOE would retain title to the LEU and would dispose of SHINE's LEU-bearing wastes if there was no available commercial disposal pathway.

4.4.3 General Atomics

GA's SGE process for recovering Mo-99 from irradiated targets has not been demonstrated at commercial scales. The facilities and target

SIDEBAR 4.1
Uranium Lease and Take-Back Program

Sections 3173 (c) and (e) of the Fiscal Year 2013 National Defense Authorization Act (P.L. 112-239) directs DOE to establish a Uranium Lease and Take-Back (ULTB) Program by January 2016 to make LEU available for the production of Mo-99 for medical use through lease contracts. The Act also requires DOE to retain responsibility for the final disposition of spent nuclear fuel and/or radioactive waste when the DOE secretary determines that commercial disposal is not available. The Act also requires DOE to recover the costs associated with the ULTB Program. Potential customers must demonstrate adequate financial assurance to cover the liabilities associated with uranium lease and take-back to be eligible to participate in the program.

The ULTB Program is coordinated between different organizations within DOE: the NNSA Production Office provides the management and leasing of LEU and the Office of Environmental Management manages the disposition of spent nuclear fuel and radioactive waste that does not have an existing disposal path.

NNSA established an intra-agency working group which coordinated the completion of various activities to establish the ULTB Program by January 2016, as required by the American Medical Isotopes Production Act (see Chapter 1 and Appendix A). Contract templates for leasing LEU and taking back spent fuel and high-level waste have been developed by DOE, and contract negotiations between DOE and potential lessees were under way when this report was being finalized for publication. NNSA reported to the present committee that one contract with MURR has been signed to support R&D activities associated with the GA project; NNSA also reported that the financial assurance requirement is proving to be somewhat challenging for some potential customers (Peter Karcz, DOE-NNSA, written communication, July 29, 2016).

materials[35] for production are available, but no regulatory approvals have been obtained. This project is not likely to bring Mo-99 to market until after March 2018.

4.4.4 Babcock & Wilcox and General Electric-Hitachi

Readiness scores for both of these projects have been included in Table 4.2 for completeness. As noted previously, however, both projects have been suspended, so they are unlikely to result in any new domestic Mo-99 production.

[35] GA would purchase or lease LEU from DOE.

4.4.5 Other Potential Mo-99 Suppliers

All of the privately supported projects described in Table 4.4 are at a low state of readiness. Some of the production technologies have been demonstrated at commercial scales, but almost all of the projects lack the necessary facilities and regulatory approvals. It is unlikely that any of the projects will bring Mo-99 to market before March 2018, and many of these projects may never be completed.

Four of the projects (Coquí, Eden, Flibe, and NWMI) propose to produce Mo-99 by fission of LEU targets[36] in reactors, a process that has been well demonstrated at commercial scale and is currently being used to produce Mo-99 in Australia and South Africa. LEU is available for sale or lease from DOE (see Sidebar 4.1). Even under the best of circumstances, however, it will take at least 5-7 years to design, construct, license, and commission the reactor and target processing facilities and commence Mo-99 production. Note particularly that

- The Coquí project has been working to construct a reactor and target processing facility for about 7 years (since 2009), but license and construction applications have not yet been submitted to the regulator.
- The Eden project proposes to use a new reactor design that has never been licensed. Reactor license and construction applications have not been submitted to the regulator.
- The Flibe project proposes to use a new reactor design with a liquid-fluoride thorium fuel system that, to the committee's knowledge, has not been technically demonstrated. Reactor license and construction applications have not been submitted to the regulator.
- The NWMI project will use a network of existing university reactors, but a new processing facility for Mo-99 recovery and purification and LEU recovery and recycle will need to be constructed and commissioned. In conjunction with the new processing facility, NWMI will have to construct and commission a facility for LEU target fabrication. Additional time will be required to develop, demonstrate, and license the process for recycling LEU from irradiated targets and fabricating new targets. Recovered LEU will need to be held for several months prior to being reused to allow sufficient time for medium-lived isotopes to decay. The company will also need to demonstrate that the Mo-99 produced from recycled targets can meet the FDA's requirements for commercial sale.

[36] These companies would also purchase or lease LEU from DOE.

- The Niowave project to produce Mo-99 using a subcritical assembly faces many of the same challenges as the SHINE project.

4.5 ECONOMIC CONSIDERATIONS

Some of the domestic Mo-99 production projects described in Sections 4.1 and 4.2 employ technologies that may have significantly different cost structures than those for conventional fission-based Mo-99 production methods. In fact, some of these projects may be able to produce Mo-99 at lower costs than current global suppliers for several reasons, including the following:

- All domestic production will be non-HEU sourced; consequently, domestic Mo-99 suppliers do not have to bear the costs for eliminating HEU from production, unlike most existing global Mo-99 suppliers. (However, some of the costs of eliminating HEU from current production are being covered by NNSA; see Chapter 5.)
- Some domestic production development costs are being offset by NNSA through cooperative agreement funding. National laboratories are also providing NNSA-funded technical support to some projects, and regulators are providing fast-track regulatory approvals.
- Supply lines from potential domestic Mo-99 suppliers to domestic users are shorter than for existing global suppliers. This lowers domestic suppliers' costs because more Mo-99 can be delivered to users for the same unit of production.
- Domestic production in new facilities may be inherently less expensive than production by global suppliers in existing (and aging) reactor and target processing facilities.

The advantage of non-HEU sourcing will be short-lived, however. Some existing global suppliers already supply Mo-99 produced with LEU targets, and others are planning to do so starting in 2017 (see Chapter 3). Marginal production costs will rise for Mo-99 made from LEU targets, but some of the costs of conversion are one-time investments,[37] which should have less effect on prices. The lower costs of production and shorter supply lines will continue to be advantageous for domestic suppliers long after conversion is completed.

Domestic suppliers will face many of the same economic and market barriers as global suppliers who plan to enter (e.g., Russia) or expand (e.g., ANSTO, Mallinckrodt, and NTP) their supplies of Mo-99 to the United

[37] As noted previously, some of these costs are being covered by NNSA.

States (see Chapter 3). At present, the main barrier to entry into the Mo-99 supply market is financial: the present low market prices for Mo-99 make it difficult to demonstrate the kind of return on investment that is needed to attract private financing to develop new domestic supplies. Current Mo-99 prices are low for several reasons:

- Historic government subsidies for Mo-99 production: most of the reactors and many of the facilities being used to produce Mo-99 were constructed with government funding and/or receive ongoing government support for operations.
- Mo-99 production capacity and marginal costs: Global suppliers currently have excess Mo-99 production capacity (see Chapter 3), and their marginal production (both irradiation and processing) costs within that excess are low.
- Oligopsony power[38]: Global Mo-99 suppliers and technetium generator suppliers are able to buy "products" (irradiation services and Mo-99, respectively) from multiple sellers. Competition among these buyers is limited—the top five Mo-99 suppliers and top four generator suppliers each supply 95 percent of their global market—by highly concentrated markets, so buyers can demand low prices as long as adequate product supplies are available. The technical and economic barriers to entry into these markets are formidable (see Chapter 3 and this chapter).
- Long-term purchasing agreement contracts: Mo-99, technetium generators, and Tc-99m radiopharmaceuticals are usually purchased under long-term proprietary contracts. These contracts usually limit the ability of sellers to increase prices.
- Pricing strategies: Technetium generator suppliers may use their generators as "loss leaders" to sell more profitable proprietary cold kits.
- Medical reimbursement policies: Reimbursement levels for medical procedures are set by government and private-payer insurance, usually based on past claim experience. The time lag between price changes and reimbursement levels can limit the ability of Mo-99/Tc-99m supply chain participants to raise prices over the short term.

[38] A type of market in which buyers of a product hold pricing power because they are small in number compared to the number of sellers of that product.

The High Level Group on the Security of Supply of Medical Radioisotopes[39] preference to allow market forces to govern Mo-99 supplies and prices also contributes to low Mo-99 prices because it reinforces many of the factors described above.

Under full-cost recovery (see Sidebar 2.4 in Chapter 2), governments would end their subsidies to reactors, forcing them to raise their prices for irradiation services. In a less price-constrained market, these irradiation-service price increases would cascade through the Mo-99/Tc-99m supply chain. However, other factors described above inhibit such cascading.

Even if new domestic suppliers are successful in entering the Mo-99 supply market, low Mo-99 prices may make it difficult for them to stay in business. Later domestic supplier entrants may have more difficulty succeeding because they will have to compete against these first entrants as well as then-existing global suppliers. Three existing global suppliers (ANSTO, Mallinckrodt, NTP) are expanding their capacities to supply Mo-99 in anticipation of Canada's exit from the market after October 2016 (see Chapter 3). Expanding supplies of Mo-99 will put further downward pressures on prices absent increased demand, likely making it difficult for new suppliers to gain a foothold in the market.

National governments, including the U.S. government, can provide incentives to push the market toward greater reliability and sustainability. Some actions are already being taken as described in Chapter 5.

4.6 FINDINGS AND RECOMMENDATIONS

FINDING 3A: The American Medical Isotopes Production Act of 2012 and financial support from the Department of Energy's National Nuclear Security Administration have stimulated private-sector efforts to establish U.S. domestic production of molybdenum-99 for medical use. However, no domestic commercial production will be established before Canada stops producing molybdenum-99 after October 2016. Potential domestic molybdenum-99 suppliers face technical, financial, regulatory, and market penetration challenges. The market challenges will likely increase after current global molybdenum-99 suppliers expand production.

As noted in Section 4.1, DOE-NNSA has entered into cooperative agreements with five U.S.-based companies to develop and demonstrate technologies for domestic production of Mo-99. Two of these companies (B&W and GEH) have suspended work on these agreements. Work by the

[39] This group operates under the Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA). See Chapter 5.

other three companies (GA, NorthStar, and SHINE) to develop domestic production continues to progress toward commercial production.

NNSA initially set an aggressive goal for its cooperative agreement partners to demonstrate a capability to produce 3,000 6-day Ci of Mo-99 per week by the end of calendar year 2013. None of the partners were able to meet this goal. None of these companies will be producing any Mo-99 for commercial sale before Canada stops producing Mo-99 after October 2016; it is also unlikely any of these companies will be producing 3,000 6-day curies of Mo-99 per week on a routine basis before Canada permanently shuts down the NRU reactor in March 2018. One partner (NorthStar) may be able to initiate commercial production of Mo-99 by the end of 2016, but the quantities produced will likely be limited to a few hundred 6-day curies per week, at least initially. In addition, the Mo-99 produced by neutron capture is of low specific activity and cannot be used in conventional Tc-99m generators. NorthStar has developed a new technetium generator system, the RadioGenix Tc-99m Generating System, to utilize low-specific-activity Mo-99.

The potential domestic Mo-99 suppliers described in Sections 4.1 and 4.2 face a variety of technical, financial, regulatory, and market challenges to establishing domestic Mo-99 production. These challenges are described in Section 4.4. The first domestic Mo-99 suppliers to enter the market are likely to have the best chance of survival. Subsequent domestic supplier entrants will have to compete against these first entrants as well as then-existing global suppliers, three of whom are expanding their production capacities. The expanding supply of Mo-99 to the market will put a further downward pressure on prices absent increased demand.

Three of the potential domestic projects (NorthStar, GA, and Northwest) will utilize a reactor that is fueled with HEU (MURR reactor) to produce Mo-99. The University of Missouri has committed to converting its reactor to LEU fuel when such fuel becomes available.[40] But the reactor will continue to operate with HEU fuel until suitable LEU fuel is available.

FINDING 3B: There is currently no domestic production of iodine-131 or xenon-133, but U.S. organizations are developing the capability to produce one or both of these isotopes.

At present, Canada supplies most of the I-131 and Xe-133 used in the United States, and IRE recently began supplying Xe-133 to the United States under an arrangement with Lantheus. Plans by domestic organiza-

[40] The U.S. government is working to develop LEU fuel for use in the MURR reactor and other high-performance research reactors in the United States. However, it will be at least a decade before such fuel is available. See NASEM (2016).

tions to produce I-131 and Xe-133 are described in Section 4.3. MURR has already received a license amendment from the NRC to produce I-131 by irradiating tellurium targets and is currently testing its process. Other potential domestic suppliers may recover I-131 and Xe-133 as part of their Mo-99 production processes.

APPENDIX 4A
FDA Regulatory Submission Process

This appendix describes the steps in obtaining regulatory approval from the Food and Drug Administration (FDA) for the commercial sale of Mo-99 and Tc-99m intended for medical use. These regulatory approval steps are illustrated schematically in Figure 4A.1.

4A.1 DRUG MASTER FILE (DMF)

A DMF is a submission to FDA that provides confidential information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of drugs administered to humans (Niazi, 2009). The submission of a DMF is made at the discretion of the application holder; it is not required by law or FDA regulation. Although a DMF is not a regulatory requirement, it can facilitate the regulatory approval process for an Investigational New Drug (IND) Application, a New Drug Application (NDA), and an Abbreviated New Drug Application (ANDA), if it provides information in support of the quality and safety of the drug. A DMF may

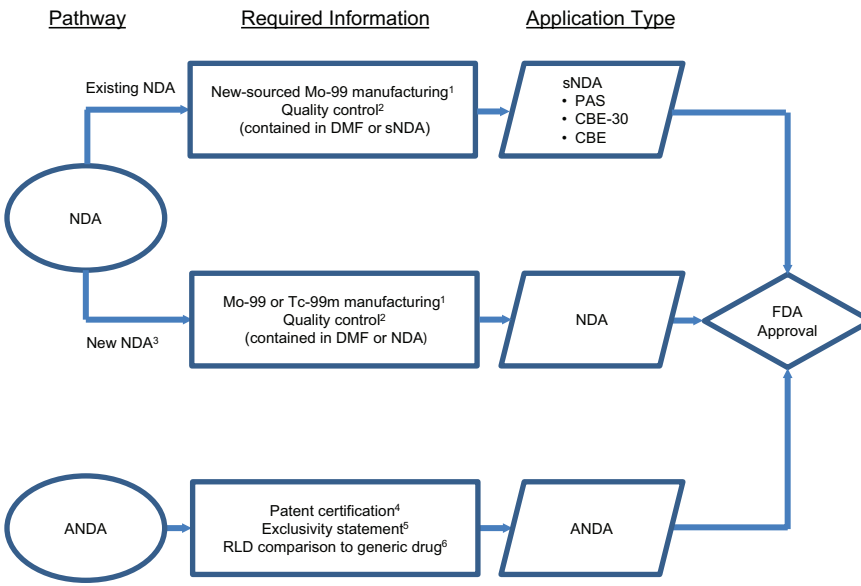


FIGURE 4A.1 FDA approval pathways for Mo-99 and Tc-99m. The flow sheet shows three different approval pathways and the required information and application type for each pathway.

FIGURE 4A.1 Notes

ANDA = abbreviated new drug application; CBE = changes being effected; CBE-30 = changes being effected in 30 days; DMF = drug master file; FDA = U.S. Food and Drug Administration; NDA = new drug application; PAS = prior approval statement; RLD = reference listed drug; sNDA = supplemental new drug application.

[1] Mo-99 manufacturing information includes (1) target information: fabrication & specification, irradiation parameters, number of targets in irradiation position in reactor, placement of targets in reactor and associated neutron fluxes, and target transport hold-up and conditions; (2) target irradiation (one run); and (3) Mo-99 purification process (separate runs).

[2] Quality control information includes (1) Mo-99 qualification: three generator runs for each generator size; comparison of Mo-99 to European Pharmacopeia monograph specification (Note: Mo-99 produced from new technologies may need different/additional specification(s) due to possible different impurity profiles; and potential for different biodistribution may require additional data); and (2) Tc-99m qualification: reconstitute the three most commonly used radiopharmaceutical kits: anionic, cationic, and neutral; Technescan MAG3 (kit for the preparation of Tc-99m mertiatide) should be included in the chosen kits.

[3] A new drug submission is required by the Health Canada for cyclotron-produced Tc-99m. It is unclear whether FDA would require an NDA submission for cyclotron-produced Tc-99m. FDA indicates the following requirements: define cyclotron energy level, target fabrication (Mo-99 enrichment), irradiation parameters, purification process, and Mo-99 qualification with kit performance data.

[4] ANDA applicants are required to submit patent certificates. The need for patent certifications depends on the patents listed for the RLD (the FDA-approved drug product) in the *Orange Book*.

[5] If the RLD is not covered by any market exclusivity at the time of ANDA submission, the ANDA applicant should provide an *exclusivity statement* in the ANDA acknowledging that there is no unexpired exclusivity for the RLD.

[6] The proposed generic drug must be the same as the RLD. *Same* means that the proposed drug has identical active ingredient(s), nonexception excipient(s), dosage form, strength, route of administration, and conditions of use as the RLD, and is bioequivalent to the RLD.

be filed for how Mo-99 is produced. A DMF may be amended when this information changes: for example, when converting target material from HEU to LEU. The DMF can be reviewed by FDA to support new drug applications.[41]

[41] See http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/UCM2007046.

4A.2 NEW DRUG APPLICATION (NDA)

An NDA is a submission to the FDA that allows drug sponsors to formally propose that the agency approve a new drug for sale and marketing in the United States. The NDA includes data gathered during animal studies and human clinical trials of an IND application (see Section 4A.3 for a description).[42]

There are three FDA drug approval pathways described in different sections of the Federal Food, Drug, and Cosmetic Act of 1984:

1. The 505(b)(1) approval pathway is for a new drug and includes human subject research to demonstrate safety and efficacy. Tc-99m pertechnetate is an approved drug, so this pathway would likely not be used for a new drug involving Tc-99m use.
2. The 505(b)(2) approval pathway is for a previously approved drug for which safety and efficacy have been approved by the FDA. For Tc-99m pertechnetate, the manufacturing process is often different. This is the likely pathway for NDAs involving Tc-99m use.
3. The 505(j) pathway is for a drug that must be equivalent to the original reference listed drug (RLD), including ingredients, manufacturing, and dosing.

The provisions of 505(b)(2) were created, in part, to help avoid unnecessary duplication of studies already performed on a previously approved drug—an RLD. As a result, the 505(b)(2) pathway can result in a more economical and faster route to approval compared to a traditional development pathway [such as 505(b)(1)].

4A.2.1 Supplemental NDA (sNDA)

A sNDA is the vehicle for companies to change a label, market a new dosage or strength of a drug, or change the way they manufacture a drug. There are four reporting categories of sNDA (FDA, 2004):

1. Major change: Prior Approval Supplement
2. Moderate change: Supplement–Changes Being Effected in 30 Days
3. Moderate change: Supplement–Changes Being Effected
4. Minor change: to be noted in the next annual report

[42] See the Federal Food, Drug, and Cosmetic Act of 1984 here: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/.

4A2.2 Abbreviated NDA (ANDA)

An ANDA is a submission to the FDA for approval of a generic drug that performs in the same way as a previously approved drug (an RLD).[43] The submission is termed *abbreviated* because it generally does not require the inclusion of animal studies and human clinical trial data to demonstrate the drug's safety and effectiveness.

A generic drug product is one that is comparable to its RLD in active ingredient(s), dosage form, strength, route of administration, and (with certain exceptions) condition of use. The inactive ingredients for generic drug products are allowed to differ from those of the RLD only in preservative, buffer, and/or antioxidant. Additional differences are generally not permitted.[44]

As of August 12, 2015, no ANDA has been submitted to the FDA for Tc-99m generator (for the production of sodium pertechnetate Tc-99m injection) (Duffy, 2015).

4A.3 INVESTIGATIONAL NEW DRUG (IND)

An IND application is submitted to FDA to seek permission to test a new drug (or biologic) in humans. This route is not typically required for sodium pertechnetate Tc-99m injection obtained from Tc-99m generator with Mo-99 produced from either HEU or LEU processes unless a new clinical indication for sodium pertechnetate Tc-99m injection is required to be studied.

4A.4 2016 USER FEES

The Prescription Drug User Fee Act was enacted in 1992 and is renewed every 5 years. It authorizes FDA to collect fees from companies that submit applications or supporting information to applications for production of human drug and biological products. These fees have played an important role in expediting the drug approval process.[45] The 2016 user fees are shown below.

Submission Fees	
NDA full fee (clinical data)	$2,374,200
NDA ½ fee (no clinical data)	$1,187,100
ANDA	$76,030

[43] See http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVDrugsandDevices/.

[44] See https://www.gpo.gov/fdsys/pkg/CFR-2012-title21-vol5/pdf/CFR-2012-title21-vol5-sec314-94.pdf.

[45] See http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/.

CMC Supplements (NDA)	No Fee
CMC Supplements (ANDA)	$29,370
Supplement (with clinical data)	$1,187,100
DMF (supporting NDA)	No fee
DMF (supporting ANDA)	$42,170
Establish and Product Fees	
Establishments (NDA product)	$585,200
Products (NDA product)	$110,370
Establishment (ANDA domestic)	$243,903
Establishment (ANDA foreign)	$258,905
Establishment (DMF domestic)	$40,867
Establishment (DMF foreign)	$55,867

User fees can be waived or reduced in the circumstances described in section 736(d) of the Federal Food, Drug, and Cosmetic Act:

- A waiver or reduction in fees is necessary to protect public health.
- The fees present a significant barrier to innovation due to limited resources or other circumstances.
- The fees exceed the anticipated costs of FDA's review of the new drug applications.

For a small business,[46] FDA will waive the application fee for its first human drug application. However, there are no small business waivers for product or establishment fees.[47]

[46] The Act defines a *small business* as a business that has fewer than 500 employees, including employees of affiliates.

[47] Product and establishment fees are defined here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm#P62_3931.

5

Progress in Eliminating Highly Enriched Uranium and Remaining Obstacles

This chapter addresses the final charge of the statement of task for this study, which directs the Academies to provide

> An assessment of the progress made by the Department of Energy and others to eliminate worldwide use of highly enriched uranium in reactor targets and medical isotope production facilities.[1] This assessment should identify key remaining obstacles for eliminating highly enriched uranium from reactor targets and medical isotope production facilities and recommend steps that could be taken to overcome the identified obstacles.

Most of the global supply of molybdenum-99 (Mo-99) for medical use is produced by irradiating targets containing highly enriched uranium (HEU) in research reactors (see Chapter 2). Following irradiation, targets are processed to recover Mo-99 and prepare it for commercial sale. The waste from target processing also contains HEU, which must be recovered, stored, and eventually disposed of. This chapter focuses on the elimination of HEU from both targets and waste.

The "others" referred to in the study charge include the following Mo-99/Tc-99m supply chain participants (see Chapter 2):

- Target suppliers: The companies that manufacture the HEU targets used for producing Mo-99.

[1] As noted in Chapter 1, this report does not address the elimination of HEU from reactor fuel. As noted in Chapter 3, some Mo-99 is currently produced in an HEU-fueled reactor.

- Irradiation services suppliers: Operators of the research reactors used to irradiate these targets to produce Mo-99.
- Mo-99 suppliers: Companies that purchase targets, arrange for these targets to be irradiated in research reactors, and operate the facilities used to process these targets and recover Mo-99 for commercial sale.

Most of the global supply of Mo-99 is produced by five suppliers (see Chapter 3):

- Australian Nuclear Science and Technology Organisation (ANSTO), Australia
- Institut National des Radioéléments (IRE), Belgium
- Mallinckrodt, Netherlands
- Nordion, Canada
- NTP Radioisotopes (NTP), South Africa

IRE, Mallinckrot, and Nordion produce Mo-99 exclusively with HEU targets; NTP produces Mo-99 with both HEU and low enriched uranium (LEU) targets; and ANSTO produces Mo-99 exclusively with LEU targets. Chapter 3 provides additional information about these suppliers.

One current global Mo-99 supplier told the committee that global suppliers were spending between $25 million and $40 million each to eliminate HEU from Mo-99 production. The committee cannot verify this estimate because suppliers consider their conversion-related costs to be business-proprietary information.

5.1 AMERICAN MEDICAL ISOTOPES PRODUCTION ACT

The American Medical Isotopes Production Act of 2012 (P.L. 112-239) contains provisions to eliminate the use of HEU for medical isotope production and encourage the development of U.S. domestic supplies of Mo-99 and associated isotopes. Section 3174 of the Act specifies that

> Effective 7 years after the date of enactment of the American Medical Isotopes Production Act of 2012, the [Nuclear Regulatory] Commission may not issue a license for the export of highly enriched uranium from the United States for the purposes of medical isotope production.[2]

[2] The export license cutoff date can be extended for up to 6 years if the Secretary of Energy certifies to Congress that "there is insufficient global supply of molybdenum-99 produced without the use of highly enriched uranium available to satisfy the domestic United States market; and . . . the export of United States-origin highly enriched uranium for the purposes

Three of the five current global Mo-99 suppliers (IRE, Mallinckrodt, and Nordion) use U.S.-origin HEU and are therefore subject to this provision.[3] Their conversion-related activities are described later in this chapter.

Section 3173 of the 2012 Act also specifies that

> The Secretary [of Energy] shall carry out a technology-neutral program[4]—(A) to evaluate and support projects for the production in the United States, without the use of highly enriched uranium, of significant quantities of molybdenum-99 for medical uses; (B) to be carried out in cooperation with non-Federal entities . . . .

And that

> The Secretary shall carry out a program to provide assistance for—(1) the development of fuels, targets, and processes for domestic molybdenum-99 production that do not use highly enriched uranium; and (2) commercial operations using the fuels, targets, and processes described in paragraph (1).

The Department of Energy's National Nuclear Security Administration (DOE-NNSA) established a technology-neutral cooperative agreement program to support domestic production of Mo-99 without HEU. It provides up to $25 million in cost sharing per agreement with potential domestic suppliers to demonstrate a capability to make at least 3,000 6-day Ci per week by 2013.[5] As noted in Chapter 4, agreements were established initially with B&W (now BWX Technologies) and GE-Hitachi in 2009 and NorthStar Medical Radioisotopes and SHINE Medical Technologies in 2010.[6]

DOE-NNSA also signed an agreement with General Atomics (GA) in 2015 to establish production of Mo-99 in cooperation with Nordion and the University of Missouri Research Reactor Center[7] (MURR). Mo-99 will be produced in the MURR reactor, which is currently fueled with HEU. The reactor will convert to LEU once a suitable fuel has been developed. The development of this fuel is under way and is not expected to be completed until at least 2027 (NASEM, 2016).

