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OPPORTUNITIES AND APPROACHES FOR SUPPLYING MOLYBDENUM-99 AND ASSOCIATED MEDICAL ISOTOPES TO GLOBAL MARKETS

PROCEEDINGS OF A SYMPOSIUM

Nuclear and Radiation Studies Board

Division on Earth and Life Studies

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

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The committees are indebted to the symposium presenters and session moderators who spent the time and effort to share their experience related to molybdenum-99 production and supply. They are listed in Appendix A.

The committees extend special thanks to the staff of the National Academies for supporting this study. Study director Dr. Ourania Kosti took the lead for organizing the symposium and was primarily responsible for shaping the symposium proceedings. Dr. Rita Guenther, senior program officer, assisted with the proceedings review and publication. Dr. Guenther also skillfully managed the logistics of the committees' meetings in Moscow, in close consultation with the Russian Academy of Sciences' committee chair, Prof. Stepan Kalmykov. Ms. Toni Greenleaf and Ms. Darlene Gros provided valuable advice on the symposium logistics and managed the travel arrangements.

This Proceedings of a Symposium was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies in making each published proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

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Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by Dr. Thomas J. Ruth, TRIUMF. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committees and the National Academies.

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Preface

The decay product of molybdenum-99 (Mo-99), technetium-99m (Tc-99m), is the most used medical isotope in diagnostic imaging worldwide. About 60-70 percent of the Mo-99 supplied globally is produced by irradiation of highly enriched uranium (HEU) solid targets in nuclear research reactors fueled by uranium. Irradiation causes uranium to fission [reaction: $^{235}U(n,f)^{99}Mo$] and to produce a number of isotopes including Mo-99, iodine-131 (I-131), and xenon-133 (Xe-133). Efforts to reduce and ultimately eliminate HEU from targets irradiated for medical isotope production are under way as part of an international threat reduction goal. In the United States, the U.S. Department of Energy's National Nuclear Security Administration (DOE-NNSA) is responsible for implementing the policy to reduce and ultimately eliminate HEU from civilian applications including medical isotope production.

Most Mo-99 in the world is supplied by companies in Australia, Belgium, Netherlands, South Africa, and, until recently, Canada.[1] Except for Australia, these companies rely on research reactors that were built in the 1950s and 1960s, and often shut down for scheduled or unscheduled maintenance. In 2009 and 2010, Mo-99/Tc-99m shortages occurred when Canada's NRU and Europe's HFR reactors were simultaneously shut down for extended periods. Supply of Mo-99 and Tc-99m is particularly sensitive to reactor shutdowns because they cannot be stockpiled for future shortages due to their short half-lives.[2]

A number of additions to the Mo-99/Tc-99m supply chain are emerging in other countries, including the United States and Russia. The United States, although the biggest consumer of Mo-99, has not produced Mo-99 since 1989. Several projects are under way to establish U.S.-based production of Mo-99 from non-HEU sources. Russia consumes small amounts of Mo-99 but has been producing this medical isotope for decades to cover the country's domestic demand and more recently for some exports of Mo-99 produced by irradiation of HEU targets. Since 2013, Russia has been increasing its Mo-99 production capacity and aspires to capture up to a 20 percent share of the global market. Details on Russia's Mo-99 production plans and associated timelines have not been announced. On one hand, the sale of Russian-produced Mo-99 to global markets could help improve supply reliability. On the other hand, the sale of Russian HEU-sourced Mo-99 could interrupt the full adoption of current market and policy trends toward production of Mo-99 from non-HEU sources.

The 2016 National Academies of Sciences, Engineering, and Medicine report (NASEM, 2016) recommended that the U.S. government pursue opportunities for engagements between U.S. and Russian scientific and technical organizations to better understand Russia's plans related to Mo-99 production. This recommendation led

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[1] According to NASEM (2016) these companies account for about 95 percent of the global supply of Mo-99 for medical use.

[2] The half-life of Mo-99 is 66 hours, and that of Tc-99m is 6 hours.

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Sidebar P.1
Statement of Task

The U.S. National Academies of Sciences, Engineering, and Medicine (the National Academies) and the Russian Academy of Sciences will organize a joint symposium to discuss opportunities and approaches for supplying molybdenum-99 (Mo-99) and associated medical isotopes (iodine-131 and xenon-133) to global markets. The symposium will address the following topics:

- Trends in global demand and supply for Mo-99 and associated medical isotopes.
- Prospects and approaches for developing new global supplies of Mo-99 and associated medical isotopes.
- Technical, regulatory, economic, and policy considerations for producing Mo-99 and associated medical isotopes for global markets using uranium fission and other processes.

The symposium presentations and discussions will be summarized in a National Academies proceedings that will be issued in English and Russian.

DOE-NNSA to ask the National Academies to host a symposium, with the objective of bringing together U.S., Russian, and other international experts to promote the establishment of working relations among global experts, especially U.S. and Russian experts, and a common understanding of global supply chain needs and requirements. The focus of the symposium was intended to be on Mo-99 production and to a lesser extent on other medical isotopes that are co-produced, for example, I-131 and Xe-133.

The symposium titled *Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets* was held July 17-18, 2017, at the International Atomic Energy Agency (IAEA) in Vienna, Austria. It was co-hosted by the National Academies and the Russian Academy of Sciences in cooperation with the IAEA. The symposium featured a range of presentations[3] on the topics listed in the statement of task (see Sidebar P.1). About 85 individuals from 17 countries participated in the symposium.[4]

The symposium was organized by a committee of U.S. experts appointed by the National Academies and a committee of Russian experts appointed by the Russian Academy of Sciences. The symposium organizing committees met four times over the course of the study. Two of these meetings were joint meetings with a quorum of U.S. and Russian committee members: in April 2017, in Moscow, Russia, to plan the symposium, and in July 2017, in Vienna, Austria, to hold the symposium and create an outline of the symposium proceedings. The third meeting took place in October 2017 in Washington, D.C., to finalize the symposium proceedings. That meeting lacked participation of Russian committee members due to the United States' temporarily suspending issuance of visas in Russia.[5] The fourth meeting took place in November 2017 in Moscow to receive comments on the symposium proceedings from the Russian committee.

This Proceedings of a Symposium was jointly authored by the U.S. and Russian symposium organizing committees and is published in both English and Russian. The committees are responsible for the overall quality and accuracy of the proceedings as a record of what transpired at the symposium. Although the symposium committees are responsible for the content of this proceedings, any views contained in the proceedings are not necessarily those of the committees, the National Academies, or the Russian Academy of Sciences. This proceedings does not contain findings, conclusions, or recommendations.

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[3] See Appendix A for the symposium agenda and Appendix B for short biographical information on the symposium organizing committee members and speakers.

[4] See Appendix C for list of symposium participants.

[5] See http://www.nbcnews.com/news/world/u-s-suspends-russia-nonimmigrant-visas-tit-tat-fallout-n794416.

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The proceedings is organized into seven chapters.

- Chapter 1 summarizes the July 17-18, 2017, symposium opening remarks from the IAEA, the National Academies, and the Russian Academy of Sciences.
- Chapter 2 provides an introduction of Mo-99/Tc-99m in nuclear medicine.
- Chapter 3 provides an overview of the current (as of July 2017) Mo-99 supply.
- Chapter 4 describes HEU- to LEU-sourced Mo-99 production conversion challenges and opportunities for research and development.
- Chapter 5 describes Mo-99 supply reliability.
- Chapter 6 describes prospects for future Mo-99 supply.
- Chapter 7 describes issues related to Mo-99 supply sustainability.

Each chapter summarizes information obtained during the presentations and discussions that took place at the symposium. The proceedings is intended for the reader with some prior knowledge on the Mo-99 supply chain and Mo-99/Tc-99m production methods. The joint committees suggest that non-expert audiences read the reports titled *Molybdenum-99 for Medical Imaging* (NASEM, 2016), *Medical Isotope Production Without Highly Enriched Uranium* (NRC, 2009), and *2017 Medical Isotope Supply Review: 99Mo/99mTc Market Demand and Production Capacity Projection 2017-2022* (OECD-NEA, 2017) for background information.

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Acronyms and Abbreviations

AIPES	Association of Imaging Producers and Equipment Suppliers
ANM	ANSTO Nuclear Medicine
ANSTO	Australian Nuclear Science and Technology Organisation
BARC	Bhabha Atomic Research Centre
CARR	China Advanced Research Reactor
CIIC	Canadian Isotope Innovations Corp
Ci	curie
CNEA	Comisión Nacional de Energía Atómica (National Atomic Energy Commission)
CNNC	China National Nuclear Corporation
CRP	coordinated research projects
CT	computed tomography
EC	European Commission
EMA	European Medicines Agency
EOB	end of bombardment
EU	European Union
FCR	full cost recovery
HEU	highly enriched uranium
HLG-MR	High-Level Group on the Security of Supply of Medical Radioisotopes
IAEA	International Atomic Energy Agency
INVAP	Investigacion Aplicade (Nuclear Engineering International)
KAERI	Korea Atomic Energy Research Institute
KJRR	Kijang Research Reactor

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LEU	low-enriched uranium
LINAC	linear accelerator
MIPR	Medical Isotope Production Reactor
Mo-99	molybdenum-99
MURR	University of Missouri Research Reactor
N/A	not applicable
NASEM	National Academies of Sciences, Engineering, and Medicine
NDA	New Drug Application
NNSA	National Nuclear Security Administration
NWMI	Northwest Medical Isotopes
OECD-NEA	Organisation for Economic Co-operation and Development's Nuclear Energy Agency
PET	positron emission tomography
RAS	Russian Academy of Sciences
RIAR	Research Institute of Atomic Reactors
RMB	Brazilian Multipurpose Research Reactor
SCK•CEN	Belgian Nuclear Research Centre
SPECT	single-photon emission computed tomography
SPECT-CT	single-photon emission computed tomography-computed tomography
Tc	technetium
U.S. DOE	U.S. Department of Energy
U.S. FDA	U.S. Food and Drug Administration
U.S. NRC	U.S. Nuclear Regulatory Commission

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Glossary

Anti-trust refers to government policy to prevent abuse of dominant position in the market or the existence of cartels (definition provided by Mr. Jan Velthuijsen, PricewaterCoopers).

Available production capacity is the maximum amount of molybdenum-99 (Mo-99) that can be produced or supplied on a routine basis (NASEM, 2016).

Breakthrough is the process of Mo-99 being co-eluted with technetium-99m (Tc-99m) from a technetium generator. The contamination of Tc-99m with Mo-99 can interfere with radiopharmaceutical production, reduce image quality, and expose patients to unnecessary radiation (NASEM, 2016).

Centralized nuclear pharmacy is a nuclear pharmacy contracted by hospitals/medical centers to produce and provide radiopharmaceuticals. Most of the nuclear pharmacies in the United States today are "centralized" nuclear pharmacies. The concept of centralized nuclear pharmacy is not widespread; most countries continue to use individual nuclear pharmacies.

Conventional molybdenum-99 production method refers to uranium fission production in a research reactor. *Alternative* molybdenum-99 production method refers to any other reactor- or nonreactor-based production method.

Elution is the process by which Tc-99m is obtained from technetium generators.

Full cost recovery is the pricing of services to recover the full cost of production of Mo-99 to ensure a sustainable supply.

Half-life (denoted as $t_{1/2}$) is the time required for half of the atoms of a given radioisotope to decay to another isotope (NASEM, 2016).

High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR, see https://www.oecd-nea.org/med-radio/security/) is a group established in 2009 by the Organisation for Economic Co-operation and Development's Nuclear Energy Agency to examine the underlying causes of global Mo-99/Tc-99m shortages and recommend

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actions to ensure adequate supplies in the future. The HLG-MR comprises approximately 40 experts representing the governments of 17 countries as well as from the European Commission and the International Atomic Energy Agency. The work of the HLG-HR was recently extended to the end of 2018.

Highly enriched uranium is uranium enriched in uranium-235 (U-235) to concentrations greater than or equal to 20 weight percent. HEU enriched to 90 percent or above is referred to as *weapons-grade* HEU. The primary concern with civilian utilization of HEU is its potential diversion by terrorists to make nuclear explosive devices (NASEM, 2016).

Highly enriched uranium-sourced Mo-99 production is a term used throughout this proceedings to indicate use of HEU targets to produce Mo-99. The use of HEU-fueled reactors for Mo-99 production is not addressed in this proceedings.

Low-enriched uranium is uranium enriched in U-235 to concentrations lower than 20 weight percent.

Neutron capture is a method to produce Mo-99 by irradiating natural or enriched Mo-98 targets and capturing a neutron (n) and transmuting to Mo-99 after emitting a gamma ray.

Outage reserve capacity is capacity maintained by irradiation facilities or processing facilities to allow rapid scale-up of Mo-99 production to meet demand when other irradiation or processing facilities shut down for scheduled or unscheduled maintenance. In recent years, Mo-99 suppliers have started to pay for the costs for maintaining the outage reserve capacity; this capacity is referred to as *paid outage reserve capacity*.

Six-day curie is the quantity used to price and sell Mo-99. It is the measurement of the remaining radioactivity of Mo-99 six days after the time of measurement.

Specific activity is radioactivity per unit mass, usually expressed as becquerel (Bq) per gram or curies (Ci) per gram (NASEM, 2016). Mo-99 produced by fission is of high specific activity, that is, more than 10,000 curies per gram (Ci/g). Mo-99 produced by neutron capture is of much lower specific activity, about 0.1-1 Ci/g.

Supply reliability refers to the current ability of the supply chain to deliver Mo-99/Tc-99m to meet demand.

Supply sustainability refers to the ability of the supply chain to continue long term to deliver Mo-99/Tc-99m to meet demand.

Uranium fission is a process to produce Mo-99 by irradiating U-235 targets.

Welfare is a term used in economics to describe the allocation of benefits (financial, health, other) between producers and consumers of a country. On the subject of Mo-99 production and supply, welfare can be transferred from one country to another, if the producing country subsidizes production by using taxpayers' money and the Mo-99 is supplied to other countries in which patients are benefited without having to carry the full costs of the Mo-99/Tc-99m testing. In this example, the producing country loses welfare and the receiving countries gain welfare.

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Overview

Participants of the July 17-18, 2017, symposium titled *Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets* examined current trends in molybdenum-99 production, prospects for new global supplies, and technical, economic, regulatory, and other considerations for supplying molybdenum-99 to global markets. The symposium was co-hosted by the National Academies of Sciences, Engineering, and Medicine and the Russian Academy of Sciences in cooperation with the International Atomic Energy Agency. It was intended to promote the establishment of working relationships among global experts, especially U.S. and Russian experts, and a common understanding of global supply chain needs and requirements. The symposium was attended by about 85 individuals from 17 countries. Discussions can be summarized as follows:

Molybdenum-99/Technetium-99m Demand (Chapter 2). The decay product of molybdenum-99, technetium-99m, is used in about 80 percent of all nuclear medicine procedures worldwide. Utilization of technetium-99m has declined globally. In the United States, the largest consumer of molybdenum-99/technetium-99m, several factors have contributed to the decline, including changes in medical insurance reimbursement policies, increased preference for competing imaging modalities, widespread acceptance and further development of appropriate use criteria, radiation exposure concerns, and more efficient use of technetium-99m. Apart from China, no other country represented at the symposium indicated a projected increase in molybdenum-99 demand in the near future.

Current Molybdenum-99 Supply (Chapter 3). As of July 2017, almost all molybdenum-99 for medical use is produced by irradiating solid uranium targets in six research reactors, and is supplied to the global market by four companies in Australia, Belgium, Netherlands, and South Africa. Existing smaller suppliers, with plans to expand production, are located in Argentina and Russia. All of these suppliers, except Russia, are either in the final stages of converting production from using highly enriched uranium (HEU) to low-enriched uranium (LEU) targets or already produce molybdenum-99 using LEU targets.

A representative of the Russian State Atomic Energy Corporation, Rosatom, noted that Russia realizes that selling non-HEU-sourced molybdenum-99 is a recognized requirement for producers aspiring to capture a share of the global market. The representative added that Rosatom, for economic reasons, has chosen not to prioritize conversion of production from using HEU to LEU targets in existing reactors but instead to invest in alternative non-HEU production methods with a goal of capturing up to a 20 percent share of the global market in the future.

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Conversion from HEU- to LEU-Sourced Molybdneum-99 Production Challenges (Chapter 4). Conversion from HEU- to LEU-sourced molybdenum-99 production has been a challenging process. Target manufacturers, reactor operators, and molybdenum-99 suppliers have had to resolve several technical problems related to LEU target fabrication and processing, target validation, and radioactive waste management. Conversion has taken two of the existing global producers about 6-7 years, and one global producer is still resolving conversion-related technical challenges. These challenges were described by several participants as greater than anticipated and requiring large capital investments. The transition to an all-LEU-sourced production has been challenging for other members of the supply chain including generator manufacturers and nuclear pharmacy operators.

The challenges of conversion from HEU- to LEU-sourced molybdenum-99 production have generated several opportunities for research and development to improve production and processing efficiencies and radioactive waste management. Three such activities were described at the symposium: Korea's high-density LEU target development, Germany's FRM-II reactor research group's proposed extraction process, and Australia's radioactive waste treatment technology.

Molybdenum-99 Supply Reliability (Chapter 5). Since the 2009-2010 molybdenum-99 supply shortages, governments and industry have taken several actions to improve the reliability of the molybdenum-99/technetium-99m supply chain. These actions include increasing production capacity and outage reserve capacity, monitoring and reviewing the supply chain to identify periods of potential risk, investing in the durability of the supply, coordinating reactor schedules, enhancing communications among supply chain participants, and developing backup agreements between producers and reactor operators. Many symposium participants noted that the supply market is more reliable today as a result of these actions. However, according to the Organisation for Economic Co-operation and Development's Nuclear Energy Agency, bringing new capacity to the market is important to reduce risks of future shortages.

Prospects for Molybdenum-99 Future Supply (Chapter 6). Several countries are planning to develop new capabilities to produce molybdenum-99. These countries include the United States, Russia, Argentina, Brazil, Canada, China, Egypt, India, Netherlands, and South Korea. All of these new capabilities involve non-HEU-based technologies. Representatives of the planned projects provided information on the current status of capability development and the projected dates when molybdenum-99 would be supplied to the market. These dates ranged from 2018 to about 2025. Representatives of Russia's three new projects that involve alternative, non HEU-based molybdenum-99 production methods, did not provide similarly detailed projections. One explanation given was that these Russian projects are at initial stages of development and it is too early to predict their success or provide a schedule for completion.

Some of the projects discussed at the symposium rely on technologies not yet proven for large-scale commercial molybdenum-99 production. Symposium participants, including some current producers, commented that the schedules for molybdenum-99 production provided by some potential producers were ambitious and do not account for the time needed for development, industrialization, and validation of the different molybdenum-99 production methods. In addition to the market-readiness challenge, other participants raised the market penetration challenge: If all aspirant molybdenum-99 producers were to enter the market, global production capacity would far exceed current demand and needed outage reserve capacity. Without an indication that global demand for molybdenum-99 is likely to increase substantially in the next few years, this additional global production capacity cannot be absorbed by the market.

It is possible, however, that introduction of new production capacity from countries that previously relied on imports to cover domestic molybdenum-99 needs has a different market effect. That is, molybdenum-99 produced by smaller local/regional producers may be preferred over molybdenum-99 purchased from global producers owing to favorable transportation logistics that improve supply reliability, possible cost advantages, and other factors. As several countries become self-sufficient for molybdenum-99 supply, existing global producers could lose part of their current supply share.

Molybdenum-99 Supply Sustainability (Chapter 7). The historic pattern of government subsidization of medical isotope production has proven to lead to market sustainability issues. To create a sustainable molybdenum-99/

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technetium-99m market, the High-Level Group on the Security of Supply of Medical Isotopes agreed on six principles in 2011; full cost recovery is one of these principles. Currently, the methodology for estimating molybdenum-99 production costs used by the different producers is not publicly disclosed and implementation of full cost recovery is self-assessed without an independent review of the assessment.

Several symposium participants offered comments on their company's or organization's views on adoption of the full cost recovery principle. These comments highlight the range of existing and anticipated differences in estimating molybdenum-99 production costs and interpreting full cost recovery.

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Opening Remarks

The symposium featured representatives from the International Atomic Energy Agency (IAEA), the National Academies of Sciences, Engineering, and Medicine (National Academies), and the Russian Academy of Sciences providing opening remarks. This chapter summarizes their addresses.

INTERNATIONAL ATOMIC ENERGY AGENCY

The IAEA is an independent international organization that is related to the United Nations system. Mr. Christophe Xerri (Department of Nuclear Energy, IAEA) and Ms. Meera Venkatesh (Department of Nuclear Sciences and Applications, IAEA) opened the symposium with welcoming remarks and introductory comments on the significance of ensuring a reliable and sustainable medical isotope supply. The IAEA has played a central role in reviewing available technologies for production of molybdenum-99 (Mo-99)/technetium-99m (Tc-99m) (see, e.g., IAEA, 2015, 2017) and assisting Member States with evaluation of options and adoption of technologies to produce Mo-99 and other medical isotopes by

1. Promoting scientific and technical cooperation and transfer of nuclear technologies to Member States; and
2. Establishing coordinated research projects (CRP) between developed and developing countries.

Mr. Joao Osso (IAEA) informed the symposium participants about a CRP titled *New Ways of Producing Tc-99m and Tc-99m Generators*. The objective of the CRP is to create guidelines for enhancing and strengthening the capabilities of Member States in developing alternative routes for the production of Mo-99/Tc-99m, in particular using linear accelerators. The CRP also aims to provide guidelines for optimization of the performance of low- and medium-specific-activity generators. The CRP was open for proposals at the time of this writing.

THE NATIONAL ACADEMIES

Dr. Ourania Kosti (National Academies) provided introductory comments on behalf of Dr. Hedvig Hricak (Memorial Sloan Kettering Cancer Center), chair of the National Academies committee that organized the symposium. She noted that the National Academies have been tasked by the U.S. government to report on issues related to medical isotope production at least three times in the recent past:

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- In 2007, the National Academies issued a report titled *Advancing Nuclear Medicine Through Innovation* (IOM and NRC, 2007). The report was authored by a committee chaired by Dr. Hedvig Hricak. It highlighted several emerging opportunities in nuclear medicine, but cautioned that "deteriorating infrastructure and loss of federal research support are jeopardizing the advancement of nuclear medicine."
- In 2009, the National Academies issued a report titled *Medical Isotope Production Without Highly Enriched Uranium* (NRC, 2009) The report was authored by a committee chaired by Dr. Christopher Whipple (ENVIRON, retired). This study was carried out under a congressional mandate contained in the Energy Policy Act of 2005 to examine the technical and economic feasibility of producing medical isotopes without highly enriched uranium (HEU). The study report concluded that production of medical isotopes without HEU was economically and technically feasible.
- In 2016, the National Academies issued a report titled *Molybdenum-99 for Medical Imaging* (NASEM, 2016). The report was authored by a committee chaired by Dr. S. James Adelstein (Harvard Medical School). That study was carried out under another congressional mandate contained in the American Medical Isotopes Production Act of 2012 to examine progress made toward establishing U.S.-based production of Mo-99 and eliminating worldwide use of HEU from reactor targets and medical isotope facilities. The study report concluded that despite efforts from both existing global suppliers and potential domestic (to the United States) suppliers, any delays in bringing additional supplies of Mo-99 to the market would increase the risks of shortages.

