We trust you will find our report useful in deciding on the best path forward for securing supply of Tc-99m for the Canadian health care system over the medium to long term.

Yours sincerely,

The Expert Review Panel on Medical Isotope Production:

Mr. Peter Goodhand, Chair

Mr. Richard Drouin

Dr. Thom Mason

Dr. Éric Turcotte

Report of the Expert Review Panel on Medical Isotope Production

Presented to the Minister of Natural Resources Canada

30 November 2009

Table of Contents

Executive Summary

The Expert Review Panel on Medical Isotope Production (the Panel) was established on June 19, 2009, to advise the Government of Canada on the most viable options for securing a predictable and reliable supply of the key medical isotope technetium-99m (Tc-99m) in the medium to long term. This report is the culmination of that work, and presents recommendations that, in our opinion, will move Canada toward a new model for sustainable and secure long-term production of medical isotopes. We recognize that the government must ultimately select the best path forward for Canada, taking into account the broader nuclear energy and health care policy considerations that are outside the mandate of the Panel.

As part of this work, an expression of interest (EOI) process was launched to solicit ideas for alternative production of molybdenum-99 (Mo-99)/technetium-99m (Tc-99m) for the Canadian market in the medium to long term. We received 22 EOIs from a range of public and private sector organizations and reviewed the EOIs against specified criteria:

- Technical Feasibility;
- Business Implementation;
- Timeliness;
- Regulatory Issues; and
- Benefits to Canadians.

The EOIs proved very useful in identifying broad classes of technology options available. We greatly appreciated the time and effort invested by the proponents — we reviewed and assessed every EOI, and they played an important role in forming the content and recommendations presented here.

We also engaged medical, technical and regulatory experts to enhance our understanding of the many considerations involved in a long-term plan to secure medical isotope supplies. Among others, we received information from:

- Atomic Energy of Canada Limited;
- the Canadian Association of Medical Radiation Technologists;
- the Canadian Association of Nuclear Medicine;
- the Canadian Association of Radiologists;
- the Canadian Association of Radiopharmaceutical Scientists;
- the Canadian Institutes of Health Research;
- the Canadian Medical Association;
- the Canadian Society of Nuclear Medicine;
- the Canadian Society of Senior Engineers;
- individual nuclear medicine specialists;

- International Safety Research Inc.;
- the Ontario Association of Nuclear Medicine;
- the Royal College of Physicians and Surgeons of Canada - Nuclear Medicine Specialty;
- SECOR Inc.;
- SNC Lavalin Inc.;
- 15 independent and internationally known technical experts;
- other national and international stakeholders; and
- a Tc-99m generator manufacturer.

Throughout, our focus and attention remained on the best interests of patients and their families and the health care needs of Canadians.

Our report is structured around major classes of technology, with each technology option assessed against the specified criteria. The technologies are:

- **Reactor technology**

  1. New multi-purpose research reactor — fission option
  2. Dedicated Isotope Facility — fission option
  3. Existing reactors — fission option

- **Accelerator technology**

  4. Linear accelerator — photo-fission option
  5. Linear accelerator — Mo-100 transmutation option
  6. Medical cyclotron — direct Tc-99m option

Sustainability and Security

Through our work and our assessments, we established parameters to define a sustainable and secure supply of Tc-99m in the medium to long term. A **sustainable** supply of Tc-99m to serve the needs of Canadian patients would:

1. be viable for the foreseeable future, likely for at least 15 to 20 years, and may include options that begin producing in the short to medium timeframe but that promise to remain viable;
2. comprise options that could each meet a meaningful portion of the Canadian demand, but that would not necessarily be exclusively Canadian-based and may or may not serve the U.S. or other markets;
3. have a sound business model that may or may not include government involvement; and
4. be free of highly enriched (weapons-grade) uranium (HEU) because of Canadian and global commitment to non-proliferation.

A **secure** supply of Tc-99m would:

5. improve redundancy at all points in the supply chain to avoid the “single point of failure” risk associated with a linear supply chain;
6. use diverse technologies to hedge against a failure that could arise if all suppliers used the same technology;
7. collocate irradiation and processing facilities to minimize decay losses and avoid shipping losses and risks; and
8. ensure sufficient capacity to accommodate short-term outages of some sources.

Establishing these parameters for sustainable and secure supply helped to frame how we assessed the likelihood of various technology options contributing to a stable isotope supply in the long term.

Key Findings for Technology Options

The most significant findings for each technology are given below. A full assessment of each technology option against all established criteria is given in Chapter 5.

1. New Multi-purpose Reactor Option

The lowest-risk path to new Mo-99/Tc-99m production capacity is to build a new multi-purpose research reactor. The research reactor also promises the most associated benefits to Canadians based on its multiple purposes.

Research reactors are shared facilities that have all the benefits associated with multi-use facilities, including the benefit of costs being spread over a large base of activities. However, this is the most expensive of the options, with high capital and operating costs. Costs associated with the processing facility, training, licensing requirements, security, and waste management are also very significant.

Revenue from isotope production would likely offset only approximately 10–15% of the costs of the reactor; building a new reactor would have to be justified, in large part, based on its other missions.

Given the established parameters for sustainability, any new reactor-based source of Mo-99 should be based on low enriched uranium (LEU) targets; some research and development (R&D) would be required to optimize the process and deal with the increased volumes of waste.

Of all the technology options, this one has the highest potential for concomitant benefit to Canadians based on the promise of the broad-based research that would be undertaken, and its associated potential for generating intellectual property, job creation and training.

2. The Dedicated Isotope Facility (DIF) Option

This option involves restarting the DIF project, which included two Multi-purpose Applied Physics Lattice Experiment (MAPLE) reactors, the New Processing Facility (NPF) and associated waste management structure. These facilities were never fully commissioned, and are in an extended shutdown state.

The DIF was designed and optimized to use HEU targets. Moreover, the design of the MAPLE reactors, the NPF and the associated waste management structure was heavily customized and dedicated to isotope production. This customization would pose significant challenges for possible modification and conversion to LEU, which, in our opinion, is mandatory for any medium- to long-term plan.

Furthermore, even if the existing infrastructure were to come at no cost, the ongoing economics for this project remain questionable because high operating costs cannot be shared across multiple uses. The fact that no dedicated isotope production reactors have been built and operated or are in planning anywhere in the world (with the exception of the DIF) suggests that others recognize the economic difficulties of this option.

Estimates for the timeline range from two to eight years. Although the best-case scenario of two years to market is attractive, we expect the timeline to be longer given the challenges with the processing facility, in addition to the licensing challenges.

3. Existing Reactor Option

Other existing research or power reactors, either domestically or internationally, could be used to irradiate targets for the production of Mo-99. Generally, projects associated with existing reactors are based on the use of modified processing facilities at AECL and the existing supply chain. Because research reactors are less powerful and consequently less efficient for isotope production, they require the use of HEU targets to achieve worthwhile yields.

While conversion to LEU would be possible, it may not be justifiable based on the limited remaining lifespan of the facilities. Nonetheless, HEU-based

options in this category should be considered as options to address short-term supply shortages.

4. Linear Accelerator — Photo-fission Option

A particle accelerator is a device that uses electric fields to accelerate ions or charge subatomic particles to high speeds in well-defined beams to bombard targets for research and isotope production.

In this option, a high-power electron linear accelerator is used to bombard a converter to produce an intense photon beam to generate Mo-99 through nuclear interactions with natural uranium.

The required accelerator is not currently available, but the development is technically low risk. Substantial R&D is needed for the target and converter design, the cooling capacity and overall process optimization.

To meet the required production levels, the accelerators would be dedicated to isotope production, and would not be available for research or any other purpose. This option suffers from poor economics because capital investment is relatively high and cannot be shared across multiple missions.

Although the cost of an individual accelerator is much less than that of a reactor, as many as four accelerators would be needed to meet Canadian demand, and they would be relatively expensive to build and operate based on the high power requirement. When costs associated with processing and waste management are included, the total costs of the option could exceed $500M.

As a fission-based approach, this option would likely fit well into the existing supply chain; however, significant quantities of nuclear waste would be generated.

5. Linear Accelerator — Mo-100 Transmutation Option

An electron linear accelerator can produce Mo-99 through the transmutation of enriched Mo-100.

The Mo-100 option requires significant R&D regarding targetry and cooling capacity, as well as the development and marketing of a new type of generator. There is some concern that hospitals may not accept the new generators, and that this new product may not be able to compete with the traditional generators, presenting significant business risk.

Currently, there is no commercial production of purified Mo-100. The cost of the quantity needed could be substantial and may prove to be a barrier to commercialization. A full recycling of Mo-100 could reduce the cost substantially by minimizing loss, but recycling is yet to be demonstrated, and significant R&D would be required.

As in the case of photo-fission, the accelerators used for Mo-100 transmutation would likely need to be dedicated to isotope production to achieve the desired production levels, making this a single-use option. Return on investment would be difficult given the current price for Mo-99 and the significant costs, which cannot be shared across multiple missions.

A significant advantage of this option from an environmental and cost point of view is that it does not generate nuclear waste.

6. Cyclotron Option

A cyclotron is also a particle accelerator device. This option is based on bombarding Mo-100 with protons to extract Tc-99m directly from the irradiated product.

This is the only option in which Tc-99m is produced directly without first generating Mo-99.

Because the production of Tc-99m using cyclotrons is at an early stage of development, it is difficult to say how much of the Canadian market could be or would be served by cyclotrons. However, it is attractive because the cyclotron infrastructure could be in place and used for other purposes, but could still offer surge capacity to augment other sources.

Although significant R&D is required, the infrastructure to undertake the research, demonstration and initial production is presently available. Therefore, costs are relatively low and timelines for the R&D are relatively short.

This option can be implemented on a gradual basis since the model is for a distributed system with each cyclotron serving only local radiopharmacies and nuclear medicine departments. Communication and collaboration between medical cyclotron operators could ensure redundancy in supply and avoid single point of failure in the supply chain.

The cyclotron option is not a complete solution; because the half-life of Tc-99m is short, only hospitals and radiopharmacies close to a cyclotron would be served. More remote locations would continue to be served by Tc-99m generators, likely through existing supply chains. As a result there will be a need for Mo-99 to meet Canadian needs for the foreseeable future, although this could coexist with direct Tc-99m production.

Difficulties with this option include the requirement for R&D associated with target design and Mo-100 recycling. This option may require more validation from a Health Canada regulatory perspective. Currently, there is no commercial production of purified Mo-100. The cost could be high and may prove to be a barrier to commercialization.

An important consideration is that this option does not produce nuclear waste, which results in economic and environmental benefits over fission-based options.

The cyclotron option has the potential to be the timeliest option. Commercial production of Tc-99m could begin between 2011 and 2014, depending primarily on results of R&D and health regulatory issues.

General Recommendations

1. Strive for diversity and redundancy throughout the supply chain.

We recommend adopting a supply strategy offering technological diversity, and redundancy at every step in the supply chain.

2. Leverage multi-use infrastructure.

We recommend investing in infrastructure that is designed to have multiple purposes and is more likely to remain useful over the long term, regardless of how the use of medical isotopes evolves.

3. Continue with international coordination, and seek processing standardization within North America.

We recommend that the government continue to inform itself of all international isotope initiatives, and work with other countries to better coordinate worldwide efforts around isotope production and distribution. We also encourage the government to start laying the groundwork now for establishing target and target processing compatibility, especially for any new sources developed in North America.

4. Recognize that HEU options are viable only in the short to medium-term.

We recommend that any option reliant on HEU be dismissed as a long-term solution. As a proponent of non-proliferation, Canada must work to eliminate HEU from civilian use. Because many options associated with existing reactors are based on using HEU targets, they should be considered only within a short-term context.

Technology-specific Recommendations

1. Make policy decisions on the requirement for a new research reactor.

We recommend that the government expeditiously engage in the replacement of the NRU reactor as we believe a multi-purpose research reactor represents the best primary option to create a sustainable source of Mo-99, recognizing that the reactor's other missions would also play a role in justifying the costs. With the National Research Universal (NRU) reactor approaching the end of its life cycle, a decision on a new research reactor is needed quickly to minimize any gap between the start-up of a new reactor and the permanent shutdown of the NRU. If the decision is to not build a new research reactor, the issue of securing supply of Tc-99m will have to be revisited in light of how cyclotron/accelerator options are advancing, and what new foreign sources of isotopes have materialized.

2. Support an R&D program for cyclotron-based Tc-99m production.

We recommend that the cyclotron option for direct production of Tc-99m, which has many attractive features, be explored further. Although this option requires significant R&D, the infrastructure and know-how to undertake that work is readily available in Canada so costs associated with the R&D remain relatively low. Assuming technical viability, the infrastructure necessary to demonstrate this approach in selected centres across Canada is already in place. Indeed, Canada has an opportunity to be a leader in this area and strengthen its existing related businesses.

3. Achieve better use of Tc-99m supply through advanced medical imaging technologies.

We recommend deployment of newer single photon emission computed tomography (SPECT) technologies (software and hardware), as well as investment in positron emission tomography (PET) technology, to reduce demand for Tc-99m now and over the longer term, which would reduce the impact of future shortages of reactor-produced isotopes.

Other Considerations

1. Linear accelerator options

The two linear accelerator options have limited prospects for multi-purpose use, require significant R&D, and may not have significant cost advantages over reactor technologies. Nonetheless, a modest R&D investment could be considered as a hedge against the risk of failure of other options. Of the two linear accelerator options, we prefer the technology based on Mo-100 transmutation since the projected economics appear better, and it largely avoids nuclear waste management issues.

2. Dedicated Isotope Facility (DIF) infrastructure

Cost and timeline estimates associated with the commissioning and licensing of the DIF varied widely. Although it may be possible to bring them into operation, the business case is such that even if the DIF facilities could be licensed immediately at no cost, the ongoing revenues from isotope sales would be insufficient to cover the ongoing operating expenses, particularly with the anticipated reduced throughput from future conversion to LEU targets. A dedicated isotope facility based on a private sector cost-recovery model would be a good solution assuming a private sector organization would be willing to accept the full commercial risk associated with this model.

Chapter 1

Introduction

The Expert Review Panel on Medical Isotope Production (the Panel) was established on June 19, 2009, to advise the Government of Canada on the most viable options for securing a predictable and reliable supply of medical isotopes[1] in the medium to long term. We, Peter Goodhand (Chair), Richard Drouin, Thom Mason and Éric Turcotte,[2] served as members of the Panel, and we sought to understand this complex issue from multiple perspectives including business, technical, medical and policy angles.

This report is the culmination of that work, and presents options that, in our opinion, will move Canada toward a new model for sustainable and secure long-term production of technetium-99m (Tc-99m), recognizing that the decision as to the best path forward for Canada must ultimately be made by government, taking into account the broader nuclear energy and health care policy considerations that are outside the scope and understanding of the Panel.

Since the inception of its nuclear fission program in the 1940s — as part of the Allied effort during the Second World War — Canada has been a world leader in the development of nuclear energy. The benefits of nuclear research and development (R&D) in Canada have extended far beyond energy, encompassing more fundamental nuclear and materials research including work leading to the 1994 Nobel Prize in Physics. Canada's nuclear program pioneered a number of medical applications of nuclear energy, including the production and use of medical isotopes. Canada's leadership in medical isotope production began with the supply of cobalt-60 for nuclear medicine procedures, which led to the world's first two cobalt-60 teletherapy cancer treatment units in London, Ontario, and Saskatoon, Saskatchewan (Ullyett, 1997). Canada's leadership continues with the National Research Universal (NRU) reactor having supplied a variety of medical isotopes including 30 - 40% of the global supply of molybdenum-99 (Mo-99). Tc-99m is the most commonly used isotope in nuclear medicine, and is produced from the radioactive decay of Mo-99 (which makes Tc-99m the daughter isotope of Mo-99).

[1] Throughout the document, unless otherwise indicated, the term "isotopes" refers to medical isotopes.
[2] See Appendix 1 for biographies of the Panel members.

