MEDICAL ISOTOPE PRODUCTION WITHOUT HIGHLY ENRICHED URANIUM

Committee on Medical Isotope Production Without Highly Enriched Uranium

Nuclear and Radiation Studies Board
Division of Earth and Life Studies

NATIONAL RESEARCH COUNCIL
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

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This study was supported by Contract/Grant No. DE-AM01-04PI45013 between the National Academy of Sciences and the U.S. Department of Energy. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the views of the organizations or agencies that provided support for the project.

International Standard Book Number-13: 978-0-309-13039-4
International Standard Book Number-10: 0-309-13039-5

Cover: Image generated from a brain perfusion scan using technetium-99m (courtesy of Satoshi Minoshima, University of Washington). Overlay: Photograph of the University of Missouri Research Reactor (MURR) core (courtesy of the University of Missouri).

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Printed in the United States of America

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Preface

This study was motivated by a conflict between the nonproliferation objectives of the Energy Policy Act of 1992, which created increasing pressures to phase out U.S. exports of highly enriched uranium (HEU) for medical isotope production, and the Energy Policy Act of 2005, which sought to increase the reliability of medical isotope supply by lifting the requirements of the 1992 Act for HEU exports to Canada, the Netherlands, Belgium, France, and Germany for medical isotope production.[1] At no time during the study were these dual objectives of securing HEU and providing a reliable supply of medical isotopes questioned by the committee—both objectives are obviously important. The question we pursued was the feasibility of achieving both.

All of the U.S. supply of the most widely used medical isotope, technetium-99m (Tc-99m), is produced by irradiating HEU targets in a reactor, extracting molybdenum-99 (Mo-99) from the targets, and collecting the Tc-99m that is produced when Mo-99 decays. No Mo-99 is currently produced domestically for medical use. The two main sources of Mo-99 for use in the United States are the National Research Universal (NRU) Reactor operated by Atomic Energy of Canada, Ltd. (AECL) at its Chalk River, Ontario, site and the High Flux Reactor (HFR) operated by the Nuclear Research and Consultancy Group at the Petten, Netherlands, site. Both reactors are over 40 years old.

[1]See Sidebar 1.3 for a discussion of these congressional amendments.

The Committee was tasked with evaluating the feasibility of converting medical isotope production of Mo-99 from HEU to low enriched uranium (LEU). For reasons discussed in Chapter 3, the report focuses on the feasibility of producing Mo-99 with LEU. In Section 630 of the Energy Policy Act of 2005, Congress defines feasibility to include consideration of cost, specifically, that "the average anticipated total cost increase from production of medical isotopes in such facilities without use of highly enriched uranium is less than 10 percent." That Mo-99 can be produced in a reactor without using HEU is not in doubt; Argentina has been producing Mo-99 with an all-LEU system since 2002. An Argentine-designed and built reactor near Sydney, Australia, will likely produce Mo-99 with LEU fuel and targets in the near future, and an Argentine company is completing construction of a Mo-99 processing facility at an all-LEU reactor near Cairo, Egypt.

As the committee began to assess the technology of isotope production and the system of production and distribution, it quickly came to understand that the system that supplies and distributes medical isotopes involves more than just cost considerations. We found that the medical community that uses Tc-99m and the industry that provides it greatly value the reliability of supply.

During the study, there were three significant medical isotope outages in the United States and one currently ongoing in Europe. The first, from November 2005 through April 2006, was the result of a Tc-99m generator supply disruption when a U.S.-based technetium generator producer, Mallinckrodt, shut down production because of a product recall. The second outage was the result of a safety-related shutdown of the NRU Reactor in Canada that began in late November 2007 and lasted about a month. The third outage was the result of the shutdown of HFR in the Netherlands that began in August 2008 and is expected to last through the middle of February 2009. At about the same time, a Mo-99 processing facility in Belgium was also shut down after radioactive iodine was inadvertently vented to the environment. The global production of Mo-99 was inadequate to meet demand during these outages, and some hospitals and clinics were forced to postpone or cancel diagnostic imaging procedures.

At the time of our study's first meeting in February 2007, AECL was working to complete two new reactors, Maple I and Maple II, which were to be dedicated to medical isotope production, and a new Mo-99 processing facility. The reactors and their associated processing facilities would have had the capacity to supply essentially all of the Mo-99 needed to meet worldwide demand if necessary and would have provided redundancy to ensure reliability. However, for reasons described in Chapter 10, AECL discontinued work on the Maple reactors in May 2008.

Planning is underway in Europe for a replacement for HFR in the Netherlands, but construction has not begun. Construction of a new

research reactor, the Jules Horowitz, has just begun in France, and it is scheduled to begin operation in 2014. As discussed in Chapter 3, other supplies could come online that could contribute to U.S. Mo-99 supply, including supplies from domestic producers.

The supply of Mo-99 in the United States is likely to be unreliable until newer production sources come online. The reliability of the current supply system is an important medical isotope concern; as noted in Chapter 10, the committee has concluded that achieving a cost difference of less than 10 percent in facilities that will need to convert from HEU- to LEU-based Mo-99 production is much less important than is reliability of supply.

Chris Whipple, *Chair*
Steve Larson, *Vice Chair*

Acknowledgments

At the start of this study, the committee had much to learn about all aspects of the radiopharmaceutical market, including the technologies involved in radiopharmaceutical production, distribution, medical application, and regulation. The cooperation we received from radioisotope producers and associated organizations was complicated by their responsibilities to protect proprietary technologies and business plans. Despite this complication, the information and cooperation that the committee received from these organizations was critical to the success of this study. This report could not have been written without the support of the people listed below who made presentations to the committee and/or met with small groups of committee members during site visits.

The committee acknowledges the excellent support it received from the project sponsor, the U.S. Department of Energy, National Nuclear Security Administration. The committee is especially grateful for the support it received from Andrew Bieniawski, Nicole Nelson-Jean, Parrish Staples, and Edward Fei.

The committee gratefully acknowledges the following people who made presentations at its information-gathering sessions:

- Henri Bonet, Institut National des Radioéléments (IRE)
- Roy Brown, Council on Radionuclides and Radiopharmaceuticals (CORAR)
- Ralph Butler, Missouri University Research Reactor (MURR)
- Jack Coffey, Cardinal Health

- Pablo Cristini, Comisión Nactional de Energía Atómica (CNEA)
- Stephen Dembek, U.S. Nuclear Regulatory Commission
- Therese Donlevy, Australian Nuclear Science and Technology Organization (ANSTO)
- Edward Fei, U.S. Department of Energy, National Nuclear Security Administration (DOE-NNSA)
- Ira Goldman, International Atomic Energy Agency (IAEA)
- Ed Lyman, Union of Concerned Scientists
- Peter Lyons, U.S. Nuclear Regulatory Commission
- Grant Malkoske, MDS-Nordion
- Brian McGee, Atomic Energy of Canada Limited (AECL)
- Nicole Nelson-Jean, DOE-NNSA
- Adrian Nunn, Bracco Research
- Evans Reynolds, Babcock & Wilcox (B&W)
- Richard Roberts, Mallinckrodt
- Marcelo Salvatore, Investigaciones Aplicadas Sociedad del Estado (INVAP)
- Dale Simpson, Mallinckrodt
- Parrish Staples, DOE-NNSA
- Orhan Suleiman, U.S. Food and Drug Administration
- George Vandegrift, Argonne National Laboratory
- Frank von Hippel, Princeton University

Small groups of committee members visited several facilities during this study to obtain first-hand information about the medical isotope production process (see Appendix C). We gratefully acknowledge the following organizations and individuals for supporting these visits:

- AECL Chalk River Laboratories (Chalk River, Ontario, Canada), Brian McGee
- ANSTO (Lucas Heights, Australia), Ian Smith and Ian Turner
- CNEA and INVAP (Buenos Aires, Argentina), Gabriel Norberto Barcelo, National Atomic Energy Commission, Pablo Cristini, CNEA, and Juan José Gil Gerbino, Marcelo Salvatore and Daniel Amaya, INVAP
- Compagnie pour l' Etude et la Réalisation de Combustibles Atomiques (CERCA; Romans, France), Henri Sztark and Laurent Hallé
- High Flux Reactor (Petten, the Netherlands), Rob Stol and Fred Wjitsma, Nuclear Research and Consultancy Group
- IRE (Fleurus, Belgium), Henri Bonet
- Mallinckrodt (Maryland Heights, MO, and Petten, the Netherlands), Dale Simpson

- MDS Nordion (Ottawa, Ontario, Canada), Grant Malkoske. Mr. Malkoske retired toward the end of the study; the committee's point of contact after his retirement was Jill Chitra
- MURR (Columbia, MO), Ralph Butler and Charlie Allen

The committee is also grateful for the excellent assistance provided by the National Research Council staff in preparing this report. Staff members who contributed to this effort are Kevin Crowley, study director and director of the Nuclear and Radiation Studies Board, Naoko Ishibe (program officer), Daniela Stricklin (program officer), Courtney Gibbs (senior program assistant), and Shaunteé Whetstone (senior program assistant).

The expertise needed to cover the areas within our scope was remarkably broad, and the committee membership reflected this diversity. The expertise of the committee members included nuclear medicine, radiopharmaceutical production, nuclear reactor design and operations, fabrication and chemical processing of uranium targets, waste management, nuclear nonproliferation, security for facilities with highly enriched uranium, economics, construction management, and risk assessment. A consequence of such diversity is that the study was an excellent learning experience for all involved. I thank the members of the committee for their dedicated efforts throughout the development of this report.

Chris Whipple, *Chair*

Reviewers

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

Mr. Pablo Adelfang, International Atomic Energy Agency
Dr. Jim Adelstein, Harvard Medical School
Dr. Carolyn Anderson, Washington University
Dr. Frank Bengel, Johns Hopkins School of Medicine
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Dr. Geoffrey Rothwell, Stanford University
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Dr. Armando Travelli, Argonne National Laboratory (retired)
Dr. Frank von Hippel, Princeton University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Dr. Harold Forsen, Bechtel Corporation, and Dr. John Bailar, University of Chicago. Appointed by the National Research Council, 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 carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the National Research Council.

Contents

Summary

This report is the product of a congressionally mandated study[1] to examine the feasibility of eliminating the use of highly enriched uranium (HEU[2]) in reactor fuel, reactor targets, and medical isotope production facilities. The report focuses primarily on the use of HEU for the production of the medical isotope molybdenum-99 (Mo-99), whose decay product, technetium-99m[3] (Tc-99m), is used in the majority of medical diagnostic imaging procedures in the United States, and secondarily on the use of HEU for research and test reactor fuel. This summary is organized around the four study charges provided by Congress and a fifth study charge negotiated between the National Academies and the study sponsor, the Department of Energy's National Nuclear Security Administration (DOE-NNSA). The fifth charge was formally approved by the sponsor and the National Academies prior to the start of the study. The complete study charge is given in Sidebar 1.2.

[1]The study was mandated by Section 630 of the Energy Policy Act of 2005 (Public Law 109-58). See Appendix A.

[2]HEU is uranium enriched in uranium-235 (U-235) to concentrations greater than or equal to 20 weight percent. Uranium enriched in U-235 to concentrations less than 20 weight percent is low enriched uranium (LEU); see Sidebar 1.1.

[3]The "m" denotes that this radionuclide is metastable.

CHARGE 1: FEASIBILITY OF PROCURING SUPPLIES OF MEDICAL ISOTOPES FROM COMMERCIAL SOURCES THAT DO NOT USE HEU

The authoring committee for this report (Appendix B) provides a detailed examination of feasibility in Chapter 10. This examination is supported by information and analyses in Chapters 2, 7, 8, and 9. The committee finds that:

- Low enriched uranium (LEU) targets that could be used for large-scale[4] production of Mo-99 have been developed and demonstrated.
- These targets could be used in reactors and processing facilities that produce large-scale quantities of medical isotopes for the U.S. market. However, existing producers might have to make modifications to their process equipment and to their chemical separations processes to use these LEU targets. The targets would also have to be compatible with existing or planned reactors. Conversions could require significant expense (tens of millions of dollars) and time (ranging from a few months to about 13 years) depending on whether it was carried out in existing or new facilities.
- At the present time there are not sufficient quantities of medical isotopes available from LEU targets to meet U.S. domestic needs. However, the committee sees no technical reasons that adequate quantities cannot be produced from LEU targets in the future.

CHARGE 2: CURRENT AND PROJECTED DEMAND AND AVAILABILITY OF MEDICAL ISOTOPES IN REGULAR CURRENT DOMESTIC USE

The committee examined the availability and demand for Mo-99 for domestic use in Chapters 3, 4, and 5. The committee finds that:

- Current (2006) demand for Mo-99 in the United States is between 5000 and 7000 6-day curies[5] per week. U.S. supply/demand probably has not changed appreciably since 2006.
- Demand growth for Mo-99/Tc-99m in the United States over the next 5 years could range from 0 to 5 percent per year with the most likely growth rate in the range of 3 to 5 percent per year.
- Demand growth for diagnostic imaging will likely continue over the long term as the U.S. population ages. The extent to which this will be

[4]That is, production of greater than 1000 6-day curies of Mo-99 per week. See Sidebar 3.1.

[5]Most producers calibrate the sale price to the number of curies present in a shipment of Mo-99 6 days after it leaves the producer's facilities. This quantity is referred to as 6-day curies. See Sidebar 3.1.

reflected in the demand for Mo-99/Tc-99m will depend strongly on whether other diagnostic imaging modalities find widespread use in the United States, which is unlikely to happen in the foreseeable future.

- Reliability of supply is impacting the availability of Mo-99 for medical use and the continuity of patient care in the United States and elsewhere. Reliability of Mo-99 supply is likely to continue to be a serious problem for the United States in the early part of the next decade without new supply sources.
- Conversion from HEU to LEU targets would remove policy uncertainties associated with the continued availability of HEU for use in Mo-99 production. However, conversion would not address any of the other supply reliability concerns associated with current HEU-based production.
- Although there are other potential foreign and domestic sources of Mo-99 supply, it will take several years for substantial supplies from these producers to become available.
- Because current supplies of Mo-99 are produced in reactors built largely at government expense, private companies that can provide new domestic supplies of Mo-99 to the market might not choose to compete without government assistance. A possible exception is Babcock & Wilcox, which has indicated that it is interested in producing Mo-99 but has not announced firm plans to build a production facility.

CHARGE 3: PROGRESS BEING MADE BY THE DEPARTMENT OF ENERGY AND OTHERS TO ELIMINATE ALL USE OF HEU IN REACTOR FUEL, REACTOR TARGETS, AND MEDICAL ISOTOPE PRODUCTION FACILITIES

An examination of the progress that is being made in eliminating HEU use is provided in Chapter 11. The committee finds that:

- DOE-NNSA, in collaboration with several other organizations, has made substantial progress in converting reactor fuels and targets to LEU through the Global Threat Reduction Initiative (GTRI). **The committee recommends that the GTRI program be continued until research and test reactors worldwide have converted their fuel and targets to LEU or have been permanently shut down and their HEU fuel has been returned to the country from which it originated.**
- Despite this progress, the GTRI program faces several challenges. There are 78 HEU-fueled research and test reactors operating throughout the world that are out of the scope of GTRI. From a purely technical perspective, it appears that most of these reactors can be converted to LEU even if they have a unique fuel design or a defense mission. **The**

committee recommends that DOE-NNSA, in cooperation with the International Atomic Energy Agency (IAEA), make an effort to maintain an up-to-date and comprehensive database of the research and test reactors of the world, including large pulse reactors, critical facilities, and reactors with a defense-orientated mission.[6] The committee also recommends that these reactors be investigated to determine if it is feasible to convert them to LEU; if so, they should become in-scope for the program.

- Converting Mo-99 production worldwide to LEU will continue to be a major challenge for GTRI and its Reduced Enrichment for Research and Test Reactors (RERTR) Program. Recommendations on additional steps that can be taken to encourage conversion are provided in response to the fifth study charge. **The committee recommends that the RERTR Program increase its focus on eliminating HEU wastes that result from Mo-99 production facilities using U.S.-origin HEU by examining options to downblend this waste or encouraging its return to the United States.**

CHARGE 4: POTENTIAL COST DIFFERENTIAL IN MEDICAL ISOTOPE PRODUCTION IN THE REACTORS AND TARGET PROCESSING FACILITIES IF THE PRODUCTS WERE DERIVED FROM PRODUCTION SYSTEMS THAT DO NOT INVOLVE FUELS AND TARGETS WITH HEU

The committee focused on costs of producing Mo-99 because it is the precursor of Tc-99m, which is by far the major medical isotope used today. The committee provides a detailed examination of Mo-99 production costs in Chapters 6 and 10. The committee estimated average costs at three points in the Mo-99/Tc-99m supply chain, Mo-99 production, technetium generators, and Tc-99m doses:

- Costs of Mo-99 production in 2008: about $225 per 6-day curie with a cost variation of about ± 40 percent.
- Average prices for technetium generators sold in the United States in 2005: about $1900 for a generator with 10 curies[7] with a variation of about ± 25 percent.
- Average prices for Tc-99m sold in the United States in 2005: about $11.00 per 30 mCi dose of Tc-99m sodium pertechnetate, with a variation greater than ± 20 percent.

[6]These reactors do not include HEU-fueled naval propulsion reactors or related test beds and training reactors.

[7]The quantity of Mo-99 in a technetium generator is typically calibrated to be the quantity present on the day or day after it is delivered to a customer. This quantity is different from the 6-day curie quantities sold by Mo-99 producers.

The committee finds that:

- The anticipated average cost increase to convert to the production of medical isotopes without the use of HEU would likely be less than 10 percent for at least three of the four current large-scale producers (MDS Nordion, Mallinckrodt, and Institut National des Radioéléments). This is true for costs and/or prices at all three points in the Mo-99/Tc-99m supply chain that were examined by the committee. In fact, a 10 percent cost increase for Mo-99 would provide very substantial resources for conversion and would have a negligible impact on the cost of common diagnostic imaging procedures. The committee has insufficient information regarding potential conversion costs for the South African producer Nuclear Technology Products Radioisotopes.

This result is based on assumed future facility operations of 30–50 years. For the High Flux Reactor (HFR) at Petten, it is assumed that development of LEU targets and processes would carry over to the to-be-built Pallas reactor, so that a long amortization period is justified. The committee is unable to assess whether the use of a 30-year operating period is consistent with Atomic Energy of Canada Limited's (AECL) long-term plans for Mo-99 production. AECL has not indicated what plans it has for producing Mo-99 beyond 2016 and was not willing to discuss with the committee what refurbishment is needed to keep National Research Universal (NRU) running until 2016. If AECL decides to get out of the business of producing Mo-99, then obviously a shorter amortization period would need to be used.

CHARGE 5: IDENTIFY ADDITIONAL STEPS THAT COULD BE TAKEN BY DOE AND MEDICAL ISOTOPE PRODUCERS TO IMPROVE THE FEASIBILITY OF SUCH CONVERSIONS

The committee recommends that Mo-99 producers and the U.S. government consider several steps to improve the feasibility of conversion; additional details are provided in Chapter 10:

- Mo-99 producers: Commit to conversion, announce a best-effort schedule for selecting and implementing an LEU-based Mo-99 production process, and identify additional needs for technical assistance. Work with industry organizations and scientific and medical societies concerned with Mo-99 production for marshalling, coordinating, and supporting an industry-wide conversion strategy.
- DOE: Make the considerable technical expertise of the DOE national laboratory system available to assist existing producers with conversion-related research and development (R&D) and examine options

to share R&D costs with existing and potential new producers that could supply the U.S. market as a means to incentivize the conversion process and encourage new domestic production. Remove disincentives to conversion by maintaining the cost of LEU so that it is no more expensive than HEU on a common U-235 mass basis.

- Department of State: Intensify the diplomatic pressure on countries that still use HEU (fuel or targets) to induce them to convert. In particular, those countries that are partners in GTRI and have made a commitment to the "minimization of HEU" should be encouraged to live up to their commitments; this includes Canada, the Netherlands, Belgium, and France.
- Food and Drug Administration (FDA): Work with industry and DOE's technical experts to ensure that there is a common understanding of LEU-based production of Mo-99 from a regulatory perspective, and also that there is a good understanding of likely FDA requirements for obtaining regulatory approvals for the use of this isotope in radiopharmaceuticals.
- U.S. Congress: Provide clear and consistent policy signals concerning conversion to LEU-based Mo-99 production. Consider additional controls on the use of U.S.-origin HEU for medical isotope production and incentives to motivate conversion and the development of domestic sources of Mo-99. Some possible incentives are described in Chapter 10.

1

Background and Study Task

Section 630 of the Energy Policy Act of 2005[1] (the 2005 Act; see Appendix A) directed the Secretary of Energy to enter into an arrangement with the National Academy of Sciences to conduct a study on the elimination of highly enriched uranium (HEU; Sidebar 1.1) in reactor fuel, reactor targets, and medical isotope production facilities. The 2005 Act specifically directed that the study should address the following four points:

1. The feasibility of procuring supplies of medical isotopes from commercial sources that do not use HEU.
2. The current and projected demand and availability of medical isotopes in regular current domestic use.
3. The progress that is being made by the Department of Energy (DOE) and others to eliminate all use of HEU in reactor fuel, reactor targets, and medical isotope production facilities.
4. The potential cost differential in medical isotope production in the reactors and target processing facilities if the products were derived from production systems that do not involve fuels and targets with HEU.

The 2005 Act defines *medical isotopes*[2] to include "molybdenum 99, iodine 131, xenon 133, and other radioactive materials used to produce

[1]Public Law 109-58.

[2]Medical isotopes are a class of radioactive isotopes (radioisotopes) that have unstable nuclei and emit radiation. This radiation is used for medical imaging and treatment. A report of the

SIDEBAR 1.1
HEU

Almost all uranium found in nature contains about 0.7 percent by weight of uranium-235 (U-235) and about 99.3 percent by weight uranium-238 (U-238) along with minor amounts of other uranium isotopes, for example, uranium-234. *Enrichment* is a process used to increase the concentration of the U-235 isotope relative to U-238. *HEU* is defined as uranium enriched to concentrations greater than or equal to 20 percent by weight in U-235. Uranium enriched to concentrations less than 20 percent by weight in U-235 is *LEU*.

Uranium is enriched by exploiting the small (three-neutron) mass difference between U-235 and U-238. Two enrichment processes are in commercial use today: an older and less efficient gaseous diffusion process that was developed during World War II and is still being used in the United States; and a more efficient gas centrifuge process that is being used in Europe, Russia, and other countries. Two centrifuge facilities are currently being constructed in the United States. A third enrichment process (laser enrichment) has been developed but is not used commercially.

Enriched uranium is used to fuel the majority of today's research and commercial nuclear reactors. Ordinary water is used as a coolant and moderator for light-water reactors (LWRs) that typically use LEU fuel enriched in U-235 up to about 5 percent by weight. The majority of commercial nuclear reactors that produce about 16 percent of the world's electrical power are LWRs. Most existing research and test reactors were designed to use HEU fuel, but many of these have been or are being converted to LEU fuel (see Chapter 11).

Most of the world's production of Mo-99 is carried out by irradiating HEU targets in research and test reactors that are fueled with LEU. With one exception, the United States is currently the world's primary supplier of HEU for Mo-99 production, either directly through DOE or indirectly through the European organization Euratom Supply Agency (ESA). The U.S.-origin HEU that is used for Mo-99 production has an enrichment of about 93 percent U-235 and was originally produced for use in nuclear weapons. The exception is South Africa, which uses its own HEU (which is 45 percent enriched) to

radiopharmaceuticals for diagnostic, therapeutic procedures or for research and development." However, this report focuses on the production and use of molybdenum-99 (Mo-99) for reasons that are described at the beginning of Chapter 2.

Section 630 of the 2005 Act determines the production of medical isotopes using low enriched uranium (LEU) to be feasible if the following conditions are met:

National Research Council and the Institute of Medicine (NRC and IOM, 2007) provides a discussion of the uses of medical isotopes in medicine and research.

produce Mo-99 in a reactor that is also fueled with HEU but is in the process of being converted to LEU.

ESA has also received HEU from Russia, and some of this HEU has been used to fuel three European reactors: the High Flux Reactor of the Institut Laue-Langevin, which is located in Grenoble, France; the Orpheus Reactor, which is located in Saclay, France; and the FRM II Reactor, which is located in Garching, Germany. (See http://www.francenuc.org/en_sources/sources_unat_e.htm for a discussion of HEU use in France.) None of these reactors is used to produce Mo-99. ESA does not publicly disclose the sources of HEU used for the manufacture of targets for medical isotope production. Most of this HEU is probably of U.S. origin, but some may also be of U.K. origin.

The primary concern with civilian use of HEU for applications such as Mo-99 production is its attractiveness for use in improvised nuclear devices by terrorists or rogue states. The amount of HEU required to achieve a sustained nuclear chain reaction (referred to as the critical mass) depends on the enrichment of U-235 as well as the design of the device. The IAEA defines a significant quantity of a nuclear material to be the approximate quantity of material from which the possibility of manufacturing a nuclear explosive device (i.e., a device that can achieve a prompt critical mass) cannot be excluded. The IAEA significant quantity for HEU is 25 kg. The HEU-based weapon used on Hiroshima, Japan, in August 1945 contained 64 kg of HEU having an average enrichment of about 80 percent. However, a well-designed nuclear explosive device could be made with less than 25 kg of HEU. The Atomic Energy Act gives the U.S. government the authority to regulate uranium that is enriched in U-235 (and also U-233) above natural abundances. Such materials are referred to as special nuclear materials. The U.S. government requires stepped-up security for facilities that handle greater than 5 kg of HEU.

As U-235 enrichment decreases, more uranium is required to achieve a prompt critical mass. It is difficult but not impossible to achieve a prompt critical mass with LEU.

- LEU targets have been developed and demonstrated for use in the reactors and target processing facilities that produce significant quantities of medical isotopes to serve U.S. needs for such isotopes.
- Sufficient quantities of medical isotopes are available from low enriched uranium targets and fuel to meet U.S. needs.
- The average anticipated total cost increase from production of medical isotopes in such facilities without the use of HEU is less than 10 percent.

During the negotiations between the National Academies and the sponsoring organization within DOE (the National Nuclear Security Adminis-

tration [DOE-NNSA]), it was jointly agreed that the following task would also be included as part of this study:[3]

> If the National Academies determine that the procurement of medical isotopes from commercial sources is not feasible as defined in Section 630 of the Energy Policy Act, it should estimate the magnitude of the cost differential and identify additional steps that could be taken by the Department of Energy and medical isotope producers to improve the feasibility of such conversions. In estimating the magnitude of cost differentials, consideration should be given to facilities utilized by both large and small producers. The National Academies should also identify any reliability of supply issues that could arise as a result of such conversions.

DOE-NNSA and the National Academies judged that this added task would assist DOE in achieving its mandate to minimize the use of HEU in civilian applications. The complete statement of task for this study is reproduced in Sidebar 1.2.

The mandate for this study reflects an effort by the U.S. Congress to balance two competing national interests: first, to ensure the continued availability of reasonably priced medical isotopes in the United States; and second, to prevent the proliferation of HEU, which could be diverted for malevolent use in nuclear explosive devices (Sidebar 1.1). A brief history of congressional actions on HEU use for medical isotope production is provided in Sidebar 1.3. Kuperman (2005, 2006) explores the motivations for and possible consequences of these actions.

At present, there are no producers of Mo-99 for medical use[4] in the United States. Almost all of the Mo-99 used worldwide is produced by just four companies, all using HEU targets:

- MDS-Nordion, which is located in Ottawa, Ontario, Canada, obtains Mo-99 under an agreement with Atomic Energy of Canada Limited (AECL), which is located at Chalk River, Canada;
- Mallinckrodt[5] near Petten, the Netherlands, extracts Mo-99 from targets irradiated in three European reactors;
- Institut National des Radioéléments (IRE) near Fleurus, Belgium, extracts Mo-99 from targets irradiated in three European reactors; and

[3]This additional task was formally approved by DOE-NNSA and the National Academies prior to the start of the study.

[4]In this report, the terms Mo-99 production, Mo-99 producer, and similar constructions refer specifically to Mo-99 produced for medical isotope use. All uranium-fueled nuclear reactors produce Mo-99 as a result of fission of U-235 contained in their reactor fuels, but this Mo-99 is not recovered for medical use.

[5]Mallinckrodt Inc., a Delaware corporation, is an indirect wholly owned subsidiary of Covidien Ltd.

SIDEBAR 1.2
Study Task

The National Academies will conduct a study and provide findings and recommendations to DOE on the production of medical isotopes without HEU. As mandated by Congress in Section 630 of the Energy Policy Act of 2005, the study will determine the following:

1. The feasibility of procuring supplies of medical isotopes from commercial sources that do not use HEU, using the definition of feasibility defined in Section 630 of the Energy Policy Act of 2005.
2. The current and projected demand and availability of medical isotopes in regular current domestic use.
3. The progress that is being made by DOE and others to eliminate all use of HEU in reactor fuel, reactor targets, and medical isotope production facilities.
4. The potential cost differential in medical isotope production in the reactors and target processing facilities if the products were derived from production systems that do not involve fuels and targets with HEU.

If the National Academies determine that the procurement of medical isotopes from commercial sources is not feasible as defined in Section 630 of the Energy Policy Act, it should estimate the magnitude of the cost differential and identify additional steps that could be taken by DOE and medical isotope producers to improve the feasibility of such conversions. In estimating the magnitude of cost differentials, consideration should be given to facilities utilized by both large and small producers. The National Academies should also identify any reliability of supply issues that could arise as a result of such conversions.

With respect to the first charge, Congress established three tests for feasibility:

1. LEU targets have been developed and demonstrated for use in the reactors and target processing facilities that produce significant quantities of medical isotopes to serve U.S. needs for such isotopes;
2. Sufficient quantities of medical isotopes are available from LEU targets and fuel to meet U.S. needs; and
3. The average anticipated total cost increase from production of medical isotopes in such facilities without the use of HEU is less than 10 percent.

- Nuclear Technology Products (NTP) Radioisotopes extracts Mo-99 from targets irradiated in a reactor near Pelindaba, South Africa.

Approximately 40–50 kg of HEU are used annually for medical isotope production (NNSA and ANSTO, 2007[6]), including annual U.S. exports of

[6]This is a report from a conference that involved almost all of the Mo-99 production community. The report was produced by a working group during the conference.

SIDEBAR 1.3
Congressional Actions on HEU Use for Medical Isotope Production

U.S. congressional efforts to reduce the use of HEU for isotope production date from the early 1990s. The Energy Policy Act of 1992 (the 1992 Act) required that foreign producers who received HEU from the United States cooperate in converting to LEU-based production. This section of the 1992 Act, which is sometimes referred to as the Schumer Amendment after its sponsor, Senator Charles Schumer (D-NY), reads, in part, as follows:

> The [Nuclear Regulatory] Commission may issue a license for the export of highly enriched uranium to be used as a fuel or target in a nuclear research or test reactor only if, in addition to any other requirement of this Act, the Commission determines that—(1) there is no alternative nuclear reactor fuel or target enriched in the isotope 235 to a lesser percent than the proposed export, that can be used in the reactor; (2) the proposed recipient of that uranium has provided assurances that, whenever an alternative nuclear reactor fuel or target can be used in that reactor, it will use that alternative in lieu of highly enriched uranium; and (3) the United States Government is actively developing an alternative nuclear reactor fuel or target that can be used in that reactor. . . . 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.

The Energy Policy Act of 2005 exempts certain HEU recipient countries, specifically Belgium, Canada, France, Germany, and the Netherlands, from some provisions of the Schumer Amendment. The section of the 2005 Act referred to as the Burr-Bond Amendment, after its sponsors, Representative Richard Burr (R-NC) and Senator Christopher (Kit) Bond (R-Mo), reads, in part, as follows:

> The [Nuclear Regulatory] Commission may issue a license authorizing the export (including shipment to and use at intermediate and ultimate consignees specified in the license) to a recipient country of highly enriched uranium for medical isotope production if, in addition to any other requirements of this Act (except subsection a.), the Commission determines that—(A) a recipient country that supplies an assurance letter to the United States Government in connection with the consideration by the Commission of the export license application has informed that United States Government that any intermediate consignees and that ultimate consignee specified in the application are required to use the highly enriched uranium solely to produce medical isotopes; and (B) the highly enriched uranium for medical isotope production will be irradiated only in a reactor in a recipient country that—(i) uses an alternative nuclear reactor fuel; or (ii) is the subject of an agreement with the United States Government to convert to an alternative nuclear reactor fuel when alternative nuclear reactor fuel can be used in the reactor.

about 15.5 kg of HEU to Canada. All of the U.S. supply of medical isotopes is provided by MDS-Nordion and Mallinckrodt, either through their own production or through backup supply agreements with each other and with IRE and NTP. The United States currently consumes about half of world production of Mo-99.

As described in the Regional Producers section of Chapter 3, there are two organizations that are or soon will be able to produce Mo-99 using LEU:

- Comisión Nactional de Energía Atómica (CNEA) in Buenos Aires, Argentina, has been producing Mo-99 using LEU since 2002. CNEA makes Mo-99 primarily for domestic and regional use.
- Australian Nuclear Science and Technology Organisation (ANSTO) in Lucas Heights, Australia, plans to begin producing Mo-99 using the CNEA-developed process in the near future.

Both of these producers are interested in becoming global suppliers. Additionally, the International Atomic Energy Agency is sponsoring a coordinated research project (discussed in Chapters 3 and 11) to help other countries develop LEU-based production for indigenous use.

STRATEGY TO ADDRESS THE STUDY CHARGE

This study was carried out by a committee of experts appointed by the president of the National Academy of Sciences acting in his capacity as chair of the National Research Council. The committee consists of 14 members with expertise that spans the issues relevant to the study task: chemistry, chemical and nuclear engineering, radiochemistry, construction and infrastructure management, economics, isotope production, nuclear medicine, nuclear security, radioactive waste management, and risk assessment. In selecting the membership of this committee, the National Research Council sought to obtain a balance between members with experience in the production and use of medical isotopes and members with relevant disciplinary expertise but no direct medical isotope experience. The committee leadership also reflects this balance: the committee chair is an academy member with demonstrated leadership capabilities but no experience in medical isotope production; the vice chair is also an academy member and has experience as a medical isotope user. Biographical sketches of the committee members are provided in Appendix B.

Given both the importance of this congressional request and the controversy surrounding the use of HEU for medical isotope production, the committee understood that it needed to reach out broadly to interested and potentially affected parties to obtain information for this study. The

committee held four meetings to receive information from subject matter experts, representatives of the medical isotope production and user communities, and congressional and federal agency staff (Appendix C).

Small groups of committee members also toured medical isotope production and/or technetium generator manufacturing facilities at AECL and MDS-Nordion (Chalk River and Ottawa, Canada, respectively), Mallinckrodt (Petten, the Netherlands, and Maryland Heights, Missouri), IRE (Fleurus, Belgium), ANSTO (Lucas Heights, Australia), and CNEA/Investigaciones Aplicadas Sociedad del Estado (INVAP; Buenos Aires, Argentina). A small group of members also toured the University of Missouri Research Reactor (MURR; Columbia, Missouri) and the reactor fuel and target fabrication facility operated by Compagnie pour l'Etude et la Réalisation de Combustibles Atomiques (CERCA; near Romans, France).

Some organizations provided proprietary information for this study through nondisclosure agreements with the National Academies. This information primarily addressed issues such as isotope production processes, future plans, and potential barriers to conversion from HEU to LEU. None of the proprietary information received by the National Academies appears in this report.

Given the broad task statement for this study, the committee recognized early on that it needed to establish boundaries to guide its inquiries. Specifically, the committee decided that:

- The study would focus on the reactor production of the medical isotope Mo-99 and its decay product Tc-99m for reasons described in Chapter 2.
- Financial feasibility of LEU production would be assessed at several points in the Mo-99 supply chain (Chapter 10).
- The discussion of the third charge of the task statement (Sidebar 1.2) would emphasize progress being made in the elimination of HEU targets for medical isotope production (Chapters 7–10) but would also discuss elimination of HEU fuel in reactors (Chapter 11).

REPORT ROADMAP

The report is organized into a number of chapters that address the elements of the study charge.

- This chapter provides the background and study task for the report.
- A short primer on Mo-99 production and use is provided in Chapter 2. It is intended primarily for nonexpert readers who wish to gain a

better understanding of how this isotope is currently being made and how its decay product, Tc-99m, is used for medical imaging.

- Mo-99 supply and supply reliability are discussed in Chapters 3 and 4.
- Current and projected Mo-99 demand is discussed in Chapter 5.
- Mo-99/Tc-99m production cost estimates are provided in Chapter 6. These estimates are used in the feasibility assessment that appears in Chapter 10.
- Several considerations for conversion of reactor targets from HEU to LEU are discussed in Chapters 7–9: technical (Chapter 7), regulatory (Chapter 8), and general approaches and timing (Chapter 9).
- The prospects and feasibility of converting HEU-based Mo-99 production to LEU-based production are discussed in Chapter 10. This chapter also contains the committee's response to the feasibility assessment portions of the study charge.
- Progress that is being made by DOE in eliminating use of HEU in reactors is discussed in Chapter 11.

An effort was made by the committee to develop chapters that could stand alone for the benefit of audiences who were not interested in reading the entire report. This results in some repetition of basic facts and concepts in the chapters that will be noticed by readers who peruse the report from beginning to end.

2

Molybdenum-99/Technetium-99m Production and Use

The congressional mandate for this study calls for an examination of the production of medical isotopes to include "molybdenum 99, iodine 131, xenon 133, and other radioactive materials used to produce radiopharmaceuticals for diagnostic and therapeutic procedures or for research and development." However, the authoring committee determined that for the purposes of addressing the statement of task for this study (Sidebar 1.2), it is sufficient to focus on the production of the medical isotope molybdenum-99 (Mo-99). This is so because:

1. The decay product of Mo-99, technetium-99m[1] (Tc-99m), is used in about two-thirds[2] of all diagnostic medical isotope procedures in the United States.
2. Between 95 and 98 percent of Mo-99 is currently being produced using highly enriched uranium (HEU) targets (NNSA and ANSTO, 2007), which was the major concern of Congress when it mandated this study.
3. Other medical isotopes such as iodine-131 (I-131) and xenon-133

[1]The symbol "m" denotes that the isotope is metastable. The nucleus of a metastable isotope has an elevated energy state and, in the case of Tc-99m, releases this energy by emitting a gamma ray. The decay process is referred to as *isomeric transition*.

[2]Higher percentages of procedures utilizing Tc-99m are estimated by some other sources. For example, NNSA and ANSTO (2007) estimated that about 70 percent of all procedures utilize Tc-99m. Some of the industry presenters at the committee's information-gathering meetings estimated that 80–85 percent of all procedures utilize Tc-99m.

(Xe-133) are by-products of the Mo-99 production process and will be sufficiently available if Mo-99 is available.

4. These other medical isotopes are not being recovered for sale by all major Mo-99 producers because they can be more cheaply produced and purchased from other sources.[3]

Point 3 deserves additional elaboration. The fission of uranium-235 (U-235) produces a spectrum of fission products (see Figure 2.5) including Mo-99, I-131, and Xe-133. These fission products are produced in the same proportions to each other whether HEU or low enriched uranium (LEU) targets are used. All of these isotopes can be recovered when the targets are processed to obtain Mo-99.

The primary purpose of this chapter is to provide a brief overview of the production and use of Mo-99 in nuclear medicine and is intended primarily for nonexpert readers. Knowledgeable readers may wish to skip directly to Chapter 3.

MOLYBDENUM-99 USE IN NUCLEAR MEDICINE

The decay product of Mo-99, Tc-99m, is the workhorse isotope in nuclear medicine for diagnostic imaging. Tc-99m is used for the detection of disease and for the study of organ structure and function. Tc-99m is especially useful for nuclear medicine procedures because it can be chemically incorporated into small molecule ligands and proteins that concentrate in specific organs or tissues when injected into the body. The isotope has a half-life of about 6 hours and emits 140 keV photons when it decays to Tc-99, a radioactive isotope with about a 214,000-year half-life. This photon energy is ideally suited for efficient detection by scintillation instruments such as gamma cameras. The data collected by the camera are analyzed to produce detailed structural and functional images. A recent report of the National Research Council and Institute of Medicine (NAS and IOM, 2007) provides a description of the imaging process.

As will be described in more detail in the following section, Tc-99m is currently produced through a multistep process that begins with the neutron irradiation of fissile U-235 contained in HEU (see Sidebar 1.1) or LEU targets in a nuclear reactor. This irradiation causes U-235 to fission and produces Mo-99 and many other fission products, including I-131 and Xe-133. Following irradiation, the targets are chemically processed to separate Mo-99 from other fission products. If desired, these other fission products can be recovered separately. The separated Mo-99, which is con-

[3]For example Russian English Venture in Isotope Supply Services (REVISS) sells Russian-produced isotopes.

tained in a solution, is then adsorbed onto an alumina (Al_2O_3) column that is contained in cylinders that are about the diameter of a large pencil. The columns are shipped to radiopharmacies and hospitals in radiation-shielded cartridges known as *technetium generators* (Figure 2.1).

The Mo-99 in the generators decays with about a 66-hour half-life to Tc-99m. The Tc-99m is typically recovered by passing a saline solution through the alumina column in the generator, a process known as *eluting* the generator. The saline removes the Tc-99m but leaves the Mo-99 in place. A technetium generator can be eluted several times a day for about a week before it needs to be replaced[4] with a fresh generator (Figure 2.2).

There are numerous Tc-99m *kits*[5] for producing radiopharmaceuticals to examine the brain, kidney, heart, bone, liver, and lung. Table 2.1 provides a selected list of Tc-99m labeled radiopharmaceuticals in use today. The list is not intended to be exhaustive but to illustrate the range of diseases and conditions where Tc-99m based diagnostic imaging is useful. Figure 2.3 provides examples of images that can be obtained from diagnostic imaging procedures.

Because of its relatively short half-life (66 hours), Mo-99 cannot be stockpiled for use. It must be made on a weekly or more frequent basis to ensure continuous availability. The processes for producing Mo-99 and technetium generators and delivering them to customers are tightly scheduled and highly time dependent. An interruption at any point in the production, transport, or delivery of Mo-99 or technetium generators can have substantial impacts on patient care, as discussed in Chapter 4.

Mo-99 PRODUCTION PROCESS

There are two primary approaches for producing the medical isotope Mo-99, as described in Appendix D: fission of U-235, which produces Mo-99 and other medically important isotopes such as I-131 and Xe-133, and neutron capture by Mo-98 to produce Mo-99. For the reasons described in Appendix D, the committee dismissed neutron capture as a viable process for producing Mo-99 in the quantities needed to meet U.S. or global demand for Mo-99. None of the four global producers of Mo-99 (Chapter 1) use the neutron capture method to produce Mo-99 because of its inefficiencies. However, this process can be used to make smaller

[4]The technetium generator is replaced after about a week because it loses its elution efficiency and also because the Tc-99m can become contaminated with Mo-99 from the column. The latter process is referred to as Mo-99 *breakthrough*. After it is replaced, the old generator may continue to be used for research that does not involve human subjects.

[5]Kits are composed of all of the required chemicals (e.g., the pharmaceutical agent, chelating compound, and saline solution) for formulating the radiopharmaceutical to which Tc-99m is added.

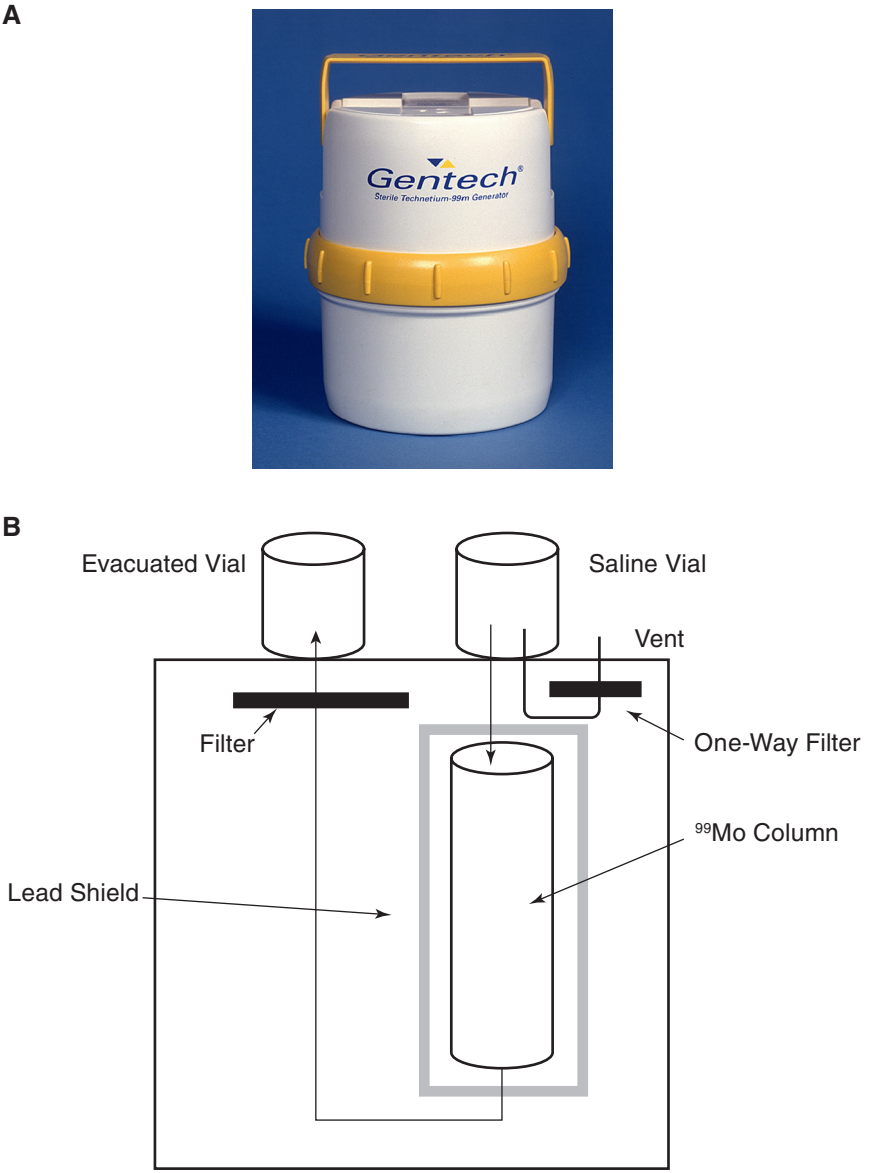

FIGURE 2.1 (a) External view of a technetium generator produced by the Australian Nuclear Science and Technology Organisation (ANSTO). SOURCE: Courtesy of ANSTO. (b) Schematic diagram showing the internal structure of a typical technetium generator.

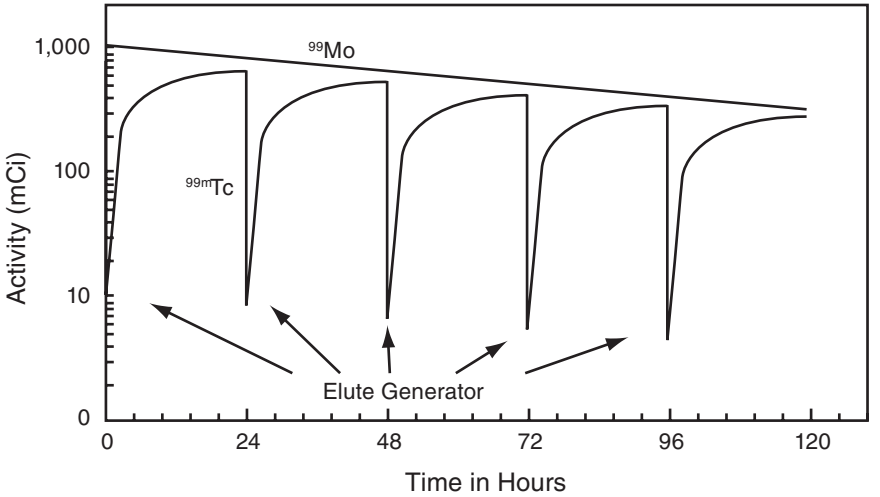

FIGURE 2.2 Plot of typical Mo-99 and Tc-99m activity on a logarithmic scale versus time for multiple elution of a technetium generator.

TABLE 2.1 Selected Examples of Tc-99m Kits for Nuclear Medicine Diagnostic Imaging

Kit Name	Imaging Procedure
Technetium Tc-99m Medronate (MDP)	Bone Scan
Technetium Tc-99m Albumin Aggregated (MAA)	Lung Perfusion
Technetium Tc-99m Pentetate (DTPA)	Kidney Scan and Function
Technetium Tc-99m Sulfur Colloid	Liver Scan Sentinel Lymph Node Localization
Technetium Tc-99m Sestamibi	Cardiac Perfusion
Technetium Tc-99m Exametazime	Brain Perfusion
Technetium Tc-99m Mebrofenin	Gall Bladder Function
Technetium Tc-99m Etidronate	Bone Scan
Technetium Tc-99m Disofenin	Gall Bladder Function
Technetium Tc-99m Succimer (DMSA)	Kidney Scan and Function
Technetium Tc-99m Tetrofosmin	Cardiac Perfusion
Technetium Tc-99m Bicisate	Brain Perfusion
Technetium Tc-99m Red Blood Cell	Blood Pool Imaging
Technetium Tc-99m Sodium Pertechnetate	Thyroid, Salivary Gland, Meckel's Scan
Technetium Tc-99m Lidofenin	Gall Bladder Function
Technetium Tc-99m Mertiatide (MAG3)	Kidney Scan and Function
Technetium Tc-99m Oxidronate (HDP)	Bone Scan

NOTE: MAA = methacrylic acid, MDP = methylene diphosphonate, DTPA = diethylene triamine pentaacetic acid, DMSA = dimercaptosuccinic acid, MAG3 = mercapto acetyl triglycine, HDP = hydroxymethylene diphosphonate.
SOURCE: Extracted from the Food and Drug Administration approved pharmaceutical list, 2008.