The report also noted Russia's aspiration to become a global producer of Mo-99 without a commitment or schedule for eliminating HEU from reactor targets. The report recommended that the U.S. government pursue opportunities for engagements between U.S. and Russian scientific and technical organizations to better understand Russia's plans related to Mo-99 production.

Dr. Kosti noted that this recommendation likely led the U.S. Department of Energy's National Nuclear Security Administration (DOE-NNSA) to ask the National Academies to host the symposium on *Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets*. The objective of the symposium was to bring together U.S., Russian, and other international experts to promote the establishment of working relationships among global experts, especially U.S. and Russian experts, and to foster a common understanding of global supply chain needs and requirements. The symposium was organized on the premise that sale of Russian-produced Mo-99 to global markets could help further improve supply reliability. However, the sale of Russian HEU-sourced Mo-99 could interrupt the full adoption of current market and policy trends toward production of Mo-99 from non-HEU sources. Russia is investing in non-HEU Mo-99 production methods because it realizes that selling non-HEU-sourced Mo-99 is a recognized requirement for producers aspiring to capture a share of the global market. (See Chapter 6 for more information.)

RUSSIAN ACADEMY OF SCIENCES

Prof. Stepan Kalmykov (Moscow State University), chair of the symposium organizing committee of the Russian Academy of Sciences, recognized the significance of collaboration and cooperation between the U.S. and Russian academies in areas of mutual interest, which include nuclear applications. Since 1959, collaboration has been conducted in the form of visits of experts, exchanges of scientific publications and materials, technical meetings, symposia, joint studies, and research projects.

In carrying out their joint activities, the two academies have cooperated often with relevant international organizations, notably the IAEA. The symposium on *Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets* is an example of the inter-academies and IAEA cooperation.

In closing, Prof. Kalmykov honored the memory of his colleague, Academician Nikolai Laverov, who passed away in 2016. Academician Laverov was vice president of the Russian Academy of Sciences and chairman of the scientific-technical Council of the State Corporation, Rosatom. An expert in the field of geology and nuclear energy, Academician Laverov was a strong proponent and supporter of exchange of knowledge and information between U.S. and Russian scientists. Academician Laverov was recognized for his scientific achievements and

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collaborative spirit in many countries outside Russia, including the United States. He was elected a foreign member of the National Academies in 2005, for his leadership in the uses of uranium and for the direction of national and international programs for the management of radioactive waste.

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2

Molybdenum-99/Technetium-99m in Nuclear Medicine

The decay product of molybdenum-99 (Mo-99), technetium-99m (Tc-99m), is used in about 80 percent of all nuclear medicine procedures worldwide. It is the isotope of choice for single-photon emission computed tomography (SPECT) because of its 140-keV gamma-ray emission, its convenient half-life of 6 hours, and availability in the form of Mo-99/Tc-99m generators.

DEMAND FOR MOLYBDENUM-99/TECHNETIUM-99M

The United States is the largest consumer of Tc-99m, carrying out 50 percent of all procedures that utilize Tc-99m worldwide, or approximately 40,000-50,000 procedures daily. Dr. Wolfgang Weber (Memorial Sloan Kettering) noted that in the United States, myocardial perfusion imaging for coronary artery disease dominates the overall demand for Tc-99m owing to the high prevalence of coronary artery disease and the relatively large amounts of Tc-99m needed to image for the disease. A second major application of Mo-99/Tc-99m is whole-body imaging for detection of bone metastases and to a lesser extent for benign bone diseases such as inflammation. Other applications include sentinel node imaging before surgery for breast cancer or melanoma, as well as for thyroid, lung, and renal imaging.

Utilization of Mo-99/Tc-99m has declined globally. The National Academies reported a 45 percent decline in Tc-99m utilization in the United States based on analysis of Medicare[1] data for the period 2006-2014 (NASEM, 2016). The decline continued in 2015 based on more recent analysis (see Figure 2.1). Dr. Ourania Kosti (National Academies) noted that the decline started in 2006 or earlier, that is, before the 2009-2010 Mo-99 shortages, for reasons not attributable to supply disruptions. Several factors contributed to the decline, including changes in medical insurance reimbursement policies, increased preference for competing imaging modalities, widespread acceptance and further development of appropriate use criteria, radiation exposure concerns, and more efficient use of Tc-99m. According to the 2016 National Academies report, these factors are likely to continue to operate and result in further decline of Mo-99 demand. Indeed, articles have been published since the release of the 2016 NASEM report, indicating additional changes in medical insurance reimbursement policies related to medical imaging aiming to reduce medical costs.[2] The 2016 National Academies report also noted a 25 percent decline

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[1] Medicare is the federal health insurance program in the United States for people 65 years of age and older and for those with permanent disabilities.

[2] See, for example, http://www.modernhealthcare.com/article/20170826/NEWS/170829906 and http://www.dailypress.com/news/.

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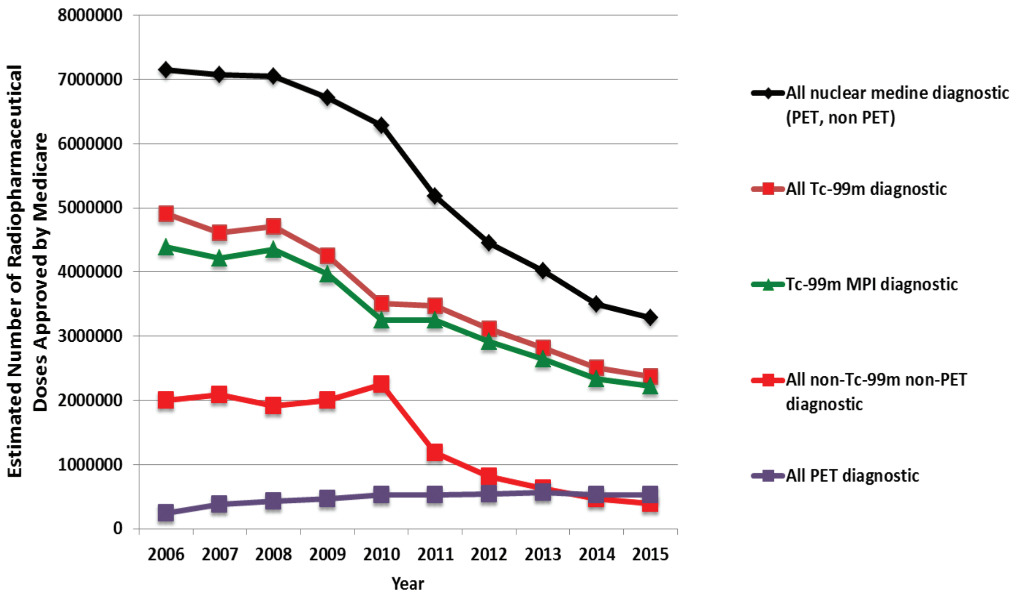

FIGURE 2.1 Estimated utilization of nuclear medicine diagnostic radiopharmaceuticals by Medicare beneficiaries: 2006-2015.
NOTE: CPT Copyright American Medical Association. All rights reserved. CPT is a registered trademark of the American Medical Association.
SOURCE: Courtesy of Dr. Kathryn Morton, University of Utah.

in I-131 and Xe-133 utilization (see Figures 2.2 and 2.3), medical isotopes that are co-produced with Mo-99 in research reactors and can be recovered for use in medical applications.

Dr. Weber noted that new camera systems that improve the resolution of Tc-99m images together with improved software for data analysis and multimodal imaging such as SPECT/computed tomography (CT) have the potential to increase the future demand for Mo-99/Tc-99m or at least keep the demand stable. However, he noted that development of new Tc-99m radiopharmaceuticals has been slow in the past two decades and therefore unlikely to contribute to increases in Tc-99m utilization in the near future. The most recent Tc-99m agent to be approved by the U.S. Food and Drug Administration was Tc-99m tilmanocept (Lymphoseek™) in 2013 (Agrawal et al., 2015). Most research and development in radiopharmaceuticals has focused primarily on positron emission tomography (PET) imaging agents owing to their higher sensitivity and easier quantification of PET signals.

The Organisation for Economic Co-operation and Development (OECD)'s Nuclear Energy Agency (NEA) considers that current

- Global demand for Mo-99 is 9,000 six-day Ci/week (2015 estimate), and
- Demand growth rate for Mo-99 is 0.5 percent for mature markets (Europe, Japan, North America, Oceania, and South Korea) and 5 percent per year for developing markets (South America, Africa, and Asia) (2014 estimates).

Dr. Jin Du (China Isotope & Radiation Corporation) confirmed that in China, Mo-99/Tc-99m utilization has increased by 5 percent during the past 5 years. He noted that the Chinese Society of Nuclear Medicine is focusing on efforts to develop nuclear medicine programs in the country and on training nuclear medicine physicians. These investments in nuclear medicine programs will likely result in further growth of Mo-99 demand in China.

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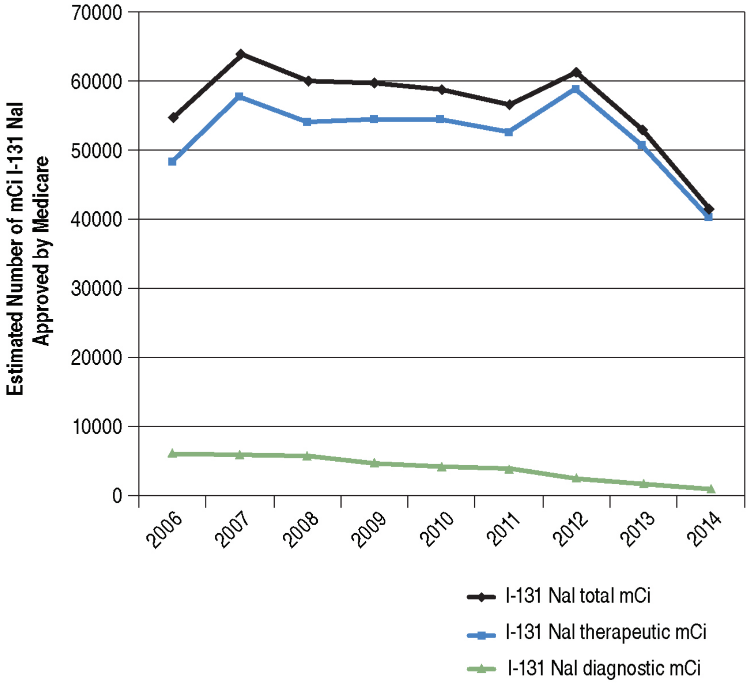

FIGURE 2.2 Estimated utilization of I-131 by Medicare beneficiaries: 2006-2014 (NASEM, 2016).

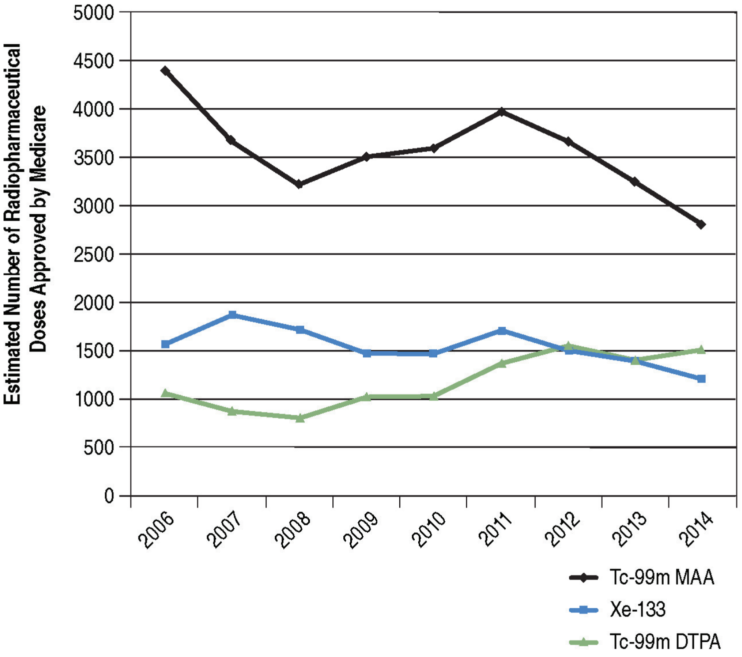

FIGURE 2.3 Estimated utilization of Xe-133 by Medicare beneficiaries, 2006-2014.
NOTE: Most of Xe-133 studies are carried out in conjunction with Tc-99m macroaggregated albumin (MAA) lung perfusion imaging for the diagnosis of pulmonary embolism. The other ventilation agent in wide use in the United States is Tc-99m pentatate (DTPA) aerosol (an off-label use of an FDA-approved agent for renal and brain imaging) (NASEM, 2016).

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Apart from China, no other country represented at the symposium indicated a projected increase in Mo-99 demand in the near future.[3]

NUCLEAR MEDICINE PROGRAM DEVELOPMENT

The IAEA has been tracking information related to trends in nuclear medicine worldwide and has reported considerable variability across countries in infrastructure, technology, and educational resources for implementing nuclear medicine practice, training, and research. Mr. Rodolfo Nuñez-Miller (IAEA) noted that Africa is the continent with the largest disparities in relation to nuclear medicine applications: of Africa's 54 countries only half have nuclear medicine programs.

The IAEA helps Member States develop, expand, and operate nuclear medicine facilities. It has focused on providing assistance for developing nuclear medicine programs in low- and medium-income countries to help overcome several challenges these countries face related to

- Training a multidisciplinary team of professionals, including physicians, medical physicists, radiographers, and radiochemists;
- Assessing the impact of introducing novel high-cost health technologies and their sustainability;
- Purchasing and utilizing high-cost equipment for nuclear medicine imaging and laboratory equipment for the nuclear pharmacy and providing for quality control;
- Managing potential increases in healthcare costs; and
- Complying with international standards where there is a lack of adequate infrastructure, quality assurance culture, and qualified human resources to do so.

The IAEA's support for nuclear medicine programs is provided through technical cooperation projects. For example, the IAEA may assist Member States in designing nuclear medicine expansion projects, capacity building, fellowship training, providing equipment and supplies, and auditing quality management. Mr. Nuñez-Miller noted that expansion or development of nuclear medicine programs requires strong and committed support from the national government. He also noted that development of nuclear medicine programs takes a long time, a minimum 4 years. This lag time from initiating the development of nuclear medicine programs to offering nuclear medicine tests needs to be considered when projecting Mo-99/Tc-99m utilization trends in emerging markets.

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[3] Mo-99 demand may be increasing in other developing and developed countries not represented at the symposium. The countries represented at the symposium are currently producing Mo-99 or have plans to produce Mo-99. Countries with no current or planned Mo-99 production were not represented at the symposium.

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3

Current Molybdenum-99 Supply

As of July 2017, almost all molybdenum-99 (Mo-99) for medical use was being produced by irradiating solid uranium targets in the six research reactors listed below (available production capacity of the reactors is shown in parentheses) and illustrated in Figure 3.1.

- BR-2, Belgium (7,800 six-day Ci/week)
- HFR, Netherlands (6,200 six-day Ci/week)
- LVR-15, Czech Republic (3,000 six-day Ci/week)
- Maria, Poland (2,700 six-day Ci/week)
- OPAL, Australia (2,150 six-day Ci/week)
- SAFARI-I, South Africa (3,000 six-day Ci/week)

All reactors except OPAL and SAFARI-I (since August 2017) irradiate highly enriched uranium (HEU) targets. Mo-99 produced in these reactors is supplied to the global market by four companies in Australia (Australian Nuclear Science and Technology Organisation [ANSTO]), Belgium (Institut National des Radioelements [IRE]), Netherlands (Curium), and South Africa (NTP Radioisotopes). In addition to these reactors, smaller amounts of Mo-99 are produced in other reactors, for example, the RBT-6 and RBT-10a (available production capacity is 1,000 six-day Ci/week) and WWR-c (350 six-day Ci/week) in Russia, and the RA-3 reactor (400 six-day Ci/week) in Argentina. The Russian reactors irradiate HEU targets, and the Argentinian reactor irradiates low-enriched uranium (LEU) targets.

All Mo-99 suppliers except those in Russia are either in the final stages of converting production from using HEU to LEU targets or already produce Mo-99 using LEU targets.

Two irradiation facilities, the OSIRIS reactor in France and the NRU reactor in Canada, contributed to the Mo-99 supply until December 2015 and October 2016, respectively. The OSIRIS reactor permanently stopped operating; the NRU reactor is kept in hot standby and could resume production until March 2018 to support global Mo-99 supply and avoid Mo-99 shortages.

The following sections summarize information that was provided at the symposium on the countries and companies that supply Mo-99 produced in currently operating reactors.

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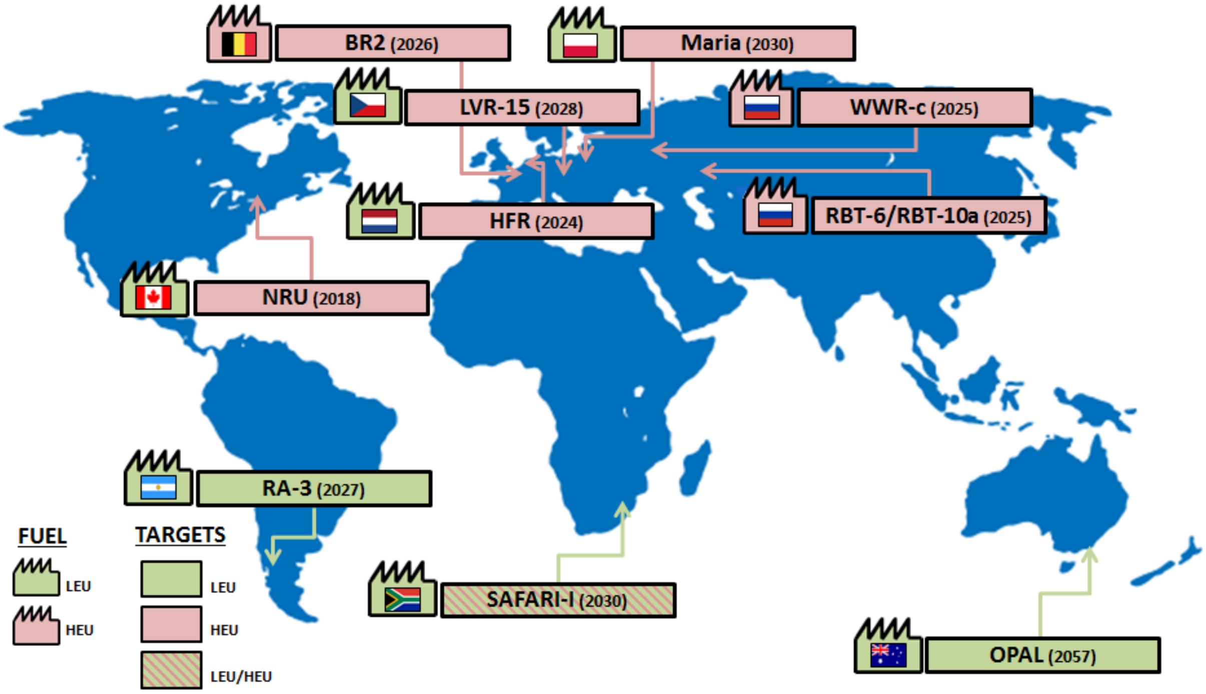

FIGURE 3.1 Current Mo-99 supply map as of July 2017.
NOTE: Most Mo-99 is produced in reactors in Belgium (BR-2), Netherlands (HFR), the Czech Republic (LVR-15), Poland (Maria), Australia (OPAL), and South Africa (SAFARI-I). Smaller amounts of Mo-99 are produced in Russia (RBT-6/RBT-10a and WWR-c) and Argentina (RA-3). The NRU reactor in Canada is on "hot standby" and could resume production until March 2018 to support global Mo-99 supply. The estimated end of operation for the reactors is shown in parentheses. The schematic indicates whether a reactor irradiates HEU or LEU targets and whether it operates using HEU or LEU fuel.

AUSTRALIA

Mr. Michael Druce represented the Australian company ANSTO located in Lucas Heights, a suburb of Sydney. ANSTO is a statutory body of the Australian government and produces Mo-99 commercially by processing LEU targets. This approach was adopted first at the HIFAR reactor and, since 2007, at the OPAL reactor. ANSTO can produce about 2,150 six-day Ci/week of Mo-99 (up from 1,200 six-day Ci/week in 2016). ANSTO's production capacity is expected to increase to 2,650 six-day Ci/week in the fourth quarter of 2017 upon commissioning of the new processing facility, which is part of the ANSTO Nuclear Medicine (ANM) project, and further increase to 3,500 six-day Ci/week in the first quarter of 2018. ANSTO also produces I-131 (by irradiating tellurium targets) and other isotopes used in nuclear medicine.

ANM is a joint initiative from the Australian government and ANSTO dedicated to commercial Mo-99 production and will be operated as a subsidiary of ANSTO. An advantage of the ANM facility is that it can maximize production and supply during critical demand periods, typically over weekends and in response to reactor outages.

Mr. Druce discussed several challenges that ANSTO faces as the company gradually expands Mo-99 production. These challenges involved

1. Ensuring that expansion of Mo-99 production did not affect other reactor activities;
2. Developing storage solutions for the additional intermediate-level radioactive waste (see Chapter 4 for a description of ANSTO's long-term radioactive waste management solution); and
3. Ensuring that emissions of noble gases such as xenon are maintained at regulatory-permissible levels.

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BELGIUM

Mr. Jean-Michel Vanderhofstadt represented the privately owned Belgian company IRE, located in Fleurus. IRE can produce 3,600 six-day Ci/week of Mo-99 (up from 2,500 six-day Ci/week in 2016) by processing HEU targets irradiated at HFR, BR2, and LVR-15 reactors. IRE also produces I-131 through fission and is the exclusive supplier of Xe-133 to the U.S. market.