A central component of the infrastructure supporting Canada's nuclear and related science and technology since 1957 has been the NRU reactor. Designed to be a flexible and robust neutron source (hence the *U* for Universal in its name), it has supported power reactor fuels development, materials testing, neutron beam research and isotope production. Over its operating life, the mission of the NRU has evolved in response to changing national priorities (Mo-99 is one example of such an emergent mission). However, the NRU reactor shutdown at Chalk River Laboratories (CRL) in December 2007 and, more recently, the 2009 outage, have served to highlight the fragility of the global Mo-99/Tc-99m supply chain. Currently, the production of these isotopes is dependent on a handful of ageing nuclear reactors, the NRU among them.

In response to the ongoing fragility of the supply chain, the Government of Canada implemented a five-point action plan to protect the health and safety of Canadians. This Panel was announced as part of that plan, and an expression of interest (EOI) process was launched to solicit ideas for alternative production of Mo-99/Tc-99m for the Canadian market in the medium to long term.

We received 22 EOIs from a range of public and private sector organizations and reviewed them against specified criteria:

- Technical Feasibility;
- Business Implementation;
- Timeliness;
- Regulatory Issues; and
- Benefits to Canadians.

We also engaged medical, technical and business experts to provide input to enhance our understanding of the many considerations involved in a long-term plan to secure isotope supplies.

Based on the information gathered, this report provides advice and recommendations to the Government of Canada on the most promising options for securing a sufficient and reliable supply of Tc-99m for the Canadian market in the medium to long term, taking into account the changing landscape of nuclear medicine imaging.

Throughout, our focus and attention remained on the best interests of patients and their families and the health care needs of Canadians. Our mandate was to focus on the medium to long term. However, we know that short-term issues also need to be addressed. We appreciate the efforts of others, including those in government and the medical community, to limit the impacts of Tc-99m shortages on patients in the short term.

Chapter 2

Panel Activities and Processes

This chapter presents our mandate and the activities we undertook in fulfilling that mandate.[3]

The timelines established for the Panel were very short given the complex nature of isotope production and use, and the extent to which stakeholders needed to be engaged for us to understand the context and options available. From the launch on June 19, 2009, to the delivery of this report on November 30, 2009, we have worked very hard to arrive at the most informed advice possible. We would like to point out that all stakeholders, and especially proponents of the expressions of interest (EOIs), were under significant time constraints. Nonetheless, proponents provided detailed information that proved invaluable in our work and integral to establishing our recommendations.

We describe our activities and processes so that readers may understand the nature and scope of our work, and view our recommendations with the knowledge of the constraints and limitations of our processes and analyses.

2.1 Mandate

When it was established, the Panel was asked to report to the Minister of Natural Resources on its assessment of the most viable options for securing supplies of Tc-99m to the Canadian health system over the medium and long term, including identifying actions that may be required of governments and others to facilitate realization of the options.[4]

The Government of Canada has put in place other initiatives and mitigation strategies in the short term to address demand for Tc-99m while supplies are still falling short. As a Panel, we have considered short-term initiatives, mitigation strategies and short-term impacts only insofar as they were relevant to longer-term considerations.

[3] See Appendix 2 for a chronology of the Panel's activities.
[4] See Appendix 3 for the Terms of Reference of the Panel.

2.2 Expressions of Interest

At the time the Panel was announced, a call for Expressions of Interest (EOI) was put out to public and private sector organizations for submissions on alternative production of Mo-99/Tc-99m. In response to the call, 22 EOIs were received, and all were assessed against the established criteria described below[5]:

- Technical Feasibility: the scientific and technical merits of projects taking into account risks associated with the introduction of new technologies and the likelihood that technologies could be realized on a commercial scale.
- Business Implementation: the business merits of the projects, taking into account the partnerships established by the proponents; funding requirements and secured resources; access to existing or new physical infrastructure; the ability of the proponents to integrate their proposal in a supply chain; cost structure and required revenue from market or other sources; and business risks associated with these elements.
- Timeliness: the schedule for implementing projects, including the risks of delays.
- Regulatory Issues: the capacity of proponents and the project to meet nuclear and medical safety standards and provide an assessment of potential issues, including nuclear and medical regulatory issues that could affect implementation: facilities; controlled nuclear materials; facility safety and security; waste management; and transportation.
- Benefits to Canadians: the benefits of implementation to Canadians, focusing on the overall ability of the project to assure supplies of Tc-99m generators to the Canadian health care system, and also considering concomitant scientific and technological benefits, economic benefits, or any other benefits to Canadians, including the creation of new intellectual property for Canadian companies, creation of Canadian businesses or strengthening of existing businesses, and development of leading-edge research infrastructure within Canada.

2.3 Other Stakeholder Engagement

To better understand the many considerations for a long-term strategy for Canada given its position in the North American and global markets for isotopes, we consulted domestic and international experts in a variety of technical and business fields, as well as with the Canadian nuclear medicine and broader medical community and their national associations. Among others, we received information from:

[5] See Appendix 4 for the Call for Expressions of Interest – Proponent's Guide.

- Atomic Energy of Canada Limited (AECL);
- the Canadian Association of Medical Radiation Technologists;
- the Canadian Association of Nuclear Medicine;
- the Canadian Association of Radiologists;
- the Canadian Association of Radiopharmaceutical Scientists;
- the Canadian Institutes of Health Research;
- the Canadian Medical Association;
- the Canadian Society of Nuclear Medicine;
- the Canadian Society of Senior Engineers;
- individual nuclear medicine specialists;
- International Safety Research Inc.;
- the Ontario Association of Nuclear Medicine;
- the Royal College of Physicians and Surgeons of Canada - Nuclear Medicine Specialty;
- SECOR Inc.;
- SNC Lavalin Inc.;
- 15 independent and internationally known technical experts;
- other national and international stakeholders; and
- a Tc-99m generator manufacturer.

Stakeholders expressed their opinions in writing and in person, and we considered all advice and information brought forward.

Through a request for proposal (RFP) process, we commissioned business and technical analyses to support our deliberations. As the consultant, SECOR Inc., was asked to perform business analyses of the isotope market and technology options. They also coordinated technical input from independent experts. Unless otherwise stated, figures and tables in this report that illustrate business/market aspects of medical isotope production were produced by SECOR.

We would like to acknowledge the significant amount of interdepartmental collaboration and engagement that included the following.

- The Canadian Nuclear Safety Commission (CNSC) and Health Canada provided an overview of the nuclear and health regulatory implications of different submissions to help us assess the EOI submissions.
- The Special Advisor to the Minister of Health on Medical Isotopes, Dr. Alexander (Sandy) McEwan, shared his views and experiences in his capacity as an advisor to the Minister of Health.
- The Health Canada Ad Hoc Health Experts Working Group on Medical Isotopes answered our health-related questions and its members presented their organization’s views and experiences.
- Representatives of AECL met with us and we visited AECL’s Chalk River Laboratories to become better informed about all aspects of the Multi-purpose Applied Physics Lattice Experiment (MAPLE) reactors and the

Dedicated Isotope Facility. We also toured the National Research Universal (NRU) reactor and received a presentation on its status, including its return to service and licence extensions.

We have also been supported by a Secretariat formed by personnel seconded from Natural Resources Canada, Health Canada and the CNSC.

2.4 Reporting

This report, presented to the Minister of Natural Resources on November 30, 2009, is the culmination of our work as a Panel and fulfills our mandate to provide advice to the government on viable options for long-term sustainability and security of supply.

The key section of this report — Chapter 5, Assessment of Options — is structured around major classes of technologies. The criteria for assessing the 22 submissions proved very useful in identifying broad classes of technology options available. Our detailed and nuanced understanding of the considerations within each technology option is the result of the time and effort invested by the proponents.

This report does not discuss each EOI individually, but we reviewed and assessed every one, and each played a role in informing the content and recommendations presented here. Information from other stakeholders was also instrumental.

Chapter 3

Background

This chapter provides a brief history of nuclear research and development (R&D), nuclear medicine and the isotope market in Canada. Further related information is provided in Chapter 4, Context.

3.1 Nuclear History

Since the discovery of radioactivity in the late 19th century, nuclear science and technology has influenced innovation in a variety of fields including energy, medicine, agriculture, archaeology, research and manufacturing. Specifically, nuclear R&D has led to significant advancements in medical imaging, cancer therapy, medical equipment sterilization, food irradiation, energy production, and materials understanding and development.

Canada has, historically and to this day, been a key player in nuclear R&D. Canada's nuclear program originated from its involvement in the Manhattan Project, a Second World War project involving the United States, the United Kingdom and Canada, which sought to develop the first atomic bomb (Tammemagi and Jackson, 2009). Although originally a military program, Canada's nuclear R&D program quickly evolved into a peaceful research and technology program. Since the end of the war in 1945, Canada has been a centre for world-renowned nuclear expertise and achievements. For example, in 1994, Dr. Bertram Brockhouse shared the Nobel Prize in Physics for his work in the 1950s at the National Research Experimental (NRX) reactor and later at the National Research Universal (NRU) reactor, which advanced the detection and analysis techniques used in the field of neutron scattering for condensed matter research (Canadian Nuclear Association, 2008b).

3.2 Nuclear Medicine

Canada's nuclear program has contributed significantly to the development and advancement of nuclear medicine, which uses radioactive materials for both diagnostic and therapeutic purposes. Canada's first foray was therapeutic, with the production of cobalt-60. That led to the 1951 development of the first teletherapy units for cancer treatment in London, Ontario, and Saskatoon, Saskatchewan, and later became diagnostic, with the use of Tc-99m and other medical isotopes (Ullyett, 1997).

Isotopes of a chemical element are atoms having the same number of protons but different numbers of neutrons in the nucleus. Some isotopes are stable while others are unstable. Radioactive isotopes (radioisotopes) are unstable isotopes that spontaneously decay with the concomitant release of ionizing particles and radiation. An isotope that spontaneously decays creates other elements or isotopes; the original isotope is called the parent isotope and the newly created element or isotope is called the daughter. Molybdenum (Mo-99) is the parent isotope of Tc-99m.

Isotopes are used in nuclear medicine in the following ways:

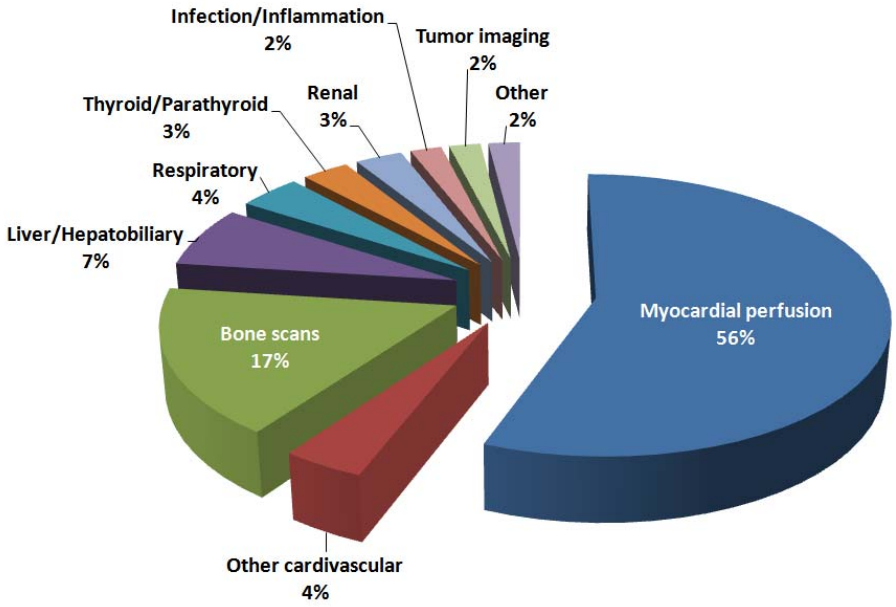
- Diagnostically - Radioisotopes, when administered in low dose to a patient, emit energy that can be captured by an external detector to produce a diagnostic image.
- Therapeutically - Radioisotopes, when injected into a patient in higher dose for therapeutic use, emit very energetic photons or particles to destroy targeted cells (e.g. cancer cells).

Of the approximately 200 radioisotopes commonly available today, almost all are artificially created (Nuclear Medicine Radiochemistry Society, 2009). The most significant quantities of radioisotopes rich in neutrons (e.g. Mo-99, I-131) come from neutron bombardment of elements in a nuclear reactor. Cyclotrons are used to produce isotopes rich in protons. Some cyclotron-produced isotopes are well-suited for radiation therapy. Others are used for nuclear imaging with single photon emission computed tomography (SPECT) or positron emission tomography (PET) technologies. A more complete discussion of technology options for isotope production is in Chapter 5, Assessment of Options.

3.3 Tc-99m

Tc-99m is the most commonly used medical isotope. It is estimated that every year 30 million patients undergo Tc-99m procedures around the world (Hansell, 2008).

Figure 3.1 breaks down the types of nuclear medicine procedures that can be done using Tc-99m.



Sources: IMV 2007 Nuclear Medicine Market Summary Report, October 2007, Burns 2007, SECOR Analysis

Figure 3.1. Medical Procedures Using Tc-99m

Tc-99m is obtained from the decay of its parent isotope Mo-99. It was discovered in 1937, and the first Mo-99/Tc-99m generator was invented at Brookhaven National Laboratory in the U.S. in 1957. General usage of Tc-99m began in the early seventies when Chalk River Laboratory established routine production of Mo-99, its parent isotope (Tammemagi and Jackson, 2009; Ullyett, 1997). Tc-99m is versatile and can be used to produce some 20 different compounds. Different Tc-99m compounds can be used to verify the function of different organs. For example, when combined with albumin particles and injected intravenously, Tc-99m is trapped in the blood vessels of the lungs, and helps to identify areas with decreased or absent blood flow (pulmonary embolism).

Additional benefits of the medical isotope Tc-99m are the low dose required for medical imaging and its short half-life of only six hours, which ensures that it

does not remain in the body very long. Moreover, the historically low cost of Tc-99m has made it attractive. The relatively low cost derives from the production of Mo-99 as a by-product of the operation of research facilities, such as the NRU, that were built and operated for a variety of public purposes. Arguably, the low cost of technetium has inhibited R&D into alternative isotopes and alternative imaging modalities, especially in applications where the technetium-based procedures are effective. For example, F-18-sodium fluoride for PET imaging was developed in 1962 as a bone imaging agent but did not progress to clinical use because of the very low cost of a Tc-99m bone scan.

The recent increase in the cost of Tc-99m makes the more accurate PET imaging alternative a stronger competitor. The ongoing reduced supply and increased cost of Tc-99m is currently driving research into finding equal or better alternatives to Tc-99m.

3.4 Medical Isotope Production in Canada

From its start in 1957, the NRU reactor has grown to provide more than half of the world's isotopes for nuclear medicine procedures, helping "over 76,000 people every day and 27 million people every year, in more than 80 countries" (Atomic Energy of Canada Limited, 2006). Besides producing Mo-99, the NRU produces iodine-131, iodine-125, xenon-133, cobalt-60, carbon-14 and iridium-192. The NRU's supply of Mo-99 has grown to 30–40% of the global demand. However, it should be noted that all Tc-99m to Canadian health care institutions comes from foreign generator manufacturers because there are no Canadian generator manufacturers and 100% of NRU supply is exported.

The NRU reactor has proven well suited to isotope production because of the "neutron efficiency" of its heavy water moderated core, its large core volume with provision for sufficient cooling to accommodate a large load of irradiation targets, and its capability for on-power refuelling, allowing extraction of irradiated targets without a reactor outage.

3.4.1 Recent History

Recent unplanned outages of the NRU reactor in December 2007, and the ongoing outage that began in May 2009, have resulted in world-wide supply shortfalls, and highlighted the fragility of the current supply chains.

Since the May 2009 outage, the supply of Tc-99m has been greatly reduced. The weekly supply of Tc-99m has fluctuated significantly, depending on the province, region or supplier (Urbain, 2009). Although the situation seems to ease some weeks, the supply does not appear to be reliable in the short-term.