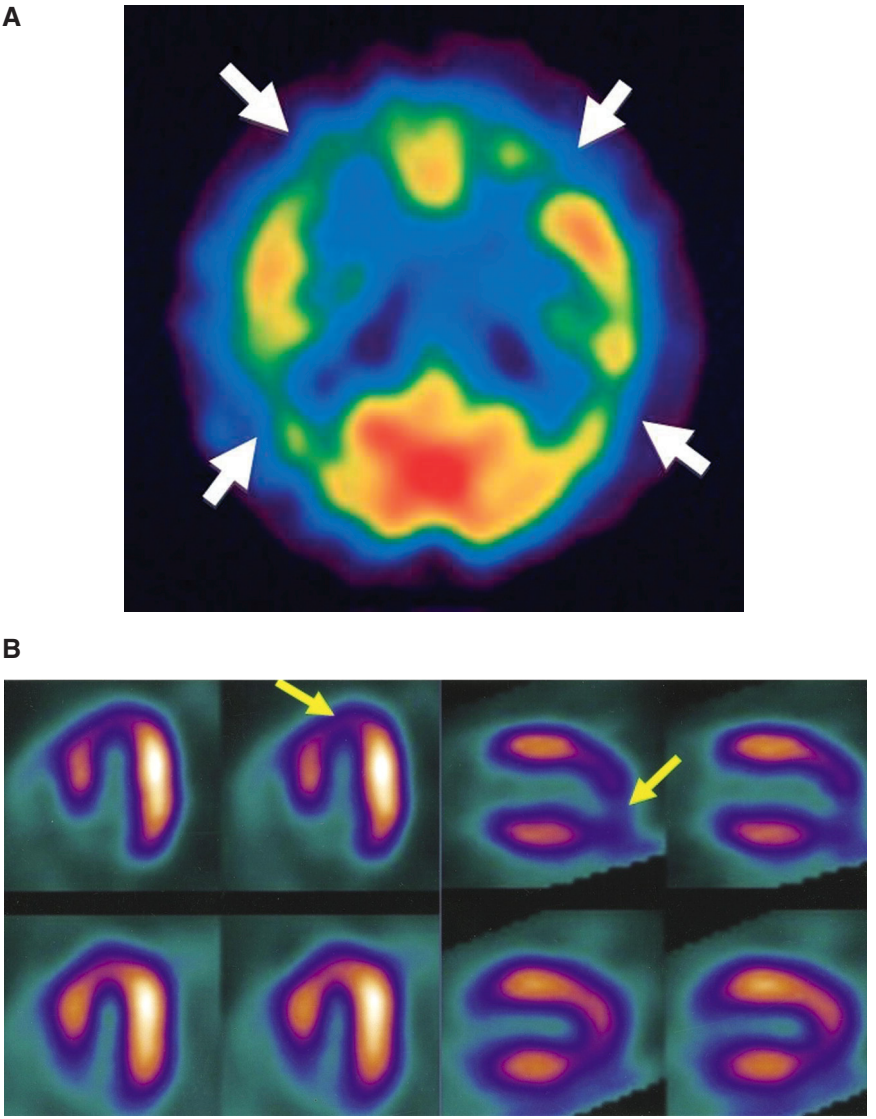

FIGURE 2.3 (a) Image acquired from a Tc-99m cerebral blood flow brain scan of a person with Alzheimer's disease. The arrows indicate areas of diminished blood flow due to the disease. SOURCE: Courtesy of Satoshi Minoshima, University of Washington. (b) Images acquired from a cardiac perfusion SPECT study at stress and rest using a Tc-99m radiotracer. The images on the top row are taken during stress, and the images at rest are shown on the bottom. The arrows indicate areas of decreased perfusion, visualized by the darker colors in the image. SOURCE: Reprinted with permission from Elsevier from Rispler et al., 2007.

quantities of Mo-99. In fact, as will be discussed in Chapter 3, the International Atomic Energy Agency has Coordinated Research Projects that are partly focused on production by this method. Additionally, Japan recently announced that it will produce Mo-99 using neutron activation to provide a stable domestic supply.[6]

This chapter focuses on the production of Mo-99 by neutron irradiation of targets containing highly enriched uranium-235 (HEU) in a nuclear reactor. This section provides an overview of this production method and is organized in terms of the following three processes:

1. Fabrication of uranium targets,
2. Irradiation of targets in a nuclear reactor,
3. Dissolution of the uranium target and recovery and purification of Mo-99.

These three processes apply whether Mo-99 is produced from HEU or LEU targets.

The equipment used to produce Mo-99 is small: The process equipment used to dissolve the targets and recover Mo-99 and (if desired) other isotopes is "bench scale" compared to most industrial chemical processing applications. In fact, this process equipment has a footprint similar to that of a large dining room table. Of course, this processing equipment must be operated inside large and heavily radiation-shielded facilities because the irradiated targets that contain Mo-99 are highly radioactive.

Fabrication of Uranium Targets

The *target* used for Mo-99 production is a material containing uranium-235 that is designed to be irradiated in a nuclear reactor. The target is designed to satisfy several requirements: First, it must be properly sized to fit into the irradiation position inside the reactor.[7] Second, it must contain a sufficient amount of U-235 to produce the required amount of Mo-99 when it is irradiated. Third, it must have good heat transfer properties to prevent overheating[8] (which could result in target failure) during irradiation. Fourth, the target must provide a barrier to the release of radioactive products, especially fission gases, during and after irradiation. Fifth, the target materials must be compatible with the chemical processing steps that will be used to recover and purify Mo-99 after the target is irradiated.

[6]http://www.jaif.or.jp/english/aij/member/2008/2008-11-26b.pdf.

[7]This requirement is reactor specific, because the locations and sizes of the irradiation positions depend on the particular design of the reactor.

[8]This heat is the by-product of nuclear reactions in the target that result from neutron bombardment.

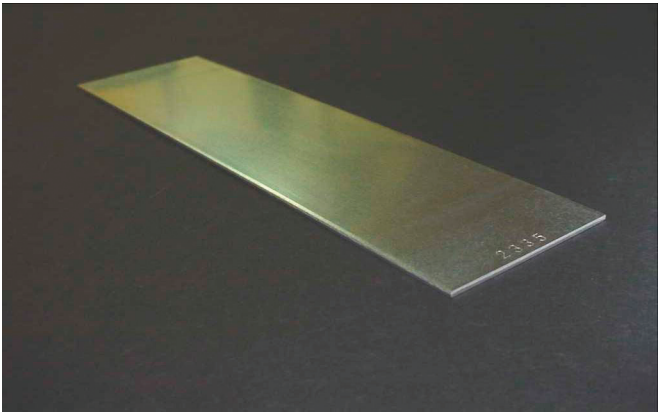

FIGURE 2.4 CNEA's high-density LEU-aluminum dispersion targets. These targets have been used since 2002 to produce Mo-99 in Argentina. The target is approximately 15 cm in length. SOURCE: Courtesy of Pablo Cristini, CNEA, Argentina.

To meet these criteria, targets are fabricated in a wide variety of shapes and compositions to meet the needs of individual Mo-99 producers. Targets may be shaped as plates (Figure 2.4), pins, or cylinders. Target compositions include uranium metal, uranium oxides, and alloys of uranium, nearly always with aluminum. Metallic targets are typically encapsulated in aluminum or stainless steel to protect the chemically reactive uranium metal or alloy and to contain the fission products produced during irradiation. This encapsulation is referred to as the target *cladding*.[9] Sometimes an intermediate barrier material such as aluminum or nickel is used to separate the cladding from the U-235 target material. Table 2.2 summarizes the types of targets used or planned to be used in the future by different producers.

Irradiation of Targets in a Nuclear Reactor

Mo-99 is produced in the uranium-bearing targets by irradiating them with thermal neutrons.[10] Some of the U-235 nuclei absorb these neutrons, which can cause them to fission. The fission of the U-235 nucleus produces two but sometimes three lower-mass nuclei referred to as *fission fragments*. Approximately 6 percent of these fission fragments are Mo-99 atoms (Figure 2.5).

[9]The target has a "sandwich" structure: The metal cladding is the "bread" and the uranium-bearing material is the "meat."

[10]A thermal neutron is a low-energy neutron of about 0.025 electron volts at room temperature. This energy is typical for neutrons in light-water (i.e., ordinary water) reactors.

TABLE 2.2 Uranium-Bearing Targets for Mo-99 Production

Target Geometry	Target Material	Target Users[a]
Plate	Uranium aluminide/ aluminum-alloy dispersion	Mallinckrodt, Institut National des Radioéléments, Nuclear Technology Products, CNEA, Australian Nuclear Science and Technology Organisation (ANSTO, OPAL reactor)
Pin	Uranium aluminum alloy in aluminum-cladding	MDS-Nordion (National Research Universal reactor)
Cylinder	UO2 deposited on the inside surface of a stainless-steel closed cylinder	Indonesian National Atomic Energy Agency (BATAN; current)
	Foil target	BATAN (planned)
	Compacted UO2 powder	MDS Nordion (Maple reactors)[b]

[a]See Chapter 3 for a discussion of these producers.
[b]In May 2008, AECL announced that it was discontinuing development work on the Maple reactors.
SOURCE: Data from George Vandegrift, Argonne National Laboratory.

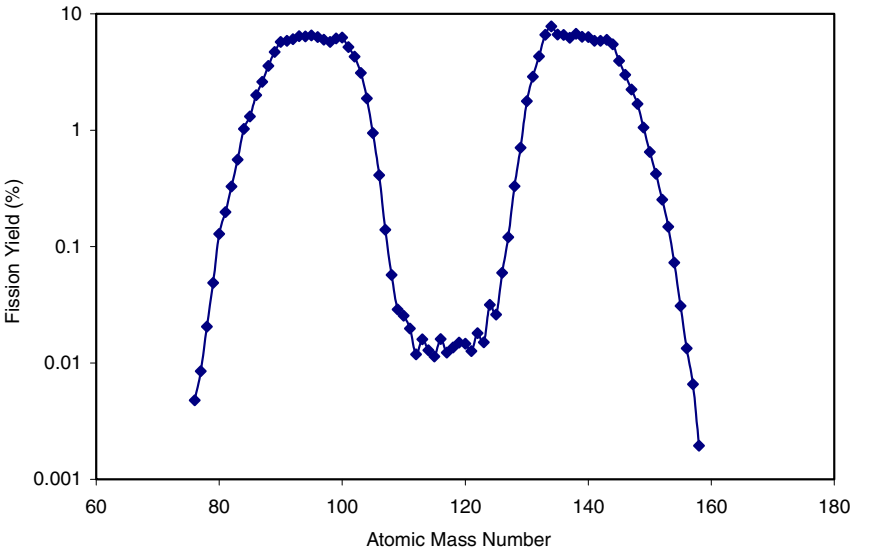

FIGURE 2.5 Fission yield for thermal neutron fission of U-235. SOURCE: Data from Joint Evaluated Fission and Fusion File, Incident-neutron data, http://www-nds.iaea.org/exfor/endf00.htm, October 2, 2006; see http://www-nds.iaea.org/sgnucdat/c1.htm.

Nuclear reactors provide an efficient source of thermal neutrons for Mo-99 production. This is why all major Mo-99 producers irradiate their targets in nuclear reactors. The amount of Mo-99 produced in a target is a function of irradiation time, the thermal neutron fission cross section for U-235,[11] the thermal neutron flux[12] on the target, the mass of U-235 in the target, and the half-life of Mo-99. For typical reactor thermal neutron fluxes on the order of 10^{14} neutrons per square centimeter per second, irradiation times of about 5 to 7 days are required to achieve near-maximum Mo-99 production in the targets.

Beyond these irradiation times, the amount of Mo-99 produced in the targets approximately balances the amount of Mo-99 being lost to radioactive decay, so further irradiation is not productive (see Sidebar 3.1). Even at maximum production, only about 3 percent of the U-235 in the target is typically consumed. The remaining U-235 along with the other fission products and target materials are treated as waste.

Dissolution and Mo-99 Recovery

Once the targets are removed from the reactor, they are cooled[13] in water typically for half a day or less before being transported to the processing facility in shielded casks. Once at the processing facility, the targets are placed into hot cells (Figure 2.6) for chemical processing. Processing is carried out quickly to recover the Mo-99 to minimize further losses from radioactive decay. About 1 percent of the Mo-99 produced in the target is lost to radioactive decay every hour after irradiation.

The apparatus in the hot cell used to process the targets and recover the Mo-99 (Figure 2.7) consists of a container for dissolving the targets, which is connected to tubing and columns for subsequent chemical separations to isolate Mo-99. The components can be easily replaced or reconfigured by a human operator using remote manipulators. The most expensive part of the separation facilities are the hot cells themselves. Hot cell facilities can cost tens of millions of dollars to construct.[14] The separation apparatus

[11]Fission cross section is usually expressed in barns, where 1 barn = 1×10^{-24} cm^2. This cross section is related to the probability that the nuclei will capture a thermal neutron and cause fission.

[12]Neutron flux is a measure of the intensity of neutron radiation. It is defined as the number of neutrons crossing a unit area of one square centimeter in one second (neutrons/cm^2-s).

[13]Cooling is a safety measure to prevent the target from being damaged because of high temperatures, to provide time for short-lived fission gases to decay, and to reduce overall radiation doses in the target processing system.

[14]For example, Ralph Butler, director of the Missouri University Research Reactor (MURR), estimated that it could cost between $30 million and $40 million to construct a new hot cell facility for Mo-99 production at MURR. The facility would have two processing lines with three or four hot cells plus one additional common hot cell. This cost estimate was character-

in the hot cell is constructed using commercially available components or components that are easily fabricated in machine or glass-blowing shops.

There are two general approaches for chemically processing targets to recover Mo-99: alkaline dissolution and acidic dissolution. The processes can be used on both HEU and LEU targets.

Alkaline Dissolution Process

Alkaline dissolution is generally used for targets that contain aluminum. This process is used by all of the major isotope producers except MDS Nordion. A sodium hydroxide (NaOH) solution is used to dissolve the entire target, including the aluminum cladding and the uranium/aluminum alloy "meat" (see footnote 9). Dissolution produces a sodium aluminate ($NaAlO_2$) solution containing sodium molybdate (Na_2MoO_4) along with small amounts of fission products and plutonium (Pu)[15] and a solid oxide/hydrated oxide residue. Hydrogen gas is evolved during dissolution. The solid residue contains uranium and most of the fission products except the alkali metals, iodine, fission gases, alkaline earths, and the elements that can act as either an acid or base such as molybdenum and aluminum. The short-lived fission gases (e.g., Xe-133) can be collected for sale or stored for decay, and I-131 can also be separated for sale if desired.

The solution is recovered by filtering to remove suspended solids, typically purified by ion exchange, and passed through a column of alumina[16] that preferentially adsorbs the molybdate (MoO_4^{-2}) ion. Mo-99 recovery yield from the solution typically exceeds 85 to 90 percent. The sorbed molybdate is typically washed with a dilute ammonium hydroxide (NH_4OH) solution and then removed from the column using a concentrated saline or ammonium hydroxide solution. Mo-99 is recovered as a highly pure product.

Acid Dissolution and Molybdenum Separations Process

Acid dissolution is generally used for uranium metal and uranium oxide targets. It is currently used by only one major producer, MDS Nordion. In contrast to the alkaline dissolution process, only the uranium metal or oxide is processed; the uranium target meat is physically separated or

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ized as "just a guess" pending completion of a conceptual design study for the facility (Ralph Butler, written communication with study director Kevin Crowley, November 24, 2008).

[15]Plutonium is produced by neutron capture of U-238 to produce U-239 which rapidly undergoes beta decay to form neptunium-239 (Np-239). Subsequently, Np-239 undergoes beta decay to form Pu-239. Plutonium may also be produced by successive neutron captures of U-235.

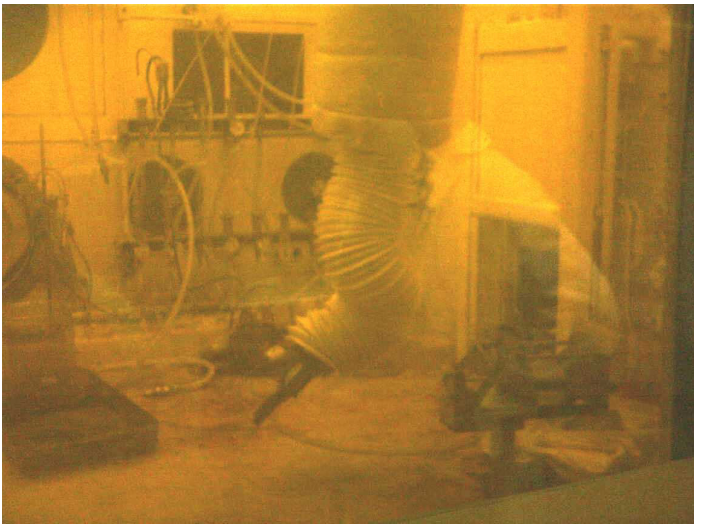
[16]In some processes ion exchange resins have been substituted for the alumina column for this separation.

A

B

FIGURE 2.6 (a) Hot cells in use at CNEA for processing of LEU targets to recover Mo-99. (b) Worker operating hot cell manipulators at MDS Nordion. SOURCE: Courtesy of CNEA and MDS Nordion, respectively.

A



B

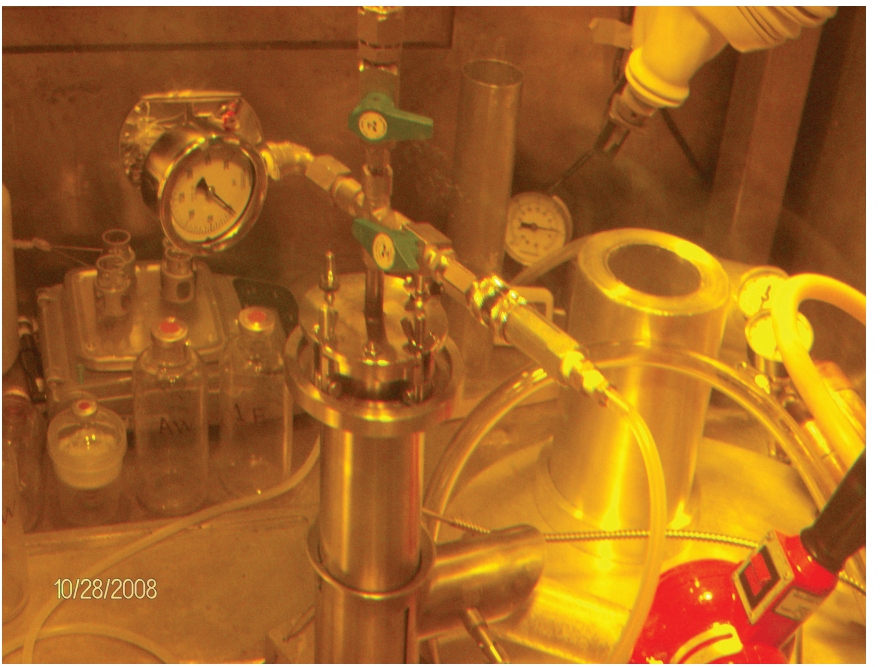


FIGURE 2.7 (a) View into a hot cell at CNEA showing the target processing equipment. (b) View into a hot cell at MURR showing the new dissolver for the LEU metal foil targets. SOURCE: Courtesy of CNEA and the University of Missouri, respectively.

leached from the target cladding and then dissolved in nitric acid. A nitrate (NO_3^-) solution containing uranium, molybdenum, and all other fission products (except volatile gases such as iodine, Xe-133, krypton-85, and nitrogen oxides) is formed.

Additional processing steps are required to recover pure molybdenum. Molybdenum can be separated from the nitrate solution by any of several separation processes. Typical separation processes include adsorption of the molybdenum on ion exchange resins and solvent extraction. Mo-99 recovery yields from these separation processes typically exceed 85 to 90 percent. The adsorbed or extracted molybdenum is washed with an appropriate solution to remove residual fission products and uranium. The wash solution becomes waste. The adsorbed molybdenum is then removed from the separation medium using an appropriate solution and recovered as a highly pure Mo-99 product.

Waste Management

Waste management is similar for both the alkaline and acid dissolution processes. In the alkaline process, the sodium aluminate and dissolved or suspended fission products that pass through the alumina column are combined with the other fission product wastes and precipitated oxide residues. This waste is stored temporarily either as-is or put into a solid form (e.g., in cement). The waste stream from the acid dissolution process includes the separated cladding and liquid waste from the Mo-99 separation or extraction processes. This liquid waste can be stored in tanks or mixed with cement to immobilize it. Most of these process wastes are stored at producers' sites or are transported to offsite storage facilities. As noted in Chapter 3, one producer (Nuclear Technology Products Radioisotopes in South Africa) is disposing of these wastes.

Approximately 97 percent of the uranium originally present in the targets ends up in the process waste. Consequently, the accumulating waste from Mo-99 production contains substantial quantities of HEU. Worldwide, tens of kilograms of this HEU waste are accumulating annually from Mo-99 production. This HEU could be recovered for reuse, but currently no producer has active plans to do so, presumably because it is less costly to purchase fresh HEU. Additionally, no Mo-99 producers currently downblend their HEU waste (by mixing it with natural or depleted uranium) to convert it to LEU.

Process Trade-offs

Both the alkaline and acid dissolution processes have been proven to be effective through many years of use with HEU targets by the major isotope

producers. Moreover, the Argentine organization CNEA has demonstrated that the alkaline process can be used with LEU targets, and work is underway (see Chapter 7) to develop an improved acid dissolution process for LEU targets. As discussed elsewhere in this report (see Chapter 10), the committee sees no technical barriers to adapting either of these processes for LEU-based Mo-99 production.

However, each of these processes has inherent advantages and disadvantages.[17] For example, alkaline processing produces very pure Mo-99, solid waste that is suitable for storage, and fission gases that can be readily isolated for sale or for storage to allow for decay. On the other hand, relative to the acid process, alkaline processing produces larger volumes[18] of processing solutions, it can require more time than the acidic process for target dissolution, and Mo-99 yields can be lower because some molybdenum may be incorporated into the solid residue. Additionally, hydrogen gas is produced in the alkaline process, which requires additional safety procedures.

Acidic processing, in contrast, generally requires shorter processing times, produces smaller volumes of processing waste, and results in slightly higher Mo-99 yields. On the other hand, additional steps have to be carried out to separate the Mo-99 from the processing solutions, and there needs to be a separate process for handling the treatment of the nitrogen oxide gases given off from the process.

These characteristics should only be viewed as generalities. All of the major producers have optimized their processing systems over many years to improve processing times, enhance recovery efficiencies, and minimize the production of liquid and solid waste.

[17]A review of both alkaline and acid dissolution processes was provided by George Vandegrift (Argonne National Laboratory) during a presentation to the Committee in 2007.

[18]The operative word here is "relative" because the liquid volumes are small (typically of the order of one or a few liters per processing batch) for either process.

3

Molybdenum-99/Technetium-99m Supply

The focus of this chapter is on the supply of molybdenum-99 (Mo-99) and technetium-99m (Tc-99m) for medical diagnostic imaging. The chapter provides a description of the global supply of Mo-99, the supply of Tc-99m in the United States, and Mo-99/Tc-99m supply chains. The information provided in this chapter is used to address the availability clause of the second charge in the statement of task for this study (see Sidebar 1.2).

PAST PRODUCTION OF Mo-99 IN THE UNITED STATES

Although there is currently no commercial production of Mo-99 in the United States, this was not always the case. Prior to 1989, Cintichem, Inc. produced Mo-99 for the U.S. market using a 5 MWt (megawatt thermal) research reactor located in Tuxedo, New York. This reactor was shut down when tritium contamination of surface waters adjacent to the reactor site was confirmed. A decision to decommission the reactor was subsequently made after a risk-benefit study carried out by Cintichem's parent company, Hoffman-LaRoche, determined that its continued operation was not justified. Cintichem offered to arrange a long-term supply agreement with the other North American supplier, the Canadian company Nordion (later MDS Nordion), to supply Mo-99 to U.S. technetium generator manufacturers (Amersham [now GE Healthcare], Mallinckrodt, and DuPont[1]).

[1]Of these three, only Mallinckrodt continues to supply technetium generators to the U.S. market.

In response to growing concerns about medical isotope availability, Congress created[2] the Isotope Production and Distribution Program and gave it the responsibility for ensuring a stable supply of isotopes, including medical radioisotopes, in the United States. In 1991, the Department of Energy (DOE) was funded by these three domestic technetium generator manufacturers to study the feasibility of using its facilities to develop a domestic supply of Mo-99 and associated fission products. As a result of this feasibility study, DOE purchased the rights to Cintichem's Mo-99 production technology[3] and associated equipment in 1991. Initially, DOE planned to produce Mo-99 using the Cintichem technology at the Omega West Reactor (OWR) and the Chemistry and Metallurgy Research (CMR) hot cell facilities at the Los Alamos National Laboratory. However, in December 1992–January 1993, a leak in the primary cooling system piping of that reactor was determined to be contributing to tritium contamination of the groundwater beneath the reactor facility. After detailed analysis, DOE decided in mid 1993 to shut down the reactor.

From mid 1993 until early 1995, DOE evaluated other alternative facilities for Mo-99 production. An Environmental Impact Statement (DOE, 1996a) prepared during 1995 evaluated these alternatives, and in 1996 DOE issued a Record of Decision (DOE, 1996b) that selected the CMR facility at Los Alamos for target fabrication and the 2 MWt Annular Core Research Reactor (ACRR) and associated hot cell facilities at Technical Area V at Sandia National Laboratories as the preferred alternatives for Mo-99 production. From late 1996 until mid 1999, DOE made capital investments and supported operating costs of the Sandia nuclear facilities to develop a Mo-99 production capability. DOE costs ranged from $20 million to $50 million, depending on whether facility operating costs were included as part of the Mo-99 project costs.

DOE issued an Expression of Interest (EOI) in 1999 to gauge commercial interest in further development of this Sandia production initiative. There was initial industrial interest in learning about the Sandia production capability. However, knowledgeable Mo-99 producers concluded that Sandia production of Mo-99 was not economically competitive with then-existing commercial Mo-99 production. The yield of Mo-99 (in terms of curies per gram of uranium-235 [U-235]) using the Cintichem technology in the

[2]Public Law 101-101. The program was managed by the Office of Nuclear Energy within the Department of Energy (DOE).

[3]Cintichem used an acidic dissolution process (now referred to as the Cintichem process) to produce Mo-99 from irradiated highly enriched uranium (HEU) targets. An improved version of this process is currently being developed for use on low enriched uranium (LEU) targets by Argonne National Laboratory. It is referred to as an *LEU-modified Cintichem process* or sometimes just *modified Cintichem process*.

Sandia facilities was about 65–80 percent that from other major producers, thus making it unattractive to the industrial sector.

One of the outcomes of the production initiative was the participation of an Albuquerque-based small business, Technology Commercialization International (TCI), in the DOE EOI information meetings. This company had existing supply arrangements for isotope distribution from Russian isotope production facilities and was interested in alternative technologies for Mo-99 production and distribution.

TCI and the Kurchatov Institute, along with Argonne National Laboratory, were funded to evaluate a Kurchatov Institute solution-based reactor concept for Mo-99 production. This initiative proceeded through demonstration of production of Mo-99 samples, and these samples were evaluated for product quality and product yield. However, TCI was not able to sustain this initiative after the conclusion of DOE funding, and ultimately the company decided to terminate its isotope production initiatives. All of TCI's business operations were terminated just as this National Academies study was initiated. Another U.S. company (Babcock & Wilcox) is now trying to commercialize the solution-reactor technology as discussed elsewhere in this chapter.

CURRENT Mo-99 SUPPLY

Between 95 and 98 percent of the world's supply of Mo-99 is produced by just four organizations (NNSA and ANSTO, 2007), all of which use HEU targets: MDS Nordion, Mallinckrodt, Institut National des Radioéléments (IRE), and Nuclear Technology Products Radioisotopes (Pty) Ltd. (NTP) (see Table 3.1 and Figure 3.1). These companies are referred to as *large-scale producers* in this report because they supply more than 1000 6-day curies[4] (see Sidebar 3.1) of Mo-99 per week to the market on a routine basis. Two of these companies (MDS Nordion and Mallinckrodt) supply all of the Mo-99 used in the United States under normal operating conditions. These companies routinely purchase Mo-99 from each other and from the other two large-scale producers to help maintain supply reliability.

The remaining world supply of Mo-99 is provided by a small number of organizations that make Mo-99 primarily for indigenous or regional use. The committee refers to these organizations as *regional producers* in this report. These producers supply considerably fewer than 1000 6-day curies per week, collectively producing only about 5 percent of the world supply

[4]The committee uses *curies* instead of the equivalent international standards (SI) unit, Becquerel, in this report because this unit is used and understood by the isotope production community. Curies can be converted to Becquerel by multiplying by 3.7×10^{10}.

TABLE 3.1 Principal Large-Scale and Regional Producers of Mo-99

Mo-99 Producer	Country	Primary Supply Regions	Percent of World Supply of Mo-99[a]	Percent of U.S. Supply of Mo-99[a]
MDS-Nordion	Canada	North America, South America, Europe, Asia	40	60
Mallinckrodt	United States, Netherlands	North America, Latin America, Europe, Middle East	25	40
IRE	Belgium	Europe	20	0
NTP	South Africa	Africa, Australia[a]	10	0
Other	Argentina, Australia, Russia	South America, Pacific-Asia, Russia	5	0

NOTE: Percentages are estimates and vary depending on global reactor production schedules.
[a]These percentages include production of Mo-99 by ANSTO. However, ANSTO shut down its production in January 2007 and has been purchasing Mo-99 while it converts its processing facilities to use the CNEA-developed LEU-based Mo-99 production process.
SOURCE: Supply quantities from Bonet et al. (2005).

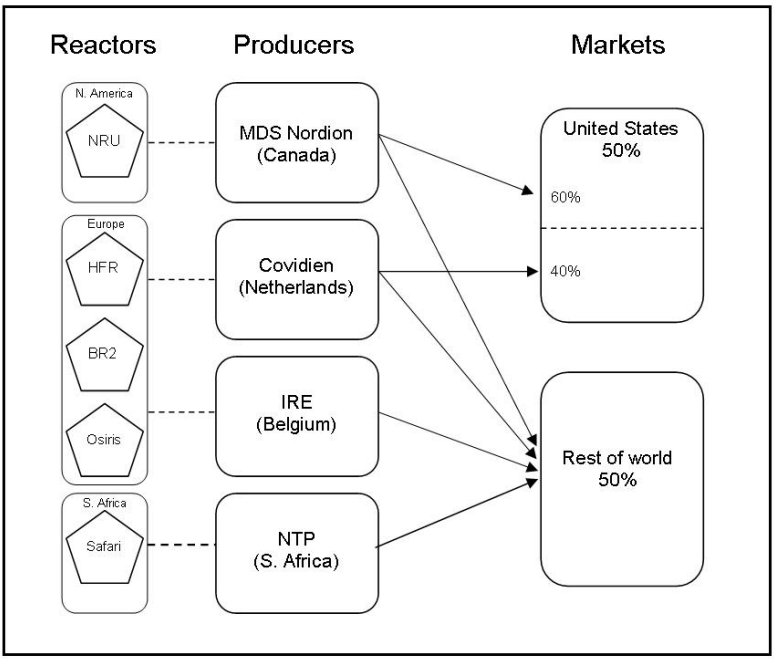


FIGURE 3.1 Large-scale global production of Mo-99 and supply to the U.S. market. NOTE: Arrows indicate only the major flows of Mo-99. There are secondary flows among producers that are not shown on the figure.

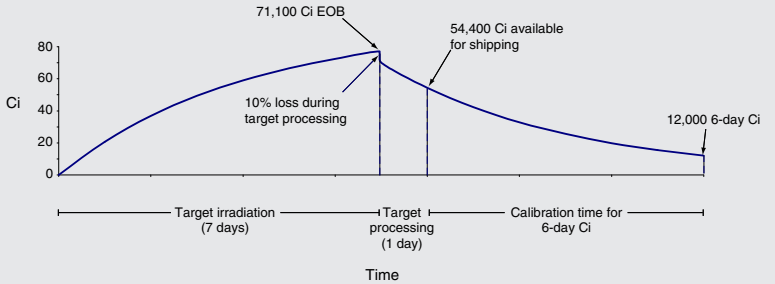
SIDEBAR 3.1
6-Day Curies

Mo-99 is priced and sold based on units of radioactivity (or *activity*) calibrated to a certain future time. Time calibration is necessary because of radioactive decay. The unit of activity used by Mo-99 producers to price and sell this isotope is the unit *curie (Ci)*, which is equal to 37 billion disintegrations per second. Most producers, and all large-scale producers, calibrate the sale price to the number of curies present in a shipment of Mo-99 6 days after it leaves the producer's facilities. This quantity is referred to as *6-day curies*.

The 6-day curie concept is schematically illustrated in the figure below, which shows the buildup and decay of Mo-99 during target irradiation, processing, and shipping. During the 5- to 7-day period of irradiation in the reactor (left side of figure) Mo-99 builds up in the target and eventually approaches a maximum as Mo-99 production is balanced by Mo-99 loss to radioactive decay. Mo-99 continues to be lost to radioactive decay after the targets are removed from the reactor, and some additional losses are incurred during target processing because of process inefficiencies (middle of figure). The amount of Mo-99 available for sale as 6-day curies (right side of figure) is only a fraction of the isotope present in the targets at the end of bombardment (EOB) by neutrons in the reactor.

The current global demand for Mo-99 is about 12,000 6-day curies per week. To produce this quantity of isotope, producers would need to irradiate enough U-235 targets to obtain about 77,000 curies of Mo-99 in the targets at EOB (left side of figure). About 54,400 curies of Mo-99 will be recovered from processing these targets, assuming a Mo-99 recovery efficiency of 90 percent (Chapter 2) and a processing time of 1 day (Table 3.4). The 12,000 6-day curies represent about 17 percent of the Mo-99 present in the targets at EOB.

The weekly global demand for Mo-99 can be supplied by the fission of about 2 g of U-235. The 54,400 curies of Mo-99 available at the end of target processing would have a mass of about 0.11 g. This mass of Mo-99 is about the amount contained in a cook's "pinch of salt." The remainder of the U-235 ends up as waste.



of Mo-99. At least two of these producers are contemplating an expansion of their supply capabilities as is discussed elsewhere in this chapter.

The short half-life for Mo-99 (66 hours) prevents it from being stockpiled for use, so Mo-99 producers must schedule the production of this isotope to meet projected demand. Producers make Mo-99 at the rate at which they can sell it, so it is reasonable to assume that Mo-99 supply is equal to Mo-99 demand, particularly when averaged over periods when there are no production or distribution disruptions.

Industry supply and demand estimates for Mo-99 are usually expressed as weekly quantities, probably because this isotope is produced on a continuous basis to meet demand. The committee follows this industry convention in this report and expresses supply quantities in terms of *6-day curies per week*.

Several estimates of the global and U.S. supply for Mo-99 have been published (e.g., Bonet and Ponsard, 2005; von Hippel and Kahn, 2006; NNSA and ANSTO, 2007). The committee is unable to verify the accuracy of these estimates because Mo-99 producers do not publicly disclose their production data. The most recent and likely the most reliable[5] of these estimates is provided in NNSA/ANSTO (2007). According to that report, the 2006[6] production of Mo-99 for medical diagnostic imaging (Chapter 2) was approximately 12,000 6-day curies per week; 2006 production for the U.S. market fluctuated between about 5,000 and 7,000 6-day curies on a weekly basis. This range reflects variations in both supply and demand in the U.S. market over the course of the year and may also reflect uncertainties about the actual supply and demand quantities. According to a representative of MDS Nordion, growth in 2006 supply has been "flat to single digit growth levels" since 2006 so "this range can be used to reflect demand/supply for this entire time period."[7]

CURRENT Mo-99 PRODUCERS

All of the organizations that currently produce Mo-99 utilize government-owned research or test reactors to irradiate targets, and some use government-owned facilities for target processing and Mo-99 recov-

[5]The committee judges that this is the most reliable currently available estimate because it is based on a workshop that was attended by three of the four global Mo-99 producers, including the two producers that supply the U.S. market, as well as several regional producers. All of these producers had an opportunity to provide information for this conference report.

[6]Publicly available supply and demand estimates for Mo-99/Tc-99m are usually at least 1–2 years old. Producers do not divulge current information.

[7]Jill Chitra, MDS Nordion, written communication with study director Kevin Crowley, November 26, 2008.

ery. Table 3.2 provides information about these reactors as well as other reactors that could be used to produce Mo-99 in the future. The principal producers are described briefly in the following sections, starting with the large-scale producers and followed by the regional producers, each in alphabetical order.

Large-Scale Producers

Mallinckrodt (Netherlands)

Mallinckrodt produces approximately 40 percent of the U.S. supply of Mo-99 and about 25 percent of world supply depending on global reactor production schedules. Production is carried out at the Petten site in the Netherlands in a joint venture with the Nuclear Research and Consultancy Group (NRG), the site operator. Production began in late 1998. Mo-99 is produced using uranium-aluminum alloy dispersion targets (Table 2.2).

The targets are irradiated in the High Flux Reactor (HFR), which is located at the Petten site, the Belgian Reactor II (BR2), which is located in Mol, Belgium, and the Osiris reactor, which is located in Saclay, France. After irradiation, the targets are processed in a Mallinckrodt-operated facility at the Petten site. That facility contains 10 hot cells, only 5 of which are apparently required to produce Mo-99. The process wastes are shipped off site for storage.[8]

IRE (Belgium)

IRE produces approximately 20 percent of the world supply of Mo-99 depending on global reactor production schedules and provides Mo-99 to the U.S. market through MDS Nordion and Mallinckrodt. It has been producing Mo-99 since 1979 at its site near Fleurus, Belgium. HEU targets are irradiated in three reactors:[9] HFR, BR2, and Osiris. The irradiated targets are transported in shielded casks on trucks to the IRE facility for processing. IRE has a dedicated bank of hot cells for target processing, a backup set of processing hot cells, and a third set of hot cells that are used intermittently for processing of strontium.

[8]Information on the number of hot cells in the facility, the number of hot cells used to produce Mo-99, and waste disposition can be found at http://ie.jrc.ec.europa.eu/publications/brochures/HFR%20brochure.pdf and http://www.wmsym.org/abstracts/2001/25/25-5.pdf.

[9]IRE also utilized a fourth reactor in Germany (FRJ-2) until it was shut down in 2006.

TABLE 3.2 Research, Test, and Isotope Production Reactors for Mo-99 Production

Reactor Name	Location	Owner	Reactor Category
Reactors Used by Large-Scale Producers of Mo-99			
NRU	Chalk River, Canada	AECL	Research
HFR	Petten, Netherlands	European Commission	Test
BR2	Mol, Belgium	Centre d'Etude de l'Energie Nucleaire (SKC-CEN)	Test
Osiris	Saclay, France	Commissariat à l'Énergie Atomique (CEA)/CEN-Saclay	Research
SAFARI-1	Pelindaba, South Africa	Nuclear Energy Corporation of South Africa (NECSA)	Research
Reactors Used by Regional Producers of Mo-99			
RA-3	Buenos Aires, Argentina	CNEA	Research
OPAL	Lucas Heights, Australia	ANSTO	Research
WWR-TS	Obninsk, Russia	Karpov Institute of Physical Chemistry	Research
Existing Reactors That Could Be Used for Mo-99 Production			
MURR	Columbia, Missouri, USA	University of Missouri	Research
G.A. Siwabessy MPR	Serpong, Tangerang (West, Java)	Badan Tenaga Nuklir Nasional (National Nuclear Energy Agency)	Research
ETRR-2	Inshas, Egypt	Atomic Energy Authority of Egypt	Research
RP-10	Peru	Instituto Peruano de Energía Nuclear	Research
RECH-1	Chile	Comisión Chilena de Energía Nuclear	Research
MARIA	Poland	Institute of Atomic Energy	Test
TRIGA II Pitesti	Romania	RAAN	Test
HANARO	S. Korea	Korea Atomic Energy Research Institute	Test
JMTR	Oarai, Ibaraki-ken, Japan	Japan Atomic Energy Research Institute	Test

Max. Power (MWt)[a]	Commissioning Date	Maximum Annual Days of Operation	Fuel Type	Target Type	Mo-99 Producer
135	1957	315	LEU	HEU	MDS Nordion
50	1961	290	LEU	HEU	Mallinckrodt IRE
100	1961	115	HEU[b]	HEU	Mallinckrodt IRE
70	1966	220	LEU	HEU	Mallinckrodt IRE
20	1965	315	HEU (45%)[c]	HEU	NTP
10	1968	230	LEU	LEU	CNEA
20	2007	340	LEU	LEU[d]	ANSTO
15	1964	190	HEU (36%)	HEU	Karpov Institute of Physical Chemistry
10	1966	339	HEU[b]	LEU	
30	1987	147	LEU	LEU	
22	1997	294	LEU	LEU	
10	1988	104	LEU		
5	1974	48	LEU		
30	1974	140	HEU (36%)		
14	1979	84	LEU		
30	1994	252	LEU		
50	1968	182	LEU		

continued

TABLE 3.2 Continued

Reactor Name	Location	Owner	Reactor Category
Reactors That Are Not Yet Operating But That Could Be Used for Mo-99 Production			
Maple reactors	Chalk River, Canada		
Jules Horowitz Reactor	Cadarache, France		
Pallas	Petten, the Netherlands[b]		
Medical Isotope Production System	Lynchburg, Virginia, USA		

[a]Reactor power is not a measure of a reactor's Mo-99 production capacity. In general, capacity depends on neutron flux and the number of targets that can be irradiated simultaneously.
[b]Reactor will be converted to LEU when suitable fuel is available.
[c]In the process of converting to LEU.
[d]LEU-based isotope production scheduled to begin in 2009.
[e]Reactors have been shut down. See Chapter 10.

MDS Nordion (Canada)

MDS Nordion provides approximately 60 percent of the U.S. supply of Mo-99 and approximately 40 percent of world supply depending on global reactor production schedules. MDS Nordion has provided 100 percent of the U.S. supply of Mo-99 on several occasions over the past several years. It obtains raw Mo-99 stock from Atomic Energy of Canada Limited (AECL), a Canadian government-owned Crown Corporation,[10] under a revenue-sharing agreement. AECL is responsible for target fabrication, target irradiation, and target processing to recover a solution containing Mo-99, as well as the management of wastes from these processes. AECL fabricates pin-type targets (Table 2.2) from HEU obtained from the United States and irradiates those targets in the National Research Universal (NRU) reactor (Table 3.2) at the Chalk River site in Ontario, Canada. The targets are processed at the Chalk River site in a single bank of hot cells. Process wastes are stored at the site. The separated Mo-99 is shipped by truck to MDS Nordion's plant in Ottawa for purification and preparation for distribution.

[10]MDS Nordion was originally part of AECL but was privatized in 1991.

Max. Power (MWt)[a]	Commissioning Date	Maximum Annual Days of Operation	Fuel Type	Target Type	Mo-99 Producer
10	[e]		LEU	HEU[f]	
100	2014 (est)		LEU[g]	LEU?	Mallinckrodt IRE
30–80	2016 (est)	300 (est)	LEU	LEU?	Mallinckrodt IRE
0.20 per unit	5 years from funding	350 (est)	LEU	LEU	B&W

[f]HEU was used in the original design.
[g]Reactor may start up with 27 percent HEU if high-density LEU fuel is not available.
[h]Anticipated location. A final decision on the site for this reactor has not been made.
SOURCES: Reactor data from IAEA (2000, Series No. 3-Nuclear research reactors of the world) and discussions with reactor operators.

NTP Radioisotopes (South Africa)[11]

NTP, a subsidiary of the South African Nuclear Energy Corporation (NECSA), produces about 10 percent of the world supply of Mo-99 and provides backup supplies to the U.S. market. It produces Mo-99 from uranium-aluminum dispersion targets (Table 2.2) fabricated in South Africa using 45 percent HEU of domestic origin. The targets are irradiated in the Safari-1 reactor (also fueled with South African HEU but it is in the process of converting to LEU fuel; see Piani, 2007), which is located at the NECSA site in Pelindaba, and processed at that same site to recover Mo-99 and I-131. The radioactive processing waste is stored to allow decay of short-lived isotopes and then disposed of by shallow land burial (IAEA, 1998).

[11]NTP declined the committee's invitation to participate in this study. The committee obtained the information in this section from the literature and informal contacts with NTP staff.

Regional Producers

There are at least three regional producers of Mo-99 for medical isotope use. Those producers are described in the following subsections.

Australian Nuclear Science and Technology Organisation (Australia)

ANSTO has been producing Mo-99 primarily to supply its domestic market, but it also supplies Tc-99m generators to 11 countries in the Asia-Pacific region. ANSTO produced Mo-99 for 25 years by irradiating 1.8–2.2 percent LEU pellets in the High Flux Australian Reactor (HIFAR) at Lucas Heights, Australia (Donlevy et al., 2000). It shut down its processing facility in 2007 to convert to a more efficient Mo-99 production process that utilizes 19.75 percent LEU targets. ANSTO has been purchasing Mo-99 from large-scale producers to satisfy its market needs during this shutdown period.

ANSTO signed a turnkey contract with the Argentine company Investigaciones Aplicadas Sociedad del Estado (INVAP) to construct a new multipurpose[12] Open Pool Australian Lightwater (OPAL) reactor and to refurbish five process hot cells for Mo-99 production. Construction was completed in 2006, and the reactor was hot commissioned in November 2006 (Figure 3.2).[13] The processing facility is designed to utilize Comisión Nactional de Energía Atómica (CNEA)-developed LEU targets and a target dissolution process to produce Mo-99. The waste from processing (a uranium solid) will be canned and stored on site.

ANSTO plans to phase the production of Mo-99[14] from its new process. Phase 1 (referred to as "Mini-moly") would supply Mo-99 to meet domestic and some export demand. A key export customer would be the United States. With success in this phase, ANSTO would become the first organization to demonstrate sustained large-scale (i.e., >1000 6-day curies per week) production of LEU-produced Mo-99. Phase 2 (referred to as "Mega-moly") would be a scaled-up facility that would greatly expand production capacity, allowing ANSTO to become a global supplier of Mo-99. The second phase would require several years and a substantial financial

[12]In addition to isotope production, the OPAL reactor supports neutron science and materials research.

[13]OPAL was shut down in July 2007 when dislodged fuel plates were discovered during refueling. A manufacturing defect in the fuel allowed individual fuel plates to shift within the fuel elements. A minor light water seepage into the heavy water moderator tanks was also discovered, but this seepage is not a safety concern and does not prevent the reactor from operating. ANSTO replaced the fuel in the reactor core and received regulatory approval to restart the reactor in May 2008.

[14]ANSTO will also separate and sell I-131.

A

B

C

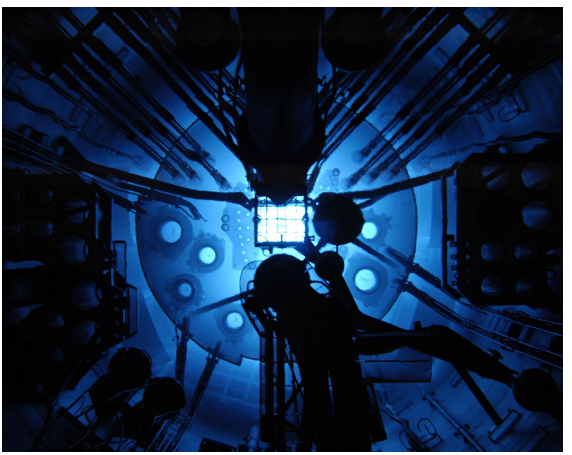


FIGURE 3.2 OPAL reactor at Lucas Heights, Australia. (a) Reactor building with steel mesh roof to protect against crash of light aircraft. (b) Reactor control room. (c) Top view of the reactor core. SOURCE: Courtesy of ANSTO.

investment to implement. It would only be undertaken if a favorable business case could be made for expanding production.