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of medical isotope production is the most effective temporary means to increase the supply of molybdenum-99 to the domestic United States market."

[3] NTP uses South African–origin HEU to produce Mo-99. See Chapter 3.

[4] That is, a program that does not favor one technology or production method for Mo-99 over another.

[5] None of the companies that established cooperative agreements with NNSA have met this capability demonstration requirement. See Chapter 4.

[6] B&W and GE-Hitachi suspended work on these projects in 2014 and 2012, respectively. See Chapter 4.

[7] Nordion has contracted with GA and MURR to carry out these activities.

DOE-NNSA has also established task-order agreements with IRE, Mallinckrodt, and NTP to provide resources and technical assistance for their conversion to LEU production. Additional information about these activities is provided later in this chapter.

5.2 TARGET CONVERSION

Most[8] of the HEU targets used to produce Mo-99 for medical use have a *sandwich* design (see Figure 2.5 in Chapter 2). The *meat* of the sandwich contains uranium-aluminum alloy (UAlx)[9] particles dispersed in aluminum alloy matrices. The meat is encapsulated in an aluminum alloy *cladding* that provides a barrier to the release of fission gases from the target meat and transfers heat from the meat to the reactor coolant. Targets are manufactured to meet suppliers' particular size specifications but are typically 3-5 cm in width, 10-15 cm in length, and about 1-2 mm in thickness.

IRE, Mallinckrodt, and NTP have contracted with CERCA to develop and manufacture LEU targets having this same sandwich design, but with modifications to the target meat and cladding to accommodate LEU. Nordion has contracted with GA to develop LEU targets for producing Mo-99 at MURR. All of these target development efforts are described in the following sections.

5.2.1 IRE and Mallinckrodt

IRE and Mallinckrodt initiated the development of LEU targets in 2010. Both companies have completed their target development efforts and are receiving commercial quantities of LEU targets from CERCA. IRE plans to begin commercial production of Mo-99 from LEU targets in 2017 and to be fully converted to LEU production in 2019. Mallinckrodt plans to be fully converted to LEU targets by the end of 2017.[10]

A LEU target having the same design and dimensions as an HEU target would produce about 5 times less Mo-99 because it would contain less

[8] Nordion uses pin-type HEU targets to produce Mo-99. Use of this target will be discontinued after CNL ceases production of Mo-99 in the NRU reactor in October 2016. See Chapters 3 and 7.

[9] UAl_2 and aluminum powder are the starting materials for dispersion targets. These materials are transformed to UAl_3/UAl_4 during the target fabrication process. The final ratio is a function of the specific processing steps employed. The resulting compound (or intermetallic compound) is referred to as "UAlx."

[10] That is, Mallinckrodt will be able to produce Mo-99 for commercial sale using LEU targets and its customers will have the necessary regulatory approvals to use this Mo-99 in technetium generators. Mallinckrodt does not expect to have a large remaining inventory of HEU targets after conversion is complete.

U-235 and more U-238.[11] IRE and Mallinckrodt have made two modifications to their LEU target designs to reduce this Mo-99 production penalty:

- The density of uranium in the target meat was increased to 2.6-2.8 grams uranium per cubic centimeter (gU/cc) by increasing the ratio of UAlx alloy to aluminum dispersant. (The density of uranium in the meat of a HEU target is about 1.9 gU/cc.)
- The volume of the target meat was increased by increasing its target/cladding thickness or increasing target length.

A harder aluminum alloy cladding was also used in the LEU targets to improve their manufacturability. The harder cladding minimizes distortion of the target meat during rolling operations.

Taken together, these design changes and changes in the irradiation protocol increased Mo-99 yields from LEU targets to about 80 percent of the yields from HEU targets. These companies plan to take additional steps to maintain their current Mo-99 production capacities (3,500 6-day Ci per week for Mallinckrodt and 3,600 6-day Ci per week for IRE; see Chapter 3) once they start producing with LEU targets: both companies plan to irradiate and process additional LEU targets, and Mallinckrodt also plans to irradiate targets in higher-flux positions and to increase Mo-99 recovery efficiencies.

5.2.2 NTP

NTP initiated the development of LEU targets in 2007 and began the routine commercial production of Mo-99 from these targets in June 2011. Approximately half of NTP's processing runs in 2015 utilized LEU targets (see Chapter 3).

NTP converted from 45 percent HEU targets to 19.75 percent LEU targets, so it only had to contend with a factor of 2.5 yield penalty[12] for Mo-99 production. NTP was able to offset some of this yield penalty by increasing the density of uranium in the target meat. At that time the company chose not to make size changes to its targets to further reduce this penalty.

Mo-99 yields from NTP's LEU targets are 20 to 25 percent lower than

[11] Neutron capture losses in a LEU target are about 15 percent higher than in a comparable HEU target (Kaichao Sun and Lin-Wen Hu, MIT Nuclear Reactor Laboratory, written communication, April 28, 2016). U-238 captures neutrons to produce actinides, making fewer neutrons available for fissioning U-235 to produce Mo-99. U-238 fission can also produce Mo-99, but the thermal fission cross section for U-238 is many orders of magnitude lower than for U-235.

[12] Assuming a neutron shielding loss of about 15 percent. See Footnote 10.

yields from its HEU targets. NTP is irradiating and processing additional LEU targets to maintain its current Mo-99 production capacity of 3,000 6-day Ci per week (see Chapter 3).

5.2.3 Nordion

GA is developing a LEU target for Nordion that is radically different in design than the HEU pin targets that Nordion now uses to produce Mo-99. The target contains LEU in the form of pellets of uranium oxide encapsulated in zirconium cladding and designed to fit and be cooled within locations in the graphite reflector in the MURR reactor (see Chapter 4). The design of the target is proprietary and details were not revealed to the committee.

The target is still in development stages and has not yet been qualified for use (see Section 5.3). GA told the committee that commercial production of Mo-99 with this technology can begin in the first half of 2018 if development and licensing activities go forward as planned (see Chapter 4).

5.2.4 Other Mo-99 Suppliers

To the committee's knowledge, the Russian Federation is the only other country besides these discussed above that uses HEU to produce Mo-99. Russian-origin HEU is currently being used to produce Mo-99 at the Karpov Institute in Obninsk and the Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad (see Chapter 3).[13] Both of these institutes produce Mo-99 by irradiating HEU targets in HEU-fueled reactors.

At present, the Russian Federation produces only enough Mo-99 for its own use and for limited export (see Chapter 3). Russia has expressed an interest in becoming a global Mo-99 supplier by expanding production at RIAR (see Chapter 3).

RIAR has carried out preliminary design work on a LEU target that it estimates could also be used to produce Mo-99. However, Russia has not made a public commitment or announced a schedule for converting its Mo-99 production to LEU targets. Such conversion would also require modifications to RIAR's target processing facilities, which could be costly, and additional regulatory approvals in export markets to use Russian-produced Mo-99.

[13] Mo-99 production is under development at the Kurchatov Institute of Atomic Energy in Moscow using a LEU-fueled aqueous solution reactor (ARGUS). Production of Mo-99/Tc-99m at other Russian institutes is discussed in Zhuikov (2014).

5.3 IRRADIATION FACILITY CONVERSION

The LEU targets described above must be qualified in each reactor that will be used to produce Mo-99 for medical use. *Qualification* is a multistep process for ensuring that the target meets preestablished technical and regulatory specifications with respect to, for example,

- Fission density
- Heat generation in the target meat from uranium fission and other nuclear reactions
- Target meat and cladding temperatures
- Target meat and cladding mechanical stability

The qualification process requires one or more test irradiations of a prototypic target under the conditions it is likely to encounter in the reactor, followed by physical examinations to identify material or structural changes. The overall objectives of this process are to ensure that target performance meets nuclear safety requirements and to obtain the information needed to develop target irradiation specifications.

The testing plan and analysis of results must be reviewed and approved by regulatory authorities before the target is considered to be qualified for use. The time required for target qualification can vary from a few months to over a year, and the time also depends on target design and fabrication requirements, as well as the availability of reactors and post-irradiation examination facilities to carry out the necessary work.

The LEU targets developed by IRE, Mallinckrodt, and NTP are similar in design to already-qualified HEU targets; consequently they have similar performance specifications and should therefore be easier to qualify. Indeed, NTP has already qualified its LEU targets for use in the SAFARI-1 reactor and, as noted previously, is producing Mo-99 from these targets on a routine basis. IRE and Mallinckrodt have qualified their targets in all of the reactors they currently use to produce medical isotopes with HEU targets (see Chapter 3).[14] However, neither of these suppliers is currently making Mo-99 for commercial sale with their LEU targets.

The LEU target being developed by GA for selective gaseous extraction has a different design than Nordion's already-qualified HEU target. This target has not yet been qualified for use.

[14] IRE also informed the committee that it plans to qualify its LEU targets in the future for use in the LV-15 Reactor (Czech Republic) and FRM II (Germany).

5.4 PROCESSING FACILITY CONVERSION

Suppliers have made or are making changes to their processing facilities and process flow sheets to accommodate LEU targets. Those changes are described in the following sections.

5.4.1 IRE, Mallinckrodt, and NTP

IRE, Mallinckrodt, and NTP use similar aqueous chemical processes (described in Chapter 2) to dissolve HEU targets and recover Mo-99: The targets are placed in a dissolver vessel and a strong base (sodium hydroxide [NaOH]) is added to dissolve aluminum in the target meat and cladding. Uranium precipitates and is separated from the process solutions by filtering. These solutions are further processed using ion exchange and distillation to separate and purify Mo-99.

The same chemical processes can be used to recover Mo-99 from LEU targets, but some process steps must be modified to accommodate changes (described previously) in target mass and composition. Not all of these process changes were anticipated prior to cold and hot testing.

Filtering of uranium after target dissolution was a more difficult process step for LEU targets than initially anticipated. The filters were being clogged prematurely by a fine-grained precipitate, subsequently identified as magnesium hydroxide. The source of the magnesium was eventually traced to the new alloy cladding used in the LEU targets.

This filtering problem was overcome by redesigning the uranium filters and/or filtering processes to accommodate the precipitate and the higher uranium loadings associated with LEU targets. Nevertheless, some suppliers have reported to the committee that LEU filtering remains a difficult process step.

Some Mo-99 suppliers reported that the liquids from LEU target dissolution contained higher-than-expected levels of radioactive tungsten[15] (tungsten-187 [W-187]). This isotope was not removed from the liquids and subsequent processing steps, so it ended up in the purified Mo-99 solutions. The source of tungsten was eventually traced to the target fabrication process used by CERCA: tungsten was introduced during TIG welding[16] of the target cladding; the introduced tungsten was activated to W-187 during target irradiation. CERCA changed its fabrication process to reduce tungsten incorporation into the target.

[15] Molybdenum and tungsten are in the same chemical family and thus have similar chemical properties.

[16] Tungsten inert gas welding. A tungsten electrode is used to produce the weld. The electrode is designed to be nonconsumable, but small amounts of tungsten can nevertheless be introduced into the welded material.

Neutron capture by U-238 in a LEU target produces about 50 times[17] more actinides (e.g., plutonium) per 6-day Ci in LEU targets than in HEU targets. These additional actinides are removed during target processing. However, one producer (Mallinckrodt) had to develop a method to identify individual actinides and their contributions to total radioactivity in purified Mo-99 at the request of the U.S. Food and Drug Administration.[18]

The current status of global Mo-99 suppliers' efforts to convert their target processing to handle LEU targets is summarized below:

- NTP processes LEU and HEU targets in different dissolver vessels but uses common hot cells for some other processing steps. (Processing equipment is replaced after each run.) NTP told the committee that it could convert entirely to Mo-99 production with LEU targets in about 8 days (the amount of time required to irradiate LEU targets in the reactor) if demand warranted.
- IRE has two sets of hot cells for producing Mo-99. It is producing Mo-99 from HEU targets in one set of hot cells while it establishes Mo-99 production from LEU targets in the other set of hot cells. IRE plans to begin producing Mo-99 with LEU targets in 2017 and to be completely converted to LEU targets by the end of 2019. The company also plans to bring a new processing facility online in the 2020s.
- Mallinckrodt also has two sets of hot cells for producing Mo-99. The company plans to begin hot testing its process for producing Mo-99 from LEU targets in one set of hot cells while it produces Mo-99 for commercial sale from HEU targets in the other set. The company plans to begin producing Mo-99 for commercial sale with LEU targets in one set of hot cells, and it plans to convert its second set of hot cells to produce Mo-99 with LEU targets once all of its HEU targets are used up.

5.4.2 Nordion

The LEU targets being developed by GA for Nordion will be processed in hot cells at MURR using selective gaseous extraction (see Chapter 4). A gas containing chlorine and oxygen will be passed through the irradiated target pellets to extract Mo-99 and some other fission isotopes. These extracted products will be transported to Nordion in Kanata, Ontario, Canada, for purification.

[17] The ratio of the U-238 atoms to U-235 atoms in LEU is ~4:1 compared to ~0.08:1 in HEU.

[18] Roy Brown, Mallinckrodt, verbal communication, October 22, 2015.

The extraction process is still in developmental stages. Processing of small batches of irradiated target material has been carried out at MURR, and information from these tests is being used to refine the technology. As noted previously, full-scale testing will not take place until MURR receives regulatory approvals. These approvals are not likely before mid-2017 at the earliest.

5.5 WASTE MANAGEMENT

The production of Mo-99 by aqueous chemical processing of irradiated HEU or LEU targets produces the following four waste streams:

- Uranium solids (alkaline target dissolution only). These solids, which contain LEU or HEU, are placed into long-term storage for reuse or disposal.
- Processing off-gases, primarily the noble gases xenon (Xe-131m, Xe-133, Xe-133m, and Xe-135) and krypton (Kr-85). These gases are stored for several months to allow time for radioactive decay. Following storage, the gases are vented to the atmosphere.
- Process liquids from target dissolution. These liquids contain fission products and neutron activation products produced during target irradiation. These wastes are typically solidified and packaged for disposal.
- Other solid wastes produced during target processing: for example, radioactively contaminated processing equipment. These wastes are also packaged for disposal.

Each Mo-99 supplier has a different approach for managing these wastes, depending on the regulations and storage/disposal facilities available in host countries. Production of Mo-99 by aqueous processing of LEU targets will produce these same types of waste streams, but some waste volumes will be larger. Current global Mo-99 suppliers are developing additional capacity to manage these wastes as part of their conversion efforts.

Production of Mo-99 from GA's selective gaseous extraction process will also produce solid and gaseous waste streams, but their compositions and volumes will likely be different than those produced by conventional aqueous processing of irradiated LEU plate targets. GA did not provide enough information to the committee to allow it to evaluate waste throughputs from its process.

Section 2.6 in Chapter 2 describes the important role that radioactive xenon (radioxenon) plays in compliance monitoring for the Comprehensive Nuclear Test Ban Treaty. The conversion of Mo-99 production from HEU to LEU targets will not change radioxenon or other off-gas production

levels; Mo-99 and radioxenon will be produced in the same relative quantities regardless of whether HEU or LEU is used. Mo-99 suppliers can reduce their radioxenon emissions if desired by increasing storage hold-up times before venting these gases to the atmosphere.

The four global Mo-99 suppliers that use HEU targets (IRE, Mallinckrodt, Nordion, NTP) will still possess large quantities of weapons-grade waste[19] even after they have converted to Mo-99 production using LEU targets. These suppliers are responsible for managing this waste consistent with the laws and regulations in their host countries. The Academies (NRC, 2009) recommended that the DOE increase its focus on eliminating the HEU wastes from Mo-99 production from U.S.-origin HEU by examining options for downblending this waste or returning it to the United States. This is a potentially difficult recommendation to execute because DOE does not own this waste and cannot compel suppliers to downblend or return it to the United States.

The DOE-NNSA Office of Material Management and Minimization has two programs that are addressing this recommendation:

- The Nuclear Material Removal Program supports the return to the United States of U.S.-origin HEU that was used in targets for the production of Mo-99, provided the material meets the receiving facility criteria.
- The Gap Program can support the in-country disposition of these materials.

NNSA reported to the committee[20] that it is working with several countries to disposition this target residual material (TRM) and has made some progress:

- Canada has agreed to return the liquid HEU TRM that is now being stored at Canadian Nuclear Laboratories (CNL) to the United States. Shipments were scheduled to begin in the summer of 2016 and continue for about 18 months.[21] Canada is evaluating disposition options for its solidified TRM.
- Argentina completed the in-country downblending of its HEU TRM in March 2016, and Indonesia completed in-country downblending of its HEU TRM in August 2016. This downblending was carried out with DOE's technical and financial support.

[19] Irradiation of HEU targets for Mo-99 production typically consumes 3 percent or less of the HEU.

[20] Rilla Hamilton, DOE-NNSA, written communication, April 20, 2016.

[21] These shipments had not begun as of September 1, 2016.

- DOE has consulted with Belgium about the possible return of HEU TRM to the United States. Belgium has not yet decided on a disposition pathway for this material.
- Netherlands has no plans to return its HEU TRM to the United States; its plans, if any, for downblending this waste are unclear.

Several other countries have produced Mo-99 with non-U.S.-origin HEU: Pakistan, Russian Federation, and South Africa. NNSA reported to the committee that "South Africa remains unreceptive to detailed discussions on [downblending this material]." DOE has not engaged Pakistan or the Russian Federal governments in any discussions on downblending.

5.6 ASSISTANCE FROM DOE-NNSA

As noted in Section 5.1 of this chapter, DOE-NNSA is providing financial support to some current global Mo-99 suppliers. Funding and authorization for this NNSA-supported work is provided by Congress through annual appropriations.[22]

Two types of support are being provided: (1) technical assistance from U.S. national laboratories to address conversion-related issues (the contracts and work scopes for this assistance are not made public), and (2) task-order agreements administered by the U.S. national laboratories to help accelerate suppliers' conversion efforts. Specific task orders are proposed by the suppliers and must be agreed to by the laboratory and DOE-NNSA before any government funding is provided. The technical and financial details of the agreements are proprietary; however, the committee was able to obtain general information about some of the work being carried out under these agreements from individual suppliers.

To date, NNSA has provided the following cost-shared support to the following organizations:

- IRE: $9.4M
- Mallinckrodt: $4.6M
- NTP and the South African Nuclear Energy Corporation (NECSA): $24.3M

5.6.1 IRE

IRE has received financial support to address conversion-related research and development issues and LEU target qualification.

[22] Rilla Hamilton, DOE-NNSA, written communication, June 8, 2016.

5.6.2 Mallinckrodt

Mallinckrodt has received financial support for several purposes:

- Supporting the purchase of an additional transport cask to ship irradiated LEU targets from reactors to Mallinckrodt's processing facility in Petten, the Netherlands. This additional cask is needed to transport the larger numbers of irradiated LEU targets required to maintain current Mo-99 production capacity of 3,500 6-day Ci per week.
- LEU target testing at Mallinckrodt's production facility in Petten.
- Technical services from Pacific Northwest National Laboratory on techniques for making alpha measurements on Mo-99 to meet regulatory requirements.
- Purchase of Mo-99 from other suppliers when one of Mallinckrodt's hot cell lines is shut down for testing and conversion to Mo-99 production with LEU targets.

5.6.3 NTP

NTP has received financial support for the acceleration of its conversion project. The support to NECSA is being used to evaluate treatment of uranium residues and the higher volumes of waste from Mo-99 production without HEU. NECSA has subcontracted with ANSTO to complete this work because ANSTO has extensive experience with waste management techniques. NNSA has not provided any funding directly to ANSTO.

5.6.4 General Atomics

GA is one of five cooperative agreement partners with DOE-NNSA to develop domestic production of Mo-99 without HEU. DOE-NNSA is providing up to $25 million in cost sharing to GA to develop a domestic production capability in cooperation with Nordion and MURR. Mo-99 will be produced with LEU targets, as noted previously. This partnership is described in more detail in Chapter 4. To date, NNSA has provided $9.7M to GA under this agreement.

5.7 ASSISTANCE FROM OTHER ORGANIZATIONS

A number of other organizations are promoting the elimination of HEU from medical isotope production through a variety of means. Some of these efforts were discussed in previous chapters of this report. These efforts include the following:

- The U.S. Nuclear Regulatory Commission (NRC) and the Food and Drug Administration (FDA) have committed to expediting the review of license amendments and applications for the production and commercial sale of Mo-99 produced without HEU.
- The U.S. technetium generator supplier Lantheus Medical Imaging is promoting the commercial sale of LEU-sourced technetium generators[23] in North American markets. It was the first company to sell these technetium generators in the United States (the first generator sales were in 2011). Lantheus has manufactured over 95 percent of the LEU-sourced technetium generators sold in the United States since early January 2013. The company has also produced an educational video and is offering webinars to its customers on Mo-99 made without HEU.
- The Centers for Medicare & Medicaid Services (CMS) have approved a $10 add-on payment under the Hospital Outpatient Prospective Payment System for use of Tc-99m doses prepared from non-HEU sources. This payment is described in Sidebar 5.1.
- UPPI, an independently owned group of university-based nuclear pharmacies, is implementing a strategy, referred to as the UPPI LEU walk, to convert its 83 nuclear pharmacies to use Mo-99 from non-HEU sources. It is also taking action to encourage private payers to offer the $10 add-on reimbursement for Tc-99m doses prepared from non-HEU sources.
- The Veterans Administration reinforced its original mission for preferential procurement of non-HEU-based Mo-99 utilization in a March 28, 2016, memorandum addressed to the 115 Veterans Administration Medical Centers performing nuclear medicine studies.
- The White House Office of Science and Technology Policy has established the Mo-99 stakeholders working group to coordinate efforts across the U.S. government and the private sector to establish a stable domestic supply of Mo-99 for medical use and eliminate the civilian use of HEU in targets and target processing facilities used to produce Mo-99. The group holds meetings in Washington, DC, about three times per year.
- NNSA sponsors an annual Mo-99 Topical Meeting to discuss progress toward achieving non-HEU production of Mo-99 with Mo-99/Tc-99m supply chain participants and other interested parties.
- The Organisation for Economic Co-operation and Development's Nuclear Energy Agency established a High Level Working Group on the Security of Supply of Medical Radioisotopes (HLG-MR).

[23] At least 95 percent of the Mo-99 in these generators is made using LEU targets.

The group is comprised of representatives from countries with interests in medical isotope production and the International Atomic Energy Agency (IAEA). The HLG-MR coordinates efforts to improve the reliability of Mo-99 supplies and to monitor conversion efforts (see Section 2.7.1 in Chapter 2).

- The IAEA convenes meetings of technical experts to discuss issues related to the elimination of HEU from medical isotope production. In October 2015, for example, the agency sponsored the technical meeting entitled *Global Capabilities for the Production and Manufacture of Molybdenum-99 Targets*.

The activities of these organizations serve various purposes and impact different parts of the Mo-99/Tc-99m supply chain. For example, the NRC and FDA efforts are intended to accelerate the elimination of HEU from Mo-99 production at the front end of the supply chain. The Lantheus, UPPI, and CMS efforts are intended to stimulate commercial demand for Mo-99/Tc-99m produced without HEU targets. Other activities provide further opportunities for technical exchanges and discussions on elimination of HEU in Mo-99 production and improving global Mo-99 supply reliability.

Several participating States in the 2016 Nuclear Security Summit (NSS) pledged[24] to make "every effort to achieve further progress with regard to minimizing and eliminating the use of highly enriched uranium (HEU) in civilian applications." These efforts include LEU alternatives for medical isotope production:

- Where technically possible convert existing molybdenum-99 (Mo-99) medical isotope production facilities to use 100% LEU targets by December 31, 2017.
- Focus efforts globally to expedite licensing approval of non-HEU-based Mo-99 and its daughter product technetium-99m (Tc-99m).
- Consistent with international trade agreements and the schedules of the major Mo-99 producers to convert to LEU targets, and subject to applicable domestic laws, end imports and exports of HEU-based Mo-99 unless the members of the Organization [sic] for Economic Cooperation and Development's Nuclear Energy Agency High Level Group on the Security of Supply of Medical Radioisotopes deem that the licensed global non-HEU production capacity of Mo-99 and its daughter product Tc-99m have become insufficient and unsustainable.

[24] NSS 2016: Gift Basket on Minimizing and Eliminating the Use of Highly Enriched Uranium in Civilian Applications. Available at http://static1.squarespace.com/static/568be36505f8e2af8023adf7/t/56febac0b654f939134d97d1/1459534530157/HEU+Minimization+Gift+Basket+for+NSS+2016.pdf.

SIDEBAR 5.1
Centers for Medicare & Medicaid Services $10.00 Add-On

In 2013, the Centers for Medicare & Medicaid Services (CMS) established a $10.00 per dose "add-on" reimbursement for imaging studies on Medicare Part B patients (i.e., outpatients in hospitals or clinic-based imaging centers) that utilize Tc-99m from non-HEU sources. This reimbursement is provided directly to the providers of the imaging studies, not to technetium generator suppliers or Mo-99 suppliers. It is intended to cover the incremental cost of Tc-99m produced without HEU under full-cost recovery principles.