IRE began its LEU conversion project in 2010 and anticipates completing it in 2018 after it resolves the technical challenges it faces during conversion. It estimates Mo-99 production capacity after conversion to be about 3,500 six-day Ci/week. IRE has not yet received approvals from drug regulators to sell LEU-sourced Mo-99. IRE plans to convert I-131 production to LEU after the Mo-99 conversion is complete, possibly in 2018, and to convert Xe-133 production in 2019.

NETHERLANDS

Mr. Roy Brown represented Curium, a new company created in April 2017 following the merging of IBA Molecular and Mallinckrodt Nuclear Medicine LLC. Curium produces Mo-99 at the Petten site in Netherlands. It can produce 4,500 six-day Ci/week (up from 3,500 six-day Ci/week in 2016) by processing HEU targets irradiated at HFR, BR-2, and Maria reactors. Curium's production capacity is expected to increase to 5,000 six-day Ci/week by the end of 2017.

Curium began its LEU conversion project in 2010 and anticipates completing it by the end of 2017. During that time the company has resolved several technical challenges and has received approval from various drug regulators to sell LEU-sourced Mo-99 (see Chapter 4 for more information provided by Mr. Brown).

SOUTH AFRICA

Mr. Gavin Ball represented the South African company NTP, a subsidiary of the South African Nuclear Energy Corporation located in Pelindaba (west of Pretoria). NTP can produce 3,500 six-day Ci/week (up from 3,000 six-day Ci/week in 2016) by processing LEU and HEU (45 percent uranium enrichment) targets irradiated at SAFARI-I. NTP has been increasing Mo-99 production from LEU targets each year: it was 38 percent in 2014; 47 percent in 2015; 77 percent in 2016, and 95-100 percent in 2017. Production has been solely LEU-sourced since August 2017. NTP also produces I-131 via fission.

NTP began its LEU conversion project in 2008 and was the first large-scale producer to achieve routine production of Mo-99 from LEU sources in 2011. The company has regulatory approvals to sell LEU-based I-131.

RUSSIA

Dr. Vladimir Risovaniy (Rosatom Headquarters), Mr. Alexey Vakulenko (JSC Isotope), Dr. Oleg Kononov (Karpov Institute), Dr. Victor Skuridin (Tomsk Polytechnic University), and Dr. Evgeniy Nesterov (Tomsk Polytechnic University) presented information on Russian institutions and their respective Mo-99/Tc-99m production and supply.

Mo-99/Tc-99 in Russia is produced in four facilities:

- Karpov Research Institute of Physical Chemistry (Karpov Institute) in Obninsk, Kaluga Region. Mo-99 at Karpov is produced by irradiating HEU targets at the WWR-c reactor.
- Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad. Mo-99 at RIAR is produced by irradiating HEU targets at the RBT-6 and RBT-10a reactors.
- The Khlopin Radium Institute in St. Petersburg. Mo-99 at the Khlopin Radium Institute is produced via neutron capture [reaction: $^{98}\text{Mo}(n,\gamma)^{99}\text{Mo}$] by irradiating Mo-98 targets in the RBMK-reactor[1] at Leningrad Nuclear Power Plant.

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[1] Russian for high-power channel-type reactor. Currently, there are 11 reactors of this type in Russia located at the Leningrad, Kursk, and Smolensk nuclear power plants.

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- The Nuclear Physics Research Institute at Tomsk Polytechnic University, in Tomsk, Siberian Federal District. Mo-99 at Tomsk Polytechnic University is also produced via neutron capture. Production at this facility was suspended in 2015 and is expected to resume in 2018.

The Karpov Institute, RIAR, and the Khlopin Radium Institute are enterprises owned and operated by the Russian State Atomic Energy Corporation, Rosatom. Mo-99 produced in these institutes is distributed to the domestic market to meet current demand estimated to be around 100 six-day Ci/week and since 2012 to the international market (Latin America, Asia, and the Middle East) by the joint stock company JSC-Isotope, also a Rosatom enterprise. In 2016, JSC Isotope supplied about one-third of Rosatom's production capacity (about 400 six-day Ci/week) and estimates its global market share to be about 5 percent.

Khlopin Radium Institute and Tomsk Polytechnic University supply the Mo-99/Tc-99m produced only to the domestic market and do not currently have additional production capacity for exports. At Khlopin Radium Institute, a stationary technetium generator is used to elute Tc-99m for distribution to the St. Petersburg area. Supply of Mo-99 from Khlopin Radium Institute is equivalent to about 10 six-day Ci/week. Supply from Tomsk Polytechnic University, which is also about 10 six-day Ci/week, is distributed to the Siberian, Ural, and Far East regions.

Russian experts from the Rosatom enterprises were asked to present on activities related to conversion from irradiating HEU to LEU targets for Mo-99 production but they chose not to do so. Instead they offered some remarks on the topic during the symposium discussion sessions.

Mr. Risovaniy noted that Russia, along with all other countries that were represented at the symposium, realizes that to enter the global Mo-99 market by selling uranium fission-based Mo-99, it needs to convert to LEU-sourced production by irradiating LEU targets. However, Rosatom has chosen not to prioritize conversion. He explained that although the company has the technical expertise to successfully convert, conversion is not an economical solution for Russia to reach the goal of capturing a large share of the Mo-99 market. This is due to the large costs of converting and maintaining LEU-sourced Mo-99 production and the challenge to recover these costs in the spirit of full cost recovery (see more on full cost recovery in Chapter 7). Rosatom is focusing on new projects that rely on alternative technologies for producing Mo-99 without HEU (see Chapter 6). Mr. Risovaniy added that if these projects fail for technical or other reasons, Rosatom may then decide to focus on conversion to LEU-sourced production at RIAR and the Karpov Institute. He did not provide an estimate of how long he thinks it would take RIAR and Karpov to convert their reactors to irradiating LEU targets, if they chose to focus on conversion. Other symposium participants highlighted that experience from Curium, and NTP showed that conversion is a longer process than anticipated. As noted earlier in this proceedings, it took existing global Mo-99 producers about 6-7 years to convert, and one global producer (IRE) is still resolving technical challenges.

Dr. Kononov confirmed that explorations related to conversion from irradiating HEU to LEU targets at the WWR-c reactor are proceeding at a slow pace by performing experiments to test a conversion plan. He also noted that the Karpov Institute is working toward expanding Mo-99 production capacity at the WWR-c reactor to 700 six-day Ci/week by changing the current uranium target configuration and chemical processing. Dr. Kononov estimated that this project could take about 2 years to complete.

ARGENTINA

Dr. Pablo Cristini represented the Argentinian government agency National Atomic Energy Commission (Comisión Nacional de Energía Atómica [CNEA]), which is in charge of the country's nuclear energy research and development. Argentina has been producing Mo-99 for medical applications since 1985 at the RA-3 reactor designed and constructed by CNEA.[2] It was the first country to convert its small-scale Mo-99 production to LEU in 2002 and has been routinely producing about 400 six-day Ci/week for several years. Production at RA-3 covers national demand and about a third of Brazil's demand. RA-3 also produces other medical isotopes and can produce xenon-133.

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[2] Dr. Cristini noted that CNEA has transferred, jointly with INVAP, the technology for fission radioisotope production with LEU to Egypt, Australia, Algeria and, more recently, to India.

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4

Conversion to Low Enriched Uranium–Sourced Production and Opportunities for Research and Development

Mr. Jeff Chamberlin (U.S. Department of Energy's National Nuclear Security Administration) commended global producers for recognizing the international threat reduction goal of eliminating highly enriched uranium (HEU) from medical isotope production facilities and investing in conversion from HEU- to low-enriched uranium (LEU)-sourced molybdenum-99 (Mo-99) production. He added that the technical progress these producers have made with conversion in a relatively short period is enormous: In 2009, a National Academies report (NRC, 2009) concluded that conversion of large-scale Mo-99 production is technically feasible and less than 10 years later (likely by the end of 2018) global production of Mo-99 would predominantly be from non-HEU sources.

However, conversion from HEU- to LEU-sourced Mo-99 production has been a challenging process, and Mo-99 producers and target manufacturers have had to resolve several technical challenges related to LEU target fabrication and processing, target validation, and radioactive waste management. The transition to an all-LEU-sourced production has also been challenging for other members of the supply chain, including generator manufacturers and nuclear pharmacy operators. Some of these challenges were discussed at the symposium and are summarized in the following sections.

TECHNICAL CHALLENGES OF CONVERSION

The experience of conversion from HEU- to LEU-sourced Mo-99 production has been similar for global producers Curium, IRE, and NTP. Conversion took about 6-7 years (IRE is still resolving some technical challenges), and the associated challenges were described by representatives of these companies as greater than anticipated and requiring high capital investments. In addition, the operating costs for maintaining LEU-sourced production are also high. Mr. Gavin Ball (NTP) noted that these challenges came with no benefit to the patient because HEU- and LEU-sourced Tc-99m are identical in terms of diagnostic potentials.

Target Fabrication and Processing

The reduction of U-235 enrichment in HEU to LEU targets is 4.7-fold. Therefore, LEU targets with the same design and dimensions as HEU targets would produce about 5 times less Mo-99 because of the lower U-235 content. This reduction in efficiency led producers to invest in improving efficiency of LEU targets by modifying the target composition.

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Mr. Roy Brown described two issues Curium faced with LEU target fabrication due to the introduction of impurities: First, the aluminum alloy cladding that was selected contained a metallic impurity that formed oxides and clogged the uranium filter used during the target processing. The company solved this issue within about 6 months by designing and validating a new uranium filter that could handle the metallic impurity load. Second, the target manufacturing process at CERCA (French acronym for Company for the Study of Atomic Fuel Creation), a subsidiary of AREVA, introduced another metallic impurity into the LEU targets, that is, contamination with radioactive tungsten (tungsten-187 [W-187]), a chemical analog of molybdenum. CERCA's Bertrand Stepnik explained that the same amount of impurity is present in HEU targets but because of the lower U-235 content in an LEU target, the relative percentage of impurity increased by a factor of five compared to the U-235 inside the HEU target. The issue, which was also faced by the other global producers who purchase targets from CERCA, was resolved after CERCA set in place certain manufacturing controls.

Target Validation

After fabrication, the LEU targets have to be validated in all the reactors used by the Mo-99 producer. For Curium and IRE, this means validation in three reactors for each company. Mr. Brown said that unexpected shutdowns of the HFR and Maria reactors and the long-scheduled shutdown of BR-2 during Curium's validation runs caused delays in the company's conversion schedule. Mr. Vanderhofstadt and Mr. Brown mentioned that IRE and Curium had to compete for reactor irradiation time to validate their targets and to stay on schedule with their conversion plans. This has proven problematic for IRE's target validation schedule and qualification of LEU targets for irradiation in the HFR reactor, a reactor both companies use for Mo-99 production.

Operational Challenges

In addition to target manufacturing and validation challenges, there are operational challenges related to LEU-sourced Mo-99 production. Because more LEU targets need to be irradiated to produce Mo-99 equivalent to that of the HEU targets, more irradiation positions within a reactor are utilized. This allows for less space in a reactor for irradiation of other targets and also requires adjusting target irradiation strategies to ensure that production of other products generated in the reactor is not affected.

Mr. Ball noted that during the transition period from HEU to LEU, NTP was producing and supplying Mo-99 from both sources, which was causing "logistical nightmares" because of the different processes and training of staff involved.

Radioactive Waste Management

LEU-sourced Mo-99 production leads to increased volumes of radioactive waste, particularly liquid waste, because of the decreased production yield. Existing global Mo-99 suppliers are developing additional capacity to manage these wastes as part of their conversion efforts and the waste management costs are high. These higher waste volumes led one producer (ANSTO) to develop a technology for radioactive waste treatment, which is described later in this chapter.

DRUG REGULATORY APPROVAL CHALLENGES

When converting target material from HEU to LEU, the Mo-99 produced needs prior approval by each national drug regulatory agency within the country the generator manufacturer markets its generators. Mr. Ira Goldman (Lantheus Medical Imaging) described the validation tests needed for U.S. Food and Drug Administration (U.S. FDA) approval, and Mr. Roy Brown (Curium) described the filing process with the regulatory agencies to receive approval to sell LEU-based Mo-99 in the United States, Europe, Canada, and Asia.

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Validation Process

Lantheus Medical Imaging purchases Mo-99 from ANSTO, IRE, and NTP for production of technetium generators aimed primarily for the U.S. market. Lantheus' supply of LEU-sourced technetium generators constitutes about 50 percent of its total supply. The company aims to convert to an all-LEU Mo-99 supply in 2018. As part of its all-LEU conversion plan, Lantheus will purchase Mo-99 supplied by ANSTO's new ANM facility. To do that the company will need to file a "prior approval supplement" with the U.S. FDA because ANM will be irradiating targets of different design from those irradiated currently by ANSTO. Mr. Goldman anticipates that the U.S. FDA approval procedure will likely be "straightforward" because ANM will be using targets and processes similar to those used by NTP, one of the current Mo-99 suppliers to Lantheus.

The validation process for Mo-99 produced at ANM will involve Lantheus performing qualification tests in three generator sizes followed by testing of kit labeling. These validation studies could take about 2 months to complete. The U.S. FDA has a 4-month statutory review period. Therefore, commercialization of technetium generators that use Mo-99 from ANM is anticipated to take about 6 months.

A similar validation process will be followed for obtaining regulatory approval for marketing IRE's LEU-sourced Mo-99 in 2018.

Drug Regulatory Submissions

Curium is both a Mo-99 producer and a technetium generator manufacturer. Mr. Brown noted that Curium's drug regulatory submissions were approved by drug regulatory authorities in Europe, the United States, and Asia within 2-4 months from the time of filing. According to Mr. Brown, the rapid approval was attributed to the commitment and collaboration between drug regulatory agencies and Curium's careful global regulatory planning, which involved coordination of the submissions to the different regulatory agencies and engagement with the regulators at different stages of the conversion project.

Curium engaged in discussions with the regulators as early as 5 years prior to the date the submissions were made in order to inform the regulators about the anticipated processes and receive feedback and provide updates as the project was progressing. Curium had regular meetings closer to submission to better understand what information the regulatory authorities were anticipating and the type of appropriate submission. Following submission, the company made "polite contact," when appropriate, to receive an update on the review schedule.

Curium had dedicated regulatory affairs groups that were tasked with investigating the submission requirements for the different regulatory authorities, coordinating submission schedules, and responding consistently to the regulators' questions and concerns. An example of schedule coordination was the filing with European and Asian regulators: The Asian regulators required that the company had EU approval prior to submitting for approval in Asia. Curium used the European Commission's work-sharing provision for submissions to European health authorities. (See Sidebar 4.1 for more information on the regulatory approval process in Europe.)

NUCLEAR PHARMACY OPERATIONAL CHALLENGES

Mr. David Pellicciarini (Cardinal Health) noted that, with respect to conversion from HEU- to LEU-sourced technetium generators, nuclear pharmacies do not need to seek any regulatory approvals. For example, they are not involved in validation studies that are part of the technetium generator approval process, although they may be asked by generator manufacturers who are seeking to have their generators approved to provide some cold kits for testing. Also, the nuclear pharmacies' radioactive material licenses are not affected by conversion from HEU- to LEU-sourced technetium generator production. Although from a regulatory perspective, conversion from HEU- to LEU-sourced Mo-99 production has no effect in the nuclear pharmacy's operations, operators face some challenges during the transition from HEU- to LEU-sourced Mo-99 production.

During the transition, some nuclear pharmacies may be dispensing radiopharmaceutical doses using both HEU- and LEU-sourced generators. Mr. Pellicciarini described three challenges that Cardinal Health's nuclear pharmacies in the United States are facing:

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Sidebar 4.1
Drug Regulatory Approval Process in Europe

Mr. Brendan Cuddy, European Medicines Agency (EMA) described the European Union's (EU's) two processes for authorizing medicines: a centralized process and a national process. In the centralized process, pharmaceutical companies submit a single marketing-authorization application to EMA, the agency that regulates the medicinal products marketing authorization through various committees. Once granted, a centralized marketing authorization is valid in all EU Member States. The majority of medicines available in the EU are authorized at the national level, following the EU Member State's national authorization procedures. Marketing of technetium generators in Europe is authorized at the national level. Several regulatory procedures were put in place to facilitate the regulatory approval process of selling low-enriched uranium (LEU)-based technetium generators in the Europe.

Regulatory authorities in Europe initially considered conversion to LEU-sourced Mo-99 production a type II variation, that is, the highest level of variation to marketing authorizations involving "substantial change to the starting material and to manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product." More recently, industry sources have reported that a number of their submissions have been classified as a type 1B variation, which is the next level of variation down and requires a simpler level of assessment.

Additional actions to minimize the risk of delay of approvals of variations in existing marketing authorizations supporting conversion from highly enriched uranium (HEU) to LEU were taken by the European Commission in the form of provisions to Commission regulation No. 1234/2008 (EU, 2008) concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products. These are work-sharing and grouping provisions.

The work-sharing provision was placed in effect to "avoid duplication of work in the evaluation of variations to the terms of several marketing authorisations. . . ." According to the provision, one authority, selected from among the competent authorities, assesses the variation on behalf of the other concerned authorities. The grouping provision was placed in effect to "facilitate the review of the variations and reduce the administrative burden." According to the provision, companies can group a set of changes that affect more than one medicinal product into one variation if all concerned marketing authorizations are affected by the exact same group of variations.

The entry into force of a mutual recognition agreement between the EU and the United States is also expected to benefit the radiopharmaceutical sector exporting to both territories. Specifically, the benefits to manufacturers are eliminating duplication of inspections from different authorities, waiving of testing of imported products, and encouraging greater international harmonization. The benefits to the regulatory authorities are encouraging greater international harmonization, better use of resources, and ability to focus on sites of higher risk.

A third provision allows for assessment of active substance master files by one regulatory authority on behalf of the others through the active substance master file work-sharing procedure. The procedure was established to harmonize assessment of submissions and avoid inconsistent decision making and requests for changes from different regulatory authorities. The provision was originally intended only to be for new active substance master files and new procedures, but following discussions between EMA and Member States, it was agreed that this work-sharing procedure would be opened for companies who have radiopharmaceutical marketing authorizations to recognize the situation that many are in, with regard to filing new active substance master files to change from HEU to LEU.

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1. Operations are less efficient. LEU doses can only be dispensed from LEU-sourced technetium generators but HEU doses can be dispensed by combining technetium from an HEU- or LEU- sourced generator. Combining Tc-99m from multiple generators allows for increased operational efficiencies. Strictly dispensing LEU doses could result in HEU-sourced generators not being fully utilized during the transition period.
2. Operations are more complex. With two generators available, nuclear technicians have to pay attention to whether the customer specifically requested an LEU-sourced dose, ensure that the LEU-sourced generator was used for that dose, and confirm that the paper trail accompanying the dose dispensed and shipped is correct. The latter is particularly important for customers who are seeking the $10 per dose additional reimbursement on purchases of radiopharmaceuticals sourced from non-HEU generators.[1]
3. Issues exist with contingency planning and traceability. Not all nuclear pharmacies within the Cardinal Health chain purchase both HEU- and LEU-sourced generators and therefore not all nuclear technicians are trained to operate in a nuclear pharmacy that dispenses doses from both HEU- and LEU-sourced generators. If one nuclear pharmacy temporarily closes and its customers need to be supported by a different nuclear pharmacy within the chain, staff may need to be trained in managing both HEU- and LEU-sourced purchases.

Mr. Pellicciarini noted that these operational challenges will be removed when full transition to LEU-sourced Mo-99 is complete.

OPPORTUNITIES FOR RESEARCH AND DEVELOPMENT

The challenges of conversion from HEU- to LEU-sourced Mo-99 production has provided several opportunities for research and development to improve production and processing efficiencies and manage the larger volumes of radioactive wastes. Although the symposium organizing committees did not solicit presentations from representatives of all research and development efforts related to Mo-99 production under way, three of these activities were described at the symposium.

High-Density Low-Enriched Uranium Target Development

Conventional HEU aluminum alloy targets have 1.1-1.4 g uranium per cubic centimeter (U/cm^3), and LEU aluminum alloy targets have 2.6-2.7 g U/cm^3. To obtain Mo-99 at "per target" levels equivalent to currently available HEU targets, the density of LEU targets needs to be 8-9 g U/cm^3. The Korea Atomic Energy Research Institute (KAERI) has been developing a process for production of high-density UAl_x[2] targets with uranium density of 3.2 g U/cm^3 with the possibility of increasing it to above 9 g U/cm^3.

Dr. Ul-Jae Park (KAERI) noted that conventional UAl_x targets are produced by using pulverized UAl_x powders through five steps of melting, casting, heat treatment, component analysis, and crushing. Aspherical powder of uranium alloys can be produced by centrifugal atomization. Using this technique KAERI can increase uranium content to 4.6 g U/cm^3 and a uranium content of 9.0 g U/cm^3 is also achievable by using U-metal powders produced by the centrifugal atomization technology.

Compared with conventional pulverized UAl_x powders, KAERI's powders have spherical shape, smoother surfaces, and smaller surface area. These differences may lead to minor differences in dissolution behaviors during the chemical process of the targets. KAERI anticipates that development of high-density LEU targets will be completed in 2021, and the institute could start supplying the targets to the global market after that.

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[1] This regulation was issued by the U.S. Centers for Medicare and Medicaid Services in 2012.

[2] UAl_x refers to a mixture of intermetallic compounds of uranium and aluminum resulting from melting and casting of a uranium-aluminum binary system.

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Future Efficient Molybdenum-99 Extraction Process

The decrease in yield per target and increase in liquid radioactive waste production following LEU-sourced Mo-99 production motivated a research team at the FRM-II reactor in Germany to develop two projects to regain yield and to reduce the amount of liquid radioactive waste produced during Mo-99 purification. These projects were summarized by Dr. Rianne Stene (FRM-II).

The first project focuses on developing a cylindrical LEU target with mechanically separable cladding. Since the cladding can be mechanically (as opposed to chemically) separated from the target before processing, the liquid wastes produced during target processing would be less. Further, the monolithic uranium foils promise increased yield. According to Dr. Stene, this target design is ready for industrial fabrication.

The second project focuses on developing a dry-chemical technique for Mo-99 processing and purification. The technique takes advantage of the chemical and physical properties of fluorides to achieve the separation of molybdenum from uranium. This project is in early development stages.