Normally the NRU supplies more than 30% of the world market. Hence its shutdown has had a significant impact on the availability of Tc-99m, with variations across countries and regions. The reduction in supply also varies across Canada, since medical isotope supplies are managed by the provinces and territories (Zakzouk, 2009).

The shutdown of the NRU has had, and continues to have, a negative impact on other countries. For example, despite the fact that the Comisión Nacional de Energía Atómica reactor in Argentina is now operating at full capacity, it is unable to meet Latin American demand during NRU's absence (SECOR, 2009a). As for Japan, although its supply is more diversified than others, the country remains significantly short of demand due to the NRU shutdown (SECOR, 2009a).

The medical community has responded by adopting mitigating strategies, which include triaging patients based on specific factors, rescheduling patients around the delivery of Tc-99m, switching to other isotope alternatives such as thallium for cardiac scans, referring patients to other imaging modalities such as PET, computed tomography (CT) scans and magnetic resonance imaging (MRI), and maximizing the use of the Tc-99m available.

While these initiatives have proven effective at managing the reduced supply of Tc-99m, they have created new pressures on the health care system. For example, referring patients to other imaging modalities has increased wait times for these other diagnostic tests. As well, the patient rescheduling has led to pressures on health human resources by requiring weekend shifts and overtime.

The reduced supply of Tc-99m has had other negative consequences on nuclear medicine and its health human resources. The Royal College of Physicians and Surgeons of Canada has noted a decrease in the number of nuclear medicine residents. The same has been observed by the Canadian Association of Medical Radiation Technologists (CAMRT) for admissions to technologist programs. Some nuclear medicine professionals have also been laid off (CAMRT, 2009).

Furthermore, there have been concerns regarding the decrease in patient referrals to nuclear diagnostic scans. Even with recently improved supply of Tc-99m, referrals are still down 10 - 25% compared with the number of referrals preceding the NRU reactor shutdown (Urbain, 2009). As a result, patients requiring Tc-99m-based nuclear diagnostic scans are being diverted to other imaging modalities and may undergo diagnostic scans that are sub-optimal, more invasive, and/or more costly.

The recent outage of the NRU has also affected the other medical isotopes produced in Chalk River. For example, Iodine-131, used for thyroid cancer management, now has to be imported from South Africa, and Health Canada had to approve the new source expeditiously. The NRU outage has increased the

workload for the regulator, necessitating expedited approval processes to allow access to new source of isotopes.

In addition to what is being done by the medical community, the government has developed and adopted short-term initiatives and mitigation strategies to manage the medical isotope shortages resulting from the NRU reactor outage. Since May 2009, Health Canada and Natural Resources Canada have been working closely with key partners and stakeholders, including provinces and territories, the health care community, international counterparts, and industry, to manage the ongoing medical isotope supply situation.

Although these short-term initiatives and mitigation strategies are essential in managing the ongoing shortage of medical isotopes, our work focuses on reviewing and assessing medium to long-term options, and formulating advice and recommendations to achieve sustainability and security of the isotope supply for Canadian patients.

Chapter 4

Context

This chapter describes the most significant contextual elements important in understanding the many facets of isotope supply and demand in the medium to long term. These elements helped to distinguish the merits and limitations of each option. The context, as described here, includes business, technical and medical considerations.

4.1 Canadian Technetium-99m Supply Chain

Technetium-99m (Tc-99m) is widely used in medical imaging and accounts for approximately 80% of nuclear medicine diagnostic procedures in Canada. It is used in the majority of nuclear medicine diagnostic tests, about 24,000 out of 30,000 nuclear medicine diagnostic scans per week (Health Canada, 2009). Because more than one dose is sometimes required per scan, total Canadian demand is estimated to be 32,000 doses per week.

Tc-99m's parent isotope, molybdenum-99 (Mo-99) has a relatively short half-life (the time required for a quantity of radioactive material to decay to half of its initial amount) of 66 hours and Tc-99m has an even shorter half-life of 6 hours. With such short half-lives, these isotopes cannot be stockpiled for later use. To assure continuous availability, Mo-99 must be produced frequently, which adds to the complexity of ensuring security of supply. An interruption in the production of Tc-99m may take up to one week before the impact is felt by hospitals. Once production is restarted, it may take up to another week before Tc-99m reaches hospitals since it takes a minimum of six days to irradiate targets, process Mo-99 and produce a generator.

Figure 4.1 demonstrates the basic linear supply chain for Tc-99m.

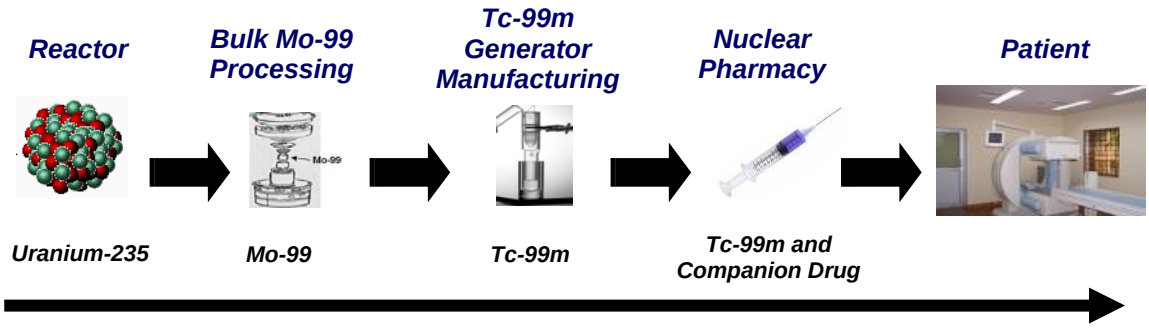
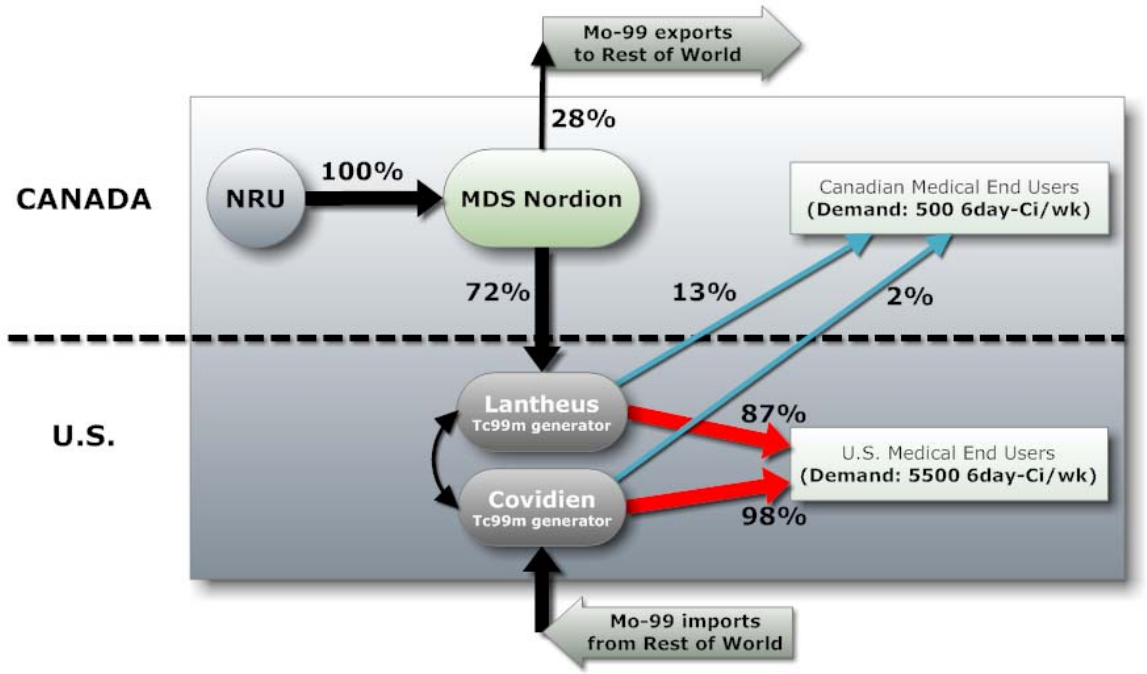


Figure 4.1. Tc-99m Supply Chain (Natural Resources Canada, 2009a)

In Canada, highly enriched uranium (HEU) is imported from the United States to be made into targets. Issues around long-term availability of HEU are discussed in section 4.5.2. The HEU targets are irradiated in the National Research Universal (NRU) reactor and processed on site for Mo-99 extraction.

Figure 4.2 shows how the raw Mo-99 supplied from the NRU makes its way through the global supply chain — with U.S. private-sector generator producers and distributors (Lantheus or Covidien), as the final supplier to Canada. The diagram highlights the fact that Tc-99m generators are not made in Canada; therefore, despite the significant portion of raw Mo-99 material supplied by Canada, our health care system is reliant on foreign private-sector manufacturers for all Tc-99m needs.



(adapted from Natural Resources Canada, 2009a)

Figure 4.2. Simplified North American Supply Chain

The Mo-99 from the NRU is shipped to the facilities of MDS Nordion in Ottawa, Ontario, for purification. Close to three-quarters of the purified Mo-99 is exported to a Tc-99m manufacturer in the United States — Lantheus Medical Imaging — and the rest (28%) is sent offshore, primarily to Japan and Latin America.

Lantheus ships back to Canada only 13% of the Tc-99m it produces, but this accounts for 85% of the Tc-99m on the Canadian market.

Tc-99m coming into Canada via Covidien generators produced in the U.S. accounts for the remaining 15% of the market. This breakdown is in contrast to the U.S. market, where half the Tc-99m comes from Covidien from European sources and the other half from Lantheus from the NRU. The more evenly distributed market share has protected U.S. health care providers from the effects of the NRU shutdown.

4.2 Global Supply Chain

Worldwide, generator manufacturers source Mo-99 principally from five government-owned and funded multi-purpose research reactors located in Canada, Europe and South Africa:

- the NRU reactor in Canada (1957);
- the BR2 reactor in Belgium (1961);
- the HFR Petten reactor in the Netherlands (1961);
- the OSIRIS reactor in France (1966); and
- the SAFARI reactor in South Africa (1965).

This reliance on five aging nuclear reactors for global supply of isotopes is driven by economics. Multi-purpose research reactors are expensive to maintain and operate and require significant capital investment.

Figure 4.3 illustrates how the five nuclear reactors feed into four supply chains built around global Mo-99 processors and Tc-99m generator manufacturers.

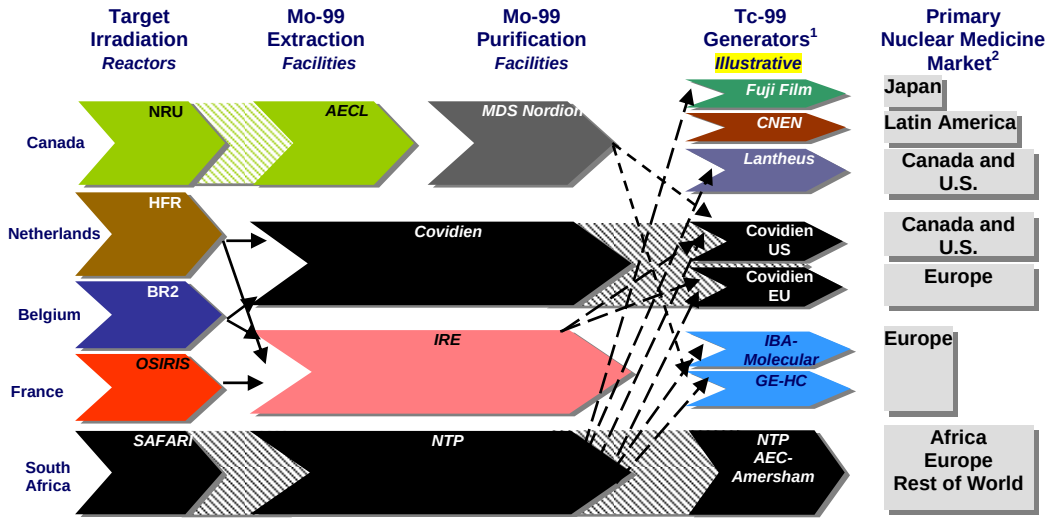
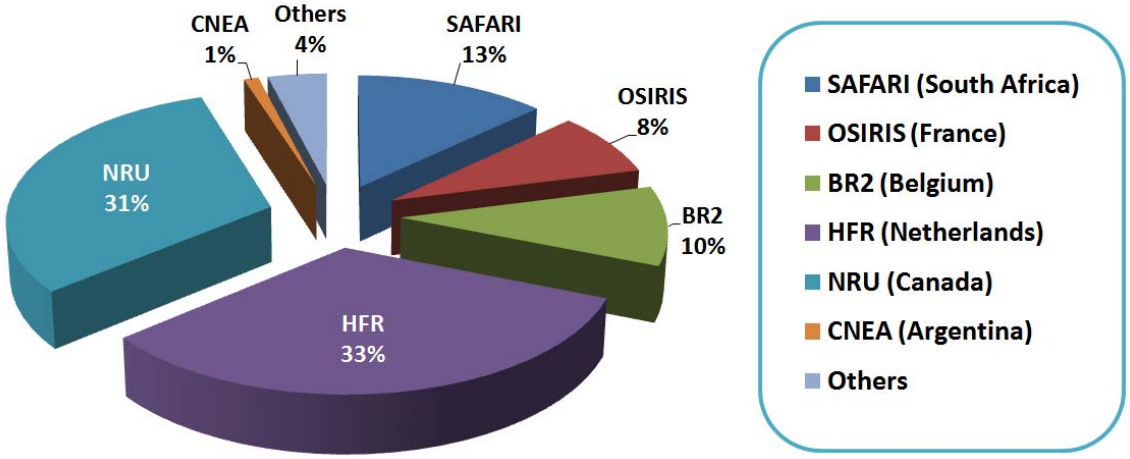


Figure 4.3. Global Supply Chains (Natural Resources Canada, 2009b)

1. Most bulk Mo-99 processors also cross-sell to other generator companies.
2. Indicates markets where majority of sales occur; distributors also serve other markets.

While Canada accounts for less than 4% of the global demand for Tc-99m generators, AECL's NRU has typically contributed 30 - 40% of the global supply of Mo-99. The NRU reactor's market share relative to other major producers is shown in Figure 4.4. Historically, exports of Mo-99 were worth approximately $100M and imports of Tc-99m represented a market value of $20M.



(adapted from Natural Resources Canada, 2009a)

Figure 4.4. 2008 Global Market Share by Reactor

The recent supply shortages have highlighted the vulnerability of centering production around a limited number of aging reactors. It must be emphasized, however, that the linear nature of the supply system for isotopes and its limited compatibility and interconnectedness creates vulnerabilities not only at the reactor end but at every link in the individual supply chains.

New sources of global supply have been slow to materialize in part because of the projected impact of Canada's Multi-purpose Applied Physics Lattice Experiment (MAPLE) reactors coming on stream (National Research Council of the National Academies, 2009). Based on HEU targets, these dedicated isotope reactors were designed with enough capacity to meet worldwide demand twice over. The limited number of producers worldwide and the limited planning for new capacity can also be attributed to the economic realities of a market in which product pricing reflects subsidized costs due to shared use of government facilities.

The market pricing of Mo-99 to date has not reflected the true costs of production because worldwide isotope production was an add-on activity using government-funded infrastructure whose primary purpose was research and development. Isotope production represented an additional public benefit that was compatible with research operations.

Because the pricing of Mo-99 production to date has reflected government-funded infrastructure without provision for full cost recovery, the ability to attract private sector involvement has been limited. Indeed, in the late 1980s and early 1990s, the U.S. government established a program to entice private sector organizations to enter the market for isotope production. Despite significant incentives, no organizations came forward because: the market is small; the price structure excludes capital costs of facilities, future waste liabilities and the full operating costs of complex nuclear facilities are significant; and out-competing subsidized production from foreign markets would be next to impossible (National Research Council of the National Academies, 2009).