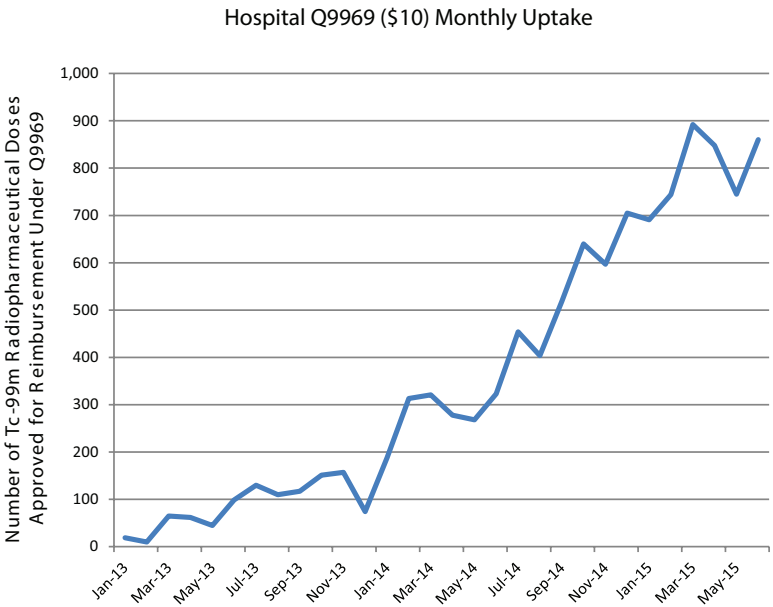

FIGURE S5.1 Number of Tc-99m doses approved for reimbursement from hospitals receiving the $10.00 add-on payment from CMS under code Q9969. CMS data show a positive trend toward utilization of the $10 add-on reimbursement. However, utilization remains low compared to total Tc-99m radiopharmaceutical doses approved by Medicare Part B. See discussion in text. SOURCE: Daniel J. Duvall, MD, Chief Medical Officer, CPI.

To qualify for this add-on reimbursement, the Tc-99m dose must be at least 95 percent non-HEU sourced. The provider requests reimbursement by entering the designated Healthcare Common Procedure Coding System (HCPCS) code, Q9969,[a] on the procedure invoice. The provider must also establish a paper trail to document the non-HEU provenance of the Tc-99m dose. This paper trail starts at the Tc-99m manufacturing facility and includes the nuclear pharmacy that dispensed Tc-99m dose.

CMS data (see Figure S5.1) show a positive trend toward utilization of the $10 add-on reimbursement. However, utilization remains low when compared to the total number of Tc-99m radiopharmaceutical doses approved for reimbursement for Medicare Part B patients. In 2014, the first full year that reimbursement was available, the CMS Medicare Part B database shows that reimbursement claims for about 1,800 doses of Tc-99m radiopharmaceuticals were approved under the Q9969 code. This is about 0.1 percent of the 1,750,000 Tc-99m radiopharmaceutical doses approved by Medicare Part B in 2014. In 2015, the number of Tc-99m radiopharmaceutical doses approved for reimbursement was estimated to be about 9,600.[b]

Many providers contend that the administrative costs required to qualify for this add-on reimbursement are greater than the reimbursement itself. These costs, whether real or perceived, probably reduce overall reimbursement requests, even at imaging centers that utilize Tc-99m from non-HEU sources. CMS has expressed a willingness to increase the add-on reimbursement amount, but CMS reported that industry has so far been unwilling to provide the cost data needed to justify such an increase.

CMS expects that the add-on reimbursement amount will decrease as costs for producing Tc-99m without HEU are incorporated into base payments for Tc-99m studies. CMS plans to eliminate the add-on reimbursement altogether once the market has transitioned away from HEU use to produce Mo-99/Tc-99m. As noted elsewhere in this chapter, this transition will likely occur in 2017 or later.

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[a] HCPCS 2016 Code Q9969: Tc-99m From Non-Highly Enriched Uranium Source, Full Cost Recovery Add-On, Per Study Dose. See https://www.hipaaspace.com/Medical_Billing/Coding/Healthcare.Common.Procedure.Coding.System/Q9969.

[b] CMS data presented to the committee. Duvall (2015) reported that about 800 monthly reimbursement requests were being received in mid-2015 for Medicare Part B patients. They did not report the number of requests approved for reimbursement, only the number submitted. Annualized, this would constitute 9,600 Tc-99m radiopharmaceutical doses per year. Data for Tc-99m radiopharmaceutical doses approved by Medicare Part B in 2015 were not available at the time this report was being finalized for publication.

- Ensure that any exports of HEU are done within the existing legal and regulatory frameworks and are either (1) for the sole purpose of producing needed medical isotopes or tied to a pledge from the facility receiving the HEU for demonstrated actions to convert to the use of LEU, or (2) for the specific purpose of disposition in the receiving country by blending down that material to LEU or by other secure means.

These efforts were agreed to by several States that host Mo-99/Tc-99m supply chain facilities, including Argentina, Australia, Canada, Czech Republic, Indonesia, the Netherlands, Poland, Republic of Korea, and the United States.

5.8 FINDINGS AND RECOMMENDATIONS

FINDING 5A: The American Medical Isotopes Production Act of 2012 is accelerating the elimination of worldwide use of U.S.-origin highly enriched uranium in targets and medical isotope production facilities. There are no insurmountable obstacles to the elimination of highly enriched uranium from medical isotope production. The four global molybdenum-99 suppliers that use highly enriched uranium have committed to eliminating its use in reactor targets and medical isotope production facilities and are making uneven progress toward this goal. This progress is being facilitated by financial support from the U.S. government and technical support from U.S. national laboratories.

The HEU-export elimination provision in the American Medical Isotopes Production Act of 2012 provides strong incentives for current Mo-99 suppliers that use U.S.-origin HEU—IRE, Mallinckrodt, and Nordion—to eliminate its use from medical isotope production. NTP is not affected by this provision because it uses South African–origin HEU to produce Mo-99. Nevertheless, NTP showed early leadership by being the first global supplier to demonstrate that it is technically and commercially feasible to convert its facilities to produce Mo-99 using LEU targets. NTP was following in the footsteps of ANSTO, which has always produced Mo-99 with LEU targets and was the first supplier to demonstrate large-scale (>1,000 6-day Ci per week) production of Mo-99 with LEU targets.

NNSA is providing financial support and U.S. national laboratories have also provided technical support to some current global suppliers to convert to Mo-99 production using LEU targets. NNSA's financial and technical assistance to IRE, Mallinckrodt, and NTP, described in Section 5.6 in this chapter, have helped these suppliers overcome technical chal-

lenges associated with conversion. The availability of this assistance likely accelerated the conversion schedules for these suppliers.

The committee judges that there are no insurmountable obstacles to the elimination of HEU from medical isotope production. As noted above, ANSTO and NTP have demonstrated that it is technically and economically feasible to produce Mo-99 without HEU. IRE and Mallinckrodt plan to use the same types of LEU targets and aqueous chemical processes that are currently being used by ANSTO and NTP to produce greater than 1,000 6-day Ci per week of Mo-99 for commercial sale on a routine basis.

Nevertheless, progress toward elimination of HEU from medical isotope production has been uneven:

- ANSTO has always produced Mo-99 without HEU.
- NTP converted from HEU to LEU targets over about a 5-year period (2007-2011) and now sells commercial quantities of Mo-99 produced with LEU targets.
- IRE initiated development of LEU targets in 2010 and plans to begin commercial production of Mo-99 with these targets in mid-2017, an elapsed time of about 8 years.
- Mallinckrodt initiated development of LEU targets in 2010 and plans to convert to LEU targets by the end of 2017, an elapsed time of about 8 years.
- Nordion, in cooperation with GA and MURR, initiated the development of LEU targets in late 2015 and plans to begin commercial production of Mo-99 with these targets in the first half of 2018, an elapsed time of about 2.5 years. As noted below, the committee views this schedule as optimistic.

This unevenness is primarily the result of suppliers' commitments to conversion and their resourcefulness in overcoming the unanticipated problems that were described in Section 5.4 of this chapter.

IRE and Mallinckrodt must complete several tasks before they can begin routine commercial production of Mo-99 with LEU targets:

- Hot testing of the Mo-99 production process with LEU targets needs to be completed. This testing may reveal additional process problems that will need to be resolved. For example, both ANSTO and NTP had to make adjustments to their process flow sheets for LEU targets to raise Mo-99 separation efficiencies to levels characteristic for HEU targets (typically 80 to 90 percent).
- A dedicated LEU target processing line needs to be set up and tested in each facility.

- Full-scale Mo-99 production runs with LEU targets will need to be made to provide data for Drug Master Files[25]; additionally, three full-scale runs will need to be made to provide Mo-99 to technetium generator suppliers for preparation of a New Drug Application (NDA) or supplemental NDA (sNDA).
- The NDA or sNDA needs to be reviewed and approved by regulatory authorities. Inspections of the Mo-99 production facilities may be carried out as part of the approval process.

The committee judges that IRE's and Mallinckrodt's schedules for converting to Mo-99 production with LEU targets in one of their two process lines are achievable if they do not encounter any unexpected delays in completing the steps outlined above. IRE has already encountered a several-month delay in completing the conversion of its first processing line because of the issues described in Section 5.4 of this chapter. Additional delays in completing these steps could push the start of commercial production into late 2017 or beyond.

Nordion will stop producing Mo-99 with HEU targets at the end of October 2016 (see Chapter 3) and plans to begin producing Mo-99 at MURR using LEU targets in the first half of 2018. The schedule for initial commercial production at MURR appears optimistic given the unexpected technical obstacles that frequently arise with these first-of-a-kind projects as well as the long regulatory lead times normally associated with the establishment of new Mo-99 production. Neither Nordion nor GA has shared detailed information about the selective gaseous extraction technology or development results. Consequently, the committee does not have sufficient information to judge whether the first-half 2018 schedule is achievable.

It is important to note that some companies will continue to produce medical isotopes in HEU-fueled reactors even after HEU is eliminated from targets and medical isotope production facilities. The reactors in Belgium (BR-2) and Missouri (MURR) have committed to conversion after suitable LEU fuel is developed. The reactors in Russia have not committed to converting to LEU fuel. See NASEM (2016) for additional information.

FINDING 5B: Several organizations have taken leadership roles in promoting the wider utilization of molybdenum-99 produced without the use of highly enriched uranium. However, progress is being impeded by several factors, including the continued availability of highly enriched uranium targets.

[25] As noted in Appendix 4A in Chapter 4, a DMF is not required by law or regulation but can facilitate the regulatory approval process.

RECOMMENDATION 5B: The U.S. government and others should take additional actions to promote the wider utilization of molybdenum-99 and technetium-99m produced without the use of highly enriched uranium targets.

Global Mo-99 suppliers are undergoing a protracted and difficult transition away from the use of mostly HEU targets to the exclusive use of LEU targets. Companies that are now producing Mo-99 with LEU targets (ANSTO and NTP) find themselves at a competitive disadvantage in the market; their costs for producing Mo-99 with LEU targets are higher, but their ability to increase prices to cover these costs is limited by the ready availability of Mo-99 produced with HEU targets. These companies described this situation to the committee as "unsustainable."

Market uptake of Mo-99/Tc-99m produced from LEU targets is lagging in spite of the commendable efforts being taken by many organizations (see Section 5.7) to increase utilization. There are at least two reasons for this situation: (1) Mo-99 produced with LEU targets provides no additional medical benefits to patients; and (2) there are ready supplies of Mo-99 produced with HEU targets to meet patient needs. In fact, the global demand for Mo-99 produced with LEU targets currently is lower than global supply capacity.

Recommendation 5B is intended to promote the wider utilization of Mo-99/Tc-99m produced without the use of HEU targets and hasten the elimination of HEU from the global supply chain. Several actions could be taken to address this recommendation. For example:

- CMS: Continue to offer the $10 add-on per dose reimbursement for Tc-99m from non-HEU sources until Tc-99m from HEU sources is no longer available for commercial sale in the United States. At the same time, accelerate the retrospective analysis of medical procedure costs that utilize Tc-99m from non-HEU sources so that reimbursement rates more closely reflect actual Tc-99m production costs.
- NNSA: Examine options to eliminate the availability of HEU for Mo-99 production to shorten the transition period. For example, NNSA could buy back U.S.-origin HEU in raw or target form from global Mo-99 suppliers once Mo-99 production with LEU targets is firmly established. This would reduce and might even eliminate the transition period for global suppliers to use up their HEU target inventories. It would also reduce the volume of HEU waste resulting from the use of these target inventories.
- Technetium generator suppliers and nuclear pharmacies: Continue to work with the medical community, their purchasing organiza-

tions, and private insurance companies to further increase the utilization of Mo-99 produced without HEU targets. UPPI's effort to encourage private payers to offer the $10 add-on reimbursement for Mo-99 produced from non-HEU sources has the potential to further accelerate the transition away from HEU use.

- U.S. Congress: Restrict or place financial penalties on the import of Mo-99 produced with HEU targets after Mo-99 produced without HEU targets becomes widely available for commercial sale in the United States.

FINDING 5C: Even after highly enriched uranium is eliminated from molybdenum-99 production, large quantities of processing wastes containing highly enriched uranium will continue to exist at multiple global locations. This weapons-grade material is a proliferation hazard. The Department of Energy's National Nuclear Security Administration is working with global suppliers and their governments to examine options for downblending or returning this material to the United States.

RECOMMENDATION 5C: The U.S. government should continue to work with global molybdenum suppliers and their regulators to reduce the proliferation hazard from processing waste from medical isotope production containing U.S.-origin highly enriched uranium. The U.S. government should also develop a global inventory of this waste if one does not already exist.

DOE-NNSA has taken several actions to implement the Academies' 2009 recommendation (NRC, 2009) to manage the HEU wastes from Mo-99 production from U.S.-origin HEU. These actions are described in Section 5.5 of this chapter. Of particular note is NNSA's work with the Canadian government to return to the United States the HEU waste that is being stored in liquid form at CNL, as well as work with Argentina and Indonesia to downblend their HEU wastes. The HEU in waste from Mo-99 production in Pakistan, South Africa, and the Russia Federation is not U.S. origin. Nevertheless, this waste is still a proliferation hazard. Recommendation 5C is intended to further improve the management of HEU wastes to reduce their proliferation hazard.

The committee leaves it to the U.S. government to determine the best way to develop the recommended global inventory of HEU wastes. Mo-99 suppliers, their host governments, and/or the IAEA may have the information needed to develop this inventory.

FINDING 5D: The government of the Russian Federation has not announced a commitment or schedule for converting molybdenum-99 production from highly enriched uranium to low enriched uranium targets. The continued sale of molybdenum-99 produced with highly enriched uranium targets to international markets could disrupt progress toward full market adoption of molybdenum-99 from non-highly enriched uranium sources.

RECOMMENDATION 5D: The U.S. government—through the U.S. Department of State, the U.S. Department of Energy's National Nuclear Security Administration, and the U.S. scientific and technical communities—should engage with the Russian government to clarify its schedule for converting molybdenum-99 production from highly enriched uranium to low enriched uranium targets. The U.S. government should pursue engagements between U.S. and Russian scientific and technical organizations to facilitate conversion.

To the committee's knowledge, the Russian Federation has not made a public commitment to eliminate HEU targets from Mo-99 production or announced a schedule for doing so. Once a decision is made to convert it could take 3 years or longer before any Mo-99 is available for commercial sale. The Russian Federation has all of the necessary technical expertise to develop LEU targets and associated Mo-99 recovery and purification processes without any outside assistance. Nevertheless, efforts to convert Russian Mo-99 production to LEU targets could encounter the obstacles described in Sections 5.2-5.4 of this chapter. This report may be helpful to Russian technologists in overcoming these obstacles.

The continued sale of Mo-99 produced with HEU targets to international markets from the Russian Federation or any other country could delay the full transition to Mo-99 production without HEU, continue the current market distortions in Mo-99 prices, and impact the sustainability of Mo-99 supplies over the long term. Several steps could be taken by the U.S. government to address Recommendation 5D.

- The U.S. government could work through the HLG-MR to obtain a better understanding of Russian plans and schedules for eliminating HEU from the targets used to produce Mo-99 for sale on international markets.
- The U.S. government, again in cooperation with the HLG-MR, could examine options for discouraging sales of Mo-99 produced with HEU targets on international markets once current global

suppliers complete their conversions to LEU targets. Such options could include policy statements and possibly even a tariff system for Mo-99 produced with HEU targets.

- The U.S. government could encourage engagements on medical isotope production between the U.S. and Russian technical communities. Such engagements could include technical exchanges that could benefit both countries and hasten Russia's entry into global markets as a supplier of Mo-99 produced with LEU targets. Such engagements could also provide opportunities for unofficial exchanges of information and views between the U.S. and Russian governments.

Russia could become an important global supplier of Mo-99 in the future. The steps suggested above could help accelerate the entry of Russian-made Mo-99 produced with LEU targets into global markets in a responsible and sustainable manner.

6

Molybdenum-99/Technetium-99m Historic and Projected Demand

This chapter addresses the demand component of the fourth charge of the statement of task for this study (see Sidebar 1.3), which directs the Academies to provide an assessment of

> The adequacy of molybdenum-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond.

This chapter focuses on assessing the current and near-future *demand* (referred to as *medical needs* in the study charge) for molybdenum-99 (Mo-99)/technetium-99m (Tc-99m) in the United States. Current and near-future *supplies* of Mo-99/Tc-99m to the United States are discussed in Chapter 7.

This fourth study charge was not mandated in the American Medical Isotopes Production Act of 2012 (Appendix A). As noted in Chapter 1, this study charge was added in consultation with the study sponsor, the Department of Energy's National Nuclear Security Administration, to assist it with its nuclear non-proliferation mission and to provide important additional information to the U.S. Congress and the medical isotope production and utilization communities.

Demand for Mo-99 is driven by demand for technetium generators, which in turn is driven by demand for Tc-99m radiopharmaceutical doses (see Figure 2.4 in Chapter 2 and Figure 3.1 in Chapter 3). Technetium generator sales are not publicly disclosed by generator suppliers, and there is no centralized source of information on numbers of Tc-99m radiopharmaceutical doses dispensed in hospital and nonhospital settings in the United

SIDEBAR 6.1
Proxy Metrics for Mo-99 Demand Assessment

The committee's assessment of Mo-99/Tc-99m demand uses proxy metrics because data on Tc-99m generator sales and Tc-99m radiopharmaceutical doses dispensed are not available. The committee made the following assumptions in developing these metrics:

1. Mo-99 supply and Mo-99 demand are in approximate balance.
2. Mo-99 supply and Tc-99m utilization (technetium generator and Tc-99m radiopharmaceutical doses) are in approximate balance.
3. The number of procedures that utilize Tc-99m and the number of Tc-99m doses dispensed are in approximate balance with Tc-99m utilization.

With respect to the first point, the short half-lives of Mo-99 (66 hours) and Tc-99m (6 hours) rule out storage of excess supply; so, to avoid inefficient wastage, weekly supply is planned to match weekly aggregate demand. However, when supply capacity temporarily falls below demand (as it did during the 2009-2010 Mo-99 supply shortages), supply can be less than weekly demand. When that occurs available doses are rationed, requiring some imaging procedures to be performed with reduced Tc-99m activity or delayed or cancelled, and some procedures to be shifted to other modalities.

Mo-99 supply is also sensitive to distribution efficiency. The activity of Mo-99 begins to decline after irradiated targets are removed from a reactor. The decline is about 1 percent per hour. Long supply-line distances can increase supply needs for Mo-99 without increased demand for Mo-99.

With respect to the second point, all of the Mo-99 produced for commercial sale is used for medical imaging and all (or almost all) is incorporated into Tc-99m generators. The number of doses of Tc-99m that can be obtained from a technetium generator will depend on its utilization efficiency. If utilization efficiencies are increased, as happened during the 2009-2010 global Mo-99 supply shortages,

States. Consequently, the committee had to develop a number of proxy metrics (see Sidebar 6.1) to assess Mo-99/Tc-99m demand trends. The data used to develop these metrics were derived from

- Published information,
- Expert opinions of medical professionals and other Mo-99/Tc-99m supply chain participants, and
- Three databases that contain information on Tc-99m radiopharmaceutical utilization in selected sectors of the U.S. health care system.

Tc-99m utilization will increase without increasing Mo-99 supplies (OECD-NEA, 2010).

With respect to the third point, the number of procedures that utilize Tc-99m and the number of Tc-99m doses dispensed correlate with Tc-99m utilization. However, changes in the frequency of use of high Tc-99m dose procedures (e.g., MPI[a,b]) will have a more substantial effect on Tc-99m utilization compared to changes in frequency of use of lower-dose procedures.[c] Consequently, Mo-99 demand correlates better with Tc-99m utilization expressed as Tc-99m doses rather than the number of procedures that utilize Tc-99m.

In the United States, trends in utilization of nuclear cardiac procedures in general, or nuclear MPI in particular, are a proxy for overall trends in utilization of Tc-99m radiopharmaceuticals. Nuclear cardiac procedures represent more than half of the nuclear medicine procedures performed in the United States (Delbeke and Segall, 2011), and Tc-99m MPI procedures represent the majority of all of the cardiac procedures performed in the United States.[d] However, the rise (in 2000-2006) and decline (in 2006-2014) of nuclear MPI (McNulty et al., 2014) have been sharper compared to other nuclear medicine procedures that utilize Tc-99m, and the factors that affected the rise and decline may be different from those for other examinations. Nuclear cardiology and MPI more specifically are not as highly utilized in other countries and therefore are not a good proxy for overall Tc-99m utilization trends in countries other than the United States.[e]

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[a] MPI is an imaging test that shows how well blood flows through regions of the heart muscle.

[b] The estimated radiation dose for Tc-99m MPI ranges from 10 to 15 mSv (see Einstein et al., 2007).

[c] For example, hepatobiliary scintigraphy or sentinel lymph node localization.

[d] Over 70 percent according to the committee's analysis of Medicare data (see Figure 6.5).

[e] In Europe, nuclear cardiology represents only 14 percent of the nuclear medicine procedures performed. See Delbeke and Segall (2011).

These data sources are identified in Table 6.1 and discussed in Section 6.2 of this chapter.

Historical Mo-99 demand trends are useful for informing projections of future demand. Such projections can be developed by examining past demand trends and assessing the factors that are likely to affect those trends in the future. Some key demand trends are identified and discussed in Section 6.4 of this chapter.

6.1 GLOBAL DEMAND FOR Mo-99/Tc-99m

The most authoritative information on the global demand for Mo-99/Tc-99m comes from periodic assessments by the Organisation for Economic

TABLE 6.1 Data on Historic Decline of Mo-99 Demand in the United States

Source	Reference	Study Period	Proxy for Mo-99/Tc-99m Demand	Estimated Decline (%)
Published Literature				
OECD-NEA[a]	OECD-NEA 2011b, 2015, 2016	2010-2015	Production capacity	25
Kaiser Permanente of Northern California	McNulty et al., 2014	2009-2011	MPI utilization	30
Six large integrated health systems	Smith-Bindman, et al., 2012	1996-2010	Nuclear medicine	35
Expert Opinions				
Nuclear cardiology	Conference call (see Appendix C)	2009-2015	MPI utilization	40
Mo-99 supply chain participants	Conference call/ site visit (see Appendix C)	2009-2015	Tc-99m generator sales and Tc-99m generator purchases	25
Committee Analysis				
	Medicare Part B data	2006-2014 2010-2014		49 29
	Nuclear Pharmacy A (Rocky Mountain area)	2008-2014 2010-2014	Radiopharmaceutical doses dispensed	42 32
	Nuclear Pharmacy B (Upper Midwest)	2008-2014 2010-2014	Radiopharmaceutical doses dispensed	29 13
			Average reported decline ~2009/2010-2014/2015[b]	**25**

[a] OECD-NEA reported data are for global Mo-99 supply and demand. However, the United States accounts for 50 percent of global demand; therefore, global demand trends are also reflected in the U.S. market.

[b] Data that contributed to the average reported decline estimate are the following: OECD-NEA, expert opinions of nuclear cardiologists and Mo-99 supply chain participants, and the committee's analysis of Medicare Part B, Nuclear Pharmacy A, and Nuclear Pharmacy B data. See text for details.

Co-operation and Development's s Nuclear Energy Agency (OECD-NEA). OECD-NEA surveys irradiation services suppliers and Mo-99 suppliers about the number of reactor operating days and Mo-99 production capacities within specified periods.

OECD-NEA has published three estimates of global demand for Mo-99 over the past 5 years:

- 2010: 12,000 6-day curies (Ci) per week (OECD-NEA, 2011b).
- 2012: 10,000 6-day Ci per week (OECD-NEA, 2012).
- 2015: 9,000 6-day Ci per week (OECD-NEA, 2015, 2016).

The 2009 Academies report on medical isotope production (NRC, 2009) estimated that global demand was 10,000 to 14,000 6-day Ci per week in 2006. This estimate was based on that report's authoring committee's discussions with global Mo-99 suppliers.

The OECD-NEA estimates show a 25 percent decline in demand for Mo-99 globally from 2010 to 2015. OECD-NEA suggests that this decline was driven by several changes in the utilization of Mo-99/Tc-99m as a result of the 2009-2010 Mo-99 supply shortages (see Chapter 3). These changes included the more efficient global distribution of available Mo-99/Tc-99m supplies, more efficient elution of technetium generators and patient scheduling, and the use of alternative imaging modalities (OECD-NEA, 2011b).

6.2 DOMESTIC DEMAND FOR Mo-99/Tc-99m

Representatives of a U.S. technetium generator supplier and a U.S.-based national nuclear pharmacy chain told the committee that the OECD-NEA-estimated 25 percent decline in global Mo-99 demand before and after the 2009-2010 shortages is also reflected in the U.S. market.[1] An analysis carried out by the committee suggests that the decline in Tc-99m use in the United States began before the 2009-2010 supply shortages:

- Published data from Kaiser Permanente of Northern California show a continuous reduction in myocardial perfusion imaging (MPI) procedures between 2000 and 2011; the reduction in MPI use from 2009 to 2011 was 30 percent (McNulty et al., 2014).
- A report on imaging utilization in six large integrated health care systems across the United States described a decrease in nuclear medicine use from 32 to 21 per 1,000 enrollees from 1996 to 2010

[1] Ira Goldman, Lantheus Medical Imaging, verbal communication, June 2, 2015; and Scott Claunch, Cardinal Health, verbal communication, August 11, 2015.

(Smith-Bindman et al., 2012), a decline of 35 percent within this period.