Synroc Waste Treatment Technology

ANSTO has for about 40 years invested in research and development of a technology called *synroc* (short for synthetic rock) to provide a matrix for immobilization and final disposal of various types of intermediate-level and high-level radioactive wastes, including long-lived actinide-rich waste streams. In the synroc process, the radioactive liquid waste is mixed with additives to create a slurry that is then dried to produce a free-flowing powder. The resultant powder is first thermally treated and then dispensed into cans and sealed. The cans are hot isostatically pressed, heated, and then pressure is applied. Under these conditions the powdered mixture is formed into a solid ceramic or glass ceramic block of well-defined composition. The canister is designed to collapse and form a cylindrical shape suitable for maximum waste storage efficiency.

Dr. Bruce Begg (ANSTO) highlighted three advantages of the synroc technology:

1. Maximum waste volume reduction that minimizes disposal costs,
2. Chemical durability of the waste form that reduces environmental risk, and
3. Versatility of the range of effective waste-form compositions that allows for treatment of different waste streams.

ANSTO is currently designing and building a synroc waste treatment plant (expected to be operational from late 2019) as part of the ANM project. The liquid waste from ANM processes will be stored for decay for at least 2 years prior to treatment by the synroc process. The synroc canisters will be sent to Australia’s proposed National Radioactive Waste Management Facility (NRWMF). The location of the NRWMF is currently being finalized and the facility is expected to start operations by the mid-2020s.

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5

Supply Reliability

The 2009-2010 molybdenum-99 (Mo-99) supply shortages that occurred when Canada's NRU and Europe's HFR reactors were simultaneously shut down for extended periods exposed the vulnerabilities of the Mo-99 supply. Vulnerabilities included the aging and not-well-maintained reactor infrastructure, less than optimum coordination of reactor operating and maintenance schedules, and lack of options for increasing production from operating reactors during shortages. Since the 2009-2010 shortages, governments and industry have taken several actions to improve the reliability of the Mo-99/Tc-99m supply chain. These actions include increasing production capacity and outage reserve capacity; monitoring and reviewing of the supply chain to identify periods of potential risk; investing in the durability of the supply; coordinating reactor schedules; enhancing communications among supply chain participants; and developing backup agreements between producers and irradiators. Many symposium participants including Mr. Roy Brown (Curium), Mr. Jean-Michel Vanderhofstadt (IRE), and Dr. Kathrine Smith (Australian Embassy and Permanent Mission to the International Atomic Energy Agency in Vienna) noted that the supply market is more reliable today because of all these actions.

Dr. Kennedy Mang'era (Canadian Isotope Innovations Corp. [CIIC]) disagreed that the existing supply chain has reached a satisfactory level of reliability. He pointed out that an unexpected simultaneous shutdown of two reactors with high Mo-99 production capacity (for example the BR-2 and HFR reactors in Europe) could still lead to severe supply shortages.[1] Dr. Smith and others responded to the comment by stating that the likelihood of the scenario of two reactors shutting down unexpectedly and simultaneously is low because of actions taken by governments and industry to prevent that scenario from happening. In addition, if this scenario were to occur, the enhanced communication channels that are in place today can mitigate the consequences of reactor shutdowns and prevent supply disruptions.

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[1] In November 2017, Mo-99 production at NTP was halted "because of non-compliance with licensing conditions." See http://m.engineeringnews.co.za/article/south-african-nuclear-body-shuts-down-key-unit-because-of-compliance-failure-2017-11-22; https://www.reuters.com/article/us-safrica-isotopes/south-african-mo-99-plant-shut-after-suspected-hydrogen-leak-idUSKBN1DM2GS?feedType=RSS&feedName=environmentNews. The shutdown lasted for more than 7 weeks and production had not restarted at the time this proceedings was at the final publication stage. AIPES anticipated that NTP's temporary shutdown would cause Mo-99 shortages in selected markets (see https://www.bnms.org.uk/radioisotope-supplies/molybdenum-supplies/).The situation was constrained due to the scheduled refueling of the OPAL reactor.

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INCREASING PRODUCTION CAPACITY AND OUTAGE RESERVE CAPACITY

As noted in Chapter 3, current Mo-99 producers have made significant investments to increase Mo-99 production capacity. Mr. Roy Brown and Mr. Gavin Ball noted that Curium and NTP have also increased paid outage reserve capacity. Other existing producers also may have increased the paid outage reserve capacity, but did not comment on that at the symposium.

MONITORING AND REVIEWING OF THE SUPPLY CHAIN

The Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA) released its first report on Mo-99 supply and demand forecast in 2012 (OECD-NEA, 2012a) and updates in 2014 (OECD-NEA, 2014a), 2015 (OECD-NEA, 2015b), 2016 (OECD-NEA, 2016), and more recently in 2017 (OECD-NEA, 2017). Dr. Smith presented the major findings of the 2017 OECD-NEA update, which provides supply projections up to 2022.

Existing supply chain participants have maintained supply during the period examined in the report with only minor disruptions. OECD-NEA projects that contribution of Mo-99 supply from alternative technologies starting in 2018 is expected to be substantial. However, since the 2016 OECD-NEA update, many prospective processing projects have been delayed, and further delays can be expected (see Figure 5.1). If no additional capacity is added from alternative technologies by mid-2018 (when the NRU reactor in Canada permanently shuts down), the level of capability to manage potential supply disruptions will be reduced. Overall, the OECD-NEA report concluded that the supply situation will require careful and well-considered planning to minimize risks and that regular monitoring and review are needed on progress toward bringing new capacity to market.

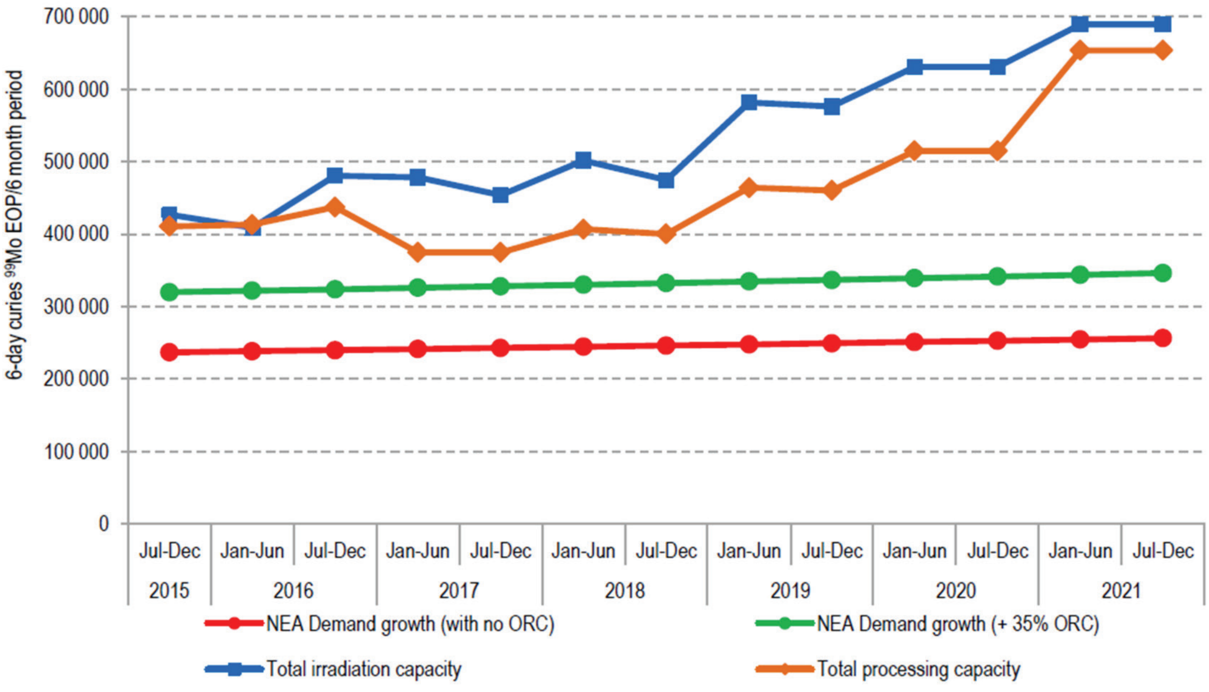

FIGURE 5.1 Modeling scenario presented by the Organisation for Economic Co-operation and Development's Nuclear Energy Agency.

NOTE: This scenario, referred to as Scenario C or Project Delayed Scenario in the OECD-NEA (2017) report, builds on the technological challenge scenario and assumes that the qualified projects that aim to produce Mo-99 are delayed by 1 year.

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INVESTING IN DURABILITY OF THE SUPPLY CHAIN

Two examples of investments in the durability of the supply chain were discussed at the symposium: in target manufacturing by CERCA and in reactor operations by the Belgian Nuclear Research Center (SCK•CEN), the operator of the BR-2 reactor.

CERCA

The 2016 National Academies report raised a concern about the vulnerability of the front end of the supply chain because one company, CERCA, provides the majority of the targets used to produce Mo-99. CERCA representatives Mr. Yann Guinard and Mr. Bertrand Stepnik estimated that since the 1970s, CERCA has manufactured more than 200,000 HEU plates, and since 2008 more than 50,000 LEU plates.

Mr. Guinard discussed the company's investment to "ensure CERCA's long-term presence as the reference supplier" of Mo-99 targets. These investments involved

- Changes in the plant environment,
- Upgrades in the existing plant to comply with applicable safety and security requirements, and
- Construction of a new building to host uranium alloy fabrication activities (to be commissioned in 2021).

CERCA is part of AREVA-NP, a subsidiary of AREVA SA, a private company that is fully owned by the French government. In the framework of the reorganization of the AREVA Group, AREVA NP will become an affiliate of Électricité de France (EDF), the French electricity utility company, under the temporary name "New NP." Mr. Guinard said that the reorganization will provide to CERCA a "sustainable financial structure."

SCK•CEN

Mr. Bernard Ponsard (SCK•CEN) noted that BR-2's 18-month maintenance and modernization operation, which ended in July 2016, aimed to improve the reactor's safe and efficient operations. Various systems and components were replaced as a precaution and, as a result, it is possible that the reactor's operating license can be extended by 10 years, that is, to 2036.

COORDINATING REACTOR SCHEDULES

Mr. Bernard Ponsard represented the Association of Imaging Producers and Equipment Suppliers' (AIPES') Security of Supply Working Group[2] and presented on the group's role in supply reliability and current activities. The group is tasked with coordinating the international scheduling of reactors that produce Mo-99 to provide global coverage during reactor shutdown periods. Participation in the scheduling efforts is at the discretion of the producer and relies upon willingness to contribute schedule information.

Initially, AIPES concentrated on European research reactors, but following the severe disruptions of Mo-99 supply in 2009-2010, the group incorporated all research reactors that supply the global market in its scheduling efforts. Today BR-2 (Belgium), HFR (Netherlands), Maria (Poland), LVR-15 (Czech Republic), SAFARI-I (South Africa), OPAL (Australia), RA-3 (Argentina), and FRM-II (Germany) contribute reactor schedules (see Figure 5.2). Ira Goldman (Lantheus), who is the current chairman of the Security of Supply Working Group, noted that AIPES has engaged the Russian State Atomic Energy Corporation, Rosatom, in many discussions about the possibility of the Russian reactors contributing schedule information to AIPES to benefit the reliability of the supply chain, but Rosatom has not agreed to do so. Mr. Alexey Vakulenko (JSC Isotope) responded to the comment by stating that Russia's reactor schedule contribution would not be relevant at this point because Mo-99 produced in Russia has not received drug regulatory approvals to be marketed in the European, U.S., and other markets. Therefore, it

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[2] Previously known as Reactors and Isotopes Working Group.

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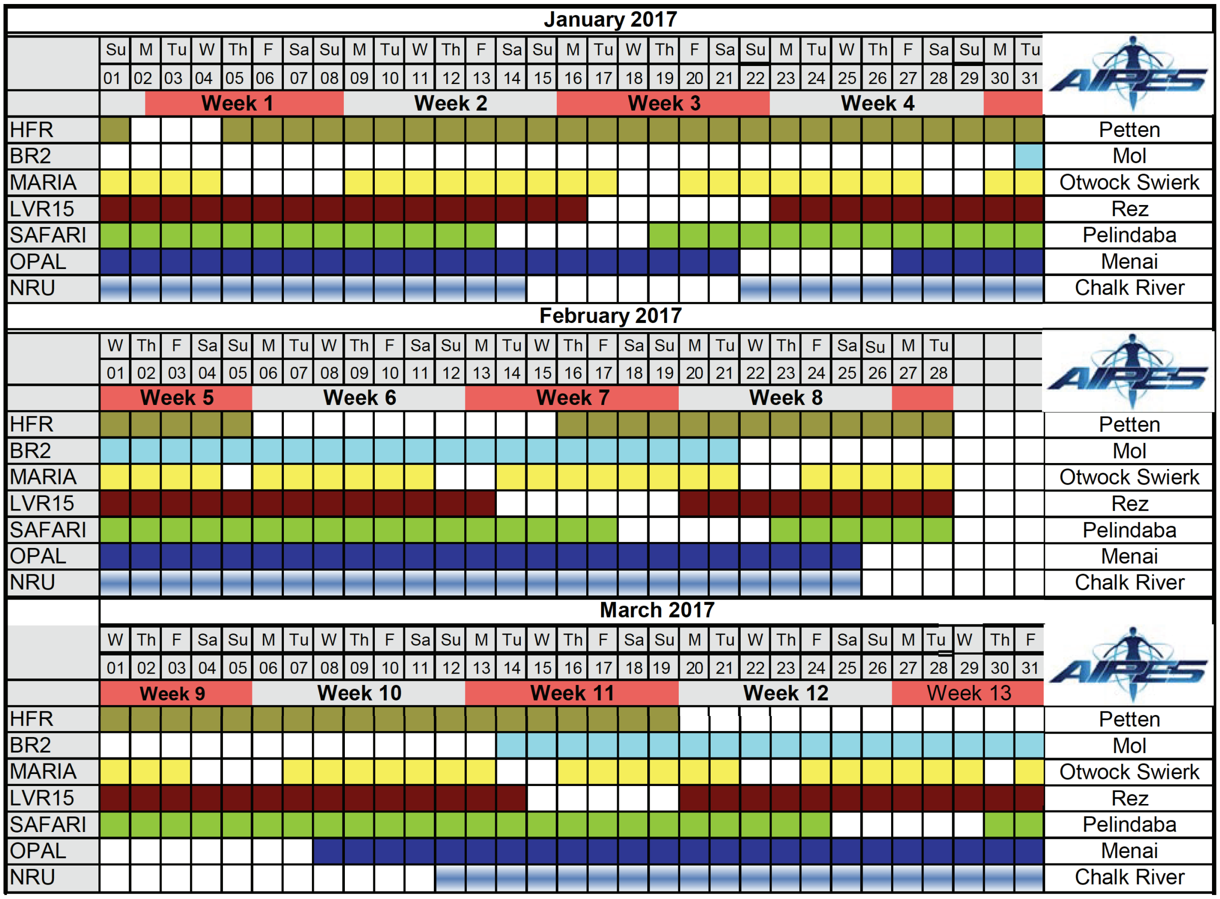

FIGURE 5.2 Reactors operating schedules, first trimester, 2017
SOURCE: Bernard Ponsard, SCK•CEN.

could not be used to mitigate potential global Mo-99 supply shortages. However, he welcomed continuing discussions between Rosatom and AIPES on the topic, especially as Russia increases its Mo-99 global market share.

AIPES has developed the AIPES Mo-99 capacity model[3] an analytical tool to improve reactor operation scheduling and to assess the impacts of schedules on global Mo-99 production. The model was developed in 2014 and is monitoring the maximum reactor capacity available per week for the global production of Mo-99 (see Figure 5.3). Mr. Ponsard noted that it is a suitable tool to assist in scheduling the reactor operating periods with respect to optimal Mo-99 production and supply and to identify periods at risk that need to be further investigated at the processor and generator manufacturer level.

AIPES has taken additional actions to improve Mo-99 production monitoring and stakeholder communication. In 2012, it created the Emergency Response Team to follow production and supply issues week by week through conference calls, if requested. This continuing follow-up allows AIPES to identify the potential for Mo-99 shortages and to define action plans with research reactors, processors, and generator manufacturers. The AIPES Emergency Response Team—currently chaired by Mr. Ponsard—is also concerned with the security of supply of other medical radiosotopes, for example Lu-177.

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[3] Previously known as the Versailles model.

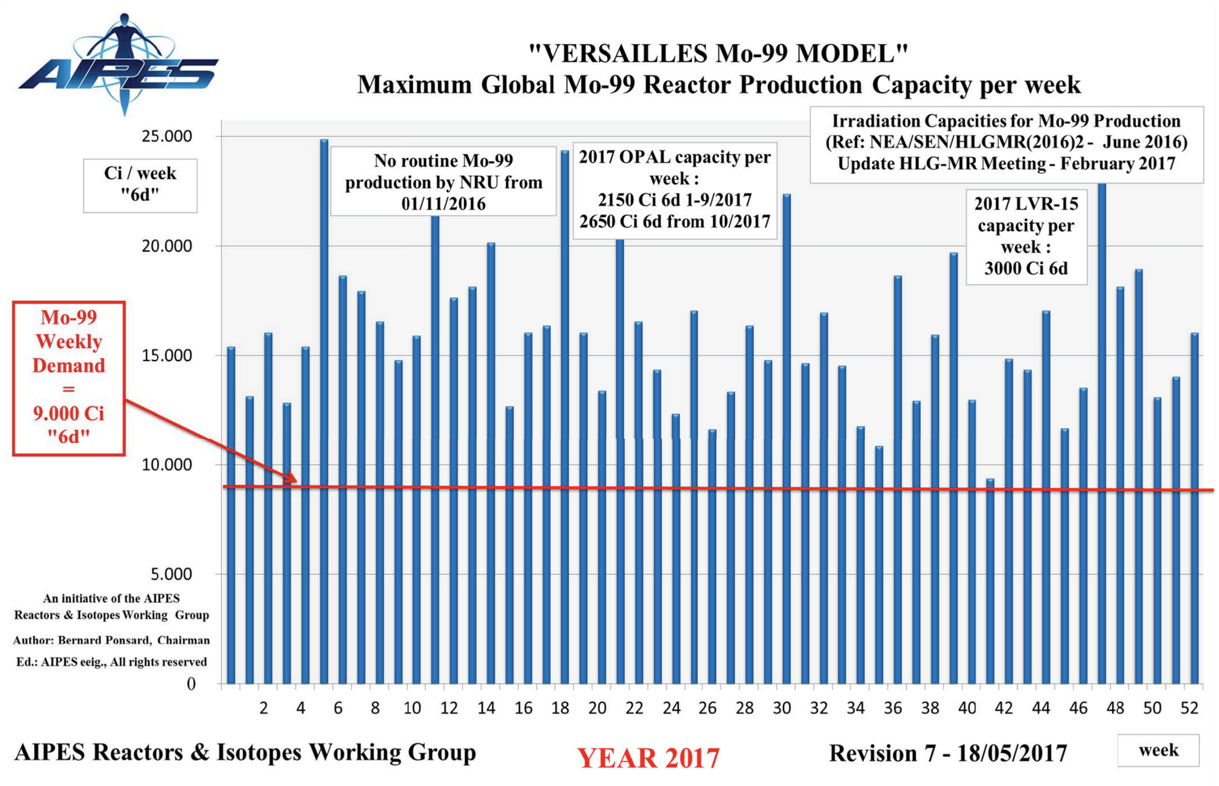

FIGURE 5.3 AIPES Mo-99 capacity model 2017.
SOURCE: Bernard Ponsard, SCK•CEN.

CREATING BACKUP AGREEMENTS

Irradiating facilities and producers have business agreements in place for backup production and supply of Mo-99. These backup agreements aim to prevent or reduce the effects of scheduled and/or unscheduled shutdowns of production facilities with the ultimate goal to prevent the potential for Mo-99 supply shortages. Three such backup agreements were mentioned at the symposium:

- Between BR-2 and HFR,
- Between OPAL and SAFARI-I, and
- Among all four global producers.

The details of the backup agreements were not discussed at the symposium.

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6

Prospects for Molybdenum-99 Future Supply

Dr. Ourania Kosti (National Academies) presented a series of speculative maps to illustrate the changes that could occur in molybdenum-99 (Mo-99) supply in the next 10-15 years (see Figures 6.1 and 6.2). The maps presented at the symposium were created using information primarily collected in the process of preparing the 2016 National Academies report and were revised for publication in this proceedings using updated information presented at the symposium. Most of the updates involved delays in Mo-99 production by several projects. Specifically:

- The Jules Horowitz Reactor (JHR), France, is expected to start operation in 2022, pushed back from 2020. The update was provided by Mr. Bernard Ponsard (SCK•CEN).
- The Kijang Research Reactor (KJRR), South Korea, is expected to start operation in 2022, pushed back from 2020. The update was provided by Dr. Ul-Jae Park (KAERI).
- The RA-10 reactor, Argentina, is expected to start operation *after* 2020; the reactor was expected to start operation in 2020. The update was provided by Dr. Pablo Cristini (National Atomic Energy Commission, Argentina).
- The FRM-II reactor, Germany, is expected to start producing Mo-99 in 2019, pushed back from 2018. The information was provided by Dr. Riane Stene (FRM-II).

Dr. Kosti noted several changes in the Mo-99 supply that could occur by 2020. For example,

- Irradiation facilities that currently irradiate HEU targets for Mo-99 production for medical use (i.e., BR-2, HFR, LVR-15, Maria) may only irradiate LEU targets.
- Existing reactor FRM-II, Germany, could start producing Mo-99 for medical use.
- One or more companies in the United States could start producing Mo-99.
- One or more companies in Canada could start producing Mo-99 or Tc-99m.
- Russia could increase Mo-99 production by introducing additional capacity from existing production facilities and/or from new projects.