ANSTO has not produced any Mo-99 since its reactor and processing facilities were shut down in 2007. It has obtained regulatory approval to begin test irradiations of LEU targets as the first step in restarting commercial Mo-99 production. These irradiations commenced in late November 2008. ANSTO hopes to begin commercial production of Mo-99 from this new process in the second quarter of 2009.[15]

CNEA (Argentina)

CNEA produces Mo-99 primarily for its domestic market and secondarily for export to other South American countries. It began producing Mo-99 using HEU targets in 1985 (Cols et al., 2000) and developed and converted to LEU-based production in 2002. CNEA manufactures its own uranium-aluminum alloy plate LEU targets (Table 2.2) from LEU purchased from the United States. The targets are irradiated in the RA-3 reactor[16] at CNEA's Ezeiza Atomic Center near Buenos Aires. Target processing is carried out in a hot cell facility at the Ezeiza site. Process wastes are also managed at the site.

At present, CNEA produces Mo-99 primarily for its own domestic market.[17] However, it could expand Mo-99 production within its current facilities by increasing target throughputs. Such an expansion would put CNEA in the ranks of large-scale producers.

Karpov Institute of Physical Chemistry (Russia)

The Karpov Institute of Physical Chemistry, located in Obninsk, Russia, has been producing Mo-99 for domestic use since 1985. It currently produces about 99 percent of the Mo-99 used in the Russian market. The institute manufactures its own HEU targets and irradiates them in the WWR-TS reactor at Obninsk. The institute processes the targets in a hot cell facility at the site to recover Mo-99 and to produce Tc-99m generators. It supplies generators to over 200 hospitals and clinics in the country.

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[15]Ian Turner, ANSTO, written communication with study director Kevin Crowley, December 10, 2008.

[16]The reactor was originally fueled with HEU but was converted to LEU in the late 1980s. The reactor is 41 years old and will probably be able to run for another 10 years. Planning has begun for a replacement reactor.

[17]Bulk Mo-99 is shipped to two private companies in Argentina that manufacture technetium generators for the domestic market and some other South American countries.

POTENTIAL FUTURE SUPPLIERS OF Mo-99

At least two U.S.-based organizations are examining the feasibility of producing Mo-99 for sale in the commercial market: Babcock & Wilcox (B&W) and Missouri University Research Reactor (MURR). The status of these efforts is described below.

Neither of these organizations is currently producing Mo-99 on a commercial basis, and both are seeking pharmaceutical partners (presumably technetium generator producers) to provide financial support and/or a long-term commitment to purchase Mo-99. At the time the committee completed work on this report (November 2008), neither organization had announced a partnership.

However, the committee is aware of efforts by both of the U.S. technetium generator manufacturers to identify alternative sources of Mo-99 supply, both domestic and foreign. There are several potential barriers to such partnerships. These include the existence of long-term supply agreements between technetium generator producers and current Mo-99 producers, the long lead times (see Chapter 9) before Mo-99 from these new operations would become available, and the risk of substantial cost or time overruns from unanticipated problems encountered during construction and start-up of these new facilities.

B&W (USA)

B&W (formerly BWX Technologies) has developed a conceptual design for a 200 kW homogeneous solution reactor, called the Medical Isotope Production System (MIPS), to produce Mo-99 (Reynolds, 2008). This reactor is conceptually similar in design to the Argus Reactor at the Kurchatov Institute in Russia, which has already been used to demonstrate the production of Mo-99 (Ball, 1999).

MIPS consists of one or more modular compact cylindrical reactor vessels that contain control rods and cooling coils and is surrounded by a neutron reflector (Figure 3.3). The reactor would operate at about 80° C and at atmospheric pressure. The reactor fuel, which also serves as the target material for Mo-99 production, is a solution containing an LEU salt, such as uranyl nitrate [$UO_2(NO_3)_2$], dissolved in water and acid. The reactor would be operated in batch mode to produce Mo-99: That is, the reactor would be operated to allow Mo-99 to build up in the salt solution; then the reactor would be shut down and the salt solution would be pumped through an ion exchange column that preferentially sorbs Mo-99. The isotope would be recovered by washing the column. If needed, the salt solution could also be periodically processed through a fuel cleanup apparatus to remove other fission products. A three-reactor system could supply about 50 percent of U.S. demand for Mo-99.

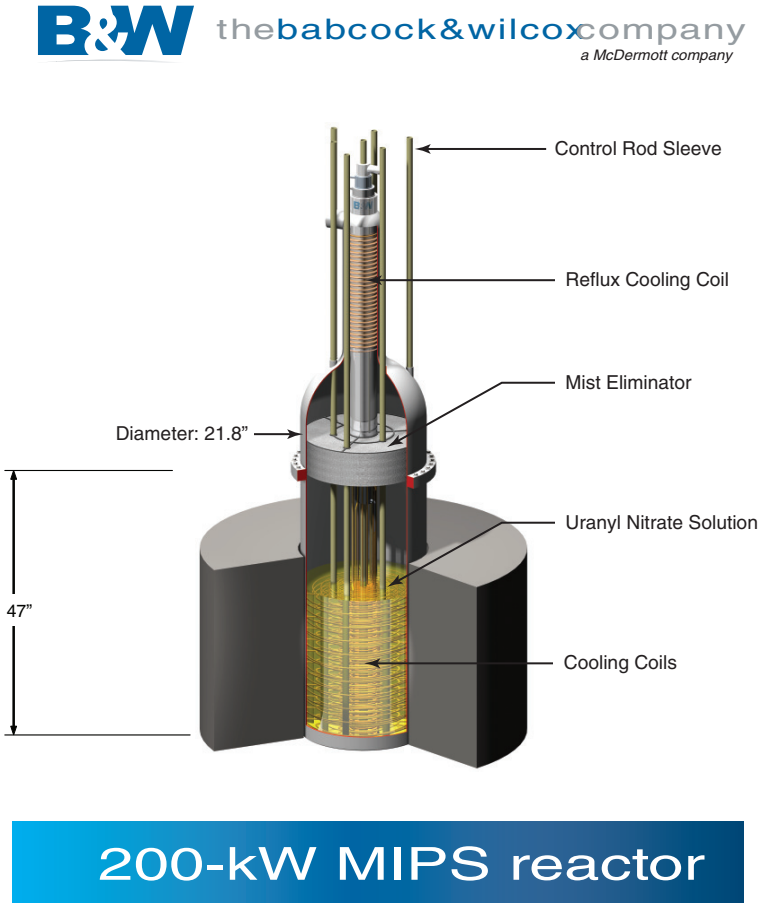

FIGURE 3.3 Schematic illustration of the aqueous homogeneous solution reactor for B&W's MIPS. The dimensions of the reactor are shown on the figure. SOURCE: Courtesy of Gary Neeley, B&W.

The reactor design is still conceptual and research and development (R&D) is underway to address several issues (e.g., Chemerisov et al., 2008; Gelis et al., 2008; Vandegrift et al., 2008; Ziegler et al., 2008). The Argentine company INVAP is performing R&D under a contract with B&W on reactor design and Mo-99 sorbent efficiency. Argonne National Laboratory is carrying out DOE-funded research to provide a better understanding of the chemistry of salt solutions in operating solution reactors and the recovery of Mo-99. Of particular concern is the potential for formation

of precipitates in the salt solution, radiation effects on the oxidation of molybdenum, and the treatment of gases produced in the reactor, especially from the decomposition of the nitrate ion. Argonne researchers report that the results to date indicate that there is a "high potential for the successful implementation of this technology" (Vandegrift et al., 2008).

B&W hopes to construct the first set of up to three commercially funded MIPS facilities at a logistically attractive location to supply Mo-99 to the U.S. market. It could also supply these systems to producers in other countries.

B&W estimates that it would take 5–6 years[18] to bring the reactor and support facilities into operation once a radiopharmaceutical partner is identified and full funding is obtained. The cost of this project is proprietary. However, this schedule assumes the successful completion of the current R&D program and the resolution of several legal and regulatory issues, including:

- *MIPS licensing:* The cost and regulatory requirements for licensing MIPS are unclear at this point and could affect its commercial viability. MIPS does not fall cleanly into any of the current licensing categories for reactors defined in 10 CFR Part 50 (Domestic Licensing of Production and Utilization Facilities).
- *Waste disposal:* The regulatory classification of the waste produced by MIPS will affect the cost and availability of disposal. Although MIPS waste is projected by B&W to meet radiological limits for low-level waste (LLW), it is not clear whether the reactor solution waste would fall under the regulatory definition for high-level waste (HLW). There is no commercial disposal pathway for waste that is classified as HLW in the United States. If Mo-99 is produced in the United States, the production wastes may be stored until there is a permanent disposal path. Waste that is classified as LLW can be disposed of in shallow land burial facilities as long as it is not greater-than-class-C (GTCC) waste. There currently is no disposal pathway for GTCC.
- *LEU availability:* LEU would be required to fuel the MIPS reactor. However, the USEC Privatization Act (Public Law 104-134) restricts the sale of enriched uranium to commercial entities. Section 3112-d of the Privatization Act allows the Secretary of Energy to sell LEU that has been down-blended from the DOE stockpile to commercial entities if three requirements are met.[19] It will take some time to carry out the administra-

[18]This time estimate has not been independently verified by the committee.

[19]The DOE Secretary must determine that any such inventory sales will not have a material adverse impact on the domestic uranium industry and that DOE will receive adequate payment if it sells this uranium. DOE must also obtain a determination from the President that the uranium to be sold is not necessary for national security.

tive actions necessary to meet these requirements. The committee was informed by a representative of the National Nuclear Security Administration that DOE should be able to complete work on these determinations in time to allow B&W to purchase LEU for its solution reactor.

Of course, Food and Drug Administration (FDA) approvals for the sale of Tc-99m from the MIPS-produced Mo-99 would also have to be obtained.

MURR (USA)

MURR is assessing the feasibility of developing the capability to supply up to half of the U.S. market needs for Mo-99 (Butler, 2008). Production would utilize the multipurpose research reactor (Table 3.2; Figure 3.4) located on the university's main campus in Columbia, Missouri, and a target processing facility that would be constructed adjacent to the reactor facility. MURR is working on target and process design, conceptual facility development, and waste disposition in cooperation with Argonne National Laboratory, CERCA, and INVAP. It is also participating in the International Atomic Energy Agency's (IAEA's) Coordinated Research Project on indigenous Mo-99 production (discussed in the next section) to demonstrate that LEU-produced Mo-99 will meet FDA requirements (see Sidebar 8.1). MURR has performed cold tests[20] to demonstrate Mo-99 recovery efficiency and successfully irradiated an annular test target containing 4.59 g LEU (19.75 percent U-235) for 140 hours in a reflector position in the reactor and processed that target using Argonne's modified Cintichem process. MURR plans to irradiate several more targets in early 2009 to optimize the modified Cintichem process for use at the facility.

MURR appears to have most of the facilities and capabilities (except hot cells) needed to produce Mo-99 for the U.S. market. The organization is producing other medical isotopes for commercial companies. It also has experience with medical isotope regulation and good manufacturing practices. The MURR reactor also appears to have sufficient capability for target irradiation. The reactor began operations in 1966 but is designed to allow replacement of all major components without extended shutdowns. The reactor is currently fueled with HEU, but it will be converted to LEU when a suitable fuel is available (see Chapter 11).

A large capital investment and up to about 5 years[21] will be required to design, construct, and license a Mo-99 production facility. The primary

[20]Cold testing is done without using radioactive material.

[21]This time estimate was provided by MURR and has not been independently verified by the committee.

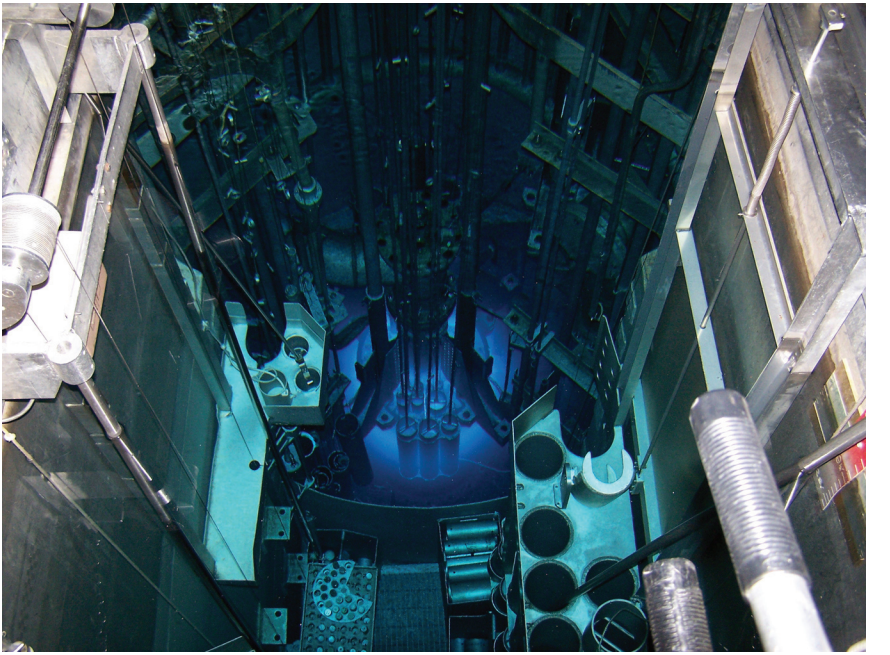

FIGURE 3.4 Top view of the MURR core. SOURCE: Courtesy of the University of Missouri.

regulatory barrier to production of Mo-99 at MURR is the disposition pathway for the waste from target processing. As was the case with the B&W project discussed previously, the classification of this waste as HLW or LLW will determine the cost and availability of disposal.

Other Potential Future Suppliers of Molybdenum-99

The IAEA has initiated a "Coordinated Research Project (CRP) on Developing Techniques for Small-Scale Indigenous Production of Mo-99 using LEU or Neutron Activation."[22] The 5-year project, which was started in 2005, is intended to foster capacity building at the local and regional levels, improve access to nuclear medicine, and support HEU minimization. This CRP is providing technical know-how and related assistance and training to assist member states in the adoption of LEU methods for producing

[22]Further information on this CRP can be found at http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_Mo99.html.

Mo-99. Two production methods are being investigated: The main method being studied is the LEU-modified Cintichem process that uses LEU foil targets. Also being studied is a method involving neutron activation of molybdenum trioxide targets for producing a gel form of molybdenum called "gel moly."[23] Seven institutions in six countries are "contract holders" in this CRP and are receiving funding for technology development, implementation, and training: Chile,[24] Libya, and Pakistan are working on the modified Cintichem process, Kazakhstan is working on the "gel moly" process, and Egypt and Romania are working on both processes. Several other organizations are assisting with technology development and training as "agreement holders," including CNEA, Indonesian National Atomic Energy Agency (BATAN, Indonesia), MURR, Korea Atomic Energy Research Institute (KAERI, Korea), Bhabha Atomic Research Centre/Board of Radiation and Isotope Technology (BARC-BRIT, India), Institute of Atomic Energy Radioisotope Centre (POLATOM, Poland), and Argonne National Laboratory. Goldman et al. (2007) provide reports on recent progress in this CRP.

As indicated by its title, the goal of this CRP is to develop *small-scale indigenous production* of Mo-99. However, many of the CRP participants have reactor facilities that could support large-scale LEU-based production of Mo-99 (e.g., Chile, Egypt, Indonesia, Pakistan, Poland, and Romania; see Table 3.2) if suitable commercial partners can be found. This would require significant investment and a partnership with a suitable generator producer and distributor. Investments might be required, for example, to augment and train the staff at the reactor facility so that Mo-99 production could be carried out on a reliable schedule. Additionally, the facility itself might need to be upgraded to enable the irradiation and processing of targets and to satisfy best radiopharmaceutical manufacturing practices. A radiopharmaceutical partner could provide financial resources, technical advice, and a predictable market for the Mo-99 produced by the facility.

The IAEA held a consultancy meeting in Vienna, Austria, in June 2007 to assess the use of homogeneous aqueous solution reactors for the production of Mo-99 and other short-lived fission-produced products. The goals of this meeting were to foster the exchange of information and also to produce a status report on the current technology state of art. This meeting could be the first step of a longer process through another CRP to be launched to assist member states with the development of this technology for Mo-99 production and other fission-produced isotopes.

[23]A discussed in Appendix D, Mo-99 produced by neutron activation has a low specific activity compared to fission-produced Mo-99. Although it can be used in technetium generators, its low specific activity reduces the quantity and duration of Tc-99m yields.

[24]See Schrader et al. (2007) for a discussion of recent progress in Chile.

TABLE 3.3 Technetium Generator Sales in the United States in 2005

	Distribution of Sales		
	Mallinkcrodt	BMS[a]	Total
Tc-99m generators shipped	56,000	36,500	92,500
Average generator size (Ci)	10[b]	16[b]	
Tc-99m doses utilized (millions)	11.2	11.7	22.9
Average generator price (US$)	1400	2080	

[a]Now Lantheus.
[b]Mallinckrodt and Bristol-Myers Squibb (BMS) generators are incorrectly transposed in the Bio-Tech Systems report.
SOURCE: Bio-Tech Systems (2006).

Tc-99m SUPPLY IN THE UNITED STATES

The most reliable estimates of Tc-99m supply in the United States that could be obtained by the committee are provided in a report by Bio-Tech Systems (2006). It quantifies Tc-99m supply in terms of technetium generator sales. The Bio-Tech Systems report estimates that over 92,000 technetium generators were sold in the United States in 2005, supplying 22.9 million doses of Tc-99m radiopharmaceutials (Table 3.3). The two U.S. distributors of technetium generators were Brystol-Meyers Squibb (BMS; now Lantheus[25]), which normally obtains Mo-99 from MDS Nordion, and Mallinckrodt.[26] Both had about an equal market share of sales based on numbers of Tc-99m doses in 2005. Normally, Tyco-Mallinckrodt's U.S. market share is about 60 percent and BMS's share is about 40 percent. However, Tyco-Mallinckrodt had a recall of its technetium generators in the last quarter of 2005, which lasted until April 2006 (see Chapter 4). BMS picked up the slack during this outage and supplied all of Mallinckrodt's regular customers, thereby increasing its market share.

Mo-99/Tc-99m SUPPLY CHAINS

Mo-99 producers have established global supply chains to ship this isotope to each other and to Tc-99m generator manufacturers using a combination of commercial and charter aircraft and ground transport services. Tc-99m generator manufacturers have also established national and regional supply chains to move generators from their production facili-

[25]BMS sold its medical imaging business to Avista Capital Partners in January 2008. The new company name (Lantheus) was announced in March 2008.

[26]Another generator manufacturer, Amersham, a British company, dropped out of the technetium generator business in the United States in 1999. Amersham is now part of GE Healthcare, which continues to operate radiopharmacies in the United States.

TABLE 3.4 Typical Process Times for Mo-99 and Tc-99m Supply Chains

Process steps	Typical process times (hr)
U-235 target irradiation and cooling	130–168 (5–7 days)
Shipping and processing of target to extract Mo-99	6–28
Mo-99 packaged and shipped	6–12
Tc-99m generator prepared and packaged	12
Tc-99m generator shipped	1–24
Tc-99m generator used by hospital or radiopharmacy	168–336 (7–14 days)

ties to hospitals and radiopharmacies using both air and ground services. Perhaps the most striking characteristic of these supply chains is their time efficiency: Because of the short half-lives for Mo-99 and Tc-99m, the revenues that can be obtained from their sale depend on how quickly they can be distributed to users. Table 3.4 shows the typical times required to move Mo-99 and Tc-99m through their supply chains, which in some cases span continents. The elapsed time between the time the irradiated targets are delivered to the processing facility and delivery of a Tc-99m dose to a patient can be as little as 25–76 hours. Actual times depend on the shipping distances and availability and frequency of transportation.

Figure 3.5 provides a schematic representation of the supply chains for U.S. producers of Mo-99 and Tc-99m generators. As noted previously, there are two suppliers of Mo-99 to the United States: MDS Nordion and Mallinckrodt. There are also two technetium generator manufacturers in the United States: Mallinckrodt and Lantheus, located in Maryland Heights, Missouri, and Billerica, Massachusetts, respectively.

MDS-Nordion ships most of its Mo-99 from Canada to the United States by air charter to technetium generator manufacturers. It supplies its key customer Lantheus and also supplies some Mo-99 to Mallinckrodt. Lantheus supplies technetium generators to markets throughout North America. Mallinckrodt ships Mo-99 from its production facility in the Netherlands to its Maryland Heights, Missouri, facility by aircraft. Mallinckrodt has an in-house facility at Maryland Heights for preparing and shipping technetium generators. Technetium generators are shipped to radiopharmacies and hospitals across the United States, Canada, and Latin America. The generators are available in a number of different curie loadings, generally ranging from less than half a curie to about 20 curies.[27]

[27]Under Department of Transportation regulations, technetium generators can be shipped by Federal Express if they contain fewer than 20 curies.

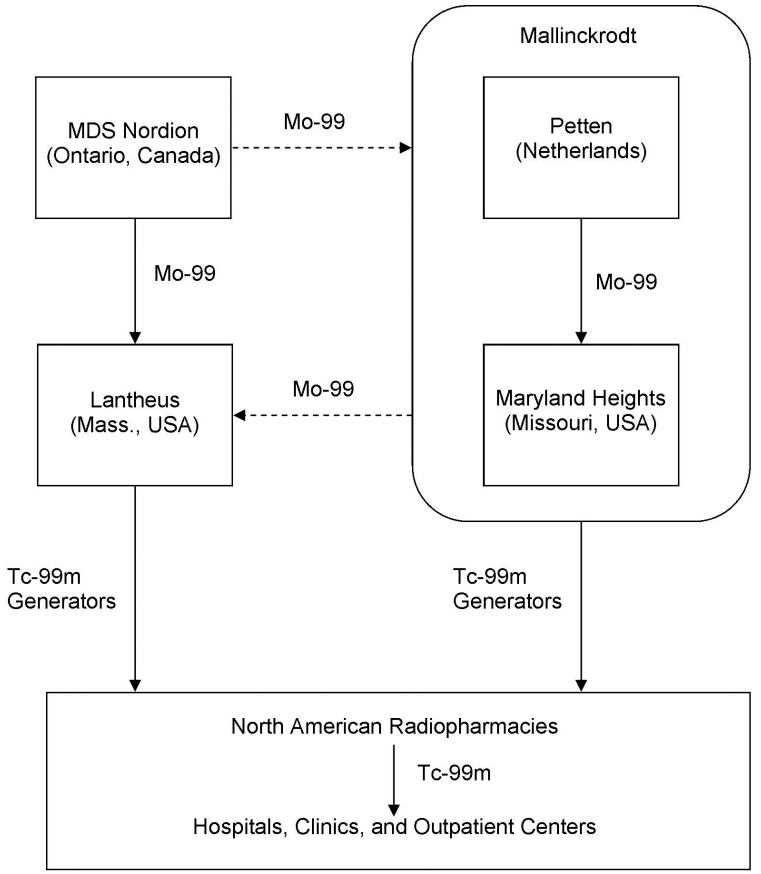

FIGURE 3.5 Supply of Mo-99, Tc-99m generators, and Tc-99m to North American markets. Dashed arrows indicate secondary flows of Mo-99 between these producers. The figure does not show other secondary flows of Mo-99 into the North American market.

SUMMARY

This chapter provides a description of the Mo-99 and Tc-99m for medical diagnostic imaging. Several important points of information provided in this chapter are summarized below:

- The 2006 global supply of Mo-99 was about 12,000 6-day curies per week. The 2006 supply to the U.S. market was between 5000 and

7000 6-day curies. U.S. supply and demand probably has not changed appreciably since 2006.

- About 95 to 98 percent of the Mo-99 produced globally, and all of the Mo-99 used in the United States, is made using HEU targets.
- Mo-99 is being produced with LEU targets by CNEA (Argentina) and is anticipated to be produced by ANSTO (Australia) using CNEA technology. This production is primarily intended for indigenous or regional use at present, but both of these organizations have expressed a desire to become global suppliers if economic conditions are favorable.
- The IAEA is supporting a coordinated research project to assist several other countries with the development of indigenous Mo-99 production using LEU, but this production is intended for domestic use only.
- Mo-99 has not been produced in the United States since 1988. Presently, Mo-99 is supplied to the U.S. market primarily by two commercial companies: MDS Nordion (Canada) and Mallinckrodt (Netherlands). These companies utilize government-constructed and -owned reactors to irradiate HEU targets. The reactors are between about 40 to 50 years old.
- Tc-99m generators are supplied to the U.S. market by two companies: Mallinckrodt (located in Missouri) and Lantheus (located in Massachusetts). Mallinckrodt generators mainly use Mo-99 produced at Petten in the Netherlands; Lantheus mainly obtains its Mo-99 from the NRU reactor at Chalk River, Ontario, via MDS Nordion.
- There are two U.S.-based organizations that are seeking support to develop domestic production of Mo-99 using LEU: B&W (located in Virginia) and MURR. However, neither organization had obtained the necessary financial support by the time this report was completed.

4

Molybdenum-99/Technetium-99m Supply Reliability

The statement of task for this study calls on the National Academies to evaluate the "availability of medical isotopes for . . . future domestic use," and also to "identify any reliability of supply issues that could arise as a result of conversions from highly enriched uranium (HEU) to low enriched uranium (LEU) production of medical isotopes" (see Sidebar 1.2). These supply reliability issues are addressed in this chapter, specifically with respect to molybdenum-99 (Mo-99) and technetium-99m (Tc-99m).

Supply reliability is primarily an issue for reactor production of Mo-99. The downstream elements of the Mo-99/Tc-99m supply chain (i.e., technetium generator production and Tc-99m distribution; see Chapter 3) are in relatively better shape with respect to reliability.[1] Mo-99 supply reliability has been a concern in the United States since the late 1980s when the Cintichem Reactor was shut down (Chapter 3). These reliability concerns arise from the following three factors:

1. Increasing demand, both domestically and globally, for Mo-99;[2]
2. Continued reliance on a small number of aging foreign reactors for Mo-99 production; and

[1]There have been some recent problems with technetium generators, but these have been less frequent and have had a smaller impact on the medical isotope user community than the disruption of Mo-99 supplies.

[2]Reliability is affected by both supply and demand; if demand grows without new production then reliability can suffer.

3. Increasing difficulty of transporting Mo-99 across international borders, especially by air.

Supply reliability is in comparatively better shape in other major world regions, notwithstanding the recent outages that are discussed elsewhere in this chapter. As noted in Chapter 3 and discussed in more detail elsewhere in this chapter, Europe is in the process of replacing two aging reactors; Australia recently commissioned a new reactor (Open Pool Australian Lightwater [OPAL]) and plans to bring a new Mo-99 production facility online in 2009; and Argentina recently upgraded its Mo-99 production facilities and has also begun planning to replace its aging reactor (RA-3).

The discussion in this chapter is organized into three sections. The first provides an examination of general Mo-99 supply reliability issues independent of whether HEU or LEU targets are used to produce this isotope. The second section provides an examination of Mo-99 supply reliability issues that could arise as a result of conversion from HEU to LEU targets. The third and final section provides findings to address the study charge.

MOLYBDENUM-99 SUPPLY RELIABILITY: GENERAL ISSUES

The general supply reliability issues that will be discussed in this section arise roughly on two timescales: days to weeks (short timescales) and months to years (long timescales). Over short timescales, supply reliability problems are primarily the result of:

1. Planned or unplanned facility outages combined with limited excess capacity for Mo-99 production elsewhere.
2. Problems with transporting Mo-99 from production facilities to technetium generator producers.

Such disruptions, although temporary, can lead to severe disruptions in diagnostic imaging procedures that can affect the continuity of patient care.

All of the reactors that produce Mo-99 must be shut down periodically for refueling and other maintenance. Even the best run and maintained reactors will be shut down on a monthly or more frequent basis for a total of at least 50 days per year (see Table 3.2). The operational programs and planned shutdowns of reactors in Europe (Belgian Reactor II [BR2], High Flux Reactor [HFR], and Osiris) and South Africa (Safari-1) are coordinated so that there is available reactor capacity for medical isotope production.[3] Also, the two European Mo-99 producers (Mallinckrodt and

[3]However, as discussed elsewhere in this chapter, unplanned shutdowns can result in insufficient reactor capacity.

SIDEBAR 4.1
Shutdown of the NRU Reactor

On November 18, 2007, AECL shut down the NRU reactor for what was intended to be 5 days of routine maintenance. During the shutdown, inspectors from Canada's nuclear regulatory agency (Canadian Nuclear Safety Commission [CNSC]) discovered that AECL had been operating the reactor without upgraded emergency backup power systems for the reactor's cooling pumps. The CNSC ordered the reactor to remain shut down until installation of these backup systems was completed.

The shutdown of the NRU caused shortages of Mo-99 in the United States and Canada, causing the cancellation of medical procedures and outcries from the medical community (see Ad Hoc Health Experts Working Group on Medical Isotopes, 2008). The Canadian Parliament passed a bill that allowed AECL to resume operation of the reactor for 120 days despite any conditions under the Nuclear Safety and Control Act relating to the installation of the emergency backup power systems.

NRU was restarted on December 16, 2007, with one of the two emergency backup systems for the cooling pumps installed; the second backup supply was installed shortly after the reactor began operating. MDS Nordion reported that it received the first batch of Mo-99 after the shutdown from AECL on December 19.

Once it became clear that NRU would have an extended shutdown (i.e., for more than a few days), Mo-99 producers in Europe and South Africa increased production of Mo-99 and took steps to distribute this isotope around the world to help offset supply disruptions (AIPES, 2007). In spite of this increased production, they were not able to replace all of the lost production.

Institut National des Radioéléments [IRE]) have agreements with multiple European reactors for target irradiation services (see Figure 3.1).

Until recently, the Canadian reactor operator Atomic Energy of Canada Limited (AECL) did not coordinate its reactor outage schedules with other reactor operators (Collier, 2008). However, after an extended shutdown in 2007 (discussed below and in Sidebar 4.1), the Canadian government announced that it was developing a new protocol for sharing information among reactor operators, isotope suppliers, and the medical establishment.

Unplanned reactor shutdowns can severely disrupt Mo-99 supplies, and these disruptions can have serious impacts on the quality of patient care. Supply disruptions can lead to the reduction of Tc-99m that is available for patient procedures. Some of these procedures can be rescheduled, but others, especially emergency procedures, cannot be postponed without potentially serious medical consequences. Such shutdowns have

SIDEBAR 4.2
A Selected Chronology of Events That Have Affected Mo-99 Supply to North America

1989	Cintichem Reactor, the only domestic supplier of Mo-99 to the United States, is permanently shut down.
1992	The U.S. Department of Energy (DOE) begins an effort to produce Mo-99 in its reactors (see Chapter 3).
1999	DOE ends its efforts to produce Mo-99 after a solicitation of private companies yields no interest (see Chapter 3).
2001	Mo-99 shipments to the United States by air are halted temporarily after the September 11 terrorist attacks.
2002	HFR is shut down for 42 days because of reactor operation safety concerns.
2005	Production of Tc-99m generators by Mallinckrodt is shut down in the United States on November 18 because of a product recall. Production is not restarted until April 2006.
2006	NRU reactor is shut down for approximately 6 days because of a technical problem.
2007	NRU reactor is shut down for 24 unplanned days by its regulator to address safety concerns.
2008	HFR is voluntarily shut down in August 2008 after a corrosion problem in the primary cooling system is discovered. The reactor is not scheduled to come back online until February 2009. IRE is shut down in August 2008 after I-131 was unexpectedly vented through a stack. The facility received approval to restart on November 4, 2008. A scheduled 5-day shutdown of NRU Reactor in December 2008 was extended for several additional days. Because HFR was also shut down at the time, there were supply shortages in the United States and Canada.

resulted from worker strikes as well as reactor maintenance and reactor upgrades that could not be taken care of during planned outages. Several unplanned shutdowns have occurred during the past 20 years (Sidebar 4.2 provides selected examples); two major reactor shutdowns occurred while this National Academies study was in progress:

- A November 2007 shutdown of the National Research Universal (NRU) reactor for scheduled maintenance was extended for almost a month after the regulator discovered that a safety upgrade had not been made (Sidebar 4.1). This outage was reported to have affected more than 50,000 patient procedures in the United States (Perkins et al., 2008), although the basis for this estimate is unclear. An unpublished survey by the Society for

Nuclear Medicine indicated that 84 percent of respondents' facilities were affected by this shutdown, and about 40 percent of respondents' facilities were operating at half capacity or below (the survey results are provided in Ad Hoc Health Experts Working Group on Medical Isotopes [2008]).

- The HFR reactor was shut down in late August 2008 after small gas bubbles of unknown origin and composition were discovered in the primary cooling system. A subsequent investigation determined that the gas bubbles were the product of corrosion of an aluminum sleeve where it contacted concrete.[4] A possible fix has been identified, but the operator now estimates that the reactor will not be restarted until February 16, 2009. At the time this shutdown occurred, the other four major production reactors (NRU in Canada; BR2 and Osiris in Europe; and Safari-1 in South Africa) were either shut down for maintenance or had scheduled shutdowns planned in the near future.

Within a week of the August 2008 shutdown of HFR, IRE also shut down its isotope production facilities in Fleurus, Belgium, after 40 GBq (a little over 1 curie) of iodine-131 (I-131) gas was unexpectedly released to the air outside the plant. The facility regulator did not approve a restart until November 4, 2008. This "perfect storm" of coincidental shutdowns is having substantial global impacts on Mo-99 availability. These outages are expected to disrupt Tc-99m supplies in Europe for at least 4–6 weeks and are also having an impact on North American markets.[5] However, the supply disruptions have been somewhat less than expected[6] because Mallinckrodt has been able to produce Mo-99 at its Petten facility from HEU targets irradiated in the Osiris reactor in France. Nevertheless, the European Association of Nuclear Medicine recently characterized the isotope supply situation as "turning from a short term shortage to a 'chronic disease.'"[7] The American Society of Nuclear Medicine has established a task force to examine alternative means for isotope production within the United States (SNM, 2008).

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[4]Pitting corrosion of aluminum materials in contact with concrete is probably the single most serious materials aging problem in research reactors. Such corrosion is particularly likely to occur in heat-affected zones close to welds in reactors and in the lining of spent fuel pools.

[5]For example, Mallinckrodt has informed its customers that they will get less Mo-99 than they have ordered.

[6]According to European press reports, customers were expecting to receive only about 30 percent of their normal deliveries of Tc-99m but were instead receiving 65–70 percent. Tc-99m supplies may further ease when the BR2 reactor restarts in late October 2008, but additional shortages are expected again in November 2008 when BR2 and Osiris shut down for scheduled maintenance. The committee has not independently verified these press reports.

[7]EANM Press Release, December 2, 2008.

Difficulties in moving radioactive material across international borders can also affect Mo-99 supply reliability, especially when air transport is involved.[8] Cross-border shipments of medical and industrial radioactive materials are regulated by individual countries, usually in accordance with the International Atomic Energy Agency's (IAEA) International Regulations for the Safe Transport of Radioactive Material (IAEA, 2004). IAEA's model regulations allow radioactive materials such as Mo-99 to be transported in commercial airliners. However, airline companies can refuse to carry these shipments, and individual airline pilots can refuse to carry shipments even if company policies allow it. The IAEA has reported (IAEA, 2004) that it is becoming increasing difficult for companies to ship radioactive materials by air.

Mo-99 producers told the committee that although cross-border shipments are still manageable, they are becoming less reliable. A representative of MDS Nordion told the committee that it avoids the use of passenger aircraft for Mo-99 shipments to the United States. Instead, it uses charter aircraft and trucks to ship Mo-99. A representative of the Australian Nuclear Science and Technology Organisation (ANSTO) reported to the committee that it encounters an "adverse" Mo-99 cross-border shipping event once every 3 weeks on average. Such events include shipments being laid off at airports or delayed in customs. These adverse events often occur without notice. They disrupt Mo-99 delivery schedules and may delay patient care.

Medical isotope producers and technetium generator manufacturers are aware of these supply reliability issues and they cooperate with each other to minimize the impacts of disruptions. For example, producers have agreements in place (including the necessary U.S. Food and Drug Administration approvals; see Sidebar 8.1) to obtain alternative supplies of Mo-99 during temporary disruptions. Mo-99 producers will also ramp up production when possible to supply each others' customers with Mo-99 or technetium generators. There is enough surge capacity at existing reactors to temporarily cover Mo-99 shortages caused by short-duration shutdowns of single reactors, but such surges cannot be maintained indefinitely because reactors need to be shut down periodically for routine maintenance and refueling. In fact, recent experience suggests that unplanned shutdowns that extend beyond about a week have the potential to cause severe supply disruptions, as demonstrated by the November 2007 shutdown of NRU that was discussed earlier in this chapter (see also Sidebar 4.2).

[8]Of course, ground-based disruptions can also occur. For example, a fire in the Chunnel between France and Britain on September 11, 2008, disrupted Tc-99m supplies to Britain during early October.

Many of the steps taken by producers to increase the reliability of Mo-99 supplies have relatively low cost, and of course the additional business that comes with supplying a competitor's customers adds to that producer's profits. However, producers have also taken some relatively high-cost steps to increase reliability that might not be seen as necessary or prudent if cost were the only business consideration. As noted in Chapter 3, for example, Mallinckrodt has 10 hot cells for Mo-99 production at its Petten, Netherlands, facility, even though other producers typically operate with fewer hot cells. MDS Nordion decided to build two Maple reactors at AECL to irradiate targets for Mo-99 production, even though one reactor had more than enough capacity to meet its current production needs.

The obsolescence of existing Mo-99 processing facilities, which consist of hot cells, the target processing equipment contained within them, and ancillary support facilities, is not a major concern for supply reliability. Some of these facilities have been operating for decades, and the committee received no reports of disruptions owing to major equipment malfunctions. Many of the major components of the hot cell itself (e.g., windows, manipulators) can be repaired or replaced. The target processing equipment contained within the cells (Figure 2.7) can be replaced with off-the-shelf items or can be easily fabricated at relatively low cost.

The greatest single threat to supply reliability is the approaching obsolescence of the aging reactors that current large-scale producers utilize to irradiate HEU targets to obtain Mo-99 (see IAEA, 2008). The continued operation of these aging reactors (Table 3.2) is a testament to their good design and construction, and to the success of reactor safety and maintenance programs. However, unlike processing facilities, not all of the components of these reactors can be easily maintained or replaced. For example, buried or concrete-encased pipes and some structural components of the reactor are difficult to access; replacing them could be expensive and could require extended (months to years) reactor shutdowns. These components include, depending on the reactor design, structural elements of the reactor core, the reflector, the reactor containment vessel, and the reactor pool liner.

The three reactors that are currently being used to irradiate targets for Mo-99 production in Europe (HFR, BR2, and Osiris) were commissioned in the 1960s (Table 3.2) and will be reaching the ends of their planned lives between about 2015 and 2020. Efforts are under way to construct two replacement reactors that could be used to produce medical isotopes. These reactors would presumably irradiate targets on a contract basis for current Mo-99 producers in Europe (Mallinckrodt and IRE) and any new producers that have nearby target processing facilities.

Ground was broken in 2007 for construction of the Jules Horowitz Reactor in Cadarache, France (Iracane, 2007). This 100 MWt materials

test reactor will be used for nuclear fuel research and the production of medical isotopes. The reactor is being constructed with funding from the Commissariat à l'Énergie Atomique (French atomic energy commission), Electricité de France, several research institutes, and AREVA. The reactor is planned to be commissioned by 2014. Construction cost for this reactor is estimated to be about 500 million euros (ESFRI, 2006).

Four organizations, including NRG and Mallinckrodt, are developing a business plan and conceptual design with research reactor builders for a new multipurpose reactor, named "Pallas," to replace HFR (van der Schaaf et al., 2008). The site for this reactor has not yet been selected but, according to NRG staff, it is likely to be built at Petten. The primary applications of this new reactor will be nuclear research and isotope production. The target date for completion of this reactor is 2016.[9]

About 40 percent of the U.S. supply of Mo-99 currently comes from Europe (Chapter 3), and so these new reactors will likely contribute to an improved reliability of supply for the United States. This assumes, of course, that the current European reactors can continue to operate until these new reactors come online. However, the other 60 percent of U.S. supply is produced in a 51-year-old Canadian reactor (NRU). When it announced its decision to discontinue work on the Maple reactors (Chapter 10), AECL also announced its intention to seek a 5-year license extension for NRU (from 2011 to 2016). A representative of the Canadian government told the committee that this upgrade would require expenditures of "hundreds of millions of dollars."[10] It is not clear to the committee whether such upgrades could be made without extended shutdowns of NRU.

In the committee's judgment, a particular concern for upgrading the NRU is the possible need to replace its aluminum reactor vessel, or calandria.[11] The original NRU calandria was replaced in the early 1970s because of corrosion, and the reactor was shut down for over 2 years while this replacement was made. There is no other reactor on the Chalk River site that could be used to produce Mo-99 during an extended outage of NRU.

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[9]Three vendors have been invited to submit designs for this reactor: Korea Atomic Energy Research Institute (KAERI, South Korea), AREVA (France), and Investigaciones Aplicadas Sociedad del Estado (INVAP, Argentina). A final design has not yet been selected, nor has funding been committed for construction. The 2016 date was characterized to the committee by NRG staff as "optimistic."

[10]Sylvana Guindon, Natural Resources Canada, verbal communication with committee chair Chris Whipple and study director Kevin Crowley, June 20, 2008.

[11]The calandria is a sealed drum-shaped vessel that contains the heavy water moderator. This vessel is penetrated by a series of horizontal fuel channels and vertical channels for control rods.

Finally, reliability of Mo-99 supply will depend on the continued availability of HEU[12] until Mo-99 producers are able to convert to LEU. Although the recently enacted Burr Amendment (Sidebar 1.3) has increased the short-term reliability of Mo-99 supply by ensuring continued access to HEU by producers in Belgium, Canada, France, Germany, and the Netherlands, its impact on long-term supply reliability is unclear. Long-term access to HEU is likely to be driven by unforeseen events that are out of Mo-99 producers' direct control. For example, the U.S. government could decide to restrict or eliminate exports of HEU in the future because of security concerns or in direct response to a terrorist attack. If that were to happen, the Burr Amendment will have decreased the reliability of supply if it has slowed conversion efforts by HEU-based producers, which appears to be the case for at least one producer, MDS Nordion (Chapter 10).

LEU CONVERSION

The conversion of Mo-99 production from HEU to LEU would increase reliability of Mo-99 supplies in one important respect: namely, it would remove longer-term uncertainties associated with the continued availability of HEU for Mo-99 production. However, Mo-99 production using LEU targets could utilize the same reactors and the same or similar processing facilities used for current HEU-based production. Consequently, the reliability-of-supply concerns described previously for current HEU-based production would also apply to LEU-based production. Additionally, conversion itself could lead to reliability of supply problems if not carried out in a technically sound manner. The technical aspects of conversion are discussed in some detail in Chapter 7.

FINDINGS

With respect to its charge to assess the availability of Mo-99 for future domestic use and identify any reliability-of-supply issues that could arise as a result of conversions from HEU- to LEU-based production, the committee finds that:

1. Reliability of supply is primarily a problem for the reactor production of Mo-99. Recent Mo-99 disruptions have impacted the availability of

[12]Continuing to make HEU available for Mo-99 production is a U.S. government policy decision, not a technical decision. From a purely technical perspective there is enough excess U.S.-controlled weapon grade HEU to supply Mo-99 production for a very long time at current rates of consumption. As discussed in Chapter 1, about 40–50 kg of HEU is used annually to support global production of Mo-99. There are hundreds of metric tons of HEU in the U.S. stockpile (http://nnsa.energy.gov/nuclear_nonproliferation/1978.htm).

this isotope for medical use and are affecting the continuity of patient care in the United States and elsewhere.

2. The supply of Mo-99 to the United States is fragile over a number of different timescales. This fragility occurs because:

- Mo-99 is highly perishable owing to its short (66-hour) half-life.
- It is produced in a small number of reactors, all of which are shut down periodically for planned and unplanned maintenance. There is limited excess capacity when a major reactor is shut down for extended periods (weeks) or more than one reactor is shut down simultaneously even for shorter periods.
- It is produced in reactors that are about 40–50 years old and have uncertain additional remaining lifetimes.
- It is not produced domestically.
- It is produced with HEU, which could be restricted in the future.
- There are long supply lines from some producers in Europe and South Africa to users in the United States.
- There can be difficulties involved in moving radioactive materials across international borders, especially by air.

As demonstrated by the 2007 NRU reactor outage and 2008 HFR outage, the sustained shutdown of reactors used by either MDS Nordion or Mallinckrodt would result in the substantial disruption of supplies to the United States and worldwide, as would the simultaneous shutdown of reactors used by both companies even for short periods.

3. AECL's May 2008 announcement that it will discontinue development work on the Maple reactors is a blow to worldwide supply reliability and increases U.S. vulnerability to supply disruptions.

4. Reliability of Mo-99 supply is likely to become a serious problem for the United States in the early part of the next decade without new or refurbished reactors: The operating license for the NRU reactor expires in 2011 and substantial investment and refurbishment will apparently be required to obtain a license extension; moreover, the European replacement reactors (Jules Horowitz and Pallas) will not yet be operational. HFR and NRU can probably continue to meet incremental growth in Mo-99 demand if those reactors can remain operational, but continued operations are not assured through the next decade. There is enough surge capacity at existing reactors to cover shortages caused by the shutdown of a single reactor, but such surges can not be maintained indefinitely.

5. Conversion from HEU-based to LEU-based production of Mo-99 would improve supply reliability because it would remove uncertainties associated with the continued availability of HEU for Mo-99 production.

However, conversion would not address any of the other supply reliability concerns associated with current HEU-based production. Moreover, conversion itself could lead to reliability-of-supply problems if not carried out in a technically sound manner.

6. Although there are other potential foreign and domestic sources of Mo-99 supply (see Chapter 3), it will take some time (5–10 years and possibly longer) for substantial supplies from these producers to become available (see also Chapter 10). As discussed in Chapter 10, government assistance is likely to be required to improve U.S. supply reliability.

5

Molybdenum-99/Technetium-99m Demand

The focus of this chapter is on the current and future demand for molybdenum-99 (Mo-99) in the United States. The committee's objective is to address explicitly the first part of the second charge of its statement of task (Sidebar 1.2) to assess the "current and projected demand and availability of medical isotopes in regular current domestic use." The second part of this charge on availability of medical isotopes was addressed in Chapter 3. The projected demand assessment focuses on potential changes in the demand for Mo-99/technetium-99m (Tc-99m) over the next 5 years in response to technical, medical, and demographic developments. The committee judged that the available data are insufficient to support projections over longer time periods.

CURRENT DEMAND FOR Mo-99

As discussed in Chapter 3, Mo-99 supply and demand are usually in balance when there are no production or other supply disruptions. The most recent and likely the most reliable estimates of current supply and demand for Mo-99 are 12,000 6-day curies per week globally and between about 5000 and 7000 6-day curies per week in the United States for the calendar year 2006 (NNSA and ANSTO, 2007).

As will be discussed elsewhere in this chapter, demand for Mo-99 in 2006 was below that for 2005 based on numbers of patient visits for nuclear medicine procedures. Patient visits were reported to be recovering in 2007 (AuntMinnie.com Staff Writers, 2008), so the current (2008) demand

for Mo-99 could be slightly higher than the 2006 estimates provided by the NNSA and ANSTO (2007) report. However, because of supply disruptions in 2007 and 2008 that were described in Chapter 4, it is not likely that all of the demand for Mo-99 in 2008 had been met.

PROJECTED DEMAND FOR MOLYBDENUM-99

The projected demand for Mo-99 is of great interest to both current producers and to potential new producers. Future demand is unknowable in a strictly quantitative sense because it will be determined by events that have yet to occur and that cannot necessarily be predicted. Several factors that could affect projected demand growth are discussed in the following sections of this chapter.

The committee used several sources of information to develop projected demand estimates for this report, including published estimates, estimates provided to the committee at its information-gathering sessions, and commercial market analyses. Some of the projected demand information gathered by the committee was provided under nondisclosure agreements. The committee has not disclosed any proprietary information in this report, but it has used proprietary information to "ground truth" its projected demand estimates.

The information sources used to develop demand growth estimates are not strictly independent. The commercially available market analyses are based on information provided by Mo-99 producers, technetium generator manufacturers, pharmaceutical companies, and hospitals. Mo-99 producers and technetium generator manufacturers use these market analyses and other information to develop their own projected demand estimates for business planning purposes. Consequently, there is likely to be some circularity of information and reasoning reflected in these various estimates.

A commercial market analysis prepared by Bio-Tech Systems, Inc. (Bio-Tech Systems, 2006)[1] provides a detailed assessment of future demand for Tc-99m. These estimates are based on the analysis of the radiopharmaceutical market, including the potential penetration of alternate imaging modalities that could substitute for Tc-99m in diagnostic imaging, as well as the impacts of demographic changes on the demand for imaging procedures. Demand for Tc-99m is an accurate indicator of Mo-99 demand

[1]The National Academies, at the committee's request, purchased the global rights to this report. The committee was not able to evaluate the methods or data used by Bio-Tech Systems to develop the estimates contained in this report and therefore cannot vouch for their accuracy. However, based on conversations with industry representatives, the committee judges that this report is generally viewed as an authoritative and valuable source of information on the diagnostic radiopharmaceutical market. The report is available in the public access file for this study.

because (as noted in Chapter 2) Mo-99 is used exclusively for diagnostic medical imaging, and all of the Mo-99 produced for this purpose is incorporated into technetium generators.