A true commercial market for reactor-produced isotopes is unlikely to exist as long as shared use of government-owned facilities represents a significant source of supply. Given recent investments in new facilities such as the OPAL reactor in Australia and the anticipated move to begin production at a new research reactor in Germany, the status quo may hold for the foreseeable future.

4.3 Market Supply and Demand

4.3.1 Market

Global demand for Tc-99m is estimated at 48 million doses per year (Natural Resources Canada, 2009a). The U.S. is the largest consumer of Tc-99m, accounting for 44% of doses; Europe represents the second largest market at 22%; followed by Japan at 14%; and the rest of the world at 16%. Canada consumes approximately 4% of global doses (Natural Resources Canada, 2009a).

The value of the Canadian market is small and was historically worth approximately $20M. However, assuming 32,000 Tc-99m doses per week, recent price increases to $25 per dose have increased the market to just over $40M. Only production options based on a multi-use infrastructure are likely to be viable because the other uses of the infrastructure can help offset costs.

4.3.2 Market Trends

Prior to the 2009 shortage, demographic and medical trends suggested that global demand for Tc-99m would grow at an average rate of between 3 - 10% per year as new markets (mostly in Asia) adopt nuclear medicine and existing markets continue to use it[i]. However, some of the current accommodations being made to manage demand may hold over the longer term, and alternative medical imaging modalities may become increasingly attractive if the price of Tc-99m continues to increase. In conversation with members of the Canadian medical community, we were told that demand is more likely to remain relatively flat over the longer-term. In Japan, where there has been significant adoption of PET technology, growth in demand for Tc-99m changed from a rate of increase of 3% per year to a rate of decrease of 3% per year[i].

On the supply side, various reactors are planning to increase production in the next two years. As shown in Figure 4.5, if production increases as projected, global isotope supply could match demand as soon as 2011, even without one of the major reactors, such as the NRU, in service (SECOR, 2009b). However, there is considerable uncertainty in this estimate. All current production facilities are old and prone to disruptions. The ability of projected new supply sources to come on stream in the time frames anticipated, and to produce the projected quantities, are subject to considerable technical and regulatory uncertainties. As such, it may be several years before demand and supply can be balanced on a sustainable basis.

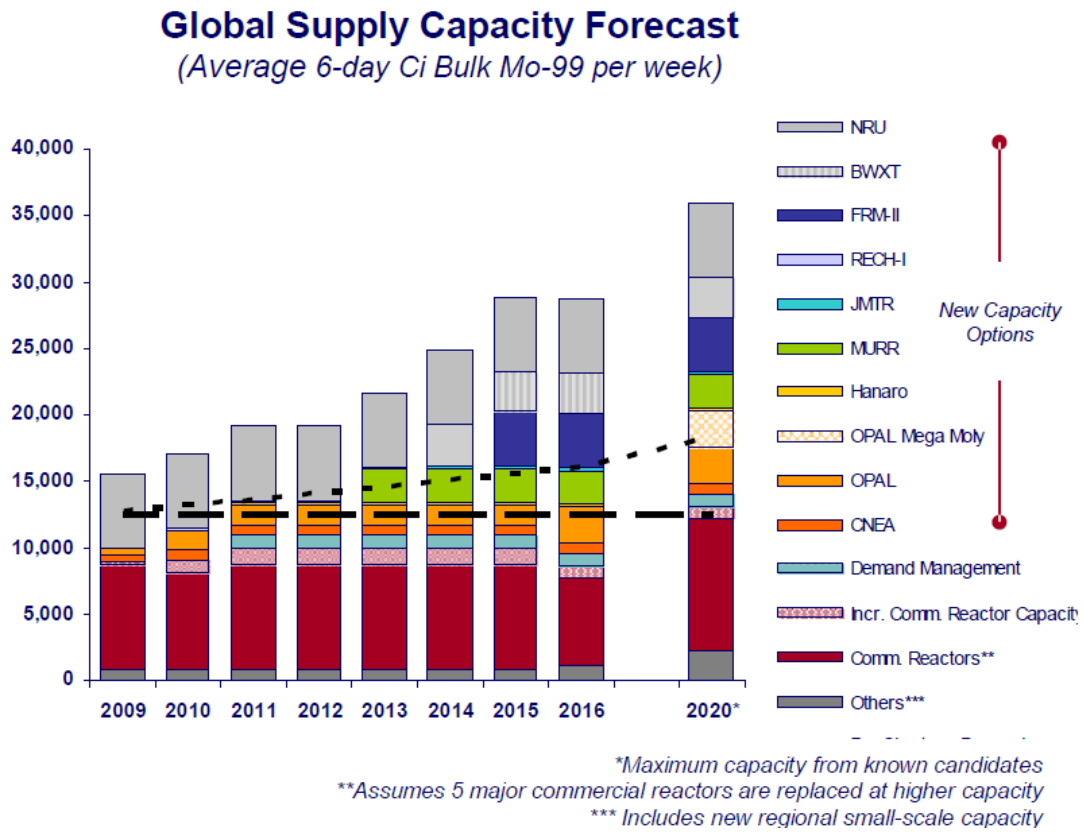


Figure 4.5. Supply Forecast to 2020[i]

Supply Uncertainties

A significant factor in determining the commercial attractiveness of new supply options is the future availability of the NRU. Three scenarios are envisioned:

1. The NRU returns to service with reliable output.
2. The NRU returns to service but with significant planned and unplanned outages.
3. The NRU does not return to service.

Scenarios 2 and 3 would tend to accelerate the timelines for new supply options. It is likely that any new Canadian entrants to the market would face significant competition regardless of the future of the NRU reactor, unless the new supply options could be brought on line before Australia reached full capacity and other suppliers, such as the University of Missouri's research reactor, came on line.

From a supply chain structure perspective, the recent NRU shutdown has removed supply primarily from the North American, Japanese and Latin American markets. To meet North America's high demand, supply is being diverted from around the world, leaving other countries with unmet demand (SECOR, 2009a). Citing fair share policies, Covidien has diverted supply to North American operations, and IRE and NTP are providing Lantheus with their available capacity.

Recent shortages have drawn attention to the market's vulnerabilities and governments and private enterprise are actively looking for ways to diversify. This drive for diversification is unlikely to subside even after the NRU comes back on line, and health care systems are unlikely to accept ongoing dependency on reactors with over 30% of the worldwide supply. We anticipate that proponents who assumed the status quo in terms of expected market share have significantly over-estimated achievable sales volumes. Moving forward, achievable market share for any supply option may be closer to 15% of the global market, as opposed to the 30% to 40% market share currently garnered by AECL's NRU reactor, and the similarly large market share garnered by the HFR in the Netherlands.

4.3.3 Pricing

Because government-owned reactor operators have not looked to recover a significant portion of their costs, being content to accept revenue from a "sideline" activity, the price of Mo-99 has been kept very low. This creates a scenario in which, indirectly, governments subsidize the private-sector Tc-99m market. The suppressed prices are so low as to make the market unattractive to commercial investors, at least at the level of production of raw Mo-99. Because Canada is a significant exporter of Mo-99, the Canadian government has effectively been subsidizing supply of Mo-99 for foreign markets.

At the highest level of global supply, the long term price will be driven by the availability of capacity to satisfy demand. Extended shortages will drive price increases, which will create the potential for alternative technology approaches.

Currently, the price of a radiopharmacy dose (20 millicuries) is approximately $25. This is more than double the 2007 price. It is unclear, as yet, whether these prices will hold once the NRU comes back on line and supply meets demand. It is unlikely to drop significantly, however, since price increases were already projected before the current shortage

Recent isotope shortages and new capital investments in processing have resulted in major supply chain players actively considering further price increases (SECOR, 2009a).

4.3.4 Impact of Tc-99m Pricing on Health Care Budgets

The cost of the Tc-99m isotope represents only a small fraction of the total cost of any nuclear medicine procedure. For example, the total cost of a bone scan, including physician fees, technician costs and time on the single-photon imaging technology (SPECT) camera, is approximately $400, while the cost of the Tc-99m radiopharmaceutical is approximately $25 per dose.

Independent analysis predicts price to be stable over the next 10 years[i]. However, the nuclear medicine community believes that more than a five-fold increase in the price for Tc-99m would reduce the attractiveness of the Tc-99m procedures. Other analyses predict that a price increase of between 2.5 and 3.0 times would be enough to make PET imaging more attractive, and thereby change the nuclear medicine landscape and the level of demand for the isotope[i].

A significant price increase for Tc-99m could have the same negative impact as an actual isotope shortage by preventing hospitals with strict budget constraints from purchasing the required medical isotopes. While gradual and planned changes in pricing can likely be accommodated, sharp jumps in price such as those seen in the past year would be more difficult to absorb because of the constraints of budget planning and cost-recovery models in publically-funded health care systems.

4.4 New and Alternate Medical Technologies

In the past two years, new SPECT technologies have appeared on the market promising faster imaging using the same amount of Tc-99m per study as older nuclear imaging technologies. These new technologies use solid state detectors, and can also perform studies using the same acquisition time but with half the Tc-99m dose. Other new software with a “count recovery” algorithm can produce diagnostic-quality images using less Tc-99m.

Availability of technology, medical imaging equipment and isotopes vary from province to province, and from hospital to hospital in Canada. Alternative nuclear medicine cameras, known as PET scanners, are a type of nuclear medicine imaging system that uses different isotopes from the gamma and SPECT gamma cameras. PET technology relies on a newer generation of isotopes that decay by positron emission. These newer isotopes are produced daily by medical cyclotrons and have short half-lives.

Although availability of these cameras is limited, large urban centres typically have them. Alternative scanning technologies such as magnetic resonance imaging (MRI) and computed tomography (CT) can also be used for some imaging needs; those imaging technologies are preferred for diagnosing

anatomic anomalies compared to nuclear medicine procedures that are typically used for assessing metabolic or functional changes. However, within the nuclear medical community, functional and anatomic imaging modalities tend to be viewed as complementary technologies rather than exchangeable alternatives.

Currently, Canada has 31 PET scanners available but they are unevenly distributed across the country. For example, the province of Quebec has 15 PET scanners. The number of PET scanners in Canada is in sharp contrast with the country's 603 SPECT gamma cameras. PET technologies provide a high quality alternative to SPECT technologies for providing physicians information for determining tissue characterizations and classifications, for the staging of cancers, for the restaging of cancers, for patient prognosis, and for monitoring the effectiveness of cancer therapies. PET scanners also offer improved lesion localization, better distinction between physiological and pathological uptake, and a shorter scan time for the patient (about 30 minutes, or half that of other imaging modalities) (Wilson, 2009).

The major barrier to adopting PET scanners is cost ($2.2M versus $700K to $1.2M for SPECT or SPECT/CT gamma cameras). If the price of Mo-99 increased 2.7 times, however, it would be enough to reduce cost differentials and encourage PET deployment[i]. Based on Japan's experience, if PET deployment accelerates in Canada, yearly demand for Tc-99m could be in decline by 2015[i].

Despite the emergence of new imaging technologies and the search for alternatives to Tc-99m, the medical community has indicated that demand for Tc-99m will remain significant in Canada and elsewhere, especially in developing nations, over the next 10 to 20 years.

4.5 Made in Canada vs. Made for Canada

As already discussed, Canada has a storied history in isotope development and supply, and the U.S. and the world have come to rely on Canada to meet demand. Although we did not explicitly place value on maintaining Canadian leadership in the area of isotope production, the assessment criteria did include consideration of "benefits to Canadians," which would help value those options that offered potential for intellectual property development, new business development and collateral economic activity. From this perspective, long-term options for isotope production that had the potential to allow Canada to continue to play a value-added role in isotope innovation rated well in this category.

Domestic self-sufficiency would require producing generators in Canada or developing a technique that does not use traditional generators. However, we would like to emphasize that domestic self-sufficiency does not necessarily result in security of supply to Canadian patients. A purely domestic supply chain that remains linear with insufficient redundancy at each step remains vulnerable to

single-point failures. Therefore, we did not place particular value on achieving an entirely Canadian-based supply chain, but instead chose to consider the options in terms of overall risk of supply disruptions from a Canadian perspective.

4.5.1 Highly Enriched Uranium (HEU)

The present technology for producing Mo-99 uses neutrons generated from a nuclear reactor to irradiate targets — usually relying on HEU.

HEU has been preferred because enriching uranium to over 90% U-235 maximizes the production of Mo-99. Although HEU is useful in optimizing production of isotopes, because it can also be used in nuclear weapons, its use in civilian applications is contra-indicated.

Nuclear non-proliferation and security concerns have led to global efforts to move away from the use of HEU. Transition to LEU for reactor fuels has made significant progress, but large-scale production of Mo-99 using LEU targetry is still being optimized.

In converting reactors from HEU (typically ~93% U-235) to LEU (< 20% U-235) targets, isotope production drops to about one-fifth of its efficiency with HEU, based on the same amount of uranium. Converting an existing processing line from HEU to LEU is costly in other ways —modification of hot cells, design of new targets, poor yields and increased waste costs.

4.5.2 U.S. Policy on Domestic Isotope Production

The U.S. has two ongoing policy interests related to medical isotopes:

- access of U.S. citizens to medical diagnostic procedures; and
- minimization or elimination of HEU from civilian uses, including medical isotope production.

The U.S. has been without a domestic source of Mo-99 since 1989 when the Cintichem reactor ceased to operate (Robertson, 2008).

The U.S. government will spend at least $20M over the next year to assist the development of domestic LEU-based production of Mo-99; further legislation under consideration would authorize an additional $163M over four years.

Current U.S. policy requires that domestic isotope production be on a commercial basis with the exception of isotopes for research or for which there are limited commercial supply options. This policy has created U.S. dependence on foreign sources of Mo-99, with Canada typically supplying half the U.S. market. The major foreign sources of Mo-99 continue to rely on HEU, including HEU from U.S. sources.

Despite growing efforts by U.S. non-proliferation proponents to restrict exports of HEU, HEU export restrictions continue to receive exemptions to respond to U.S. dependence on foreign isotope production. However, House Resolution 3276, *American Medical Isotopes Production Act* of 2009, questions the reliability of foreign suppliers and seeks to commit significant funding to the establishment of a domestic source of Mo-99, based on LEU (U.S. Committee on Energy and Commerce, 2009). This legislation would also result in the elimination of exports of HEU for isotope production in Canada within a 7- to 10-year period (U.S. Committee on Energy and Commerce, 2009). On November 5, 2009 this legislation was passed by the House of Representatives by a vote of 400 to 17.

When Australia's recently commissioned OPAL reactor based on LEU comes on stream, there will be increased pressure on others to convert. Given the significant costs associated with conversion, it does not make sense to invest in conversion for facilities nearing the end of their operating life. Equally, given the outlook for HEU supply and the support for non-proliferation objectives, establishing a new HEU-based production capability is not prudent.

4.6 Existing Infrastructure in Canada

Canada has a mature and well-established infrastructure for producing Mo-99. Its advanced nuclear technology and know-how may play a vital role in alternative methods of production.

The core existing facilities are located primarily at AECL's Chalk River Laboratories. They include the Nuclear Fuel Fabrication Facility, the NRU reactor, the Mo-99 Production Facility (MPF) and ground tile holes for storing nuclear waste. The MPF has been the only operating Mo-99-processing facility in North America since 1984.

The NRU reactor, vital for both nuclear energy research and the production of medical isotopes, is over 50 years old and in the midst of a significant shutdown for repairs.

The NRU is licensed by the Canadian Nuclear Safety Commission (CNSC) to operate until October 2011. AECL plans to apply for licence renewal to operate until at least 2016. Although our focus was on the long and medium term, we did take into account the timeliness of technology options and whether they would potentially come on line before 2016. If the NRU did not bridge the gap between 2010 and 2016, the isotope market and nuclear medicine landscape in the medium and long term would be affected.