Dr. Kosti presented additional changes that could occur by 2030 and further change the Mo-99 supply chain map. For example, by 2030, it is possible that

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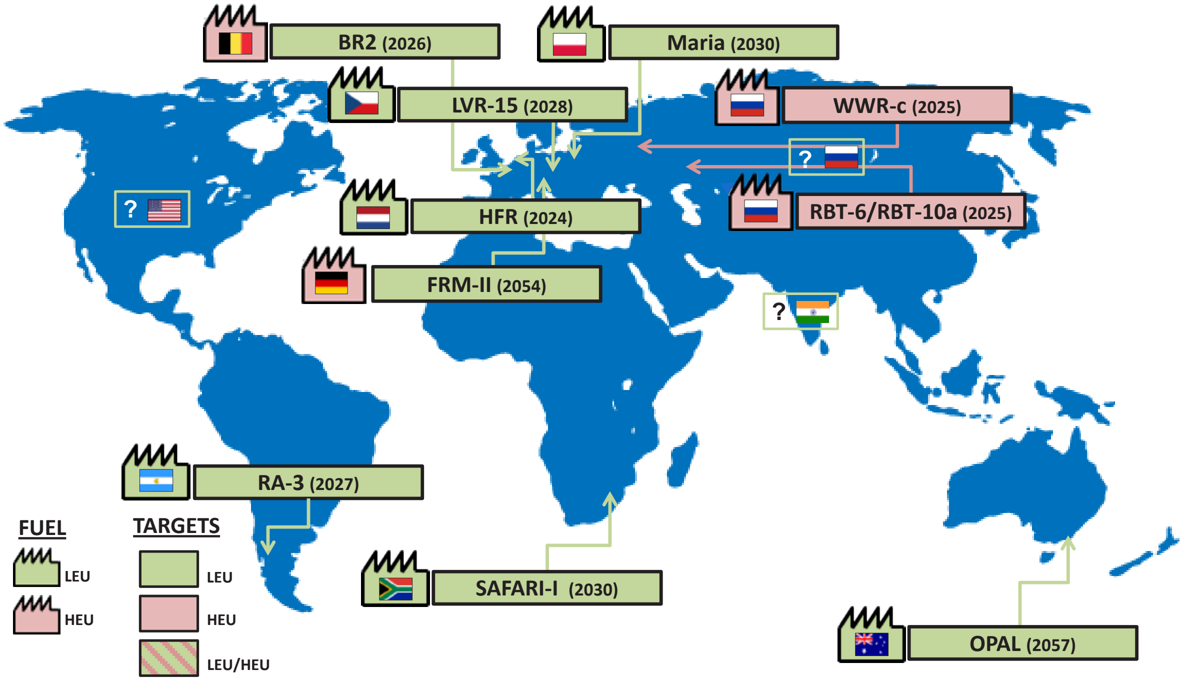

FIGURE 6.1 Speculative map of Mo-99 supply in 2020. If compared to Figure 3.1, several changes to the global supply of Mo-99 may occur by 2020: (a) Reactors that irradiated highly enriched uranium (HEU) targets for Mo-99 production in July 2017 (BR-2, HFR, LVR-15, Maria, and SAFARI-I) will likely be irradiating low-enriched uranium (LEU) targets by 2020. Russia's reactors will likely continue to irradiate HEU targets, if they still produce Mo-99. (b) Canada's NRU reactor will have permanently shut down. (c) The United States, Russia, and India may have started producing Mo-99 using non-HEU-sourced production methods. The question marks on the left of the three country flags indicate the uncertainties associated with the production plans and schedules.

- Several changes in the European reactor inventory could occur:
  - BR2,[1] Maria, LVR-15, and HFR will have reached the end of their operating lives and permanently shut down.
  - JHR (France), a reactor currently under construction, could start production of Mo-99 in 2022.
  - New reactor PALLAS (Netherlands) could start producing Mo-99 around 2026.
- SAFARI-I[2] in South Africa could stop producing Mo-99 when its current operating license expires in 2030.
- Several new projects could be completed and producers in Argentina, Brazil, China, Egypt, India, Japan, and South Korea could start producing Mo-99 for domestic and regional supplies.

POTENTIAL NEW MOLYBDENUM-99 SUPPLIERS

Several countries are planning to develop new capabilities to produce Mo-99. The symposium organizing committees invited many of these potential new producers to provide brief presentations on the status of the Mo-99 production projects. Updates on the production plans of the projects represented at the symposium are summarized by country in the sections that follow.

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[1] As noted in Chapter 5, it is possible that the reactor's operating license can be extended by 10 years, that is, to 2036.

[2] Mr. Gavin Ball (NTP) noted that the reactor's management team is investing in a plant-life extension program. It is possible that the reactor will operate beyond 2030.

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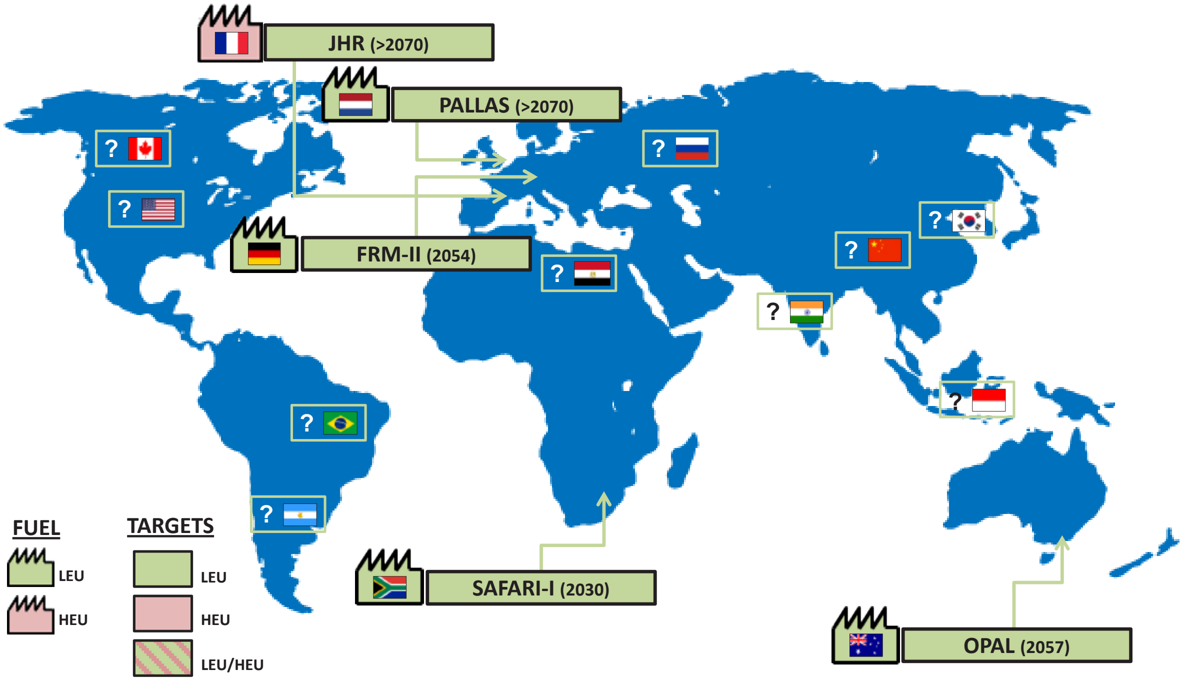

FIGURE 6.2 Speculative map of Mo-99 supply in 2030. If compared to Figure 5.1, several changes to the global supply of Mo-99 may occur by 2030: (a) Several reactors will have reached the end of their operating license (BR-2, HFR, LVR-15, and Maria) and permanently shut down. (b) Three reactors (JHR, PALLAS, and FRM-II) may start producing Mo-99. (c) Several countries including Brazil, Canada, Egypt, South Korea may start producing Mo-99 using non-HEU-sourced production methods. The question marks on the left of the country flags indicate the uncertainties associated with the production plans and schedules.

Representatives from Algeria, Brazil, Japan, Indonesia, and the United States' Niowave and Eden Radioisotopes were unable to participate; an invited potential producer from Poland responded that the Mo-99 production project has been halted; a representative from Nordion, Canada, was unable to provide an update on the collaborative project with General Atomics and the University of Missouri Research Reactor Center. Updates on the production plans of those projects that were not represented at the symposium are not summarized in this proceedings.

The United States

Several private-sector companies in the United States are planning to produce Mo-99 for medical use. Three of these companies (General Atomics, NorthStar Medical Radioisotopes, and SHINE Medical Technologies) have signed cooperative agreements with the Department of Energy's National Nuclear Security Administration (DOE-NNSA). Each project carried out by these companies has been awarded $25M in cost sharing for work that contributes directly to the establishment of Mo-99 production capability. NorthStar and SHINE representatives provided updates on their Mo-99 production projects. As noted earlier, the General Atomics project was not represented at the symposium. In addition to the two cooperative agreement projects, representatives of three private companies working toward establishing U.S.-based production of Mo-99 without DOE-NNSA funding presented their projects at the symposium.

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NorthStar Medical Radioisotopes

NorthStar, a company located in Beloit, Wisconsin, is pursuing two processes to establish capabilities to supply Mo-99 to the U.S. and global markets. These are:

1. A neutron capture of molybdenum-98 using neutrons produced in a research reactor and
2. A photon-induced transmutation of molybdenum-100 [reaction: $^{100}Mo(\gamma,n)^{99}Mo$] using photons produced with electron accelerators.

Dr. James Harvey who represented NorthStar noted that the company intends to run both of these production processes in parallel in the future because "they provide redundancy and have different strengths in terms of approaching and serving the market." NorthStar's neutron capture process is the most advanced in terms of market readiness and could be market ready for Mo-99 production in early 2018. NorthStar's photon-induced transmutation process could be market ready for Mo-99 production at the end of 2019.[3]

The Mo-99 produced by NorthStar's two processes has low specific activity and cannot be loaded directly to conventional technetium generators. NorthStar has developed a new technetium generator system, the RadioGenix Tc-99m Generating System, to utilize low-specific-activity Mo-99. The RadioGenix system is a platform technology that NorthStar has used for other isotopes such as actinium/bismuth and tungsten/rhenium, and has been specifically developed for Mo-99/Tc-99m production. Tc-99m generated from the RadioGenix system meets the U.S. and European pharmacopeia standards for Tc-99m.

The RadioGenix Tc-99m Generating System was subject to a New Drug Application (NDA) by the U.S. Food and Drug Administration (U.S. FDA). Dr. Harvey noted that the regulatory approval process has been long: NorthStar met with the U.S. FDA to outline a path to NDA submission in 2010 and submitted the NDA in 2013. As of July 2017 the company was awaiting approval of a resubmission of the NDA to start producing Mo-99. He noted that the 7-year regulatory approval process compared in length with the conversion from the HEU to LEU production process, which was estimated by global producers to also take 6-7 years.

The RadioGenix system is not intended to be a "mobile" system similar to today's conventional technetium generators, which are shipped to nuclear pharmacies daily. Instead, nuclear pharmacies certified to use the RadioGenix system will be equipped with the system, will be trained to use it, and will be receiving Mo-99 solution from NorthStar to load on the generator for Tc-99m elution. Dr. Harvey recognized that the RadioGenix system's footprint is much larger than today's conventional technetium generators but noted that it occupies about the same footprint as four of the conventional generators in their respective secondary shields. He also noted that it is intended for the U.S. centralized nuclear pharmacies, which are typically larger than hospital-based nuclear pharmacies. Mr. David Pellicciarini (Cardinal Health), who represented the largest centralized nuclear pharmacy chain in the United States, agreed that larger Cardinal Health facilities would likely be able to accommodate the RadioGenix system but added that smaller facilities within the Cardinal Health chain may be challenged.

SHINE

SHINE, a Wisconsin-based company, plans to use deuterium/tritium accelerator technology to induce subcritical fissioning of U-235 in an LEU uranyl sulfate solution. SHINE plans to build eight accelerator-driven operating assemblies to produce up to 4,000 six-day Ci/week of Mo-99 for U.S. and global supply. The company also plans to supply I-131 and Xe-133.

Ms. Katrina Pitas, who represented SHINE, noted that the proposed process is cost-effective and generates less nuclear waste than conventional Mo-99 production methods. She added that the proposed process produces high-specific-activity Mo-99, compatible with existing technetium generators, without the need for a nuclear reactor.

SHINE's facility in Janesville, Wisconsin, will be an integrated facility for medical isotope production, processing, and target (uranyl sulfate solution) production. The target in the proposed production method is expected

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[3] The information was provided by Mr. Peter Kartz (Department of Energy) at the 2017 Mo-99 Topical Meeting in Montreal, Canada, in September 2017.

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to last the lifetime of the facility, but if this ends up not being the case, Ms. Pitas noted that SHINE will have the capability to remove impurities from the solution or to create a new solution.

SHINE submitted a facility construction permit application to the U.S. Nuclear Regulatory Commission (U.S. NRC) in 2013 and received approval in 2016. SHINE has entered into supply agreements with GE Healthcare, Lantheus Medical Imaging, and the Chinese company HTA Co., Ltd. The company anticipates starting medical isotope production in 2020.

Dr. Boris Zhuikov (Russian Academy of Sciences) commented on SHINE's proposed production technology being an attractive alternative to uranium fission in a nuclear reactor, but noted that the company has not yet demonstrated the capability of the proposed system to produce high-specific-activity Mo-99. He added that developers of the SHINE technology would benefit from discussions with Russian investigators at Kurchatov Institute who used the Argus Reactor[4] to test small-scale production of Mo-99 using LEU solution in 2014.

Northwest Medical Isotopes

Northwest Medical Isotopes (NWMI) plans to produce Mo-99 by irradiating LEU targets in a network of existing university research reactors. Ms. Carolyn Haass, who represented the company at the symposium, said that two of these reactors have been identified publicly and are the University of Missouri Research Reactor and Oregon State University's TRIGA Reactor. A third reactor is being explored. For NWMI's project, targets would be processed in a radioisotope production facility (RPF). The RPF will be located in Columbia, Missouri. In addition, the RPF will be used to recover uranium from the dissolved LEU solution and recycle it back into new LEU target material. A construction permit application for the RPF was submitted to the U.S. NRC in two parts: Environmental Report in January 2015 and Safety Report in July 2015. A decision is expected in January 2018. NWMI's production capacity is 3,500 six-day Ci of Mo-99/week with the potential to increase it to 5,000 six-day Ci/week.

NWMI's project proposes recycling and recovering LEU to minimize radioactive waste generation. The recycling process is proprietary. Ms. Haass outlined a high-level summary of the LEU recycling and recovery process.

1. First-stage recovery. Mo-99 anion exchange (IX) column LEU stream is held in lag storage tanks to allow decay of select radionuclides. The decayed uranium solution is diluted and pumped through first-stage IX columns to separate bulk fission product contaminants. Uranium is then eluted from IX column, and concentrator/condenser is then used to concentrate eluate for second-stage IX uranium recovery. Waste from the dilution is sampled and sent to a high-dose liquid waste accumulation tank. Condensate is sent to a low-dose liquid waste accumulation tank.
2. Second-stage recovery. Interim uranium product solution is processed through a second-stage IX column to remove trace contaminants. Uranium is then eluted from the IX columns and a concentrator/condenser is used to control the volume of recycled uranium product. The final uranium product solution is sampled to confirm that it meets recycle specifications. Waste generated from the second-stage recovery is sampled and sent to the high-dose liquid waste accumulation tank. Condensate is sent to a low-dose liquid waste accumulation tank.
3. Product uranium lag storage. Product uranium lag storage allows for U-237 decay so that the recovered LEU can be contact-handled during LEU target fabrication.

Coquí RadioPharmaceuticals

Coquí RadioPharmaceuticals, a Puerto Rico–based company, plans to produce Mo-99 by irradiating LEU targets in two 10-megawatt (MW) LEU-fueled research reactors similar to Australia's INVAP-designed OPAL reactor. Ms. Carmen Bigles noted that the company plans to build these reactors and associated Mo-99 production

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[4] The Argus Reactor was the first solution reactor designed in the former Soviet Union in the 1980s. Currently this reactor is used for testing and experiments and not for regular medical isotope production.

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facility on the "Duct Island" site at Oak Ridge, Tennessee. Coquí aims to produce Mo-99 to meet greater than 50 percent of U.S. demand and for exports. The company's plan calls for start of construction of the reactors in 2020 and production of Mo-99 in 2023.

Flibe Energy

Flibe Energy, located in Huntsville, Alabama, aims to develop a 250-MWe liquid fluoride thorium reactor (LFTR) for the main purpose of electrical power generation and a secondary purpose of medical isotope production. Thorium in the reactor fuel captures a neutron and is transmuted to uranium-233 (U-233), which is fissile. The fission of U-233 with neutrons produces a spectrum of fission products including noble metals, molybdenum, and noble gases such as xenon. Removal of noble metals from liquid-fluoride reactors was demonstrated during the operation of the Molten-Salt Reactor Experiment at Oak Ridge National Laboratory in the mid-1960s, but separation of Mo-99 has not yet been demonstrated. Because LFTRs are designed to operate continuously for the lifetime of the plant, Mo-99 can be removed from the liquid fuel stream along with other noble metal fission products as part of the normal operation of the reactor's chemistry management system.

Dr. Matthew Lish, who represented Flibe Energy, described the company's proposed production method as a long-term strategic plan for securing future Mo-99 supply. Upon funding, the company is targeting application for licensing of a demonstration reactor in approximately 5 years (around 2022). The demonstration reactor would be 2-5 megawatts thermal (MWT) capable of producing about 7,000 six-day Ci/week per MWT.

Russia

Representatives of the Russian State Atomic Energy Corporation, Rosatom, Mr. Risovaniy (Rosatom Headquarters), Mr. Vakulenko (JSC Isotope), and Dr. Kononov (Karpov Institute), discussed three prospects for producing Mo-99 from non-HEU sources in Russia. The goal of these projects carried out by Rosatom is to expand supply to the global market to reach up to a 20 percent share:

1. Production in an aqueous homogeneous reactor (or solution reactor). In 2015, Rosatom made a decision to construct a proof-of-concept solution reactor in Sarov (Nizhniy Novgorod region) dedicated to Mo-99 production. Construction started in 2017 and is expected to be completed in 2018; operation of the reactor is expected to start in 2019. Mo-99 production capacity from one solution reactor is about 250 six-day Ci/week and can be scaled up by installing more reactors. The advantages of solution reactors for medical isotope production were not discussed at the symposium but they are comprehensively discussed elsewhere (IAEA, 2008).
2. Production in nuclear power plants with RBMK reactors. Karpov Institute is exploring the possibility of producing Mo-99 in RBMK nuclear power plant reactors by irradiating LEU targets. Mr. Vakulenko and Dr. Kononov noted that key features of RBMK reactors allow the production of medical isotopes without affecting the reactor's main purpose of operation, which is production of electricity. One of these key features is the ability to take the targets that are irradiated at periphery channels of the reactor for processing while the reactor is still operating to produce electricity.

   The technology for producing radionuclides in an RBMK reactor was demonstrated at the Leningrad Nuclear Power Plant in the early 1990s, and starting in 2001 several targets have been irradiated at that site to produce medical isotopes including Mo-98 targets for small-scale production of Mo-99. To date, irradiation of uranium targets for Mo-99 has not been demonstrated in an RBMK.

   Rosatom is planning to test production at the RBMK reactor at Smolensk Nuclear Power Plant, the youngest of the three RBMK reactors[5] currently operating in Russia. Karpov Institute is working on designing LEU targets for irradiation at Smolensk and on optimizing the target chemical processing. Dr. Kononov noted that validation of LEU target irradiation could start in early 2018. In his view this is

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[5] The RBMK reactor at Smolensk is expected to be decommissioned in 2034.

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a promising non-HEU-sourced Mo-99 production method with the potential to produce large amounts of Mo-99, about 2,000 six-day Ci/week.

3. Production via neutron capture in high-flux reactors. Rosatom is exploring the possibility of irradiating enriched Mo-98 targets in high-flux reactors such as the SM-3 reactor at RIAR (flux up to $5.0 \times 10^{15}/(\mathrm{cm}^2\ \mathrm{s})$) for the production of Mo-99. This project is based on a new method of Mo-98 activation, currently at early stages of investigation, which uses nanopowder and the Szilard-Chalmers effect. Preliminary calculations have shown that the specific activity of Mo-99 produced with this method is around 50-70 Ci/g, which is higher than that achieved by conventional neutron activation. Mr. Risovaniy appeared to favor this production method of Mo-99 production because of some benefits it offers, including relatively low production costs and low waste generation.

Mr. Vakulenko explained that Rosatom's goal to capture a large (up to 20 percent) share of the global Mo-99 market relies on the success of one or more of these three projects. He added that all projects are at initial stages of development, and it is too early to predict their success and provide timelines for completion. When asked by several symposium participants to provide further clarity on the schedule for deciding which project Rosatom will pursue further, he said that he anticipates JSC Isotope will make a decision in 2018 on which method of production from non-HEU sources appears to be the most promising from technological, economic, and market perspectives, and focus on the market readiness of that production method.

A fourth prospect for Mo-99 production in Russia is under development at Tomsk Polytechnic University and was presented by Prof. Victor Skuridin and Dr. Evgeniy Nesterov. This project aims to build on the university's existing Mo-99 production capabilities (see Chapter 3) by irradiating enriched Mo-98 targets and activating both thermal and resonance neutrons to increase the reaction cross-sections and achieve higher-specific-activity Mo-99 than conventional neutron activation. Tomsk Polytechnic University has tested this method at its IRT-T 6 reactor, a 6-MW reactor with neutron flux equal to $1.7 \times 10^{14}/(\mathrm{cm}^2\ \mathrm{s})$. Mo-99 of specific activity up to 15 Ci/g (at the end of bombardment) has been achieved. The group is working on optimizing the reflector geometry to increase activity to 50 Ci/g or higher.

Mo-99 produced with this method can be loaded on generators that are not much larger than conventional generators, and breakthrough is within limits for authorization of distribution within Russia. (It was later noted that Mo-99 produced via neutron activation methods would not be suitable for loading on conventional generators for distribution in Europe or the United States because of failure to meet U.S. or European pharmacopoeia specifications for technetium due to breakthrough.) Tomsk Polytechnic University, in collaboration with the IAEA, is developing regional production using this method, estimated to be market ready in a few years.

Dr. Nesterov noted that, in an effort to reduce costs of purchasing Mo-98,[6] Tomsk Polytechnic University is exploring a procedure for reusing Mo-98 so that only 100g of enriched material is expended over a 5-year operation. The radioactive waste generated during the process is only a small fraction (1/10,000) of the produced material activity as opposed to uranium fission, which produces waste that is of 10 times higher activity than that of the product.

Argentina

In 2010, CNEA announced the decision to carry out a project that involves the design, construction, licensing, and operation of a new multipurpose nuclear reactor, RA-10. RA-10 will be a 30-MW reactor, dedicating about half of its operation to medical isotope production. The reactor will be able to produce 2,500 six-day Ci/week of Mo-99 to cover domestic supplies and expand international supplies. The reactor will also be producing 400 Ci of I-131 per week via fission. Dr. Pablo Cristini (CNEA) noted that construction of the RA-10 reactor started in May 2017 and the reactor is expected to start producing Mo-99 after 2020.

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[6] The cost is about $200 per gram of Mo-98.