- A group of nuclear cardiology experts working at institutions across the United States estimated that the decline in MPI in their practices was about 40 percent during the period 2009-2015.[2]

The committee's analysis of Tc-99m utilization in the United States used data from the following two sources:

1. Publicly available Medicare Part B data[3] on outpatient services for the period 2006-2014. These data are summarized by billing code for specific diagnostic and therapeutic radiopharmaceutical doses approved for Medicare Part B reimbursement. These billing codes are known as the Healthcare Common Procedure Coding System (HCPCS) and are administered by the Centers for Medicare & Medicaid Services (CMS).[4]
2. Data on radiopharmaceutical doses dispensed at two nuclear pharmacies in the United States[5] during the period 2008-2014. Nuclear Pharmacy A is located in the Rocky Mountain area and Nuclear Pharmacy B in the Upper Midwest. Both nuclear pharmacies dispense unit doses for inpatients and outpatients of all ages.

These data are discussed in the following subsections.

6.2.1 Medicare Part B Data

Medicare is the federal health insurance program for people 65 years of age and older and those with permanent disabilities. Individuals enrolled in Medicare account for about 15 percent of the total population in the

[2] These experts provided this information to the committee on a June 2, 2015, conference call; see Appendix C.

[3] Centers for Medicare & Medicaid Services (CMS), Part B National Summary Data File. Available at https://www.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/Part-B-National-Summary-Data-File/Overview.html (accessed September 15, 2015). Permissions for this intended use of the American Medical Association (AMA) content were not required as this falls within "Fair Use." Communication between Academies staff (Ourania Kosti) and AMA's Licensing Manager (Cheryl Ashe).

[4] HCPCS are based on Current Procedural Technology (CPT) codes developed, maintained, and copyrighted by AMA. CPT codes were developed to describe procedures and are assigned to every task and service a medical practitioner may provide to a patient. HCPCS codes were developed for billing purposes.

[5] Data from these two nuclear pharmacies were provided to the Academies and permission to use these data was granted provided that the names of the nuclear pharmacies were not disclosed.

United States (Henry J. Kaiser Family Foundation, 2016a); Medicare's share of total personal health care spending in the United States was 22 percent in 2013 (MedPAC, 2015). Medicare's structure is described in Rajaram and Bilimoria (2015).

The committee used publicly available Medicare Part B data to assess trends in utilization of Tc-99m radiopharmaceuticals based on counts of HCPCS codes that were approved for reimbursement in particular years. The *number of HCPCS codes* approved for reimbursement each year equals the *number of doses* of a radiopharmaceutical approved for reimbursement for that same year, which is also equal to the *number of procedures* using a radiopharmaceutical approved for reimbursement that year. The only exception relates to doses for Tc-99m-sestamibi and tetrafosmin used for Tc-99m MPI; a complete Tc-99m MPI procedure typically utilizes two doses: one administered at rest and another during either an exercise or pharmacological stress. Appendix D provides the list of the radiopharmaceuticals and their HCPCS codes as well as the grouping of the HCPCS codes for the committee's analysis.

An increasing number of Medicare beneficiaries are transitioning from Medicare Part B to Medicare Part C (also known as Medicare Advantage), a program that allows beneficiaries to receive Medicare-covered benefits by enrolling in private health plans: for example, health maintenance organizations and preferred provider organizations (Rajaram and Bilimoria, 2015). These Medicare-approved private plans provide all benefits covered under Medicare Parts A and B. However, services performed under Medicare Advantage are not reflected in the publicly available Medicare Part B National Summary Data. Medicare Advantage beneficiaries represented 16 percent of the total Medicare beneficiaries in 2006 and 31 percent of the total Medicare beneficiaries in 2014 (Henry J. Kaiser Family Foundation, 2016b).

The migration of beneficiaries from Medicare Part B to Part C (Medicare Advantage) introduces a systemic bias into the Medicare Part B National Summary Data on approved radiopharmaceutical doses. If one assumes that Tc-99m utilization rates by Medicare Part B and Part C beneficiaries is similar, then this bias can be removed by adjusting the data for each year as follows:

$$N = \frac{MB}{(1 - MA)}$$

Where

N = Committee's estimated number of Tc-99m radiopharmaceutical doses approved by Medicare in that year for both Medicare Part B and Part C (Medicare Advantage) beneficiaries.
MB = Number of radiopharmaceutical doses approved for reimbursement by Medicare Part B in that year.
MA = Percent (expressed as a decimal) of Medicare beneficiaries enrolled in Medicare Part C (Medicare Advantage) in that year.

The committee adjusted Medicare Part B data for Medicare Advantage enrollments using the equation above. The committee's estimates of Tc-99m radiopharmaceutical doses approved by Medicare are presented in Figure 6.1. Tc-99m diagnostic radiopharmaceutical utilization declined 49 percent from 2006 to 2014 (from an estimated 4.9 million to 2.5 million doses) and about 29 percent from 2010 to 2014 (blue line in Figure 6.1). These trends were driven primarily by reductions in utilization of Tc-99m doses for MPI (green line in Figure 6.1). MPI agents Tc-99m-sestamibi and tetrafosmin were estimated to account for more than 90 percent of all Tc-99m doses approved for reimbursement by Medicare.[6]

Utilization of radiopharmaceutical doses for all nuclear medicine diagnostic procedures declined 51 percent from 2006 to 2014 (from an estimated 7.2 million to 3.5 million; black line in Figure 6.1). Non-Tc-99m/non-positron emission tomography (PET) diagnostic utilization was relatively constant from 2006 to 2008; increased about 15 percent from 2008 to 2010; and declined about 50 percent from 2010 to 2011 (red line in Figure 6.1). The 2008-2010 increase and 2010-2011 decrease were likely driven by changes in utilization of thallium-201, which is used in myocardial scintigraphy for evaluating cardiac disorders. Thallium-201 myocardial scintigraphy is an alternative diagnostic test that replaced Tc-99m MPI during the 2009-2010 Mo-99/Tc-99m shortages. The quality of scans with thallium-201 is inferior compared to the quality of those acquired with Tc-99m MPI and the radiation dose to the patient is higher.

The decline in utilization of nuclear medicine diagnostic procedures during the period 2006-2014 does not include PET radiopharmaceutical utilization. In fact, PET utilization, which accounts for less than 4 percent of all nuclear diagnostic procedures in 2006, increased twofold from 2006 to 2014 among Medicare beneficiaries (purple line in Figure 6.1). In 2014 it accounted for about 15 percent of all nuclear diagnostic procedures among Medicare beneficiaries. Moreover, the utilization of other advanced imaging

[6] Tc-99m MPI accounts for about 50 percent of all Tc-99m doses in the general population. This discrepancy with the Medicare data is believed to be age-specific.

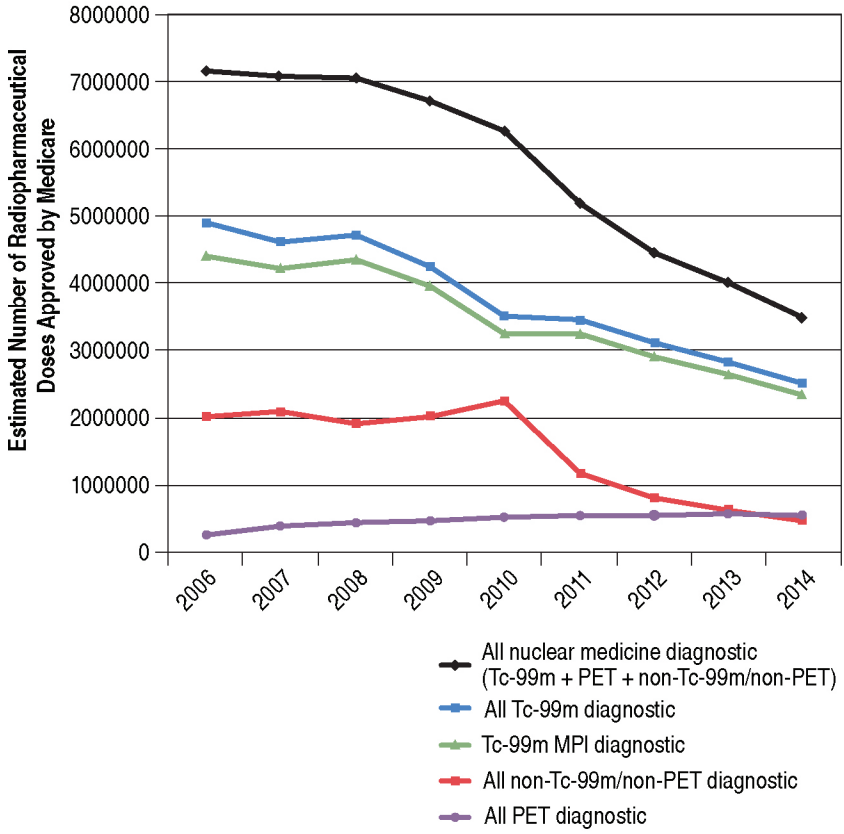

FIGURE 6.1 Estimated utilization of nuclear medicine diagnostic radiopharmaceuticals by Medicare beneficiaries: 2006-2014. NOTE: CPT Copyright American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association.

procedures such as computed tomography (CT) and magnetic resonance imaging (MRI) also increased among Medicare beneficiaries during this period.[7] These data are not shown.

[7] For this analysis the committee used CPT codes for one common MRI and CT procedure: MRI of the lumbar spine (CPT codes 72148, 72149, 72158) and CT of the abdomen +/–pelvis (CPT codes 74150, 74160, 74170, 74146, 74177, 74178). The data were also adjusted for Medicare Advantage enrollments. The following workload changes were observed from 2006 through 2014: about +13 percent for MRI of the lumbosacral spine, about +28 percent for CT abdomen and/or pelvis, and about +135 percent for CT pulmonary angiograms.

6.2.2 Nuclear Pharmacy Data

The committee analyzed the number of radiopharmaceutical doses dispensed at two nuclear pharmacies (Nuclear Pharmacy A and Nuclear Pharmacy B, described previously) in the United States during the period 2008-2014. About 95 percent of the nuclear medicine doses delivered by these nuclear pharmacies were to outpatients and 5 percent were to inpatients.

Data from Nuclear Pharmacy A show a 42 percent decline in utilization of Tc-99m radiopharmaceutical doses from 2008 to 2014 and a 32 percent decline from 2010 to 2014 (blue line in Figure 6.2). This decline is similar to those for non-PET nuclear medicine radiopharmaceutical doses (orange line in Figure 6.2) and Tc-99m MPI diagnostic doses (green line

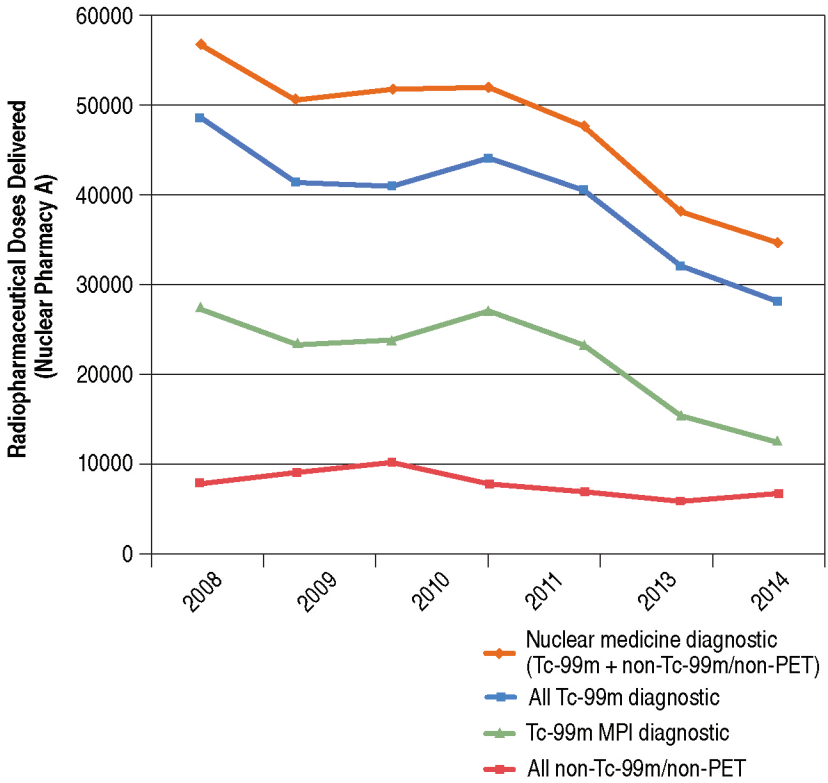

FIGURE 6.2 Radiopharmaceutical doses dispensed at Nuclear Pharmacy A: 2008 to 2014. PET radiopharmaceuticals are not included in this analysis.

in Figure 6.2). Trends in Tc-99m utilization in Nuclear Pharmacy A were less driven by Tc-99m MPI compared to Medicare (see Figure 6.1). More specifically, Tc-99m MPI accounted for about half of all of the Tc-99m doses, a finding consistent with existing data for the general population. Also, there was not as dramatic a decline in non-Tc-99m/non-PET utilization from 2010 to 2011 (red line in Figure 6.2) compared to Medicare (red line in Figure 6.1).

Data from Nuclear Pharmacy B (see Figure 6.3) show a 29 percent decrease in utilization of Tc-99m radiopharmaceutical doses from 2008 to 2014 and a 13 percent decline from 2010 to 2014 (blue line in Figure 6.3). The decline in Tc-99 utilization (blue line in Figure 6.3) is similar to that for Tc-99m MPI diagnostic doses (green line in Figure 6.3) and for non-PET

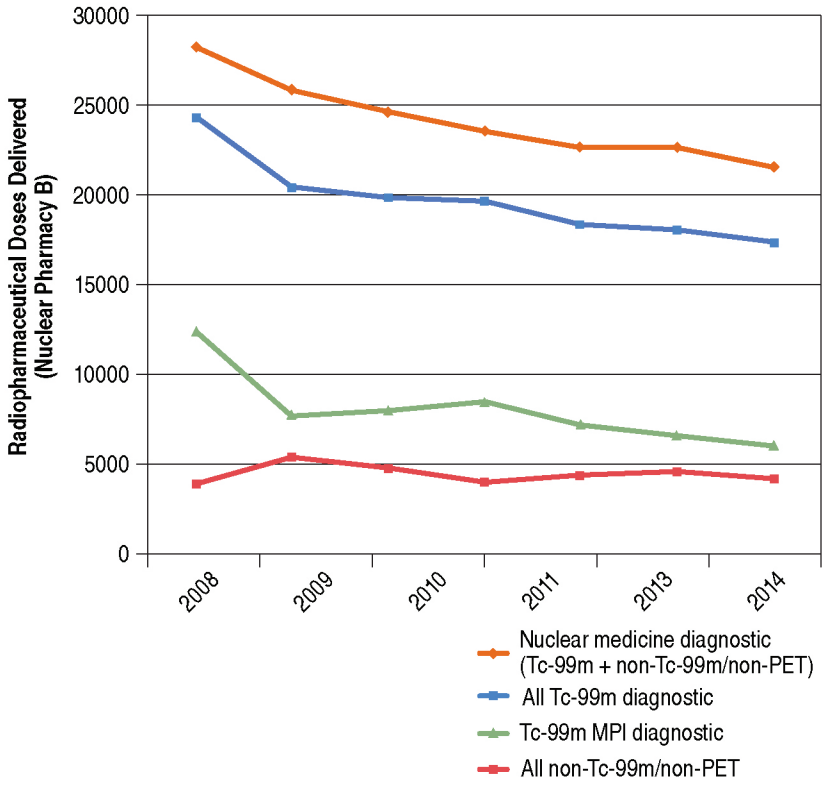

FIGURE 6.3 Radiopharmaceutical doses dispensed at Nuclear Pharmacy B: 2008 to 2014. PET radiopharmaceuticals are not included in this analysis.

nuclear medicine radiopharmaceutical doses (orange line in Figure 6.3). Trends in Tc-99m utilization were not driven by Tc-99m MPI to the same degree as for Medicare patients (compare the green lines in Figures 6.1 and 6.3). Also there was not as dramatic a decline in non-Tc-99m/non-PET utilization from 2010 to 2011 (red line in Figure 6.3). The overall trends in radiopharmaceutical utilization in Nuclear Pharmacy A were similar to those observed for Nuclear Pharmacy B.

6.2.3 Discussion

Available data from published reports, expert opinions, and the committee's independent analysis of data from Medicare Part B data and two nuclear pharmacies indicate that

- Mo-99/Tc-99m utilization in the United States has been declining for at least a decade. The decline started before the 2009-2010 Mo-99/Tc-99m supply shortages and continued until at least through 2014-2015, the latest period of available data.
- The decline is reflected in all nuclear imaging procedures except PET.

The observed decline in demand for Tc-99m ranges from 13 to 40 percent for the period 2009-2010 to 2014-2015 and is on average about 25 percent (see Table 6.1). This is a similar magnitude of decline as observed in global Mo-99 demand for the same period (see Section 6.1 in this chapter).

The observed variability in decline across the different data sets could be caused by age and geographic variability. Age and geographic (IOM, 2013) variation in health care utilization is well documented in the medical literature. Age variation may also explain the differences in MPI utilization between the Medicare and the nuclear pharmacy data sets. The Medicare population is 65 years of age and older, whereas the populations served by the two nuclear pharmacies are of all ages. Older populations are more likely to be diagnosed with heart disease and have MPI procedures.

6.3 FUTURE GLOBAL DEMAND FOR Mo-99/Tc-99m

Past attempts to estimate future Mo-99/Tc-99m demand have met with limited success, primarily because of the difficulties in forecasting medical, economic, and market developments that affect future demand. The previous Academies medical isotopes report (NRC, 2009) estimated that Mo-99/Tc-99m demand in the United States would grow between 3 percent and 5 percent per year for the period 2008-2012 "if there are no major disruptions in Mo-99/Tc-99m supplies and no major changes in

health care policies or practices" (NRC, 2009, p. 78). However, there was a major recession in the late 2000s, a supply disruption in 2009-2010, and there were also important changes in health care policies and practices during these periods. The Academies' growth forecast proved to be overly optimistic at least in part because of these unforeseen developments.

OECD-NEA has revised its future Mo-99 demand estimates downward in response to new data on utilization trends. In 2011, for example, OECD-NEA estimated a 25 percent increase in Tc-99m utilization in mature markets (Europe, Japan, North America, Oceania, and South Korea) from 2010-2020 and a 40 percent increase in emerging markets (South America, Africa, and Asia[8]) for the same period (OECD-NEA, 2011b). These estimates were revised in 2015 to 0.5 percent and 5 percent per year, respectively, based on then-current information from supply chain participants (OECD-NEA, 2015).[9] As noted in Section 6.1 of this chapter, OECD-NEA also adjusted its Mo-99 demand projections from 12,000 6-day Ci per week in 2010 to 9,000 6-day Ci per week in 2015.

OECD-NEA's projected demand increase in mature markets (0.5 percent per year) is driven by population aging, which as noted previously should increase the demand for Tc-99m-based procedures. Projected out 5 years, this demand increase would amount to an additional 225 6-day Ci per week over the current estimated global demand (9,000 6-day Ci per week). This is essentially a stable demand.

Emerging markets accounted for about 16 percent of the global demand for Mo-99 in 2015 (OECD-NEA, 2015). OECD-NEA assumed that this portion of the market would grow at 5 percent per year because of population aging (especially in China), economic growth, and expansion of the health care sector in these countries. However, data to support this projected demand are limited. Moreover, some of the demand growth in emerging markets is likely to be met by regional Mo-99 suppliers (see Chapter 3) and will not affect Mo-99 supplies in mature markets.

Mature markets are estimated to account for the remaining 84 percent of global demand (OECD-NEA, 2015). As noted previously, the United States has historically accounted for about half of the global demand for Mo-99/Tc-99m. Therefore, at least over the next 5 years, Mo-99/Tc-99m utilization in the United States will drive global demand.

[8] But not including Japan or the Republic of Korea.

[9] The OECD-NEA does not presently have sufficient data to make new estimated growth rates.

6.4 FUTURE DOMESTIC DEMAND FOR Mo-99/Tc-99m

The committee has refrained from developing quantitative estimates of future demand for Mo-99/Tc-99m because it is unable to forecast future medical, economic, and market developments that could affect demand trends. The committee instead identified factors that have affected Mo-99/Tc-99m utilization in the past and that might affect future utilization, especially in the near term (i.e., over the next 5 years). These factors are described in the next two subsections.

6.4.1 Factors That Could Decrease Future Demand for Mo-99/Tc-99m

The committee identified eight factors that could decrease future demand for Mo-99/Tc-99m in the United States:

- Reduced reimbursements for medical imaging procedures
- Transitioning away from the fee-for-service health care model
- Decline in the number of nuclear medicine experts
- More efficient use of technetium generators and Tc-99m-based radiopharmaceuticals
- Widespread acceptance and further development of appropriate use criteria
- Slow progress in new Tc-99m radiopharmaceutical development
- Increasing preference for competing imaging modalities
- Radiation exposure concerns

These factors are described in the following subsections. The committee judges that the first six of these factors could be particularly important for modulating domestic demand over the next 5 years.

6.4.4.1 Reduced Reimbursements for Medical Imaging Procedures

Per capita, health care costs in the United States are twice the average of other developed countries, and the percentage of the U.S. gross domestic product spent on health care continues to grow. Efforts to control these costs in recent years have resulted in reduced reimbursements for medical imaging procedures. These reductions were triggered by a 2005 report to Congress that noted that the growth rate for imaging procedures far exceeded rates for other medical services. The report raised concerns about the appropriateness of the imaging services being provided (GAO, 2008; MedPAC, 2015). Many of these services were provided in private offices.

The federal government has addressed these concerns by changing reimbursement policies to limit office-based medical imaging. The most

important of these changes was the Deficit Reduction Act of 2005 (P.L. 109-171). Congress enacted special payment rules, effective January 1, 2007, that limit reimbursements for the technical component of imaging services[10] performed in private offices. These special payment rules eliminated financial incentives for performing studies such as nuclear MPI in private offices. In 2009, CMS implemented a strategy to *bundle* services, frequently provided together as an episode of care, into one code and to reimburse a fixed amount for the bundle without adjustment for services actually provided. This new reimbursement policy discouraged providers from performing tests having little clinical value-added[11] because the costs would have to be borne by the provider, not the payer (Ferrari et al., 2014).

These changes in reimbursement policies resulted in an abrupt and nearly threefold reduction in the number of office-based nuclear medicine procedures (primarily MPI studies) performed from 2008-2010 (see Figure 6.4), and they likely played a significant role in the observed decline in nuclear medicine procedures from about 2007 to today. These changes are also likely to affect future health care practices and to further reduce the demand for nuclear imaging (and Mo-99/Tc-99m).

6.4.4.2 *Transitioning Away from the Fee-for-Service Health Care Model*

There are two major changes in the traditional fee-for-service health care model: capitation and value-based adjustments. The fee-for-service model encourages providers to offer more billable services, whereas the capitated and value-based models incentivize providers to reduce spending.

- Capitation gives providers a prepaid fixed payment based on expected annual spending for each enrolled patient. This payment is not determined by the services actually offered, so providers have no financial incentive to perform imaging studies that provide little added clinical value.
- Value-based adjustments, such as Medicare's Hospital Value-Based Purchasing (CMS, 2015) system, reward hospitals for efficiency as

[10] Most imaging procedures permit separate reimbursement for generating the image (*technical component*) and reading and interpreting the images generated (the *professional component*). Under these special payment rules, reimbursements for the technical component of imaging services provided in a physician office setting cannot be greater than the same service provided in a hospital outpatient setting.

[11] There is some overlap in the information provided by the different imaging modalities. In the fee-for-service model of health care, there is motivation to employ multiple imaging modalities because an additional test may provide some unique useful information for disease diagnosis. But this approach is expensive and often has limited return.

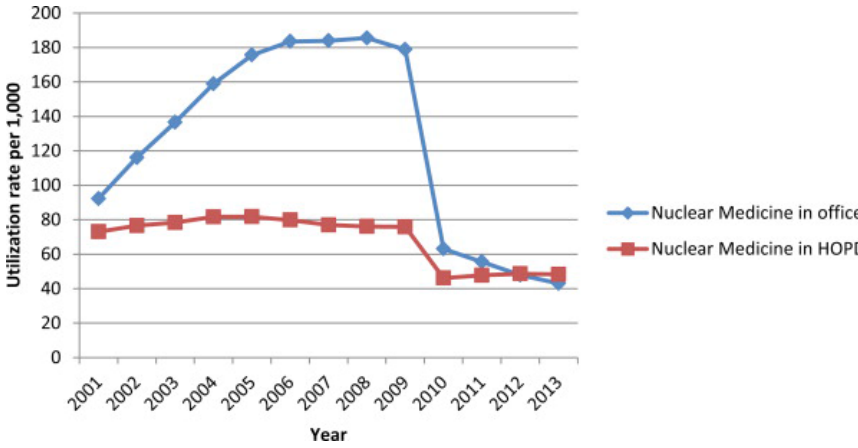

FIGURE 6.4 Utilization of office-based and hospital-based outpatient nuclear medicine imaging services per 1,000 beneficiaries: 2001-2013. Changes in reimbursement policies implemented in 2007 resulted in an abrupt and nearly threefold reduction in the number of office-based nuclear medicine procedures (primarily myocardial perfusion studies) performed from 2008-2010. NOTE: HOPD = Hospital Outpatient Department. SOURCE: Patel et al. (2015). Copyright 2015, with permission from Elsevier.

measured by the costs of individual episodes of care starting from 3 days prior to admission to 30 days after discharge.

The switch from fee-for-service to capitation and value-based health care models could further reduce the number of imaging procedures performed, including those utilizing Mo-99/Tc-99m.

The full transition from fee-for-service to capitated or value-based payments will occur over many years. The U.S. Department of Health and Human Services (HHS) announced a goal of transitioning 85 percent of Medicare fee-for-service reimbursements into fee-for-value payments by 2016 (HHS, 2015). At the end of 2014, CMS estimated that 20 percent of Medicare payments were made under the fee-for-value model.