In addition to the aging but operational facilities mentioned above, the Chalk River site hosts the DIF, which is not operational. The DIF project started in the 1990s with the goal of replacing the isotope production capability of the NRU

reactor. The 10 MW reactors were conceived as a dedicated facility for producing molybdenum and select other isotopes for medical use. The project also involved building the New Processing Facility (NPF), which was to be an integrated part of the dedicated production line. An above-ground canister for storing processed HEU waste was built at Chalk River Laboratories (CRL) as part of the production complex.

On May 16, 2008, the Government of Canada announced that it accepted the decision of the Board of Directors of AECL to terminate the DIF project. The reactors have experienced licensing, technical and economic impediments that remain unresolved to this day. AECL has noted that the decision was based on a series of reviews that considered the costs of further development, as well as the time frame and risks involved with continuing the project (AECL, 2008).

Currently, the MAPLE reactors are in an extended shutdown state, the NPF was never fully commissioned and the amount of work associated with commissioning and licensing this infrastructure is uncertain.

Besides Chalk River Laboratories, MDS Nordion has processing facilities in its complex in Ottawa. At these facilities, MDS Nordion conducts further chemical purifications and quality control testing for the Mo-99 prior to shipping it to technetium generator manufacturers abroad.

Another area where Canada has strong and advanced expertise is particle accelerator technology. Research centres and private sector companies are involved in manufacturing, exporting, building and operating a wide range of particle accelerators. This includes compact medical cyclotrons, electron beam industrial irradiators, electron linear accelerators for radiotherapy or for research, and large research accelerators for synchrotron radiation and high-energy research.

The McMaster Nuclear Reactor (MNR) has in the past produced Mo-99 as a backup to NRU. This was accomplished using the HEU plate fuel that at the time (70s) was used to power the reactor. This was at a time when demand was much lower than today and the processing infrastructure suitable for dealing with this type of target does not currently exist. In addition MNR has converted to LEU fuel and it’s relatively low power makes it difficult to produce meaningful quantities of Mo-99 without the use of HEU.

4.7 Risk of Unproven Technologies

New and innovative techniques are unproven technologies by definition, and investing in them involves risk. All options for alternate isotope supply, but one, are unproven on a commercial scale. Only options based on new or existing multi-purpose research reactors can be considered proven. The risks for all other options would be based on their level of development in the innovation spectrum, that is, whether they were still in the R&D stage or had progressed to the demonstration stage.

Risks associated with technology development can be mitigated by:

- investments in a range of technological approaches;
- limited investment for pilot projects;
- good project management with well-planned, phased R&D and appropriate stage-gating; and
- use or development of multi-use infrastructure that can support a broad-based research program so that failure of one project does not significantly change the value of the infrastructure.

The risks associated with research, development and demonstration, and ways to mitigate these risks were given due consideration in formulating our recommendations.

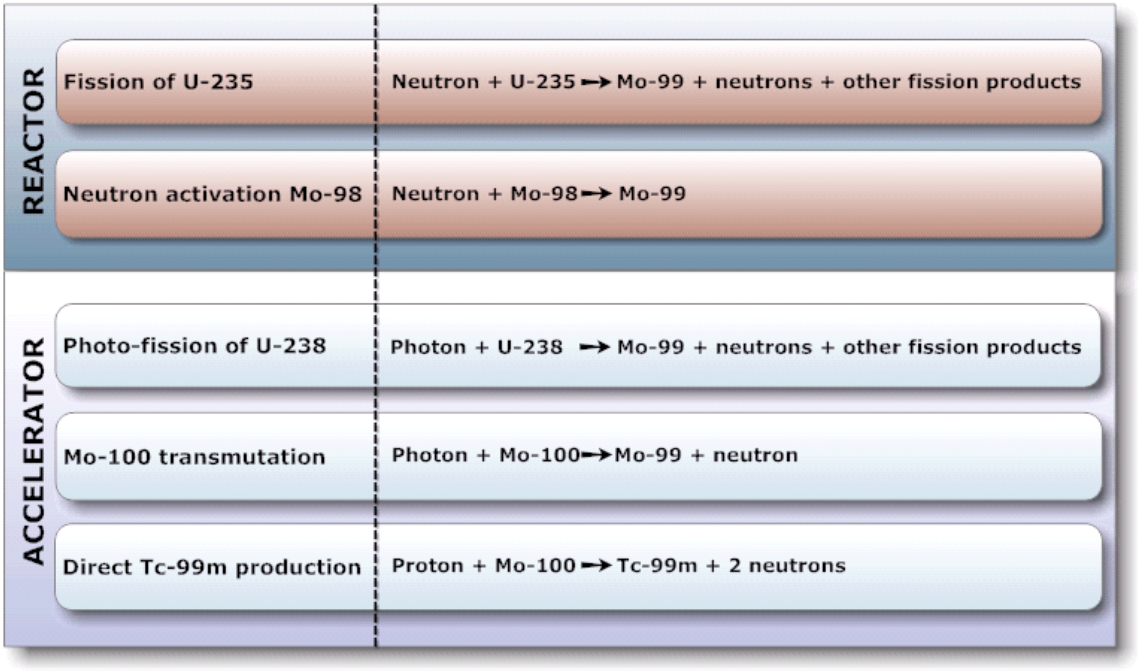
[i] Analyses commissioned from SECOR, 2009.

Chapter 5

Assessment of Options

5.1 Overarching Discussion

To better understand the various technological options below, it is useful to understand the “routes” to molybdenum-99/technetium-99m (Mo-99/Tc-99m):



We have established classes of technology for the options under consideration. These are:

- **Reactor technology:**
    1. New multi-purpose research reactor — fission option
    2. Dedicated Isotope Facility (DIF) — fission option
    3. Existing reactor — fission option

- **Accelerator technology:**
    4. Linear accelerator — photo-fission option
    5. Linear accelerator — Mo-100 transmutation option
    6. Cyclotron — direct Tc-99m option

The classification of options was developed based on the expressions of interest (EOIs) received and input from other stakeholders, including members of the medical community. Note that no proposals based on Mo-98 neutron activation were received. Although the EOIs are not discussed individually, they were essential in helping us understand the nuances of the technological options available.

5.1.1 Comparative Assessment

This section provides a head-to-head comparison of the technologies against the established criteria. We discuss only those aspects of the technologies that we consider germane in distinguishing among the options. More detailed assessments of each technology option follow.

5.1.2 Overview

The costs, timelines and other key characteristics of the technology options are listed in Table 5.1. The data were estimated based on information contained in EOIs and expert technical and business assessments commissioned by the Panel. Although there is considerable uncertainty in the numbers, they are useful in understanding the relative differences between the technology options.

Table 5.1. Summary Information for Each Technology Option

Technology	Cost	Timeline (to first production)	Capacity (percentage of Canadian demand **)
Multi-purpose research reactor	> $500M	2015–2020	500% ***
DIF	$50–250M	2011–2017	2800% (before conversion to LEU)*
Other Existing Reactors	$50–250M	2011–2013	Varies up to and possibly exceeding 100%
Accelerator — Photo-fission	$250–500M (for 4 accelerator facilities)	2013–2015	100% Using 4 accelerators
Accelerator — Mo-100 Transmutation	$50–250M (for 2 accelerator facilities)	2013–2015	Over 100% Using 2 accelerators
Cyclotron	< $50M (for 5 new and 3 existing cyclotron facilities)	2011–2014	180% Using 8 cyclotrons

* *Capacity to make Mo-99 with a reactor using LEU targets is limited more by the efficiency of the processing facility than by the reactor itself.*

** *Based on an estimated Canadian demand for Tc-99m of 32,000 doses (470 6-day Ci of bulk Mo-99) per week*

*** *Based on estimated reactor capacity, without considering limitations of a processing facility*

5.1.3 Sustainability and Security

The objective of this work is to find a sustainable and secure supply of Tc-99m for Canadians. This does not necessarily imply a need to create an entirely domestic supply of Tc-99m, although a fully integrated Canadian-based supply chain may help give priority to Canadians in times of international crisis. Market dominance by a single Canadian supplier, however, would expose Canadians to significant risk if there were a failure in that supply chain.

Through our work and our assessments, we established parameters to define a sustainable and secure supply of Tc-99m in the medium to long term. A **sustainable** supply of Tc-99m to serve the needs of Canadian patients would:

1. be viable for the foreseeable future, likely for at least 15 to 20 years, and may include options that begin producing in the short to medium timeframe but that promise to remain viable;
2. comprise options that could each meet a meaningful portion of the Canadian demand, but that would not necessarily be exclusively Canadian-based and may or may not serve the U.S. or other markets;
3. have a sound business model that may or may not include government involvement; and
4. be free of highly enriched (weapons-grade) uranium (HEU) because of Canadian and global commitment to non-proliferation.

A **secure** supply of Tc-99m would:

5. improve redundancy at all points in the supply chain to avoid the “single point of failure” risk associated with a linear supply chain;
6. use diverse technologies to hedge against a failure that could arise if all suppliers used the same technology;
7. collocate irradiation and processing facilities to minimize decay losses and avoid shipping losses and risks; and
8. ensure sufficient capacity to accommodate short-term outages of some sources.

Establishing these parameters for sustainable and secure supply helped to frame how we assessed the likelihood of various technology options contributing to stable isotope supply in the long term.

Given the vulnerabilities of the existing supply chain for Tc-99m, we were looking for medium- to long-term options that would result in a more distributed, diversified and redundant supply system that would remove the single point of failure risk inherent in the current linear supply chain.

Based on our analysis, cyclotron-based and linear accelerator-based options may be technically viable, although further research and development (R&D) is

required. Therefore, we believe there exists the possibility of introducing diversity and redundancy into the supply chain.

The cyclotron-based option is attractive because it could be entirely Canadian-based. By producing Tc-99m directly, this option obviates the need for foreign suppliers of generators and represents a regionally controlled option largely immune to international forces. However, cyclotron technology cannot serve the needs of more remote hospitals in Canada because the significant transportation distance/time would be impractical given the amount of decay that would occur. The cyclotron option, therefore, cannot reach 100% of the Canadian market even if it is scaled to supply 100% of the Canadian demand. Nonetheless, the distributed nature of this option would provide sufficient redundancy and capacity in times of shortage to ensure that Canadians would have access to required tests.

The output of the cyclotrons could be increased to fully serve the needs of large centres, leaving more generators available to be used by remote locations. The multi-use nature of cyclotrons means that during times of shortage of Tc-99m, activities on the cyclotrons could be re-prioritized so as to quickly ramp up production of the isotope, assuming a sufficient number of cyclotrons were available across Canada. Even if only limited amounts of Tc-99m were produced during times of sufficient global supply, there could be capacity in the system to moderate any disruptions in the generator supply chain.

The Mo-100 transmutation option would have similar benefits to the cyclotron option, although the economic and ancillary benefits of this option are less attractive. The linear accelerator-based options would also serve to improve diversity and redundancy, but for those that rely on existing processing capability or existing generator manufacturers, there would not be any guarantee that Canadians would get preferential access to the product during times of global shortage, although such shortages would be less likely given the improved diversity and redundancy.

If several of the proposed new foreign sources come on line, global capacity could exceed demand at some point between 2011 and 2017, although we anticipate ongoing fragility in the first half of that period. In that period, an unplanned permanent shutdown of any of the major reactors would create a situation of significant shortage. The ongoing fragility of the global market will have to be addressed by new sources appearing globally. Recent proposals for new sources have been driven by shortages; as these shortages are alleviated, pressures to expedite new sources will diminish, making uncertain the speed with which these new sources will come on line.

Moreover, the price of reactor-based Mo-99 is not expected to increase enough to reach a break-even point that would lead to a pure commercial market.

Assuming that the cyclotron option proves technically viable, a network of cyclotrons based in major medical centres could be used in combination with either domestic or foreign reactor-based supply to reliably meet Canadian demand. However, care should be taken to avoid having cyclotrons servicing so much of the market that other suppliers find the remaining market unattractive.

5.1.4 Technical Feasibility

All of the options under discussion are considered potentially technically feasible, given varying amounts of R&D, time, investment and effort. Options at an earlier stage of the innovation cycle have a higher technical risk, however.

Only reactor-based production of Mo-99 is proven on a commercial scale, albeit one with limited cost recovery by government-owned producers. We consider all cyclotron and accelerator-based options to require significant amounts of R&D, and to have the associated level of risk. Nonetheless, the benefits that would stem from these options are significant enough to justify investment in an R&D program for one or more of these options.

A technical comparison of the options is given in Table 5.2.

Table 5. 2. Summary of Technological Risks

Technology	Significant R&D / Technical Risk
New Multi-purpose Research Reactor	• Proven technology with low risk, assuming use of existing reactor design • LEU target processing optimization required
DIF	• Testing/development required to prepare a comprehensive safety case for licensing • For conversion to LEU, target processing optimization and modification of the NPF would be required
Existing Reactors	• Varies depending on specific option, but may include: • Processing R&D • Safety analyses
Accelerator — Photo-fission	• Risks associated with developing a high-energy linear accelerator with supra-conductivity • Targetry/cooling must be tested at high-beam powers • Yield uncertain • Target processing optimization required
Accelerator — Mo-100	• Risks associated with developing a linear accelerator with the required specifications • Target/converter design and cooling has not been commercially tested • Availability of Mo-100 • Recycling strategy is high risk • Technical and market risks associated with new generators • Issues around specific activity, impurities and a higher elution volume pose a licensing risk
Cyclotron	• Mo-100 target design has not been commercially tested • Availability of Mo-100 • Mo-100 target recycling has significant risk • Issues around specific activity, impurities and labelling efficiency are significant and pose licensing risk

Orange — Significant R&D and significant risk
Yellow — Limited R&D but technical challenges
Green — Proven technology

Processing

Fission-based options require complex processing of radioactive product post-fission. Cost estimates for establishing a new processing facility range from $40M to $400M, depending on the throughput and whether it is a new or refurbished facility[i]. Estimated costs for a new LEU processing facility at the Missouri University Research Reactor (MURR) are currently at $140M, and do not include final waste disposition, which is assumed to be handled by the U.S. Department of Energy (likely at Savannah River Site). The costs are considerable, with significant uncertainty, and proponents of EOIs generally did not give these costs due consideration. Some proponents assumed that Atomic Energy of Canada Limited (AECL) or others would receive the irradiated targets and would undertake the processing.

It is not clear whether AECL would be able to easily accept targets from others. The molybdenum-99 production facility is old (established in 1984), and there are no redundant hot cells within this facility to accommodate new types of irradiated targets, or to conduct the R&D that would be necessary to optimize a new process.

The New Processing Facility (NPF) at Chalk River was built as part of the integrated DIF. This set of hot cells was never fully commissioned because the project was terminated. AECL maintains that these hot cells were optimized for HEU processing and designed so tightly around the specifications for the processing of Multi-purpose Applied Physics Lattice Experiment (MAPLE) targets that the costs associated with modifying them for a different purpose would be as high as to approach the costs of a new facility. A full evaluation of this assertion is outside the scope of this committee, but if a new multipurpose research reactor at Chalk River were to include Mo-99 production, it would make sense to carefully evaluate the suitability of a modified NPF as an element of the production complex to realize the attendant savings of repurposed infrastructure.

In sum, the costs associated with building or modifying and operating a processing facility are not trivial. As the government assesses new sources of Tc-99m supply, special attention should be given to these costs when considering any new fission-based plan. In any relevant request for proposal process, planning and costing of appropriate processing arrangements should be verified.

HEU

Given Canada's commitment to non-proliferation of weapons-grade nuclear products, no new projects requiring HEU should be initiated. Furthermore, proposed legislation in the U.S. may cut off supply of HEU within 7 to 10 years. Therefore, we do not consider HEU-based options sustainable over the medium to long term.

As well, given the significant costs associated with conversion from HEU to LEU, it is not sensible to convert facilities nearing the end of their operating life. Therefore, options based on existing reactors that use HEU targets were considered to be unsustainable since conversion is not an option.