Table 5.1 provides information on historical (2002–2005) and forecast (2006–2012) growth rates for nuclear medicine procedures. The table shows total nuclear medicine procedures in the United States, the subset of those procedures[2] that utilize Tc-99m (Tc-99m procedures), and Tc-99m doses.[3] Several important observations can be made from this information:

- Tc-99m was used in about two-thirds of all nuclear medicine procedures performed in the United States in 2005; this ratio is expected to decline to slightly less than 60 percent by 2012 (although in absolute numbers, there is a projected growth in procedures using Tc-99m). This relative decline is reflected by the slightly lower annual projected growth rates for Tc-99m procedures (sixth column in Table 5.1) compared to the annual projected growth rates for all nuclear medicine procedures (third column in Table 5.1). According to Bio-Tech Systems, this decline will primarily be due to the increased use of fluorine-18 labeled fluorodeoxyglucose (FDG) for some imaging procedures. FDG is described elsewhere in this chapter.
- Annual growth rates for Tc-99m dose utilization (last column in Table 5.1) are expected to increase at a slightly higher rate (about 1 percent) than the annual growth in Tc-99m procedures. This could reflect a change in the proportion of cardiology procedures (which are projected to decrease as a percentage of all Tc-99m procedures; in 2005 they comprised about 60 percent of such procedures) to other general nuclear medicine procedures.
- Historical annual growth rates for Tc-99m doses were above 8 percent early in this decade but are projected to decrease to between about 4 and 6 percent between 2006 and 2012. This growth rate is below the projected rate of growth of Tc-99m generator sales (see Table 5.2), which are projected to increase between about 7.5 percent and 9.4 percent per year between 2006 and 2012. As noted in the tables, the growth in sales for Tc-99m dose utilization is not expected to keep pace with Tc-99m generator sales growth rates.

The estimates for projected growth in Tc-99m from the Bio-Tech Systems report (4–6 percent) are slightly lower that the growth estimates

[2]A nuclear medicine procedure is a medical procedure that utilizes medical isotopes such as Tc-99m. The terms "procedures" and "studies" are used interchangeably. A number of common Tc-99m procedures are listed in Table 2.1.

[3]A Tc-99m dose contains millicurie (mCi) quantities of Tc-99m. Typical Tc-99m doses for diagnostic imaging procedures range from about 15 to 30 mCi.

TABLE 5.1 Historical (2002–2005) and Forecast (2006–2012) U.S. Demand for Nuclear Medicine Procedures, Tc-99m Procedures, and Tc-99m Doses

Year	Total nuclear medicine procedures (millions)	Annual growth rate of nuclear medicine procedures (%)	Total Tc-99m procedures (millions)	Tc-99m procedures as % of nuclear medicine procedures	Annual growth rate of Tc-99m procedures (%)	Total Tc-99m doses utilized (millions)	Annual growth rate of Tc-99m dose utilization (%)
2002	14.1	6.7	10.2	72.2	5.4	17.7	8.7
2003	15.3	8.3	10.7	70.0	5.0	19.1	8.0
2004	16.1	5.4	11.1	68.6	3.2	20.2	5.9
2005	16.9	4.7	11.3	66.8	2.0	21.1	4.6
2006	17.7	4.7	11.7	66.0	3.5	22.1	4.5
2007	18.7	5.8	12.1	64.5	3.4	23.0	4.0
2008	19.8	6.0	12.6	63.5	4.4	24.3	5.5
2009	21.1	6.4	13.2	62.7	5.0	25.7	6.1
2010	22.4	6.1	13.8	61.5	4.2	27.1	5.3
2011	23.8	6.3	14.3	60.2	3.9	28.5	5.1
2012	25.3	6.3	14.9	59.1	4.3	30.0	5.2

NOTES: Data on procedures and doses are rounded from the original source. The 2002–2005 data are historical estimates; 2006–2012 data are forecast estimates.
SOURCE: Bio-Tech Systems (2006, Exhibit 1-10).

TABLE 5.2 Sales of Technetium in the United States, 2002–2012

Year	Technetium generator sales ($ millions)	% Growth (annual)	Average price per dose Tc-99m ($)	% Growth (annual)
2002	115.9	13.0	6.55	4.0
2003	129.9	12.1	6.80	3.8
2004	142.6	9.8	7.05	3.7
2005	154.3	8.3	7.30	3.5
2006	166.9	8.1	7.55	3.4
2007	179.3	7.5	7.80	3.3
2008	195.2	8.9	8.05	3.2
2009	213.6	9.4	8.30	3.1
2010	231.7	8.5	8.55	3.0
2011	250.6	8.2	8.80	2.9
2012	271.2	8.2	9.05	2.8

NOTES: Data on procedures and doses are rounded from the original source. The 2002–2005 data are historical estimates; 2006–2012 data are forecast estimates.
SOURCE: Bio-Tech Systems (2006, Exhibit 1-11).

that the committee received from the other sources, which range from about 5 to 8 percent per year. One respondent told the committee that it was using a growth rate that was roughly half that figure for prudent business planning purposes. The NNSA and ANSTO (2007) report cites an annual projected worldwide growth rate of between 5 and 10 percent. This is substantially higher than the other estimates obtained by the committee. However, the global potential for future growth is probably greater than that for the United States because of the large populations and relatively small market penetrations of nuclear medicine technologies.

FACTORS THAT COULD AFFECT PROJECTED DEMAND

There are several factors that could affect the projected demand growth for Mo-99/Tc-99m in the United States. For example:

- Radiopharmaceutical market changes could affect supplies of (or prices[4] for) Mo-99/Tc-99m.

[4]Under ideal market conditions, as the price of an item increases, suppliers are willing to provide more units of that item because they can cover the increasing marginal costs of production. The Mo-99 production industry does not appear to follow this ideal condition, however. As price increases, companies can increase supply to a point at little or no additional marginal cost. However, once a company reaches its supply capacity, it cannot increase supply in the short run at any price.

- Changes in health care practices, such as insurance coverage for certain procedures, could affect the demand for diagnostic imaging.
- Demographic changes, for example, the aging U.S. population, could affect the demand for medical care, including demand for diagnostic imaging procedures.
- Some Mo-99/Tc-99m use could be displaced by other diagnostic imaging modalities.

These factors are briefly described in the following sections.

Changes in Radiopharmaceutical Markets

There have been substantial changes in the technetium generator manufacturing market in the past decade as has already been described in this report: GE Healthcare dropped out of the technetium generator business in the United States in 1999, leaving the market to two companies: Mallinckrodt and Bristol-Myers Squibb (BMS). In 2008, BMS sold its medical imaging business to a venture capitalist firm (Avista Capital Partners), and a reorganized company, Lantheus, was launched that same year.

The departure of GE Healthcare from the technetium generator market in the United States has increased the pricing power of the remaining two companies. Indeed, the Bio-Tech Systems report notes that prices for Tc-99m have been advancing more rapidly since the exit of GE Healthcare from the market, and that BMS (now Lantheus) has been especially aggressive in raising its prices. Technetium generator price increases are being moderated to a certain extent by the long-term contracts that generator manufacturers have in place with many customers. Nevertheless, prices could increase substantially as these contracts expire and are renegotiated.

Limits on Medicare and private insurance reimbursements for diagnostic imaging procedures may help to moderate future price increases for technetium generators and Tc-99m. Reimbursements for diagnostic imaging procedures are made directly to hospitals and clinics; these organizations, in turn, are responsible for allocating the costs of those procedures for materials, for example, Tc-99m, labor, and facility usage. Although Tc-99m is generally a small part of the total cost of most diagnostic imaging procedures, the ability of technetium generating manufacturers (and Mo-99 producers) to increase prices will likely be limited by reimbursement rates for the diagnostic procedures themselves. Moreover, technetium generator companies and Mo-99 producers will have to compete with each other and with hospitals/clinics for a portion of any reimbursement increases. Vertically integrated producers such as Mallinckrodt may have more flexibility to set prices for Mo-99 because they also control pricing for technetium generators.

Another recent and important market development is the early 2008 expiration of the patent owned by Lantheus for the diagnostic radiopharmaceutical Cardiolite (generic name sestamibi; see Table 2.1) that is used in cardiac perfusion[5] procedures. Generic sestamibi radiopharmaceuticals are now being introduced by several companies.[6] The availability of generics is likely to have a substantial impact on prices for Cardiolite and other cardiac perfusion agents. Companies that produce and sell these agents might seek a higher return on Tc-99m sales to help maintain profits. However, Medicare and insurance company reimbursements may limit these efforts. Reimbursement for diagnostic imaging procedures covers the cost of Tc-99m, any associated radiopharmaceuticals, and the procedure. Any increase in the costs of producing or selling Tc-99m might have to be absorbed by the producers or hospitals if reimbursement limits are not raised.

Changes in Health Care Practices

Changes in health care practices could have substantial positive or negative impacts on the demand for Mo-99/Tc-99m. There was a substantial decline in patient visits for nuclear medicine procedures—from 17.2 million visits in 2005 to 15.2 million visits in 2006 (IMV Ltd.[7]; Forrest, 2007), presumably because of changes in health care delivery or administration practices. Although the committee is not able to evaluate the exact cause of this decrease, it was able to confirm that the reported reduction is real and also that recovery to date is incomplete. As the present report was in National Academies review, IMV reported[8] that the number of patient visits for nuclear medicine procedures in the United States had increased by 3 percent to 15.7 million from 2006 to 2007.

There are several other changes that are having a downside impact on nuclear medicine procedures, and especially cardiology procedures:

- Reimbursement cuts mandated by the Deficit Reduction Act of 2005 (Public Law 109-171). Recently, Medicare announced that it had spent $1.8 billion less on imaging services in 2007 as a result of this act.

[5]Bio-Tech Systems (2006) estimates that this myocardial imaging comprises almost 60 percent of all Tc-99m based diagnostic imaging procedures.

[6]Bio-Tech Systems (2006) notes that Cardinal Health, Draximage, and Teva Pharmaceuticals are planning to introduce generic products for perfusion imaging. Cardinal Health received approval while the present report was in preparation.

[7]The committee relied on a summary of this report published by IMV Ltd., IMV Medical Information Division, Des Plaines, Illinois and available at http://www.marketresearch.com.

[8]The data were reported in an article published on AuntMinnie.com on November 11, 2008, entitled "IMV: Nuclear med procedures up in 2007."

- Widespread acceptance of the updated and more restrictive 2007 Appropriateness Criteria of the American Society of Nuclear Cardiology (ASNC) and American College of Cardiology Foundation (ACCF) for performing cardiac nuclear stress tests.[9]
- Insurance company preapproval requirements for medical procedures, which are likely to spread.

In this cost-constrained environment, there is limited support for the development of new nuclear medicine tracers or technology improvements in cameras, quantification, and reconstruction algorithms.

Displacement by Other Diagnostic Imaging Modalities

There are alternative imaging modalities that could potentially reduce the future demand for Tc-99m based radiopharmaceuticals. Some potentially important alternatives are discussed in this section. The committee has focused this discussion on current and potentially new imaging modalities for cardiac and bone scanning, because these procedures account for over 75 percent of Mo-99/Tc-99m use (Bio-Tech Systems, 2006). If there are substantial changes in Mo-99/Tc-99m demand over next 5 years they are most likely to occur because of changes in the numbers of these procedures. The remaining 25 percent of Mo-99/Tc-99m use is broadly spread among multiple clinical indications, such as kidney function, cerebral perfusion, lung perfusion, gastric function, bladder function, thyroid scanning, and joint imaging. The committee judges that, in aggregate, these studies are likely to remain numerically stable over the next 5–7 years. Of course, it is also possible that new Tc-99m kits (Table 2.1) could be developed over the next 5 years that would expand the use of this isotope for diagnostic imaging.

The information in the following sections is based primarily on direct experience of the committee's medical experts.

Radioisotope Alternatives

The most widely used radioisotopic alternative to Tc-99m for perfusion imaging is thalium-201 (Tl-201). Tl-201 has strong biologic features for use in cardiac imaging: when injected intravenously, it is perfused into cardiac muscle. This radionuclide has serious limitations, however. The energy of gamma emission (about 80 keV) is less than optimal for detection with gamma cameras, so images are not as high quality as those for

[9]ASNC/ACCF appropriateness criteria for Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT MPI).

Tc-99m (which has a 140 keV emission). Tl-201 also provides relatively large radiation dose to the patient, especially to kidneys. Also, this isotope is normally produced in commercial cyclotrons and is relatively expensive to make compared to Tc-99m. Nevertheless, Tl-201 continues to enjoy a moderate but consistent application in cardiology, often in conjunction with Tc-99m agents. However, there is no compelling reason for the current levels of Tl-201 use to markedly increase in nuclear cardiology applications except when there are prolonged shortages of Tc-99m generators.

Positron Emission Tomography (PET) Imaging

The use of positron emission tomography (PET) is expanding rapidly in the United States because it provides higher-resolution images than Tc-99m scans, and because PET data provide more accurate quantitative information about underlying biologic processes (see, e.g., Kudo, 2007). At the present time there are between 1 million and 2 million PET procedures performed annually in the United States, and there are approximately 1600 U.S. sites registered as PET facilities with the Centers for Medicare & Medicaid Services (CMS).[10] Although the pace of purchase of new machines has slowed markedly recently for economic reasons, the number of patients being imaged with PET is continuing to expand using current excess capacity, and the rate of growth of PET procedures is projected to continue to be in double digits through 2012. PET imaging could potentially compete with many of the common indications for which Tc-99m radiotracers are used.

There are three PET radiotracers approved for use and reimbursable by CMS that could compete with Tc-99m in cardiovascular procedures. The most widely used is rubidium-82 (Rb-82), which is obtained from a strontium-82 (Sr-82)/Rb-82 generator (see Bateman et al., 2006).[11] The primary advantage of Rb-82 over Tc-99m tracers is that perfusion reserve[12] can be measured quantitatively. However, Sr-82 has a short half-life (25 days) and must be made in a commercial cyclotron of 70 MeV or more, and the Sr-82/Rb-82 generator system is expensive. Moreover, imaging is complex to perform and requires significant infrastructure. Most private cardiology practices do not have the infrastructure or capabilities to perform this procedure.

[10]http://www.cms.hhs.gov/MedicareApprovedFacilitie/NOPR/list.asp

[11]The short half-life of Rb-82 (75 seconds) requires that it be produced at the site of clinical use. It is obtained by elution from a generator loaded with the parent isotope Sr-82. This Sr-82/Rb-82 generator has the same general design concept as an Mo-99/Tc-99m generator.

[12]Perfusion reserve is the capacity of flow through a blood vessel system in an organ under a stress or stimulus.

A second type of positron tracer that has been useful in measuring coronary perfusion is nitrogen-13 (N-13) ammonia. This radiotracer has about a 10 minute half-life and must be continuously produced on a hospital-based cyclotron. There are growing numbers of hospital-based cyclotrons that are being installed, and it is possible that N-13 ammonia will be more widely used in the future. However, this is unlikely to displace Tc-99m use in cardiology given the demographics of use and referral patterns.

A third type of positron tracer that could have an impact on Tc-99m use in cardiology is fluorine-18-labeled FDG. FDG has been shown to have increased uptake in plaque, especially in the common carotid arteries but also in coronary arteries. FDG myocardial viability assessment has been performed for some time, but it is not used for perfusion assessment, which is the basis for Tc-99m use.

A number of myocardial perfusion agents are also under development (Higuchi et al., 2008) that could potentially displace Tc-99m. F-18 labeled BMS-747158, for example, is a promising cardiac tracer because it is cleared largely in first pass in the myocardium in proportion to blood flow. This tracer will probably compete with Rb-82 myocardial imaging, but the committee judges that it is unlikely to have a major impact on nuclear cardiology practice and use of Tc-99m tracers over the next 5 years for the reasons described below.

The bulk of nuclear cardiology procedures are performed in the offices of specially trained cardiologists, who have expertise in the use of the gamma camera and Tc-99m compounds, but have not extended their practice to PET. In addition, the economic cost of replacing the less expensive and clinically well-accepted gamma camera and technetium perfusion agents with PET is usually not cost-effective for the relatively low procedure volume that is common in many private cardiology practices. Also, PET requires additional training to interpret and the more complicated performance procedures require additional support personnel, such as medical physicists, in addition to the usual nuclear medicine technologists.

According to the Bio-Tech Systems report (2006), about 50 percent of Tc-99m use is dedicated to cardiovascular applications. The major advantage of Tc-99m for routine cardiovascular procedures is that it can be performed readily in an outpatient setting as an adjunct to the cardiologist office practice, the equipment is easy to maintain, and the images are generated by simple computer systems.

There are a number of agents in preclinical development or are being evaluated in clinical trials under a Food and Drug Administration (FDA)-approved Investigational New Drug (IND) application. However, the committee judges that these research radiopharmaceuticals will have little or no impact on the number of currently used Tc-99m labeled cardiology drugs during the next 5–7 years.

Fluorine-18 (F-18) bone scanning is generally regarded by nuclear medicine experts as diagnostically superior to the use of Tc-99m methylene diphosphonate (MDP) with planar or even SPECT imaging (Apolo et al., 2008). The availability of more than 1,600 PET facilities in the United States has led to FDG production and distribution through a network of commercial cyclotrons. These facilities have excess capacity for the raw material of FDG production, namely F-18, and these manufacturers have a strong economic incentive to produce more F-18 labeled radiotracers. F-18 is easy and inexpensive to produce as a generic product and a United States Pharmacopeia monograph exists that describes well-accepted methodology as a clinical-grade product. This agent is attractive for bone scanning because it is a simple salt (NaF) with a simple chemistry. Moreover, before the introduction of Tc-99m MDP and like agents for bone scanning, F-18 was covered for bone scanning under an approved New Drug Application (NDA; see Sidebar 8.1) issued by the FDA.

However, F-18 for bone scanning has been relatively slow to penetrate the oncology market for several related reasons: (1) The NDA lapsed and was withdrawn by the original manufacturer; (2) F-18 procedures are not reimbursed by CMS or most insurance companies because of a lack of clinical efficacy data that shows improved clinical benefit in comparison to Tc-99m MDP; and (3) despite having an approved NDA in the past, the FDA made a recent decision to require additional clinical data on effectiveness prior to reinstituting NDA approval. Recently, a consortium of radiopharmacy companies, instrumentation manufacturers, and professional societies began development of a clinical trial comparing Tc-99m MDP and F-18 bone scanning for detection of metastases in patients with prostate, breast, and lung cancer. Data collection is projected to be completed by 2010, and this information will be submitted to the FDA with the goal of obtaining an NDA as a basis for subsequent reimbursement requests through CMS. A likely timeframe for approval and the degree to which this will reduce Tc-99m MDP use for bone scanning is uncertain.

As is the case with cardiovascular applications of Tc-99m compounds, the ease and simplicity of use and the ease of reimbursement of Tc-99m bone scanning agents in comparison to PET scanning has inhibited wide-scale implementation of PET bone scanning with F-18. The committee judges that before Tc-99m bone scanning will be replaced, the important technical, regulatory, and reimbursement hurdles described above will need to be addressed.

Other Imaging Modalities

Intra-arterial contrast coronary angiography has been considered the gold standard for detecting coronary artery disease. This is particularly use-

ful prior to surgery because the technique gives accurate information about coronary anatomy. The disadvantage of this technique is that it is invasive, requires relatively high doses of radiation as well as intra-arterial contrast, and is associated with both morbidity and mortality, albeit at relatively low rates. Because of its high negative predictive value, Tc-99m perfusion imaging is usually done prior to intra-arterial coronary angiography to reduce the number of patients who need this more complicated procedure.

An advantage of Tc-99m perfusion imaging is the recent discovery that the site of blockage in acute coronary syndromes is often in arteries that are subcritical in terms of their stenosis,[13] often a 30 to 40 percent reduction in diameter of the involved vessel. This is related to the involvement of the wall of the artery and the destruction of the underlying endothelium to create an eccentric change in the vessel diameter. It is also thought that perfusion changes on Tc-99m stress imaging may reflect defects in the perfusion bed of these vessels even when their lumen, or lining, is not completely compromised.

Computed tomography (CT) imaging is becoming widely used for coronary angiography, in conjunction with calcium scoring that indicates where deposits of calcium are located in coronary arteries. Although many cardiology offices have purchased CT machines, their use for coronary angiography is still unproven, and there are technical problems, including interferences from calcium deposits in the coronary artery, that limit the sensitivity of this method. Moreover, CT angiography is likely to be complementary to Tc-99m radiotracer use, not a replacement technology because it provides no direct information about myocardial ischemia or left ventricular function.

Other molecular imaging modalities that potentially could be used as replacements for Tc-99m include nanocarriers, magnetic resonance imaging (MRI), and ultrasound. MRI of the myocardium has been touted as being highly effective for exploring biochemistry and perfusion of the myocardium. MRI is ideally suited to the assessment of cardiac morphology, contractile function, myocardial perfusion, and infarction (Shah et al., 2005; Hudsmith and Neubauer, 2008).[14] At the time of this writing, however, MRI per se has not made major inroads into clinical practice of evaluating cardiovascular patients in most parts of the United States. The reason for this probably reflects the lack of specialized expertise and equipment that would be required to replace what is current practice. In fact, in almost all instances, MRI, CT, and ultrasound are complementary to Tc-99m radiotracer use, not competitors.

[13]Stenosis is the abnormal narrowing of a blood vessel.

[14]For a recent review of this field, see also *Nature Clinical Practice Cardiovascular Medicine* (2008), Volume 5, Supplement 2: Cardiovascular Molecular Imaging for Clinicians.

Demographic Changes

Current estimates of the projected demand for Mo-99/Tc-99m are based primarily on demographic factors. The U.S. population is aging, and the front edge of the baby boomer generation is reaching retirement age. As this population continues to age, its needs for diagnostic imaging will likely increase. For example, with respect to cardiovascular use of Tc-99m, as long as there are no major changes in the amounts of public and private insurance, it seems likely that patients will choose their individual cardiology providers, who will preferentially use the facilities that they are familiar with (such as Tc-99m radiotracers and gamma cameras) in the development of treatment plans. In part this is because of an inherent conservatism in regulatory patterns as well, which make it more difficult for new techniques, no matter how meritorious, to be widely accepted and reimbursed in less than about a 5-year timeframe.

FINDINGS AND DISCUSSION

With respect to the study charge to estimate current and future demand for Mo-99 in the United States, the committee finds that:

- Demand for Mo-99 in the United States in 2006 fluctuated between 5000 and 7000 6-day curies (Sidebar 3.1) per week.
- Estimates of future demand growth for Mo-99 evaluated by the committee range from about 3 percent to 10 percent. These estimates are for both U.S. and global demand. The committee judges that demand growth for Mo-99/Tc-99m in the United States could range from 0 percent to 5 percent per year for the next 5 years, with the most likely growth rate in the range of 3 percent to 5 percent per year. These estimates assume that there are no major disruptions in Mo-99/Tc-99m supplies and no major changes in health care policies or practices.
- The demand growth for diagnostic imaging modalities will likely continue over the long term as the U.S. population ages. The extent that this will be reflected in demand for Mo-99/Tc-99m will depend strongly on whether other diagnostic imaging modalities take hold in the market.
- During the next 5 years, imaging modalities (e.g., PET, CT, MR) that could potentially displace Tc-99m use for medical diagnostic imaging probably will not find widespread use in the United States. The current practice of favoring clinical use of Tc-99m radiopharmaceuticals will continue for the foreseeable future.

Note that global demand for Mo-99/Tc-99m could grow more rapidly than demand in the United States in the mid to long term as nuclear medi-

cine technologies find more widespread application, especially in developing countries. At present, almost all of the Mo-99/Tc-99m produced in the world is consumed by developed countries. There is a huge potential market for these isotopes in those countries that hold most of the world's peoples such as India and China. Their demand for Mo-99 will almost certainly increase substantially as the increasingly affluent segments of their populations demand improved health care. The relative low cost and ease of use of Tc-99m installations that rely on conventional gamma cameras will give these modalities a competitive advantage over PET, CT, and MRI.

What is not clear at this point is whether these developing countries will develop indigenous production of Mo-99 or will purchase this isotope on world markets. If countries choose to purchase Mo-99 there could be significant impacts on Mo-99 supplies, supply reliability (Chapter 4), and prices in the United States. Although these impacts are likely to occur on timescales that are beyond the 5-year focus of this report, they should be of intense interest to Mo-99 producers who are contemplating conversion from highly enriched uranium (HEU)- to low enriched uranium (LEU)-based production or the construction of new facilities. It seems likely that, absent the development of truly superior imaging technologies, there will continue to be a flourishing long-term global market for these isotopes.

Finally, although it is beyond the scope of this report, decisions by developing countries to produce Mo-99 domestically also have implications for HEU minimization. It will be important for the U.S. government, especially the Department of State and the Department of Energy-National Nuclear Security Administration, as well as the International Atomic Energy Agency to encourage these countries to take the LEU path for Mo-99 production.

6

Molybdenum-99/Technetium-99m Production Costs

The focus of this chapter is on the cost of producing medical isotopes, specifically molybdenum-99 (Mo-99) and its decay product technetium-99m (Tc-99m), from highly enriched uranium (HEU)-based production systems. This cost information is used in Chapter 10 to address the fourth charge of the study task (Sidebar 1.2), which calls for an assessment of the "potential cost differential in medical isotope production in the reactors and target processing facilities if the products were derived from production systems that do not involve fuels and targets with HEU."

The study charge does not specify the point in the medical isotope supply chain (Figure 3.5) at which this potential cost differential is to be estimated. The committee received a range of opinions about how such estimates should be made from participants at its information-gathering meetings. Representatives of some isotope production organizations suggested that the congressional language clearly called for this estimate to be made at the point of Mo-99 production. Other participants suggested that this estimate should be made at the point of Tc-99m use (i.e., at the patient) because Congress is most concerned about the patient impacts of any medical isotope cost increases that might result from conversion to low enriched uranium (LEU)-based production.

At its first information-gathering meeting (see Appendix C), the committee invited Dr. Peter Lyons[1] to provide a background briefing on the

[1]Dr. Lyons was on the staff of the Senate Energy and Natural Resources Committee and played a key staff role in developing the language for this study. Dr. Lyons is now a member of the Nuclear Regulatory Commission.

study task, and also to clarify whether Congress intended to specify the point in the supply chain where this cost differential was to be estimated. Dr. Lyons told the committee that Congress did not intend to specify a particular point in the supply chain, and he recommended that the committee should use its best judgment in deciding how to develop these estimates.

The committee recognizes that its report will have several audiences (e.g., the sponsor: Department of Energy-National Nuclear Security Administration [DOE-NNSA]), Congress, and medical isotope producers and users) that will be interested in costs at different points in the supply chain. The committee also recognizes that its report could be used by Congress and NNSA to inform future policy decisions that could affect the availability of HEU for medical isotope production. The committee judged that its report would be most useful to all of these audiences and purposes if it provided cost estimates at several points in the supply chain.

The committee concluded that it could develop reasonably accurate cost estimates at the following three points in the supply chain:

1. Costs to medical isotope producers for making Mo-99;
2. Costs to radiopharmacies, hospitals, and clinics for purchasing technetium generators loaded with Mo-99;
3. Costs to patients (or their insurance companies) for purchasing Tc-99m doses obtained from these technetium generators.

The next section of this chapter describes how the committee estimated costs at these three points in the Mo-99/Tc-99m supply chain. Subsequent sections present the cost estimates. The timeframes for the estimates are specified where they are presented.

APPROACHES USED TO ESTIMATE COSTS

It is important to recognize that the cost estimates developed by the committee do not need to be exact to meet the needs of this study. The National Academies were asked by Congress to estimate the potential cost differential for producing Mo-99 from HEU-based versus LEU-based production systems. As discussed in Chapter 10, the variability in costs identified in this chapter, which are substantial and judged by the committee to be real, greatly simplifies the analysis.

In conventional business terms, the cost of producing an article includes both the fixed costs associated with construction of the facilities used for production as well as the variable costs attributable to production and distribution. When that article is sold, the price to the purchaser of that article reflects the producer's cost for making it, plus a premium that reflects the

value added by the production step, plus any product delivery costs. The premium represents the producer's gross profit for selling the article.

The committee initially set out to develop cost estimates using this business approach. Accordingly, costs for Mo-99/Tc-99m through the supply chain (Figure 3.5) were defined as follows:

- *Mo-99 producer.* The cost of producing Mo-99 includes the fixed costs for constructing the Mo-99 production facility and that portion of the reactor that is attributable to production. The variable costs include both direct expenses for production (e.g., materials, labor, facilities, and services) and indirect expenses (e.g., facility maintenance, safety, and security) that are attributable to production.
- *Tc-99m generator producer.* The cost of producing a Tc-99m generator includes the gross cost of the Mo-99 (i.e., the price paid by the technetium generator producer for the Mo-99 plus any delivery charges) plus the fixed and variable costs associated with producing the generator.
- *Radiopharmacy, hospital, or clinic.* The cost of producing a Tc-99m dose includes the net cost of the Tc-99m generator (i.e., the price paid by the radiopharmacy or hospital for the Tc-99m generator, plus any associated delivery charges, minus any refunds[2] received by the radiopharmacy or hospital when the generator is returned to the producer) plus the fixed and variable costs associated with producing the dose.
- *Patient.* The cost for the Tc-99m dose used in the medical isotope procedure includes the cost of the Tc-99m dose to the hospital plus any hospital costs associated with preparing and administering the dose.

As the study progressed it became clear to the committee that this approach was impractical for several reasons. First, the committee was not able to obtain detailed cost/price breakdowns for production because companies consider this information to be proprietary.[3] Second, some of the fixed costs for producing Mo-99, especially the construction of reactors used to irradiate targets, were borne decades ago by state-owned entities. Reactor construction is expensive, and nobody knows what portions of these costs are attributable to Mo-99 production.

Finally, and perhaps more important, the committee came to understand that there is no single cost or price for Mo-99/Tc-99m at any point in the supply chain. The costs to Mo-99 producers are different because they are located in different countries, operate under different currencies, and

[2]Technetium generator producers may reuse the generator case and shielding.

[3]The National Academies did receive proprietary information from some companies under nondisclosure agreements. However, these companies were unwilling to provide cost or price information.

have different cost structures for materials, labor, facilities, and services. Information obtained by the committee suggests that the costs for producing this isotope probably vary by at least 35 to 40 percent across all large-scale producers. This variation is substantially larger than the 10 percent cost feasibility test established by Congress (Sidebar 1.2).

The costs to a radiopharmacy or hospital for purchasing technetium generators are also highly variable. Tc-99m generator producers publish list prices for Tc-99m generators, but the committee was told by several companies that nobody pays list prices. Costs are negotiated with each purchaser and are affected by market mechanisms. These include producers' pricing power due to normal supply/demand balances as well as the ability of purchasers to obtain discounts through long-term and bulk purchasing agreements.

The cost to a patient for a Tc-99m radiopharmaceutical is controlled largely by the reimbursement policies of the Centers for Medicare & Medicaid Services and private health insurance. Reimbursement levels vary by insurer and by procedure. Some insurers bundle the reimbursement for Tc-99m with the reimbursement for the nuclear medicine procedure.[4] Other insurers will only reimburse the hospital for the actual cost for the Tc-99m radiopharmaceutical; the hospital is not allowed to add on any additional overhead charges associated, for example, with assaying or administering the radiopharmaceutical. This practice is expected to become universal in the United States in the years ahead as insurance companies seek to contain the costs for medical care. If that occurs, the cost to the patient for Tc-99m radiopharmaceuticals will be the same as the cost to hospitals or clinics.

Third, it is clear to the committee that the producers' costs for making Mo-99 defined above does not include all of the actual costs of producing this isotope. All large-scale producers irradiate targets in multipurpose reactors that were constructed either partly or wholly with government funding.[5] These reactors serve many other users, and it is not at all clear how costs are apportioned to these users for the services they receive. At best, users probably cover only a share of operational costs and may or may not cover part of the capital costs of the facilities.[6]

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[4]Reimbursement rates for nuclear medicine procedures can typically range from hundreds to thousands of dollars. The cost of the Tc-99m dose used in the procedure is typically on the order of $10.

[5]For example, Mallinckrodt and Institut National des Radioéléments (IRE) utilize government-owned reactors in Europe for irradiating targets; MDS Nordion obtains Mo-99 from Atomic Energy of Canada Ltd (AECL) in Chalk River, Canada. AECL is a Canadian Crown Corporation that is wholly owned by the Canadian government. See Chapter 2.

[6]Comparable new multipurpose facilities (e.g., the Open Pool Australian Lightwater [OPAL] reactor; see Table 3.2) cost hundreds of millions of U.S. dollars to construct.

Fourth, and finally, international exchange rates may also have a substantial impact on market prices and costs. All of the Mo-99 consumed in the United States is produced in other countries. Producers' costs are denominated in the currencies of host countries, but Mo-99 prices are set in U.S. dollars. Consequently, swings in exchange rates can substantially impact market costs and prices. Recent U.S. currency devaluations can have substantial impacts on medical isotope pricing and could in fact make it more difficult to bring new foreign supplies of Mo-99 into the U.S. market.

The committee decided to use a variety of approaches for developing cost estimates for the three points in the supply chain (i.e., for Mo-99 production, technetium generators, and Tc-99m doses). The committee used actual cost information in some cases, and it was able to deduce costs by compiling available information in other cases. The committee attempted where possible to develop multiple cost estimates at each point in the supply chain, both to improve its confidence in the estimates and also to understand cost variability. However, in some specific cases it was difficult for the committee to differentiate between "costs" and "prices" based on available information. Some of the estimates provided in this chapter probably represent a mix of both.

The approaches for estimating costs are described in more detail in the following sections. In some cases the committee has been intentionally vague about sources of information used to estimate costs. This was done to protect proprietary information and to make it impossible to trace cost estimates back to particular companies. The committee has not divulged any proprietary information in this report. Finally, it is important to note that all of the cost estimates provided in this report are in U.S. dollars.

Costs of Producing Mo-99

For the purpose of this report, the committee defines Mo-99 production costs as the costs to the producer for making a unit quantity of Mo-99 that can be sold to a technetium generator manufacturer. As noted in the preceding section, these costs do not necessarily include all of the costs for producing Mo-99 because producers probably do not pay the full costs for using reactor facilities.

As discussed in Chapter 3, the quantity of Mo-99 available for sale from an irradiated target is much less than the total quantity of Mo-99 produced in the target because of radioactive decay and process losses. Standard industry practice is to sell bulk Mo-99 on a calibrated "6-day curie," which is nominally the quantity of Mo-99 remaining 6 days after the Mo-99 leaves the producer's facility (see Sidebar 3.1). The committee will express the cost of producing Mo-99 in terms of 6-day curies.

The committee estimated the cost of producing a 6-day curie using two types of information. The committee was able to develop a cost estimate based on its understanding of the production process and its understanding of costs[7] at some key parts of the process. The committee was able to verify that this estimate was reasonable by checking it against public sources of information about producers' revenues and the quantities of these isotopes that these producers supply to the market.

The committee's best estimate of average production costs for a 6-day curie of Mo-99 is about $225. However, there is likely to be a wide variation in production costs among producers because of the factors described previously in this chapter. The committee could not gather sufficient information to develop a quantitative estimate of the distribution of costs. However, based on the information it received, the committee judges that a reasonable estimate in the variation in production costs is probably on the order of $100. In other words, the cost for producing Mo-99 probably range from about $125 to $325 per 6-day curie. The overall cost of producing 12,000 6-day curies of Mo-99 per week to meet 2006 demand at $225 per 6-day curies is about $140 million.

At the National Nuclear Security Administration (NNSA) and Australian Nuclear Science and Technology Organisation (ANSTO) conference in Sydney in December 2007, a representative of ANSTO informed the participants that a gram of Mo-99 was "worth" (i.e., could be sold for) about $46 million. Assuming a specific activity for Mo-99 of 4.8×10^5 Ci/g, a curie of Mo-99 is worth about $96 and a 6-day curie is worth about $470. This selling price is just over twice the average cost of production that was estimated by the committee.

Costs for Technetium Generators

Technetium generators are also sold on the basis of a calibrated quantity of Mo-99. However, the calibration is not based on 6-day curies, but rather on the number of curies that are contained in the generator on the day of or day after its delivery to the radiopharmacy, hospital, or clinic. The committee will refer to this calibrated quantity as *technetium generator curies*.[8]

[7]No producers provided cost estimates to the committee or were asked to confirm such estimates.

[8]As shown in Table 3.4, technetium generator producers can deliver technetium generators to radiopharmacies, hospitals, and clinics a day or two after they receive Mo-99. Depending on the timing of its delivery, the technetium generator can contain up to about twice the number of 6-day curies that were delivered to the technetium generator manufacturer by the Mo-99 producer.

The generators contain less than a curie to about 20 curies of Mo-99.[9] The cost of shipping the generator to the hospital, radiopharmacy, or clinic will generally depend on the shipping mode and distance. For the purposes of this discussion the committee will neglect the shipping cost in the estimate of technetium generator costs, which is likely to be small in comparison to the costs of the generator itself and because it will vary from place to place.

Technetium generator manufacturers publish list prices that can be used as a first step in estimating costs. The 2008 price list for a technetium generator sold by the Australian company ANSTO Radiopharmaceuticals and Industrials (ARI),[10] for example, is plotted in Figure 6.1. There are two notable features about the data in this plot. First, list prices for 120 GBq (about 3.25 curies) and smaller generators define two linear trends that can be represented by the equation

$$P = a\ \mathrm{GA} + \mathrm{FP}, \tag{6.1}$$

where P is the generator price in Australian dollars, GA is the quantity of technetium generator curies, and FP is the fixed price. The slope of the line, a, is the incremental price per GBq[11] of Mo-99. The intercept of the line with the y-axis, b, represents the fixed part of the price for the technetium generator. Part of this price is presumably refunded if the generator is returned to the producer.

The two data trends shown in the figure represent two different calibration days. The right-most (lower) data trend shows the prices for generators calibrated for Thursday delivery but actually delivered on Wednesday; the left-most (upper) data trend shows the prices for generators calibrated on Monday but actually delivered the previous Friday. The price differences (i.e., difference in the slopes) between the data trends can be almost exactly explained by the extra 2 days of radioactive decay for generators on the upper curve. Also note that the intercepts of the two curves are approximately equal, providing some confidence that they represent the fixed portion of the generator price.

The second notable feature of this plot is the list price for 370 GBq (10 Ci) technetium generators: The list price is identical for both calibration days but falls along the data trend for Thursday calibration. Generators of this size are more typical of those sold in the United States, as will be discussed later in this section.

[9]As noted in Chapter 3, Department of Transportation regulations allow technetium generators to be shipped by Federal Express if they contain less than 20 curies.

[10]ARI is a wholly owned subsidiary of ANSTO.

[11]The price per curie can be obtained by multiplying this price per GBq by 37.

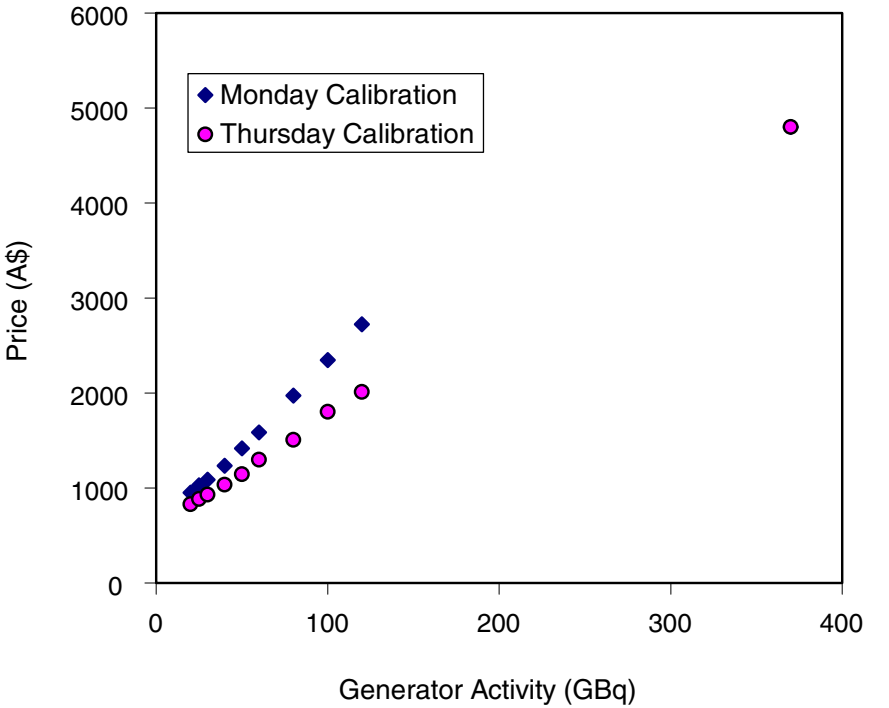

FIGURE 6.1 List prices in 2008 for ARI technetium generators sold in Australia on two different calibration days. NOTES: 100 GBq = 2.7 Ci. These data should not be used for estimating actual costs for the reasons explained in the text. SOURCE: Data from ANSTO/ARI.

As noted previously in this chapter, almost nobody pays list prices for technetium generators. Consequently, the prices shown in Figure 6.1 should not be used for cost estimation purposes. It is also important to recognize that these generators are sold in a different market (Australia and Pacific countries) in a different currency and do not necessarily reflect U.S. market prices. In contrast to the United States, Australian and Pacific markets place different social values on health care and have different structures for pricing and reimbursing medical treatments.

The committee obtained a proprietary generator list price for another technetium generator producer that supplies the U.S. market. It shows the same slope and intercept behavior as Figure 6.1, especially for smaller generators, but the slopes and intercept values are substantially different. Nevertheless, Figure 6.1 is useful because it illustrates an important fact about

technetium generator pricing: For a given generator producer, the incremental cost of a technetium generator curie of Mo-99 is approximately the same regardless of the size of the generator, and there is also a fixed-price component that is independent of generator size. This observation led the committee to conclude that it should develop estimates for the technetium generators rather than the Mo-99 that is contained within them.

The committee used two sources of information to estimate technetium generator prices. First, Bio-Tech Systems (2006) reported that average prices for Mallinckrodt and BMS (now Lantheus) generators in 2005 were $1,400 and $2,080, respectively. Bio-Tech Systems (2006) also reported that the average Mallinckrodt generator size was 10 Ci, and the average BMS generator size was 16 Ci (see Table 3.3).[12]

Second, the committee obtained the radiopharmaceutical price list for Fraser Health, a large health authority in British Columbia, which contains technetium generator prices for two companies.[13] This price list was negotiated in 2005, the same year covered by the Bio-Tech Systems report described previously, and is valid for purchases during the period 2005–2008. The prices were quoted in Canadian dollars (C$). In 2005, a Canadian dollar was worth about US$0.83.[14] The low and high prices for each generator size are C$1,800 (US$1,490 in 2005) and C$2,300 (US$1,910 in 2005), respectively, for a 7.5 Ci generator and C$2,300 (US$1,910 in 2005) and C$2,800 (US$2,320 in 2005), respectively, for a 10 Ci generator. The price variations reflect different bundles for different numbers of generator purchases.

The cost variation for technetium generators sold to Fraser Health is about 12 percent for the 7.5 Ci generator and 10 percent for the 10 Ci generator. It is interesting to note the prices for 10 Ci generators sold to Fraser Health generator are much higher than the average price of a BMS generator. Of course, the latter price is an average and the former represents prospective prices for generators to be sold over a 3-year period. This dataset is too sparse to develop quantitative distributions of generator costs.

Costs for Tc-99m

Tc-99m is produced from technetium generators as a sodium pertechnetate solution ($NaTcO_4$); the quantity of Tc-99m contained in the solution

[12]As noted in Table 3.3 the sizes of Mallinckrodt and BMS generators are incorrectly transposed in the Bio-Tech Systems (2006) report.

[13]Fraser Health requested that the committee not name the companies. Fraser Health is a large health care company that can obtain competitive prices based on the numbers of generators it purchases.

[14]This exchange rate is based on the average daily interbank exchange rate for 2005 listed on the Bank of Canada website. As of December 2008, C$1.00 was approximately equal to US$0.80.

is expressed in terms of activity, usually in units of millicuries (mCi). Tc-99m sodium pertechnetate is sold as individual doses for single diagnostic imaging procedures, typically ranging from about 20 mCi to 35 mCi. It is also sold in bulk quantities up to several hundred millicuries, which would be used for multiple procedures.[15]

The committee obtained information on Tc-99m sodium pertechnetate prices from several sources. The Bio-Tech Systems (2006) report provides average prices per dose of Tc-99m sodium pertechnetate from hospital and radiopharmacy sales in 2005. It reports that average prices range from $8.20 for hospital/clinic sales and $7.20 for radiopharmacy sales. The dose size is not specified.

The committee obtained 2008 data on actual prices for Tc-99m sodium pertechnetate sold by several radiopharmacies. These prices were obtained from three large U.S. health care organizations that purchase Tc-99m sodium pertechnetate from these radiopharmacies. Price quotes are provided for individual Tc-99m pertechnetate doses and for bulk Tc-99m sodium pertechnetate. Most of the prices fall in the range from $0.28 to $0.45 per mCi, but two prices were much higher, about $0.90 per mCi.[16]

The committee estimated the cost for a dose of Tc-99m sodium pertechnetate by taking the middle of the price range noted above, neglecting the highest two prices, and multiplying by a dose size of 30 mCi. The result is about $11.00. The cost range, again neglecting the highest two estimates, is greater than ± 20 percent. The committee did not obtain enough data to develop quantitative distributions of technetium dose costs.

DISCUSSION AND FINDINGS

The committee estimates the following costs/prices for medical isotopes at three points in the Mo-99/Tc-99m supply chain.

- *Cost for Mo-99 production in 2008*: about $225 per 6-day curie with a cost variation of about ± 40 percent.
- *Price for technetium generators in 2005*: The "average" cost of a 10 Ci generator is about $1,900 with a variation of about ± 25 percent.
- *Price for a Tc-99m dose in 2008*: about $11.00 per dose of Tc-99m sodium pertechnetate, with a price variation of over ± 20 percent based on the information that was available to the committee.

[15]The amount of Tc-99m used in a single medical isotope procedure depends on the procedure itself and the body mass of the patient.

[16]The $0.90/mCi prices were not for standard dose quantities and may reflect higher labor costs associated with preparation and assaying.

7

Conversion to LEU-Based Production of Molybdenum-99: Technical Considerations

The objective of this chapter is to describe and discuss the important technical considerations for conversion of molybdenum-99 (Mo-99) production from highly enriched uranium (HEU) to low enriched uranium (LEU). This chapter is intended to support the discussion of conversion feasibility that appears in Chapter 10.

The focus of this chapter is on conversion of the HEU targets that are currently being used to produce Mo-99 for medical use (Chapter 2). With two exceptions, all of the reactors that are currently being used for large-scale production of Mo-99 (Chapter 3) have already been converted to LEU fuel. The exceptions are the Safari-1 Reactor in South Africa and the Belgian Reactor II (BR2) in Belgium. Safari-1 is in the process of converting (see Chapter 3), and BR2 will convert when a suitable LEU fuel becomes available. A general discussion of research reactor fuel conversion is provided in Chapter 11.

TARGET DESIGN AND PROCESSING

As noted in Chapter 1, almost all of the Mo-99 produced for medical use in the world today is made using HEU targets. These targets consist of an HEU "meat," usually a uranium oxide or uranium metal alloy, contained within a metal or metal alloy cladding (Chapter 2). Three basic approaches exist for converting these targets to LEU:

- Direct replacement of the HEU in the target with LEU (with an increase in the number of targets that are irradiated).
- Increase the mass of U-235 in the LEU target by increasing target size.
- Increase the mass of U-235 in the target by changing the composition of the target meat.

These approaches are described in the following sections.

Direct Replacement of the HEU in the Target with LEU

HEU and LEU have essentially the same physical and chemical properties, so the direct replacement of HEU by LEU in the target meat would pose no particular target design, fabrication, or testing challenges. The LEU target would have the same geometry, heat transfer, and chemical processing properties as the equivalent HEU target and could be irradiated and processed in essentially the same manner. Assuming the same target design and uranium density, the yield of Mo-99 from the LEU target would be only about 20 percent of the HEU target it replaces owing to its reduced uranium-235 (U-235) mass and increased neutron capture.[1] Consequently, approximately five times as many LEU targets would have to be irradiated and processed to produce the same amount of Mo-99 as a single HEU target, and up to five times as much volume of waste from target processing might be produced as a result. Some producers have suggested that their facilities might not be able to accommodate these higher throughput requirements without substantial modification.

Facility modifications might not be necessary, however, if certain process changes are made. Current target dissolution processes (see Chapter 2) operate well below solubility limits using containers that are small relative to the hot cells in which they sit. Higher throughputs could be accommodated by increasing container sizes and/or increasing material concentrations in the solvent.[2] Liquid waste can also be converted to solids by precipitation, evaporation, or calcination to substantially reduce its volume. Moreover, given its lower U-235 enrichment, this solid waste can be more closely packed together in storage containers and facilities without increasing criticality risks. Because the LEU targets produce the same amount of fission heat and heat-producing fission products as HEU targets

[1]Most HEU targets have 93 percent U-235 enrichments; LEU targets would have 19.75 percent enrichments. Neutron capture in LEU targets (primarily by uranium-238 [U-238]) would be about 15 percent higher than in equivalent-sized HEU targets.