6.4.4.3 Decline in the Number of Nuclear Medicine Experts

General nuclear medicine (excluding nuclear cardiology) is practiced by physicians certified in nuclear medicine and nuclear radiology or radiologists who are not specialty trained in nuclear medicine.[12] The number of physicians with training in nuclear medicine and nuclear radiology is cur-

[12] All radiologists have some nuclear medical experience as part of their residency.

rently low and declining as practicing physicians retire. Few physicians are certified in nuclear medicine each year by the American Board of Nuclear Medicine: an average of 74 physicians per year were certified from 2004 through 2013 nationwide (ABMS, 2015). The number of radiologists who opt for fellowships in nuclear radiology is even lower: an average of 6 radiologists per year opted for fellowships from 2004 through 2014 nationwide. In comparison, about 1,200 physicians were certified in diagnostic radiology each year (ABMS, 2015).

Radiologists who are not specialty trained in nuclear medicine now provide the majority of professional services in the practice of general (noncardiac) nuclear medicine because there are a limited number of specialty-trained physicians in nuclear medicine. The lack of specialty expertise in nuclear medicine among radiologists is likely to influence practice preferences in favor of alternate imaging modalities. The selection of alternate modalities by physicians could further reduce demand for Mo-99/Tc-99m in their practices.

The number of cardiologists with training in nuclear cardiology remains relatively steady (ABIM, 2015). On average, about 66 percent of all cardiologists in the United States obtain additional credentials in nuclear cardiology through the Certification Board of Nuclear Cardiology (CBNC). CBNC awarded primary certification to 571 cardiologists in 2014.[13] Cardiologists trained in nuclear cardiology will likely continue to utilize Tc-99m MPI in their practices until superior imaging modalities gain widespread acceptance and until reimbursement and the infrastructure exists to permit migration to these alternatives.

6.4.4.4 More Efficient Use of Technetium Generators and Tc-99m-Based Radiopharmaceuticals

Regional commercial nuclear pharmacies have replaced many hospital-based nuclear pharmacies over the last few decades. These commercial nuclear pharmacies have improved the efficiency of technetium generator utilization by more effectively matching generator supplies with Tc-99m radiopharmaceutical demand, primarily through economies of scale and more effective scheduling. Nuclear pharmacies and Tc-99m end users (hospitals and clinics) implemented other procedural changes to improve Tc-99m utilization efficiencies during the 2009-2010 Mo-99 supply shortages. These included the following:

- More frequent technetium generator elutions to increase Tc-99m yields (see discussion in Section 2.5.5 in Chapter 2).

[13] See http://www.cccvi.org/cbnc/content_152.cfm?navID=49.

- Use of appropriate software to track Tc-99m utilization and estimate Tc-99m activities needed daily or weekly to allow generator sizes and delivery schedules to be optimized.
- Adjustments to imaging schedules to better utilize available Tc-99m supplies, including grouping exams that use the same radiopharmaceuticals.
- Refinements of imaging protocols to reduce the activity administered to patients without compromising image quality.
- Use of more sensitive imaging equipment (solid-state detectors) to reduce the activity administered to patients (Gambhir et al., 2009).

Further penetration of these procedural changes in nuclear pharmacies and imaging centers could further increase Tc-99m utilization efficiencies and decrease demand for Mo-99/Tc-99m.

6.4.4.5 Widespread Acceptance and Further Development of Appropriate Use Criteria

The initial motivation for developing and promoting Appropriate Use Criteria (AUC) arose from concerns about costs and harms associated with unnecessary imaging.[14] Introduction of AUC has impacted clinical practice since around 2005, especially in cardiology, and it has resulted in lower use of some imaging procedures when minimal or no patient benefit is expected.

The definition of an appropriate diagnostic or therapeutic procedure is "one in which the expected clinical benefit exceeds the risks of the procedure by a sufficiently wide margin such that the procedure is generally considered acceptable or reasonable care" (Mann et al., 2015). AUC currently do not strongly support the use of one imaging modality over another; instead, they provide a score or categorical assignment as to the appropriateness of an imaging study in a given clinical setting.

AUC often score multiple types of imaging modalities similarly, allowing flexibility to the ordering physician to decide on the appropriate imaging modality and to incorporate secondary considerations (e.g., safety, cost,

[14] The methods for the development of AUC have evolved over time. The following process is used at present: A multidisciplinary panel of experts first develops a list of possible clinical indications for the tests based on patients' symptoms at the time of presentation, and it reviews the literature that assesses the performance of the tests in various clinical settings. Once the list of indications and the literature review have been vetted, a rating panel is convened. Each panel member independently rates each test for each indication using a 9-point scale, where 1-3 is "rarely appropriate," 4-6 "may be appropriate," and 7-9 is "appropriate." One or more additional rounds of scoring occur when the rating panel members interact and each panel member is allowed to change his/her score based on panel discussions. The process ends when consensus is reached for the indications being assessed.

local expertise, availability, and patient preference) in the decision-making process (Hendel et al., 2013).

AUC are broadly used in decisions for diagnostic or therapeutic procedures in cardiology and have likely contributed to the decline in imaging studies utilizing Tc-99m. The use of AUC in other disciplines could lead to the further decline in imaging procedures, including those that utilize Tc-99m, if those AUC were to give greater weight to alternate imaging modalities.

6.4.4.6 Slow Progress in New Tc-99m Radiopharmaceutical Development

Several Tc-99m radiopharmaceuticals have been removed from the U.S. market over the past 25 years (see Table 6.2). Additionally, there has been slow progress during the past decade in developing new Tc-99m radiopharmaceuticals that could stimulate demand for Mo-99/Tc-99m.[15]

The most recent Tc-99m agent to be approved by the Food and Drug Administration (FDA) was Tc-99m tilmanocept (Lymphoseek™), which is used for imaging the lymph nodes in cancer patients (Azad et al., 2015). FDA approval of this agent occurred in 2013.

According to the U.S. National Institutes of Health database of active clinical trials (ClinicalTrials.gov), only one novel FDA-approved Tc-99m agent, Tc-99m-EC-DG (Ethylenedicysteine-Deoxyglucose), is currently being evaluated in a multicenter Phase 3 (NIH, 2008) study.[16] Another 10 clinical trials are evaluating off-label Tc-99m agents (i.e., agents used for different indications than those described in the FDA-approved drug label).[17] A few Tc-99m radiopharmaceuticals are at various stages of preclinical study development.[18]

Most new radiopharmaceutical development is for PET imaging. Nuclear imaging with PET offers many advantages over single-photon emission computerized tomography (SPECT). These include better image quality due to improvement in resolution, better hybrid integration with

[15] Developers of a potential new radiopharmaceutical must weigh the costs of research and regulatory approval against the potential downstream profits of an approved drug. If future reimbursements for the new drug are judged to be low, then the expected downstream profits will be smaller, and development of the radiopharmaceutical will be less attractive.

[16] The purpose of this study is to determine if the images of the primary lesions of lung cancer and any metastatic lesions seen from the investigational SPECT/CT Tc-99m-EC-DG scans are the same as the PET/CT 18F-FDG scans.

[17] Search performed by the committee on February 28, 2016.

[18] For example: Tc-99m etarfolatide to evaluate response to treatment in patients with metastatic ovarian and lung cancer, Tc-Annexin V-128 as an *in vivo* apoptosis imaging marker, and Tc-99m-PSMA to diagnose prostate cancer.

TABLE 6.2 List of Tc-99m Agents Discontinued from the U.S. Market

Tc-99m-Radiopharmaceutical	Year Approved by the FDA	Year Discontinued	Reason for Discontinuance
Tc-99m-Arcitumomab (CEA Scan™)	1996	2006	Low sales
Tc-99m-Fanolesomab (NeutroSpec™)	2004	2005	Reported life-threatening adverse effects
Tc-99m-Apcitide (AcuTect™)	1998	2005	Low sales
Tc-99m-Teboroxime (Cardiotec™)	1991	ca. 1994	Low sales

CT and MRI, and the capacity for quantitative imaging (Kudo, 2007). Two new PET agents received FDA approval in 2016.[19]

6.4.4.7 Increasing Preference for Competing Imaging Modalities

Advancements in medical imaging have enabled the development of new imaging modalities for disease diagnosis, some of which compete with SPECT imaging. For example, cardiac ischemia can be diagnosed using six different procedures: MPI SPECT, cardiac CT angiography (CCTA), stress echocardiography, cardiac PET MPI, coronary artery calcium scoring, and cardiac MRI perfusion. The relative utilization of these procedures for all noninvasive cardiac imaging procedures among Medicare B recipients 2014 is shown in Figure 6.5. Tc-99m MPI SPECT is the most utilized cardiac imaging procedure today, accounting for 72 percent of cardiac imaging performed in the United States. Cardiac MRI scans (performed for any purpose) comprise less than 1 percent, and cardiac PET comprises about 4 percent.

The choice of imaging modality to diagnose cardiac ischemia and disease in general is often dictated by available infrastructure (equipment and expertise), cost, and amount of reimbursement. These factors are less favorable today for MRI and PET than for SPECT imaging. At present, infrastructure does not exist for any substantive conversion of Tc-99m MPI SPECT to cardiac MRI or PET in the United States. Even if utilization of Tc-99m MPI SPECT undergoes further decline, the volume is likely to

[19] These are Ga-68 DOTATATE (produced with a Somakit-TATE kit), a PET agent for neuroendocrine tumor diagnosis and follow-up, and F-18 FACBC (F-18 fluciclovine) for prostate cancer recurrence.

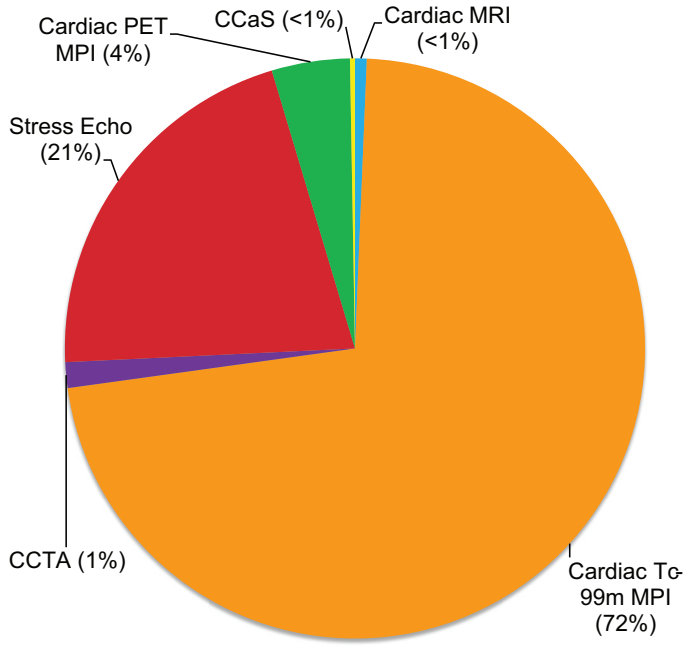

FIGURE 6.5 Relative frequency of cardiac imaging procedures performed among Medicare Part B beneficiaries in the United States. NOTES: CcaS = coronary artery calcium scoring; CCTA = cardiac computed tomography angiography; stress echo = stress echocardiography. SOURCE: Produced by the committee using 2014 Medicare Part B data from relevant CPT codes for imaging procedures.

remain high compared to alternate modalities for cardiac imaging. Other factors such as physician preferences and expertise as well as patient-specific factors will continue to affect the choice of imaging modalities in the future.

6.4.4.8 Radiation Exposure Concerns

A report released by the National Council on Radiation Protection and Measurements in early 2009 indicated that Americans were exposed to about six times as much ionizing radiation from medical diagnostic procedures in 2006 than in 1980 (3 mSv per capita per year compared to 0.5 mSv) (NCRP, 2009). The increased exposures in medical diagnostic imaging were driven primarily by the increased usage of higher-dose procedures,

particularly CT and nuclear medicine (especially nuclear cardiology) (Lin, 2010; Mettler et al., 2009). Physician and patient concerns about the potential health consequences of these increased exposures, especially related to cancer, have driven efforts to reduce patient exposures by eliminating unnecessary procedures (see discussion on AUC in Section 6.4.4.5 in this chapter) and reducing the radiation doses received from these procedures. The *Image Gently* and *Image Wisely* initiatives[20] are notable examples of these efforts.

Advancements in gamma cameras and image processing software have improved image quality while lowering radiation doses. Such software is already in wide use in nuclear medicine and is therefore unlikely to result in substantial further dose reductions in nuclear medicine studies. Further dose reductions are most likely to be obtained from further reduction in unnecessary imaging procedures.

6.4.2 Factors That Could Increase Future Demand for Mo-99/Tc-99m

The committee identified two factors that could increase future demand for Mo-99/Tc-99m in the United States:

- Aging populations
- Greater access to health care

These factors are described in the following two subsections.

6.4.2.1 Aging Populations

The need for health care services in the United States will increase as the population ages, and the U.S. population is aging. About 15 percent of the U.S. population is currently 65 and older (48 million of the 320 million total current population); this segment of the population is expected to nearly double by 2030 (72 million of the 358 million total projected population), when the median postwar baby boom generation is expected to reach 75 years of age, and stabilize thereafter (Ortman et al., 2014).

This change in the population age structure, together with trends in obesity and diabetes, are expected to lead to the increased incidence of coronary heart disease in the United States: from about 17 million cases in 2015 to 21 million cases in 2018 to 30 million cases by 2027.[21] These

[20] See http://www.imagewisely.org/ and http://www.imagegently.org/.

[21] These predictions come from the Future Elderly Model, a microsimulation model developed to examine health and health care costs. This model has been used in many predictions of health and health spending. See Gaudette et al. (2015) and NASEM (2015).

trends will likely result in increased demand for cardiac imaging procedures that utilize Tc-99m.

6.4.2.2 Greater Access to Health Care

The 2014 Affordable Care Act (P.L. 111-148) requires almost all citizens to be covered by health insurance, either through their employer or purchased from the government or a third-party provider. The rate of uninsured adults in the United States dropped by about 7 percent, from 18 percent before the fourth quarter of 2013 (just before the Affordable Care Act took effect) to 11 percent in the second quarter of 2015 (Marken, 2015). The increase in insured Americans could result in some additional growth in Tc-99m-based imaging procedures. However, many of the Tc-99m MPI SPECT scans performed in the United States are already covered by Medicare, so the growth in Tc-99m-based imaging procedures could be less than for imaging procedures in general.

6.5 DOMESTIC DEMAND FOR I-131 AND Xe-133 AND FUTURE PROJECTIONS

The committee is not aware of any published estimates of future demand for the medical isotopes I-131 and Xe-133. Some marketing companies collect survey data on utilization of these medical isotopes, but their analyses are based on low participation rates and their estimates may therefore have limited accuracy.

The committee analyzed Medicare Part B data to assess historic trends in I-131 and Xe-133 utilization using the same methodology described in Section 6.2 of this chapter. Medicare reports the amount of I-131 activity (in microcuries [μCi] or millicuries [mCi]) administered in procedures, not the number of radiopharmaceutical doses. Medicare reports Xe-133 utilization in terms of doses, similar to reporting on Tc-99m-based radiopharmaceuticals.

6.5.1 Iodine-131

The committee's analysis of Medicare Part B data showed a 24 percent decline in total I-131 utilization for both therapeutic and diagnostic purposes from 2006 to 2014 (black line in Figure 6.6). The decline in I-131 utilization for diagnostic purposes began around 2008 and continued through 2014 (green line in Figure 6.6). I-131 utilization for therapeutic purposes declined slightly from 2007 to 2011, increased slightly from 2011 to 2012, and declined sharply (about 40 percent) from 2012 to 2014 (blue line in Figure 6.6).

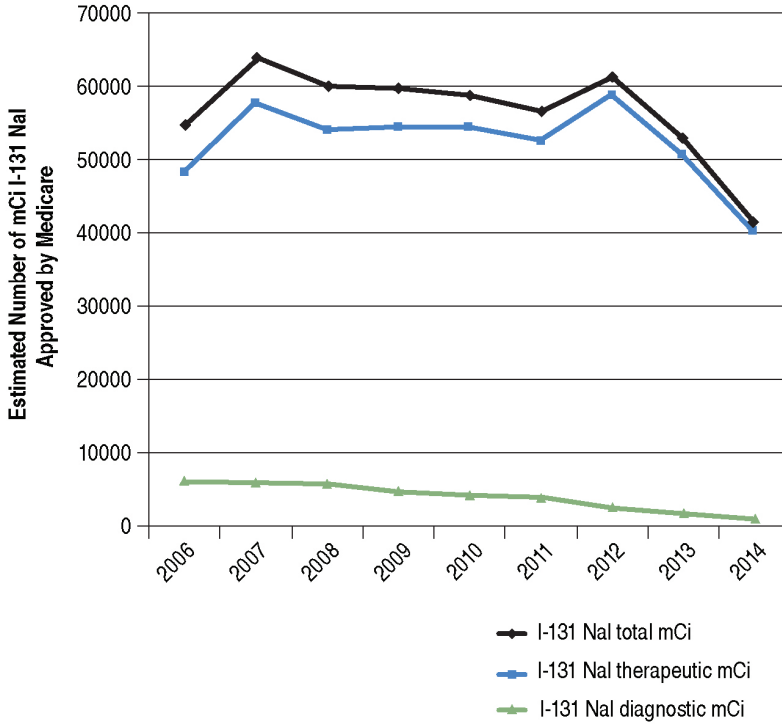

FIGURE 6.6 Estimated utilization of I-131 by Medicare beneficiaries: 2006-2014. SOURCE: Produced by the committee using Medicare Part B data. Medicare Part B describes I-131 utilization per μCi or mCi amount.

Approximately 20 percent of thyroid cancers diagnosed in the United States are among individuals 65 years and older[22] and therefore eligible for Medicare. Consequently, the exact percent of decline observed by the committee's analysis of Medicare Part B data may not be representative of the entire U.S. population.

Most I-131-NaI used today is for the treatment of hyperthyroid disorders and thyroid cancer. The American Thyroid Association (ATA) revised its guidelines for the management of these diseases in 2009 (Cooper et al., 2009). The revised guidelines include a recommendation to not use I-131-NaI to treat patients who are at *very low risk* of cancer recurrence after surgery, and also to use reduced doses of I-131-NaI to treat patients who are at *low risk* of recurrence and have no residual disease after surgery

[22] See http://seer.cancer.gov/statfacts/html/thyro.html.

(Haugen et al., 2016). The latter recommendation was supported by two studies published in 2012 (Mallick et al., 2012; Schlumberger et al., 2012).

These and other recommendations by ATA have contributed to the decline in I-131 utilization in therapy observed in Figure 6.6. I-131 utilization for treatment of hyperthyroidism has remained relatively stable and is expected to remain so in the near future.

I-131 utilization for diagnostic purposes overall is only about 10 percent of the doses used for therapy. Diagnostic applications for I-131 include the following:

- Measuring thyroid uptake and imaging the thyroid for the diagnosis of thyroid disease.
- Imaging the thyroids of thyroid cancer patients to demonstrate presence of remnant or metastasis and the need for I-131 therapy.

Iodine-131 for thyroid imaging is being replaced by I-123[23] because it is less likely to damage thyroid cells during imaging. The practice of imaging the thyroid before I-131 therapy is also becoming less common because of the low sensitivity of thyroid scans (using either I-123 or I-131) for detecting remnant or metastasis and concerns about decreased uptake of the subsequent therapeutic dose by the remnant thyroid tissue or metastatic cells.[24] These changes in practice have contributed to the decline in I-131 used in diagnostic procedures.

The committee anticipates that it may take the medical community a few additional years to fully adopt the ATA recommendations. Therefore, it is possible that Na I-131 used in therapy and I-131 used in diagnosis will further decline in the near future.

6.5.2 Xenon-133

Xe-133 is the only FDA-approved agent for pulmonary ventilation studies in the United States. Most of these studies are done in conjunction with Tc-99m macroaggregated albumin (MAA) lung perfusion imaging for the diagnosis of pulmonary embolism. The other ventilation agent in wide use in the United States is Tc-99m DTPA aerosol (an off-label use of an FDA-approved agent).[25] Tc-99m Technegas™ (Tc-99m delivered as an ultrafine carbon dust) is approved only for use outside the United States.

[23] I-123 has a half-life of about 13.2 hours. It decays to tellurium-123 via electron capture and emits a gamma ray with a predominant energy of 159 kiloelectron volts (keV).

[24] Described in the medical literature as *stunning*.

[25] Tc-99m-DTPA is FDA approved as a renal and brain imaging agent (see Table 2.1, Chapter 2) but its off-label use in ventilation imaging is more common than its FDA-approved use in renal and brain imaging.

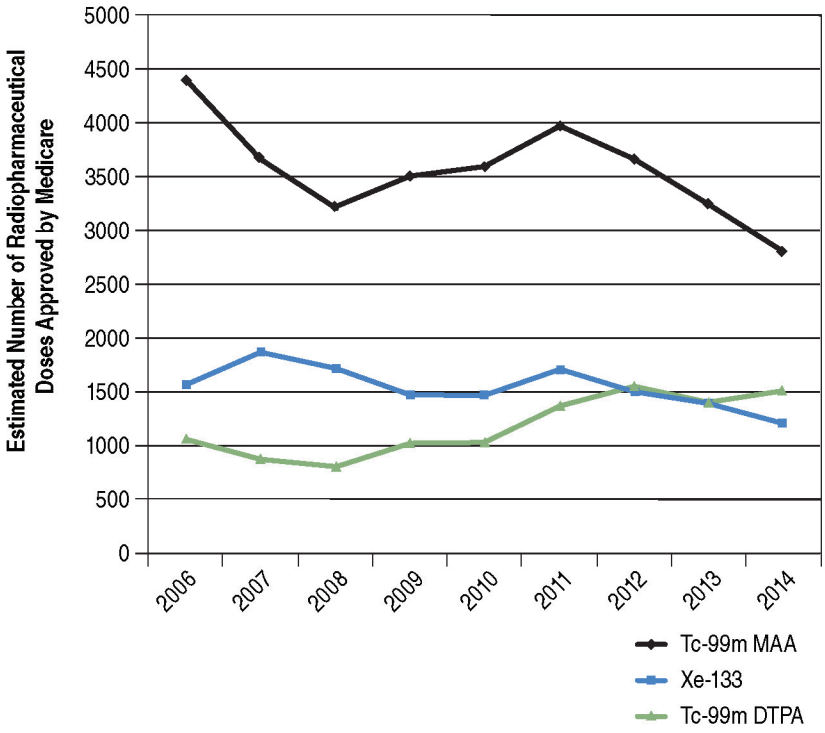

FIGURE 6.7 Estimated utilization of Xe-133 by Medicare beneficiaries, 2006-2014. Most of Xe-133 studies are carried out in conjunction with Tc-99m macroaggregated albumin (MAA) lung perfusion imaging for the diagnosis of pulmonary embolism. The other ventilation agent in wide use in the United States is Tc-99m pentatate (DTPA) aerosol (an off-label use of an FDA-approved agent for renal and brain imaging.

Xe-133 utilization declined 24 percent during the period 2006 to 2014 among Medicare beneficiaries (blue line in Figure 6.7). Tc-99m-MAA utilization for lung perfusion declined by about 36 percent during this same period (black line in Figure 6.7) while use of Tc-99m DTPA aerosol increased by about 43 percent (green line in Figure 6.7). These trends suggest that Tc-99m DTPA aerosol is replacing Xe-133 for pulmonary ventilation studies. There may be several reasons for this shift, but it is primarily because Xe-133 studies

- Must be carried out in a room with a negative ambient air pressure relative to outside hallways and with an exhaust vent to remove xenon gas.
- Require an additional piece of equipment (a gas delivery system) with associated quality control procedures.
- Provide limited projection images.

The committee judges that it is likely that Tc-99m DTPA aerosol will continue to replace Xe-133 in the near future because of the above factors. In addition, Xe-133 utilization could decline further if FDA approves Technegas™ for use in the United States and cost and reimbursement arrangements favor it over the other alternatives. Technegas is generally accepted to be superior to either Xe-133 or Tc-99m DTPA aerosol for pulmonary ventilation imaging (Jögi et al., 2010).

Technegas is manufactured in Australia by Cyclomedica Australia Pty Ltd. The Australian manufacturer has (intermittently) been trying to obtain FDA approval for Technegas for many years.

6.6 FINDING

The committee developed one finding to address the demand side of the fourth study charge to assess the "adequacy of molybdenum-99 supplies to meet future domestic medical needs, particularly in 2016 and beyond." The finding is presented below.

FINDING 4A: Domestic demand for molybdenum-99/technetium-99m for medical use has been declining for at least a decade. The decline began well before the global Mo-99 supply shortages in 2009-2010 and is reflected in nuclear imaging procedures that utilize technetium-99m. The average decline in domestic molybdenum-99/technetium-99m utilization from 2009-2010 to 2014-2015 was about 25 percent, similar to the estimated decline in global molybdenum-99 demand for that same period. Some of the factors responsible for the decline in domestic demand will continue to operate into the future, making it unlikely that domestic demand will increase significantly over the next 5 years. International demand for molybdenum-99 for medical use may increase over the next 5 years primarily because of higher utilization in emerging Asian markets.

OECD-NEA estimates that global demand for Mo-99 in 2015 was about 9,000 6-day Ci per week, a decrease of about 25 percent since 2010. This estimate is based on data provided by Mo-99 suppliers and is likely to

be reliable. The committee's analysis presented in this chapter indicates that Mo-99/Tc-99m utilization in the United States has also declined on average about 25 percent since 2009-2010 (see Table 6.1). Moreover, Mo-99/Tc-99m utilization in the United States has been declining for at least a decade, starting well before the 2009-2010 Mo-99 global supply shortages and continuing through the most recent available data in 2014-2015. This decline is reflected in all nuclear imaging procedures except PET.

OECD-NEA's latest estimates for future growth in global demand for Mo-99 are 0.5 percent in mature markets (including the United States) and 5 percent in emerging markets (e.g., Asia). The demand growth in mature markets is expected to be driven by aging populations, whereas growth in emerging markets is expected to be driven by aging population, economic growth, and expansion of the health care sector.