Since we would not pursue new HEU-based projects, reopening the DIF should be considered only if it includes a well-articulated plan to move to LEU targets. The existing infrastructure, primarily the processing facility, was tightly designed around the original HEU-based requirements, and adapting to new requirements involves considerable risk and cost.

All three accelerator options do not use HEU targets, and are therefore attractive from a non-proliferation perspective.

5.1.5 Business Implementation

Because prices for Mo-99 are low, economic viability is difficult to achieve. World prices for Mo-99 have been kept artificially low by current producers, who have been selling isotopes below full cost because they regard isotope production as a sideline to their primary research activities. This pricing creates a marketplace that would be unattractive to most private sector investors.

In considering the economic viability of each option, it is important to establish the point of entry into the market since this affects both the achievable margin and an organization's ability to compete against the existing suppliers. Based on the EOIs received, the proposed entry point into the supply chain for isotopes differs from option to option, as listed in Figure 5.1.

[i] Based on analysis commissioned from SECOR.

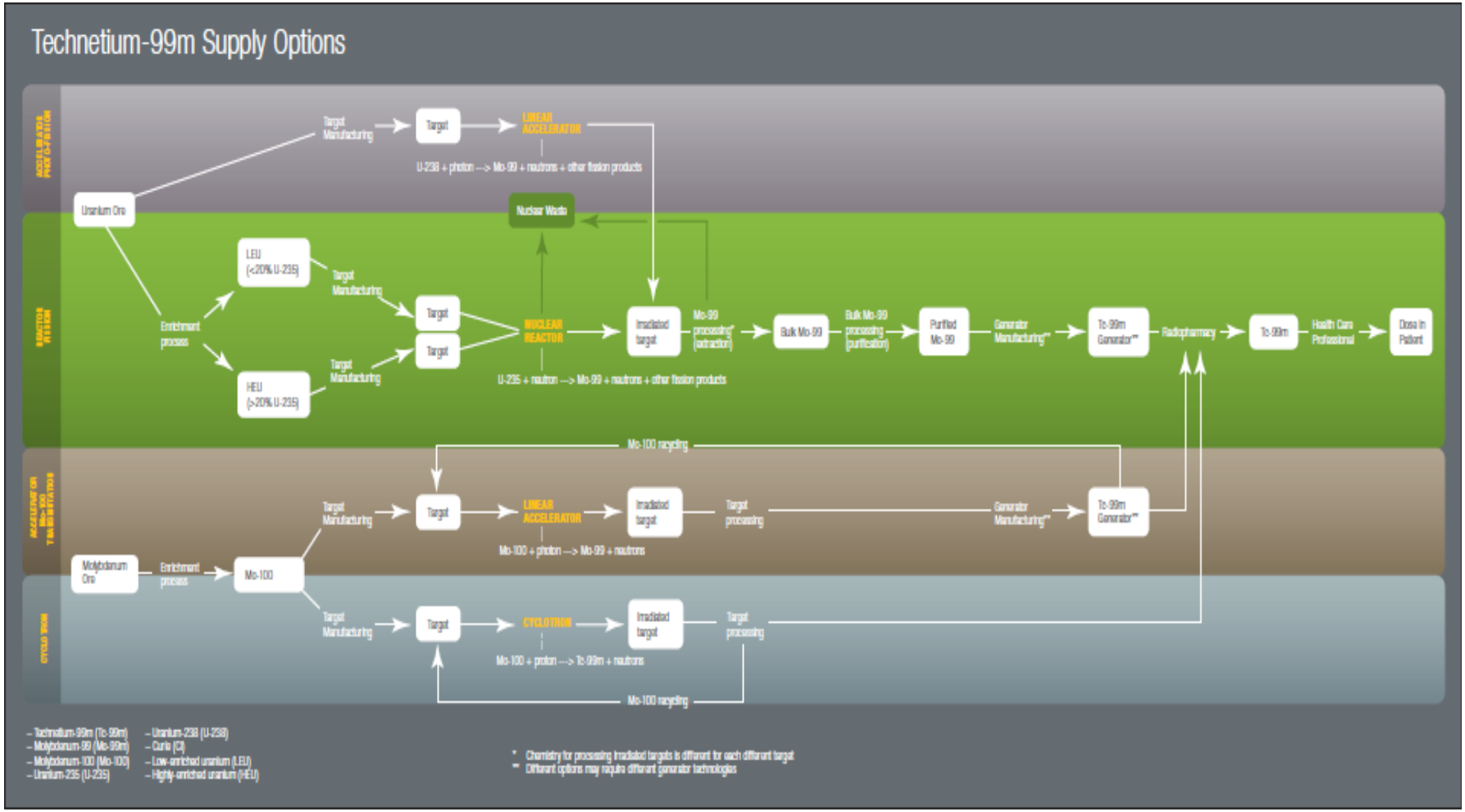


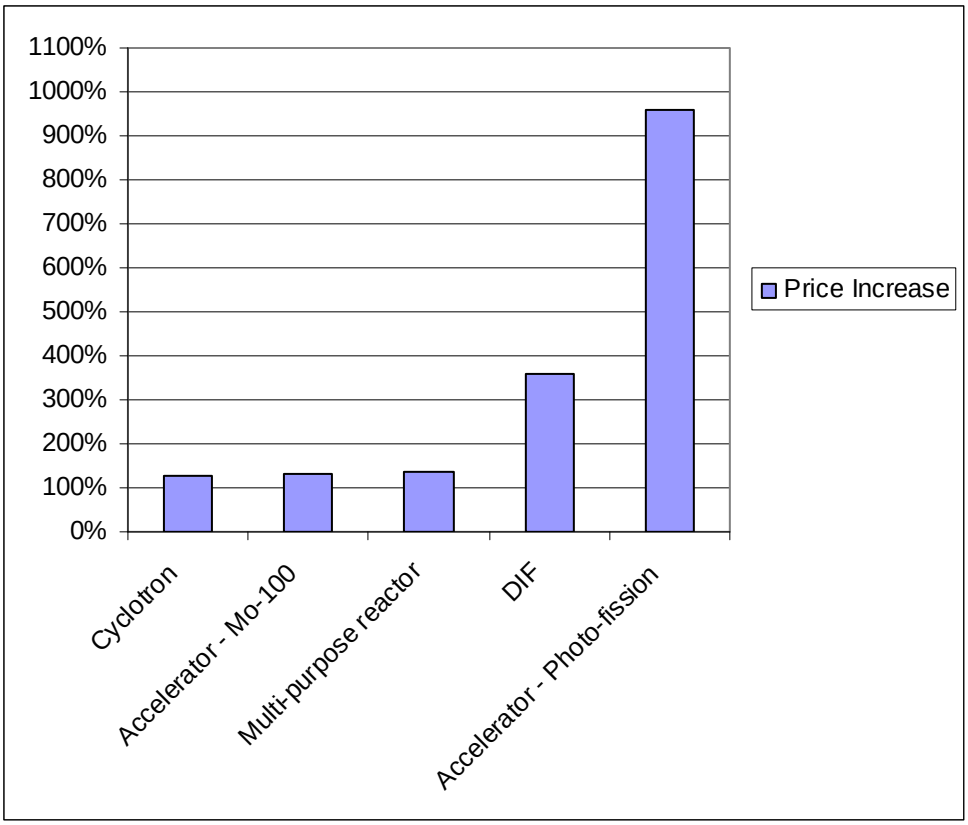
Figure 5.1. Comparison of Likely Points of Product Entry into Supply Chain

The implications for entering the market at different points along the supply chain are discussed further in the subsections on each technology option. However, in general, EOIs tended to be incomplete from a supply-chain perspective, and this aspect should be given attention in any work that follows this report.

Missions / Uses

Prices are expected to remain relatively stable around the $25 per dose mark; however, market share for individual Mo-99 producers is expected to decrease based the market's drive to diversify supply. For single-use options such as the DIF and photo-fission options, where large-volume sales would be required to offset the large capital and operating costs, the decreasing trends in market share make the economics less favourable. The multi-use options (the research reactors and the cyclotrons) are less affected by these trends.

As shown in Figure 5.2, assuming flat demand growth, analyses suggest that price increases of more than 3 times would be necessary for the DIF and photo-fission options to achieve positive net present values (NPV). However, with this magnitude of price increase, other imaging technologies such as positron emission tomography (PET) become increasingly attractive, reducing demand for Tc-99m and then compromising the commercial viability of these options. Therefore, the available data suggests that the economics for these options will be unattractive under almost any future scenario. Note that although the estimates in Figure 5.2 are highly uncertain, the graph remains useful in providing a picture of the relative economic attractiveness of the various options.



Note: Multi-purpose reactor estimate is based on allocation of 20% of reactor costs

Figure 5.2. Price increases needed to achieve a positive Net Present Value[i]

The multi-purpose reactor (assuming an allocation of 20% of reactor costs), cyclotron and Mo-100 transmutation options all become viable with relatively modest price increases, suggesting that it would be possible for them to find a niche in a future market scenario. In a scenario where demand is assumed to grow at 3% per year, these options become even more attractive[i].

Environmental and Waste Management

Waste management issues, which are particularly significant for any fission-based option, were not well addressed by proponents of EOIs. Proponents generally did not appear to understand the requirements for handling waste nor to acknowledge the costs of waste management, handling, storage and disposal.

Many submissions seemed to be based on a tacit assumption that AECL would accept the waste from any isotope-related activities. The U.S. Department of Energy is expected to use the Savannah River Site to accept all U.S. isotope-related waste at no cost so as to remove the waste costs from the “isotope books.” Such a strategy may be considered in Canada as well, and should be

examined as one method of encouraging new entrants into the isotope market, especially if new options are likely to be fission-based. The long-term disposition of target waste presents similar challenges to spent power reactor fuel, but on a smaller scale.

Avoidance of fission products and nuclear waste streams is a significant advantage of the Mo-100 linear accelerator and cyclotron options over the reactor-based and photo-fission accelerator options.

Although it is true that the medical cyclotrons would consume less electricity than the proposed linear accelerators, the magnitude of the difference, especially compared with the environmental impact of reactor-based technologies, is small and would not be a basis for choosing among the technologies.

5.1.6 Timeliness

The technology options vary considerably in their projected timelines for commercial production, as shown in Figure 5.3

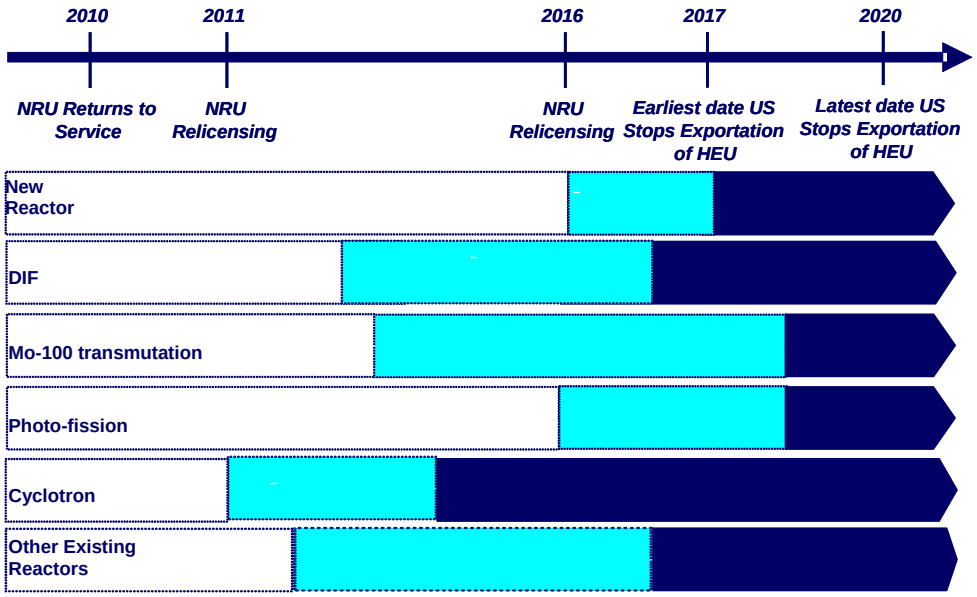


Figure 5.3. Timeline for Introduction of Technology Options[i] (where the light blue bar is range for coming on stream, and the dark bar is commercial production)

The cyclotron option has the earliest predicted market entry at 2011; some technical experts consider this an optimistic estimate and suggest 2013 would be more realistic. Licensing concerns associated with this option could also significantly affect the timeline, and initial cyclotron-based product will enter the market in small quantities.

For the DIF option, the timeline estimates varied considerably. Estimates for the timeline range from two to eight years. Although the best-case scenario of two years to market is attractive, we expect the timeline to be longer given the challenges with the processing facility, in addition to the licensing challenges.

The new research reactor has the longest timeline, creating urgency for a policy decision on the need for a new reactor. Given the expected remaining operating life of the NRU, a decision is needed within the next year.

5.1.7 Regulatory Issues

The CNSC and Health Canada indicated that all options are potentially licensable from both the nuclear and health perspectives, removing regulatory issues as a basis for distinguishing among the options. It is worth noting that the nuclear safety and licensing requirements are significantly less for non-reactor-based options. However, the cyclotron option raises the most questions related to health regulatory requirements since the direct production of Tc-99m is a novel method and there are significant concerns around the purity and specific activity of the product. The new generator technology required for the Accelerator – Mo-100 option may also require significant health licensing effort.

5.1.8 Benefits to Canadians

All the multi-use options, including the multi-purpose research reactor option and the cyclotron option, have considerable ancillary benefits stemming from their other purposes. For these options, much of the benefit comes from the potential for the creation of intellectual property, job creation, training and discovery that comes from R&D activities. However, the scope of R&D associated with the cyclotron option (isotope development and proton-therapy) is narrower in comparison to the scope associated with a multi-purpose research reactor.

We acknowledge that linear accelerators have many uses; however, achieving sufficient production capacity would require a set of dedicated accelerators, making them unavailable for other benefit.

5.1.9 Summary

All the options have their merits and limitations. Table 5.3 provides a high-level summary of how each option fares against the considerations integral in establishing a sustainable and secure long-term plan.

Table 5.3. Overall Comparison of Options

Technology Option	Redundancy/Diversity	HEU/LEU	Multi-use	Processing	Environmental and Waste Management	R&D Required	Cost
New multi-purpose research reactor	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology	• No HEU • Designed for LEU targets from outset	• Multi-use facility • Economics improved • Offers broadest spectrum of auxiliary benefits from R&D and other isotopes	• Processing facility needs to accommodate high throughput (LEU) • Process development and optimization may be needed for LEU	• Large amounts of waste with associated costs and environmental concerns	• Limited	• > $500M
DIF	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology • May worsen security of supply by driving out other participants	• HEU • Conversion to LEU required • Costly and difficult	• Single-use facility • High capital and operating costs are not shared • Poor economics	• Processing facility needs to accommodate high throughput (LEU) • Conversion difficult • Some R&D required	• Large amounts of waste with the associated costs and environmental concerns	• Moderate	• $50–250M (without conversion to LEU)
Existing reactors	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • No improvement in diversity of technology	• HEU • Conversion to LEU required	• May detract from current missions of the reactors	• Processing facility may be far away • Process development and optimization may be needed	• Large amounts of waste with associated costs and environmental concerns	• Moderate	• $50–250M
Accelerator — photo-fission	• Redundancy of raw Mo-99 production but other parts of supply chain remain vulnerable • Diversity of technology	• N/A[6]; targets made from natural uranium	• Single-use facility • Facilities would have to be dedicated to Mo-99	• New processing facilities would be required at considerable cost	• Waste with associated costs and environmental concerns	• Significant	• $250–500M
Accelerator — Mo-100 trans-mutation	• Redundancy across supply chain • Diversity of technology	• N/A; targets made from Mo-100	• Single-use facility • Facilities would have to be dedicated to Mo-99	• New generators required • Market acceptance questionable	• No significant waste	• Significant	• $50–250M
Cyclotron	• Redundancy across supply chain • Diversity of technology	• N/A; targets made from Mo-100	• Multi-use facility • Used for R&D; PET isotopes	• Processing R&D required	• No significant waste	• Significant	• < $50M

Yellow: Neutral Green: Positive Orange: Negative

[6] N/A is used to mean “not applicable”

5.2 New Multi-purpose Research Reactor Option

5.2.1 Technology Description

Virtually all of the Mo-99/Tc-99m commercially available today is produced via fission of U-235 targets in nuclear reactors. From this perspective, the lowest risk path to new Mo-99/Tc-99m production capacity in Canada is a new multi-purpose research reactor. The research reactor also promises the most attendant benefit to Canadians based on its multiple purposes.