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Brazil

Dr. Cristini (CNEA) and Mr. Osso (IAEA) were asked to comment on the status of the Brazilian reactor RMB (Brazilian Multipurpose Research Reactor), a "twin" reactor in terms of design to the RA-10 reactor in Argentina. They noted that the project had been proceeding slowly for 2-3 years because of lack of financing from the Brazilian government. The project was recently revived, and the RMB reactor may start operating around 2023. The reactor's capacity will be 1,000 six-day Ci/week intended to cover domestic demand (estimated to be around 350-400 six-day Ci/week) and some regional supplies.

Canada

The Canadian government has invested in four projects to produce Mo-99 and Tc-99m via nonfission to cover Canadian demand for Mo-99 (and Tc-99m) which is currently about 500 six-day Ci/week. Two projects were discussed at the symposium:

- TRIUMF's project, which aims to produce Tc-99m via the ^{100}Mo(p,2n)^{99m}Tc reaction using cyclotrons and
- Canadian Isotope Innovations Corporation's (CIIC's) project, which aims to produce Mo-99 via the ^{100}Mo(γ,n)^{99}Mo reaction using linear accelerators.

Mr. Ken Buckley (TRIUMF) and Dr. Kennedy Mang'era (CIIC) said that the approaches Canada is currently exploring have several advantages over the current fission-based Mo-99 production and supply approaches. These advantages include

- Diversification of technologies used for Mo-99/Tc-99m supply,
- Decentralization of Mo-99/Tc-99m supply,
- Lower costs associated with construction and operation of Mo-99/Tc-99m facilities, and
- Scalability of supply.

Some project-specific information is provided in the following sections.

TRIUMF

TRIUMF collaborates with four other institutions (University of British Columbia, British Columbia Cancer Agency, Centre for Probe Development and Commercialization, and Lawson Health Research Institute) to produce Tc-99m in cyclotrons. The consortium was tasked with

- Demonstrating routine, reliable commercial-scale production of Tc-99m,
- Obtaining regulatory approval for clinical use of the produced Tc-99m in humans,
- Establishing a business plan for Tc-99m distribution, and
- Commercializing the technology to other producers.

Mr. Buckley noted that the TRIUMF consortium alone, which includes three cyclotrons of suitable energy for Tc-99m production, can provide about 134,000 GBq (3,600 Ci) Tc-99m[7] annually. There are 15 cyclotrons in Canada that in total could provide 1,388,000 GBq (37,500 Ci) Tc-99m annually from enriched Mo-100, which is over half the demand for Tc-99m in Canada. He added that Tc-99m produced using the TRIUMF technology may be priced differently depending on the size of the cyclotron used for production. For example, Tc-99m produced using a small, 16-MeV/100 μA cyclotron, which has a lower production yield, will be more expensive compared to that produced using a 24-MeV/500 μA cyclotron, which has a higher production yield.

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[7] The concept of the six-day curie of Mo-99 is not relevant for direct Tc-99m production by cyclotrons where Mo-99 plays no role.

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Cyclotrons are routinely used for production of positron emission tomography (PET) medical isotopes, but commercial-scale production for Tc-99m was first demonstrated by TRIUMF. Because this is a novel production method for direct production of Tc-99m, TRIUMF is required to file a new drug submission to Health Canada. For the submission, TRIUMF will utilize data on the performance of cyclotron-produced Tc-99m from two studies:

1. A small clinical trial to show that the clinical results of technetium produced directly from cyclotrons are not inferior to the clinical results obtained from generator-derived technetium and
2. A kit labeling study to validate the labeling performance of cyclotron-produced technetium.

The project is anticipated to be market-ready in 2018. The TRIUMF consortium formed the company ARTMS Products to disseminate and commercialize the technology to other producers. In May 2017, Alliance Medical in the UK entered into an agreement with ARTMS to receive the required products and procedures for the production of Tc-99m using cyclotrons.

Canadian Isotope Innovations Corporation

CIIC proposes to use a linear accelerator (LINAC) to produce Mo-99 from enriched Mo-100 at a facility in Saskatoon, Canada. CIIC is currently validating the technology, and key processes are complete or in advanced development stages. Dr. Mang'era noted that a pilot facility has been operational since 2015 with a capacity for 100 Ci/week of Mo-99 (calibrated 1 day post-end of bombardment [EOB]). CIIC has completed the design and developed a business plan for a larger facility with capacity to produce about 1,100 Ci/week of Mo-99 that would be operational 3 years after funding is secured. The company's business approach relies on the company shipping Mo-99 solution to its customers for extraction of Tc-99m at the customer's site using the CIIC-supplied separation generator, the Next-Gen LSA Generator. CIIC would then reclaim and recover the Mo-100, which will be recycled into fresh Mo-100 enriched targets.

Dr. Mang'era noted that the success of CIIC's business plan relies on

- Secure supply of enriched Mo-100 for target preparation,
- Development of the Next-Gen LSA Generator,
- Health Canada and U.S. FDA approvals of the Next-Gen LSA Generator,
- Market acceptance of alternative nonfission Mo-99/Tc-99m sources,
- Private-investment fundraising for business plan execution, and
- Implementation of full cost recovery by Mo-99/Tc-99m producers.

China

China imports Mo-99 from NTP, ANSTO, and IRE to cover its demand, which is currently estimated at 280-300 six-day Ci/week but is growing at a rate of approximately 5 percent per year. (Mr. Joao Osso [IAEA] pointed out that demand for Mo-99 in China remains very low, if one accounts for the country's large population.) Dr. Jin Du (China Isotope & Radiation Corporation) noted that the growing demand has led the China National Nuclear Corporation (CNNC) to explore domestic production of Mo-99.

CNNC is a large state-owned enterprise under the direct management of the central government of China. Several radioisotope producers within CNNC have attempted to establish Mo-99 production using different methods, but plans were abandoned in the early 2000s due to high production costs.

Dr. Du discussed two current projects in China aiming to produce Mo-99 to cover domestic needs:

- China Advanced Research Reactor (CARR), a 60-MW reactor located in Fangshan District, Beijing. CARR started operating in 2010 and aims to produce 1,000 six-day Ci/week of Mo-99. Testing of Mo-99 production at CARR is expected to start in 2020. The reactor will also produce iodine-131 (by irradiating tellurium targets) and other isotopes used in nuclear medicine.

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- Research and development of the Medical Isotope Production Reactor (MIPR) project, an aqueous homogeneous reactor to be operated by NPIC. The production capacity for Mo-99 will be about 2,000 six-day Ci/week. NPIC applied for a construction permit in May 2017, but a schedule for starting Mo-99 production has not been made public. The reactor will also produce iodine-131 and strontium-89.

Egypt

Egypt has produced about 70-75 six-day Ci/week of Mo-99 every 2 weeks since 2015 by irradiating LEU targets at the Egyptian Atomic Energy Authority's ETRR-2 complex located at Inshas (a suburb of Cairo). Production at ETRR-2 covers part of Egypt's Mo-99 demand estimated to be 40-80 six-day Ci/week. Dr. Mostafa Abd Elaal, who represented the Egyptian Atomic Energy Authority, noted that the agency aims to increase production to 200 six-day Ci/week within the next 1-3 years and—with IAEA support—to 400 six-day Ci/week after that.

India

India currently imports Mo-99 from Russia and Belgium to cover most of the country's demand and produces small amounts of low-specific-activity Mo-99 by neutron capture in the Dhruva research reactor owned and operated by Bhabha Atomic Research Centre (BARC). Dr. Anupam Mathur (Department of Atomic Energy) noted that BARC is currently working with the Argentinian company INVAP to develop capability to produce about 300 six-day Ci/week of high-specific-activity Mo-99 by irradiating LEU targets at the new Apsara reactor or Dhruva reactor. Mo-99 produced at the Apsara or Dhruva reactors will cover domestic needs (estimated at about 200 six-day Ci/week) and for supply to the international market (100 six-day Ci/week).

LEU target design has been completed by BARC, and some natural uranium "dummy" targets have been prepared and sent to INVAP for testing. BARC faces a technical challenge related to different irradiation protocols between INVAP and the Indian reactors (Apsara and Dhruva), which may affect Mo-99 production yield. Production of Mo-99 at Apsara or Dhruva reactors is estimated to start in 2019.

Netherlands

The PALLAS reactor in Netherlands, is an initiative for the future replacement of the HFR when it reaches its end of operations around 2025. The PALLAS reactor is a separate legal entity from NRG (the operator of the HFR), conceptualized in 2013. It will be a 20- to 25-MW reactor, built specifically for medical isotope production on the same site as HFR in Petten, 50 kilometers north of Amsterdam. Mr. Hermen van der Lugt noted that PALLAS has contracted with the designer of the nonnuclear facilities and buildings. PALLAS issued an award to the designer of the nuclear island in January 2018. A licensable design is expected to be completed by 2019 and construction by 2025. The PALLAS reactor will have a capacity for Mo-99 production at least at the level of the HFR capacity. It will also produce a range of other isotopes for medical use.

South Korea

South Korea currently imports Mo-99 from Australia, South Africa, and Russia to cover all of its demand, which is about 150 six-day Ci/week. The Korean government launched the new research reactor project in 2012 to build the 15-MW Kijang Research Reactor (KJRR) to produce Mo-99, I-131, Ir-192, and other medical isotopes. Dr. Ul-Jae Park (Korea Atomic Energy Research Institute) noted that production of Mo-99 at KJRR is expected to start in 2022, a delay of about 2 years since the previous schedule estimate, because of additional seismic specifications imposed by the South Korean regulatory authority following the September 2016 earthquake near the site. These additional regulatory specifications have also added to the cost of construction of the proposed reactor.

Dr. Park noted that South Korea aspires to become the first large-scale Mo-99 producer in Asia and change the existing Asian supply chain, which relies on reactors in Europe, Australia, and South Africa. Initially KJRR

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will produce about 500 six-day Ci/week and gradually increase to 2,000 by 2025. Most of the Mo-99 produced at KJRR will be available to the global market.

MARKET-READINESS AND PENETRATION CHALLENGES

Mr. Gavin Ball (NTP) commented on the often ambitious schedules of new potential producers entering the Mo-99 market. Specifically, he thought that many potential producers underestimate the time needed for development, industrialization, and validation of both conventional and alternative technologies. He added that receiving regulatory approvals to construct, operate, and sell medical isotopes can also be long processes. Therefore, many of the projects presented at the symposium are unlikely to be market ready by the dates presented at the symposium (and summarized in Table 6.1).

In addition to the market-readiness challenge, other symposium participants commented on the market penetration challenge that potential new producers will likely face. This is because potential new producers will have to compete with existing global producers who currently can meet demand and the additional 30 percent outage reserve capacity recommended by the Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA) and have marketing and management experience in doing so. Some additional production capacity has been recognized as needed by organizations such as the OECD-NEA to minimize risks of shortages, especially after the NRU reactor in Canada permanently shuts down in March 2018; however, there has not been an analysis on how much added capacity is needed to ensure a long-term sustainable Mo-99 supply.

U.S. National Academies' committee member Dr. Gene Peterson (Los Alamos National Laboratory) noted that with the large number of new projects aiming to produce Mo-99 within the next 5-10 years, production capacity could increase to over three times the current available capacity (see Table 6.1). Without an indication that global demand for Mo-99 is likely to increase substantially in the next few years this additional production capacity cannot possibly be absorbed by the market. IRE's Jean-Michel Vanderhofstadt agreed with the comment and added that the excess capacity would disrupt the dynamics of the Mo-99 market, a market that is already "not greatly profitable." He could not elaborate further to avoid violating antitrust policies.

Representatives of two new Mo-99 projects responded to the comment on market penetration raised by Dr. Peterson and Mr. Vanderhofstadt. Dr. Cristini (CNEA) said that any potential producer and its investors are free to use funds as they judge appropriate. Argentina's CNEA, for example, has built what the company considers a viable business plan by investing in the RA-10 reactor to supply Mo-99 domestically and regionally. Dr. Harvey noted that NorthStar's investment team is committed to taking appropriate actions to overcome the market penetration challenge.

The challenges that new producers might face to build a technically and commercially competitive business were recognized by several symposium participants. Others noted that it is a mistake to conclude that some aspiring domestic/regional and global producers will not succeed in establishing production capacity. For example, a participant noted that it is possible that smaller local or regional producers could be preferred over global producers when selling Mo-99 in the local or regional markets because of favorable logistics of transportation, possible cost advantages, and other factors. As several countries become self-sufficient in terms of Mo-99 supply or rely on regional supplies (for example the representative from South Korea noted that the country aims to become the first large-scale supplier in Asia), existing global producers could lose part of their current supply share.

A potential solution to existing and new producers not having to compete for a share of the existing market is to increase demand for Mo-99. Mr. Vanderhofstadt, in his capacity as president of the Association of Imaging Producers and Equipment Suppliers (AIPES), said that AIPES engages with the European and U.S. nuclear medicine associations to stimulate development of new Tc-based compounds for single-photon emission computed tomography (SPECT) and SPECT/CT. However, this is a long-term (maybe 20-year or so) project and will not provide a solution to the market-sharing problem in the short run. In a separate discussion at the symposium Mr. Vanderhofstadt admitted that IRE follows the trend in nuclear medicine and is investing in PET radiopharmaceuticals. Other companies such as Lantheus Medical Imaging are also investing in development of PET (and not SPECT) radiopharmaceuticals.

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TABLE 6.1 Current Mo-99 Producers and New Projects Presented at the Symposium

Company/Project	Method	Reactor	Production Capacity (6-day Ci/week)	Anticipated Production Year	Plans for Expansion (Mo-99 expressed in 6-day Ci/week)
Existing Global Producers					
ANSTO	Fission of U-235 (LEU)	OPAL	2,150	Producing currently	2,650 by Q4 2017 3,500 by Q1 2018
Curium	Fission of U-235 (HEU)	HFR, BR2, Maria	4,500	Producing currently; converting to LEU	5,000 in Q4 2017 ~4,500 in 2018
IRE	Fission of U-235 (HEU)	HFR, BR2, and LVR-15	3,600	Producing currently; converting to LEU	3,500 in 2018
NTP	Fission of U-235 (LEU)	SAFARI-I	3,500	Producing currently	N/A
Existing Smaller Producers					
RIAR	Fission of U-235 (HEU)	RBT-6 and RBT-10a	1,000	Producing currently	2,000 by 2019
Karpov Institute	Fission of U-235 (HEU)	WWR-c	350	Producing currently	700 by 2020
Argentina	Fission of U-235 (LEU)	RA-3	400	Producing currently	N/A
Tomsk Polytechnic University	Neutron capture	IRT-T 6	~10	Resuming production in 2018	N/A
Khlopin Radium Institute	Neutron capture	RBMK, Leningrad Nuclear Power Plant	~10	Producing currently	N/A
Egypt	Fission of U-235 (LEU)	ETRR-2	75	Producing currently	200-400 after 2020
New Projects					
United States					
NorthStar	Neutron capture	MURR	~3,000 six-day Ci	2018	>3,000 six-day Ci
NorthStar	Photon-induced transmutation of Mo-100	N/A	~3,000 six-day Ci	2019	>3,000 six-day Ci
SHINE	Fission of U-235 (accelerator-driven) (LEU)	N/A	~4,000	2020	–
NWMI	Fission of U-235 (LEU)	MURR, Oregon State University	3,500	Not provided	5,000
Coquí	Fission of U-235 (LEU)	To be built in Oak Ridge, Tennessee	2,500	2023	
Flibe Energy	Fission of U-233 generated from Th-232	To be built	>9,000	After 2022	

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Russia					
Rosatom	Fission of U-235 in aqueous homogeneous reactor (LEU)	Sarov	250	Not provided	Scaled-up production
Rosatom	Neutron capture	SM-3	Not provided	Not provided	
Rosatom	Fission of U-235 (LEU)	RBMK	2,000	Not provided	
Canada					
TRIUMF	Direct production of Tc-99m (cyclotron)	N/A	Equivalent of about 250	2018	
CIIC	Photon-induced transmutation of molybdenum-100 (LINAC)	N/A	1,200	Not provided	
Argentina	Fission of U-235 (LEU)	RA-10	2,500	2021	
Brazil	Fission of U-235 (LEU)	RMB	1,000	2023	
China	Fission of U-235 (LEU)	CARR	1,000	After 2020	
	Fission of U-235 in aqueous homogeneous reactor (LEU)	MIPR	2,000	Not provided	
India	Fission of U-235 (LEU)	Apsara or Dhruva	300	2019	
Netherlands	Fission of U-235 (LEU)	PALLAS	≥6,200	2025	
South Korea	Fission of U-235 (LEU)	KJRR	500	2022	2,000 by 2025

NOTES: New projects aiming to produce Mo-99 that were not presented at the symposium are not summarized on this table.
For acronyms and abbreviations, see same-title section at the beginning of this proceedings.

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7

Molybdenum-99 Supply Sustainability

Historically, reactor operators have charged suppliers of molybdenum-99 (Mo-99) only for the marginal operating costs associated with target irradiation and not for costs related to reactor general operation, maintenance, and decommissioning (OECD-NEA, 2010). These costs were absorbed by the governments that own the reactors because the reactors were constructed for purposes other than medical isotope production. International organizations such as the Organisation for Economic Co-operation and Development's Nuclear Energy Agency (OECD-NEA) have recognized that as medical isotope production is progressively becoming a larger part of reactors' workloads, the historic pattern of government subsidization has proven to lead to Mo-99 market sustainability issues. To create a sustainable Mo-99/Tc-99m market, the High-Level Group on the Security of Supply of Medical Isotopes agreed on six principles in 2011 (OECD-NEA, 2011), one of which is full cost recovery (FCR). FCR was a central topic of discussions at the symposium.

Mr. Jan Willem Velthuijsen (PricewaterhouseCoopers) noted that FCR is not a price-setting tool but rather a methodology to define cost elements and determine the cost associated with Mo-99 production. He added that private industry would go beyond implementing FCR to make profit.

GOVERNMENT SUBSIDIZATION OF MOLYBDENUM-99 PRODUCTION

Mr. Velthuijsen provided the economist's perspectives on the problems caused by government subsidization of Mo-99 production:

1. Welfare loss. When Mo-99/Tc-99m prices remain low due to government subsidies, there is little incentive to use Mo-99/Tc-99m efficiently. Inefficient utilization of Mo-99/Tc-99m leads to several problems including increasing radioactive waste.
2. Transfer of welfare. Taxpayers pay for the subsidies provided by governments in countries with reactors used for Mo-99 production. Healthcare consumers in countries that consume Mo-99/Tc-99m without producing it domestically benefit disproportionately from the subsidies.
3. No incentive for new capital through private investments. Because Mo-99 prices remain low, new Mo-99 producers struggle to ensure a viable business case with private funding alone.

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Mr. Velthuijsen recognized that governments still have large incentives to subsidize Mo-99 production to ensure availability. For example, delay of private investments in Mo-99 production (either to support new production or maintenance and upgrades at existing Mo-99-producing facilities) could lead to governments stepping in and offering the needed funds to ensure that no shortages occur. This, in his view, starts a vicious cycle of continued subsidy provision (Figure 7.1).

Uneven subsidization of the supply is also problematic. Mr. Velthuijsen explained that if one supply chain participant is still being subsidized by its government, existing nonsubsidized suppliers are forced to lower the price for which they sell Mo-99 and therefore are not able to earn back their investments for maintenance and upgrades of the production facilities or for conversion from highly enriched uranium (HEU)- to low-enriched uranium (LEU)-sourced production. Eventually, these nonsubsidized suppliers face the risk of being pushed out of the market. New potential suppliers who plan to enter the market at FCR face the same challenges.

Implementation of FCR would lead to increases in prices of Mo-99/Tc-99m, medical isotopes that have traditionally been underpriced. Mr. Velthuijsen noted that the market's willingness to increase prices depends on availability of alternatives to Mo-99/Tc-99m imaging, pass-through of price increases along the supply chain, and willingness to pay more for Tc-99m imaging.

PROGRESS TOWARD FULL COST RECOVERY

Evaluating the progress made by existing producers toward FCR is difficult because of the large variability in the ownership structure of production facilities such as research reactors used to produce Mo-99. Some of the reactors currently used for Mo-99 production are publicly owned. For example, Mr. Velthuijsen noted that HFR (Netherlands) is owned by the European Commission; OPAL (Australia), Maria (Poland), SAFARI-I (South Africa), and RA-3 (Argentina) are owned by national governments. LVR-15 (Czech Republic), BR-2 (Belgium), RIAR (Russia), and Karpov (Russia) are owned by research institutes that are indirectly controlled by the government.

Since introducing the concept of FCR in 2011 (OECD-NEA, 2011) and guidance for FCR implementation in 2012 (OECD-NEA, 2012b), OECD-NEA has twice reviewed progress made by supply participants toward implementing FCR: in 2012 (the report was released in 2013, see OECD-NEA, 2013) and more recently in 2014 (OECD-NEA, 2014b).

The 2012 review found that most reactor operators and processors are gradually implementing FCR for Mo-99 production, but progress toward FCR is uneven. According to the OECD-NEA report, Australia and South Africa are the two countries self-reporting full implementation of FCR. Little additional progress was made from 2012 to 2014 in implementing FCR. This led the OECD-NEA to develop the Joint Declaration on the Security of Supply of Medical Radioisotopes (Sidebar 7.1). The purpose of the Joint Declaration was to "provide a more formal and coordinated political commitment by governments of the countries participating in the HLG-MR that would foster the necessary changes needed across the supply chain, both in producing and user countries."

Information for OECD-NEA's review on implementation of FCR is obtained through self-assessments from

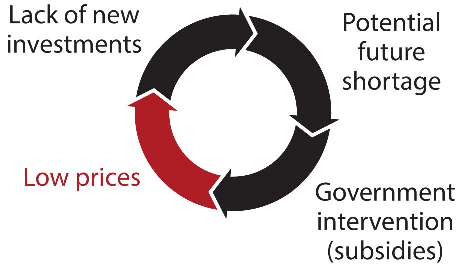

FIGURE 7.1 Vicious cycle of continued subsidization that threatens market sustainability.
SOURCE: Jan Willem Velthuijsen, PwC, Europe.