The committee judges that demand for Mo-99/Tc-99m in the United States is unlikely to grow significantly over the next 5 years primarily because of changes in health care policies, reimbursement rules, and medical practices. Some of these changes will take several additional years to be fully implemented across the U.S. health care system and therefore will continue to put downward pressures on domestic demand; these pressures may not be offset by potential growth factors such as aging of the U.S. population and greater access to health care.

7

Molybdenum-99/ Technetium-99m Supply

This chapter addresses the supply component of the fourth charge of the statement of task for this study (see Sidebar 1.3 in Chapter 1), which directs the Academies to provide an assessment of

> The adequacy of molybdenum-99 [Mo-99] supplies to meet future domestic medical needs, particularly in 2016 and beyond.

The demand component of this study charge was addressed in Chapter 6.

The committee interprets the term "beyond" in the study charge to mean the next 5 years (i.e., until about 2021). The committee judges that there are too many uncertainties in Mo-99 supply and demand (see Chapter 6) to look any further into the future.

This chapter is divided into three sections: Section 7.1 describes the factors that will affect future Mo-99 supplies. Section 7.2 describes the adequacy of Mo-99 supplies to meet future global demand, drawing on the careful work of the Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA). Section 7.3 provides the committee's finding and recommendation on the adequacy of Mo-99 supplies to meet future domestic demand.

7.1 FUTURE AVAILABLE SUPPLY CAPACITY

Several key points important to future available supply capacity were established in Chapters 3-6:

- Current global demand for Mo-99 is estimated to be about 9,000 6-day curies (Ci) per week, about half of which is consumed in the United States. It is unlikely that domestic demand for Mo-99 will increase significantly over the next 5 years (see Chapter 6).
- The United States imports Mo-99 to meet all of its domestic needs from five global suppliers in Australia, Canada, Europe, and South Africa (see Chapter 3); there is no domestic production of Mo-99 at present (see Chapter 4).
- Canada (NRU/Nordion) will stop supplying Mo-99 after October 2016. Canada will then become a supplier of last resort until the end of March 2018 (see Chapter 3). Nordion plans to resume supplying Mo-99 produced at the University of Missouri Research Reactor Center (MURR) in 2018 (see Chapter 4).

Nordion's exit from the Mo-99 supply chain after October 2016 will reduce available supply capacity and could affect the adequacy of Mo-99 supplies to the United States and other countries; the reduction will persist until this lost capacity is restored by Nordion or other suppliers.

Future supplies of Mo-99 will be affected by five factors:

- Current available global capacity to supply Mo-99
- Reductions in available global supply capacity after Canada stops producing Mo-99
- Planned additions to available global supply capacity by current irradiation services suppliers and/or Mo-99 suppliers
- Potential additions to available domestic supply capacity
- Other potential sources of Mo-99/Tc-99m supplies

These factors are discussed in the following subsections.

7.1.1 Current Available Global Capacity to Supply Mo-99

About 95 percent of the global supply of Mo-99 is produced by seven irradiation services suppliers and distributed by five Mo-99 global suppliers (see Chapter 3):

- Belgian Reactor-2 (BR-2) at Mol, Belgium. Mo-99 produced in this reactor is supplied to global markets by the Institut National des Radioélements (IRE) and Mallinckrodt.
- High Flux Reactor (HFR) at Petten, the Netherlands. Mo-99 produced in this reactor is supplied to global markets by IRE and Mallinckrodt.

- LVR-15 at Rez, Czech Republic. Mo-99 produced in this reactor is supplied to global markets by IRE.
- Maria at Otwock-Swierk, Poland. Mo-99 produced in this reactor is supplied to global markets by Mallinckrodt.
- National Research Universal (NRU) at the Canadian Nuclear Laboratories (CNL), Chalk River, Ontario. Mo-99 produced in this reactor is supplied to global markets by Nordion.
- Open Pool Australian Lightwater (OPAL) at Lucas Heights, Australia. Mo-99 produced in this reactor is supplied to global markets by the Australian Nuclear Science and Technology Organisation (ANSTO).
- South Africa Fundamental Atomic Research Installation 1 (SAFARI-1) at Pelindaba, South Africa. Mo-99 produced in this reactor is supplied to global markets by Nuclear Technology Products (NTP).

These seven irradiation services suppliers have a combined Mo-99 production capacity[1] of about 28,000 6-day Ci per week[2] (see Table 3.2 in Chapter 3). This is about three times higher than the current weekly global demand for Mo-99 of 9,000 6-day Ci. The five global Mo-99 suppliers have a combined irradiated target processing capacity of about 16,000 6-day Ci per week (see Table 3.3 in Chapter 3). This is slightly less than twice the current weekly global demand for Mo-99.

7.1.2 Reductions in Available Global Supply Capacity

The NRU reactor in Canada is scheduled to stop production of Mo-99 after October 2016 and permanently shut down at the end of March 2018 (see Chapter 3). During the period November 2016 through March 2018—referred to here as the *contingency* period—the NRU reactor could potentially resume production to support global Mo-99 supply if there is a shortage (NRCan, 2015). The associated CNL and Nordion facilities required for target processing and Mo-99 purification (see Chapter 3) will be kept in a *hot standby* mode during this contingency period.

The Canadian government has emphasized that the NRU reactor capacity during this contingency period should not be viewed as *outage reserve capacity* (ORC, see Sidebar 3.1 in Chapter 3) that the market can expect to draw upon as a matter of normal course of business. Instead, it should be viewed as a *supply of last resort* that will be used *only* in the

[1] Not accounting for reactor downtime for scheduled or unscheduled maintenance.

[2] All 6-day Ci estimates in this chapter are referenced to end of target processing. See Chapter 3.

event of unexpected shortages that cannot be mitigated through other means (Brady and Pruneau, 2015). The decision to resume Mo-99 production in NRU will be made by the Canadian government in consultation with other stakeholders.

The Canadian government has not publicly described the supply shortage triggers that would lead it to order a restart of Mo-99 production at NRU during the contingency period.[3] The Canadian government is instead focusing on establishing communication channels with relevant stakeholders so that it can receive the information it needs to inform a restart decision. These stakeholders include the Canadian federal agencies National Resources Canada and Health Canada; international organizations with information on reactor outage schedules such as the Association of Imaging Producers & Equipment Suppliers; global Mo-99 suppliers; and other national governments, including the United States.[4] The Canadian and U.S. governments, for example, have convened a bilateral working group to discuss Canada's plans to resume Mo-99 production at NRU if significant shortages develop during the contingency period. The details of these discussions are not public.

NRU/Nordion's ability to restart Mo-99 production and supply during the contingency period is subject to the availability of

- Highly enriched uranium (HEU) targets,
- An active operating license for NRU[5] and an operating reactor, and
- Readiness at CNL and Nordion to process irradiated targets and to purify Mo-99 for commercial sale.

CNL informed the committee that it expects to have sufficient HEU targets available to respond to Mo-99 supply shortages during the contingency period. NRU should also be available to produce Mo-99 during the contingency period unless it is shut down for scheduled or unscheduled maintenance. NRU has had a lengthy unscheduled outage in 2009-2010 (see Table 3.5 in Chapter 3).

Representatives of CNL and Nordion told the committee that they plan to maintain their target processing and Mo-99 purification facilities (see Chapter 3) in standby mode during the contingency period. They also plan to retain the staff that operate these facilities and may conduct training exercises to help maintain production readiness.

[3] A representative of CNL implied that the Canadian government does not intend to publicly release quantitative details of this information (Niall O'Dea, CNL, May 2016, OSTP Mo-99 Stakeholder meeting).

[4] Niall O'Dea, CNL, May 2016, OSTP Mo-99 Stakeholder meeting.

[5] These licenses are granted to CNL by the Canadian Nuclear Safety Commission.

The shutdown of NRU will result in loss of almost 20 percent of current global Mo-99 production capacity. It will also idle Nordion's Mo-99 processing capacity until its new project with General Atomics and MURR comes online, probably after March 2018 (see Chapter 4).

NRU/Nordion have in the past been able to increase Mo-99 production and supply on short notice to fill supply gaps. They are a particularly important supply source for the United States because of their *excess capacity production model* and close geographic proximity:

- NRU has the capacity to produce Mo-99 in excess of what is needed to meet Nordion's normal customer demand. This excess can be dispatched to customers on short notice.
- Mo-99 shipments from Nordion can arrive in the United States within about 24 hours of when they are requested. Consequently, there is relatively little Mo-99 lost to decay during shipment. Nordion ships Mo-99 to the United States using chartered aircraft, which adds flexibility and convenience.

This supply flexibility will be maintained during the contingency period, but it will be lost after March 2018.

7.1.3 Planned Additions to Available Global Supply Capacity

Several current global Mo-99 suppliers plan to expand their capacities to supply Mo-99 on a routine basis[6] starting in 2017, and new global or regional Mo-99 suppliers plan to enter the market later this decade (see Chapter 3).

Some current global supplies are planning to increase their available supply capacities:

- ANSTO plans to increase available supply capacity from 1,100 to 3,500 6-day Ci per week by mid-2017.
- Mallinckrodt plans to increase Mo-99 supply capacity from 3,500 to 5,000 6-day Ci per week in 2017.
- NTP plans to increase available supply capacity from 3,000 to 3,500 6-day Ci per week in 2017.

One current irradiation services supplier plans to expand its Mo-99 production capacity:

[6] This routine supply is different than ORC, which is intended to meet temporary supply shortages during planned or unplanned shutdowns of other facilities. ORC-based production is not intended to be sustained indefinitely.

- HFR plans to increase its Mo-99 production capacity from 5,400 to 6,200 6-day Ci per week starting in 2017.

Additionally, BR-2 is considering a gradual expansion of its Mo-99 production capacity from 7,800 6-day Ci per week to 10,530 6-day Ci per week (this expansion is not included in Figure 7.1 because it has not been decided).

Two additional European research reactors may become irradiation services suppliers:

- FRM-II, Germany, could start producing Mo-99 in 2018.
- Jules Horowitz Reactor (JHR), France, is expected to start operation in 2020 and could produce Mo-99 thereafter.

And several countries may expand Mo-99 supplies to global or regional markets:

- Russia plans to capture about a 20 percent share of the world Mo-99 market. There is no published schedule for Russia's expansion plan.[7]
- South Korea plans to build the Kijang Research Reactor and start producing Mo-99 in 2020 for domestic and eventual regional consumption.
- Argentina plans to build a new reactor with a weekly Mo-99 production capacity of 2,500 6-day Ci to cover domestic and regional supply needs. Argentina plans to have this reactor operational by 2020.
- Brazil plans to build a reactor with a weekly Mo-99 production capacity of 1,000 6-day Ci. This reactor, if built, would start producing Mo-99 after 2021.

Figure 7.1 shows the timeline for these projects. The schedule estimates shown in the figure were provided by suppliers and were not independently verified by the committee. Some of the timelines are likely optimistic. Reactor and radiochemical facility construction and commissioning projects are complex undertakings. These projects often experience unanticipated technical upsets and schedule delays.

The available supply capacity by current Mo-99 suppliers is estimated to be about 15,880 6-day Ci per week during the first three quarters of 2016 (see Table 3.3 in Chapter 3). Nordion's Mo-99 processing capacity,

[7] It is also unclear at present whether Russia will use HEU or low enriched uranium (LEU) targets to produce Mo-99. See Chapter 5.

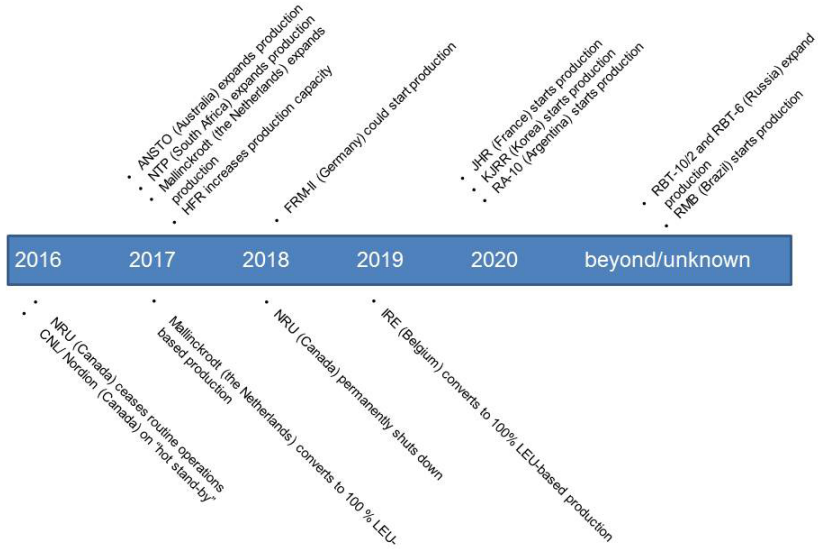

FIGURE 7.1 Expected changes to Mo-99 global supplies for the period 2016-2020.

currently about 4,680 6-day Ci per week, will drop to zero after October 2016. The scheduled expansions in available supply capacity by ANSTO, Mallinckrodt, and NTP will add about 4,400 6-day Ci per week in 2017, about 300 6-day Ci per week less than the capacity loss from Nordion.

7.1.4 Potential Additions to Available Domestic Supply Capacity

Several private-sector companies in the United States are planning to produce Mo-99 for medical use. These efforts are described in Chapter 4. Three companies have signed cooperative agreements with the Department of Energy's National Nuclear Security Administration (DOE-NNSA) and are actively working[8] to develop domestic Mo-99 supply capabilities:

- General Atomics, in collaboration with Nordion and MURR
- NorthStar Medical Radioisotopes
- SHINE Medical Technologies

[8] Two other companies, Babcock & Wilcox and General Electric-Hitachi, also signed cooperative agreements with NNSA but subsequently suspended their projects. See Chapter 4.

At least five other private-sector companies (also described in Chapter 4) are actively planning to develop domestic Mo-99 supply capabilities:

- Coquí RadioPharmaceuticals
- Eden Radioisotopes
- Flibe Energy
- Niowave
- Northwest Medical Isotopes

The NNSA-supported Mo-99 production projects are further along the development path than are production projects initiated by the private sector. As discussed in Chapter 4, none of these projects will be supplying Mo-99 to domestic markets by October 2016 when the NRU reactor ceases routine production. One project (NorthStar) may be supplying Mo-99 to domestic markets in 2018. It is unclear whether any of the five other private-sector projects will ever be completed (see Chapter 4).

7.1.5 Other Potential Sources of Mo-99/Tc-99m Supply

As discussed in Chapter 3, at least two of the four Canadian government-funded projects for Tc-99m production (Canadian Isotope Innovations and Advanced Cyclotron Systems) intend to supply Tc-99m to the U.S. market. However, these suppliers must obtain Food and Drug Administration approval to sell cyclotron-produced Tc-99m in the United States, and they will have to demonstrate the ability to produce this isotope reliably and cost-effectively. Even if successful, these suppliers are unlikely to provide more than a few hundred 6-day Ci per week to the U.S. market during the contingency period.

7.2 OECD-NEA ANALYSIS OF Mo-99 SUPPLY AND DEMAND

OECD-NEA has published several reports on Mo-99/Tc-99m market demand and projections (OECD-NEA, 2011b, 2012, 2014b, 2015, 2016). These reports are intended to inform policy makers, Mo-99 supply chain participants, and the medical community about *high-risk periods* for Mo-99 supply shortages. High-risk periods are defined in the latest reports as the periods when supply is near or below demand plus a 35 percent ORC. The OECD-NEA-recommended 35 percent ORC is based on the (n–1) criterion established by the High-level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) (see Chapter 3):

> In the HLG-MR principles, it was proposed that a processor should hold sufficient paid reserve capacity to replace the largest supplier of irradiated

> targets in their supply chain and likewise participants further down the supply chain should hold similar levels of ORC. This is the so-called (n-1) criterion. (OECD-NEA, 2015, p. 7)

The 2016 OECD-NEA report presents three scenarios for Mo-99 capacity and supply for the period 2016-2021.These scenarios are described in Sidebar 7.1. OECD-NEA concluded that

> the current irradiator and processor supply chain should be sufficient, and if well maintained, planned, and scheduled, be able to manage an unplanned outage of a reactor or a processor [in the 2016-2021 period]. (OECD-NEA, 2016, p. 21)

OECD-NEA also concluded that, starting in 2017, the capability to manage an unplanned outage will be reduced because of the planned exit of NRU/Nordion from the market. The organization highlighted the need to add irradiation and processing capacity by 2017 to offset this reduced capacity.

7.3 FINDING AND RECOMMENDATION

The committee analyzed the adequacy of Mo-99 supplies to meet domestic demand until about 2021 using the information provided in Chapters 3-6. The results of this analysis are presented below in one finding and one recommendation:

FINDING 4B: Global supplies of molybdenum-99 are adequate at present to meet U.S. domestic needs. However, available supply capacity will be reduced substantially after October 2016 when the Canadian supplier shuts down, and supply capacity could be reduced further in 2017-2018 when European suppliers convert to low enriched uranium targets and the Australian supplier starts up a new target processing facility, especially if these suppliers encounter conversion and/or start-up delays. The committee judges that there is a substantial (>50 percent) likelihood of severe molybdenum-99/technetium-99m supply shortages after October 2016, lasting at least until current global suppliers complete their planned capacity expansions.

RECOMMENDATION 4B: The U.S. government should continue to work with the Canadian government to ensure that there is an executable and well-communicated plan in place to restart Canadian supply of molybdenum-99 after October 2016.

SIDEBAR 7.1
OECD's 2016 Molybdenum-99 Supply Review

The latest OECD-NEA review of Mo-99/Tc-99m demand and production capacity was released in June 2016 (OECD-NEA, 2016). It provides the organization's findings for the period 2016-2021 based on three scenarios:

Scenario A or Reference Scenario: This is a baseline case that only includes irradiation and processing capacity contributed by existing suppliers (including Russia and Argentina) and added production capacity by existing suppliers that have plans to expand production by 2021.

For this scenario, OECD-NEA finds that processing capacity is close to the demand growth + 35 percent ORC from 2017 to 2021 (see Figure S7.1, *Top*).

Scenario B or Technological Challenge Scenario: This is a case that builds on the reference scenario and adds production capacity from some *qualified* (according to OECD-NEA) projects that aim to establish Mo-99 production[a] by 2021. In this scenario it is assumed that only the fission-based projects are likely to start Mo-99 production on their announced commissioning dates because of the proven technology and established market distribution. Projects that are exploring reactor- or non-reactor-based *alternative technologies* are assumed to have 50 percent probability of starting full-scale production on their announced commissioning dates because these technologies are not proven for large-scale commercial Mo-99 production and the market distribution is not established.

For this scenario, OECD-NEA finds that processing capacity appears to be sufficient to meet projected demand + 35 percent ORC even without all planned qualified projects being included in the total processing capacity (see Figure S7.1, *Middle*).

Scenario C or Project Delayed Scenario. This is a case that builds on the technological challenge scenario and assumes that the qualified projects that aim to produce Mo-99 and conversion to LEU production by existing suppliers are delayed by 1 year.

For this scenario, OECD-NEA finds that total processing capacity is close to the NEA demand + 35 percent ORC in 2017 (see Figure S7.1, *Bottom*). This, according to OECD-NEA, highlights the importance of introducing the new capacity in Australia within 2017.

See OECD-NEA (2016) for a detailed description of the different scenarios and projection periods.

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[a] The qualified projects included in the analysis are NorthStar, GA, SHINE, South Korea, Argentina, and JHR. U.S. projects such as Coquí, Northwest, Perma-Fix, and Niowave were not considered qualified by OECD-NEA because there were insufficient technical and project data made available to OECD-NEA by these projects for various reasons (Kevin Charlton, OECD-NEA, written communication, September 15, 2015).

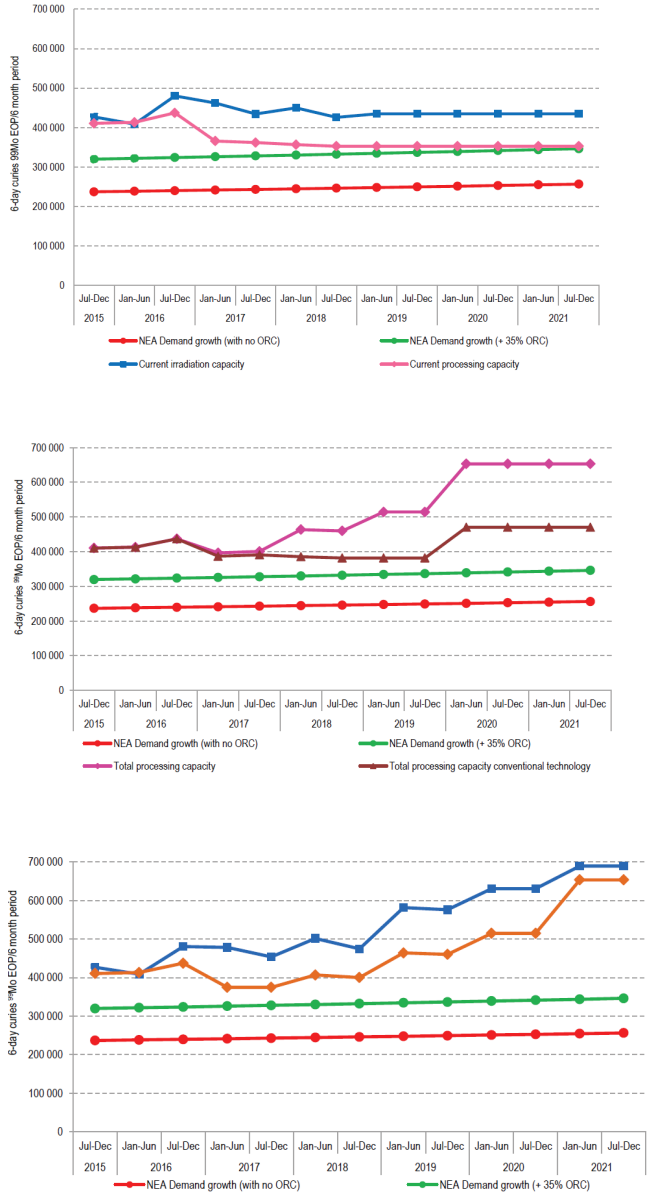

FIGURE S7.1 Selected modeling scenarios presented by OECD-NEA (2016). *Top*: Scenario A or Reference scenario. *Middle*: Scenario B or Technological Challenge scenario. *Bottom*: Scenario C or Project Delayed scenario. See text for brief descriptions of the different scenarios. NOTE: EOP = end of processing; ORC = outage reserve capacity. SOURCE: OECD-NEA (2016).

Current available supply capacity, about 15,880 6-day Ci of Mo-99 per week, is more than adequate *at present* to meet current global (~9,000 6-day Ci per week) and U.S. (~50 percent of global) demand. However, this supply capacity will be reduced to about 11,200 6-day Ci per week when NRU stops producing Mo-99 after October 2016. This represents about a 25 percent ORC, well below the 35 percent ORC recommended by OECD-NEA. Planned expansions by current suppliers, if realized, would restore most of the available supply capacity lost after October 2016 (see Figure 3.3 in Chapter 3).

A number of efforts are under way by current global Mo-99 suppliers and potential new domestic Mo-99 suppliers to fill the expected supply gap (see Section 7.1.3 in this chapter). The organizations responsible for these efforts have put forward what the committee considers to be *best-case* schedules for bringing new Mo-99 supplies to market. Several of these schedules have already slipped during the course of this study; additional slippage would be entirely unsurprising.

The number of irradiation services suppliers will be reduced from seven to six after NRU stops producing Mo-99. Four of the remaining suppliers use reactors that are over 50 years old (BR-2, HFR, LVR-15, and SAFARI-1), and one supplier also uses a reactor that is over 40 years old (Maria) (see Table 3.2 in Chapter 3). Irradiation services suppliers put great emphasis on maintenance so that their reactors can continue to operate safely and reliably. However, the potential for unplanned reactor maintenance outages increases as reactors age. Indeed, several of the reactors used to produce Mo-99 have already had unplanned and extended outages for major repairs (see Table 3.6 in Chapter 3). Such outages *may well* occur in the future.

Unplanned outages of Mo-99 suppliers could also reduce available supply capacity below current global demand. The number of global Mo-99 suppliers will be reduced from five to four after Canada stops supplying Mo-99. Three of these suppliers (IRE, Mallinckrodt, and NTP) are capable of supplying one-third or more of current global demand for Mo-99 (see Table 3.2 in Chapter 3). The loss of any one of these suppliers after October 2016 could result in severe global Mo-99 supply shortages.

Three global Mo-99 suppliers are currently making substantial modifications to their target processing facilities:

- IRE and Mallinckrodt are converting their facilities to process LEU targets and will be running two parallel processing lines (one for LEU targets and one for HEU targets) in 2017 and possibly 2018 (Chapter 5).
- ANSTO is constructing a new target processing facility (completion is planned for mid-2017) and will be implementing a target dis-

> solution and Mo-99 recovery process in that facility that contains elements of ANSTO's and NTP's current processes (see Chapter 3).

The potential for unexpected supply disruptions increases any time a supplier moves to a new facility or implements a new process. For example, ANSTO encountered a several-month delay in starting up its current target processing facility. IRE and Mallinckrodt have encountered unexpected delays in converting to low enriched uranium targets.[9] Such delays are a normal part of the start-up process for complex facilities but are difficult to anticipate or schedule.

IRE, Mallinckrodt, and NTP expect to lose about 20 percent[10] of their available supply capacity after conversion to LEU because of reduced uranium-235 (U-235) loadings and increased neutron capture (see Section 5.2 in Chapter 5). They are planning to increase target throughputs and make other changes to restore this lost capacity. Delays in these efforts could further reduce supply capacities.

NTP and ANSTO rely on one reactor each (SAFARI-1 and OPAL, respectively) for all of their target irradiations. They have no backup irradiation services suppliers. Consequently, their *entire* available supply capacity will be lost whenever these reactors shut down, whether for planned or unplanned maintenance. The reactor operators coordinate the planned outages for these reactors to minimize potential supply disruptions. However, unplanned outages of one of both of these reactors could result in severe supply shortages, especially if the outages extend over multiple weeks.