The decision to build a new research reactor is a major science and technology policy decision for Canada that would be centred around the long-term positioning of Canada within the global scientific and nuclear communities, and, to a lesser extent, the need for isotope production. Such a decision is outside the scope of this Panel. It is clear, however, that if a new research reactor were to be built, isotope production, based on LEU targets, should be included as one of the core missions.

As a Panel, we would like to stress the urgency of deciding the future of AECL and the need for a new research reactor in Canada. These decisions, although driven by factors other than isotopes, will play a large role in determining the best long-term strategies for securing isotopes for Canada. Because the current NRU licence expires in 2011 and its licence extension to 2016 and beyond is not guaranteed, any decision to build a new reactor should be made within the next year to allow the possibility of the new reactor coming on stream prior to the end of life of the NRU.

5.2.2 Technical Feasibility

Research reactors are proven technology, and fission of U-235 targets in a nuclear reactor followed by appropriate processing is the one proven way to achieve commercial levels of production of Mo-99.

It is clear that the cost, timeline and risks associated with a new research reactor can be minimized by choosing an existing reactor design and limiting its capabilities. As scientific infrastructure intended for use for 50 years or more, however, a new research reactor should aim to realize value from the substantial investment over its intended life. Designing for flexibility to serve the broadest range of purposes maximizes the chance that the reactor will be able to adapt to serve as-yet unimagined needs many years from now. Indeed, it was this flexibility and adaptability in the design of the NRU reactor that has allowed it to remain a critical piece of global nuclear infrastructure for more than 50 years. Also, if Canada is to remain in the power reactor business, it may be prudent to consider the needs of the CANDU community. The challenge is to design a new facility that possesses sufficient breadth to justify and sustain a long-term

commitment without building in so much capability and flexibility that the costs and risks become too high.

Processing

In any work to further explore a research reactor option, care should be taken to include the processing facility in the overall costing and scheduling.

Cost estimates for a new processing facility range from $40M to $400M dollars, depending on the capacity and whether it is a new-build or a refurbishment.

A new processing facility would require substantial R&D to demonstrate the efficiency, quality and purity of the product.

To mitigate transportation issues and costly, time-intensive environmental assessments, collocation of the processing facility and the reactor would be important.

Finally, to achieve redundancy at the level of Mo-99 processing, consideration should be given to having a truly redundant processing line or to attaining compatibility with other processing facilities in North America.

HEU

To this day, the Mo-99 targets used in most reactors continue to be HEU-based; however, because of global non-proliferation efforts and pending U.S. legislation, any new reactor should be designed to produce Mo-99 using LEU targets.

Generally, LEU production requires roughly five times more uranium and associated material than the current HEU method. Consequently, the volume of nuclear waste from LEU production would be five times more than the waste generated by the current method and a larger amount of plutonium (Pu-239, half-life of 24110 years) produced from U-238. As a result, consideration should be given to having the appropriate waste management structure.

5.2.3 Business Implementation

The multi-purpose research reactor is the most expensive of all the technology options with a cost between $500M and $1.2B, depending on the features of the reactor and the missions it is intended to serve. Operating expenses ranging from $35M to $70M also need to be considered. In their estimates, proponents typically did not include the costs of the processing facility, nor the costs associated with training, licensing requirements, security and waste management, all of which are very significant.

As mentioned, the capital costs and ongoing operating costs of a new reactor are high, and these would be borne, at least in large part, by the federal government. A public-private model in which the government would fund a multi-purpose reactor and the private sector would finance infrastructure dedicated to isotopes (i.e. processing infrastructure) might be viable.

Mission / Uses

Research reactors are shared facilities that have the benefit of costs being spread over a large base of activities. Multi-use infrastructure creates an opportunity for other missions to make the overall venture commercially viable and/or a sound investment of public monies.

It is expected that revenue from isotope production would only offset approximately 10–15% of the costs of the reactor. Therefore, isotopes alone are not reason enough to invest in a new research reactor. However, if a new research reactor were justifiable based on its other missions, it would be important to include isotope production as one of its missions.

Environmental and Waste Management

For any fission-based option, nuclear waste management, storage and disposal present significant long-term liabilities and are significant considerations that should be addressed from the start. It is estimated that the cost for waste management for a new multi-purpose research reactor could reach $10M annually. The burden of waste management has historically been the responsibility of the federal government.

An environmentally sound solution to store, and later, dispose of the nuclear waste is a must in any future project for Mo-99 production from fission. Chalk River Laboratories has infrastructure in place that has been used or built to manage waste from Mo-99 production. Careful examination of the adequacy and adaptability of the existing facilities is required to assess their usability in a future modern and environmentally sound Mo-99 production program.

The use of LEU would meet non-proliferation objectives but would increase the volume of uranium waste. However, preliminary studies suggest that more efficient Mo-99 extraction processes, in addition to more efficient waste volume reduction processes, may help overcome the waste volume issue (Vandegrift, 2006).

5.2.4 Timeliness

The timeline proposed for this option is 5 to 10 years, making it among the slowest to market of all options considered. As the scope and novelty of the reactor design increases, the risk to the timeline also increases.

5.2.5 Regulatory Issues

Nuclear

A multi-purpose research reactor would be a Class I nuclear facility with the entire incumbent regulatory requirements, including an Environmental Assessment. However, there are no obvious barriers to licensing. Use of an existing design would reduce the technical, licensing, construction and operational risks.

Health

Use of LEU targets would significantly change the impurity profile of the Mo-99 produced, and would require additional validation from a Health Canada regulatory perspective prior to commercial production. However, Tc-99m generators based on LEU targets from Australia's OPAL reactor have been approved for use in Canada.

5.2.6 Benefits to Canadians

Of all the classes of technology proposed, this one has the highest potential for concomitant benefit to Canadians based on the promise of the broad-based research that would be undertaken, and its associated potential for generating intellectual property, job creation and training. It would also be integral in maintaining and growing the existing nuclear industry in Canada.

We strongly recommend technology options that can serve multiple purposes. Because of the multiple uses of the research reactor, it would have the broadest base of ancillary benefits and would tend to be the most adaptable to a changing marketplace.

5.2.7 Pros and Cons

Table 5.4. Pros and Cons for the New Multi-purpose Research Reactor Option

Pros	Cons
Technical: • Designed to use LEU targets from the beginning • Targets may be designed to be compatible with other processing facilities **Business:** • Proven technique for isotope production **Benefits:** • Important infrastructure for broad-based R&D supporting basic science, reactor development, medical research and materials development • Potential for creation of intellectual property and spin-off businesses • Infrastructure for new isotope research • Important in training and retaining highly qualified people • Important in supporting existing and future CANDU power reactors beyond the NRU • Creation of knowledge-based jobs • Builds on the significant nuclear expertise and infrastructure Canada already has in place	**Business:** • Significant investment • Costly to build ($500M to $1.2B or more) • Costly to operate ($45 to $70M) • Additional costs associated with the need for a processing facility, licensing, security and waste management • Revenue from isotope production would offset only a small fraction (10-15%) of reactor costs **Environmental:** • Creation of significant quantities of nuclear waste **Timeline:** • Long timeline to completion (5 to 10 years)

5.3 Dedicated Isotope Facility Option

5.3.1 Technology Description

We received a number of EOIs proposing to restart the DIF project, which includes two MAPLE reactors, the NPF and its associated waste management structure. As with most reactor-based production of Mo-99/Tc-99m, the DIF option would produce the required isotopes through fission of U-235 targets in the MAPLE reactors.

During commissioning of the MAPLE reactors in 2003, AECL measured a positive Power Coefficient of Reactivity (PCR), when a negative PCR had been predicted. This raised concerns with the regulator, the CNSC. AECL undertook to overcome the issues. However, in 2008, AECL terminated the project, and the DIF facilities were put into an extended shutdown state. Currently, neither the reactors nor the processing facility are authorized by the CNSC for routine operation.

The submissions we received offered a range of paths for completion of the DIF project, with or without substantial modifications to the technology and/or existing facilities. The submissions sought to build on the significant investment and existing infrastructure that is already in an advanced state of completion.

Notably, the DIF option represents a complete production line including: the reactors, the processing facilities, the waste management structure and storage.

5.3.2 Technical Feasibility

Production of Mo-99/Tc-99m via fission of U-235 targets in a nuclear reactor is proven technology. Experts agree that, with certain modifications and/or regulatory approvals, the DIF project could be successfully commissioned and licensed to produce the required isotopes; however, the costs and timelines are very uncertain.

The design of the MAPLE reactors, the NPF and the associated waste management structure was heavily customized and dedicated to isotope production alone. The design customization has ultimately imposed significant challenges around possible modification and re-use of these facilities. This introduces significant risk for the submissions received by this Panel as well as with planning a conversion to LEU, which is a requirement of any medium- to long-term plan.

Processing

Modifications to the target and/or to the core may present difficulties in adjusting the NPF and associated waste management structure to the new designs and may run up significant costs. Further, most of the DIF-based submissions envisaged converting to LEU in the future but with interim use of HEU targets. As mentioned, the limitations of the NPF and associated waste management structure with regard to target type could present challenges and were not sufficiently explored by the proponents.

HEU

Significant R&D would be required to convert the DIF to LEU targets and the feasibility of converting the NPF and associated waste management structure from HEU to LEU targets has not been sufficiently evaluated. Because the processing of LEU targets generates higher waste volumes, the capacity of the HEU-designed NPF and associated waste management structure may not be sufficient to produce enough product to cover operating costs.

5.3.3 Business Implementation

Benefits of the DIF option include the use of some existing infrastructure, simple insertion of MAPLE-produced Mo-99/Tc-99m into the existing supply chain and some redundancy of supply from having two reactors. There would, however, be no redundancy in processing.

According to recent estimates, the high operating cost of the DIF would not be offset by the revenue from the sale of isotopes[i]. This is before taking into account the substantial waste management costs. When these are factored in, the economics become even more unattractive.

On the basis of current prices and with expected sales volumes, even if the existing infrastructure were available at no cost, the economics for this option are poor because of the problems with single-use facilities for isotope production.

Estimates for the timeline range from two to eight years. Although the best-case scenario of two years to market is attractive, we expect the timeline would be longer given the challenges with the processing facility and the licensing challenges.

Mission / Uses

The DIF option is a single-use infrastructure for isotope production. Return on investment for the DIF would be dependent on the size of market share it could secure. Ongoing global diversification efforts would make this market share smaller than the NRU's current market share. Moreover, LEU conversion would limit capacity, and DIF would likely produce roughly half of typical NRU output.

A dedicated facility purely based on a private sector cost-recovery model would be a good solution, but it is unlikely that a private sector organization would be interested in accepting the full commercial risk associated with this approach.

Environmental and Waste Management

Although the waste management infrastructure is in place at the Chalk River site, the ongoing costs of waste handling and storage could nonetheless be significant, depending on the processes used.

As well, independent experts have raised concerns about the volume of waste that would be generated using LEU targets and whether the existing DIF facilities could accommodate it.

5.3.4 Timeliness

The timelines suggested by proponents of the DIF option are relatively short based on the fact that the infrastructure is largely in place. The additional work projected by proponents focuses on process commissioning and safety analyses, which are expected to have relatively short timelines. These timelines are in contrast with AECL claims that successful commissioning and licensing could take up to eight years. The true timeline likely falls somewhere between two and eight years, given the challenges with the processing facility and licensing, and may not be significantly different from other options.

The conversion to LEU, including the associated R&D and facility modifications, will take time, but not likely beyond the anticipated elimination of HEU in seven to ten years.

5.3.5 Regulatory Issues

Nuclear

Input received from the CNSC suggests that the licensing history of the DIF puts any submission to resume this project under intense nuclear regulatory scrutiny. This implies some uncertainty in terms of licensing. For any change to the reactor configuration, a new safety case would have to be prepared. Also, an amendment to the Non-Power Reactor Operating Licence (NPROL) for the MAPLE reactors and possibly to the Chalk River site Nuclear Research and Test Establishment Operating Licence (NRTEOL) (due to the changes to the MPF processes) would be required. Both amendments may require an Environmental Assessment, although these would likely be combined.

The CNSC has indicated that some proponents of EOIs did not appropriately account for the length of time required for CNSC staff review, or the CNSC public hearing process, putting at risk the aggressive timelines proposed.

Eventual conversion to LEU will also require additional nuclear regulatory licensing and approval before commercial production of Mo-99/Tc-99m from LEU targets.

Health

Since Mo-99/Tc-99m from a MAPLE reactor would be fission-based and would have similar characteristics to existing Mo-99/Tc-99m, no significant health regulatory barriers are anticipated. However, conversion to LEU targets would significantly change the impurity profile of the Mo-99 produced, which would require additional Health Canada approval before commercial production.

5.3.6 Benefits to Canadians

The Chalk River site has been a centre of excellence in nuclear technology, and although the DIF itself provides no R&D benefits, maintaining this site would help preserve Canadian expertise and intellectual assets.

5.3.7 Pros and Cons

Table 5.5. Pros and Cons for the DIF Option

Pros	Cons
Technical: • Reactor fission is a proven technique for Mo-99 production • Substantial infrastructure in an advanced state of readiness • Comprehensive production line: reactors, processing facilities and waste management system • Modern and efficient design of waste processing and reduction of fissile waste volume **Business:** • Existing supply chain **Security:** • Two reactors to ensure redundancy during outages **Timeline:** • Timeline to production could be as short as two years **Benefits:** • Builds on the significant nuclear expertise and infrastructure already in place	**Technical:** • Processing facility is a prototype of a novel and unproven approach. Target design is also new. • Commissioning has not been completed. • LEU conversion, which is essential for any long-term solution, will be challenging • Customized design may not allow modification or conversion to LEU targets **Business:** • Economics are poor because not a multi-use facility **Environmental**: • Significant quantities of nuclear waste **Regulatory:** • Concerns regarding the power coefficient of reactivity need to be resolved with the CNSC

5.4 Existing Reactor Option

5.4.1 Technology Description

We received several EOIs suggesting the use of existing research or power reactors, either domestically or internationally, to irradiate U-235 targets for the production of Mo-99. The processes described in the submissions are similar, if not identical, to current proven reactor-based medical isotope production methods. As well, the EOIs generally propose to use an existing processing facility and the existing supply chain. While most, if not all, of these projects were technically feasible, none of them fit within our definition of providing sustainable and secure supply over the medium to long term.

As well, submissions regarding existing reactors relied, in most cases, on the use of HEU targets. As discussed in Chapter 4, Context, HEU is unlikely to be available beyond 10 years based on global non-proliferation efforts, as well as proposed U.S. legislation. Therefore, an option based on using existing reactors in Canada or abroad is unsustainable over the long term. For options based in other countries, it is unclear that there is any role for Canada other than as a customer for isotopes, and possibly to facilitate coordination of LEU target design and processing to permit redundancy.

While conversion to LEU would be possible, most of the infrastructure being proposed for use is relatively old and the costs of conversion would likely not be justifiable based on the limited remaining life span of the facilities.