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Sidebar 7.1
Joint Declaration on the Security of Supply of Medical Radioisotopes

The Joint Declaration on the Security of Supply of Medical Radioisotopes (OECD-NEA, 2015b) seeks to ensure the security of supply of molybdenum-99. The 14 countries that adhere to the declaration state that:

WE COMMIT, with the aim of jointly promoting an internationally consistent approach to ensuring the long-term secure supply of medical radioisotopes, to implement the HLG-MR principles in a timely and effective manner, and to:

- Take co-ordinated steps, within our countries' powers, to ensure that ^{99}Mo or ^{99m}Tc producers and, where applicable, generator manufacturers in our countries implement a verifiable process for introducing full-cost recovery at all facilities that are part of the global supply chain for ^{99m}Tc;
- Encourage the necessary actions undertaken by ^{99}Mo processing facilities or ^{99m}Tc producers in our countries to ensure availability of reserve capacity capable of replacing the largest supplier of irradiated targets in their respective supply chain;
- Take the necessary actions to facilitate the availability of ^{99m}Tc, produced on an economically sustainable basis, as outlined in the HLG-MR principles;
- Encourage all countries involved in any aspect of the ^{99m}Tc supply chain, and that are not party to the present Joint Declaration, to take the same approach in a co-ordinated manner;
- Take the necessary actions described above by the end of December 2014 or as soon as technically and contractually feasible thereafter, aware of the need for early action to avoid potential shortages of medical radioisotopes that could arise from 2016;
- Report on an annual basis to the OECD Nuclear Energy Agency (NEA) on the progress made at the national level and support an annual review of the progress made at the international level, both in light of this Joint Declaration.

Mo-99 supply chain participants. Mr. Velthuijsen pointed out that self-assessments are not entirely reliable or representative of the countries' progress toward FCR because there is no transparency in the methodology used to assess it and/or each country may interpret FCR differently. Also, there is no auditing in place to ensure that the self-assessment is accurate. Mr. Velthuijsen outlined several ways that governments can help with implementation of FCR in the Mo-99 market, for example, by auditing supply chain participants for implementation of FCR or earmarking government subsidies for research performed in reactors that also produce Mo-99. The willingness of the supply chain participants to be subject to government auditing for FCR compliance was not discussed at the symposium.

Mr. Velthuijsen offered his views on the status of some existing and new Mo-99 production projects that appear not to comply with the FCR principle:

- Belgium's BR-2 receives support from the government for waste management and security of the reactor.
- Netherlands' HFR reactor received a subsidy for its last refurbishment.
- Argentina's RA-3 reactor receives support from the government for capital expenditures and waste management. The new RA-10 reactor is paid for with government funds.

PERSPECTIVES ON FULL COST RECOVERY

Several symposium participants offered comments on their company's or organization's views on FCR. These comments highlight the range of anticipated differences in implementation of FCR in the Mo-99/Tc-99m supply market in the future.

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- Existing global producers (ANSTO, NTP, IRE, Curium) highlighted the importance of realistic pricing of Mo-99/Tc-99m and of FCR being implemented throughout the supply chain. They all noted some progress toward FCR at the reactor level since the principle was issued by OECD-NEA.

  Mr. Jean-Michel Vanderhofstadt said that IRE is negotiating contracts with irradiating facilities based on FCR. To his knowledge the only cost not covered for the irradiation services that IRE receives is initial capital investments for building the reactors because they were built for other purposes many years ago. He added that because of FCR, irradiation costs have increased 400 percent over the past few years. Russia's Oleg Kononov (Karpov Institute) provided a similar comment, stating that for Mo-99 production in the WWR-c reactor, the only costs not expected to be recovered are the costs for building the reactor.
- Some representatives of new projects that involve construction of new facilities dedicated to medical isotope/Mo-99 production said that implementation of FCR is crucial to the success of their projects. These representatives included Jim Harvey (NorthStar), Katrina Pitas (SHINE), Carolyn Haass (NWMI), Kennedy Mang'era (CIIC), and Ken Buckley (TRIUMF). Mr. Risovaniy (Rosatom) agreed that implementation of FCR for the aqueous homogeneous reactor project that involves construction of a new production facility is essential.
- Implementation of FCR for projects that involve construction of new reactors differed based on whether the reactor to be constructed will be dedicated to medical isotope production or is also intended for research activities.
  - Construction of the multipurpose RA-10 reactor in Argentina is subsidized by the Argentinian government.
  - Phase 1[1] of the PALLAS reactor in Netherlands, which will be dedicated to Mo-99 production, is funded by the Department of Economic Affairs and the province of North Holland. The loans received for Phase 1 need to be repaid during subsequent phases.
- Representatives of projects that involve medical isotope production as a secondary purpose and power generation as a primary purpose claimed that most production costs will be recovered by power generation. Two such projects were described at the symposium: Rosatom's project to produce Mo-99 in RBMK reactors and Flibe Energy's project to produce Mo-99 in thorium reactors.

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[1] Phase 1 involves design, construction licensing, and development of the business case to secure the financing for the next phase.

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Appendixes

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Appendix A

Agenda

SYMPOSIUM DAY 1: MONDAY, JULY 17, 2017

International Atomic Energy Agency
Board Room A
M Building

9:00 Opening Session

Welcome
Meera Venkatesh, *International Atomic Energy Agency* (5 min)
Christophe Xerri, *International Atomic Energy Agency* (5 min)

Statement from the U.S. and Russian Academies
Stepan Kalmykov, *co-chair, Russian Academy of Sciences* (on behalf of the symposium organizing committees) (10 min)

9:20 Plenary Session
Moderator: Alexander Bychkov, *Permanent Mission of the Russian Federation to the International Organizations in Vienna*

Mo-99 production: Past, present, and future
Hedvig Hricak, *co-chair*, *U.S. National Academies* (on behalf of the symposium organizing committees) (10 min)

Russia's role in global molybdenum-99 supply
Alexey Vakulenko, *JSC V/O IZOTOP, Russian Federation* (20 min)

Establishing and expanding nuclear medicine programs
Rodolfo Nuñez-Miller, *International Atomic Energy Agency* (10 min)
Wolfgang Weber, *Memorial Sloan Kettering, United States* (10 min)

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Plenary session discussion (15 min)

10:30 BREAK

10:50 Molybdenum-99 Supply Reliability: Session 1
Moderator: Jack Coffey, *Enigma Biomedical Group*

Organisation for Economic Co-operation and Development-Nuclear Energy Agency's principles to address molybdneum-99 supply reliability and the organization's global market demand and production capacity projections
Kath Smith, *High-Level Group on the Security of Supply of Medical Radioisotopes* (15 min)

The European Commission's efforts to evaluate the supply of medical radioisotopes
Margarida Goulart, *European Commission* (15 min)

Reactor schedule coordination for molybdenum-99 supply reliability
Bernard Ponsard, *AIPES Reactors & Isotopes Working Group* (15 min)

Investments in AREVA's target production facility to improve long-term sustainable security of molybdenum-99 supply
Yann Guinard, *AREVA, France* (15 min)

Session 1 discussion (20 min)

12:10 Molybdenum-99 Supply: Session 2 (Part 1)
Moderator: Rania Kosti, *U.S. National Academies*

Existing global suppliers: Current production and future plans
Roy Brown, *Curium* (10 min)
Michael Druce, *ANSTO, Australia* (10 min)
Gavin Ball, *NTP, South Africa* (10 min)
Jean-Michel Vanderhofstadt, *IRE, Belgium* (10 min)

12:50 LUNCH

14:30 Molybdenum-99 Supply: Session 2 (Part 2)
Moderator: Rania Kosti, *U.S. National Academies*

New projects for regional or global molybdenum-99 supply
James Harvey, *NorthStar, United States* (10 min)
Katrina Pitas, *SHINE, United States* (10 min)
Carolyn Haass, *Northwest Medical Isotopes, LLC, United States* (10 min)
Carmen Bigles, *Coquí Radio Pharmaceuticals, United States* (10 min)
Matthew Lish, *Flibe Energy, United States* (10 min)
Hermen van der Lugt, *PALLAS Reactor, Netherlands* (10 min)
Oleg Kononov, *Karpov Scientific Research Institute of Physics and Chemistry, Russian Federation* (10 min)
Ken Buckley, *TRIUMF, Canada* (10 min)
Kennedy Mang'era, *Canadian Isotope Innovations Corp*. (10 min)
Jin Du, *China Isotope & Radiation Corporation* (10 min)

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Anupam Mathur, *Department of Atomic Energy, India* (10 min)
Ul-Jae Park, *Korea Atomic Energy Research Institute* (10 min)
Pablo Cristini, *National Atomic Energy Commission, Argentina* (10 min)
Mostafa Abd Elaal, *Egyptian Atomic Energy Authority* (10 min)

Session 2 discussion (30 min)

17:30 Late afternoon break and closing remarks
(Participants move to MO2 Foyer)

19:30 Adjourn symposium day 1

SYMPOSIUM DAY 2: TUESDAY, JULY 18, 2017

Board Room A
M Building

9:00 Welcome
Stepan Kalmykov, *co-chair*, *Russian Academy of Sciences committee* (on behalf of the two Academies) (5 min)

9:05 Technical Considerations: Session 3
Moderator: Boris Zhuikov, *Russian Academy of Sciences*

Conversion to low enriched uranium-based molybdenum-99 production
Jean-Michel Vanderhofstadt, *IRE, Belgium* (10 min)
Roy Brown, *Curium* (10 min)
Gavin Ball, *NTP, South Africa* (10 min)
Vladimir Risovaniy, *Rosatom, Russian Federation* (10 min)

Production expansion
Michael Druce, *ANSTO, Australia* (10 min)

Prospects for the use of activation of molybdenum for the production of technetium-99m generators
Victor Skuridin, *Tomsk Polytechnic University, Russian Federation* (15 min)

High-density low-enriched uranium targets production
Bertrand Stepnik, *AREVA, France* (15 min)
Kinam Kim, *Korea Atomic Energy Research Institute* (15 min)

Session 3 discussion (20 min)

11:40 BREAK

12:00 Regulatory Considerations: Session 4
Moderator: Joao Alberto Osso Junior, *International Atomic Energy Agency*

European Medicines Agency's regulatory considerations
Brendan Cuddy, *European Medicines Agency* (20 min, pre-recorded)

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Perspectives from Tc-99m generator manufacturers
Ira Goldman, *Lantheus Medical Imaging, United States* (10 min)
Roy Brown, *Curium, Netherlands* (10 min)

Perspectives from a nuclear pharmacy
David Pellicciarini, *Cardinal Health, United States* (15 min)

Session 4 discussion (15 min)

13:15 LUNCH

14:30 Economic Considerations: Session 5
Moderator: Charles Ferguson, *Federation of American Scientists*

Molybdenum-99 supply economics
Jan Willem Velthuijsen, *PwC Europe* (20 min)

Low-enriched uranium-based molybdenum-99 production
Gavin Ball, *NTP* (5 min)
Michael Druce, *ANSTO* (5 min)

Session 5 discussion (25 min)

15:30 BREAK

15:50 Chemical Processing and Waste Management: Session 6
Moderator: Sergey Yudintsev, *Russian Academy of Sciences*

Chemical processing and waste management following neutron activation
Evgeniy Nesterov, *Tomsk Polytechnic University, Russian Federation* (10 min)

Development of a novel dry chemical uranium molybdenum separation: Research for a future efficient Mo-99 extraction process
Riane Stene, *FRM-II, Germany* (10 min)

Waste management in HEU versus LEU-based molybdenum-99 production
Jean-Michel Vanderhofstadt, *IRE, Belgium* (15 min)

Synroc Technology for the Management of molybdenum-99 Waste
Bruce Begg, *ANSTO, Australia* (10 min)

Recycling processed LEU for reuse as target material
Carolyn Haass, *Northwest Medical Isotopes, LLC, United States* (10 min)

Session 6 discussion (30 min)

17:20 Closing remarks
Stepan Kalmykov, *co-chair*, *Russian Academy of Sciences*

17:30 Adjourn symposium

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Appendix B

Biographical Sketches of Committee Members, Presenters, and Moderators

Mostafa Abdelaal is a molybdenum-99 production operator at the Radioisotope Production Factory at the Egyptian Atomic Energy Authority (EAEA). He worked at EAEA in 2007 and then obtained a master's degree in 2012 and a doctorate in radiochemistry in 2016. Beside molybdenum-99 and iodine-131 production, he works as a researcher in the field of radioisotopes production and labeling.

Gavin Ball serves as group executive for operations at NTP Radioisotopes where he is responsible for safe, efficient, and sustainable production operations of the company's radioisotope production plants in South Africa. He has been involved in the nuclear industry for 30 years and has more than 20 years' experience in isotope production. During this period he has specifically been involved in key leadership roles in the highly enriched uranium (HEU) to low-enriched uranium (LEU) conversion projects.

Bruce Begg is an executive manager within Nuclear Business at the Australian Nuclear Science and Technology Organisation (ANSTO), with responsibility for identifying and developing strategic commercial opportunities for ANSTO. He has more than 20 years' experience with ANSTO's synroc technology, from initially leading its technical development to now overseeing its commercialization.

Carmen Bigles is president and CEO of Coquí RadioPharmaceuticals Corp. (Coquí Pharma), a company founded in 2009 with the goal of establishing a medical radioisotope production facility in the United States. Prior to founding Coquí Pharma, Bigles co-founded and served as chief financial officer of the Caribbean Radiation Oncology Center in Puerto Rico. Bigles was born in San Juan, Puerto Rico, and received her education in Florida and Puerto Rico. In 1997, she earned a bachelor's degree in mathematics from Interamerican University in San Juan and subsequently master's degrees in architecture and suburban and town planning from the University of Miami in 2000.

Roy Brown is currently the vice president of Government Affairs & Strategic Alliances for Curium. His principal responsibility is engaging with state and federal legislators, regulatory agencies, and trade associations to educate and advocate on behalf of Curium. He is also engaged in the long-term strategy for radionuclide supply. He has more than 30 years of experience in the nuclear medicine industry. He holds a B.S. in radiation biophysics from the University of Kansas and an M.A. in business administration from Webster University.

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Ken Buckley has a bachelor of science degree in physics from McMaster University. He has more than 30 years' experience in the production and use of medical radioisotopes, particularly in the field of positron emission tomography (PET). His experience includes accelerator operation and maintenance, targetry development, automated radiochemistry development, and PET camera characterization. Since 2011 he has been the project manager for the TRIUMF-led collaboration of five institutions establishing cyclotron-based direct production of Tc-99m. In 2015 the collaboration won the Natural Sciences and Engineering Research Council Brockhouse Canada Prize for Interdisciplinary Research in Science and Engineering.

Alexander Bychkov is the representative of Rosatom in Vienna and has the post of senior counsellor of the Russian Permanent Mission for International Organizations in Vienna. He is out-of-staff adviser to the director general of Rosatom and visiting professor at the National Nuclear Research University MEPhI (Moscow Engineering Physics Institute). Before that he was a deputy director general of the International Atomic Energy Agency (IAEA) until February 2015 and a director general of the Research Institute of Atomic Reactors in Dimitrovgrad, Russia, until 2011. He graduated with a degree in chemistry from Moscow State University in 1982 and received his doctorate in 1998. His main areas of activity cover nuclear fuel-cycle subjects, including nuclear fuel, fast reactors and high-level waste, radionuclide technologies, and research reactor applications. Bychkov is a co-author of more than 160 scientific works.

Jack L. Coffey serves as a consultant with Enigma Biomedical Group and Cerveau Technologies Inc., focusing on radiopharmaceutical development with primary emphasis on supplier and manufacturing site qualification, U.S. Food and Drug Administration compliance, and manufacturing process improvements. His experience at Cardinal Health Nuclear Pharmacy Services (2003-2012) and Syncor International Corporation (1984-2003) has included regulatory compliance auditing, quality and regulatory affairs management, as well as an officer of a publicly held corporation. As a scientist at Oak Ridge Associated Universities (1974-1984) he conducted radiopharmaceutical research focused specifically on determining radiation doses to patients and members of the public from radioactive materials. Coffey chaired the Council on Radionuclides and Radiopharmaceuticals (CORAR) from 2011 to 2012. He received a B.S. in chemistry and biology from the University of the Cumberlands and an M.S. in radiation biology from the University of Tennessee.

Pablo Cristini, born in 1958, is an Argentine radiochemist, who graduated from the University of Buenos Aires in 1985. In 1979, he joined the Comisión Nacional de Energía Atómica (CNEA) of Argentina, participating in the Fission Mo-99 Production Project. In 1991 he became the head of the CNEA fission Mo-99 production plant and since 2005 has been manager of radioisotope production, responsible for the conversion of Mo-99 production from HEU to LEU. He is author or co-author of more than 30 scientific papers and publications. He had technical responsibility for transference of technology of Mo-99 production with LEU to the Australian Nuclear Science and Technology Organisation, the Egyptian Atomic Energy Authority, the Nuclear Research Center of Draria, Algeria, and the Board of Radiation and Isotope Technology (BRIT) in India.

Brendan Cuddy joined the European Medicines Agency as a scientific administrator in October 2002. Cuddy is currently head of the Manufacturing and Quality Compliance Service and is chairman of the Good Manufacturing and Distribution Practice Inspectors Working Group (GMDP IWG). The service plays a key role in collaborating and communicating with international partners on setting and recognizing GMP standards, making better use of inspectional resources, and exchanging information on the availability of already authorized medicines. Cuddy obtained his degree in chemistry from the University of Dublin, Trinity College in Ireland. He holds a master's degree from the National University of Ireland in quality and operations management and a postgraduate diploma in pharmaceutical manufacturing technology from University of Dublin, Trinity College, which satisfies the educational requirements for Qualified Person.

Michael Druce is Nuclear Business's chief technology officer and manager of Client Office activities for the new ANM Plant. He provides technical support for Nuclear Business Projects and Operations. Druce has extensive experience in the development and manufacture of radioisotopes for both medical and industrial applications. He provides technical advice on ANSTO projects and consulting services to other organizations. He is the technical director for the new ANM Mo-99 Plant and is responsible for preparing the plant for operations. He holds bachelor of applied science (chemistry) and master of business administration degrees. He graduated from the Australian School of Nuclear Technology and the Australian Institute of Company Directors. He has more than 30 years of experience with both reactor- and cyclotron-based radioisotopes. He is based at ANSTO's Lucas Heights campus.

Jin Du is the chief technology officer at China Isotope & Radiation Corporation. Dr. Du received his B.S. (1986) in chemical engineering from the Wuhan Institute of Chemical Technology and Ph.D. (2001) in chemistry from the University of Jyvaskyla, Finland. He started as a research fellow in medical radioisotopes and radiopharmaceuticals fields at China Institute of Atomic Energy in 1986, and then moved to the Japan Atomic Energy Research Institute (1996), MAP Medical Technologies, Oy, Finland (1997), and Peking University Health Research Center (2002). He accepted a senior research position in the China Isotope & Radiation Corporation (2006) and then was promoted to chief technology officer in 2016 where his main responsibility is research and development of new medical radioisotopes and radiopharmaceuticals.

Charles Ferguson has been the president of the Federation of American Scientists (FAS) since January 1, 2010. From February 1998 to August 2000, Ferguson worked for FAS on nuclear proliferation and arms control issues as a senior research analyst. Previously, from 2002 to 2004, Ferguson had been with the Monterey Institute's Center for Nonproliferation Studies (CNS) as its scientist-in-residence. He also has consulted with the Oak Ridge National Laboratory, Sandia National Laboratories, and the National Nuclear Security Administration. From 2000 to 2002, he served as a physical scientist in the Office of the Senior Coordinator for Nuclear Safety at the U.S. Department of State, where he helped develop U.S. government policies on nuclear safety and security issues. After graduating with distinction from the U.S. Naval Academy, he served as an officer on a fleet ballistic missile submarine and studied nuclear engineering at the Naval Nuclear Power School. Ferguson received his undergraduate degree in physics from the U.S. Naval Academy in Annapolis, Maryland, and his M.A. and Ph.D. degrees, also in physics, from Boston University in Massachusetts. Dr. Ferguson is the incoming director of the National Academies' Nuclear and Radiation Studies Board.

Ira Goldman is director, Strategic Supply and Government Relations, Lantheus Medical Imaging (LMI). He is co-chair of the Isotope Supply Committee, Council on Radioisotopes and Radiopharmaceuticals (CORAR), and vice chair of the Reactor and Isotopes Working Group, Association of Imaging Producers and Equipment Suppliers (European Industrial Association for Nuclear Medicine and Molecular Imaging). Goldman is responsible for developing, implementing, and monitoring corporate strategy and actions for acquisition of a globally diversified and reliable supply of Mo-99, including strategic planning for Mo-99 and Tc-99m, analysis of global Mo-99 supply options; establishing and expanding relationships with global suppliers for a reliable and high-quality supply of Mo-99 and materials; and managing projects for technical evaluation of various Mo-99 and Tc-99m production technologies. He is also responsible for legislative and governmental relations and assists with new business development for medical radioisotopes.

Margarida Goulart has a pharmaceutical sciences degree, a medical degree, and a Ph.D. in genetic toxicology, and worked as a researcher and university professor for several years, in toxicology of organic and inorganic compounds and radioactive elements, in Portugal (National Institute of Nuclear Technology) and the United States (Brown University, University of North Carolina). She is currently a permanent staff member of the European Commission (EC) as a research programme officer in the Joint Research Centre's (JRC's) Euratom Coordination Unit, responsible mainly for the coordination of nuclear security and nuclear science application activities, including cooperation between the EC and the International Atomic Energy Agency (Seibersdorf and Monaco labs) and the JRC contribution to EC actions toward security of the supply of medical radioisotopes.

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Yann Guinard is the managing director of CERCA™ at AREVA NP. He joined AREVA in 2009, and was previously the vice president in charge of strategy of AREVA's Fuel Business Unit. Prior to that, he held several management positions in various industries, with a focus on aerospace. He holds master's degrees in public affairs and business administration.

Carolyn Haass is the chief operating officer of Northwest Medical Isotopes. She has more than 30 years of experience in multidisciplinary complex nuclear, chemical, hazardous, and mixed waste engineering, procurement, construction, and project management projects in both the government and private industry. She was a regulator with the U.S. Department of Energy for more than 10 years and has extensive communication experience in the nuclear and environmental industry including day-to-day interface with regulators, safety boards, Congress, stakeholders, tribal nations, public, media, community leaders, and decision makers. Haass earned a bachelor of science degree in chemistry and metallurgical engineering from Colorado School of Mines.

James Harvey holds a Ph.D. in nuclear chemistry. He has 44 years of experience in both federal and private positions in nuclear research, development, and commercial applications of radioactive materials. He has held principal investigator roles on a number of grants and cooperative agreements and grants with various federal agencies. He has extensive experience working within and with various Department of Energy programs including environmental cleanup and radioisotope production applications. He has served as the chief science officer of NorthStar Medical Technologies, LLC for the past 12 years.