[2]Increasing material concentrations in the solvent could lead to criticality problems if HEU targets are used but would not be a problem for LEU targets.

with the same Mo-99 yield, heat management requirements would also be the same.

Another consideration for direct replacement is reactor irradiation capacity. Most of the world's supply of Mo-99 is produced by irradiating HEU targets in multipurpose, multiuser facilities (Table 3.2). Reactor operators' ability to accommodate larger numbers of LEU targets could be limited because of other user demands on reactor resources.

Increase the Mass of U-235 in the LEU Target by Increasing Target Size

Additional U-235 could be incorporated into an LEU target by increasing the volume of the target material (i.e., the target meat). This approach would reduce target throughput requirements in the reactor but would not substantially change the other material throughput requirements described previously. Also, space limitations in the reactor target irradiation positions might preclude the use of substantially larger targets.

Increase the Mass of U-235 in the Target by Changing the Composition of the Target Meat

The HEU targets[3] used for most current Mo-99 production are uranium-aluminum alloys (Table 2.2) having uranium densities approaching 1.6 g/cm^3. To obtain an equivalent mass of U-235 in an LEU target of the same size, a uranium density of about 8 g/cm^3 would be required. Higher-density LEU targets could be made of several materials:

- *Uranium metal targets.* Argonne National Laboratory has led the development of a uranium metal target (Figure 7.1) in cooperation with several organizations. Recent progress is described by Vandegrift et al. (2007), Bakel et al. (2008), and Wiencek et al. (2008).[4,5] The target consists of a thin (typically 100- to 150- micron) LEU metal foil wrapped in an

[3]Although the focus of this discussion is on targets, the same considerations apply for the conversion of reactor fuel from HEU to LEU as will be discussed in Chapter 11. Targets and fuels have the same basic sandwich design and differ primarily in size and configuration.

[4] The primary participants are Comisión Nactional de Energía Atómica (CNEA, Argentina), MURR (United States), and Indonesian National Atomic Energy Agency (BATAN). CNEA is providing advice on target design and has carried out tests on irradiated foils. BATAN and the Australian Nuclear Science and Technology Organisation (ANSTO) have also test-irradiated these foils. MURR is evaluating target fabrication approaches and modeling target thermal properties. In early November 2008, MURR also began irradiating and processing small (5 g) targets.

[5]Compagnie pour l' Etude et la Réalisation de Combustibles Atomiques (CERCA, France) is also investigating LEU foil targets in cooperation with the Missouri University Research Reactor (Allen et al., 2007).

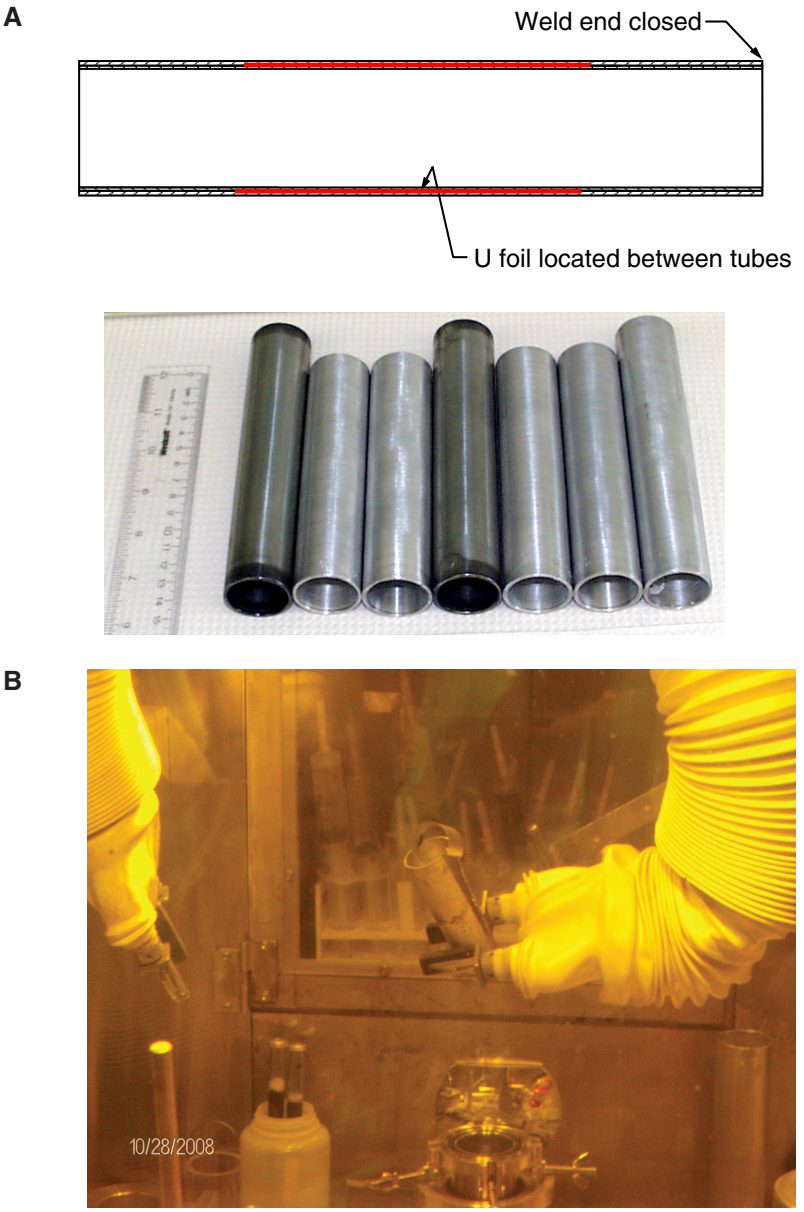

FIGURE 7.1 (a) LEU metal foil targets developed by Argonne National Laboratory. (b) Views into the hot cell at the Missouri University Research Reactor (MURR) showing the irradiated LEU foil target being removed from the target cladding in preparation for dissolution. SOURCES: Courtesy of George Vandergrift, Argonne National Laboratory, and the University of Missouri, respectively.

aluminum or nickel foil barrier and encapsulated in a cylindrical aluminum cladding. The aluminum or nickel foil serves as a recoil barrier and prevents the uranium foil from bonding with the aluminum cladding. The cylindrical design was selected to improve target structural integrity and heat transfer and facilitate physical target disassembly after irradiation.[6] However, these targets could also be fabricated as plates (see Allen et al., 2007). The primary advantage of this target material is its high uranium density (~19 g/cm^3): Gram for gram, uranium foil targets can produce as much or more Mo-99 than currently used HEU targets under the same irradiation conditions.[7] The uranium foil is potentially compatible with the alkaline[8] and acidic dissolution processes that are currently employed by large-scale producers.[9]

The foils used for this development work have been produced by Argonne National Laboratory by hot and cold rolling and by the Korea Atomic Energy Research Institute (KAERI, South Korea) using a casting method (Kim et al., 2004).[10] The KAERI foils are economical to produce but contain pinholes and surface irregularities and are of uneven thicknesses. These irregularities would not necessarily preclude the use of these foils for Mo-99 production, but could make it more difficult to qualify the targets for use and more expensive to produce targets on a production basis. Cold rolling these foils would eliminate these irregularities but is labor intensive. KAERI is working on improving the consistency of its foils,[11] and Argonne is investigating other potential sources for obtaining large quantities of these foils.[12] Work is underway at the University of Missouri to develop foil target designs that can be used for high volume production of Mo-99 (Solbrekken et al., 2008).

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[6]After the target is irradiated the aluminum cladding and foil sandwich are mechanically separated and the uranium foil is chemically processed. The separation of the foil from the cladding prior to processing reduces the mass of material that must be chemically dissolved, which is another advantage of this target design.

[7]For example, the HEU targets now being used by the Institut National des Radioéléments (IRE) to produce Mo-99 contain 3.7 g of U-235. If the HEU meat in these targets were replaced with an LEU metal foil of the same thickness, it would contain 16.6 g of U-235 (Wiencek et al., 2008).

[8]The alkaline process requires the use of hydrogen peroxide to oxidize the uranium metal.

[9]Argonne National Laboratory has also developed a modified Cintichem process to dissolve these targets and recover Mo-99. This process has Mo-99 recovery efficiencies of over 90 percent, which is similar to the recovery efficiencies for the alkaline and acidic processes that are currently being used by large-scale producers. See Bakel et al. (2008) for recent progress.

[10]Hot rolling refers to heating metal above its recrystalization temperature before rolling to form sheets. Cold rolling is conducted at room temperature to maintain a metal's original crystalline structure. Casting involves melting the metal and pouring it into a mold.

[11]George Vandegrift, Argonne National Laboratory, written communication, July 14, 2008.

[12]The Y-12 site in Tennessee has the equipment and materials to produce these foils, for example.

- *Uranium-aluminum dispersion targets*. CNEA has developed and is using high-density LEU-aluminum dispersion targets to produce Mo-99 for its domestic market (Kohut et al., 2000; Cestau et al., 2008). The target meat has a uranium density of about 2.9 g/cm^3 (IAEA, 2003, Annex 1), which is obtained by increasing the ratio of uranium aluminide to aluminum in the target meat. The aluminum serves as a binder in the target meat. The mass of U-235 in the target meat is about twice that of conventional uranium-aluminum alloy targets. These targets are compatible with the alkaline dissolution processes that are currently used by most large-scale Mo-99 producers (see Chapter 2). However, these targets would still not have enough U-235 mass to serve as direct replacements for the HEU targets used by current producers.
- *Uranium silicide targets*. Uranium silicide (U_3Si_2) was initially developed as an LEU replacement fuel for research reactors (see Chapter 11). Its use as a target material would represent a natural extension of that application. The primary advantage of this material is its higher uranium density[13] (4.8 g/cm^3) relative to uranium-aluminum dispersions and its ease of fabrication into targets (see Kolar and Wolterbeek, 2004). However, uranium silicide is difficult to dissolve[14] and cannot be processed using conventional alkaline or acidic dissolution processes (Chapter 2).
- *Uranium-molybdenum targets*. As described in Chapter 11, work is currently under way to develop high-density LEU fuels using uranium-molybdenum alloys. The goal of this work is to develop fuels that have uranium densities in the range of 7–9 g/cm^3, which are within the range needed for direct replacement of HEU in targets. However, uranium-molybdenum alloys are unsuitable for use for Mo-99 production because of their high Mo-98 content. The Mo-98 in the target would dilute the Mo-99 produced during irradiation, reducing its specific activity sufficiently to make it unusable.[15]

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[13]Uranium silicide fuel having a uranium density of 4.8 g/cm^3 has been qualified for use in research and test reactors (USNRC, 1988). Argonne has fabricated fuel plates with uranium densities of up to 6.1 g/cm^3, and CERCA has fabricated fuel plates with uranium densities of up to 6.0 g/cm^3, but these have not been qualified for use as reactor fuel. See http://www.rertr.anl.gov/QualFuel.html and Durand et al. (1992).

[14]The Argonne National Laboratory study (Buchhold and Vandegrift, 1995) on processing uranium silicide concluded that: (1) Neither of the alkaline solvents that are typically used to dissolve uranium-aluminum alloy targets (NaOH or NaOH/NaNO3) dissolves uranium silicide. (2) Uranium silicide can be dissolved in NaOH if hydrogen peroxide is added. This solvent dissolves uranium silicide at an acceptable rate, but agglomerates of the material form during dissolution and must be broken up to obtain rapid dissolution. (3) Uranium silicide will dissolve in nitric acid, but gelatinous silicic acid forms unless the Si concentration is maintained at less than 0.1 molar. (4) The fluoride ion dissolves uranium silicide but complicates waste treatment and disposal because of its corrosive nature. See also Cols et al. (2000).

[15]Researchers at Delft University are investigating methods to separate Mo-99 from Mo-98; see Appendix D.

The design of the LEU target has important implications for target dissolution, Mo-99 recovery, and waste management (see Chapter 2 for a discussion of these issues). The two principal processes that are currently used for HEU target dissolution and Mo-99 recovery are broadly similar (Chapter 2): Irradiated HEU targets are dissolved in acidic or alkaline solutions, and Mo-99 is recovered through a series of chemical processing steps followed by sorption onto an alumina column or other media. Over the years, Mo-99 producers have added proprietary improvements to their processes to reduce processing time, reduce product impurities, and improve Mo-99 recovery. These processes are technically mature and have allowed producers to achieve good consistency in the quantity and quality of their Mo-99 product.

Producers would probably prefer to convert to LEU-based production without having to make major changes to their target dissolution and Mo-99 recovery processes. The ideal approach for conversion is exemplified by the path taken by CNEA when it developed high-density LEU-aluminum dispersion targets. These targets were described previously. The CNEA-developed target is the same size and approximately the same U-235 mass as the HEU target it replaced. CNEA was able to produce this target by increasing the uranium density and thickness of the target meat and reducing the cladding thickness. As a result, CNEA had to make relatively minor adjustments to its target dissolution and Mo-99 recovery processes during conversion. Moreover, CNEA was able to convert to LEU-based production while maintaining HEU-based production—and to carry out both of these activities in a single set of hot cells. Cestau et al. (2007) reported that the efficiency and stability of CNEA's LEU-based process is similar to the HEU-based process it replaced.

Mallinckrodt, IRE, and MDS Nordion will probably not be able to follow this conversion path, primarily because there are no LEU-aluminum or LEU-oxide materials with sufficiently high uranium densities (~ 9 g /cm^3) to serve as direct replacement for HEU targets, nor are such materials on the horizon. These producers could certainly develop LEU-aluminum targets following the CNEA approach, but they would still have to irradiate, process, and manage up to two or three times more targets and wastes. Alternatively, these producers could use LEU metal targets but would likely have to modify their target dissolution processes. However, because LEU metal targets have such high uranium densities, material throughputs (both for target irradiation and processing) would likely be smaller than for currently used processes.

Nuclear Technology Products (NTP) Radioisotopes uses 45 percent HEU to produce Mo-99 instead of the 93 percent HEU that is used by the other three large-scale producers. Consequently, it must process approximately twice as much HEU material to produce the same amount of

Mo-99 as other large-scale producers. NTP could probably convert to LEU targets using a CNEA-type target design without markedly increasing target throughput or processing requirements.

RESEARCH AND DEVELOPMENT (R&D) TO SUPPORT TARGET CONVERSION

As the foregoing discussion illustrates, there are a number of technical options available to producers for converting to LEU-based targets for production of Mo-99. However, there is no "best" or "one size fits all" approach. Each producer must choose a conversion path based on its own assessment of cost, time, and technical practicability. R&D will be essential for making wise selections. Some of the necessary R&D is already in progress (e.g., LEU metal foil targets) or has been completed (e.g., high density LEU-aluminum dispersion targets). This work provides a good starting point for understanding the range of available conversion options.

Producers will need to focus their R&D on specific target design and fabrication, process development, and waste management operations. Although these operations are discrete and can in principle be investigated separately, R&D will be more effective in terms of cost, time, and outcomes if these operations are treated as a system to be optimized for LEU-based production. The work being carried out by Argonne National Laboratory and its collaborators, which was described previously in this chapter, is a good example of a systems-focused approach. In its discussions with large-scale producers, however, the committee did not see any clear evidence of such a systems-level focus.[16] This is likely due (at least in part) to the fact that most producers do not have all of the R&D capabilities in-house that are needed to address such systems-optimization problems. Also, because producers consider their processes to be proprietary they may be reluctant to seek outside assistance.

The primary objective of systems-focused R&D is to develop LEU targets that are well suited to downstream process operations, beginning with their irradiation in reactors and subsequent chemical processing through waste management (including consideration of recovery of uranium from process wastes). Systems-focused R&D might proceed as follows:

- *Target fabrication.* Development work on LEU targets would be initially aimed at producing designs that mimic (to the extent feasible given the forgoing discussion on target design options) the characteristics of currently utilized HEU targets. This would serve to reduce the number of changes in downstream target irradiation and processing operations.

[16]Producers did not share all of the details of their R&D work with the committee.

Ideally, the targets would be roughly equivalent in U-235 mass to the HEU targets they would replace so that they produce roughly equivalent amounts of Mo-99.

- *Process development.* To the extent that process changes are required to accommodate LEU targets, R&D would focus on target dissolution efficiency, Mo-99 recovery efficiency and purity, and minimization of process waste streams.
- *Waste management.* The vast majority of the uranium in the target eventually becomes waste no matter what process is used; only a very small fraction (typically about 3 percent) of the U-235 in the target undergoes fission. However, the volume and form of the waste can have a substantial impact on the difficulty and costs for its management, storage, and ultimate disposal.

The committee was told by some producers that there are numerous process uncertainties that must be performed at both the front and back ends of the Mo-99 production process before conversion to LEU-based production will be feasible. At the front end, the important uncertainties include the target dissolution rates, chemistry, and process liquid properties. At the back end, important uncertainties include product yields, product quality and consistency, and waste volumes. Some producers have cited the lack of available hot cell space as an impediment to addressing these uncertainties.

In the committee's judgment, much if not most of the necessary process development work can be resolved at relatively low cost using well-established process development and testing procedures. Current producers have decades of experience in handling and processing HEU targets to recover Mo-99. Conversion to LEU-based production is not likely to require substantial changes to current processing equipment or processing flow sheets. Consequently, access to hot cells would not be required for most of the needed R&D work. Target processing equipment is small—it would easily fit on a large laboratory bench (see Chapter 2). This makes it possible to carry out testing at full scale and at relatively low cost.

Most of the front-end process uncertainties can be resolved through "cold" (i.e., nonradioactive) testing. Such testing allows LEU target materials to be evaluated using conventional wet-laboratory facilities. Because target irradiation times for Mo-99 production are short and U-235 burn-ups in the targets are low, unirradiated LEU targets have essentially the same material and chemical properties as irradiated LEU targets. Consequently, issues such as the following can be evaluated with cold testing on unirradiated targets: efficiencies and sizes of separations equipment, reagent volumes and concentrations, dissolution rates, dissolution chemistry, treatment of process gases, and process liquid throughputs. In the case

of alkaline dissolution, uranium precipitation rates and filtration rates can also be determined.

Many of the important back-end uncertainties can be assessed through tracer testing ("slightly hot" testing) using only very small amounts of radioactive material. These tests could use stable Mo-98 that is spiked with tracer amounts of Mo-99 and radioactive impurities of concern for target processing to determine Mo-99 recovery efficiencies and purity. Because only tracer amounts are used, these tests could probably be carried out in hoods.

Of course, full-scale testing with irradiated LEU targets would be required to demonstrate that the process works as designed. Additionally, some process uncertainties that can only be resolved through full-scale testing with irradiated LEU targets, for example, product purity testing. These tests could probably be carried out in a single hot cell over a period of a few weeks to months.

To the committee's knowledge, none of the major producers are doing much actual development work[17] on LEU targets and process, including the use of cold or slightly hot testing as part of their conversion strategies. The committee views this as a missed opportunity.

FINDINGS

Several important technical considerations for converting Mo-99 production from HEU targets to LEU targets were described and discussed in this chapter. Based on this information, the committee finds that:

- There are three basic approaches for converting HEU targets to LEU: Direct replacement of HEU in the target with LEU; increasing the mass in U-235 in the target by increasing target size; or increasing the mass of U-235 in the target by changing target composition. Each approach has advantages and disadvantages.
- There are no technical barriers to conversion of Mo-99 production from HEU targets to LEU targets. Production using LEU targets is technically feasible and in fact is being carried out by CNEA in Argentina and shortly will be applied by the Australian National Nuclear Science and Technology Organisation (ANSTO) using CNEA technology (see Chapter 3). The committee sees no technical barriers to scaling up to large-scale

[17]HEU-based producers did not provide details of any development work aimed at conversion, either in presentations to the committee or in discussions during site visits. On this basis the committee assumes that development work such as is described above has not been done. The committee is aware of a conversion feasibility study that was carried out by Atomic Energy of Canada Limited (AECL), but that organization was unwilling to share the results of that study with the committee.

production. However, such scale-up could require additional investments in facilities and personnel.

- There is no single "best" approach for conversion: Each producer must choose a conversion path based on its own assessment of cost, time, and technical practicability. There are opportunities for modifying current target or process designs that would allow producers to convert within their existing facilities.
- R&D will be essential for making wise selections about conversion approaches. Most of the needed R&D can be carried out using cold testing and radioactive tracer testing at full scale and at relatively low cost in conventional laboratory facilities. Except for some specific testing needs, access to expensive hot cell facilities would not be required.
- Based on the information presented to it by producers, the committee did not see any evidence that such R&D was being carried out.

Additional information about the prospects for conversion for existing HEU-based Mo-99 producers is provided in Chapter 10.

8

Conversion to LEU-Based Production of Molybdenum-99: Regulatory Considerations

The objective of this chapter is to describe and discuss the important regulatory considerations for conversion of Mo-99 production from highly enriched uranium (HEU) to low enriched uranium (LEU). This chapter is also intended to support the discussion of conversion feasibility that appears in Chapter 10.

This chapter will focus on the following three regulatory issues:

1. Physical security for HEU;
2. Drug quality and purity; and
3. Commercial sale of radiopharmaceuticals manufactured from Mo-99.

The committee selected these regulatory considerations for discussion because it judged that they had the greatest potential to impact Mo-99 producers' decisions to convert to LEU-based production.

PHYSICAL SECURITY FOR HEU

At the beginning of this study, the committee hypothesized that HEU-based medical isotope producers might reap substantial savings in security costs by converting to LEU-based production systems. Civilian nuclear fuel cycle facilities that handle *Formula Quantities of Special Nuclear Materials*[1]

[1]Special Nuclear Material is defined in Title 1 of the Atomic Energy Act of 1954. It includes plutonium, uranium-233, or uranium enriched in the isotopes uranium-233 or uranium-235. The formula quantity for HEU is a quantity greater than 5 kg.

are required to establish security plans and systems to prevent theft, diversion, or radiological sabotage of HEU. Security guidelines are established by the International Atomic Energy Agency (IAEA, 1999) and promulgated in part or in whole in regulations by national authorities. In the United States, for example, civilian facilities possessing formula quantities of special nuclear materials fall under the authority of the Nuclear Regulatory Commission and must meet the requirements in Title 10, Part 73 of the *Code of Federal Regulations* (10 CFR Part 73) entitled Physical Protection of Plants and Materials and also 10 CFR Part 74 entitled Material Control and Accounting of Special Nuclear Materials. The regulations require that each facility have access controls, physical barriers, armed guards, and material inventory systems to secure special nuclear materials. These security systems are costly, and so the committee hypothesized that substantial cost savings might be realized by converting to LEU-based production because LEU does not fall under the same formula quantity requirements.

After visiting HEU and LEU production and potential production facilities[2] and discussing security requirements with facility staff and national regulators, the committee concluded that the cost savings from conversion of existing HEU-based production to LEU-based production would likely be small,[3] primarily for the following reasons:

1. Many Mo-99 producers utilize facilities that are located on multipurpose sites. These sites are required to have high security because they contain sensitive facilities or store HEU. For example, the Atomic Energy Canada Ltd. (AECL) Chalk River site in Ontario, Canada, has HEU spent fuel and HEU waste from the past production of Mo-99. The ANSTO site in Australia has HEU fuel onsite from a shutdown reactor. High security will be required as long as this HEU remains on site.
2. Current HEU-based producers may possess less than formula quantities of HEU at their facilities or are exempt from the security regulations that govern formula quantities.[4] HEU is shipped to the target manufacturers

[2]Small groups of committee members and staff visited major HEU-based production facilities in Canada (Atomic Energy of Canada Limited [AECL]), Belgium (Institut National des Radioéléments), and the Netherlands (Petten); LEU-based production facilities in Australia (Australian Nuclear Science and Technology Organisation [ANSTO]]) and Argentina (Comisión Nactional de Energía Atómica [CNEA]); one potential domestic production facility in Missouri (Missouri University Research Reactor [MURR]); and a fuel manufacturing facility in France (Compagnie pour l' Etude et la Réalisation de Combustibles Atomiques [CERCA]). See Appendix C.

[3]This discussion does not address the nonproliferation benefits of civilian HEU elimination, which was the primary motivation behind the Schumer Amendment (see Sidebar 1.3). See Chapter 11 for a discussion of HEU minimization efforts.

[4]For example, 10 CFR Part 73, which regulates facilities that contain formula quantities of HEU (Category 1 facilities) does not apply to research reactor facilities in the United States (e.g., MURR) even if they possess quantities of HEU greater than formula quantities.

(e.g., AECL in Canada; CERCA in France), which manufacture and store the HEU and targets until they are needed by the isotope producers. The targets can be shipped to the reactors in less-than-formula quantities.[5]

3. The security requirements for all nuclear facilities, including the research and test reactors that are used to irradiate targets for medical isotope production, were raised in many countries, including the United States, following the September 11, 2001, terrorist attacks on the United States. Consequently, the costs of security have increased even for facilities that use only LEU for medical isotope production or other purposes. However, these costs are still lower than those for facilities that store greater than formula quantities of HEU.

DRUG QUALITY AND PURITY

The second issue of concern to producers is the regulatory requirements for drug quality and purity. Some producers have questioned whether Mo-99 made from LEU targets will have the same quality and consistency as that made from HEU targets. Experience to date with LEU-based production indicates that Mo-99 purity and consistency should not be an impediment to conversion. ANSTO produced Mo-99 for medical isotope use with 1.8–2.2 percent LEU targets until 2007, when it shut down its HEU-fueled reactor (High Flux Australian Reactor) and prepared to start up its LEU-fueled replacement reactor (Open Pool Australian Lightwater reactor) and produce Mo-99 using 19.75 percent LEU targets. ANSTO reported to the committee that the Mo-99 produced from the 1.8–2.2 percent LEU targets, and Mo-99 produced from test batches of 19.75 percent LEU targets, had lower impurities than HEU-based Mo-99 and met British Pharmacopeia limits for impurities.[6] ANSTO was carrying out low-activity Mo-99 production trials as the present report was being finalized for release. A representative of ANSTO reported that the quality of Mo-99 from these runs was high and equivalent to the quality of HEU-based Mo-99 it was receiving from large-scale commercial suppliers.[7] CNEA has been producing Mo-99 using 19.75 percent LEU targets since 2002. A representative of that organization told the committee that Mo-99 purity has been consistently higher than that produced using HEU targets. Purity data for CNEA-produced Mo-99 is presented by Durán (2005).

[5]The costs of transporting larger quantities of HEU from storage to target producers would likely be significantly higher than the costs of transporting LEU. However, such transport occurs relatively infrequently compared to transport of targets.

[6]There is no U.S. Pharmacopeia (USP) for Mo-99 because it is not used for diagnostic imaging procedures. However, there is a USP for Tc-99m.

[7]Ian Turner, ANSTO, written communication with study director Kevin Crowley, December 10, 2008.

The presence of higher concentrations of alpha emitters in LEU process streams has been cited by some producers as a potential conversion uncertainty (see Vandegrift, 2005). Irradiated LEU targets will contain higher concentrations of neptunium-239 (Np-239) and its daughter product plutonium-239 (Pu-239)[8] than equivalent HEU targets. However, HEU targets contain higher concentrations of uranium-234 (U-234), which has a higher activity and shorter half-life[9] than either U-238 or U-235. The total concentrations of alpha-emitting isotopes are not appreciably different in either target type, and both uranium and plutonium isotopes can be effectively removed during target processing.

COMMERCIAL SALE OF RADIOPHARMACEUTICALS

The third issue of concern to producers involves regulatory approvals for commercial sale of radiopharmaceuticals manufactured from Mo-99. This issue was brought to the committee's attention by the Council on Radionuclides and Radiopharmaceuticals (CORAR)[10] at the committee's first meeting (Appendix C) and was characterized by a representative of that organization as a potentially significant barrier to conversion, especially for radiopharmaceuticals that are used in the United States. The issue was also raised by some other producers at the committee's subsequent meetings.

Because the focus of this report is Mo-99 production and use in the United States, this discussion will focus on U.S. regulatory processes. However, similar processes are used by regulatory agencies in other countries. In the United States, the Food and Drug Administration (FDA) is responsible for regulating the production and use of medical isotopes. The FDA is responsible for approving the use of Tc-99m in radiolabeled compounds intended for human use, but not the production of the Mo-99 precursor. However, when the process for producing Mo-99 is changed, the FDA must approve the use of Tc-99m derived from that isotope. The approval process is described briefly in Sidebar 8.1.

A current technetium generator producer who wanted to utilize a new source[11] of Mo-99 would be required to submit a Supplemental New Drug

[8]LEU targets contain more U-238 than HEU targets. Neutron capture by U-238 during target irradiation produces small amounts of Np-239, which decays with about a 2.3-day half-life to produce Pu-239.

[9]The half-life of U-234 is 2.45×10^5 years, versus 7.04×10^8 years for U-235 and 4.47×10^9 years for U-238.

[10]CORAR is an association of North American companies involved in the manufacture and distribution of radionuclides, radiopharmaceuticals, and sealed sources for medicine and life science research.

[11]For the purposes of this discussion, a "new source" includes Mo-99 obtained from a new supplier and/or from a new production process such as an LEU-based process.

SIDEBAR 8.1
FDA Approval Process

Technetium-99m, used in radiolabeled compounds intended for human use, is regulated by the FDA under the Food, Drug, and Cosmetic Act. The production of the Mo-99 precursor to Tc-99m is not regulated by the FDA if it is used only as a radiochemical. However, if the Mo-99 is to be used to make Tc-99m for radiolabeled compounds, its producer typically submits a Drug Master File (DMF) to the FDA; however, a DMF is not strictly required. The DMF describes the facility in which the Mo-99 is made; the production process itself, including any raw materials used in production; and product test methods, specifications, stability, and release criteria. The DMF is not approved by the FDA; instead, it is used as a source of information when FDA approval is sought to sell Tc-99m radiolabeled compounds made with that producer's Mo-99.

A company seeking to sell a radiolabeled compound (e.g., a technetium generator producer) is required to submit an NDA to the FDA and pay a one-time application fee (in 2008, this fee was $1,178,000). The NDA is tied to one or more specific DMFs; the NDA for a radiolabeled compound, for example, would be tied to the DMFs for Mo-99 and any other raw materials used to make that compound. Like the DMF, the NDA describes the facilities, processes, test methods, and specifications for producing the radiolabeled compound. The FDA must review and approve the NDA before that radiolabeled compound can be sold for human use.

When a Mo-99 producer makes major changes to the process or raw materials it uses to make that isotope, it submits an updated DMF to the FDA. Any company (e.g., a technetium generator producer) that wants to use the Mo-99 produced under this updated DMF may find it necessary to submit an sNDA to obtain FDA approval to use that isotope. There is no fee for this submission, but there is a cost to the company for preparing the sNDA (described elsewhere in this chapter). To obtain FDA approval of the sNDA, the company must demonstrate that the Mo-99 precursor and Tc-99m product derived from it meet product specifications on three full production batches of Mo-99. A single production batch for a large-scale producer can contain hundreds to thousands of 6-day curies recovered from multiple targets.

An sNDA is required any time there are significant changes to the Mo-99 production process. However, if the changes to the Mo-99 production process are judged by the company to be minor, it could elect to submit a Change Being Effected (CBE) notification to the FDA instead of an sNDA. The CBE informs the FDA about the change but does not provide analytical testing data. The FDA would review the CBE and could approve it or direct the company to submit an sNDA.

Application (sNDA) to the FDA (see Sidebar 8.1). The committee was told by representatives of CORAR (see also Brown, 2005) and some Mo-99 producers that a great deal of time and effort would likely be required to develop and submit an sNDA, particularly to support the three required production runs to test the new product: Protocols must be developed for

the production runs; generators must be prepared; the Tc-99m must be eluted; radiopharmaceuticals must be prepared and tested; all of this information must be compiled; and the sNDA must be written and submitted.

The committee received presentations from industry and the FDA (see Appendix C) concerning the time, cost, and uncertainties for regulatory approvals. Perhaps the most striking aspect of the presentations was the vast difference in what industry representatives expected from the FDA—a complex, tedious, expensive, and unpredictable process—and the simple, straightforward, and readily achievable approval process described by the FDA presenter.

Industry representatives provided the committee with several examples of the difficulties they have encountered in obtaining FDA approvals for new sources of Mo-99. These included a "difficult" process for obtaining approval for a backup supplier of Mo-99 who used the same production and processing protocols in an already-approved NDA (it was reported to the committee that approval took almost a year and cost more than $200,000), and another approval that took almost 2 years. A representative of CORAR suggested that the FDA could require clinical trials before it would approve the use of LEU-based Mo-99.

The FDA presenter told the committee that the review time for an NDA typically takes between 6 and 10 months. He also noted that engaging the FDA early during the process of developing the NDA can help ensure that the approval process runs smoothly. A consultant working for MURR who has long experience with the FDA approval process estimated it would take a minimum of about 4–6 months after submission of the necessary paperwork and cost about $84,000 to obtain approval for using Mo-99 from a new LEU-based process at the MURR reactor (MURR, 2006). A current Mo-99 producer told the committee that not all FDA approvals require long lead times. This producer obtained emergency approval of a backup Mo-99 supply in less than a week.

Technetium generator producers are well acquainted with the FDA approval process and have a good understanding of its requirements. If LEU-based Mo-99 can be produced with similar chemical characteristics similar to HEU-based Mo-99—and current experience in Argentina and Australia indicates that it can—it is hard for the committee to see any rational basis for expectations of substantial delays in FDA approvals if producers submit high-quality sNDAs and work with FDA staff throughout the approval process. It is especially difficult for the committee to see how the FDA would ever require clinical trials as part of an sNDA for a new Mo-99 source. Mo-99 is a well-known isotope that can be produced with low impurities using either an HEU- or LEU-based process. Clinical trials would be a useless exercise in any case because they can be used to detect only gross adverse drug effects.

Based on information provided to the committee by industry and the FDA, it seems likely that regulatory approval for new sources of LEU-produced Mo-99/Tc-99m would require at least 4 months and as long as 18 months depending on the quality of the application and issues raised by the FDA during the review process. The cost of the process is difficult to estimate but would likely be in the range of multiple tens to hundreds of thousands of dollars.

It is important to recognize that these cost estimates represent only the direct costs for regulatory approvals. There are also likely to be indirect costs for such approvals, including, for example, any opportunity costs associated with lost sales of Mo-99, technetium generators, or radiopharmaceutical kits as a result of the regulatory process. However, these regulatory costs are likely to be small in comparison to the physical costs of conversion.

FINDINGS

Three important regulatory considerations for converting Mo-99 production from HEU targets to LEU targets are described and discussed in this chapter: (1) physical security for HEU, (2) drug quality and purity, and (3) commercial sale of radiopharmaceuticals manufactured from Mo-99. On the basis of this information, the committee finds that:

- Converting from HEU- to LEU-based production is unlikely to produce substantial savings in security costs, including transportation security costs.
- The purity of Mo-99 produced from HEU targets and LEU targets is not significantly different. Mo-99 produced from LEU targets using standard production methods and practices can meet regulatory requirements for use in radiopharmaceutical production.
- FDA approval for LEU-based production of Mo-99 should not be a substantial barrier to conversion. Such approvals would require at least 4 months and as long as 18 months depending on the quality of the application and issues raised by the FDA during the review process. The cost of the process is likely to be in the range of multiple tens to hundreds of thousands of dollars. Clinical testing is unlikely to be required by the FDA for such approvals.

9

Conversion to LEU-Based Production of Molybdenum-99: General Approaches and Timing

The objective of this chapter is to describe and discuss general approaches and timing for conversion to low enriched uranium (LEU)-based production of Mo-99. Like the preceeding two chapters, this chapter is intended to support the discussion of conversion feasibility that appears in Chapter 10.

GENERAL APPROACHES FOR CONVERSION

Highly enriched uranium (HEU)-based Mo-99 producers have two basic options for converting to LEU-based production:

1. Brownfield: Convert an existing processing facility from HEU-based production to LEU-based production, or convert an unused facility that contains hot cells to LEU-based production.
2. Greenfield: Construct a new processing facility that is designed specifically for LEU-based production.

For the purposes of this discussion, a "processing facility" is a facility that contains hot cells and ancillary support equipment to receive and process irradiated LEU targets (see Chapter 2), recover and purify Mo-99, and manage wastes. The facilities upstream and downstream of this processing facility—that is, the reactor used for target irradiation and the facility used to prepare technetium generators—are likely to

be usable for either HEU- or LEU-based production with little or no modifications.[1]

Brownfield Conversion

The major advantage of Brownfield conversion is its potential cost effectiveness: It is substantially less costly to replace process equipment in an existing facility[2] than to construct a new facility. However, if not properly managed and scheduled, conversion of an existing processing facility could interrupt ongoing Mo-99 production activities and result in unnecessary cost, time, and personnel radiation exposures.

The best current example of a successful Brownfield conversion is the Mo-99 processing facility in Argentina. As discussed in Chapter 7, the facility operator, Comisión Nacional de Energía Atómica (CNEA), was able to convert to LEU-based production in the same set of hot cells that were being used for HEU-based production. Moreover, this conversion was made without interrupting Mo-99 production. This conversion was possible for two reasons: First, conversion did not require substantial changes to existing target dissolution and Mo-99 recovery processes; consequently, substantial equipment modifications were not required. Second, CNEA produces Mo-99 only once a week, and so there was sufficient hot cell down time to perform the necessary process development and conversion work.

Conversion within a single set of hot cells might be more difficult when substantial process changes are required: major equipment modifications or replacements might be needed, and cross-contamination of processing lines could occur. Such conversion would also be more difficult when production is carried out more than once a week.[3] Regulatory requirements may also be a barrier to conversion within the same set of hot cells. As noted in Sidebar 8.1, the Food and Drug Administration (FDA) supplemental New Drug Application approval process requires three full-scale production runs of Mo-99 on the equipment that will be used for commercial production. The process equipment must be set up for those runs but cannot be used for commercial production until FDA approval is obtained. Such approval could take several months.

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[1]For example, the rigs used to irradiate targets in the reactor might need to be modified if the LEU targets have a different geometry than the HEU targets they are replacing, but changes to the reactor facility itself would likely not be required.

[2]This statement assumes that major facility modifications are not required. It could be costly to make major modifications to an existing facility to accommodate new process equipment.

[3]Mo-99 could be shut down to allow for conversion if Mo-99 could be purchased from other sources until regulatory approvals were received to restart production with the new process.

In cases where conversion cannot be made within the same set of hot cells, Brownfield conversion may only be possible if there are additional hot cells available in the facility or nearby. Research and development (R&D) could be carried out in hot cells in other facilities as well. Those hot cells could be used initially to carry out the R&D needed to support conversion and would eventually become the new LEU-based processing facility. This facility could be run in parallel with the HEU-based processing facility as long as needed to complete the conversion process. The two production facilities could be run in parallel, for example, to shake out the new process and train personnel. As will be discussed in Chapter 10, at least three of the existing large-scale Mo-99 producers (Mallinckrodt, Institut National des Radioéléments [IRE], and MDS Nordion) could likely convert using this approach.

Greenfield Construction

Greenfield construction is advantageous primarily because it would not interfere with current Mo-99 production activities, and also because the new facilities can be custom-designed to meet current and projected future Mo-99 production needs. However, construction is likely to be substantially more expensive.

There are no recent examples of Greenfield construction for Mo-99 production. The Australian producer (Australian Nuclear Science and Technology Organisation [ANSTO]) is in the process of converting from an inefficient LEU-based process to a more efficient process using technology that was engineered and scaled up by the Argentine company Investigaciones Aplicadas Sociedad del Estado (INVAP) and CNEA from the CNEA-developed LEU-based process (see Chapter 3). ANSTO's existing hot cell facility was substantially refurbished by INVAP (which also constructed the Open Pool Australian Lightwater [OPAL] reactor) as part of this conversion process. The new LEU-based processing facility designed and being constructed near Cairo, Egypt, by INVAP is an example of a Greenfield facility. However, this country is not an existing Mo-99 producer and plans to produce primarily for its own domestic needs and possibly to supply other countries in the region.

TIMING FOR CONVERSION

The time required for conversion will depend largely on which approach (Brownfield or Greenfield) is used. Both approaches share some common development steps that would require about the same amount of time, most notably for target design and fabrication and process development and testing (Chapter 7). Once this testing is completed, the setup and testing

of process lines in the facilities and regulatory approvals[4] would also take about the same amount of time. However, the time required to construct or convert the facility itself would be substantially different as discussed in the following two subsections.

Greenfield Construction

Greenfield construction generally requires much longer lead times than Brownfield conversion. The exact timing would depend on the nature of the facilities to be constructed as illustrated with the following two examples:

1. Construction of a new reactor and processing facility, the latter consisting of hot cells and ancillary support equipment; or
2. Construction of a new processing facility at or near an existing reactor.

In the first case, the reactor and processing facility would likely be constructed concurrently. After construction is completed, cold commissioning of the processing line and pretraining of staff would be carried out. Hot commissioning of the processing line would normally be carried out once the reactor is operational and the first targets are irradiated.

The time interval between the start of construction and commissioning of reactors built during the past two decades (e.g., Egyptian Testing Research Reactor II [ETRR2] in Egypt, Forschungsneutronenquelle Heinz Maier-Leibnitz [FRM II] in Germany, and OPAL in Australia) has been 6 to 8 years.[5] Production facilities might be constructed in less time, but of course they could not be operated until after the reactor was commissioned.

This construction and commissioning time interval does not include the preconstruction period, which begins with the decision to build, extends through the tender solicitation and selection process, and ends with the award of a construction contract. This typically requires another 2–3 years. Up to an additional 1–2 years[6] would be required to obtain regulatory approvals to produce Mo-99 (see Chapter 8). The estimate of the total time required to bring new Mo-99 production to market is thus 9–13 years. This estimate does not account for any unanticipated startup delays as has oc-

[4]Regulatory approvals could take longer if the producer had no previous experience with Mo-99 production.

[5]Isotope production reactors (Maple reactors) were constructed in Canada but were never commissioned; see Chapter 3.

[6]The longer time period could apply if Mo-99 is being produced for export because Mo-99 producers would have to help their customers obtain regulatory approvals in customers' home countries.

curred for some recently constructed reactors (see discussion of the Maple and OPAL reactors in Chapter 3).

In the second case, there is little experience to draw on, in fact none for a large-scale producer of Mo-99 during the last several decades. The Argentinean company INVAP is finishing construction and starting commissioning of a turnkey integrated facility for producing Mo-99 from LEU targets irradiated in ETRR2, but to the committee's knowledge this is not now planned to be large-scale production. Such a facility, using proven technology,[7] can be designed and constructed in 2–3 years. An additional 1–2 years would likely be required for cold and hot commissioning, training of staff, and regulatory approvals.

Two U.S.-based organizations are seeking partners for Greenfield construction of Mo-99 production facilities in the United States: The Missouri University Research Reactor (MURR) is seeking support to construct a facility for LEU-based production using its existing multipurpose reactor (Chapter 3). MURR estimates that it could take 3–4 years to fund and construct this facility. MURR estimates that additional time, perhaps another year, would be required for process commissioning and associated regulatory approvals.

Babcock & Wilcox (B&W) is seeking a radiopharmaceutical partner for a medical isotope production reactor and associated processing facilities at its Lynchburg, Virginia, site (Chapter 3). The company estimates that construction would require 5 years if the regulatory issues described in Chapter 3 can be addressed in a timely manner. Again, additional time, perhaps 6 to 18 months, would be required to transition to this or any other new isotope production facility into production because of FDA approval protocols.

For these Greenfield construction examples, the minimum time required to bring new Mo-99 production to market ranges from about 4 to 9 years.

Brownfield Conversion

Brownfield conversion shares some similarities with the second case for a Greenfield construction, except that the processing facility already exists. The time required to convert the facility is probably less than building a new facility from scratch. As noted previously, two recent examples of such conversions are CNEA (Argentina) and ANSTO (Australia).[8] The time for conversion of the CNEA facility was very short (on the order of

[7]This facility will produce Mo-99 using the CNEA-developed process that was scaled up and engineered by INVAP.

[8]ANSTO was a Brownfield conversion in the sense that its existing hot cell facility was refurbished to accommodate a new LEU process.

a year) but, as discussed previously, this conversion was unique because it did not require major changes to the target dissolution and Mo-99 recovery processes. Conversion of the ANSTO facility began in January 2007 and is still under way.[9] Facility commissioning has been delayed because of startup problems with the OPAL reactor. As noted previously, ANSTO was carrying out low-activity Mo-99 production trials but had not yet commenced commercial production when this report was being finalized.

The time required for a Brownfield conversion will depend on the nature of that conversion. If the conversion requires the refurbishment of existing hot cells, it could require as little as 1–2 years once the process development work is completed. Personnel training and regulatory approvals would take an additional 1–2 years. On the other hand, if existing facilities can be adapted to an LEU-based process, the conversion time could be reduced to the time required to modify the process equipment, train staff, and obtain regulatory approvals. This could be as little as a few months to about 2 years once the process development work is completed.

FINDINGS

This chapter provides a description and discussion of some general approaches to converting from HEU-based to LEU-based production of Mo-99. The chapter also describes the timing requirements for such conversion. On the basis of this information, the committee finds that:

- There are two general approaches for converting from HEU-based production to LEU-based production: Brownfield (conversion within an existing processing facility or an unused facility with hot cells) or greenfield (construction of a new processing facility). Brownfield conversion is generally less expensive and takes less time but could interfere with ongoing Mo-99 production operations. Greenfield construction is generally more expensive, but the facility can be custom-designed to meet current and projected Mo-99 production needs, and conversion would not interfere with ongoing Mo-99 production activities.
- Brownfield conversions can be carried out in as little as a few months to about 2 years once the necessary process development work is completed. Greenfield construction can require 9–13 years from the decision to build to startup of Mo-99 production if a new reactor and processing facility are constructed or about 4–6 years for construction and startup of a new processing facility.

[9]Although physical installation began in 2007, substantial effort had begun prior to this date including planning and preparatory work which was initiated in 2005.

10

Conversion to LEU-Based Production of Molybdenum-99: Prospects and Feasibility

The focus of this chapter is on the first and last charges of the statement of task for this study (Sidebar 1.2). The first charge calls on the National Academies to assess "the feasibility of procuring supplies of medical isotopes from commercial sources that do not use highly enriched uranium [HEU]." The last charge calls for additional information if these feasibility criteria are not met:

> If the National Academies determine that the procurement of medical isotopes from commercial sources is not feasible as defined in Section 630 of the Energy Policy Act, it should estimate the magnitude of the cost differential and identify additional steps that could be taken by the Department of Energy [DOE] and medical isotope producers to improve the feasibility of such conversions. In estimating the magnitude of cost differentials, consideration should be given to facilities utilized by both large and small producers. The National Academies should also identify any reliability of supply issues that could arise as a result of such conversions.

This chapter is organized in four sections. The first provides a review of the current status of conversion efforts by large-scale molybdenum-99 (Mo-99) producers, the second addresses conversion feasibility, the third suggests additional steps to improve feasibility of conversions, and the fourth presents findings and recommendations.

CURRENT STATUS OF CONVERSION

As discussed in Chapters 1 and 3, the U.S. supply of Mo-99 is produced primarily by two companies, MDS Nordion and Mallinckrodt, at their facilities in Canada and the Netherlands, respectively (Table 3.1). Two other companies provide backup supplies of Mo-99 to North America: Institut National des Radioéléments (IRE) in Belgium and Nuclear Technology Products (NTP) in South Africa. All four of these companies produce Mo-99 using HEU targets.[1] Conversion prospects for these four producers are described briefly in the following sections.

MDS Nordion (Canada)

As was noted in Chapter 3, MDS Nordion obtains impure Mo-99 under a revenue-sharing agreement with Atomic Energy of Canada, Ltd. (AECL) a Canadian Crown Corporation. AECL produces Mo-99 at its Chalk River, Ontario, site by irradiating HEU targets in the National Research Universal (NRU) reactor (Table 3.2) and processing those targets in an onsite hot cell facility. Mo-99 production was planned to be shifted to a new facility at the Chalk River site, but this plan was never realized for the reasons described below.

In August 1996, AECL agreed to construct two new reactors and a processing facility for MDS Nordion at the Chalk River site. These facilities, referred to as the Dedicated Isotope Facilities (DIF), include two reactors (referred to as the Maple reactors; Sidebar 10.1) and a New Processing Facility (NPF) with five hot cells to process irradiated targets and to manage the resulting solid, liquid, and gaseous wastes from the Mo-99 extraction process.[2]

Construction of the DIF, including the Maple-1 reactor, was completed by AECL in 2000. However, Maple-1 hot commissioning was halted by the Canadian Nuclear Safety Commission because of a technical problem with the reactor (see Sidebar 10.1). The delay in commissioning the reactor resulted in large cost overruns[3] and culminated in mediation proceedings initiated by MDS Nordion. A settlement was announced in early 2006: According to a representative of MDS Nordion, the settlement involved the

[1]The targets used by NTP are 45 percent HEU, not the 93 percent HEU used by the other producers.

[2]The DIF was designed to irradiate and process HEU targets of a different design than the HEU targets that are currently being irradiated in NRU (see Table 2.2).