The committee agrees in principle with OECD-NEA that

> the current irradiator and processor supply chain should be sufficient, and if well maintained, planned, and scheduled, be able to manage an unplanned outage of a reactor or a processor [in the 2016-2021 period]. (OECD-NEA, 2016, p. 21)

However, the committee judges that it will be difficult to achieve a "well-maintained, planned, and scheduled supply chain" in light of the factors discussed above. The committee therefore finds (Finding 4B above) that there is a substantial (>50 percent) likelihood of severe molybdenum-99/technetium-99m supply shortages after October 2016, lasting at least until the planned production expansions described in Section 7.1.3 of this chapter are completed. In particular, unplanned outages at IRE, Mallinckrodt, or NTP would likely cause severe Mo-99 supply shortages, and delays by

[9] NTP, which already produces a portion of its supply with LEU targets, also encountered unexpected delays.

[10] OECD-NEA (2016) currently estimates production capacity losses to be 10 percent because some steps have already been taken by suppliers to overcome them.

ANSTO in expanding its available supply capacity will extend the period of global supply vulnerability. This period of vulnerability could last into 2018 and possibly beyond if there are substantial delays in completing these production expansions.

The committee recommends (see Recommendation 4B above) that the U.S. government should continue to work with the Canadian government to ensure that there is an executable and well-communicated plan in place to restart emergency production of molybdenum-99 in Canada if there are extended unplanned facility outages. The committee is particularly concerned about the potential for unplanned outages in global Mo-99 supplier facilities and the impacts of those outages on global Mo-99 supplies.

If such unplanned outages occur, the Canadian government might have only 1 week or at most 2 weeks to restart Mo-99 production in NRU to avoid severe global Mo-99 supply shortages. The decision and consultation processes will have to be well established and practiced to execute on this schedule. Of course, once a restart decision was made, NRU/Nordion will have to be operationally ready to resume Mo-99 production and supply. This will require that both organizations maintain an adequately sized and trained staff to operate the target irradiation and processing facilities during the contingency period.

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Appendix A

The American Medical Isotopes Production Act of 2012

Subtitle F—American Medical Isotopes Production

SEC. 3171. SHORT TITLE.

This subtitle may be cited as the "American Medical Isotopes Production Act of 2012".

SEC. 3172. DEFINITIONS.

In this subtitle:

(1) DEPARTMENT.—The term "Department" means the Department of Energy.

(2) HIGHLY ENRICHED URANIUM.—The term "highly enriched uranium" means uranium enriched to 20 percent or greater in the isotope U–235.

(3) LOW ENRICHED URANIUM.—The term "low enriched uranium" means uranium enriched to less than 20 percent in the isotope U–235.

(4) SECRETARY.—The term "Secretary" means the Secretary of Energy.

SEC. 3173. IMPROVING THE RELIABILITY OF DOMESTIC MEDICAL ISOTOPE SUPPLY.

(a) MEDICAL ISOTOPE DEVELOPMENT PROJECTS.—

(1) IN GENERAL.—The Secretary shall carry out a technology-neutral program—

(A) to evaluate and support projects for the production in the United States, without the use of highly enriched uranium, of significant quantities of molybdenum-99 for medical uses;

(B) to be carried out in cooperation with non-Federal entities; and

(C) the costs of which shall be shared in accordance with section 988 of the Energy Policy Act of 2005 (42 U.S.C. 16352).

(2) CRITERIA.—Projects shall be evaluated against the following primary criteria:

(A) The length of time necessary for the proposed project to begin production of molybdenum-99 for medical uses within the United States.

(B) The capability of the proposed project to produce a significant percentage of United States demand for molybdenum-99 for medical uses.

(C) The capability of the proposed project to produce molybdenum-99 in a cost-effective manner.

(D) The cost of the proposed project.

(3) EXEMPTION.—An existing reactor in the United States fueled with highly enriched uranium shall not be disqualified from the program if the Secretary determines that—

(A) there is no alternative nuclear reactor fuel, enriched in the isotope U–235 to less than 20 percent, that can be used in that reactor;

(B) the reactor operator has provided assurances that, whenever an alternative nuclear reactor fuel, enriched in the isotope U–235 to less than 20 percent, can be used in that reactor, it will use that alternative in lieu of highly enriched uranium; and

(C) the reactor operator has provided a current report on the status of its efforts to convert the reactor to an alternative nuclear reactor fuel enriched in the isotope U–235 to less than 20 percent, and an anticipated schedule for completion of conversion.

(4) PUBLIC PARTICIPATION AND REVIEW.—The Secretary shall—

(A) develop a program plan and annually update the program plan through public workshops; and

(B) use the Nuclear Science Advisory Committee to conduct annual reviews of the progress made in achieving the program goals and make recommendations to improve program effectiveness.

(b) DEVELOPMENT ASSISTANCE.—The Secretary shall carry out a program to provide assistance for—

(1) the development of fuels, targets, and processes for domestic molybdenum-99 production that do not use highly enriched uranium; and

(2) commercial operations using the fuels, targets, and processes described in paragraph (1).

(c) URANIUM LEASE AND TAKE-BACK.—

(1) IN GENERAL.—The Secretary shall establish a program to make low enriched uranium available, through lease contracts, for irradiation for the production of molybdenum-99 for medical uses.

(2) TITLE.—The lease contracts shall provide for the producers of the molybdenum-99 to take title to and be responsible for the molybdenum-99 created by the irradiation, processing, or purification of uranium leased under this section.

(3) DUTIES.—

(A) SECRETARY.—The lease contracts shall require the Secretary—

(i) to retain responsibility for the final disposition of spent nuclear fuel created by the irradiation, processing, or purification of uranium leased under this section for the production of medical isotopes; and

(ii) to take title to and be responsible for the final disposition of radioactive waste created by the irradiation, processing, or purification of uranium leased under this section for which the Secretary determines the producer does not have access to a disposal path.

(B) PRODUCER.—The producer of the spent nuclear fuel and radioactive waste shall accurately characterize, appropriately package, and transport the spent nuclear fuel and radioactive waste prior to acceptance by the Department.

(4) COMPENSATION.—

(A) IN GENERAL.—Subject to subparagraph (B), the lease contracts shall provide for compensation in cash amounts equivalent to prevailing market rates for the sale of comparable uranium products and for compensation in cash amounts equivalent to the net present value of the cost to the Federal Government for—

(i) the final disposition of spent nuclear fuel and radioactive waste for which the Department is responsible under paragraph (3); and

(ii) other costs associated with carrying out the uranium lease and take-back program authorized by this subsection.

(B) DISCOUNT RATE.—The discount rate used to determine the net present value of costs described in subparagraph (A)(ii) shall be not greater than the average interest rate on marketable Treasury securities.

(5) AUTHORIZED USE OF FUNDS.—Subject to the availability of appropriations, the Secretary may obligate and expend funds received under leases entered into under this subsection, which shall remain available until expended, for the purpose of carrying out the activities authorized by this subtitle, including activities related to the final disposition of spent nuclear fuel and radioactive waste for which the Department is responsible under paragraph (3).

(6) EXCHANGE OF URANIUM FOR SERVICES.—The Secretary shall not barter or otherwise sell or transfer uranium in any form in exchange for—

(A) services related to the final disposition of the spent nuclear fuel and radioactive waste for which the Department is responsible under paragraph (3); or

(B) any other services associated with carrying out the uranium lease and take-back program authorized by this subsection.

(d) COORDINATION OF ENVIRONMENTAL REVIEWS.—The Department and the Nuclear Regulatory Commission shall ensure to the maximum extent practicable that environmental reviews for the production of the medical isotopes shall complement and not duplicate each review.

(e) OPERATIONAL DATE.—The Secretary shall establish a program as described in subsection (c)(3) not later than 3 years after the date of enactment of this Act.

(f) RADIOACTIVE WASTE.—Notwithstanding section 2 of the Nuclear Waste Policy Act of 1982 (42 U.S.C. 10101), radioactive material resulting from the production of medical isotopes that has been permanently removed from a reactor or subcritical assembly and for which there is no further use shall be considered low-level radioactive waste if the material is acceptable under Federal requirements for disposal as low-level radioactive waste.

SEC. 3174. EXPORTS.

Section 134 of the Atomic Energy Act of 1954 (42 U.S.C. 2160d) is amended by striking subsection c. and inserting the following:

"c. MEDICAL PRODUCTION LICENSE SUNSET.—Effective 7 years after the date of enactment of the American Medical Isotopes Production Act of 2012, the Commission may not issue a license for the export of

highly enriched uranium from the United States for the purposes of medical isotope production.

"d. MEDICAL PRODUCTION LICENSE EXTENSION.—The period referred to in subsection c. may be extended for no more than 6 years if, no earlier than 6 years after the date of enactment of the American Medical Isotopes Production Act of 2012, the Secretary of Energy certifies to the Committee on Energy and Commerce of the House of Representatives and the Committee on Energy and Natural Resources of the Senate that—

"(1) there is insufficient global supply of molybdenum-99 produced without the use of highly enriched uranium available to satisfy the domestic United States market; and

"(2) the export of United States-origin highly enriched uranium for the purposes of medical isotope production is the most effective temporary means to increase the supply of molybdenum-99 to the domestic United States market.

"e. PUBLIC NOTICE.—To ensure public review and comment, the development of the certification described in subsection d. shall be carried out through announcement in the Federal Register.

"f. JOINT CERTIFICATION.—

"(1) IN GENERAL.—In accordance with paragraph (2), the ban on the export of highly enriched uranium for purposes of medical isotope production referred to in subsections c. and d. shall not go into effect unless the Secretary of Energy and the Secretary of Health and Human Services have jointly certified that—

"(A) there is a sufficient supply of molybdenum-99 produced without the use of highly enriched uranium available to meet the needs of patients in the United States; and

"(B) it is not necessary to export United States-origin highly enriched uranium for the purposes of medical isotope production in order to meet United States patient needs.

"(2) TIME OF CERTIFICATION.—The joint certification under paragraph (1) shall be made not later than 7 years after the date of enactment of the American Medical Isotopes Production Act of 2012, except that, if the period referred to in subsection c. is extended under subsection d., the 7-year deadline under this paragraph shall be extended by a period equal to the period of such extension under subsection d.

"g. SUSPENSION OF MEDICAL PRODUCTION LICENSE.—At any time after the restriction of export licenses provided for in subsection c. becomes effective, if there is a critical shortage in the supply of molybdenum-99 available to satisfy the domestic United States medical isotope needs, the restriction of export licenses may be suspended for a period of no more than 12 months, if—

"(1) the Secretary of Energy certifies to the Congress that the export of United States-origin highly enriched uranium for the purposes of medical isotope production is the only effective temporary means to increase the supply of molybdenum-99 necessary to meet United States medical isotope needs during that period; and

"(2) the Congress enacts a Joint Resolution approving the temporary suspension of the restriction of export licenses.

"h. DEFINITIONS.—As used in this section—

"(1) the term 'alternative nuclear reactor fuel or target' means a nuclear reactor fuel or target which is enriched to less than 20 percent in the isotope U–235;

"(2) the term 'highly enriched uranium' means uranium enriched to 20 percent or more in the isotope U–235;

"(3) a fuel or target 'can be used' in a nuclear research or test reactor if—

"(A) the fuel or target has been qualified by the Reduced Enrichment Research and Test Reactor Program of the Department of Energy; and

"(B) use of the fuel or target will permit the large majority of ongoing and planned experiments and medical isotope production to be conducted in the reactor without a large percentage increase in the total cost of operating the reactor; and

"(4) the term 'medical isotope' includes molybdenum-99, iodine-131, xenon-133, and other radioactive materials used to produce a radiopharmaceutical for diagnostic or therapeutic procedures or for research and development.".

SEC. 3175. REPORT ON DISPOSITION OF EXPORTS.

Not later than 1 year after the date of the enactment of this Act, the Chairman of the Nuclear Regulatory Commission, after consulting with other relevant agencies, shall submit to the Congress a report detailing the current disposition of previous United States exports of highly enriched uranium used as fuel or targets in a nuclear research or test reactor, including—

(1) their location;

(2) whether they are irradiated;

(3) whether they have been used for the purpose stated in their export license;

(4) whether they have been used for an alternative purpose and, if so, whether such alternative purpose has been explicitly approved by the Commission;

(5) the year of export, and reimportation, if applicable;

(6) their current physical and chemical forms; and

(7) whether they are being stored in a manner which adequately protects against theft and unauthorized access.

SEC. 3176. DOMESTIC MEDICAL ISOTOPE PRODUCTION.

(a) IN GENERAL.—Chapter 10 of the Atomic Energy Act of 1954 (42 U.S.C. 2131 et seq.) is amended by adding at the end the following:

"SEC. 112. DOMESTIC MEDICAL ISOTOPE PRODUCTION.

"a. The Commission may issue a license, or grant an amendment to an existing license, for the use in the United States of highly enriched uranium as a target for medical isotope production in a nuclear reactor, only if, in addition to any other requirement of this Act—

"(1) the Commission determines that—

"(A) there is no alternative medical isotope production target that can be used in that reactor; and

"(B) the proposed recipient of the medical isotope production target has provided assurances that, whenever an alternative medical isotope production target can be used in that reactor, it will use that alternative in lieu of highly enriched uranium; and

"(2) the Secretary of Energy has certified that the United States Government is actively supporting the development of an alternative medical isotope production target that can be used in that reactor.

"b. As used in this section—

"(1) the term 'alternative medical isotope production target' means a nuclear reactor target which is enriched to less than 20 percent of the isotope U–235;

"(2) a target 'can be used' in a nuclear research or test reactor if—

"(A) the target has been qualified by the Reduced Enrichment Research and Test Reactor Program of the Department of Energy; and

"(B) use of the target will permit the large majority of ongoing and planned experiments and medical isotope production to be conducted in the reactor without a large percentage increase in the total cost of operating the reactor;

"(3) the term 'highly enriched uranium' means uranium enriched to 20 percent or more in the isotope U–235; and

"(4) the term 'medical isotope' includes molybdenum-99, iodine-131, xenon-133, and other radioactive materials used to produce a radiopharmaceutical for diagnostic or therapeutic procedures or for research and development.".

(b) TABLE OF CONTENTS.—The table of contents for the Atomic Energy Act of 1954 is amended by inserting the following new item at the end of the items relating to chapter 10 of title I:

"Sec. 112. Domestic medical isotope production."

SEC. 3177. ANNUAL DEPARTMENT REPORTS.

(a) IN GENERAL.—Not later than 1 year after the date of enactment of this Act, and annually thereafter for 5 years, the Secretary shall report to Congress on Department actions to support the production in the United States, without the use of highly enriched uranium, of molybdenum-99 for medical uses.

(b) CONTENTS.—The reports shall include the following:

(1) For medical isotope development projects—

(A) the names of any recipients of Department support under section 3173;

(B) the amount of Department funding committed to each project;

(C) the milestones expected to be reached for each project during the year for which support is provided;

(D) how each project is expected to support the increased production of molybdenum-99 for medical uses;

(E) the findings of the evaluation of projects under section 3173(a)(2); and

(F) the ultimate use of any Department funds used to support projects under section 3173.

(2) A description of actions taken in the previous year by the Secretary to ensure the safe disposition of spent nuclear fuel and radioactive waste for which the Department is responsible under section 3173(c).

SEC. 3178. NATIONAL ACADEMY OF SCIENCES REPORT.

(a) IN GENERAL.—The Secretary shall enter into an arrangement with the National Academy of Sciences to conduct a study of the state of molybdenum-99 production and utilization, to be provided to Congress not later than 5 years after the date of enactment of this Act.

(b) CONTENTS.—The report shall include the following:

(1) For molybdenum-99 production—

(A) a list of all facilities in the world producing molybdenum-99 for medical uses, including an indication of whether these facilities use highly enriched uranium in any way;

(B) a review of international production of molybdenum-99 over the previous 5 years, including—

(i) whether any new production was brought online;

(ii) whether any facilities halted production unexpectedly; and

(iii) whether any facilities used for production were decommissioned or otherwise permanently removed from service; and

(C) an assessment of progress made in the previous 5 years toward establishing domestic production of molybdenum-99 for medical uses, including the extent to which other medical isotopes that have been produced with molybdenum-99, such as iodine-131 and xenon-133, are being used for medical purposes.

(2) An assessment of the progress made by the Department and others to eliminate all worldwide use of highly enriched uranium in reactor fuel, reactor targets, and medical isotope production facilities.

Appendix B

Committee and Staff Biographies

S. James Adelstein, Ph.D., M.D. (NAM), *Chair*, is the Paul C. Cabot Distinguished Professor of Medical Biophysics (Emeritus) at Harvard Medical School and a nuclear medicine specialist. His research interests include radionuclide dosimetry, the molecular and cellular effects of radiation, and the diagnosis and experimental treatment of cancer using radionuclides. He is a member of several professional organizations, including the Radiation Research Society and the Society of Nuclear Medicine and Molecular Imaging, and he is an elected fellow of both the American College of Nuclear Medicine and the American Association for the Advancement of Science. He was chair of the National Academies Board on Radiation Effects Research from 2002 to 2005 and vice chair of the Nuclear and Radiation Studies Board from 2005 to 2009, and he served on several National Academies committees. He also has served on public and private committees that have addressed issues concerning radiation protection, research collaboration, and biomedical isotopes. He received a B.S., an M.S., and a Ph.D. from the Massachusetts Institute of Technology and an M.D. from the Harvard Medical School. He served as dean for academic programs at Harvard Medical School from 1978 to 1998. He was elected to the Institute of Medicine (now the National Academy of Medicine) in 1985.

Thomas J. Ruth, Ph.D., V*ice-Chair*, is emeritus senior research scientist at TRIUMF and emeritus senior scientist at the British Columbia Cancer Research Centre. He holds adjunct professorships in chemistry at Simon Fraser University, physics at the University of Victoria, and medicine at the University of British Columbia. Dr. Ruth is a leader in the production

and application of radioisotopes for research in the physical and biological sciences. He has served on a multitude of national and international committees, including the National Academies Committee on Biomedical Isotopes (1993-1995), Committee on State of the Science in Nuclear Medicine (2006-2007), Committee on Medical Isotope Production without Highly Enriched Uranium (2007-2009), and Committee on an Assessment and Outlook for Nuclear Physics (2010-2012). He currently serves as an expert on radioisotope production for the International Atomic Energy Agency (IAEA) and was appointed by the IAEA director general to serve on the Standing Advisory Group on Nuclear Applications. He previously served on the Nuclear Science Advisory Committee's (NSAC's) Subcommittee on Isotopes for the Nuclear Physics Program of the U.S. Department of Energy (2009 and 2014) and on another NSAC subcommittee to review the National Nuclear Security Administration's program for removing highly enriched uranium from civilian use and supporting the development of U.S. sources of molybdenum-99. Dr. Ruth has published more than 290 peer-reviewed papers and book chapters. He received an M.A. in nuclear chemistry from the College of William and Mary and a Ph.D. in nuclear spectroscopy from Clark University. He is the 2011 recipient of the Michael J. Welch Award from the Society of Nuclear Medicine for his contributions to radiopharmaceutical chemistry. In 2015, along with five of his colleagues, Dr. Ruth received the Natural Sciences and Engineering Research Council of Canada's Brockhouse Award for their work in producing Tc-99m using medical cyclotrons.

Lin-Wen Hu, Ph.D., is director for research and services and principal research scientist at the Massachusetts Institute of Technology (MIT) Nuclear Reactor Laboratory (NRL), which operates the 6-megawatt MIT Research Reactor (MITR). Dr. Hu directs NRL's research and utilization program and leads the development, design, and safety reviews of major reactor irradiation facilities and experiments. She also serves as MITR's technical lead for the U.S. Department of Energy's Advanced Test Reactor National User Facility at Idaho National Laboratory, of which MITR is a partner facility; as the group leader of the research and test reactors working group of the nuclear technology subcommittee of International Standards Organization (ISO/TC85/SC6/WG2); and as a steering committee member of the International Group of Research Reactors. Her research interests include advanced nuclear energy systems; research reactor design, safety analysis, and applications in advanced fuel and materials irradiations; radioisotope production; and enhanced heat transfer of engineered fluids and nanostructure materials. Current research projects include the MITR low enriched uranium fuel conversion study and fluoride salt-cooled high-temperature reactor development. Dr. Hu is a licensed professional

engineer in the Commonwealth of Massachusetts and previously held a senior reactor operator license for the MITR. She has been active in the Isotope and Radiation (IRD) professional division of the American Nuclear Society since 1996 and is currently a member of the IRD Executive Committee. She has authored or coauthored more than 190 peer-reviewed journal papers, conference papers, and technical reports. She received an S.M. and a Ph.D. in nuclear engineering from MIT.

Joseph C. Hung, Ph.D., is professor of pharmacy and professor of radiology, Mayo Clinic College of Medicine, and consultant and director of radiopharmaceutical operations and enterprise Food and Drug Administration responsible official, Mayo Clinic. He is certified by the American Board of Science in Nuclear Medicine (certified as a nuclear medicine scientist in radiopharmaceuticals and radiochemistry) and by the Board of Pharmaceutical Specialties (certified as a nuclear pharmacist). Dr. Hung has served as chair of the Nuclear Pharmacy Practice Section, Academy of Pharmacy Practice and Management, American Pharmacists Association (APhA); president of the Chinese American Society of Nuclear Medicine (SNM); chair of the Committee on Pharmacopeia, SNM; and acting chair of the Expert Committee on Radiopharmaceuticals and Imaging Agents, United States Pharmacopeia. He was inducted as a fellow of the American Society of Health-System Pharmacists in 1995 and as an APhA fellow in 1996. He received a B.S. in pharmacy from Taipei Medical University and an M.S. and a Ph.D. in nuclear pharmacy from the University of Oklahoma Health Sciences Center.

Robert T. Jubin, Ph.D., is project manager for the U.S. Department of Energy's Fuel Cycle Technologies—Material Recovery and Waste Form Development Programs at Oak Ridge National Laboratory. He has more than 40 years of experience with nuclear fuel reprocessing, including solvent extraction and development of advanced centrifugal contactors; management of volatile radionuclides; and management of gaseous radioactive wastes. His solvent extraction experience includes an extended assignment with the Commissariat à l'énergie atomique et aux énergies alternatives at Fontenay-aux-Roses, near Paris, France, where he helped to develop the DIAMEX process for separation of actinides and lanthanides from high-level liquid wastes. Dr. Jubin is a member of the American Institute of Chemical Engineers and received its 2013 Robert E. Wilson Award for outstanding chemical engineering contributions and achievements in the nuclear industry. He also chairs the American Society of Mechanical Engineers' Gas Processing Subcommittee. He received a B.S. in chemical engineering from the University of Akron and an M.S. in engineering management and a Ph.D. in

chemical engineering, both from the University of Tennessee. He retired from the U.S. Air Force Reserve in 2007 at the rank of colonel.

Emmett B. Keeler, Ph.D. (NAM), is a professor in the Pardee RAND Graduate School and an adjunct professor at the University of California, Los Angeles, Public Health School, where he has taught about cost-effectiveness, cost-benefit, and decision analysis in medicine and public health for many years. He led the multisite Improving Chronic Illness Care Evaluation and the Management of Childbirth Patient Outcomes Research Team. He also analyzed health outcomes and episodes of spending for the RAND Health Insurance Experiment. His recent work has examined the costs of lung cancer screening and policies to promote cost-lowering new technologies. An elected member of the National Academy of Medicine (NAM), Dr. Keeler has participated in Institute of Medicine committees on the polygraph, on incorporating uncertainty into environmental decisions, the economic costs of uninsurance, the use of health measures in regulatory analysis, national health accounts, and geographic variation in health care spending. Dr. Keeler received a Ph.D. in mathematics from Harvard University.

Gerald L. Kulcinski, Ph.D. (NAE), is the Grainger Professor of Nuclear Engineering, Emeritus, and the director of the Fusion Technology Institute at the University of Wisconsin–Madison. He was the associate dean of research for the College of Engineering from 2001 to 2014. His current research involves the assessment of the technological and environmental aspects of the production of electricity from renewable, fossil, and nuclear energy sources. He has published more than 300 peer-reviewed scientific articles, more than 300 additional reports and articles in conference proceedings, and is a coauthor or contributor to four books. He was elected to the National Academy of Engineering in 1993 and was awarded the National Aeronautics and Space Administration (NASA) Public Service Medal in 1993 and the NASA Exceptional Public Service Medal in 2010. Dr. Kulcinski received a B.S. in chemical engineering and a Ph.D. in nuclear engineering from the University of Wisconsin–Madison.

Jason S. Lewis, Ph.D., is the Emily Tow Jackson Endowed Chair, vice chair of research in radiology, chief attending of the Radiochemistry & Imaging Sciences Service, and director of the Radiochemistry & Molecular Imaging Probe Core at Memorial Sloan Kettering Cancer Center (MSKCC). He holds a joint appointment in the Molecular Pharmacology and Chemistry Program at the Sloan Kettering Institute and in radiology at the Weill Cornell Medical College in New York. Dr. Lewis received a B.S. and an M.S. in chemistry from the University of Essex and a Ph.D. in biochemistry

from the University of Kent; he did his postdoctoral work at the Washington University School of Medicine (WUSM). Subsequently, he joined the WUSM faculty as an assistant professor of radiology (2003-2008), after which he joined MSKCC. Dr. Lewis's research program is a molecular imaging-based program focused on radiopharmaceutical development as well as the study of multimodality (PET, CT, and MRI) small- and biomolecule-based agents and their clinical translation. He has published more than 130 peer-reviewed articles as well as numerous book chapters and reviews. His research is supported by grants from the National Institutes of Health.