Hedvig Hricak is chair of the Department of Radiology at Memorial Sloan-Kettering Cancer Center. As a member of the Institute of Medicine/National Academy of Medicine, her contributions have included chairing the Committee on the State of the Science of Nuclear Medicine (2006-2007) and the Committee on Research Directions in Human Biological Effects of Low-Level Ionizing Radiation (2012), and serving as vice chair of the Committee on Tracking Radiation Doses from Medical Diagnostic Procedures (2012). She served on the Nuclear and Radiation Studies Board of the National Academy of Sciences from 2008 to 2014.

Stepan Kalmykov is the head scientist at the Laboratory of Radioecological and Radiation Problems of the Institute of Physical Chemistry of Moscow State University and the head of the Division of Nuclear and Radiation Medicine of the National Research Center Kurchatov Institute. His research focuses on actinide speciation, colloid-facilitated radionuclide migration, surface complexation modeling, determination of low-level activities, and nuclear medicine and radiopharmaceutical chemistry. He is a member of the Scientific Council on Radiochemistry (a partnership between the Russian Academy of Sciences and Rosatom), the International Nuclear Chemistry Society, the Scientific Secretary of the National Committee of Russian Chemists, and the American Chemical Society.

Kinam Kim is a senior researcher at Korea Atomic Energy Research Institute (KAERI). He received his Ph.D. in material science and engineering from Hanyang University, Korea, in 2013. He began his career at KAERI in 2013 as a researcher working on producing and studying research reactor fuels. Since April 2017, he has worked as a project manager developing atomized powder-based high-density LEU dispersion targets.

Matthew Lish is a graduate of the University of North Carolina at Chapel Hill with a bachelor of science degree in chemistry, and the University of Tennessee at Knoxville with a doctorate in nuclear engineering, concentrating in system dynamics, instrumentation, and control. Lish currently works as a reactor dynamicist at Flibe Energy in Hunstville, Alabama, where he is developing a closed-fuel-cycle thorium nuclear reactor known as the liquid fluoride thorium reactor, or "lifter" (LFTR). His areas of interest include reactor dynamics and simulation, inorganic separations chemistry, chemical process engineering, reactor dynamics, and radiation-hardened electronics for signal processing.

Hermen van der Lugt is director of PALLAS. PALLAS is responsible for all required preparations for the construction of the PALLAS reactor in Petten, Netherlands. The PALLAS reactor will take over the current role of

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the HFR reactor in the supply chain of isotopes. Activities include requirements specification, reactor design, and nuclear and conventional licensing. The PALLAS organization develops a business case for PALLAS that enables private investors to fund the construction and operation.

Kennedy Mang'era is chief operating officer (COO) at the Canadian Isotope Innovations Corp (CIIC), based in Saskatoon, Canada. Mang'era was previously director of the radiopharmacy for Winnipeg Health, a technical/scientific leader for the Prairie Isotope Production Enterprise, and head of the Radiopharmaceuticals Research Group. In these roles, he led critical research initiatives into isotope production technologies prior to joining the commercialization private company, CIIC, as a founder and COO. Mang'era is an adjunct professor at the University of Winnipeg, and is past president of the Canadian Association of Radiopharmaceutical Scientists.

Anupam Mathur is a scientist working in the Radiopharmaceuticals Program of the Board of Radiation and Isotope Technology (BRIT), Department of Atomic Energy, India. He joined the department after completing 1 year of training in radiochemistry from Bhabha Atomic Research Centre, India. Currently, he is involved in bulk production of a few regular ready-to-use injectable radiopharmaceuticals based on radioisotopes such as ^{131}I/^{32}P/^{153}Sm/^{177}Lu supplied by BRIT for clinical end use. His research interests include designing of novel ^{68}Ga/^{99m}Tc/ ^{188}Re/^{177}Lu-labeled molecules for varied diagnostic and therapeutic applications.

Boris Myasoedov is deputy secretary general for science of the Russian Academy of Sciences (RAS), head of laboratories at both the RAS Vernadsky Institute of Geochemistry and Analytical Chemistry and the RAS Frumkin Institute of Physical Chemistry and Electrochemistry. His scientific activity covers such fields as the fundamental chemistry of actinides, fuel reprocessing, partitioning of radioactive waste, and environmental protection. Myasoedov graduated from D.I. Mendeleev Chemical-Technology Institute in Moscow in 1954 and earned a Ph.D. in radiochemistry from the Vernadsky Institute in 1965 and his full doctorate in 1975 from the same institute. He was elected to the Russian Academy of Sciences in 1994 and has been awarded two State Prizes for his research on the chemistry of transplutonium elements (1986 and 2001), the Khlopin Prize for his studies of the chemistry of protactinium (1974), and the Ipatiev Prize of the RAS Presidium in 2003.

Evgeniy Nesterov is a research scientist in Laboratory No. 31 at the Nuclear Reactor, Institute of Physics and Technology, Tomsk Polytechnic University. He has 16 years of experience in research on and development on medical isotopes production and applications. Nesterov's Ph.D. thesis was about production of Tc-99m generators. He has published more than 80 articles and is co-author of 8 patents.

Rodolfo Núñez-Miller is a board-certified nuclear medicine physician with more than 20 years' experience in the field of nuclear medicine and molecular imaging. His background training was in internal medicine. Currently, he works as technical officer at the headquarters of the International Atomic Energy Agency in Vienna, Austria.

Joao Osso, from Brazil, holds the degrees of Ph.D. in nuclear chemistry from the University of Manchester, England, M.Sc. in nuclear engineering from the Federal University of Rio de Janeiro (UFRJ), Brazil, and B.Sc in chemistry from the University of Sao Paulo (USP), Brazil. He had more than 34 years of experience in the field of radioisotope and radiopharmaceutical production in Brazil before joining the International Atomic Energy Agency (IAEA) in February 2014. He is currently the head of the Radioisotope Products and Radiation Technology Section of the Division of Physical and Chemical Sciences at the IAEA in Vienna, Austria.

Ul-Jae Park works for the RI Research Division at the Korea Atomic Energy Research Institute (KAERI).

David Pellicciarini is vice president, Pharmacy Safety, Practice, and Technical Operations for Cardinal Health Nuclear Pharmacy Services (NPS). NPS operates 130 nuclear pharmacies, 30 positron emission tomography (PET) drug manufacturing facilities, and other radioactive drug manufacturing facilities. Pellicciarini has 25 years of experience in the radiopharmaceutical industry, including nuclear pharmacy, SPECT drug manufacturing, and PET

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drug manufacturing. He holds a B.S. in physics from the University of Nevada, Reno, and an M.B.A. from the University of California at Los Angeles. He is a certified health physicist (by the American Board of Health Physics).

Eugene Peterson is executive advisor to Los Alamos National Laboratory's associate director for chemistry, life, and earth sciences and is leading the laboratory's strategic planning efforts for the Science of Signatures Science Pillar. Previously, he was the chemistry division leader at Los Alamos, where he was responsible for 350 chemical professionals and a budget of approximately $150 million. Before his tenure as chemistry division leader, Peterson specialized in medical isotope production and applications research and development. Peterson served on the National Academies Committee on Medical Isotope Production Without Highly Enriched Uranium (2007-2009) and the Committee on the State of Molybdenum-99 Production and Utilization and Progress Toward Eliminating Use of Highly Enriched Uranium (2014-2016). He received his B.S. from the Illinois Benedictine College and his Ph.D. in inorganic chemistry from Arizona State University.

Katrina Pitas is vice president, Business Development, of SHINE Medical Technologies, Inc. Before joining SHINE in 2011, Pitas did research and development work for Phoenix Nuclear Labs. In her capacity as vice president of Business Development, she has played a key leadership role in implementing SHINE's strategic vision and driving SHINE's growth and development. Pitas was a key player in securing early funding for SHINE, and has also made important contributions to SHINE's regulatory efforts. Pitas received her undergraduate degree in physics from Carleton College, and before joining Phoenix Nuclear Labs, she gained experience living in both China and Japan.

Bernard Ponsard has a master's degree in physics (1983) and a master of science degree in nuclear energy (1985) from the Université Catholique de Louvain, Belgium. He joined the Belgian Nuclear Research Centre (SCK•CEN) in Mol in 1985 as a reactor physicist at the BR2 high-flux material testing reactor. He is currently head of the Radioisotopes and Silicon Production Unit at the BR2 reactor and is in charge of the strategic development of new medical radioisotopes for nuclear medicine, new radioisotopes for industrial applications, and new products for the semiconductor industry within SCK's Institute for Nuclear Materials Science (NMS). He was chairman of the AIPES Reactors & Isotopes Working Group from 2010 until 2017 for securing the global supply of medical radioisotopes as Mo-99/Tc-99m. He is currently co-chair of the AIPES Security of Supply Working Group, chair of the Emergency Response Team, and chair of the European Observatory Working Group for the European Supply of Medical Radioisotopes—Global Reactor Scheduling and Mo-99 Supply Monitoring.

Yuri Shiyan is the director of the Russian Academy of Sciences (RAS) Committee on International Security and Arms Control and the head of the Office for Coordination of International Scientific Programs and Projects. He has worked in this capacity for more than 25 years, facilitating collaborative efforts and exchanges between international partners and Soviet/Russian scientists, engineers, and medical professionals. From 2004 through 2005, he served as an expert to the International Atomic Energy Agency Nuclear Fuel Subcommittee. For the past several years, he has served as coordinator of the RAS and National Academy of Sciences committees on counterterrorism and nonproliferation. Further, he has assisted several joint U.S.-Russian projects focusing on various aspects of the nuclear fuel cycle, including the storage of spent nuclear fuel.

Viktor Skuridin is the head of Laboratory No. 31 at the Nuclear Reactor, Institute of Physics and Technology, Tomsk Polytechnic University (TPU). He has 50 years of experience in medical isotopes production and applications research and development. He is leader of a research group in nuclear medicine at TPU. He is co-author of more than 150 articles and 30 patents. He is an Honored Worker of Science and Technics of the Russian Federation and holder of various other prizes.

Katherine (Kath) Smith is currently the counsellor nuclear at the Australian Embassy and Permanent Mission to the United Nations in Vienna. In this role, she develops briefs that underpin policy; participates in the Australian delegations to meetings convened by the United Nations; and manages relationships and facilitates interactions

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and dealings between Australian Departments and Agencies and the International Atomic Energy Agency (IAEA), the OCED Nuclear Energy Agency (in Paris), and other nations/agencies. She also contributes to research related to nuclear waste forms and related materials. This role is fully funded by the Australian Nuclear Science and Technology Organisation (ANSTO).

Riane Stene graduated from the University of Texas at El Paso with a bachelor's degree in chemistry. She then moved to the Pacific Northwest to pursue a master's degree in radiochemistry from Washington State University. Currently, she is working on her Ph.D. as a joint student between the Technical University of Munich and Philipps University Marburg. Her Ph.D. research focuses on the dry chemical separation of molybdenum from uranium. After she earns her Ph.D., she would like to continue working in the field of molybdenum-99 production for medical use.

Bertrand Stepnik is working at AREVA. He is head of the CERCA research and development department. He has an engineering degree and a Ph.D. in physics. He is AREVA's expert in uranium metallurgy.

Jean-Michel Vanderhofstadt serves as the chief executive officer of L'Institut National des Radioéléments (IRE); general manager of its subsidiary IRE-Environment and Lifescience Technology (IRE-ELiT SA), specializing in the production of medical radioisotopes for nuclear medicine; and president of TransRad, an IRE subsidiary company specializing in the transport of radioactive and nuclear material. Vanderhofstad also currently serves as the vice president and treasurer of the Association of Imaging Producers and Equipment Suppliers, which represents many of the major pharmaceutical and imaging equipment companies in the field of nuclear medicine in Europe; is the board director of BioWin, a local government-funded organization drawing together stakeholders (companies, research centers, and universities) involved in innovative research and development projects and/or skills development in the field of health biotechnology and medical technologies; and is an associate professor at the University of Liège, Belgium. Vanderhofstadt graduated from the University of Liège where he obtained a degree of industrial pharmacist and from the Free University of Brussels where he earned a post-degree in business management.

Jan Willem Velthuijsen is chief economist at PwC (PricewaterhouseCoopers) Europe. At PwC, he is responsible for the Competition & Regulation team, which supports companies, governments, and regulators on questions about market definition, competition, market entry, liberalization of markets, privatization, and state aid. He has worked in numerous industries, such as energy, financials, telecoms, transport and logistics, and healthcare. For 3 years, he has been responsible for the Thoughtleadership Programme of PwC Europe. He holds a chair in economics at the University of Groningen and is a visiting professor at the University of Oklahoma.

Meera Venkatesh is director of the Division of Physical and Chemical Sciences in the Department of Nuclear Applications at the International Atomic Energy Agency (IAEA). She is responsible for programs on radioisotope production and applications, radiation technology, and nuclear sciences. Before joining the IAEA in 2011, she worked for 34 years at the Indian Department of Atomic Energy, beginning as a young researcher in the area of radioisotopes and radiopharmaceuticals and growing to lead the Radioisotope and Radiopharmaceuticals Program for which she received awards of excellence from the Indian Nuclear Society and the Department of Atomic Energy, India. She has authored more than 200 papers in international journals and several book chapters and is an editor of two international journals. She has guided 12 Ph.D. students in areas of her expertise and is passionate about promoting peaceful applications of nuclear technologies.

Wolfgang Weber is a nuclear medicine physician with expertise in molecular imaging and targeted radionuclide therapy—particularly in the use of positron emission tomography in oncology. In addition to his role as chief of the Molecular Imaging and Therapy Service, he also serves as director of the Laurent and Alberta Gerschel Positron Emission Tomography Center at Memorial Sloan Kettering.

Christophe Xerri has 25 years of experience in nuclear fuel cycle and waste management. Before his appointment

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to the International Atomic Energy Agency, he served from 2011 to 2015 as counsellor for Nuclear Affairs to the French Embassy in Japan and in Mongolia. He joined COGEMA (now AREVA) in 1991, in the field of spent fuel and waste management. He then moved to uranium mining and enrichment technology. Later, he worked in nonproliferation and international relations, and then was assigned to the office of the president of AREVA. He moved to Japan in 2007 and became vice president of Mitsubishi Nuclear Fuel in 2009, where he was also involved in handling the consequences of the earthquake and tsunami of March 2011.

Sergey Yudintsev is head of the Laboratory of Radiogeology and Radiogeoecology at the Institute of Geology of Ore Deposits, Petrography, Mineralogy, and Geochemistry of the Russian Academy of Sciences (IGEM RAS). He is a specialist in the field of management of radioactive waste derived in the closed nuclear fuel cycle. He graduated from Moscow State University (1981, geochemistry) and received his Ph.D. (1989) and Dr.Sc. (2009) degrees from the IGEM RAS. He was elected as a corresponding member of the RAS in 2011. He is now involved in research on geochemical-mineralogical aspects of safe radioactive waste disposal, including searching for new matrices for isolation of long-lived actinides and fission products. Dr. Yudintsev has published more than 250 papers in Russian and international journals and presented these results at a number of international conferences. He participated in the meetings of the Russian and American experts (Global Nuclear Energy Partnership and Advanced Fuel Cycle Initiative workshops).

Boris L. Zhuikov is head of the Laboratory of Radioisotope Complex of the Institute for Nuclear Research (INR) of the Russian Academy of Sciences in Moscow. He is responsible for the radioisotope investigation and production program at INR, including medical isotope investigation and production. He has been the project leader on a number of successful mutual U.S.-Russian Global Initiatives for Proliferation Prevention (GIPP) projects for development of medical isotope production. Zhuikov has been at INR since 1987. Prior to his employment at INR he was a research scientist at the Joint Institute for Nuclear Research, an international research center for nuclear sciences located at Dubna, Moscow Oblast. Zhuikov is author and co-author of more than 200 scientific and popular science publications including a review of medical isotope production in Russia. He is a member of the Scientific Council of the Institute for Nuclear Research of the Russian Academy of Sciences, the Russian Society of Nuclear Medicine, the American Nuclear Society, and the International Society of Nuclear Chemistry. He holds a B.Sc. in chemistry and a Ph.D. in radiochemistry from Moscow State University.

STAFF

Ourania (Rania) Kosti joined the staff of the Nuclear and Radiation Studies Board (NRSB) of the National Academies of Sciences, Engineering, and Medicine in January 2011. Prior to her current appointment, she was a postdoctoral fellow at the Lombardi Comprehensive Cancer Center at Georgetown University Hospital in Washington, D.C., where she conducted research on biomarker development for early cancer detection using case-control epidemiologic study designs. She focused primarily on prostate, breast, and liver cancers and identification of those individuals who are at high risk of developing malignancies. Kosti also trained at the National Cancer Institute (2005-2007). She received a B.Sc. in biochemistry from the University of Surrey, UK, an M.Sc. in molecular medicine from University College London, and a Ph.D. in molecular endocrinology from St. Bartholomew's Hospital in London, UK. Kosti's interests within the NRSB focus on radiation health effects.

Rita Guenther, senior program officer for the National Academy of Sciences' Committee on International Security and Arms Control (CISAC), is the responsible staff officer for this project. Recipient of a Fulbright-Hays Doctoral Dissertation Research Fellowship, Guenther manages CISAC's Russia Dialogue. She has worked on or led several cooperative U.S.-Russian and Indo-U.S. projects, including a joint U.S.-Russian workshop on the future of the nuclear security environment in 2015; a study on indigenization of Russian nuclear material protection, control, and accounting programs; and Indo-U.S. workshops on science and technology for nuclear material security and on science and technology to counter terrorism. The Office of Science and Technology Policy and the Office of the Science and Technology Advisor to the Secretary of State has consulted her concerning reforms in Russian science.

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Guenther received the National Academies distinguished service award in 2007. She speaks Russian fluently and holds an M.A. in Russian studies and a Ph.D. in history from Georgetown University.

Frances Marshall has been the project manager for the Research Reactor Fuel Cycle project in the Research Reactor Section at the International Atomic Energy Agency (IAEA), responsible for supporting Member States with research reactor fuel cycle issues since 2014. Prior to joining IAEA, she was manager of the Advanced Test Reactor (ATR) National Scientific User Facility (NSUF) Program at Idaho National Laboratory (INL) in the United States. She co-led the team to establish the ATR NSUF. At INL, Marshall supported and led projects in the areas of irradiation experiments, nuclear power plant engineering, nuclear power plant probabilistic risk analysis, and regulatory assessment. Marshall earned a bachelor's degree in nuclear engineering from the University of Virginia (UVA) and a master's degree in chemical engineering from the University of Idaho, and is a registered professional engineer. She held a reactor operator license on the UVA Reactor and worked in the commercial nuclear power industry as a startup engineer, plant systems engineer, and reactor engineer for 9 years prior to working at INL.

Tom Hanlon is a nuclear engineer in the Research Reactor Section at the International Atomic Energy Agency, responsible for project activities related to the low-enriched uranium conversions of Miniature Neutron Source Reactors (MNSRs) and production of Mo-99 without the use of highly enriched uranium. Prior to joining the IAEA, Hanlon served as a technical advisor to the National Nuclear Security Administration's (NNSA's) Mo-99 Program. He has also served as a project and program manager at the Y-12 National Security Complex and as an accelerator specialist at the Oak Ridge National Laboratory's Spallation Neutron Source. Hanlon holds a master of business administration degree from the College of William and Mary, a master of science degree in applied physics from the University of Tennessee, and bachelor of arts degrees in both physics and music from Ripon College.

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Appendix C

List of Participants

Last Name	First Name	Country	Organization—Official Name
Ahmad	Umar Farouk	Nigeria	Bayero University, Kano
Ball	Gavin	South Africa	NTP Radioisotopes SOC, Ltd.
Begg	Bruce	Australia	Australian Nuclear Science & Technology Organisation
Bigles	Carmen	USA	Coquí RadioPharmaceuticals Corp.
Brown	Roy	USA	Curium
Buchheim	Georg	Germany	Siemens Healthineers
Buckley	Ken	Canada	TRIUMF
Bychkov	Alexander	Russia	Embassy of the Russian Federation
Chamberlin	Jeff	USA	National Nuclear Security Administration
Chiba	Hiroyuki	Japan	Marubeni Utility Services, Ltd.
Cholakian	Egon	USA	Harvard University/NIH
Coffey	Jack	USA	Enigma Biomedical Group
Cox	Brett	USA	National Nuclear Security Administration
Cristini	Pablo	Argentina	National Atomic Energy Commission
Critch	Christopher	Canada	Nordion
Dambele	Musa	Nigeria	Bayero University, Kano
Dhavle	Jaidev	Austria	International Atomic Energy Agency
Doss	Michael	USA	Cardinal Health
Druce	Michael	Australia	Australian Nuclear Science & Technology Organisation
Du	Jin	China	China Isotope & Radiation Corporation
Elaal	Mostafa Abd	Egypt	Egyptian Atomic Energy Authority

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Last Name	First Name	Country	Organization—Official Name
Falaleyev	Andrey Gerkurievich	Russia	Language Exchange Translations
Ferguson	Charles	USA	Federation of American Scientists
Goldman	Ira	USA	Lantheus Medical Imaging
Goulart	Margarida	EU	European Commission
Guastella	Michael	USA	Council on Radionuclides and Radiopharmaceuticals, Inc.
Guenther	Rita	USA	National Academies
Guinard	Yann	France	AREVA
Guo	Chunsheng	China	HTA Co., Ltd.
Haass	Carolyn	USA	Northwest Medical Isotopes, LLC
Hanlon	Tom	Austria	International Atomic Energy Agency
Harvey	James	USA	NorthStar Medical Technologies, LLC
Hricak	Hedvig	USA	Memorial Sloan Kettering Cancer Center
Kalmykov	Stepan	Russia	Moscow State University
Kim	Kinam	Korea	Korea Atomic Energy Research Institute
Kononov	Oleg	Russia	Karpov Scientific Research Institute of Physics and Chemistry
Kosti	Ourania	USA	National Academies
Laas	Roman	Russia	Tomsk Polytechnic University
Lish	Matthew	USA	Flibe Energy
Malofeeva	Elena	Russia	Language Exchange Translations
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Messina	George	USA	NorthStar Medical Technologies, LLC
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Raseruthe	Fannie Ben	South Africa	NTP Radioisotopes SOC, Ltd.
Risovaniy	Vladimir	Russia	Rosatom
Rodriguez	Stephanie	USA	U.S. Permanent Mission to International Organizations in Vienna
Sano	Masaaki	Japan	Marubeni Utility Services, Ltd.
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Skuridin	Viktor	Russia	Tomsk Polytechnic University
Smith	Katherine	Australia	Australian Embassy and Permanent Mission to the United Nations in Vienna
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