[3]A representative of MDS Nordion reported to the committee that the original budget for the project was $145 million, but the company spent over $350 million on the project. The committee has not independently confirmed these figures, nor does it know what AECL spent on the project.

SIDEBAR 10.1
Maple Reactors

The Maple-1 and Maple-2 reactors are 10-MWt pool-type dedicated medical isotope production reactors fueled with LEU. When operated at their design capacities, the output of Mo-99 from one of the two reactors would have been roughly equal to current worldwide demand.

These reactors were designed to operate with HEU targets. The decision to use HEU targets was controversial because at the time the construction of the Maples was initiated, there was an international push, led by the United States. and supported by IAEA, to eliminate the civilian use of HEU (see Chapter 11).

AECL discovered that the reactor had a positive power coefficient of reactivity in June 2003, after the Maple-1 reactor had been operated at a reactor power of 8 MW. This behavior was unanticipated and, because its origin could not be identified, it was deemed by the regulator (the Canadian Nuclear Safety Commission) to be a safety issue. AECL engaged the services of organizations such as Brookhaven National Laboratory, Idaho National Laboratory, and INVAP, an Argentinian company that designs research reactors, from 2005 to 2008 for computer simulations and development of a test program to identify the cause of the discrepancy between the predicted negative and measured positive coefficient of reactivity of the reactor, but a cause was never determined. In May 2008, AECL halted work on Maple-1 and announced that it was discontinuing the project.

transfer of ownership of the DIF from MDS Nordion to AECL, assumption by AECL of all future capital and operating costs, and a $25 million cash payment to MDS Nordion. In return, AECL agreed to supply medical isotopes to MDS Nordion under a 40-year revenue-sharing arrangement.

As noted in Sidebar 10.1, work to understand and correct the technical problems with the Maple reactors continued until May 2008, when AECL announced that it was discontinuing that work.[4] AECL also announced that it intended to seek a 5-year extension of the operating license for NRU (from 2011 to 2016) to maintain production of Mo-99 for the intermediate term. As noted in Chapter 4, this life extension will reportedly cost several hundreds of millions of dollars. Natural Resources Canada, a Canadian federal department, has been charged by the Canadian government with developing contingency plans for medical isotope production by AECL. The goals of this planning are to (1) avoid unplanned outages at NRU, (2) help

[4]Following this decision, AECL was served with a notice of arbitration proceedings. MDS Nordion is seeking to compel AECL to meet its contractual obligations under the 2006 agreement. MDS Nordion has also filed a $1.6 billion lawsuit against AECL and the government of Canada for breach of contract and interference with economic relations.

the health care community manage any disruptions, and (3) arrange for an international backup supply of Mo-99.[5]

The committee was told by AECL and MDS Nordion representatives that conversion of the DIF to low enriched uranium (LEU)-based production was under consideration prior to the May 2008 announcement. This work was apparently a continuation of a conversion feasibility study that was initiated in the late 1990s by these organizations; that study is described by Malkoske et al. (2003).[6,7] That study was organized into three phases: a Phase 1 feasibility study; a Phase 2 development program; and a Phase 3 implementation program.

The Phase 1 study determined that it was technically feasible to convert the Maple reactors to LEU targets but that significant technical work was required, regulatory approvals would be needed, and the costs associated with conversion would be significant. A design concept for an LEU target was reportedly developed that could provide the basis for engineering qualification, development, and assessment of potential technical issues for converting NPF to LEU-based production. The feasibility study also identified potential capacity and throughput problems in the NPF associated with processing the larger volumes of LEU targets that were anticipated as a result of conversion.

Phase 2 focused on process and technology development and was jointly carried out by MDS Nordion, AECL, SGN (a subsidiary of the French company AREVA), and Argonne National Laboratory. The work in this program was focused on ways to overcome the capacity and throughput problems identified in Phase 1 as well as improvements to the waste processing system. Phase 2 was to have been completed in 2004 (Malkoske, 2003) but it was not clear whether this work was completed.[8] The Phase 3 program was never implemented.

This conversion feasibility study was apparently restarted by AECL and MDS Nordion while this National Academies study was in progress. The

[5]Sylvana Guindon, Natural Resources Canada, verbal communication with committee chair Chris Whipple and study director Kevin Crowley, June 20, 2008.

[6]The committee was given a high-level briefing on this study by MDS Nordion but was not provided with any company-produced written documentation. The committee was also able to obtain and review correspondence from Argonne National Laboratory about its research and development collaborations with MDS Nordion. This correspondence is in the public access file for this study.

[7]This program was initiated after a 1997 exchange of diplomatic notes between the Canadian and U.S. governments concerning the conversion of medical isotope production and processing facilities to LEU.

[8]As noted in footnote 6, the committee obtained copies of correspondence between DOE and Argonne National Laboratory concerning Argonne's work for AECL and MDS Nordion during this Phase 2 program. The program appeared to be making good progress into 2002 when it was terminated.

committee understands that three conversion options were investigated: (1) Convert the NPF before it is hot commissioned; (2) retrofit the facility to handle LEU targets after hot commissioning with HEU targets; or (3) build a new facility for processing LEU targets while using the NPF to process HEU targets. An MDS Nordion representative told the committee that conversion of the NPF before hot commissioning was preferable from both a cost and logistical standpoint but that there might not be enough time to complete conversion and establish a reliable supply of Mo-99 with an LEU-based process before the scheduled NRU relicensing period in 2011. The representative noted that retrofitting the NPF once HEU-based production begins would be costly and would disrupt isotope production.

The committee agrees with the MDS Nordion representative's assessment that conversion prior to hot commissioning is the most attractive alternative from both a timing and cost standpoint. In fact, it would have been even more attractive from a timing and cost standpoint to have designed the new reactors and processing facility to irradiate and process LEU targets: AECL and MDS Nordion could have continued to irradiate and process HEU targets in its current facilities (the NRU reactor and hot cell process line) while the LEU process was brought online. This would have allowed conversion without supply disruptions and would probably have been the most cost-effective conversion option.

AECL's decision to discontinue work on the Maple reactors (and presumably the NPF) potentially complicates its conversion options. A representative of Natural Resources Canada told the committee that AECL has determined that converting NRU to irradiate LEU targets is a "deal breaker" because of cost. However, this representative also confirmed that the government had done no independent evaluation of costs but was instead relying on AECL's estimates.[9]

On the other hand, assuming life extension to 2016, AECL's decision to continue to produce Mo-99 in the NRU reactor eliminates the time pressures to hot commission the NPF; consequently, if AECL were to reconsider its decision to abandon the DIF, including the Maple reactors, there would still be time to convert that facility to process LEU targets. The necessary target design, irradiation, and process development work could be carried out using the NRU reactor[10] and the NPF while HEU-based isotope production continues in the current facilities. As discussed in Chapter 7, much of the needed development work could be carried out with cold and radioactive tracer tests that do not require the use of hot cells.

[9]Sylvana Guindon, Natural Resources Canada, verbal communication with committee chair Chris Whipple and study director Kevin Crowley, June 20, 2008.

[10]NRU is a large multipurpose research reactor that could likely accommodate work on LEU target development as well as irradiations of HEU targets for Mo-99 production.

Perhaps the two most significant potential obstacles to conversion to LEU-based Mo-99 production at Chalk River are strategic and financial, which are intertwined:

- What are AECL's long-term plans for medical isotope production?
- Who pays for conversion?

Under the 1996 agreement with AECL to develop the DIF, MDS Nordion was responsible for paying the costs of conversion. The committee understands that this part of the original agreement is still intact. At present, MDS Nordion has no business reason to convert to LEU-based production under its current agreement with AECL. Even if a business case could be made, however, MDS Nordion might be reluctant to foot the costs of conversion without some assurance of a long-term commitment by AECL to produce Mo-99. The decision to discontinue work on the Maple reactors would appear to call this commitment into question.

The decision to discontinue work on the Maple reactors is not consistent with AECL continuing to produce Mo-99 over the long term. The committee assumes that the worst-case scenario for fixing the Maple reactors involves the replacement of the reactor cores. The cost of such replacements would likely be small (tens of millions of dollars) in comparison to the cost of building a new reactor (hundreds of millions of dollars) or refurbishing NRU (also hundreds of millions of dollars according to a representative of Natural Resources Canada, as noted previously). Further, it is unclear how such extensive refurbishment work could be carried out without affecting the reliability of Mo-99 supply, especially if the NRU reactor needed to be shut down for extended periods of time. The extended shutdown of NRU without a backup source of production would have dire consequences for Mo-99 supply worldwide.

AECL could probably contract with another organization to fix the Maple reactors—and, if desired, to convert the NPF to LEU-based production—if it does not have the necessary in-house technical expertise or resources to do the work itself. The committee judges that there is enough time to fix the Maple reactors and refurbish the NPF before 2016 if work begins within the next year (see Chapter 9 on timing).

The committee submitted a list of questions to AECL concerning its future plans for the Maple reactors, NPF, and LEU conversion (see Appendix E).[11]

[11]The questions were submitted to Richard Cote, AECL's chief financial officer who is also in charge of AECL's Mo-99 production program, and also to William Pilkington, AECL's vice president and chief nuclear officer.

AECL declined to provide either a verbal or a written response to the committee's request for information.[12]

AECL's decision to abandon the Maple reactors has probably put on hold any plans to convert to LEU-based production until the long-term Mo-99 supply issue is settled. The long-term prospects for conversion are likely poor absent a strong push from the U.S. or Canadian governments. The Canadian government is currently reviewing its options for AECL and could decide to sell all or part of it.[13] This is another complicating factor in any conversion decision.

Mallinckrodt (Netherlands)

As discussed in Chapter 3, Mallinckrodt has an agreement with the Nuclear Research and Consultancy Group (NRG) to irradiate HEU targets in the High Flux Reactor (HFR) at the Petten site in the Netherlands. Mallinckrodt also processes the irradiated targets at a hot cell facility on that site.

In late 2007, NRG and Mallinckrodt announced that they would begin an assessment of the feasibility of converting to LEU targets. The initial focus of this assessment is to develop an LEU target that is usable in the Pallas reactor, which is being planned to replace HFR in about 2016.[14] NRG will then determine if this LEU target can be used in HFR. NRG staff told the committee that development work on LEU targets could be supported by experimental irradiations within the current HFR operating license but would require a change in NRG's hot cells (to allow it to process LEU targets) but that this was not seen as a significant obstacle.

Mallinckrodt is examining two options for obtaining Mo-99 from processes that do not use HEU. First, it is assessing the feasibility of converting its current Mo-99 processing facility at Petten to accommodate LEU targets. This includes an examination of a range of possible target materials and alternative processing approaches. In 2007, Mallinckrodt reported to the

[12]An assistant to Mr. Cote did set up a phone conference with study director Kevin Crowley for the purpose of discussing how answers to the committee's questions might be provided. However, that phone conference was subsequently canceled by Mr. Cote and was never rescheduled.

[13]In 2008, the Canadian government hired National Bank Financial to advise on the options for the future of AECL. Those options could range from the outright sale of AECL to a public-private partnership to inject capital and stability into the company. The core focus of AECL has been its CANDU reactor business, and its continued viability in that business will likely depend on its ability to continue to attract contracts to support existing CANDU reactors and new reactor designs. The NRU reactor is the only remaining irradiation platform at AECL for CANDU reactor fuel and core materials and testing.

[14]As noted in Chapter 3, 2016 is an optimistic date. A reactor design has not yet been selected nor has funding been committed.

committee that the level of annual investment in this development work was in "six figures." However, the committee does not know the basis for these estimates; it is the committee's assessment that the company is investigating different LEU processes but has not selected a particular process for in-depth development work.

Mallinckrodt has not developed a detailed cost estimate for the construction of a new processing facility, but a representative reported to the committee that such a facility could cost several tens of millions of dollars. The company also reported that all of the LEU-based technologies examined to date are likely to result in increased production costs.

Mallinckrodt's second focus is on the identification of other production technologies that do not utilize HEU. The company was unwilling to share detailed information with the committee on the options under consideration, but it seems likely that the company is examining options to obtain Mo-99 from current and/or potentially new LEU-based producers. The committee is aware of two organizations that are seeking to partner with organizations such as Mallinckrodt to provide Mo-99: the Missouri University Research Reactor (MURR) and Babcock & Wilcox (B&W). The capabilities of these organizations are discussed in Chapter 3.

Mallinckrodt indicated to the committee that converting within its current facility was not possible based on processing cycle times and reliability of supply. However, the committee was not convinced that such conversion was infeasible. Because of the large number (10) of available hot cells for Mo-99 production in its Petten facility, Mallinckrodt would appear to be well positioned to convert to LEU-based production without the need for major new construction, especially if it could use a hot cell elsewhere on the site or at another site for process development work. As discussed in Chapter 7, much of the needed process development work could be done without hot cells.

The committee has not undertaken a detailed analysis of the Mallinckrodt facility to assess its suitability for conversion. Instead, the committee's judgment is based on the number of hot cells available at the Mallinckrodt facility relative to the number of hot cells that are used by other Mo-99 producers (typically about five hot cells) to process targets and recover Mo-99.

However, the rate-limiting step for conversion could well be the schedule for developing LEU targets that are compatible for use in both the existing reactor (HFR) and in the Pallas reactor that is planned to replace it. Although targets are simple in their design, it takes time to develop, test, and qualify targets for routine use for Mo-99 production. The process is not unlike that required for fuel except that physical requirements for targets may be easier to meet given their shorter residence times in reactors.[15]

[15]See also the discussion of the Belgian Reactor II (BR2) in the next section.

Conversion might be possible within 3–5 years if LEU targets can be developed for HFR; otherwise, conversion would not take place until the new reactor is up and operating. As discussed in Chapter 3, this is planned to occur in 2016 (i.e., in about 8 years). As noted in Chapter 4, HFR is estimated to reach the end of its operating life by 2020.

Lantheus (United States)

As discussed in Chapter 3, Lantheus is the other main supplier of technetium generators to the North American market. It does not produce Mo-99 itself and therefore has no direct role to play in LEU conversion. Its key Mo-99 supplier is MDS Nordion.[16]

However, Lantheus could play an important indirect role in conversion by signing a Mo-99 purchase agreement with an LEU-based producer. The committee learned through a reliable source that Lantheus is in talks with at least one potential producer about establishing a purchasing agreement for LEU-based Mo-99.

IRE (Belgium)

A representative of IRE told the committee that it has no plans to convert to LEU targets at present and is doing no research or development work on conversion. However, there appears to be ample hot cell space within the existing facility at IRE that could be used for conversion if desired. As noted in Chapter 3, IRE currently processes its HEU targets in a dedicated bank of hot cells. It has a backup set of processing hot cells that are rarely, if ever, used for target processing, and a third set of hot cells that are used intermittently for strontium recovery. Either of the latter two sets of hot cells could be used for target and process development and conversion.

Both IRE and Mallinckrodt rely primarily on HFR for target irradiation. Consequently, it is possible that IRE would be forced to convert to an LEU-based process if LEU targets are successfully developed for HFR or its Pallas replacement. It could be hard for IRE to justify the continued use of HEU targets once an LEU replacement target is developed and demonstrated for use in these reactors.

Of course, LEU targets would also have to be developed for use in the BR2 and Osiris reactors if they are to continue to be used for Mo-99 production. These could be the same target designs that are used in HFR

[16]This company may have agreements with other producers for backup supplies of Mo-99, but the committee was not able to obtain any information from the company because it declined to participate in this study.

and its replacement or targets of a different design that are compatible with Mallinckrodt's and IRE's processing equipment. The loss of BR2 and Osiris for Mo-99 production could have an impact on supply reliability during outages at HFR (and later the Pallas reactor). Compatible LEU targets would also have to be designed for use in the Jules Horowitz Reactor (JHR, Table 3.2) if that reactor is to be used for Mo-99 production.

NTP Radioisotopes (South Africa)

NTP Radioisotopes is currently working to convert its reactor fuel to LEU (see Chapter 3), but the committee is aware of no plans at present to convert to LEU targets for Mo-99 production. The organization declined to participate in this study, so the committee was unable to obtain the information needed to determine whether there is adequate existing hot cell space at NTP to support target conversion. As noted in Chapter 3, NTP uses domestic HEU enriched to 45 percent for Mo-99 production. It could continue to use its domestic supply even if the remainder of the world converted to LEU-based Mo-99 production. As noted in Chapter 7, NTP could probably convert to LEU-based production using Comisión Nacional de Energía Atómica (CNEA)-type targets without a significant increase in target throughput.

CONVERSION FEASIBILITY

Congress specified that production of medical isotopes is deemed to be feasible if the following three conditions are met (see Sidebar 1.2):

1. LEU targets have been developed and demonstrated for use in the reactors and target processing facilities that produce significant quantities of medical isotopes to serve U.S. needs for such isotopes;
2. Sufficient quantities of medical isotopes are available from low enriched uranium targets and fuel to meet United States needs; and
3. The average anticipated total cost increase from production of medical isotopes in such facilities without the use of HEU is less than 10 percent.

In the sections that follow the committee provides its assessment of whether current production of LEU-based Mo-99 is sufficiently mature and cost-effective to satisfy these three congressionally specified conditions.

Condition 1

LEU targets have been developed and demonstrated for use in the reactors and target processing facilities that produce significant quantities of medical isotopes to serve U.S. needs for such isotopes.

At present, neither MDS Nordion nor Mallinckrodt is producing Mo-99 using LEU targets nor have they announced plans to begin such production. For this reason, Condition 1 is not met. However, this literal interpretation is not helpful for differentiating between the *technical feasibility* of producing significant quantities of medical isotopes (and specifically the isotope Mo-99) using LEU targets and the *economic feasibility* of such production. Economic feasibility is the focus of the third condition established by Congress and is discussed later in this chapter.

The committee judged that a more informative approach to address this first condition is to divide it into two parts that focus specifically on technical feasibility:

I. Have LEU targets been developed and demonstrated for large-scale production of Mo-99?

II. Could these targets be used in reactors and processing facilities that produce significant quantities of medical isotopes for the U.S. market?

With respect to the first question, at least two LEU target designs have been developed that could support the large-scale production of Mo-99 (see discussion in Chapter 7): (1) uranium metal foil targets developed by Argonne National Laboratory in collaboration with several other organizations and (2) high-density uranium-aluminum dispersion targets developed by CNEA. The uranium metal targets have been tested for Mo-99 production but are not being used at present to produce Mo-99 commercially; however, the committee sees no technical barriers to their use for such production. The high-density uranium-aluminum dispersion targets are being used by CNEA for Mo-99 production on a commercial basis, although in less-than-large-scale quantities at present. The Australian Nuclear Science and Technology Organisation (ANSTO) plans to begin large-scale production of Mo-99 using this equipment in the near future as described in the Regional Producers section of Chapter 3.

With respect to the second question, the committee sees no technical barriers to the use of LEU targets for large-scale production of Mo-99 by producers that currently supply the U.S. market. There is nothing unusual about the materials used in these targets that would prevent them from being irradiated and processed in a wide range of reactors and processing facilities. The NRU reactor and HFR were converted from HEU to LEU fuel in 1991 and 2006, respectively. There is little difference between the materials and designs used in these targets and the materials and designs used for the fuels for the reactors in which these targets are irradiated.[17]

[17]In other words, any design that was qualified as a fuel would also qualify as a target. However, the reverse is not necessarily true; reactor targets are designed to be irradiated only for

Current suppliers to the U.S. market might have to make modifications to their target processing equipment to use these LEU targets. However, as was discussed previously in this chapter, these suppliers can probably convert to LEU-based production within currently built facilities. There is unlikely to be a need to construct expensive new facilities to accommodate such conversion. Of course, the LEU targets would also need to be compatible with the reactors.

There are also potential new suppliers to the U.S. market that would utilize LEU-based Mo-99 production systems. These include ANSTO, CNEA, MURR, and B&W. Any one of these producers is potentially capable of large-scale production, and at least one (MURR) has announced its interest in supplying up to one-half of the U.S. market for Mo-99.

Condition 2

Sufficient quantities of medical isotopes are available from LEU targets and fuel to meet U.S. needs.

At present, there are not sufficient quantities of medical isotopes available from LEU targets to meet even a fraction of U.S. needs. The committee sees no technical reasons that adequate quantities cannot be produced, however, for the reasons described in the preceding section. As noted in Chapter 4, the reliability of the supply of medical isotopes is poor, with numerous interruptions in recent years due in part to reliance on reactors that have exceeded their design lifetimes. The current Mo-99 production system cannot meet global demand when either NRU or HFR is down for extended periods for maintenance or repair. Conversion to LEU targets is unlikely to either endanger production capacity or fix problems associated with reliance on aged reactors.

The committee has seen no demonstrated evidence that current large-scale producers are taking any of the necessary steps to convert to LEU-based production. The committee judges that conversion within existing facilities could be carried out in as little as a few months to 2 years as discussed in Chapter 9. Moreover, as discussed in the preceding section, new suppliers of Mo-99 are potentially poised to enter the U.S. market, although it would likely take at least 5–6 years for substantial new supplies to become available from these sources.

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short periods of time (typically a few days to a week) and have low burn-ups of the uranium meat. Some target designs would likely not hold up under the higher burn-up conditions that are routinely experienced by reactor fuels.

Condition 3

The average anticipated total cost increase from production of medical isotopes in such facilities without the use of HEU is less than 10 percent.

The committee was told by congressional staff (see beginning of Chapter 6) that the 10 percent criterion is an arbitrary benchmark for feasibility. The committee notes that this 10 percent criterion is less than the cost variations for Mo-99 production at the three points in the supply chain discussed in Chapter 6: costs vary by up to 40 percent for Mo-99 production; costs vary by at least 25 percent for technetium generators; and costs vary by at least 20 percent for a Tc-99m dose. The existence of such large cost variations reinforces a key message of Chapter 4 that supply reliability is also important to Tc-99m users; it also calls into question whether the 10 percent criterion is an appropriate benchmark for feasibility.

Nevertheless, the committee has assessed whether the cost increases for LEU-based Mo-99 production would be less than 10 percent by ignoring these cost variations and considering only the change in the "average" costs of production. The committee used the following approach to perform this assessment: First, the committee estimated the additional revenues that would be available to support conversion to LEU-based Mo-99 production if the average costs at these three points in the supply chain were increased by exactly 10 percent. Then the committee assessed whether these additional revenues would be sufficient to support conversion to LEU-based production if they were made available to current large-scale HEU-based producers in proportion to their market shares for Mo-99 production.

The following two datasets were used as input to this analysis (see Table 10.1):

1. The average unit cost of Mo-99/Tc-99m at three points in the supply chain from Chapter 6: specifically, the average cost of a 6-day curie of Mo-99, the average cost of a technetium generator, and the average cost of a Tc-99m dose. The committee provides estimates at these three points because, as noted in Chapter 6, this report will have several audiences, for example, the sponsor (DOE-National Nuclear Security Administration [NNSA]), Congress, and medical isotope producers and users, that will be interested in costs at different points in the supply chain.
2. Mo-99/Tc-99m supply quantities at these three points in the supply chain from Chapter 3: specifically, the number of 6-day curies of Mo-99 sold in the United States and globally in 2006, and the number of technetium generators and Tc-99m doses sold in the United States in 2005. The use of 2005 cost data for technetium generators is likely conservative; the

TABLE 10.1 Present Values of Potentially Available Revenues from a 10 Percent Increase in the Average Unit Costs at Three Points in the Mo-99/Tc-99m Supply Chain

				Present-Value Estimates (real discount rate)[c]			
				7%		3.5%	
Point in Supply Chain	Unit	Average Unit Cost (US$)[a]	Number of Annual Units Sold in U.S. (global)[b]	Present Value of 55-Year Revenue Accumulation in U.S. (global)	Present Value of 30-Year Revenue Accumulation in U.S. (global)	Present Value of 55-Year Revenue Accumulation in U.S. (global)	Present Value of 30-Year Revenue Accumulation in U.S. (global)
Mo-99 production	6-day curie	225	312,000 (624,000)	100 (195)	85 (175)	170 (340)	130 (260)
Technetium generators	10 Ci generator	1900	92,500 (185,000)	245 (490)	220 (435)	425 (855)	325 (645)
Tc-99m	30 mCi dose	11	20,000,000 (40,000,000)	305 (615)	275 (545)	535 (1070)	405 (810)

[a] From Chapter 6.
[b] From Chapter 3.
[c] Present-value estimates are given in millions of U.S. dollars and are rounded to the nearest $5 million.

committee understands that technetium generator producers have raised prices since 2005 (see also Chapter 5).

The committee multiplied the average unit costs from the item one by 10 percent to obtain the potential average unit revenues to support conversion for the three points in the supply chain. It then multiplied those unit revenues by the number of units sold from item 2 to obtain annual available revenues for the three points in the supply chain. The estimated annual available global revenues for technetium generators and Tc-99m doses were obtained by doubling the U.S. revenues.[18]

The committee then estimated the *present values* of these U.S. and global revenues assuming that they are accumulated over the life of the production facility; the analytical approach is described in Appendix F. These present-value estimates can be thought of as the current value of potential future revenues to producers today to support conversion. The committee provides four different estimates of present values based on two different assumed discount rates and two different assumed revenue accumulation periods. The assumptions are as follows:

- *Discount rates*. Real (i.e., inflation adjusted) discount rates of 7 percent and 3.5 percent were used in the estimates: The 7 percent real discount rate is the typical midpoint estimate of U.S. firms' pretax return on investment, although estimates range from 4.5 percent to 10 percent. The U.S. Office of Management and Budget also uses 7 percent for federal cost-effectiveness studies (OMB, 1996). The 3.5 percent discount rate is sometimes used to make public-sector investment decisions (e.g., it is used in the United Kingdom in public-sector cost-benefit analyses; see HM Treasury [2003] and Moore et al. [2004]). One could make arguments for using either discount rate because medical isotope production is a public-private partnership activity as discussed in Chapter 3.
- *Revenue accumulation periods*. The reactors and hot cell facilities that are used to produce Mo-99 have lifetimes of at least 25–50 years. Two different accumulation periods that are consistent with these facility lifetimes were used in the estimates: a 55-year period assuming an initial 5-year facility construction/modification period and a 50-year operating life, and a 30-year period assuming an initial 5-year facility construction/modification period and 25-year operating life. Because conversion efforts

[18]As discussed in Chapter 3, the United States consumes about half of the global supply of Mo-99. For the purposes of this analysis, the committee also assumed that the United States consumes half of the global supplies of technetium generators and Tc-99m doses. The committee judges that this assumption is reasonable because Mo-99 is used for the same types of diagnostic procedures worldwide.

at Petten would focus on a target design and process that would be compatible with both the current HFR and with the to-be-built Pallas reactor, the use of a long operating lifetime is justified. This would also be the case for IRE, which currently uses HFR and presumably would also use Pallas. The committee is unable to assess whether the use of a 30-year period is consistent with AECL's long-term plans for Mo-99 production. AECL has not indicated what plans it has for producing Mo-99 beyond 2016, and it was not willing to discuss with the committee what refurbishment is needed to keep NRU running until 2016. If AECL decides to get out of the business of producing Mo-99 then obviously a shorter amortization period would need to be used.

- *Growth in Mo-99 demand*. The committee assumed that there will be no growth in Mo-99 demand in the future, even though a 3–5 percent annual growth rate was deemed likely by the committee for at least the next 5 years (see Chapter 5). This no-growth assumption is "conservative" because it produces a lower present-value estimate than would be the case if demand growth were included in the analysis.
- *Growth in Mo-99 prices*. The committee assumed that there will be no growth in Mo-99 prices, even though there have been recent substantial price increases and could be additional increases in the future. This is also a conservative assumption.

The numerical results of the committee's analysis are shown in Table 10.1.

For the purpose of assessing feasibility, we will consider the present-value estimates made using the most conservative assumptions about discount rates (7 percent real) and accumulation periods (30 years). For these assumptions the present values at the three points in the supply chain are as follows:

- *Based on a 10 percent increase in Mo-99 production costs:* the present value is about $175 million based on global[19] Mo-99 production levels.
- *Based on a 10 percent increase in technetium generator costs:* the present value is about $435 million based on global Mo-99 production levels.
- *Based on a 10 percent increase in the cost of Tc-99m doses:* the present value is about $545 million based on global Mo-99 production levels.

[19]The committee judged that global, rather than U.S., revenues should be used for this analysis because the two suppliers to the U.S. market, MDS Nordion and Mallinckrodt, are global producers.

Of course, as shown in Table 10.1, considerably more revenues would be available if longer accumulation periods or a lower discount rate were assumed.

To determine whether revenues of this magnitude would be sufficient to support conversion to LEU-based production, it is necessary to understand what steps are required to convert. Although these steps will likely be somewhat different for each producer, some general observations can be made. First, conversion will likely not require the construction of new reactors to irradiate LEU targets. For the reasons discussed in Chapter 7, LEU targets should be compatible in current reactors, although some target development work will be required and the rigs that are used to irradiate HEU targets in the reactor may need to be modified to accommodate LEU targets. The reactors that are now used to produce HEU-based Mo-99 are aging and will eventually need to be replaced. However, this is true whether HEU or LEU targets are used.

Second, there will be some research and development (R&D) work required to modify current HEU-based processes for producing Mo-99 to accommodate LEU targets. Much of this work can be carried out in conventional wet laboratories, and the primary costs are for the experts who will carry out this work.

Third, likely the greatest potential expense for conversion would be the need to modify existing hot cell facilities or construct new hot cell facilities to accommodate the LEU-based process. This might be required, for example, if there is not enough additional hot cell space in the facilities that are being used for HEU-based production. Alternatively, a company could shut down the HEU process to convert the facility, but the opportunity costs, that is, the cost of lost production, would then have to be considered as a cost of conversion.

To assess whether conversion could be carried out with these additional revenues the committee considers the most conservative case: $175 million available for conversion based on a 10 percent increase in Mo-99 production costs. As shown in Table 10.1, considerably more revenue would be available to support conversion if the 10 percent cost increase were applied at either of the other two points in the supply chain. The revenues available to individual producers for conversion can be estimated by multiplying $175 million by producers' market shares (Table 3.1) for Mo-99 production.[20] The results are as follows:

- $70 million for MDS Nordion based on its 40 percent global market share;

[20]Of course, producers' market shares can change over time, but the committee judges that this assumption is sufficient for the purposes of this analysis.

- $44 million for Mallinckrodt based on its 25 percent global market share; and
- $35 million for IRE based on its 20 percent global market share.

The committee judges that these additional revenues would be more than sufficient if conversion could be carried out within producers' existing facilities. This appears to be the case for all three of these producers: As noted previously in this chapter, AECL could convert within the NPF facility; IRE could convert one of its backup sets of hot cells; and Mallinckrodt could convert some of its existing hot cells. In these cases, additional conversion costs would likely be much less than the present values of these additional revenues, likely no more than a few millions to the low tens of millions of dollars for minor facility modifications,[21] LEU target and process development and implementation work, and regulatory approvals.

Conversion *might* also be feasible even if extensive facility modification or new facility construction is required to support conversion. As noted in Chapter 2, for example, MURR estimates that it would cost between $30 million and $40 million to construct a facility adjacent to its reactor with two complete process lines that could be used to process either the uranium metal foil targets developed by Argonne National Laboratory or the LEU dispersion plate targets developed by CNEA. Each process line would have either three or four hot cells plus one additional common cell. Consequently, the committee judges that the $70 million in additional revenues available to MDS Nordion is probably more than sufficient to convert within existing facilities at the Chalk River site, even if some refurbishment of hot cells is required. Similarly, the $44 million in revenues available to Mallinckrodt for conversion would almost certainly support conversion within its existing facility even if the processing equipment needed to be modified. As noted previously, IRE told the committee that it has no plans to convert and did not provide a cost estimate for conversion. However, the committee judges it very unlikely that new facility construction would be required given the number of hot cells available to that organization.

The committee judges that conversion is most certainly feasible for all large-scale producers based on the present value of additional revenues that would be available from a 10 percent cost increase in technetium generators or Tc-99m doses—even if producers had to build completely new facilities to process LEU targets. As shown in Table 10.1, the present value of revenues available from a 10 percent cost increase in technetium generators ($435 million globally) is more than twice the revenues available from a 10 percent increase in Mo-99 production costs ($170 million). The present

[21]For example, modification of the hot cells themselves or the process equipment contained within them.

value of revenues available from a 10 percent cost increase in Tc-99m doses ($545 million globally) is more than three times the revenues available from a 10 percent increase in Mo-99 production costs.

The forgoing discussion focused on fixed costs primarily associated with facility modifications and other one-time expenditures such as regulatory approvals. There could also be differences in variable costs that are not accounted for by this analysis. Such costs include labor, materials (e.g., for targets and chemical reagents), services (e.g., irradiation, waste management, and utilities), maintenance and repair, and taxes. The variable cost differences, if any, will depend on the specific conversion pathway selected by each producer. Because none of the four large-scale producers have selected a conversion pathway, it is not possible to estimate these variable cost differences.

CNEA recently presented a comparison of its variable costs for producing Mo-99 using LEU and HEU targets (Cestau et al., 2008). As discussed in Chapter 7, CNEA converted from HEU- to LEU-based production in 2002. It estimated its variable costs for Mo-99 production for the 4 years prior to (1998–2001) and 5 years following (2003–2007) conversion. Costs were presented in three categories: (1) labor; (2) materials; and (3) services, maintenance, taxes, and miscellaneous. The costs were presented as present-value (see Appendix F) estimates normalized on a per curie basis for the number of curies produced in 2007. The results of the study can be summarized as follows:

- Labor costs (for LEU-based production) increased by about 26 percent (compared to HEU-based production) primarily due to the increased costs associated with fabricating LEU targets (more steps are required to fabricate these targets).
- Costs for materials decreased by about 1.9 percent.
- Costs for services, maintenance, taxes, and miscellaneous decreased by about 1.7 percent.
- Overall costs for LEU-based production compared to HEU-based production increased by about 5 percent.

This cost increase is less than the 10 percent feasibility criterion mandated by Congress. However, the committee emphasizes again that HEU-based production costs are producer specific, and the variable costs of producing Mo-99 from LEU-based systems will also be producer specific and will depend on the conversion pathway selected. Nevertheless, this example illustrates that production of Mo-99 from LEU-based systems can be obtained for less than a 10 percent cost increase.

As noted at the beginning of Chapter 1, one of the balancing interests that motivated this study was ensuring the continued availability of reason-

ably priced medical isotopes in the United States. For most medical patients and their insurance companies, the term "reasonably priced" does not apply to a 6-day curie of Mo-99 or a Tc-99m dose, but rather to the price for a medical isotope procedure. Although the analysis presented in this section has not addressed the impacts of medical isotope cost increases on the prices for such medical procedures, those impacts can be easily assessed.

Note that cost increases near the top of the supply chain (e.g., cost increases for Mo-99 production) will have diminishing impacts on prices as they are translated down the supply chain (e.g., the price for a medical isotope procedure). For example, using the cost/price estimates developed in this section, a 10 percent cost increase for a 6-day curie of Mo-99, if translated down the supply chain, would result in about a 4.5 percent price increase for a technetium generator or about a 2.5 percent price increase for a Tc-99m dose. The impact on the price of a medical isotope procedure would be even smaller, as illustrated by the following example.

In calendar year 2007, the Centers for Medicare & Medical Services reimbursement rates for two of the most common diagnostic imaging procedures, whole body bone imaging (CPT/HCPCS[22] code 78306) and myocardial perfusion imaging (CPT/HCPCS code 78460), were $240.79 and $253.65, respectively. These reimbursement rates include the cost of the Tc-99m dose used in the procedures. A 10 percent increase in the cost of the Mo-99 that is used to produce the Tc-99m doses would translate to about a 0.1 percent increase in the prices of these procedures. A 10 percent increase in the price of a Tc-99m dose itself would only translate to about a 0.4 percent increase in these procedure prices. In other words, the increases in the prices of these medical procedures would be trivial given a 10 percent cost increase at any point in the Mo-99/Tc-99m supply chain.

Consequently, if the congressionally mandated 10 percent cost increase for Mo-99 production is intended primarily to reduce impacts of price increases on patients, the committee concludes that cost increases for Mo-99 production many times greater than 10 percent would not result in substantial increases in prices to patients, assuming that such costs are passed along without added margins. In fact, the committee is aware of substantial recent price increases in the costs of Mo-99 and Tc-99m generators that exceed the 10 percent criterion set by Congress. These increases have not had any apparent impact on the availability or price of diagnostic imaging procedures.

[22]CPT® (Common Procedural Terminology) and HCPCS (Healthcare Common Procedural Coding System) are coding conventions used to designate various medical procedures.

ADDITIONAL STEPS TO IMPROVE THE FEASIBILITY OF CONVERSION

The last charge of the study task is to identify additional steps that could be taken by DOE and medical isotope producers to improve the feasibility of conversion to LEU-based production if such conversion is not currently judged to be feasible. As noted in the preceding section, the committee judged that conversion is feasible under the 10 percent cost criterion defined by Congress. However, no large-scale producers are currently producing LEU-based Mo-99 nor have they announced their intention to convert to LEU-based production.

There is a good reason that current large-scale producers have not yet converted to LEU-based production: namely, there is no good business reason at present for doing so. Under current market conditions, producers would realize little or no direct revenue benefit from conversion, because it would not enhance product quality[23] nor would it reduce the cost of production. In fact, conversion could require an up-front financial investment that would require producers to increase prices or accept lower rates of return on the commercial sale of Mo-99. The committee judges that additional steps need to be taken by producers and the U.S. government to improve the near-term feasibility of the conversion. Several possible steps are identified by the committee in the following discussion.

Mo-99 Producers

The three large-scale Mo-99 producers that cooperated in this study (Mallinckrodt, IRE, and MDS Nordion) have acknowledged the security concerns that are driving global HEU minimization efforts, and representatives of two of those producers (Mallinckrodt and MDS Nordion) told the committee that they see conversion as inevitable if commercially feasible (see also NNSA and ANSTO, 2007). The Canadian government has also committed to conversion to LEU targets as soon as it is feasible to do so.[24] An industry association, Council on Radionuclides and Radiopharmaceuticals (CORAR) has expressed support for conversion but at the same time has asserted that conversion technologies are unproven.

The work being carried out by Argonne National Laboratory and its collaborators on LEU-based production as well as the development of a

[23]However, there could be indirect benefits of conversion, for example, being seen to support international security objectives associated with HEU minimization.

[24]On September 4, 1997, the U.S. Embassy and the Canadian Ministry of Foreign Affairs exchanged diplomatic notes that offered Canadian assurances that LEU targets would be used to produce Mo-99 when such targets became available, provided that their use did not result in a large percentage increase in costs.

commercially viable LEU-based production system by CNEA have shown two viable pathways for conversion. However, the committee has not seen any evidence that large-scale producers are taking the necessary steps or have committed to a schedule for conversion. In fact, the recent developments at AECL appear to call the Canadian conversion commitment into question.

Perhaps the most important step that Mo-99 producers can take at this time to improve the feasibility of conversion is to (1) announce their commitment to convert; (2) announce a best-effort schedule for conversion; and (3) identify needs for technical assistance, if any, to enable conversion. The committee judges that these steps would result in the following benefits:

- The commitment and schedule announcements would demonstrate that the industry is taking leadership of this important effort; it would also help to protect the industry against externally imposed solutions that might not be in its best long-term interests or in the best interests of medical patients.
- These announcements would serve as an important source of peer pressure within the industry that could help to push along producers that might be reluctant to convert. This step is critical for creating the "level playing field" that producers have identified as an essential precondition for conversion (NNSA and ANSTO, 2007).
- The identification of technical assistance needs would be an important first step in focusing the considerable R&D assets available in the U.S. national laboratories and from other technical organizations on conversion. Additional discussion of this issue is provided in a following section.

Industry organizations such as CORAR and its European sister organization, the Association of Imaging Producers and Equipment Suppliers (AIPES), working with the scientific and medical societies concerned with Mo-99 production, can play key roles in marshaling, coordinating, and supporting an industry-wide conversion effort.

DOE

The committee judges that DOE, and specifically NNSA, can also take additional steps to improve the feasibility of conversion. First, DOE can expand on the good work being carried out by Argonne National Laboratory and the Idaho National Laboratory that is currently supporting conversion (see Chapters 2, 3, and 7) by making the considerable technical expertise of the DOE national laboratory system[25] available to assist

[25]This includes the laboratories run by the Office of Science, Office of Environmental Management, and Office of Nuclear Energy, which have considerable expertise with nuclear and chemical processing.

producers with conversion-related R&D. As noted in Chapter 7, producers generally lack the necessary expertise to do much of the R&D work that will be required for conversion. DOE could encourage producers to establish Cooperative Research and Development Agreements with national laboratories for this work and should examine options to share costs with producers as a means to incentivize the conversion process. Additional funding from Congress might be needed to allow DOE to provide technical assistance on a cost-sharing basis.[26] Technical assistance by DOE could be structured to further HEU minimization goals. For example, cost sharing could be made available only after a producer has announced a commitment and schedule to convert to LEU-based production. To be effective, this technical assistance must be available to all producers who currently supply or might supply Mo-99 to the U.S. market[27] and must be appropriately focused and scheduled to meet conversion timelines.

DOE can also work with organizations in other countries (especially through its cooperation in support of mechanisms like the International Atomic Energy Agency's [IAEA] Coordinated Research Project mentioned elsewhere in the report) to provide technical assistance to producers. CNEA and its sister organization Investigaciones Aplicadas Sociedad del Estado (INVAP) are global leaders in LEU-based isotope production technology, having converted their own process from HEU to LEU, and having built all-LEU production systems in Australia and Egypt. There are public-sector technical organizations in other countries with missions similar to the U.S. national laboratories that can potentially provide technical R&D assistance as well.

Second, DOE could examine other opportunities available to it to encourage conversion. One possible opportunity in this regard is policies concerning pricing for HEU and LEU. The committee was told by DOE that its sales prices for enriched uranium for research reactors and targets includes all costs associated with the production of the enriched uranium product. This includes the fair market value for the uranium starting material as well as the full costs for the services required to produce the finished enriched uranium product. However, depending on the number and terms

[26]Section 31 of the Atomic Energy Act of 1954 authorized the Atomic Energy Commission (and now DOE) to provide such assistance: "The Commission is directed to exercise its powers in such manner as to insure the continued conduct of research and development and training activities in the fields specified below, by private or public institutions or persons, and to assist in the acquisition of an ever-expanding fund of theoretical and practical knowledge in such fields. To this end the Commission is authorized and directed to make arrangements (including contracts, agreements, and loans) for the conduct of research and development activities relating to– . . . (3) utilization of special nuclear material and radioactive material for medical, biological, agricultural, health, or military purposes. . . ."

[27]Of course, DOE could as a matter of policy give funding priority to domestic producers.

of its long-term contracts with enriched-uranium buyers, DOE's prices[28] for HEU and LEU will not necessarily represent the current costs of producing this material. In fact, during this study, DOE prices for HEU were significantly lower than LEU on a common uranium-235 (U-235) mass basis (the committee received this information from both DOE and from a buyer of enriched uranium). Although the cost of uranium is a relatively small part of the cost of producing Mo-99, maintaining the cost of LEU so that it is at least no more expensive than HEU on a common U-235 mass basis would help to improve the economics of conversion.

Department of State

The Department of State plays an important diplomatic role in ongoing U.S. efforts to promote the conversion of medical isotope production from HEU to LEU. For example, the department negotiated the 1997 memorandum of understanding with the Embassy of Canada on conversion of medical isotope production to LEU (footnote 24) and is an important partner with the DOE on the Global Threat Reduction Initiative (GTRI, see Chapter 11). The committee judges that there may be opportunities for the department to intensify diplomatic pressure on countries that still use HEU for reactor fuel and targets to induce them to convert. In particular, those countries that are partners in the GTRI and have made a commitment to the "minimization of HEU" should be encouraged to live up to their commitment; this includes Canada, the Netherlands, Belgium, and France.

Food and Drug Administration (FDA)

As discussed in Chapter 8, the FDA is responsible for regulating the commercial sale of radiopharmaceuticals derived from Mo-99. Technetium generator producers have cited FDA regulations as a potentially significant obstacle to conversion because of the cost and time required to obtain FDA approvals for the sale of radiopharmaceuticals made with LEU-based Mo-99.

The industry-wide conversion to an LEU-based Mo-99 production process is likely to raise several generic issues about Mo-99 processing and purity. The committee judges that there may be opportunities for industry and its associations and DOE's technical experts to work with the FDA well in advance of industry-wide conversion to ensure that (1) there is a common understanding of LEU-based processes from a regulatory perspective and (2) that there is a good understanding of likely FDA requirements for obtaining regulatory approvals.

[28]Actual prices set by DOE for HEU and LEU are considered business-sensitive information.

The committee is not suggesting that the FDA lower its review requirements or give the industry special consideration. The industry is ultimately responsible for submitting technically sound and supportable supplemental new drug applications (see Sidebar 8.1) for FDA review. Instead, the committee is suggesting that advanced discussions can help to clarify expectations and help industry to develop technically strong applications that can be processed expeditiously by FDA staff.

U.S. Congress

Conversion to LEU-based production of Mo-99 would serve a broader public good—namely, improved national security through the worldwide reduction of civilian HEU commerce. As discussed in Chapter 11, minimizing civilian use of HEU is a major component of the GTRI. There are currently no financial or competitive reasons for industry to convert to LEU-based production. The only reason for conversion is to support HEU minimization goals. One could argue that private industry should not be expected to shoulder the entire cost of obtaining this benefit, but that governments should also bear part of this burden. As noted in Chapter 3, governments are already involved indirectly in the production of Mo-99 through the support they provide to construct and operate reactors and processing facilities. However, there are additional steps that governments can take to hasten conversion.

The U.S. government is sending inconsistent signals to current HEU-based producers about the urgency of converting to LEU-based production. On the one hand, the government is aggressively promoting conversion to LEU-based production through the GTRI. This study is part of that effort. On the other hand, the U.S. Congress has sheathed one of its most powerful tools for promoting conversion—the Schumer Amendment (see Sidebar 1.3). Clear and consistent policy signals from the U.S. government concerning conversion to LEU-based Mo-99 production and the importance of domestic production are essential for establishing a strategic trajectory for conversion efforts.

There are a number of tactical tools available to the Congress to promote the implementation of such a strategy. The committee provides some examples below.

1. Fund government cost sharing on R&D to support conversion as described previously.

2. Condition the supply of U.S.-origin HEU for medical isotope production. Past efforts to restrict the use of U.S.-origin HEU for medical isotope production have so far been unsuccessful. Congress has at least two options for using its control of the U.S. HEU supply to promote conversion:

- Reinstate the Schumer Amendment (see Sidebar 1.3) with a specific date to phase out the use of U.S.-origin HEU for Mo-99 production. A 7- to 10-year phase-out period would likely allow enough time for all current HEU-based producers to convert (see Chapter 9).
- Phase in a ban more gradually by prohibiting the export of U.S.-origin HEU for medical isotope production in new reactors. As noted in Chapter 3, at least two new reactors are expected to come online in Europe over the next 8 years. Converting these reactors to use LEU targets would probably promote the conversion of all European reactors to LEU targets.[29] This phase-in period could be followed by a total ban on HEU exports for Mo-99 production.

3. Provide temporary financial incentives for the production and/or purchase of LEU-based Mo-99. Several approaches are possible. For example, a production incentive could help to establish new domestic suppliers of LEU-based Mo-99 (e.g., MURR and B&W), improve production capacity, and therefore help to improve supply reliability. However, such production incentives could discourage foreign producers from converting to LEU-based production because new domestic production could reduce demand for foreign-produced Mo-99.

A purchase incentive, on the other hand, would allow U.S.-based technetium generator producers to purchase LEU-based Mo-99 instead of HEU-based Mo-99 from both foreign and domestic producers. Such incentives could help establish domestic supplies and at the same time encourage foreign producers who sell Mo-99 to the U.S. market to convert. This would help to provide the "level playing field" for conversion that is desired by current producers because it would not discriminate between domestic and foreign production and would provide some "headroom" for higher LEU-based Mo-99 prices that would help to cover producers' costs of conversion. Such incentives could be especially effective if they were coordinated with the phase-out of U.S.-origin HEU for medical isotope production to provide both a carrot and a stick for conversion.

Any policies enacted by Congress must satisfy at least three important goals: (1) improve the reliability of Mo-99 supplies, especially domestic supplies; (2) avoid directing industry how to convert or selecting particular producers for preferential treatment; and (3) provide a level playing field for current producers who will need to convert and new producers who can supply the market with LEU-based Mo-99.

[29]It would probably not be feasible to process HEU and LEU targets on the same process line, and so producers would have to choose a single design for Mo-99 production. There would be a strong reliability incentive to use a design that was compatible with a newer reactor.