Kathryn A. Morton, M.D., is professor of radiology at the University of Utah with specialty training in diagnostic radiology and nuclear medicine. She previously served as chief of nuclear medicine at four academic centers (Veterans Affairs medical centers in Portland, Oregon, and Salt Lake City, Utah; Wake Forest University Medical Center; and University of Utah). Dr. Morton has 30 years of clinical experience with PET, PET/CT, conventional nuclear medicine, and diagnostic radiology. She also has academic experience as a researcher in imaging and molecular and cellular biology. She has served on more than 100 National Institutes of Health study sections and is the past chairman of the Grant Programs Committee for the Radiological Society of North America. She received an M.D. from the University of Utah.

Eugene J. Peterson, Ph.D., is executive advisor to Los Alamos National Laboratory's associate director for chemistry, life, and earth sciences and is leading the laboratory's strategic planning efforts for the Science of Signatures science pillar. Previously, he was the chemistry division leader at Los Alamos, where he was responsible for 350 chemical professionals and a budget of approximately $150 million. Before his tenure as chemistry division leader, Dr. Peterson specialized in medical isotope production and applications research and development. He was responsible for technical management of the laboratory's isotope production efforts and associated research and development, business management of isotope distribution and marketing, and procuring adequate funding for these programs. Notable program successes during his tenure included the construction of a new $23.5 million 100 MeV Isotope Production Facility at the Los Alamos Neutron Science Center for the production of accelerator isotopes and the lease by the U.S. Department of Energy of the laboratory's cryogenic distillation columns for the separation and purification of isotopes of carbon, nitrogen, and oxygen to the private sector. Dr. Peterson served on the National Academies Committee on Medical Isotope Production without

Highly Enriched Uranium. He received a B.S. from the Illinois Benedictine College and a Ph.D. in inorganic chemistry from Arizona State University.

Tor Raubenheimer, Ph.D., is a professor at the Stanford Linear Accelerator Center (SLAC) National Accelerator Laboratory and Stanford University. He is an expert in accelerator physics and design, especially for high-energy linear accelerators. Since 2011, Prof. Raubenheimer has been leading the accelerator physics design for the LCLS-II, a new high-power X-ray free electron laser based on a 4 GeV superconducting RF linac. He previously served as division director for the SLAC Accelerator Research Division, where he helped launch the Facility for Advanced Accelerator Experimental Tests as well as Large Hadron Collider accelerator research and muon accelerator research and development efforts at SLAC. Prior, he was head of the International Linear Collider Division and head of accelerator physics for the Next Linear Collider Project. He has authored more than 40 refereed journal articles and 250 conference papers. He is a fellow of the American Physical Society and has received its Division of Beam Physics Dissertation Award (1994) as well as the U.S. Particle Accelerator School Prize for Achievement in Accelerator Physics and Technology (2001). Prof. Raubenheimer received a B.S. in physics and computer science from Dartmouth College and a Ph.D. in applied physics from Stanford University.

Henry D. Royal, M.D., is professor of radiology at Washington University School of Medicine in St. Louis and associate director of nuclear medicine at the Mallinckrodt Institute of Radiology. He is trained in internal medicine and nuclear medicine and has been practicing nuclear medicine for 40 years, working in both academic and hospital settings. Dr. Royal was a member of the American Board of Nuclear Medicine from 1993 to 1999 and served as its executive director from 2004 to 2014. He also served as president of the Society of Nuclear Medicine from 2003 to 2004 and received its Lifetime Achievement Award in 2008. Dr. Royal was a member of the U.S. delegation to the United Nations Scientific Committee on the Effects of Atomic Radiation from 2002 to 2005; co-team leader of the health effects section of the International Atomic Energy Agency's International Chernobyl Project; a member of the Presidential Advisory Committee on Human Radiation Experiments; chair of the National Council on Radiation Protection and Measurements Scientific Committee on Radiation Effects on the Thyroid; and scientific chair of the Veterans' Advisory Committee on Environmental Hazards (2001 to 2010). He has been listed in "Best Doctors in America" since 1992. He received an M.D. from St. Louis University.

Felicia L. Taw, Ph.D., is group leader of the Nuclear and Radiochemistry Group at Los Alamos National Laboratory (LANL). This group, which

comprises approximately 100 staff, undertakes research and development and provides operational support for the lab's stockpile stewardship, threat reduction, and global security missions. Specific capability and program areas include nuclear forensics, treaty monitoring, weapons assessment, nuclear chemistry, radiochemistry, radioanalytical measurements, mass separations and mass spectrometry, and analytical chemistry. Dr. Taw previously served as deputy group leader for the Inorganic, Isotope, and Actinide Chemistry Group, where she helped manage the production of medical isotopes in support of LANL's isotope program, as well as research and operations in actinide and inorganic chemistry. She also previously served as the Chemistry Division's project manager for the National Nuclear Security Administration's Mo-99 Production Program. She has contributed to research on spent nuclear fuel, the development of gamma and neutron detectors, actinide chemistry, and fundamental inorganic and organic chemistry. Dr. Taw was a director's postdoctoral fellow at LANL and received a Ph.D. in organometallic chemistry from the University of North Carolina at Chapel Hill.

Staff

Kevin D. Crowley, Ph.D., *Study Director*, is senior board director of the Nuclear and Radiation Studies Board (NRSB) at the National Academies of Sciences, Engineering, and Medicine in Washington, DC. He is responsible for planning and managing the NRSB's portfolio of studies on radiation health effects, radioactive waste management and environmental cleanup, and nuclear security and terrorism and has personally directed or codirected more than 25 Academies studies in these and other subject areas. Dr. Crowley also is the principal investigator of the Academies' Radiation Effects Research Foundation project, which provides scientific support for the long-term study of health effects arising from exposures to ionizing radiation among World War II atomic-bombing survivors. Dr. Crowley held positions at Miami University of Ohio, the University of Oklahoma, and the U.S. Geological Survey before joining the Academies staff in 1993. He received his M.A. and Ph.D. degrees in geology from Princeton University.

Ourania (Rania) Kosti, Ph.D., *Senior Program Officer*, joined the staff of the Nuclear and Radiation Studies Board (NRSB) of the National Academies of Sciences, Engineering, and Medicine in January 2011. Prior to her current appointment, she was a postdoctoral fellow at the Lombardi Comprehensive Cancer Center at Georgetown University Hospital in Washington, DC, where she conducted research on biomarker development for early cancer detection using case-control epidemiologic study designs. She focused primarily on prostate, breast, and liver cancers and trying to

identify those individuals who are at high risk of developing malignancies. Dr. Kosti also trained at the National Cancer Institute (NCI) (2005-2007). She received a B.Sc. in biochemistry from the University of Surrey, UK, an M.Sc. in molecular medicine from University College London, and a Ph.D. in molecular endocrinology from St. Bartholomew's Hospital in London, UK. Dr. Kosti's interests within the NRSB focus on radiation health effects.

Appendix C

Presentations and Site Visits

FEBRUARY 12, 2015, WASHINGTON, DC

- Department of Energy-National Nuclear Security Administration Activities Related to Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium: Recommendations for This NAS [National Academy of Sciences] Study. Jeffrey Chamberlin, Director, Office of Conversion, Material Management and Minimization, Department of Energy (DOE)-National Nuclear Security Administration (NNSA); Rilla Hamilton, Mo-99 Program Director, Office of Conversion, Material Management and Minimization, DOE-NNSA
- U.S. Nuclear Industry Initiatives for the Development of Molybdenum-99 Production Methods Without Highly Enriched Uranium: Recommendations for This NAS Study. Michael Guastella, Council on Radionuclides and Radiopharmaceuticals
- International Efforts Related to Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium: Recommendations for This NAS Study. Kevin Charlton, Organisation for Economic Co-operation and Development, Nuclear Energy Agency
- Production of Molybdenum-99 Without Highly Enriched Uranium: Perspectives from the Union of Concerned Scientists and Recommendations for This NAS Study. Ed Lyman, Union of Concerned Scientists

- Perspectives from Professional Societies and Recommendations for This NAS Study. Vasken Dilsizian, American Society of Nuclear Cardiology; Sue Bunning, Society of Nuclear Medicine and Molecular Imaging; Jeffrey Norenberg, National Association of Nuclear Pharmacies

MAY 11-13, 2015, BURR RIDGE, ILLINOIS

- Mallinckrodt Pharmaceuticals. Roy Brown, Senior Director, Strategic Alliances, Mallinckrodt Pharmaceuticals
- NorthStar Medical Technologies. James Harvey, Senior VP and Chief Science Officer, NorthStar Medical Radioisotopes LLC
- SHINE Medical Technologies. Gregory Piefer, Chief Executive Officer, SHINE Medical Technologies, Inc.
- Oak Ridge National Laboratory. Chris Bryan, Irradiations Manager, High Flux Isotope Reactor, Oak Ridge National Laboratory
- Argonne National Laboratory. Amanda Youker, Chemist, Nuclear Engineering Division; Sergey Chemerisov, Facility Manager of the Linac and Van de Graaff Accelerator Facility, Nuclear Engineering Division; Peter Tkac, Chemist, Nuclear Engineering Division
- Los Alamos National Laboratory. Greg Dale, Mo-99 Program Lead and R&D Engineer, Los Alamos National Laboratory
- Y-12 National Security Complex. John Creasy, Program Manager for Advanced Reactor & Materials Design, Y-12 National Security Complex
- Savannah River National Laboratory. James Klein, Advisory Engineer, Savannah River National Laboratory
- University of Missouri Research Reactor Center. Ralph Butler, Director, University of Missouri Research Reactor Center
- General Atomics. John Saurwein, Project Manager, Reactor-Based Mo-99 Production System Project, General Atomics
- Nordion, Tom Burnett, President, Medical Isotopes, Nordion

JUNE 2, 2015, CONFERENCE CALL

- Current and Future Trends of Utilization of Nuclear Cardiology Procedures and Competing Technologies. Dr. Marcelo Di Carli, Brigham and Women's Hospital; Dr. Robert Gropler, Washington University School of Medicine in St Louis Raymond; Dr. Louise Thomson, Cedars-Sinai Los Angeles; Dr. William VanDecker, Temple University Hospital

JULY 22, 2015, CONFERENCE CALL

- IMV's Methodology for the 2015 Nuclear Medicine Market Outlook Report. Gail Prochaska, Vice President, IMV Medical Information Division; Lorna Young, Senior Director, Market Research
- Experts Views on Mo-99 Current and Future Demand. Dr. Victor A. Ferrari, Penn Medicine; Dr. Linda D. Gillam, Atlantic Health System; Dr. Michael H. Picard, Massachusetts General Hospital

AUGUST 12-13, 2015, WASHINGTON, DC

- Uranium Lease and Take-Back Program. Peter Karcz, Office of Material Management and Minimization (NA-23), National Nuclear Security Administration; Hitesh Nigam, Office of Nuclear Materials Disposition (EM-22), Department of Energy, Office of Environmental Management
- FDA's Role in Mo-99 Production and Utilization. Eric Duffy, Division Director, Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration
- U.S. Nuclear Regulatory Commission Licensing Activities Related to Molybdenum-99 Production. Steven Lynch, Project Manager, Office of Nuclear Reactor Regulation, U.S. Nuclear Regulatory Commission
- EU Observatory on the Supply of Medical Radioisotopes. Remigiusz Barańczyk, Head of Nuclear Fuel Market Observatory Sector, Euratom Supply Agency
- TechneLite® Generators Manufactured with LEU-based Mo-99. Ira Goldman, Senior Director, Global Strategic Supply and Government Relations, Lantheus Medical Imaging
- Northwest Medical Isotopes Mo-99 Production Program. Carolyn Haass, Chief Operating Officer, Northwest Medical Isotope, LLC
- Tc-99m Payment Economics. Daniel Duvall, Medical Officer, Center for Medicare, Hospital and Ambulatory Policy Group, Centers for Medicare & Medicaid Services
- Economics of Global Radioisotope Production. Kevin Charlton, Senior Analyst, Nuclear Energy Agency, Organisation for Economic Co-operation and Development Supply Chain for Molybdenum-99 Generators. Scott Claunch, Director, Pharmacy Safety and Practice, Industry and Government Affairs, Cardinal Health Pharmacy

NOVEMBER 3, 2015, WASHINGTON, DC

- Uranium Lease and Take-Back Program—an Update. Peter Karcz, Office of Material Management and Minimization (NA-23), National Nuclear Security Administration; Theresa Kliczewski, Environmental specialist, Department of Energy, Office of Environmental Management
- U.S. Nuclear Regulatory Commission's Role in Disposition of Radioactive Waste Resulting from Molybdenum-99 Production. Steven Lynch, Project Manager, Office of Nuclear Reactor Regulation, U.S. Nuclear Regulatory Commission
- The Effect of Emissions from Fission-Based Medical Isotope Production on Nuclear Explosion Detection. Tim Evans, Office of Nuclear Verification (NA-243), NNSA; Ted Bowyer, Pacific Northwest National Laboratory
- Coquí's Mo-99 Production Program. Carmen Irene Bigles, President & CEO, Coquí Radio Pharmaceuticals Corp.
- Niowave's Mo-99 Production Program. Terry L. Grimm, President & Senior Scientist, Niowave, Inc.
- Perma-Fix Medical Mo-99 Production Program. Lou Centofanti, President and Chief Executive Officer, Perma-Fix
- UPPI's LEU Walk. John Witkowski, President, United Pharmacy Partners

DECEMBER 16, 2015, OTTAWA, ONTARIO, CANADA

- NRCan's Role in Establishing Policies and Programs for Securing Supply of Mo-99/Tc-99, and Other Radioisotopes in Canada. Daniel Brady, Deputy Director, Nuclear Science & Technology, Natural Resources Canada
- CIIC's Project for Producing Tc-99m for Medical Use. Mark de Jong, Chief Technology Officer, Canadian Isotope Innovations Corp.; Kennedy Mang'era, Chief Operating Officer, Canadian Isotope Innovations Corp.; James George, Chief Executive Officer, Canadian Isotope Innovations Corp.
- PIPE's Project for Producing Tc-99m for Medical Use. Chris Saunders, Prairie Isotope Production Enterprise; Sandor Demeter, Section Head of Nuclear Medicine at the Health Sciences Centre, Winnipeg MB, Co-Director of the Winnipeg Great West Life Positron Emission Tomography program, Associate Professor with the Department of Radiology (primary) and Community Health Sciences

- TRIUMF's Project for Producing Tc-99m for Medical Use. Ken Buckley, Project Manager; Technical Support: Targetry, TRIUMF
- ACSI's Oroject for Producing Tc-99m Using Medium Energy, High Current Cyclotrons. Brigitte Guérin, Full Professor, Department of Nuclear Medicine and Radiobiology, Université de Sherbrooke; Alex Zyuzin, Director Research and Business Development, Advanced Cyclotron Systems, Inc. (ACSI)

MARCH 30, 2016, CONFERENCE CALL

- Uranium Lease and Take-Back Program—an Update. Peter Karcz, Office of Material Management and Minimization, National Nuclear Security Administration; Hitesh Nigam, Office of Nuclear Materials Disposition, Department of Energy, Office of Environmental Management; Theresa Kliczewski, Environmental specialist, Department of Energy, Office of Environmental Management; John Myers, DOE/EM

APRIL 20, 2016, WASHINGTON, DC

- Department of Energy-National Nuclear Security Administration: Closing Remarks and Suggestions Related to the Academies Study. Jeffrey Chamberlin, Director, Office of Conversion, Material Management and Minimization, Department of Energy (DOE)-National Nuclear Security Administration (NNSA); Rilla Hamilton, Mo-99 Program Director, Office of Conversion, Material Management and Minimization, DOE-NNSA

JULY 8, 2016, CONFERENCE CALL

- 2016 Medical Isotope Supply Review: 99Mo/99mTc Market Demand and Production Capacity Projection, 2016-2021. Kevin Charlton, Senior Analyst, Nuclear Energy Agency, OECD

SITE VISITS

- May 12, 2015: Argonne National Laboratory, Argonne, IL
- May 14, 2015: University of Missouri Research Reactor Center, Columbia, MO
- July 13-17, 2015: Russian Academy of Sciences, Moscow, Russia, and Russian Institute of Atomic Reactors Dimitrovgrad, Russia
- August 11, 2015: Cardinal Health Pharmacy, Beltsville, MD

- September 28-29, 2015: NTP Radioisotopes SOC, Ltd., and South African Fundamental Atomic Research Installation 1, Pretoria, South Africa
- October 19-22, 2015: CERCA, Paris, France; IRE, Fleurus, Belgium; Mallinckrodt and High Flux Reactor, Petten, the Netherlands
- December 14, 2015: Nordion, Kanata, Ontario, Canada
- December 15, 2015: Canadian Nuclear Laboratories, Chalk River, Ontario, Canada
- January 18-19, 2016: Australian Nuclear Science and Technology Organisation (ANSTO), Lucas Heights, Australia
- February 4, 2016: Lantheus Medical Imaging, N. Billerica, MA

Appendix D

List of Radiopharmaceuticals and Associated Codes Used in the Committee's Medicare Data and Nuclear Pharmacy Data Analyses

All Nuclear Medicine Diagnostic	HCPCS	Category				
		All Tc-99m diagnostic	Tc-99m MPI diagnostic	All non-Tc-99m/non-PET diagnostic	All PET diagnostic	Nuclear medicine diagnostic (non-PET)
Sestamibi (Cardiolite)	A9500	X	X			X
Tetrofosmin (Myoview)	A9502	X	X			X
Tl-201 chloride	A9505			X		X
N-13 ammonia	A9526				X	
Rb-82, diagnostic, per study dose to 60 mCi	A9555				X	
Medronate (MDP)	A9503	X				X
Tc-99m Oxidronate (TechneScan, HDP)	A9561	X				X
Pyrophosphate	A9538	X				X
Sodium fluoride F-18, diagnostic, per study dose, up to 30 millicuries	A9580				X	
Disofenin (Hepatolite)	A9510	X				X
Mebrofenin (Choletec)	A9537	X				X
Mertiatide (MAG-3)	A9562	X				X
Succimer (DMSA)	A9551	X				X
Tc-99m glucoheptonate (glucoheptate)	A9550	X				X
Tc-99m pentatate (DTPA)	A9539	X				X
I-125 sodium iothalamate (Glofil-125)	A9554			X		X
I-123 NaI, per 100 uCi, capsules, diagnostic	A9516			X		X

I-123 NaI per mCi, diagnostic	A9509			X		X
I-131 NaI capsule per mCi, diagnostic	A9528			X		X
I-131 NaI solution per mCi, diagnostic	A9529			X		X
I-131 NaI per uCi	A9531			X		X
Pertechnetate per mCi	A9512	X				X
Macroaggregated albumin (MAA)	A9540	X				X
Xe-133	A9558			X		X
Tc-99m pentatate aerosol	A9567	X				X
In-111 pentetreotide (Octreoscan)	A9565/9572			X		X
I-131 iobenguane (MIBG), diagnostic, per 0.5 mCi	A9508			X		X
I -123 iobenguane MIBG, diagnostic, up to 15 mCi	A9582			X		X
Fluorodeoxyglucose F-18 FDG, diagnostic	A9552				X	
Exametazime (Ceretec)	A9521	X				X
Bicisate (Neurolite)	A9557	X		X		X
I-123 ioflupane (DATscan)	A9584					X
In-111 Pentetate, Diagnostic CSF, per 0.5 mCi	A9548					X
F18 Florbetapir (Amyvid)	A9586				X	
In-111 oxyquinoline (oxine)	A9547			X		X

continued

All Nuclear Medicine Diagnostic	HCPCS	Category				
		All Tc-99m diagnostic	Tc-99m MPI diagnostic	All non-Tc-99m/non-PET diagnostic	All PET diagnostic	Nuclear medicine diagnostic (non-PET)
Exametazime (HMPAO) autologous WBC's	A9569	X				X
In-111 labeled autologous WBC's	A9570					X
Sulfur colloid	A9541	X				X
Labeled red cells	A9560	X				X
Ga-67 citrate per mCi	A9556			X		X
In-111 ibiritumomab tiuxetan (Zevalin), diagnostic	A9542			X		X
I-131 tositumomab (Bexxar), diagnostic	A9544			X		X
Co57/58 cyanocobalamin	A9546			X		X
Cr-51 sodium chromate	A9553			X		X
Co-57 cyanocobalamin	A9559			X		X
Arcitumomab (CEA Scan)	A9568	X				X
In-111 capromab pendetide (Prostascint)	A9507			X		X
In-111 labeled autologous platelets	A9571			X		X
I-131 human serum albumin	A9524			X		X

NOTE: Categories correspond to the labels used in Figures 6.1-6.3 and 6.6 and 6.7 in Chapter 6.

Appendix E

Acronyms

2D	Two-dimensional
3D	Three-dimensional
ABIM	American Board of Internal Medicine
ABMS	American Board of Medical Specialties
ABNM	American Board of Nuclear Medicine
ABR	American Board of Radiology
ACGME	Accreditation Council for Graduate Medical Education
ACSI	Advanced Cyclotron Systems, Inc
AECL	Atomic Energy of Canada Limited
AIPES	Association of Imaging Producers and Equipment Suppliers
AMA	American Medical Association
AMIPA	American Medical Isotopes Production Act
ANDA	Abbreviated new drug application
ANL	Argonne National Laboratory
ANSTO	Australian Nuclear Science and Technology Organisation
ASNM	American Society of Nuclear Medicine
ATA	American Thyroid Association
AUC	Appropriate Use Criteria
B&W	Babcock & Wilcox (now BWX Technologies)
BATAN	Badan Tenaga Nuklir Nasional
Bq	Becquerel
BR-2	Belgian Reactor II

CAD	Coronary artery disease
CANDU	CANada Deuterium Uranium
CBNC	Certifying Board of Nuclear Cardiology
CCaS	Coronary artery calcium scoring
CCTA	Cardiac computed tomography angiography
CEA	Commissariat à l'énergie atomique et aux énergies alternatives
CEA Scan™	Carcinoembryonic antigen scan (Tradename for arcitumomab)
CERCA	Compagnie pour l'Etude et la Réalisation de CombustiblesAtomiques
Ci	Curie
CIAE	China Institute of Atomic Energy
CIIC	Canadian Isotope Innovations Corporation
CMS	Centers for Medicare & Medicaid Services
CNEA	Comisión Nacional de Energía Atómica
CNL	Canadian Nuclear Laboratories
CNSC	Canadian Nuclear Safety Commission
CORAR	Council of Radionculides and Radiopharmaceuticals
CPT	Current Procedural Terminology
CRCHUS	Centre de Recherche du Centre Hospitalier Universitaire de Sherbrooke
CRP	Coordinated Research Project
CT	Computed tomography
DOE	U.S. Department of Energy
DTPA	Diethylene triamine pentaacetic acid
EOP	End of processing
FDA	U.S. Food and Drug Administration
FRM-II	Forschungsreaktors München II reactor
FY	Fiscal year
GA	General Atomics
GAO	U.S. Government Accountability Office
GE	General Electric
GEHC	General Electric Health Care
GTRI	Global Threat Reduction Initiative
HANARO	High-flux Advanced Neutron Application ReactOr
HCPCS	Healthcare Common Procedural Code System

HEU	Highly enriched uranium
HFIR	High Flux Isotope Reactor
HFR	High Flux Reactor
HHS	U.S. Department of Health and Human Services
HIFAR	High Flux Australian Reactor
HLG-MR	High-level Group on the Security of Supply of Medical Radioisotopes
HLW	High-level waste
IAEA	International Atomic Energy Agency
INVAP	Investigación Aplicada
IOM	Institute of Medicine
IRE	Institut National des Radioéléments
JHR	Jules Horowitz Reactor
KAERI	Korea Atomic Energy Research Institute
KJRR	Kijang Research Reactor
LEU	Low enriched uranium
LLW	Low-level waste
LMI	Lantheus Medical Imaging
MAA	Macroaggregated albumin
MAG3 (or MAG-3)	Mercaptoacetyltriglycine
MAPLE	Multipurpose Applied Physics Lattice Experiment reactor
MIPS	Medical Isotopes Production System
MIR	Modernized international reactor
MIT	Massachusetts Institute of Technology
MOX	Mixed oxide
MPI	Myocardial perfusion imaging
MRI	Magnetic resonance imaging
MTR	Materials test reactor
MURR	Missouri University Research Reactor Center
MYRRHA	Multi-purpose hYbrid Research Reactor for High-tech Applications
NASEM	National Academies of Sciences, Engineering, and Medicine
NCRP	National Council on Radiation Protection and Measurements
NDA	New Drug Application

NEA	Nuclear Energy Agency
NECSA	Nuclear Energy Corporation of South Africa
NEI	Nuclear Energy Institute
NNSA	National Nuclear Security Administration
NRC	U.S. Nuclear Regulatory Commission
NRCan	Natural Resources Canada
NRG	Nuclear Research and Consultancy Group
NRU	National Research Universal Reactor
NTP	Nuclear Technology Products SOC Ltd.
OECD	Organisation for Economic Co-operation and Development
OPAL	Open-Pool Australian Lightwater Reactor
ORC	Outage reserve capacity
ORNL	Oak Ridge National Laboratory
OSTP	(The White House) Office of Science and Technology Policy
PET	Positron emission tomography
PIPE	Prairie Isotope Production Enterprise
PNNL	Pacific Northwest National Laboratory
RAS	Russian Academy of Sciences
RIAR	Scientific Research Institute of Atomic Reactors
RMB	Brazilian Multipurpose Research Reactor
SAFARI-1	South Africa Fundamental Atomic Research Installation 1 reactor
sANDA	Supplemental ANDA
SCK•CEN	Dutch: Studiecentrum voor Kernenergie; French: Centre d'Étude de l'énergie Nucléaire; English: Belgian Nuclear Research Center
SGE	Selective gas extraction
SHINE	Subcritical Hybrid Intense Neutron Emitter
sNDA	Supplemental NDA
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computed tomography
SRA	Southern Radioisotopes Alliance Inc.
TIG	Tungsten inert gas
TRIGA	Training, Research, Isotopes, General Atomics
TRIUMF	A consortium of Canadian universities, formerly Tri-University Meson Facility
TRM	Target Residual Material

UPPI	United Pharmacy Partners LLC
WBC	White blood cell
WNN	World Nuclear News