FINDINGS AND RECOMMENDATIONS

The committee developed the following findings based on its assessment of the first and last charges in its study task: With respect to the first charge to assess "the feasibility of procuring supplies of medical isotopes from commercial sources that do not use HEU," the committee finds that:

- LEU targets that could be used for large-scale production of Mo-99 have been developed and demonstrated.
- These targets could be used in reactors and processing facilities that produce large-scale quantities of medical isotopes for the U.S. market. However, producers might have to make modifications to their facilities or process equipment to use these targets (see Chapter 7) and the targets must be compatible with existing reactors.
- At present, there are not sufficient quantities of medical isotopes available from LEU targets to meet U.S. domestic needs. However, the committee sees no technical reasons that adequate quantities cannot be produced from LEU targets.
- The anticipated total cost increase from production of medical isotopes without the use of HEU would be less than 10 percent for at least three of the four[30] current large-scale producers (Mallinckrodt, IRE, and MDS Nordion[31]). This is true for costs at three points in the Mo-99/Tc-99m supply chain: Mo-99 production, technetium generators, or Tc-99m doses. In fact, a 10 percent cost increase for Mo-99 would provide very substantial resources for conversion and would have a negligible impact on the cost of common diagnostic imaging procedures.

The committee recommends that producers and the U.S. government consider several steps to improve the feasibility of conversion. The steps discussed in this chapter include the following:

- *Mo-99 producers.* Commit to conversion, announce a best-effort schedule for selecting and implementing an LEU-based Mo-99 production process, and identify additional needs for technical assistance. Work with industry organizations and scientific and medical societies concerned

[30]The South African producer, NTP Radioisotopes, declined to participate in this study. This organization uses South African HEU for Mo-99 production. It is in the process of converting its reactor to LEU fuel but to the committee's knowledge has not announced a schedule for converting to LEU targets.

[31]The finding that MDS Nordion could convert for less than a 10 percent cost increase assumes that AECL intends to continue production of Mo-99 over the long term as discussed elsewhere in this chapter.

with Mo-99 production for marshalling, coordinating, and supporting an industry-wide conversion strategy.

- *DOE*. Make the considerable technical expertise of the DOE national laboratory system available to assist producers with conversion-related R&D and examine options to share R&D costs with producers that supply the U.S. market as a means to incentivize the conversion process and encourage domestic production. Maintain the cost of LEU so that it is at least no more expensive than HEU on a common U-235 mass basis.
- *Department of State*. Intensify the diplomatic pressure on countries that still use HEU (fuel or targets) to induce them to convert. In particular, countries that are partners in the GTRI (see Chapter 11) and have made a commitment to the "minimization of HEU" should be encouraged to live up to their commitment; this includes Canada, the Netherlands, Belgium, and France.
- *FDA*. Work with the industry and DOE's technical experts to ensure that there is a common understanding of LEU-based production of Mo-99 from a regulatory perspective and that there is a good understanding of likely FDA requirements for obtaining regulatory approvals of this isotope in radiopharmaceuticals.
- *Congress*. Provide clear and consistent policy signals concerning conversion to LEU-based Mo-99 production. Consider additional controls on the use of U.S.-origin HEU for medical isotope production and incentives to technetium generator producers that purchase LEU-based Mo-99 to motivate conversion and the development of domestic sources of Mo-99. Specific actions that could be taken are described in the preceding section.

11

Progress in Eliminating HEU Use

The focus of this chapter is on the third charge of the statement of task for this study (Sidebar 1.2), which calls for an assessment of "The progress that is being made by the DOE and others to eliminate all use of HEU in reactor fuel, reactor targets, and medical isotope production facilities." Presently, the Department of Energy's (DOE's) highly enriched uranium (HEU; see Sidebar 1.1) elimination efforts are being carried out under the Global Threat Reduction Initiative (GTRI). This initiative is focused on the minimization of HEU in *civilian* research and test reactor fuels and targets. Research and test reactors that have defense-related missions and naval reactors used to power surface vessels and submarines are out of the scope of this program.[1]

Nuclear research and test reactors (Sidebar 11.1) have been in operation for more than 60 years. They underpin the development of power and propulsion reactors and are major research tools in the fields of nuclear physics and engineering, nuclear chemistry, materials science, and biology, and they contribute to scientific and technological advances in medicine, industry, and agriculture. Research reactors have become indispensable for the production of medical isotopes to supply a rapidly increasing demand

[1]The amount of HEU in storage or use in declared Nuclear Weapon States for defense and naval propulsion purposes dwarfs the amount of HEU that is currently being used for civilian research reactor fuel and targets. The HEU under the control of the defense establishment is maintained under high security conditions to prevent its diversion for use by rogue states or terrorists.

SIDEBAR 11.1
Research and Test Reactors

Research and test reactors are used primary as a source of neutrons for scientific and technical research and development applications and for the industrial production of isotopes. They are designed with high-power-density cores to produce a high thermal neutron flux (typically 10^{14}–10^{15} neutrons per square centimeter per second) but have much lower thermal outputs (typically < 100 MW thermal) than reactors used to produce electricity (typically ≥ 3,000 MW thermal). These reactors have a wide range of designs, but typically comprise a cluster of fuel elements and control rods in a pool or tank of water with graphite, beryllium, or heavy-water reflectors. The cores and reflectors typically contain empty channels for irradiation of targets and test materials, and some reactors are designed with apertures in their pool or tank walls through which neutron beams can be accessed.

HEU is well suited as a fuel for these reactors because it provides a high density of U-235, which allows high neutron fluxes to be obtained in a compact core configuration. Maintaining this high performance can be a substantial technical challenge when converting these reactors to use LEU fuel because existing fuel designs result in U-235 densities that are too low. Conversion may require a redesign of the fuel elements and/or the development of LEU fuel material that has high U-235 densities. This fuel material must be stable under the irradiation conditions that exist in these high-performance cores. As discussed in the text, suitable replacement LEU fuels have not been developed for some very-high-power-density reactors; these reactors cannot be converted until such fuels are developed. The development of such fuels is a major current focus of the RERTR program.

for diagnostic and therapeutic procedures based on nuclear medicine techniques. More than 700 research reactors are known to have been commissioned worldwide, and 240 of these are currently in operation in 55 countries (Table 11.1); another 9 reactors are in various stages of construction and several more are planned.

Since 1975, significantly more research and test reactors have shut down each year than have started up. Of the 240 operating research reactors, 203 are or were fueled with HEU. Almost all of these reactors are supplied with HEU of U.S. or Russian origin with only a small number supplied with HEU produced in the People's Republic of China (simply referred to as China in the following discussion).

The commerce in HEU for research reactors was recognized as a potential source of nuclear weapons-usable material beginning in the mid 1970s. Increasing concerns about the proliferation of HEU prompted the formation of the Reduced Enrichment for Research and Test Reactors (RERTR)

TABLE 11.1 Country List of Research and Test Reactors as of December 2008

	Reactors Worldwide					HEU-Fueled Reactors Identified for Conversion by the GTRI				
Country	Operational	Under construction	Planned	Shutdown	Decommis-sioned	Total	Fully converted	Partially converted	Shutdown before conversion	Not converted
Albania										
Algeria	2									
Argentina	5			2		2	2			0
Australia	1			2	1	1	1			
Austria	1			2		2	1	1		
Bangladesh	1									
Belarus					1					
Belgium	4			2		1				1
Brazil	4					1	1			
Bulgaria				1		1				1
Canada	8	2[a]	1[b]	5	3	6	3			3
Chile	1			1		2	1			1
China	14	2		2		8	2		1	5
Colombia	1					1	1			
Cuba										
Czech Republic	3				2	2	1			1
Democratic P.R. of Korea	1									
Democratic Rep. of the Congo	1			1						
Denmark				2	1	1	1			
Ecuador										
Egypt	2									
European Union				1						
Finland	1				1					

TABLE 11.1 Continued

	Reactors Worldwide					HEU-Fueled Reactors Identified for Conversion by the GTRI				
Country	Operational	Under construction	Planned	Shutdown	Decommis-sioned	Total	Fully converted	Partially converted	Shutdown before conversion	Not converted
France	12		1	14	5	7	1		1	5
Georgia				1						
Germany	12			11	23	5	2		2	1
Ghana	1					1				1
Greece	2			1		1	1			
Hungary	2				1	1				1
India	5	1			4	1				1
Indonesia	3		1							
Iran, Islamic Republic of	5					2	1			1
Iraq				2						
Israel	2					1				1
Italy	4			5	5	1				1
Jamaica	1					1				1
Japan	13			7	3	7	2			5
Jordan										
Kazakhstan	3					4				4
Korea, Republic of	2			2		1				1
Latvia				2						
Libyan Arab Jamahiriya	1					2	2			
Madagascar										
Malaysia	1									
Mexico	3				1	1		1		
Morocco		1								
Myanmar										

continued

TABLE 11.1 Continued

	Reactors Worldwide					HEU-Fueled Reactors Identified for Conversion by the GTRI				
Country	Operational	Under construction	Planned	Shutdown	Decommis-sioned	Total	Fully converted	Partially converted	Shutdown before conversion	Not converted
Netherlands	3				2	3	2			1
Nigeria	1					1				1
Norway	2									
Pakistan	2					2	1			1
Peru	2									
Philippines				1		1	1			
Poland	1			2	2	1				1
Portugal	1					1	1			
Romania	2			1	1	1	1			
Russian Federation	49	1		36	11	12				12
Saudi Arabia										
Serbia	1			1						
Serbia and Montenegro										
Slovakia										
Slovenia	1					1	1			
South Africa	1					1		1		
Spain				1	3					
Sri Lanka										
Sweden				3	1	2	2			
Switzerland	3			2	1	2	1			1
Syrian Arab Republic	1					1				1
Taiwan	1	1		3	2	1	1			
Thailand	1	1								
Tunisia			1							

TABLE 11.1 Continued

	Reactors Worldwide					HEU-Fueled Reactors Identified for Conversion by the GTRI				
Country	Operational	Under construction	Planned	Shutdown	Decommis-sioned	Total	Fully converted	Partially converted	Shutdown before conversion	Not converted
Turkey	1			2		1		1		
Ukraine	1			2		1	1			
United Kingdom	2			7	27	2				2
United States	41			117	69	28	17			11
Uruguay				1						
Uzbekistan	1					2	1			1
Venezuela				1						
Vietnam	1					1		1		
TOTAL, WORLD	240	9	4	246	170	129	53	5	4	67

NOTES: There are currently 203 HEU-fueled reactors in operation worldwide; 125 of these operating reactors are in scope of the GTRI and 78 operating reactors are out of scope of the GTRI. See text for discussion.

[a]Maple-1 and Maple-2 reactors; development discontinued in May 2008.

[b]Maple X, which is planned as a materials test reactor and to take over the experimental program of the NRU reactor and support CANDU reactor development.

SOURCES: Data from the IAEA Research Reactor Database (http://www.iaea.org/worldatom/rrdb/) and a written communication to the committee from DOE-NNSA.

program[2] by DOE in 1978. This concern was reiterated over the period 1978–1980 by the International Nuclear Fuel Cycle Evaluation (INFCE) sponsored by the International Atomic Energy Agency (IAEA). At about that time the somewhat arbitrary[3] definition of HEU as uranium enriched in

[2]The objectives of this program are to reduce and eventually eliminate all commerce in HEU for research and test reactors by developing, testing, and qualifying higher density fuels and targets as well as the conversion procedures to allow reactors to operate safely and efficiently on LEU with a minimal loss in reactor performance.

[3]Glaser (2006) reviewed the rationale for selecting the less than 20 percent enrichment criterion for LEU. He concluded (pp. 18–19) that "Uranium fuel below 20% virtually elimi-

the fissile isotope U-235 to 20 percent or more (≥ 20 percent) was internationally accepted (see Sidebar 1.1). The main program objective of RERTR was to reduce and eventually eliminate all commerce in HEU for research reactors. Around the same time as INFCE, the former Soviet Union initiated a similar program to reduce the enrichment of fuel for research reactors in its client states, initially from 80 or 90 percent to 36 percent. However, this Soviet program did not become widely known in the West until the Russian Federation (RF) became a full partner in RERTR in 1993.[4]

The progress that DOE and others have made to eliminate the use of HEU in research reactors is largely a result of the RERTR program and falls neatly into two major periods: 1978–2004, when RERTR and associated spent fuel return programs had modest resources and progress was relatively slow; and 2004–present, when RERTR and associated fuel return programs became part of the GTRI.

RERTR PROGRESS: 1978–2004

The RERTR program has been focused on conversion of HEU research reactor fuel as well as conversion of HEU targets that are used to produce medical isotopes, because both fuel and targets contain direct-use material.[5] The progress made by the RERTR program during this period is described below.

Research Reactor Fuel

The primary concern of the RERTR at its inception was the elimination of HEU reactor fuel. Efforts on elimination were concentrated on the conversion of reactors to low enriched uranium (LEU) fuels, and especially on the development, testing, and qualification of higher density LEU fuels (see Chapter 7) for use in reactors that could not convert to using existing qualified LEU fuels without incurring a significant technical penalty in performance (see Sidebar 11.1).

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nates the possibility that the material could be directly used for the construction of a nuclear explosive device. Specifically, as some straightforward considerations show, LEU cannot be used in a simple gun-type device, both because of its large critical mass and the corresponding neutron emission rate. Simultaneously and coincidentally, at an enrichment level between 15–20%, plutonium production is sufficiently suppressed to minimize the total strategic value of the material if implosion-type technology is available. For both reasons, the 20% limit represents a reasonable and even optimum choice as a conversion goal for research reactors."

[4]The Russians essentially declared themselves to be partners at the October 1993 RERTR Conference in Japan.

[5]Direct-use material is directly usable in nuclear weapons. Such materials include HEU and separated plutonium.

The RERTR program work was led by DOE with help from the Department of State (DOS), which provided diplomatic assistance, and Argonne National Laboratory (ANL), which provided technical assistance. In the early 1990s, a significant role in the program was also played by an ad hoc group of research reactor operators from around the world known as the Edlow Group.[6] This group successfully lobbied for the reinstatement of the Foreign Research Reactor Spent Nuclear Fuel (FRRSNF) Acceptance Program, which came into force in May 1996, initially for a 10-year period. In 1997, a tripartite initiative involving the United States, RF, and IAEA, known as the Russian Research Reactor Fuel Return (RRRFR) program, was also initiated.

The FRRSNF Acceptance Program accepts the return of certain fuels containing HEU of U.S. origin. Aluminum-clad fuel is returned to the Savannah River site (SRS) in South Carolina, and TRIGA reactor fuel is returned to the Idaho National Laboratory (INL). DOE pays for fuel returns from other-than-high-income countries. High-income countries pay for their own fuel returns. There are other types of spent fuel (e.g., spent fuel with zirconium alloy cladding and oxide pellets as fuel meat) from demonstration reactors and one-off reactors such as the pebble bed reactor and a ship reactor in Germany and mixed oxide-burning fast breeder reactors in France and the United Kingdom. For the most part, the large spent fuel inventories from these shutdown reactors and some special experimental fuels (e.g., nitride fuel) and HEU booster rods are still in Europe and were never considered to be part of RERTR or the spent fuel return programs.

The importance of these spent fuel return programs to the success of RERTR in this period cannot be overemphasized. Other than the altruism of complying with RERTR principles, the return of a research reactor's HEU spent fuel to safe and secure facilities in the United States and Russia is the only tangible incentive for a reactor to convert to LEU.

Over the 26-year initial period of the RERTR program, only 38 U.S.-designed research and test reactors were converted from HEU fuel to LEU fuel, and not a single Russian-designed reactor was converted. During the same period, more than 200 research reactors, the majority fueled with HEU, permanently shut down because of obsolescence, problems with aging materials and facilities, and (in a very few cases) the perceived cost of conversion.

Given the large number of reactor shutdowns relative to conversions during this period, an outsider might conclude that the RERTR program

[6]The group was named after its leader, Jack Edlow, of the Edlow International Company, who advised the ad hoc group of research reactor owners and operators on how to effectively convey their request for reinstatement of the spent fuel return program to the appropriate branches of the U.S. government through meetings with and letters to senior officials.

was waiting for time to accomplish its job. However, this characterization would be unfair. The modest funding of RERTR during the period, the long lead times required to develop, test, and qualify new high-density reactor fuels, and the time required to test a series of mixed LEU and HEU fuel cores[7] all conspired to slow progress. Given these facts, it could be argued that progress was even better than might have been realistically anticipated. Of the new reactors commissioned during this period only one of significant power, Forschungsneutronenquelle Heinz Maier-Leibnitz (FRM II)[8] in Munich, Germany, as well as a few Chinese Miniature Neutron Source Reactors[9] (MNSRs) were started up with HEU.

It was recognized from the beginning of the RERTR program that to convert many research reactors, particularly materials testing reactors and high-flux/high-performance reactors, without a serious loss of performance would require the development of higher density LEU fuels. ANL provided technical leadership for the development of high-density LEU fuels working in collaboration with the international community of fuel developers for research reactors. The program successfully developed and qualified LEU silicide fuels. These fuels have uranium densities of up to 4.8 g U/cm^3 compared with typical aluminum-based HEU fuel densities of 1.6 g U/cm^3.

The FRRSNF was also successful during the initial period of the RERTR program, transporting enough fresh and spent HEU (much of the latter which had lost its self-protection[10]) to make several nuclear weapons to safe and secure facilities at SRS and INL. Meanwhile, the RRRFR program accomplished fresh HEU return shipments from Serbia, Romania, Bulgaria, Libyan Arab Jamahirya (Libya), and Uzbekistan to safe and secure facilities in the RF. All of this Russian-origin fuel is scheduled to be downblended to

[7]For many reactors, conversion from HEU to LEU fuel takes place in stages by gradually replacing the HEU fuel elements with LEU fuel elements. The replacement can take up to 10 years per reactor for design and testing of mixed LEU and HEU cores to ensure that conversion could be carried out safely.

[8]The research reactor FRM-II began routine operation in April 2005. It is fueled with Russian HEU purchased by the Euratom Supply Agency.

[9]The Chinese-built MNSRs are low-power (27 kW) research reactors used primarily for neutron activation analysis, education, and training. The reactor cores contain less than 1 kg of HEU that is enriched in U-235 to 90 percent or greater. According to IAEA's current research reactor database, there are four MNSRs in China and one each in Ghana, Iran, Nigeria, Pakistan, and Syria.

[10]During their residence in a reactor, fuels and targets become radioactive as the result of the buildup of highly radioactive fission products such as Cs-137. This radioactivity is said to give the fuel or target "self protection" because it makes those materials difficult and hazardous to handle without specialized expertise and facilities. However, the targets used for medical isotope production are typically irradiated for only a few days, so there is not much buildup of fission products. Thus, the targets (and the waste resulting from their processing) lose their self protection in a relatively short time (1 to 2 years) after removal from the reactor (e.g., von Hippel and Kahn [2006]; see also Vandegrift et al. [2007]).

LEU. Unfortunately, no Russian-origin HEU spent fuel was returned under the program during this period.

Targets for Isotope Production

RERTR target conversion efforts were focused primarily on targets used to produce medical isotopes. As was the case for reactor fuel, it was recognized that conversion required the development of new target designs to accommodate the required five-fold increase in the amount of LEU to contain the same amount of fissionable U-235 as HEU (see Chapter 7). By the mid 1990s, MDS Nordion in Canada, the largest producer of molybdenum-99 (Mo-99), was using as much or more HEU per year in its targets as some high-flux research reactors used in fuel. Moreover, target burn-ups are only about 3 percent; consequently, the waste[11] from target processing is still HEU and loses its so-called self-protection after a short period.

All four large-scale producers of Mo-99 were using HEU targets during this period (and are still doing so): MDS Nordion obtains Mo-99 from HEU targets that are irradiated in the National Research Universal (NRU) reactor in Canada; Mallinckrodt and the Institut National des Radioéléments (IRE) obtain Mo-99 from HEU targets that are irradiated in the Belgian Reactor II (BR2), the High Flux Reactor in the Netherlands, and the Osiris reactor in France; and Nuclear Technology Products (NTP) Radioisotopes obtains Mo-99 from targets that are irradiated in the Safari-1 reactor in South Africa. See Chapters 2 and 3 for additional information about these producers.

Two important conversion-related actions were accomplished during this initial period. First, ANL, supported by research reactors in Indonesia and Argentina, began a program to develop higher density LEU targets using uranium metal foil. These targets are described in Chapter 7. Second, the Comisión Nacional de Energía Atómica (CNEA), an important regional Mo-99 producer in Argentina, converted to LEU-based Mo-99 production using high-density aluminum-uranium dispersion targets in 2002. These targets are also described in Chapter 7. It would be accurate to say that this conversion was the result of the RERTR program and CNEA's desire to market an LEU-based Mo-99 production process to other countries. CNEA relied heavily on the scientific literature and the advice from ANL for target design and dissolution process development.

Note that the Australian Nuclear Science and Technology Organisation (ANSTO) was also producing Mo-99 during this period using 1.8–2.2 per-

[11]None of this HEU waste from Mo-99 production has been returned to the country of origin. It remains in storage at isotope producers' sites or in offsite facilities.

cent LEU targets. ANSTO is in the process of converting to the LEU targets and dissolution process developed by CNEA (see Chapter 3).

RERTR PROGRESS: 2004 TO PRESENT

In May 2004, within DOE's National Nuclear Security Administration (NNSA), GTRI became a vital part of the U.S. National Security Strategy:[12]

> To keep fissile material out of the hands of rogue states and terrorists . . . we must address the danger posed by inadequately safeguarded nuclear and radiological materials worldwide. The Administration is leading a global effort to reduce and secure such materials as quickly as possible through several initiatives including the Global Threat Reduction Initiative (GTRI).

In the same timeframe, other policy statements relating to the use of HEU in the civilian community were made. During the analysis concerning recommencement of the recovery of spent fuel by the RERTR program, part of the final Environmental Impact Statement issued by DOE stated:[13]

> A key goal of United States' nuclear weapons nonproliferation policy is to reduce international civil commerce in HEU, since HEU can be used directly in the production of nuclear weapons.

IAEA's director general also announced that agency's position on HEU elimination during this period:[14]

> The countries involved should join forces to step up their efforts towards minimizing and eventually eliminating the civilian use of HEU. Joint research should be conducted to address the remaining technical hurdles involved in converting from HEU to LEU the operations of facilities (including research and large pulse reactors as well as critical facilities) and the production processes for medical isotopes.

The United States and Russia have also expressed strong support for civilian HEU elimination as evidenced by the February 24, 2005, Joint Statement by President George W. Bush and President Vladimir V. Putin on nuclear security cooperation:

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[12]The National Security Strategy of the United States of America, March 2006.
[13]http://www.epa.gov/EPA-IMPACT/1996/May/Day-17/pr-16570.txt.html.
[14]http://www.iaea.org/NewsCenter/Statements/2006/ebsp2006n010.html.

> The United States and Russia will continue to work jointly to develop low-enriched uranium fuel for use in any U.S.- and Russian-design research reactors in third countries now using high-enriched uranium fuel, and to return fresh and spent high-enriched uranium from U.S.- and Russian-design research reactors in third countries.

With its broad mission to reduce and protect vulnerable nuclear and radiological material located at civilian sites worldwide, the GTRI automatically subsumed the mission of RERTR and associated fuel return programs into its portfolio.

During this second period, the RERTR program received increased funding, increased visibility, and much more direct involvement by senior DOE-NNSA leadership resulting in accelerated progress. Increased funding led to acceleration in reactor conversion, fuel development, and a major new effort to promote the development of an LEU fuel fabrication facility. The demonstration of leadership by example through the recent U.S. domestic conversions of Florida, Texas A&M, and Purdue University research reactors has been accompanied by an increased rate of international reactor conversions. A more collaborative international approach is demonstrated by the Global Initiative to Combat Nuclear Terrorism, which includes principles and actions to address HEU minimization. This initiative has been adopted by 75 partner countries, including Belgium, Canada, France, and the Netherlands.

The creation of GTRI during this period has directly resulted in:

- Direct coordination between RERTR and the HEU fuel return programs for the U.S.-origin and Russian-origin HEU, the FRRSNF, and the RRRFR program, respectively;
- Development of a standardized incentive and implementation policy;
- Greatly increased collaboration with IAEA to develop several Coordinated Research Projects (CRPs).

In 1978 RERTR was a good idea for reducing the proliferation of weapons-usable HEU. After the September 11, 2001, attacks on the United States, it was seen by many as an even better idea. Surprisingly, however, it took more than 2 years for it to be reflected in significantly increased funding for the GTRI program in the United States.

Research Reactor Fuel

The GTRI has a strategic plan to convert 125 reactors of the remaining 203 HEU-fueled reactors still planned to be operating by 2018

(Table 11.1; Figure 11.1) and thereby minimize the commerce in HEU for research reactors but unfortunately not eliminate it. As shown in Table 11.1, four reactors that were identified for conversion within the GTRI have been shut down. The remaining 78 research reactors have defense-related missions, unique fuels, special-purpose designs, or are located in countries that currently do not cooperate fully with the United States on reactor conversion programs. These 78 reactors are not targeted for conversion under the GTRI and are in fact considered to be out-of-scope of that initiative. DOE-NNSA maintains a substantial and fluid list of these reactors.[15]

HEU will continue to be transported to these out-of-scope reactors until they are eventually shut down, and also to the nuclear navies of the world, most of whose propulsion reactors are HEU fueled.[16] As a consequence, the original RERTR mission has been effectively modified from the goal to eliminate commerce in HEU for research reactors to a lesser goal of minimization.

As of December 2008, the status of the conversion program is as follows (see Figure 11.1):

- 58 reactors have been fully or partially converted and 4 reactors were shut down before conversion; 38 of these conversions took place between 1978 and 2004 and 20 conversions (including conversions of 2 Chinese reactors) took place between 2004 and present;
- 40 reactors are estimated to be able to convert using existing qualified LEU fuels; and
- 27 reactors are planned for conversion with advanced LEU fuels that still need to be developed and qualified. A new high-density uranium-molybdenum (U-Mo) alloy fuel is under development that would allow the conversion of at least 19 of these reactors. Additional analysis is required to determine whether any of the remaining 8 reactors can be converted using this fuel.

The GTRI program is focusing much effort on the development of these advanced high-density fuels, particularly U-Mo alloy fuels, with the goal of qualifying these advanced fuels by 2010.

As noted above, the GTRI has converted 20 reactors in the period of nearly 4 years since it assumed responsibility for RERTR. This represents

[15]Not all states have reported on their out-of-scope reactors, and IAEA inspectors do not visit research sites in weapons states to verify the presence of such reactors. Many of these out-of-scope reactors are located in Russia. DOE-NNSA and IAEA have information on some, but probably not all, of these reactors.

[16]France uses LEU fuels in its propulsion systems.

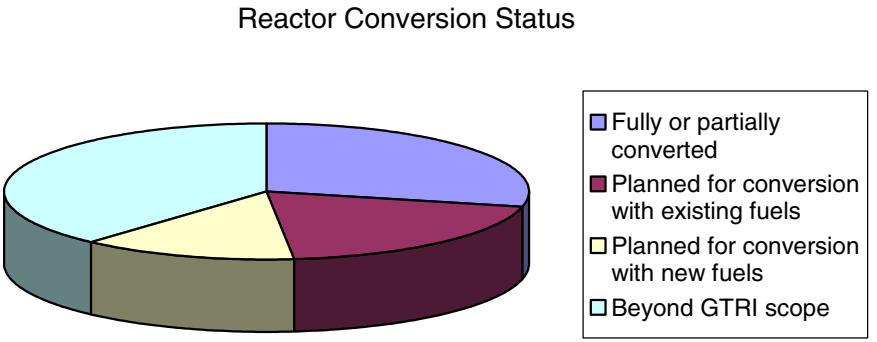

FIGURE 11.1 Current status of the program for converting research and test reactors from HEU to LEU.

a considerable acceleration over the pre-GTRI conversion rates, which averaged about 1.5 conversions per year. Moreover, the rate of conversions will likely increase over the next few years if funding levels are maintained, technical resources remain committed to conversion, and the government cooperation continues in countries where conversions are to be carried out.

The future success of GTRI in converting the remaining HEU-fueled reactors will also depend on the successful development of higher density fuels based on U-Mo alloys. Following the successful development of uranium silicide fuels, the program turned to the development of U-Mo alloys in an aluminum matrix with an initial goal of achieving densities in the range of 7–9 g U/cm^3. The program moved forward slowly, initially with limited funding. By 2004, hopes for the rapid qualification of such fuels had been severely dampened by failures of U-Mo dispersions in both plate and tube geometries in research reactors in Belgium, France, and Russia. These failures were all traced to the development of unstable interaction layers between the U-Mo fuel particles and the Al matrix, which caused swelling and decohesion of the fuel "meat" (Figure 11.2).

One promising remedy that has been identified is to add 2–4 weight percent of silicon to the fuel matrix, which appears to drastically reduce the rate of swelling. Also, increasing the weight percent of Mo to 7–10 percent allows the fuels to perform in a stable manner under irradiation, even without the addition of silicon (Figure 11.3). These approaches, along with other proposed material fixes and improvements in the fabrication technology for fuel plates, provide some confidence that the qualification

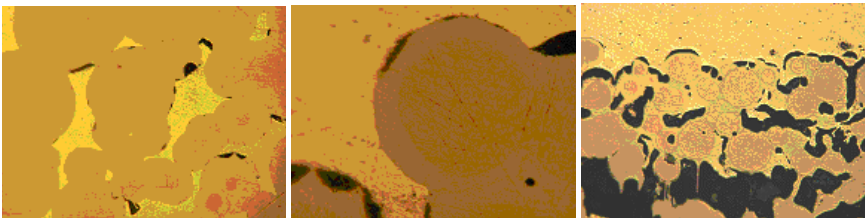

FIGURE 11.2 Micrographs of U-Mo fuels showing (left image) interaction layers around the U-Mo particles (yellow areas), (middle image) lenticular-shaped voids at the interfaces with Al matrix (black areas), and (left image) decohesion of the fuel meat. SOURCE: Courtesy of Patrick Lemoine, Commissariat à l'Energie Atomique (CEA), France.

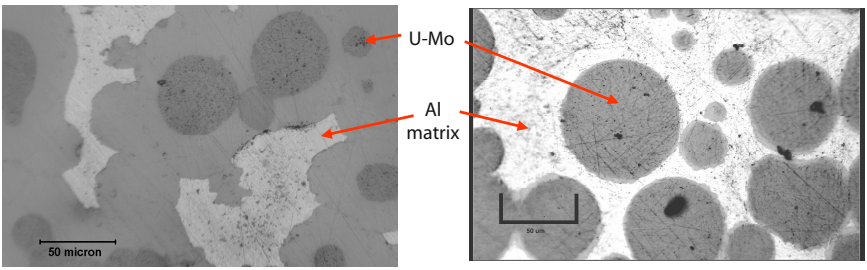

FIGURE 11.3 Micrographs of irradiated U-Mo fuel material before (left) and after (right) the addition of silicon. SOURCE: Courtesy of Idaho National Laboratory.

of a second generation of U-Mo dispersion fuel having densities of about 8.5 g U/cm^3 will be viable over the next 2 to 3 years.

ANL has been joined by INL as lead technical laboratory on new fuel development, and investigations have been initiated with the research reactor fuel development community worldwide. The partners are in Argentina, Canada, France, South Korea, and Russia, including both national laboratories and commercial fuel developers. This collaboration is a concerted effort to understand the swelling behavior of U-Mo fuels and overcome it. In a parallel effort, work to develop more advanced fuels (described below) is well underway.

Uranium silicide and U-Mo fuels are not suitable to convert all remaining reactors, however. In particular, five high-performance reactors in the United States (the Advanced Test Reactor [ATR] at INL; the High Flux Isotope Reactor [HFIR] at the Oak Ridge National Laboratory; the National

Bureau of Standards Reactor [NBSR] at the National Institute of Standards and Technology in Maryland; the Missouri University Research Reactor [MURR] at the University of Missouri; and the Massachusetts Institute of Technology [MIT] reactor) will require higher density fuels. U-Mo monolithic fuel with a density of approximately 16 g U/cm^3 is under development for this purpose. This fuel has not yet been qualified for use. GTRI identifies 27 research reactors that could utilize this U-Mo monolithic fuel for conversion.[17]

U-Mo-Al dispersion fuels having densities of 8–9 g U/cm^3 are also under development. Candidate reactors for using this fuel are BR2 in Belgium, and the remote handling facility, ORPHEE, and the Jules Horowitz Reactor, all in France. Conversion feasibility studies need to be completed for these reactors. The Jules Horwowitz Reactor is under construction (see Table 3.2) and is slated to begin operation in 2014. It will use uranium silicide fuel having a 28 percent enrichment until the U-Mo-Al dispersion fuel is qualified.

In Russia, fuel is qualified for specific reactors with focus on macroscopic behavior of fuel assemblies, and the fuel may be available for some reactors as early as the end of fiscal year 2009. Reactor-specific conversion efforts will continue for several years for Russian-designed reactors.

In Europe, data collection for fuel qualification will be more basic and widely applicable but must be reviewed by each country's regulator before use. The GTRI is planning a joint fuel qualification program with all the key European stakeholders. Preliminary evaluations suggest that the fuel testing for European dispersion qualification could be completed in roughly 3 years (i.e., by the end of 2011), which would culminate in an element test in BR2 (see Koonen, 2008). This element test would represent the final step in dispersion fuel qualification and as a lead test assembly for the BR2. The United States will provide fuel performance data and fuel design support required to complete this effort.

The monolithic fuel qualification effort is primarily focused on supplying fuel for the U.S. reactors and potentially the FRM-II reactor, but this fuel could also potentially be used with reactors that could also use U-Mo-Al dispersion fuel. Fuel tests will be performed to support qualification of the "base" fuel form that supports conversion of MIT, MURR, and NBSR by the end of 2011, assuming a 1-year review by the U.S. Nuclear Regulatory Commission.

Additional tests will be performed to enable qualification of "complex" fuel forms (which support conversion of ATR, HFIR, and potentially FRM-II) by the end of 2013. Although the dispersion fuel can use existing

[17]The work on high-density U-Mo monolithic fuels does not provide a pathway for conversion to high-density U-Mo targets, because the stable Mo-98 in the targets would dilute the Mo-99 produced by fission. See Chapter 7.

commercial fuel supply infrastructure, the supply of monolithic fuel will require the development of new fuel fabrication capability.

The HEU spent fuel return programs in the United States and Russia have played an important role in encouraging reactor operators and their authorities to convert. The importance of these programs is further underlined by the fact that the Edlow Group has remained together and renewed their call for a further extension of the FRRSNF as its termination date approached in 2006. Partially as a result of their efforts, the program was extended for another 10 years, to 2016, which almost reaches the strategic goal of the GTRI to complete the "in-scope" conversions by 2018.

In Bratislava in February 2006, the United States and the RF pledged to continue work to return fresh and spent fuel from the U.S.- and RF-designed research reactors in third-world countries. In addition to committing to specific goals, as described below, this Bratislava Initiative[18] also resulted in an agreement to provide progress reports every 6 months on accomplishments. These reports have proven to be a useful mechanism to drive programs forward at an accelerated pace. The seventh such report was made on June 7, 2008.

This initiative resulted in 336 kg of fresh and 157 kg of spent Russian origin HEU fuel (enough for about 20 nuclear weapons; see Sidebar 1.1) being returned during this period (compared with only 105 kg of fresh HEU during the previous period). These shipments included the first return of Russian-origin HEU spent fuel in RRRFR program history. That fuel was returned from Uzbekistan, the Czech Republic, and Latvia.[19] As of June 2008, FRRSNF had returned a grand total of 1146 kg of HEU in 41 shipments from 28 countries and RRRFR a grand total of 598 kg of HEU to safe and secure facilities in the United States and the RF, respectively.[20] Approximately 40 percent of the HEU that the program has targeted for return has actually been returned to date.

The 1146 kg returned to date is only about 20 percent of the 7335 kg U.S.-origin HEU that is abroad. However, NNSA has "moved the goal posts" and now considers 6016 kg of the total, which is located in Belgium, Canada, France, and the United Kingdom, to be "Material considered to be secure or to have an acceptable disposition path." If one accepts this statement, then almost 91 percent of the "planned" U.S. origin HEU has

[18]A fact sheet concerning the details if this initiative can be accessed from DOS at http://www.state.gov/p/eur/rls/prsrl/2005/42694.htm.

[19]An additional 155 kilograms of HEU research reactor fuel was returned to Russia from Hungary in October 2008.

[20]The results were presented by Jeff Chamberlin, Nuclear Removal Coordinator for the National Nuclear Security Administration, at the 2008 INMM Annual Conference in July 2008.

already been removed, and the ongoing program will be mainly repatriation of LEU from converted reactors.

Although the overwhelming majority of operating research reactors in the world were designed either in the United States or the former Soviet Union, several other countries have designed and built research reactors in their own countries and/or foreign countries. These include Argentina, Canada, China, France, Germany, and the United Kingdom. Since the inception of RERTR, the only new reactor to be fueled by a significant quantity of HEU was FRM II in Germany, which may become an unfortunate precedent in the future.[21] Although China is not officially a full partner in the conversion program, its announcement of the conversion of the 125 MW High Flux Engineering Test Reactor (HFETR) and associated HFETR-China[22] is an encouraging sign that China too is moving to replace HEU fuel with LEU fuel.

The IAEA-sponsored CRP involving China, IAEA, and the GTRI has enabled feasibility studies and conversion safety analyses to be conducted for several MNSRs both within and outside of China.[23] The feasibility studies were completed in May of 2008. It has been determined that conversion of the MNSRs to LEU fuel is feasible without any compromises to performance or safety. Publication of an IAEA TecDoc that reports the results of this CRP is planned for sometime in 2009 that reports the results of this CRP. The Chinese have signed tripartite project and supply agreements with IAEA and Ghana, Syria, and Nigeria to take back the spent fuel from their MNSRs. China has also indicated in writing to IAEA that it would also take back the spent fuel from Iran and Pakistan.[24]

Targets for Isotope Production

All four large-scale producers still obtain Mo-99 from HEU targets. However, some progress on target conversion has been made since 2004. Following Argentina, another small producer, the Indonesian National Atomic Energy Agency (BATAN), is close to LEU conversion using the foil

[21]Nikolay Arkhangelsky (Rosatom, Russia), one of the world's foremost research reactor experts, asserted in a November 2008 presentation that a limited number of very high power research reactors fueled with HEU may be required in the future to obtain sufficient neutron fluxes for some applied scientific experiments. He argues that such fluxes cannot be obtained using LEU.

[22]These reactors are located near Chengdu in Sichuan province and have been fully converted to LEU silicide fuel. The Min Jiang Test Reactor (MJTR) on the same site uses irradiated fuel from the HFETR and will convert to using LEU fuel when the current supply of HEU fuel is exhausted.

[23]The CRP is described at http://www.iaea.org/OurWork/ST/NE/NEFW/rrg_MNSR.html.

[24]The information on China's plans was provided to the committee in a written communication from Ira Goldman at IAEA.

targets and a modified Cintichem process pioneered by ANL. Successful processing of irradiated LEU foil targets has been demonstrated (Briyatmoko et al., 2007).

As noted previously, the Australian replacement reactor, OPAL, will use CNEA's high-density LEU target design and dissolution process. As described in Chapter 7, ANSTO is expected to become a large-scale producer of Mo-99.

A CRP initiated by IAEA and supported by GTRI is developing techniques for small-scale indigenous producers of Mo-99 using fission of LEU or neutron activation. This initiative is described in Chapter 3. The CRP has contracts involving the irradiation of LEU foil targets with Chile, Libya, Pakistan, and Romania, while Argentina, India, Indonesia, Korea, and the United States (ANL, MURR) are providing technical support through memoranda of understanding.[25] Poland and Egypt made successful requests to participate in the CRP after it had begun and are now actively involved. If the CRP achieves its goal, all new indigenous producers of Mo-99 will use LEU target technology or neutron activation technology freely provided through the supporters of the CRP. Clearly, this is notable progress toward the minimization of HEU at research reactors.

As noted in Chapters 7 and 10, conversion of the targets used for Mo-99 production to LEU is technically feasible for all current processes, including those used by the four large-scale producers. In the cases of Argentina and Indonesia, conversion has been demonstrated not to affect product purity or product yield (Chapter 8). At present, GTRI has a limited ability to support conversion efforts, especially in a financial sense. While the reluctance of major producers to convert is understandable from a business standpoint, pressure to convert may grow as international efforts to minimize the civilian use of HEU intensifies. As discussed in Chapter 10, DOE can play an important role in conversion by providing technical support and, working with DOS, through continuing diplomatic interactions with producers' home countries.

Finally, the committee notes that little or no progress has been made by the GTRI in minimizing the HEU waste resulting from medical isotope production. This waste is accumulating at producers' sites or at regional storage facilities (see Chapter 3). Of particular concern is the liquid HEU waste that is stored in the fissile solution storage tank (FISS tank) at the Chalk River, Ontario, site. The quantity of HEU in the tank has not been publicly disclosed, but the tank is likely to contain well in excess of 100 kg of HEU.[26]

[25]The four major commercially based isotope producers are observers in the CRP and have also provided some technical support.

[26]AECL stopped adding HEU waste to the tanks sometime between 2001 and 2006 and is now grouting the waste and storing it onsite. A final disposition pathway has not been determined.

The fact that the FISS tank wastes at Chalk River have not been solidified has led to speculation within the committee that these materials are seen as a hedge against a cutoff of HEU exports to Canada by the United States. HEU could be extracted from these liquid wastes and used to produce targets.[27]

At least two options exist for eliminating this waste. First, the wastes could be converted to LEU by adding natural or depleted uranium, a process known as "downblending." Downblending would likely be a relatively simple step for the liquid wastes at Chalk River if there is enough space in the FISS tanks to accommodate additional material. Downblending solidified HEU wastes, which exist in calcined or grouted waste forms, would likely require mechanical treatment to introduce depleted or natural uranium so that the mixture could not be easily separated. These solid wastes might have to be dissolved before they could be downblended, which could be difficult. A substantial volume of radioactive waste would be generated from this process.

The second option would be to return the waste from processing U.S.-origin HEU to the United States for downblending and storage. The liquid wastes would have to be solidified before they could be shipped, but the existing solid wastes might be shippable in their current forms. Whether there is a current legal and policy framework to return these wastes to the United States is unclear to the committee.

Finally, in addition to the HEU wastes from Mo-99 production, Atomic Energy of Canada Limited (AECL) is also storing about 45 kg of HEU that was intended for use for Mo-99 production in the Maple reactors. This material has apparently become surplus in light of AECL's decision to discontinue work on these reactors (see Chapter 10). At the time the present report was being completed, AECL had not announced whether it would return this HEU to the United States.

FINDINGS AND RECOMMENDATIONS

The third charge of the statement of task calls for an assessment of the progress that is being made by DOE and others to eliminate all use of HEU in reactor fuel, reactor targets, and medical isotope production facilities. The committee has developed the following findings and recommendations to address this task:

1. The committee finds that DOE-NNSA, in collaboration with ANL/INL and with the assistance of IAEA through the RERTR program, has made substantial progress in converting reactors and targets. In particular,

[27]A representative of IRE informed the committee that reprocessing of Mo-99 production wastes to recover HEU is an option for that organization as well if it cannot obtain fresh HEU.

substantial progress has been made in converting HEU-fueled reactors to LEU fuels. New technologies for LEU-based production (i.e., targets and processing) of Mo-99 have been developed by ANL and tested by some small producers. However, these technologies have yet to be adopted by large-scale producers of Mo-99.

2. Minimization of the commerce in civilian HEU and its use in research reactors worldwide, together with the return of research reactor spent nuclear fuel and HEU waste from isotope production to safe and secure facilities in their countries of origin, will help to reduce proliferation risks. The committee finds that the GTRI has made substantial contributions to these minimization and return goals: The period 1978–2004 was marked by slow but steady progress, whereas progress accelerated during the period 2004 to the present. **The committee recommends that the GTRI be continued until research and test reactors worldwide have converted fuel and targets to LEU or permanently shut down and their HEU fuel has been returned to the country from which it originated.**

3. Despite these successes, the committee finds that the program faces several challenges. First, the startup and continued operation of the HEU-fueled FRM II reactor in Germany sets an unfortunate precedent for possible future construction of HEU-fueled research reactors. Second, there are 78 HEU-fueled research and test reactors operating throughout the world that are out of scope of GTRI. The majority of these are old and by the end of the current GTRI program their numbers are likely to be much fewer. Nevertheless, from a purely technical perspective, it is difficult to understand why most of these reactors cannot be converted. **The committee recommends that DOE-NNSA, in cooperation with IAEA, make an effort to maintain an up-to-date and comprehensive database of the research and test reactors of the world, including large pulse reactors, critical facilities, and reactors with a defense-orientated mission.**[28] **The committee also recommends that these reactors should be investigated to determine if it is feasible to convert them to LEU; if so, they should become in-scope for the program.**

4. Finally, the committee finds that converting Mo-99 production worldwide to LEU will continue to be a major challenge for the reasons described in detail elsewhere in this report. Chapter 10 lists some actions that DOE and other parties can take to accelerate the conversion to LEU-based Mo-99 production. **The committee recommends that the RERTR 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 encouraging its return to the United States.**

[28]These reactors do not include HEU-fueled naval propulsion reactors or related test beds and training reactors.

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Appendix A

Section 630 of the Energy Policy Act of 2005

SEC. 630. MEDICAL ISOTOPE PRODUCTION.

Section 134 of the Atomic Energy Act of 1954 (42 U.S.C. 2160d) is amended—

(1) in subsection a., by striking "a. The Commission" and inserting "a. IN GENERAL.—Except as provided in subsection b., the Commission";

(2) by redesignating subsection b. as subsection c.; and

(3) by inserting after subsection a. the following:

"b. MEDICAL ISOTOPE PRODUCTION.—

"(1) DEFINITIONS.—In this subsection:

"(A) HIGHLY ENRICHED URANIUM.—The term 'highly enriched uranium' means uranium enriched to include concentration of U–235 above 20 percent.

"(B) MEDICAL ISOTOPE.—The term 'medical isotope' includes Molybdenum 99, Iodine 131, Xenon 133, and other radioactive materials used to produce a radiopharmaceutical for diagnostic, therapeutic procedures or for research and development.

"(C) RADIOPHARMACEUTICAL.—The term 'radiopharmaceutical' means a radioactive isotope that—

"(i) contains byproduct material combined with chemical or biological material; and

"(ii) is designed to accumulate temporarily in a part of

the body for therapeutic purposes or for enabling the production of a useful image for use in a diagnosis of a medical condition.

"(D) RECIPIENT COUNTRY.—The term 'recipient country' means Canada, Belgium, France, Germany, and the Netherlands.

"(2) LICENSES.—The Commission may issue a license authorizing the export (including shipment to and use at intermediate and ultimate consignees specified in the license) to a recipient country of highly enriched uranium for medical isotope production if, in addition to any other requirements of this Act (except subsection a.), the Commission determines that—

"(A) a recipient country that supplies an assurance letter to the United States Government in connection with the consideration by the Commission of the export license application has informed the United States Government that any intermediate consignees and the ultimate consignee specified in the application are required to use the highly enriched uranium solely to produce medical isotopes; and

"(B) the highly enriched uranium for medical isotope production will be irradiated only in a reactor in a recipient country that—

"(i) uses an alternative nuclear reactor fuel; or

"(ii) is the subject of an agreement with the United States Government to convert to an alternative nuclear reactor fuel when alternative nuclear reactor fuel can be used in the reactor.

"(3) REVIEW OF PHYSICAL PROTECTION REQUIREMENTS.—

"(A) IN GENERAL.—The Commission shall review the adequacy of physical protection requirements that, as of the date of an application under paragraph (2), are applicable to the transportation and storage of highly enriched uranium for medical isotope production or control of residual material after irradiation and extraction of medical isotopes.

"(B) IMPOSITION OF ADDITIONAL REQUIREMENTS.—If the Commission determines that additional physical protection requirements are necessary (including a limit on the quantity of highly enriched uranium that may be contained in a single shipment), the Commission shall impose such requirements as license conditions or through other appropriate means.

"(4) FIRST REPORT TO CONGRESS.—

"(A) NAS STUDY.—The Secretary shall enter into an

arrangement with the National Academy of Sciences to conduct a study to determine—

"(i) the feasibility of procuring supplies of medical isotopes from commercial sources that do not use highly enriched uranium;

"(ii) the current and projected demand and availability of medical isotopes in regular current domestic use;

"(iii) the progress that is being made by the Department of Energy and others to eliminate all use of highly enriched uranium in reactor fuel, reactor targets, and medical isotope production facilities; and

"(iv) the potential cost differential in medical isotope production in the reactors and target processing facilities if the products were derived from production systems that do not involve fuels and targets with highly enriched uranium.

"(B) FEASIBILITY.—For the purpose of this subsection, the use of low enriched uranium to produce medical isotopes shall be determined to be feasible if—

"(i) low enriched uranium targets have been developed and demonstrated for use in the reactors and target processing facilities that produce significant quantities of medical isotopes to serve United States needs for such isotopes;

"(ii) sufficient quantities of medical isotopes are available from low enriched uranium targets and fuel to meet United States domestic needs; and

"(iii) the average anticipated total cost increase from production of medical isotopes in such facilities without use of highly enriched uranium is less than 10 percent.

"(C) REPORT BY THE SECRETARY.—Not later than 5 years after the date of enactment of the Energy Policy Act of 2005, the Secretary shall submit to Congress a report that—

"(i) contains the findings of the National Academy of Sciences made in the study under subparagraph (A); and

"(ii) discloses the existence of any commitments from commercial producers to provide domestic requirements for medical isotopes without use of highly enriched uranium consistent with the feasibility criteria described in subparagraph (B) not later than the date that is 4 years after the date of submission of the report.

"(5) SECOND REPORT TO CONGRESS.—If the study of theNational Academy of Sciences determines under paragraph (4)(A)(i) that the procurement of supplies of medical isotopes from commercial sources that do not use highly enriched uranium

is feasible, but the Secretary is unable to report the existence of commitments under paragraph (4)(C)(ii), not later than the date that is 6 years after the date of enactment of the Energy Policy Act of 2005, the Secretary shall submit to Congress a report that describes options for developing domestic supplies of medical isotopes in quantities that are adequate to meet domestic demand without the use of highly enriched uranium consistent with the cost increase described in paragraph (4)(B)(iii).

"(6) CERTIFICATION.—At such time as commercial facilities that do not use highly enriched uranium are capable of meeting domestic requirements for medical isotopes, within the cost increase described in paragraph (4)(B)(iii) and without impairing the reliable supply of medical isotopes for domestic utilization, the Secretary shall submit to Congress a certification to that effect.

"(7) SUNSET PROVISION.—After the Secretary submits a certification under paragraph (6), the Commission shall, by rule, terminate its review of export license applications under this subsection.".

Appendix B

Biographical Sketches of Committee Members

Chris G. Whipple, *Chair*, is a principal in the Emeryville, California, office of ENVIRON International Corporation, an environmental consulting firm. His professional interests are in risk assessment, and he has consulted widely in this field for private clients and government agencies. Much of his work involves radioactive materials or mercury. Dr. Whipple is a member of the National Academy of Engineering, and he currently serves as co-chair of the Academies' Report Review Committee. He previously served as chair of the National Research Council's (NRC's) Board on Radioactive Waste Management and as a member of the Board on Environmental Studies and Toxicology. He has served on and chaired numerous NRC committees and is a long-time member of the National Council on Radiation Protection and Measurements. Dr. Whipple received his B.S. in engineering science from Purdue University and his M.S. and Ph.D. in engineering science from the California Institute of Technology.

Steven M. Larson, *Vice Chair*, is attending physician, Department of Radiology, member, Memorial Sloan Kettering Cancer Center, and professor, Department of Radiology, Weill Cornell University Medical Center. Dr. Larson is chief of nuclear medicine service, vice chairman for radiology research, and director of the Laurent and Alberta Gerschel Positron Emission Tomography Center, Department of Radiology Memorial Hospital. Dr. Larson is also laboratory head, Molecular Pharmacology and Chemistry Program, and co-director of the Ludwig Trust Center for Immunotherapy of Sloan Kettering Institute. Dr. Larson's research focus is molecular imag-

ing and targeted radiotherapy, particularly positron emission tomography (PET) and radioantibody-targeted therapy in oncology. He is a fellow of both the American College of Nuclear Physicians and the American College of Radiology. He is currently director of the American Board of Nuclear Medicine. He is the author and coauthor of more than 500 scholarly publications and has been awarded numerous honors including the Wylie medal of the U.S. Food and Drug Administration, the Academy of Molecular Imaging Distinguished Scientist Award (2007), the Wagner Lecture Medal of the Society of Nuclear Medicine, the Hevesy Awards of both the European and the U.S. Society of Nuclear Medicine, Radiology Researcher of the Year (2004) and the Pendergrass Awards of the Radiologic Society of North America. He is a member of the Institute of Medicine of the National Academy of Sciences (NAS).

Cynthia Atkins-Duffin is an authority on physical and chemical behavior of actinide and fission product elements. She is the E Program Manager (Energy, Environment and Non-Proliferation) in the Global Security Directorate at Lawrence Livermore National Laboratory. Prior to this assignment she was the deputy associate director for strategic planning and resources in the Energy and Environment Directorate. Previously she has served as the Applied Energy Technologies program leader and the Yucca Mountain Program deputy program leader. In addition, she was deputy materials program leader in the Chemistry and Materials Science Directorate from 1999 to 2002, and deputy director of the Glenn T. Seaborg Institute for Transactinium Science from 1996 to 1999. Earlier she was principal investigator in the hydrology and radionuclide migration program within the nuclear weapons programs. Dr. Atkins-Duffin's honors include the Chemistry and Materials Science Directorate Award (2001), the Energy Directorate Award (2000), and the American Institute of Chemists Award for Outstanding Undergraduate in Chemistry. She has authored or coauthored more than 40 refereed publications and given about 80 presentations. Dr. Atkins-Duffin received her Ph.D. in inorganic chemistry from Purdue University and her B.S. in chemistry from Worcester Polytechnic Institute.

Anthony Boardman is Van Dusen Professor of Business Administration in the Strategy and Business Economics Division at the University of British Columbia (UBC). His research interests include analysis of the effects of ownership on performance, privatization, public-private partnerships, cost-benefit and cost-effectiveness analyses, and strategic management in for-profit and nonprofit organizations. He is coauthor of a textbook, *Cost-Benefit Analysis: Concepts and Practice*. Dr. Boardman has extensive industry and consulting experience with a wide range of organizations in the private and public sectors. He has been a member of the Pharmacoeconomic Initiative

of British Columbia (1995–2001) and is currently serving a second, 5-year term as a member of the Patented Medicine Prices Review Board in Canada. Prior to taking up his position at UBC he taught at the Wharton School, University of Pennsylvania. Dr. Boardman studied for his undergraduate degree at the University of Kent at Canterbury in England and obtained his Ph.D. from Carnegie Mellon University in Pittsburgh.

Jeff Bostock retired from Lockheed Martin Energy Systems, Inc., as vice president for engineering and construction with responsibility for all engineering activities within the Oak Ridge nuclear complex. He has extensive experience managing projects as a Department of Energy (DOE) contractor. He has also served as vice president of defense and manufacturing and manager of the Oak Ridge Y-12 plant, a nuclear weapons fabrication and manufacturing facility. His career at Y-12 included engineering and managerial positions in all of the various manufacturing, assembly, security, and program management organizations. He also served as manager of the Paducah Gaseous Diffusion Plant. He was a member of the committees that produced the NRC reports, *Proliferation Concerns: Assessing U.S. Efforts to Help Contain Nuclear and Other Dangerous Materials* and *Technologies in the Former Soviet Union and Protecting Nuclear Weapons Material in Russia*. Mr. Bostock has also served as a panel member for the annual NRC assessment of the National Institute of Standards and Technology Measurement and Standards Laboratories. He was also a member of the NRC Committee on Oversight and Assessment of Department of Energy Project Management between 2000 and 2005. Mr. Bostock has a B.S. in industrial engineering from Pennsylvania State University and an M.S. in industrial management from the University of Tennessee. He is a graduate of the Pittsburgh Management Program for Executives.

G. Brian Estes is a consulting engineer and retired rear admiral, U.S. Navy Civil Engineer Corps. He has extensive experience in construction management, project delivery methods, federal contracting practices, and DOE environmental management projects. He was a member of the NRC Committee for Oversight and Assessment of Department of Energy Project Management, the Committee on Outsourcing of Design and Construction Management Services for Federal Facilities, and the Committee to Assess the Policies and Practices of the DOE to Design, Manage, and Procure Environmental Restoration, Waste Management, and Other Construction Projects, and has served on four other NRC committees, three of which have dealt with DOE. He is currently a member of the NRC Board on Infrastructure and the Constructed Environment (BICE) and the Department of Energy Environmental Management Advisory Board (EMAB). He holds a B.S. in civil engineering from the University of Maine, an M.S. in civil

engineering from the University of Illinois, and is a registered professional engineer in Illinois and Virginia.

Milton Levenson is nationally recognized for his ability to apply creative new insights to major engineering challenges in the nuclear industry and for his organizational and leadership skills. Currently an independent consultant, Mr. Levenson is a chemical engineer with 65 years of experience in nuclear energy and related fields. His technical experience includes work related to nuclear safety, fuel cycle, water reactors, advanced reactors, and remote control. His professional experience includes research and operations positions at the Oak Ridge National Laboratory, the Argonne National Laboratory, Electric Power Research Institute, and Bechtel, where he retired as vice president. He was elected to the National Academy of Engineering in 1976. Mr. Levenson is a fellow and past president of the American Nuclear Society, a fellow of the American Institute of Chemical Engineers (AIChE), and a recipient of the AIChE Robert E. Wilson Award in Nuclear Chemical Engineering. He is the author of more than 150 publications and presentations and holds three U.S. patents. Mr. Levenson has served on several NRC committees and has also served on the Nuclear and Radiation Studies Board.

Irvin Osborne-Lee is an associate professor and head of the Department of Chemical Engineering at Prairie View A&M University. Previously, he spent 13 years in the Chemical Technology Division of Oak Ridge National Laboratory. His expertise is in developing disposition pathways and treatment methods for problematic wastes. He has authored or coauthored about 50 papers in this area. He is also committed to positively impacting society through academic enterprise: educating and empowering students, motivating and inspiring faculty, and building key research programs. His honors and awards include the 2001 Appreciation Award of the National Society of Black Engineers and the Service to Society Award of AIChE, in which he has held a number of positions. Dr. Osborne-Lee is a member of AIChE, the National Organization for the Professional Advancement of Black Chemists and Chemical Engineers, Sigma Xi, and the National Council of Black Engineers and Scientists. He is currently a member of the board of directors for the Gulf Coast Waste Disposal Authority and was previously a director of AIChE. He received his Ph.D., M.E., and B.S. degrees in chemical engineering from the University of Texas, Austin in 1985, 1983, and 1979, respectively.

Gene Peterson did his postdoctoral work in chemistry and materials sciences at the Los Alamos National Laboratory in the area of thermochemical water splitting for hydrogen production. He joined the Argonne National Labora-

tory in 1978, performing research in the area of actinide chemistry, and in 1979, he joined the Los Alamos National Laboratory where he is currently the Chemistry Division leader. The Chemistry Division is a multiprogram capability organization that consists of 320 chemical professionals with a budget of approximately $100 million. At the Los Alamos National Laboratory, Dr. Peterson has specialized in medical isotope production and applications research and development (R&D). He has successfully managed large multidisciplinary programs in these areas at Los Alamos for more than 15 years. A notable program success during his tenure was the construction of a new $23.5 million 100 MeV Isotope Production Facility at the Los Alamos Neutron Science Center (LANSCE) for the production of accelerator isotopes. Throughout his years of service at the Los Alamos National Laboratory, he has worked on many unique projects and has more than 60 peer-reviewed publications in areas involving coordination chemistry, lanthanide and actinide chemistry, synthetic chemistry, inorganic geochemistry, environmental chemistry, materials processing, analytical chemistry, nuclear and radiochemistry, and biomedical research. He is currently participating in the development of the Center for Isotopes in Medicine within the Advanced Studies Institute, which is a joint collaboration among the University of California, the Los Alamos National Laboratory, and the New Mexico State Universities, including the University of New Mexico. Radiopharmaceutical R&D focused on isotopes produced at LANSCE will be a major thrust area of this center within the Advanced Studies Institute. Dr. Peterson received his B.S. degree from the Illinois Benedictine College in Lisle, Illinois, in 1971 and his Ph.D. in inorganic chemistry from the Arizona State University in 1976.

Richard C. Reba was a postdoctoral research fellow in nuclear medicine at the Johns Hopkins Medical Institutions. He subsequently served on the faculties of the Johns Hopkins University, George Washington University, and the University of Chicago, and he is board certified by the American Board of Internal Medicine and the American Board of Nuclear Medicine. He is an elected fellow of the American College of Physicians and the American College of Nuclear Physicians. He has been a consultant for several federal government departments and agencies, including the National Institutes of Health, DOE, Veterans' Administration, and Federal Aviation Agency, and international agencies, such as the International Atomic Energy Agency (IAEA). He has been a member of six federal government advisory committees charted by the U.S. Congress, and he has been a member of three previous NAS/NRC committees. Dr. Reba has been elected president of the largest scientific nuclear medicine organization, the Society of Nuclear Medicine, and the largest socioeconomic nuclear medicine organization, the American College of Nuclear Physicians. His research interests have been

in the area of drug development, specifically the research and application of single photon emission computed tomography (SPECT) and PET radiopharmaceuticals for the diagnosis and treatment of human disease. Dr. Reba currently serves on the faculty of Georgetown University in Washington, D.C., as professor of radiology (nuclear medicine) and internal medicine (cardiology) and as a staff physician in the Department of Nuclear Medicine of the Clinical Center of the National Institutes of Health in Bethesda, Maryland. Dr. Reba is author or coauthor of 330 scientific papers, book chapters and reviews.

Iain Ritchie is recently retired from IAEA where he spent the final 13 years of his career highlighted by a distinguished service award and appointment by the director general as crosscutting coordinator for research reactors. This responsibility for coordinating all of the agency's activities on research reactors included liaison with Reduced Enrichment for Research and Test Reactors and the Global Threat Reduction Initiative. Prior to joining the agency, Dr. Ritchie had a career as a research scientist spanning more than 25 years at the Whiteshell Nuclear Laboratories of Atomic Energy of Canada Limited. Among the highlights of this period was the management of a proton accelerator, direction of a group carrying out radiation damage experiments, and the appointment as adjunct professor of physics at the University of Manitoba. He is an expert in the field of defects in metals and has authored more than 200 technical papers and reports. In 1992 he received the Canadian Institute of Mining Metallurgy Award for Materials Engineering and in 1993 an R&D 100 Award for development of an innovative ultrasonic technique. Dr. Ritchie earned his B.S. in physics and Ph.D. in metals physics from the University of Wales in the United Kingdom.

Thomas Ruth is the head of the life science program at TRIUMF and senior scientist at the British Columbia Cancer Research Centre. In addition, Dr. Ruth is adjunct professor of pharmaceutical sciences and medicine at the University of British Columbia, chemistry at Simon Fraser University, and physics at the University of Victoria. He is a leader in the production and application of radioisotopes for research in the physical and biological sciences. His efforts at establishing PET as a quantitative tool for in vivo biochemistry has been recognized by the Canadian Nuclear Medicine Society's highest award of meritorious status. He has served on a multitude of committees, including the Institute of Medicine's Committee on Medical Isotopes and on the NRC's Committee on the State of the Science in Nuclear Medicine. In addition he serves as an expert on radioisotope production for IAEA. He has published more than 225 peer-reviewed papers and book chapters. Dr. Ruth received his Ph.D. in nuclear spectroscopy from Clark University.

Raymond G. Wymer is former director of the Chemical Technology Division, Oak Ridge National Laboratory and is now a consultant for the laboratory, DOE, and its contractors on all aspects of nuclear fuel and radioactive waste management. He is an associate member of the National Academies and is a member of the National Academies Board on Nuclear and Radiation Studies. He served on a United Nations Special Commission team to Iraq in the mid 1990s evaluating Iraq's uranium enrichment capability by chemical exchange. He is coauthor of a book *Chemistry in Nuclear Technology* and co-edited a book on *Light Water Reactor Fuel Reprocessing*. He was an editor of the journal *Radiochimica Acta* for more than 10 years until his retirement. Dr. Wymer is an adjunct professor in the Department of Civil and Environmental Engineering at Vanderbilt University. He has received recognition for his contributions in the nuclear area, including the Robert E. Wilson Award in Nuclear Chemical Engineering from AIChE for outstanding work on the nuclear fuel cycle. He received a B.A. from Memphis State University and an M.A. and a Ph.D from Vanderbilt University.

Jasmina Vujic is professor and chair in the Department of Nuclear Engineering at the University of California at Berkeley (UCB). She is also a director of an interdepartmental cutting-edge computing facility that provides computing services for advanced research and teaching to the College of Engineering departments at UCB. Before joining the Berkeley faculty, she worked at Argonne National Laboratory. Dr. Vujic is an internationally recognized expert in the advanced method development for nuclear reactor analysis and design, as well as for medical applications of radiation. Her fields of specialization also include radiation detection and measurement, nuclear reactor physics, neutron and photon transport, radiation protections, and engineering aspects of medical imaging and cancer therapy. Her general geometry collision probability code GTRAN2 has been licensed to General Electric and Toshiba. Also, the GTRAN2 code was chosen by DOE in 1991 as the computational methodology for assembly design of the modular high-temperature gas-cooled reactor core for tritium production. Dr. Vujic and a colleague developed a program in bionuclear and radiological physics for students in the bioengineering program. She has worked on diverse problems ranging from reactor core design to analysis of the neutronic behavior of fissile materials in geologic repositories, to modeling radiation transport for medical diagnostics in boron neutron capture therapy and for nuclear medicine imaging. She is holder of one U.S. patent and author of a book and 240 technical publications, including over 60 papers published in leading archival journals, and several awarded papers. She has been consulting for General Electric, Transware, VeriTainer, Aerotest Operations, and other companies. Dr. Vujic received the Prytanean Faculty Award and several other awards including an American Nuclear Society

best paper and best program awards and the 1991 Argonne National Laboratory Annual Exceptional Performance Award. She earned her B.Sc. in electrical and nuclear engineering and an M.Sc. in engineering physics from the University of Belgrade, and an M.Sc. and her Ph.D. in nuclear science from the University of Michigan.

Appendix C

Presentations and Visits

WASHINGTON, D.C., FEBRUARY 15–16, 2007

- Department of Energy-National Nuclear Security Administration, Office of Global Threat Reduction, Nicole Nelson-Jean, DOE-NNSA, Office of North and South American Threat Reduction; Parrish Staples, DOE-NNSA, Office of Global Threat Reduction
- Initiatives for the Development of Commercially Viable Mo-99 Production Methods Using LEU, Roy W. Brown, Council on Radionuclides and Radiopharmaceuticals (CORAR)
- Conversion of Molybdenum-99 (Mo-99) Production to LEU Target Technology, Grant Malkoske, MDS-Nordion
- OPAL (Open Pool Australian Lightwater) Reactor and Molybdenum-99, Therese Donlevy, Australian Nuclear Science and Technology Organisation (ANSTO)
- Mallinckrodt's Approach to HEU to LEU Conversion, Richard A. Roberts, Tyco Health Care/Mallinckrodt
- The Security Imperative of Eliminating Commercial Use of HEU, Ed S. Lyman, Union of Concerned Scientists
- Cost of Converting from HEU to LEU Targets for Medical Radioisotope Production, Frank von Hippel, Princeton University
- IAEA Input to NAS Study on Medical Radioisotope Production without HEU, Ira Goldman, International Atomic Energy Agency (IAEA)

WASHINGTON, D.C., APRIL 10–11, 2007

- ANL Perspective on Conversion of Mo-99 Production from High to Low Enriched Uranium, George Vandegrift, Argonne National Laboratory (ANL)
- Commercial Production of Fission Mo-99 from LEU Targets in Argentina, Pablo Cristini and Marcelo Salvatore, Comisión Nacional de Energia Atómica (CNEA) and INVAP (Investigaciones Aplicadas Sociedad del Estado)
- Commercial Production of Fission Radioisotopes from LEU Targets in Argentina, Pablo Cristini, CNEA
- FDA's Regulatory Role in Medical Isotope Production, Orhan Suleiman, Food and Drug Administration (FDA)
- NRC's Process for Licensing Exports of Highly Enriched Uranium (HEU) Medical Isotope Target Material, Stephen Dembek, U.S. Nuclear Regulatory Commission (NRC)
- Highly Enriched Uranium (HEU) Exports for Medical Isotope Production, Edward T. Fei, NNSA
- Conversion of Molybdenum-99 (Mo-99) Production to LEU Target Technology, Grant Malkoske, MDS Nordion
- Mallinckrodt's Mo-99 Process & Progress to LEU Conversion, Dale Simpson, Tyco Healthcare/Mallinckrodt
- Ion Beam Applications: Past, Present, and Future, Henri Bonet, Institute National des Radioéléments (IRE)

WASHINGTON, D.C., JUNE 11–12, 2007

- Global Threat Reduction Initiative–Reactor Conversion Program–Molybdenum-99 Production with LEU, Parrish Staples, DOE-NNSA
- Drug Master File Development and FDA Filings for LEU-Produced Medical Radionuclides, Roy Brown, CORAR
- Cardinal Health Nuclear Pharmacy Services, Jack Coffey, Cardinal Health
- The Cost of Developing Imaging Agents for Routine Clinical Use, Adrian Nunn, Bracco Research
- Status of IAEA Mo-99 Activities, Ira Goldman, IAEA
- National Academy of Sciences: Medical Isotope Production Study, Ralph Butler, University of Missouri Research Reactor (MURR)
- AECL's Medical Isotope Production, Brian McGee, Atomic Energy of Canada Limited (AECL)

ST. LOUIS, MISSOURI, OCTOBER 15–17, 2007

- Supporting the Nation's Nuclear Medicine Research–Update, Ralph A. Butler, MURR
- Efforts by Current Commercial Mo-99 Producers to Examine LEU Technologies, Roy W. Brown, CORAR

SITE VISITS

- August 20–21, 2007: Visit to AECL Chalk River Laboratories (Chalk River, Ontario, Canada) and MDS Nordion (Kanata, Ontario, Canada)
- December 17–18, 2007: Visit to ANSTO (Lucas Heights, Australia)
- March 10–12, 2008: Visit to IRE (Fleures, Belguim), CERCA (Romans, France) and Mallinckrodt (Petten, the Netherlands)
- June 5–6, 2008: Visit to CNEA (Buenos Aires, Argentina)

Appendix D

Alternative Molybdenum-99 Production Processes

There are two primary processes for producing molybdenum-99 (Mo-99): fission of uranium-235 (U-235) and neutron capture of molybdenum-98 (Mo-98). These are shown schematically in Figures D.1 and D.2, respectively. The fission of U-235 produces a large number of fission products, including Mo-99. The mass distribution of these fission products is shown in Figure 2.5.

The rate of production, which is of interest here, is proportional to several conditions as illustrated in the equation below:

$$R \propto n \, \phi \, \sigma$$

where

R = rate of reaction (i.e., number of reactions per unit time and volume), which is related to the amount of the new substance that can be produced
n = the number of target nuclei present (i.e., the target nuclei density in atoms per unit volume)
ϕ = the flux of particles causing the reaction (neutrons per cm^2 per second)
σ = the probability that the reaction will occur, expressed as an area

To understand whether a particular method is better than another these parameters must be considered as illustrated in the following comparisons.

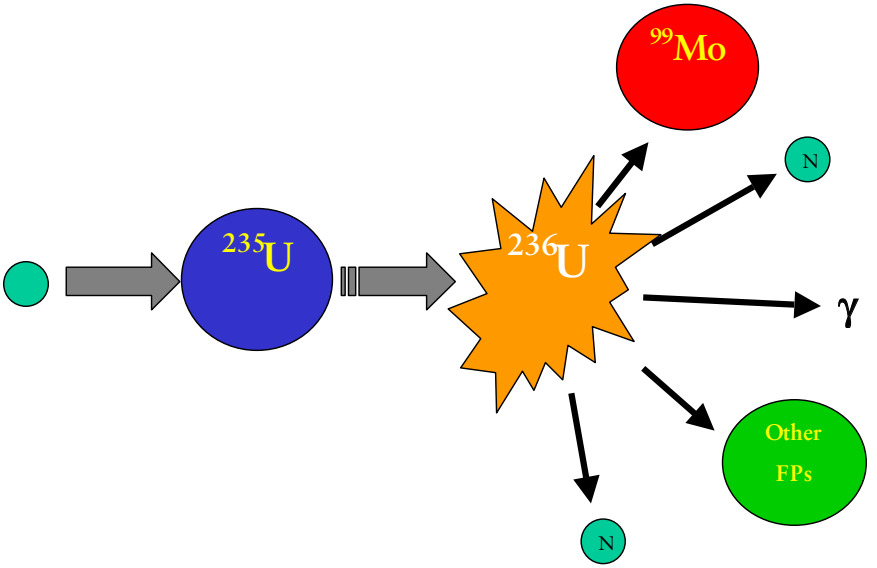

FIGURE D.1 Schematic representation of the uranium-235 fission process. N = neutrons and FPs = fission products.

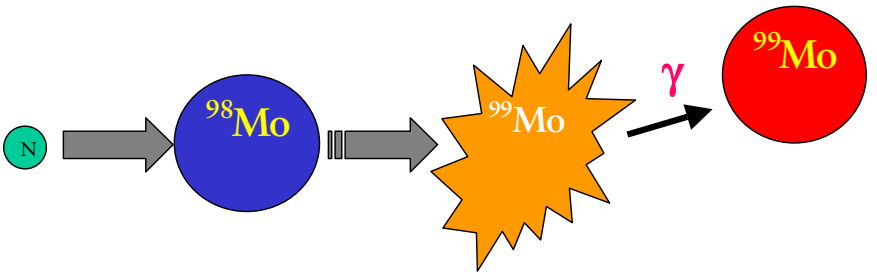

FIGURE D.2 Production of Mo-99 from neutron capture. N = neutron.

$$^{98}\mathrm{Mo}(\mathrm{n},\gamma)^{99}\mathrm{Mo}$$

The most commonly used alternative method for producing Mo-99 involves the neutron capture on an enriched target of Mo-98 (natural occurrence of Mo-98 is 24.13 percent), which is illustrated schematically in Figure D.2.

The fission cross section for thermal fission of U-235 is approximately 600 barns[1] which represents a very high probability. Of this, approximately

[1] 1 barn = 1×10^{-24} cm^2.

6.1 percent results in the production of Mo-99 or about 37 barns. The production cross section for the $^{98}Mo(n,\gamma)^{99}Mo$ reaction is about 0.13 barn for thermal neutrons, a factor of almost 300 less than the fission process even accounting for the 6.1 percent fission yield for Mo-99.

There are 6 stable isotopes (92, 93, 94, 95, 96, 97) of Mo and two very long-lived isotopes (98 is $>10^{12}$ years and 100 is $>10^{18}$ years). Both Mo-98 and Mo-100 have long enough half-lives that they exist in nature and can be used as target material. Thus the ability to produce large amounts of Mo-99 from the direct reaction route would depend upon the availability of a high flux reactor that could compensate for the lower cross section. For example, typical fluxes from the National Research Universal (NRU) reactor are around 1.5×10^{14} neutrons per cm^2 per second while the High Flux Isotope Reactor (HFIR) at Oak Ridge has a flux of 10^{15} neutrons per cm^2 per second, more than enough to be competitive in producing large amounts of Mo-99 via the (n,γ) approach.[2] However, these additional neutrons are not free and would add to the costs of producing Mo-99 by this method.

However, the Mo-99 produced by this process has a very low specific activity[3,4] because most of the Mo in the product is Mo-98. The specific activity for fission-produced Mo-99 is two to four orders of magnitude higher than from the neutron capture process (Ottinger and Collins, 1996). This has practical implications for using neutron capture Mo-99 in medical isotope procedures: First, the technetium generators that are used for fission-produced Mo-99 would have to be redesigned to use neutron capture-produced Mo-99. A larger technetium generator column would be needed, which would increase the size of the generator and the size and weight of its shield. A larger volume of liquid would be required to elute Tc-99m from the column, which would require all of the current Tc-99m kits (e.g., see Table 2.1) to be reformulated. In addition, the useful lifetime of the generator would be reduced due to the potential for higher breakthrough[5] of the Mo-99. This would require users to purchase additional generators.

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[2]If desired, the isotope could also be enriched in Mo-98 using mass separation processes.

[3]Specific activity is defined as the amount of radioactivity per unit mass as is usually expressed in terms of Becquerel's per gram or curies per gram.

[4]Delft University researchers are examining the feasibility of using Szilard Chalmers reactions to increase specific activities. However, the yields from this process are likely to be small, and a great deal of development work would likely be required to get to a useful, practical process, if indeed it is possible at all. See http://www.tudelft.nl/live/pagina.jsp?id=29b23a65-485b-44ee-9210-f460e363c2c6&lang=en. Accessed October 23, 2008.

[5]When the generator is eluted to obtain Tc-99m a very small amount of Mo-99 is released. The generator can no longer be used when the amount of Mo-99 in the eluted solution exceeds a certain level. The amount of breakthrough is roughly proportional to the amount of molybdenum present, both radioactive Mo-99 and nonradioactive Mo-98.

TABLE D.1 Comparison of Fission and Neutron Produced ^{99}Mo

$^{235}U(n,f)^{99}Mo$	$^{98}Mo(n,\gamma)^{99}Mo$
Produces high specific activity ^{99}Mo	Produces low specific activity Mo-99
Requires enriched ^{235}U target	Requires highly enriched Mo-98 target
Complex chemical processing	Simple chemical processing
Requires dedicated processing facility	Requires high flux neutron source
Generates high-level radioactive waste	Generates minimal waste

SOURCE: Modified from S. Mirzadeh, Oak Ridge National Laboratory.

Table D.1 compares the two methods of production.

Another point to consider, although of secondary importance, is the fact that several other radionuclides of medical importance are coproduced in the fission process and would require an alternative source (in particular ^{131}I and ^{133}Xe) in the case of a neutron capture process.

To make use of the neutron capture approach a number of technical challenges must be overcome not the least of which is the availability of the desired Tc-99m in a useful chemical form and of the same quality as the fission product for use with the many radiopharmaceutical *kits* now on the market. This point applies for all of the alternative processes discussed below.

ACCELERATOR PRODUCTION

There have been a number of proposals for accelerator production of Mo-99 as well as for direct production of Tc-99m. One accelerator-based approach essentially mimics the reactor production route in that the accelerator becomes the source of neutrons, which are then used to produce fission in a blanket of U-235 surrounding the neutron source. The required fluxes would be difficult to achieve in the required geometry to be competitive with reactor-generated neutrons. Such an accelerator would be expensive to build and operate although less expensive than a new reactor. Another approach would be to use an electron beam to generate high-intensity photons which in turn would be used to initiate a nuclear reaction on enriched Mo such that $^{100}Mo(\gamma,n)^{99}Mo$ creates the desired product (TRIUMF, 2008). The same issues as discussed above holds for this approach in addition to the technical challenges associated with producing a high-energy electron machine with sufficient beam flux to be able to produce sufficient Mo-99 to be competitive. That said, there are discussions around the design of electron linacs capable of accelerating tens of milliamps of electrons.

For both of these accelerator approaches multiple machines would be required since the fluxes of neutrons and photons would not be sufficiently

high to be competitive with a reactor. The cost of construction and operation of multiple machines would have to be analyzed to determine if a business case could be made for these approaches.

Another approach is photo-fission of U-238 using natural or depleted uranium targets. The challenge is the same as is mentioned for the other photon induced reaction (^{100}Mo(γ,n)^{99}Mo); that is, the need for a very high intensity beam to overcome the factor of about 1000 smaller cross section for this reaction versus neutron fission of U-235, although the fission yields are almost identical (approximately 6 percent).

The other option that has been explored is the direct production of Tc-99m from the ^{100}Mo(p,2n)^{99m}Tc. The biggest disadvantage with this approach is that the final product (the one used in nuclear medicine procedures) is directly produced and has a short half-life (6 hours). Thus, its usefulness would be greatly hampered if it needed to be shipped great distances to the end users. Even a network of suppliers would face a challenge. Takács et al. (2002) report that the cross section for the direct production of Tc-99m from enriched Mo-99 would be approximately 17 mCi/μAh. At this level even a very high beam current facility (500μA protons) and irradiation periods of a day (i.e., 24 hours), the most that could be produced in a single facility would be < 200 Ci per day. To meet the needs of the United States there would have to be more than 25 cyclotrons dedicated to this process. This does not take into account the losses associated with transport and chemical efficiencies for separating the Tc-99m from the target matrix. A single site might be able to become self-sufficient but this would not help the larger community.

Takács et al. (2002, 2003) explored the production of Mo-99 from the ^{100}Mo(p,pn)^{99}Mo reaction. Their results indicated a thick target yield (40–45 MeV) of 3.8 mCi/μAh. The daily production for a similar cyclotron would be about 50 Ci thus about 100 cyclotrons would be required for this approach.

The other approach would be through the spallation (high-energy projectile collides with the target nucleus with enough energy that a very large array of products is produced) of a target to produce Mo-99. The production rate of Mo-99 from most reasonable target materials would be at best many orders of magnitude lower than the reactor methods and two orders of magnitude lower than the above accelerator reactions and thus not a viable approach.

From this analysis there are few viable alternative approaches to the supply of Mo-99 or Tc-99m for widespread distribution. With the termination of the Maple reactor project, alternative approaches need to be explored in comparison to the cost of constructing and commissioning a new reactor facility, especially with photon-induced fission with U-238.

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Appendix E

Correspondence with Atomic Energy of Canada Limited

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

Nuclear and Radiation Studies Board

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July 23, 2008

Richard Cote
AECL
2251 Speakman Drive
Mississauga, Ontario
L5K 1B2

Dear Mr. Cote:

As a follow-up to my July 17 email message, I am sending along a list of questions (Attachment 1) from the Committee on Medical Isotope Production without Highly Enriched Uranium. This committee was appointed by the National Academies to carry out a U.S. Government-mandated study to assess the feasibility (including costs) of eliminating the use of highly enriched uranium (HEU) in medical isotope production; the impacts of HEU elimination on the reliability of medical isotope supply; and the progress being made by the Department of Energy and others to eliminate the use of HEU in research reactors, targets, and medical isotope production facilities. AECL's responses to these questions will help ensure that the committee's report to the U.S. Government is accurate and complete.

In connection with question 6 in the attachment, the committee requests that AECL provide a copy of its feasibility study on converting the Dedicated Isotope Facility to process low enriched uranium targets.

We recognize that some of the information we have requested may be business sensitive. The National Academies are willing to execute a non-disclosure agreement with AECL to facilitate access to this information. If desired by AECL, I can also arrange for a small group of committee and staff to visit your facility to review the feasibility study and discuss the questions in the attachment.

Please feel free to call me if you have questions or need additional information about this request or our study.

Sincerely,

Kevin Crowley
Study Director

ATTACHMENT
Questions to AECL

Note: The National Academies have been asked by the United States Government to evaluate the feasibility (including costs) of eliminating HEU use in medical isotope production; the impacts of such elimination on the reliability of medical isotope supply; and the progress being made by the Department of Energy and others to eliminate HEU use in research reactors, targets, and medical isotope production facilities. The following questions to AECL were developed by the National Academies Committee on Medical Isotope Production without Highly Enriched Uranium. These questions are designed to elicit the information the committee needs to develop a complete and accurate report on medical isotope production to the United States Government.

1. NRU life extension and potential impacts on Mo-99 production: AECL has announced plans to extend the operation of the NRU reactor from 2011 to 2016. The committee was told by Natural Resources Canada staff that this extension would involve "hundreds of millions" of dollars of work. (a) What replacements of major equipment or refurbishment does AECL anticipate will be necessary for NRU life extension? Is replacement of the calandria included in the planned work? (b) Can this work be carried out without an extended shutdown of NRU? (c) What impacts, if any, will this life extension work have on Mo-99 production at Chalk River? (d) How will AECL ensure that there are no supply disruptions while this life extension work is carried out?

2. Progress in understanding the positive coefficient of reactivity in the Maple Reactors: AECL announced in May 2008 that it was discontinuing development work on the Maple Reactors: (a) What progress had AECL made in understanding the coefficient of reactivity in the Maple Reactor prior to this announcement? Specifically, what tests had been run and data collected? (b) Was the decision to discontinue development work based on a technical judgment that the cause of the positive coefficient of reactivity was unlikely to be understood or fixed?

3. Plans for the Dedicated Isotope Facility: (a) What are AECL's plans for the Maple Reactors and New Processing Facility (e.g., mothball them, demolish them, sell them)? (b) Does AECL have any plans/interest in using the New Processing Facility for future Mo-99 production? (c) Has AECL carried out any studies or sought any advice on the feasibility of replacing the Maple reactor cores? If so, how much time would be required to design, build, install, and test new cores? (d) Would AECL consider an offer from an outside party to operate the Maples and New Processing Facility? (e) Could an outside party legally operate such facilities on the Chalk River Site?

4. Long-term Mo-99 supplies from Chalk River: The press has reported that it is MDS' position that AECL is obliged to provide Mo-99 for 40 years to meet its contract obligations. If AECL agrees, how will it acquire Mo-99 after the NRU reactor is shut down?

5. Development of an LEU-based Mo-99 production process: The committee understands that R&D work has been carried out at Chalk River to develop a conceptual design for an LEU target. (a) What was the nature of that work? (b) Was a physical LEU target ever developed? (c) Has any cold testing or radiotracer testing been carried out on unirradiated LEU targets to investigate target processing/Mo-99 recovery? (d) Have LEU targets having a similar design to NRU fuel been developed or tested?

6. Conversion of the Dedicated Isotope Facility to LEU-based production: The committee understands that AECL carried out a study to assess the feasibility of converting the Dedicated Isotope Facility to process LEU targets. (a) What were the results of that study? (b) Can the facility be converted to LEU-based Mo-99 production without major modifications? What would be the cost and time required for conversion? (c) If not, what modifications are required, and what would be the cost and time required for making them?

7. Coordinating the development of an LEU-based process with HEU-based production: (a) Is AECL carrying out or have any plans to carry out R&D work on conversion of Mo-99 production to LEU targets? (b) Are there any technical impediments to carrying out such R&D work using the NRU and New Processing Facility while HEU-based production is maintained in current facilities? (c) Is there enough spare irradiation capacity in the NRU to carry out such work?

8. Management of HEU waste from target processing: (a) Has AECL considered down-blending the HEU wastes from isotope production at Chalk River? (b) Does AECL have any plans to return these wastes to the United States?

9. Costs of producing Mo-99: The press has reported that AECL provides a $50 million annual subsidy to Mo-99 production at Chalk River. (a) Is this estimate accurate? If not, what is the annual subsidy? (b) What fraction of the federal government's subsidy to AECL for the operation of the NRU and other facilities is allocated to isotope production activities?

Appendix F

Present Value Calculation

In simple terms, a dollar received in the future is worth less than a dollar received today. One reason for this is inflation—a general increase in the prices of all goods and services. Suppose we assume, however, that there is no inflation or, equivalently that amounts measured in nominal (sometimes called current) dollars are converted into amounts measured in real (sometimes called constant) dollars. Individuals would still prefer a real (inflation-adjusted) dollar today to a real dollar in the future.

There are two main reasons. First, today's dollar could be invested and would yield a positive real return, thereby providing the opportunity to buy more goods in the future. Second, all things being equal, individuals would rather consume now than in the future. This means that the value of a dollar received in the future is discounted relative to a dollar received now. Mathematically, the present value, PV, of \$1 received in one year is

$$PV = \frac{1}{1+i}$$

where i is the appropriate real discount rate; it might, for example, reflect a company's real return on investment or an individual's real saving rate. The present value of \$1 received in n years' time is

$$PV = \frac{1}{(1+i)^n}$$

This term is called the *present value factor* or the *discount factor*. It equals the present value of $1 received in n years when the discount rate is i, compounded annually. For example, if a company receives $1 in 30 years time, and it uses a discount rate of 7 percent, then the present value factor is $1/(1 + .07)^{30} = 0.13$. In other words, $1 in 30 years' time is equivalent to 13 cents today. As amounts are received further in the future, n increases and the present value of that amount decreases.

Table 10.1 supposes that firms receive an incremental increase in revenues each year over a fixed number of years, 55 or 30. Such payment streams are called an annuity. The present value of an annuity of $1 received each year for 30 years, denoted a_i^n, equals

$$a_i^n = \frac{1}{(1+i)^1} + \frac{1}{(1+i)^2} + \quad + \frac{1}{(1+i)^n}$$

This can be shown to equal

$$a_i^n = \frac{1-(1+i)^{-n}}{i}$$

Thus, for example, the present value of an annuity of $1 per year received for 30 years at a discount rate of 7 percent would equal $12.41. Consequently, the present value of $7.02 million per year[1] for 30 years at a discount rate of 7 percent would equal $\$7.02 \times 12.41$ million = $87.1 million. This amount is rounded down to $85 million in Table 10.1.

[1] $\$225 \times 312{,}000 \times 0.10 = \$7.02$ million.

Appendix G

Glossary

6-day curies: The number of curies present in a shipment of Mo-99 6 days after it leaves a producer's facilities.
6-day curies per week: The number of 6-day curies supplied in a week.

Barns: A unit of measure of the fission cross section; 1 barn = 1×10^{-24} cm^2.
Becquerel (Bq): The SI derived unit of radioactivity, one Becquerel is equal to one radioactive disintegration per second.
Breakthrough: The contamination of Mo-99 in the Tc-99m eluted from the column of a technetium generator that occurs after prolonged use.
Brownfield conversion: Conversion within an existing processing facility or an unused facility with hot cells.

Calandria: A sealed drum-shaped vessel that contains the heavy-water moderator for the reactor. This vessel is penetrated by a series of horizontal fuel channels and vertical channels for control rods.
Casting: The process of melting a metal and pouring into a mold.
Cold rolling: Process in which metal sheets are rolled at room temperature to maintain the metal's original crystalline structure.
Cold testing: Testing conducted without the use of radioactive material.
Curie (Ci): A unit of radioactivity, defined as 1 Ci = 3.7×10^{10} decays per second.

Direct-use material: Material that is directly usable in nuclear weapons. Such materials include highly enriched uranium (HEU) and separated plutonium.

Dissolution: The process of putting a material into solution.

Downblend: Dilution of HEU with depleted uranium or natural uranium to convert it into low enriched uranium (LEU).

Drug master file (DMF): A document submitted to the Food and Drug Administration (FDA) by a Mo-99 producer describing the facility in which the Mo-99 is made; the production process itself, including any raw materials used in production; and product test methods, specifications, stability, and release criteria that may be used as a source of information when FDA approval is sought.

Eluting: Recovering an isotope (Tc-99m) by passing a saline solution through the alumina column of the generator.

Enriched uranium: Uranium with a higher concentration of the U-235 isotope than found naturally.

Enrichment: Process used to increase the concentration of the uranium-235 (U-235) isotope in a material relative to U-238.

Fission: Process whereby a large atomic nucleus (such as uranium) is split into two (and sometimes three) smaller nuclei.

Fission cross-section: Probability that a nucleus will capture a neutron and fission, usually expressed in barns.

Fission fragments: Smaller atomic fragments resulting from fission of a large nucleus.

Formula quantities: Special nuclear material in strategic quantities. For HEU this quantity is greater than 5 kg.

Greater-Than-Class-C waste: Radioactive waste that contains concentrations of certain radionuclides above the Class C limits in 10 CFR §61.55.

Greenfield construction: Construction of new facilities for producing and/or processing Mo-99.

Half-life: The time required for a quantity of radioactive material to decay to half of its initial value.

High-level waste: Highly radioactive materials containing fission products and transuranic elements produced as a byproduct of the reactions that occur inside nuclear reactors.

Highly enriched uranium: Uranium enriched to concentrations greater than or equal to 20 percent by weight of U-235.

Hot cell: Shielded workspace for working with highly radioactive materials.

Hot rolling: Heating metal above its recrystalization temperature before rolling it to form sheets.

Isomeric transition: Radioactive decay process in which the nucleus of a metastable isotope has an elevated energy state and releases this energy by emitting a gamma ray.

Large-scale producer: Producers of Mo-99 who supply more than 1000 6-day curies of Mo-99 per week to the market on a routine basis.

Low enriched uranium: Uranium enriched to concentrations less than 20 percent by weight of U-235.

Medical isotopes: Class of radioactive isotopes (radioisotopes) that have unstable nuclei and emit radiation. This radiation is used for medical imaging and treatment.

Neutron capture: Process involving the capture of neutrons by an atomic nucleus to form a heavier nucleus.

Neutron flux: Measure of the intensity of neutron radiation, defined as the number of neutrons crossing a unit area of a square centimeter in one second (neutrons/cm^2-s).

New drug application (NDA): A written application to the Food and Drug Administration seeking approval to sell a pharmaceutical in the United States.

Perfusion: Delivery of arterial blood to biological tissue.

Perfusion reserve: Capacity of flow through a blood vessel system in an organ under a stress or stimulus.

Regional producers: Producers who supply Mo-99 for indigenous or regional use in less than large-scale quantities.

Significant quantity: Approximate quantity of material from which the possibility of manufacturing a nuclear explosive device (i.e., a device that can achieve a prompt critical mass) cannot be excluded.

Special nuclear materials: Fissile material or material that is capable of sustaining a chain reaction of nuclear fission. It includes plutonium and uranium enriched in the isotopes U-233 or U-235.

Stenosis: Abnormal narrowing of a blood vessel.

Supplemental new drug application (sNDA): Additional written documentation submitted for approval by the FDA when a producer makes major changes to the process or raw materials it uses to make a pharmaceutical.

Target: Material containing U-235 that is designed to be irradiated in a nuclear reactor.

Target cladding: Target encapsulation of aluminum or stainless steel that serves to protect the chemically reactive uranium metal or alloy and to contain the fission products produced during irradiation.

Target meat: Uranium-bearing material in the target.

Tc-99m kits: Chemicals (e.g., pharmaceutical agent, chelating compound, and saline solution) used to formulate a radiopharmaceutical to which Tc-99m is added.

Technetium generator: Device used to store Mo-99 and extract its decay product Tc-99m.

Technetium generator curies: Calibrated quantity of Mo-99 based on the number of curies that are contained in the generator on the day of or day after its delivery to the radiopharmacy, hospital, or clinic.

Thermal neutron: Low-energy neutron of about 0.025 electron volts at room temperature.

Tracer testing: Evaluation of the separations methods and processing of targets using very small amounts of radioactive material.

Appendix H

Acronyms

ACCF	American College of Cardiology Foundation
ACRR	Annular Core Research Reactor
AECL	Atomic Energy of Canada Limited
AIPES	Association of Imaging Producers and Equipment Suppliers
ANL	Argonne National Laboratory
ANSTO	Australian Nuclear Science and Technology Organisation
ARI	ANSTO Radiopharmaceuticals and Industrials
ASNC	American Society of Nuclear Cardiology
ATR	Advanced Test Reactor
B&W	Babcock & Wilcox
BARC/BRIT	Bhabha Atomic Research Centre/Board of Radiation and Isotope Technology
BATAN	Indonesian National Atomic Energy Agency
BMS	Bristol-Myers Squibb
BR2	Belgian Reactor II
CERCA	Compagnie pour l' Etude et la Réalisation de Combustibles Atomiques
CFR	Code of Federal Regulations
CMR	Chemistry and Metallurgy Research
CMS	Centers for Medicare & Medicaid Services
CNEA	Comisión Nactional de Energía Atómica
CNSC	Canadian Nuclear Safety Commission

CORAR	Council on Radionuclides and Radiopharmaceuticals
CRADA	Cooperative Research and Development Agreement
CRP	Coordinated Research Project
CT	Computed tomography
DIF	Dedicated Isotope Facilities
DMF	Drug Master File
DOE	U.S. Department of Energy
DOE-NNSA	U.S. Department of Energy, National Nuclear Security Administration
DOS	U.S. Department of State
EOB	End of bombardment
EOI	Expression of interest
ESFRI	European Strategy Forum on Research Infrastructures
ETRR-2	Egyptian Testing Research Reactor II
FDA	U.S. Food and Drug Administration
FDG	2-deoxy-2-[^{18}F] fluoro-D-glucose (also called fluordeoxyglucose)
FISS	Fissile solution storage
FRM-II	Forschungsneutronenquelle Heinz Maier-Leibnitz (German: Research Reactor Munich II)
FRRSNF	Foreign Research Reactor Spent Nuclear Fuel
GE	General Electric
GTCC	Greater-than-class C
GTRI	Global Threat Reduction Initiative
HEU	Highly enriched uranium
HFETR-C	High Flux Engineering Test Reactor- China
HFIR	High Flux Isotope Reactor
HFR	High Flux Reactor
HIFAR	High Flux Australian Reactor
HLW	High-level waste
IAEA	International Atomic Energy Agency
INFCE	International Nuclear Fuel Cycle Evaluation
INL	Idaho National Laboratory
INVAP	Investigaciones Aplicadas Sociedad del Estado
IRE	Institut National des Radioéléments
KAERI	Korea Atomic Energy Research Institute

LEU	Low enriched uranium
LLW	Low-leve waste
MDP	Methylene diphosphonate
MIPS	Medical Isotope Production System
MIT	Massachusetts Institute of Technology
MNSR	Miniature Neutron Source Reactor
MOU	Memorandum of understanding
MRI	Magnetic resonance imaging
MTR	Materials Test Reactor
MURR	Missouri University Research Reactor
NBSR	National Bureau of Standards Reactor
NDA	New Drug Application
NECSA	Nuclear Energy Corporation of South Africa
NNSA	National Nuclear Security Administration
NPF	New processing facility
NRG	Nuclear Research and Consultancy Group
NRU	National Research Universal (reactor)
NTP	Nuclear Technology Products
OPAL	Open Pool Australian Lightwater (reactor)
OWR	Omega West Reactor
PET	Positron emission tomography
POLATOM	Institute of Atomic Energy Radioisotope Centre
R&D	Research and development
RERTR	Reduced Enrichment for Research and Test Reactors
RF	Russian Federation
RRRFR	Russian Research Reactor Fuel Return
sNDA	Supplemental New Drug Application
SPECT	Single photon emission computed tomography
SRS	Savannah River site
TCI	Technology Commercialization International
USNRC	U.S. Nuclear Regulatory Commission
USP	United States Pharmacopeia