Existing Research Reactors

McMaster University submitted an EOI proposing to use its on-campus research reactor to irradiate the HEU targets used in the 1970s when the university provided backup isotope supply when the NRU reactor was down for vessel replacement. This option raises several long-term issues. The targets proposed are not compatible with the processing facility at AECL today. Work would be required to modify AECL's processing line to accommodate these targets. The neutron flux of the McMaster reactor is low and its cooling capacity limited, resulting in limited yield even with HEU targets. Indeed, given the already low yield, conversion to LEU targets would not be feasible other than as a backup option. The location of the reactor on the university campus raises safety and security concerns around storage and transportation of the targets before and after irradiation. Also, losses due to decay during shipping time from Hamilton to Chalk River result in amounts of end-product that may not justify the effort required. But most significantly from the perspective of this Panel, the use of HEU excludes this project from consideration for the medium to long term.

However, the use of HEU would not preclude this project from being considered for the short term as a “bridging” option. Indeed, we are aware that this project is being discussed within forums looking at short-term strategies. We believe that the use of McMaster University’s reactor as a back-up option is best considered alongside all other such short-term options, and is therefore better handled by those tasked with the short term.

Similarly, submissions related to the use of any other existing research reactor in North America or elsewhere should be considered within the context of the need for short-term or bridging options, and will not be discussed further here.

Power Reactors

The on-line re-fuelling feature of CANDU power reactors is such that it would allow for a limited number of channels in the reactor to be used for the irradiation of targets.

Although this is technically possible, no owner/operator of a CANDU power plant has expressed a willingness to pursue the idea. It is unlikely that any organization would be willing to allow a new and likely unprofitable line of business to detract from its critical mission of electricity production. Beyond the HEU and processing concerns that apply to all projects within this class of technology, obtaining the necessary changes to the existing operating licences from the CNSC would not be trivial.

5.4.2 Technical Feasibility

This option is based on the one proven method for Mo-99/Tc-99m production — fission of U-235 targets in a nuclear reactor followed by appropriate processing. Furthermore, it is based on the use of currently operating facilities, so the technical risks are very low. In some cases, changes to existing processing facilities would be required.

That being said, the production of Mo-99 requires a very high neutron flux, higher than what is currently available in the proposed existing reactors. As a result, there is some risk that work would be required to optimize yield. As well, the irradiation of fissile material targets requires adequate cooling to remove the fission heat; these existing facilities likely cannot provide that. Nevertheless, the overall technical risk remains very low.

Processing

The use of any reactor for isotope production should be compatible with a processing facility in existence or to be constructed as part of the project. Modifications to existing processing facilities to accommodate existing reactors' targets would present significant challenges and would be very costly. Estimates for a new processing facility are also costly, $40M to $400M, depending on the capacity and whether it is a new-build or a refurbishment.

As well, most projects would require shipping of Mo-99 to processing facilities, thus reducing already low production volumes, and adding to the risk in the supply chain. However, establishing commonality of targets between reactors could improve redundancy of supply.

HEU

Most of the submissions based on the use of existing reactors to produce Mo-99 relied on the use of HEU targets. As mentioned above, while conversion to LEU would be possible, most of the infrastructure being proposed for use is relatively old and the costs of conversion would likely not be justifiable based on the remaining lifespan of the facilities. As such, the existing reactor option is outside our definition of providing sustainable and secure supply over the medium to long term.

5.4.3 Business Implementation

These submissions, especially the university-based ones, would all be almost entirely reliant on government funding for implementation. Based on the production rates achievable, the cost–benefit ratio is poor. Nonetheless, government funding of one or more of these projects as short-term backup options may be justifiable based on the health needs of Canadian patients.

Mission / Uses

Existing research reactors are shared infrastructure, sharing costs over a larger base of activities and able to leverage existing funding. Because the market for Tc-99m is relatively small, multi-use infrastructure makes both business and economic sense because it creates an opportunity for other missions to make the overall venture commercially viable and/or a sound investment of public monies.

In the case of power reactors, however, the mission of producing electricity is so critical that owners/operators would be unlikely to place that purpose at risk to produce Mo-99.

Environmental and Waste Management

Existing reactors and processing facilities may not have the appropriate waste management facilities in place to accommodate a new mission of isotope production.

Modifications to existing waste management infrastructure could present significant challenges and be very costly.

5.4.4 Timeliness

The timelines proposed for these projects are in the range of one and a half to three years. These are among the quickest to market of all options considered. However, they are considered a short- to medium-term option since they are HEU-based; conversion to LEU would have a much longer timeline, would be riskier, and would likely be infeasible given the age, mandate and/or neutron-flux of the reactors in question.

5.4.5 Regulatory Issues

Nuclear

All of the options in this class propose the use of currently licensed facilities. Although changes to the existing licences would be required to allow for the introduction of HEU targets, the regulatory issues are moderate. Licence amendments would be required for a revised safety case covering any associated changes to a reactor facility or mode of operation. For power reactors, a licence modification to permit Mo-99 production would require significant work to ensure continued safe operation of such facilities.

Also, if an existing processing facility needs to be modified, a licence amendment would be required.

In addition, depending on the extent of the modification to a nuclear facility, an Environmental Assessment may be required.

Health

Since Mo-99/Tc-99m from an existing reactor would be fission-based and have similar characteristics to existing Mo-99/Tc-99m, no significant health regulatory barriers are anticipated. However, use of LEU targets would significantly change the impurity profile of the Mo-99 produced, and would require additional validation from a Health Canada regulatory perspective prior to commercial production, although LEU-based product has been licensed in Canada.

5.4.6 Benefits to Canadians

Beyond improving the security of supply of Mo-99/Tc-99m, these projects present few benefits to Canadians. Projects undertaken at research centres, including universities, may have the attendant benefit of helping to justify ongoing support for important R&D infrastructure in Canada.

5.4.7 Pros and Cons

Table 5.6. Pros and Cons for the Existing Reactor Class of Technology Option

Pros	Cons
Technical: • Takes advantage of existing infrastructure • Based on proven technology, and in the case of McMaster University, it has been done before **Timeline:** • Possible quick implementation **Benefits:** • Universities are keen to be a part of the solution and the project may benefit them • May provide the justification needed to continue funding existing nuclear R&D infrastructure in Canada	**Technical:** • Aging reactors • Often reliant on aging AECL processing infrastructure • In some cases, the proposed targets are not compatible with the existing process • Production rates are low in many cases • Need for shipping to a processing facility reduces already low production volumes • Safety and security concerns associated with handling HEU on a university campus or in a densely populated area • Target storage and waste management must be done off site • HEU-based, which precludes it from being considered a sustainable long-term option

5.5 Linear Accelerator — Photo-Fission Option

5.5.1 Technology Description

A particle accelerator is a device that uses electric fields to accelerate ions or charged subatomic particles to high speeds in well-defined beams to bombard targets for research and radioisotope production. The most commonly accelerated particles are electrons and protons (hydrogen nuclei). The path of the acceleration can be straight (linear accelerator) or circular (cyclotron, synchrotron, etc.), depending on the design and the acceleration technique.

In this option, a high-power electron linear accelerator is used to bombard a converter to produce an intense photon beam to generate Mo-99 through photo-nuclear interactions with natural uranium. This is a fission-based option similar to the reactor fission options except that this involves the fission of U-238 and not U-235.

5.5.2 Technical Feasibility

An accelerator facility based on 100-kW power requires modest development, and has a high probability of success. In the case of photo-fission, an adequate, shielded and protected processing facility is required.

The photo-fission method requires higher power to compensate for the low efficiency of the production and improve yield. More specifically, the operation of an electron linear accelerator requires a significant amount of electricity to produce the electron beam because only part of the beam is converted by the photo-converter and subsequently only part of that converted energy will interact with the target. The energy is lost through heat, which makes cooling capacity an important consideration that requires further development and testing.

Substantial R&D is needed to establish an efficient process and high-quality product on a commercial scale.

Processing

Because this technology is also fission-based, the processing of the irradiated targets is not substantially different from the way it is currently done, although increased volumes may reduce production rate of bulk Mo-99. Although there is relatively low technical risk, it is costly. Cost estimates for a new processing facility range from $40M to $400M, depending on the capacity and whether it is a new-build or a refurbishment. In general, proponents of EOIs did not appropriately account for the costs associated with this aspect of production.

HEU

Because this option is based on fission of U-238, the isotope that comprises 99.3% of natural uranium, enrichment of U-235 (i.e., use of HEU) is not relevant.

5.5.3 Business Implementation

Many aspects of the business case are uncertain at this time given the significant amounts of R&D necessary to better understand the potential of this approach. Although the cost of an accelerator is much less than that of a reactor, the accelerators needed for these options would be relatively expensive based on the high power needed. The cost of one accelerator is estimated at more than $50M, and as many as four accelerators would be required to serve the Canadian market. When costs associated with required buildings, processing and waste management are included, the total costs of the option could exceed $500M.

The raw material is natural uranium, which is readily available in Canada at low cost.

This option's fission-based approach introduces several cons, especially around waste, but it also presents some advantages. Once the targets come out of the accelerator, they are not substantially different from targets irradiated in reactors; therefore, the new technology can fit into the existing supply chain for Tc-99m generators. This would be advantageous because it is likely that the new supply would easily find a buyer in one of the dominant players in the existing market. The downside is that this option would do nothing, other than add capacity, to improve the dynamics of this supply chain, and alone would not necessarily address some of the weak points further downstream.

Mission / Uses

To meet the required throughput, the accelerators would be dedicated to isotope production. Although photo-fission could produce a few other medical isotopes (iodine-131 and xenon-133), the infrastructure would not be available for research or any other application. As a result, this option would be a single-use infrastructure that suffers from poor economics because the high capital investment cannot be justified for the small Canadian market for isotopes, and there is no opportunity to share costs with other missions.

Environmental and Waste Management

The photo-fission option produces significant nuclear waste, important from both an environmental and an economic point of view. Waste management carries all the environmental concerns associated with the management and long-term storage of nuclear waste, including the costs.

5.5.4 Timeliness

This option could be implemented in the 2013–2015 timeframe; however, the significant R&D required makes the timeline highly uncertain. The fission product processing facility that would be required would be a three- to five-year program. If an existing facility could be retrofitted to handle the fission products, this timeline could be shortened. However, our information on the current infrastructure, including its limitations and issues, indicates that a suitable retrofit is unlikely.

5.5.5 Regulatory Issues

Nuclear

Particle accelerators under 50 MeV energy are Class II nuclear facilities. Licensing a Class II nuclear facility is usually straightforward considering the relatively low risk posed by operating such facilities compared with other nuclear facilities. A new processing facility for fission products would require a Class I facility licence with an Environmental Assessment similar to that for any Class I nuclear facility.

Health

Regarding health regulatory requirements, significant review and licensing assessment would be required by Health Canada since the process is substantially different from the conventional Mo-99 production process.

5.5.6 Benefits to Canadians

Linear accelerator technologies are Canadian-born and -based. If successful in serving the domestic market, the photo-fission technology could be exported and provide the basis for new Canadian businesses. Note that Canada already has a long history and strong reputation for accelerator development and sales. Several Canadian companies currently provide accelerator technology and compete on a global scale.

5.5.7 Pros and Cons

Table 5.7: Pros and Cons for the Linear Accelerator — Photo-fission Option

Pros	Cons
Technical: • Accelerator technology already exists and the power required is attainable with some development • Does not require enriched uranium **Business:** • Compatible with the existing supply chain and would introduce diversity of supply **Regulatory:** • Licensing requirements for accelerators are significantly lower than for reactors **Benefits:** • Medical isotopes such as iodine-131 and xenon-133 could also be produced • Potential for creation of intellectual property and spin-off businesses • Unique Canadian technology	**Technical:** • Considerable R&D required to develop converter and targets to handle high power deposition • Transportation of radioactive targets is challenging **Business:** • Costs of the photo-fission option are high and could approach $500M or more, including R&D and the development of four new dedicated accelerator facilities • This option alone would not significantly change the dynamics of the existing supply chain and may not address risk of a single point failure further down the supply chain • Costs associated with a new processing facility would be significant • Magnitude of power requirements constrain placement of facility **Environmental:** • Photo-fission would generate significant quantities of nuclear waste, which implies environmental concerns and high costs for waste management

5.6 Linear Accelerator — Mo-100 Transmutation Option

5.6.1 Technology Description

As previously mentioned, an electron linear accelerator can produce Mo-99 through the activation of enriched Mo-100. For the activation of Mo-100, the linear accelerator produces a high-energy electron beam that is directed at a photo-converter. The impact of the beam with the photo-converter produces secondary radiation that moves on to hit a second target composed of enriched Mo-100. The impact of the radiation on this target causes the removal of one neutron from Mo-100 thus producing Mo-99.

5.6.2 Technical Feasibility

As in the case of photo-fission, although technically feasible, this production method requires a photo-converter system and a target, both of which still require significant R&D to address issues in design and cooling capacity.

Standard generators would not be suitable and “dry gel” generators would be required. Although this technology was developed in India over 25 years ago, some R&D would be required to evaluate fragility associated with this design such as the moly “breakthrough”[7] problem.

Processing

Processing has not been done on a commercial scale and requires significant R&D, adding to the risk.

HEU

In this option, the target is made from Mo-100, not uranium, so HEU is not relevant.

5.6.3 Business Implementation

As with the photo-fission option, business implementation of the Mo-100 transmutation option depends on many factors not defined at this time. In addition to the cost of building an appropriate accelerator, the costs of developing the targetry, extraction and processing need to be taken into account.

[7] Breakthrough is excessive Mo-99 contamination in the Tc-99m eluted from a generator. Regulatory limits in Canada specify that the maximum acceptable limit beyond which the generator fails the breakthrough test is 0.15 µCi of Mo-99 per mCi of Tc-99m.

Currently, there is no commercial production of Mo-100. The cost could be substantial and may prove to be a barrier to commercialization. A full recycling of the raw materials would reduce the cost substantially by minimizing loss, but recycling is yet to be demonstrated and significant R&D would be required. Moreover, this recycling would require the users of the generators to return them, which may present a logistical problem.

Capacity per unit is estimated at 200–300 curies per week, although some proponents estimated more; two facilities would likely be needed to meet the Canadian weekly demand of 500 curies. The estimated costs of this option are $34 to $64M. It is worthwhile to note that although the two accelerator facilities do create some redundancy in the system, they cannot truly be considered backups to each other because one alone could not meet Canadian demand.

Accelerators can easily be turned on and off, which would optimize operating costs because they would run only when required. From this point of view, this option offers the possibility of truly redundant capacity that could be easily activated in times of need.

The Mo-100 option requires the development and marketing of a new type of generator. Significant costs would be associated with development of this new product. Hospitals and central radiopharmacies would have to purchase and install a new generator, which could be expensive and carries risks associated with liquid and gas leaks. Many hospitals may not accept the new generators and the new generators would have to compete with the traditional generators already in the marketplace, presenting significant business risk.

Mission / Uses

As in the case of photo-fission, the accelerators used for Mo-100 transmutation would need to be dedicated to isotope production to achieve the desired throughput, making this a single-use option. Return on investment would be difficult given the small Canadian market and the significant capital and operating costs.

Environmental and Waste Management

The Mo-100 transmutation option does not generate nuclear waste, which represents a significant advantage of this option from an environmental point of view.

5.6.4 Timeliness

The timeline for R&D and for building the accelerators would not be extensive, although there is a risk of failure of the R&D. The estimated timeframe for production is 2013–2015, which is the same as for the photo-fission option.

5.6.5 Regulatory Issues

Nuclear

Particle accelerators under 50 MeV energy are Class II nuclear facilities. Licensing a Class II nuclear facility is usually straightforward considering the relatively low risk posed by operating such facilities compared with other nuclear facilities.

There would likely not be any barriers to the licensing of a processing facility for Mo-100.

Health

Regarding health regulatory requirements, substantial review and licensing assessment is required by Health Canada since the process is substantially different from the conventional Mo-99 production process. Concerns related to impurities (molybdenum-94, yttrium-91 from zirconium, niobium-99), specific activity and higher elution volumes may present challenges to licensing.

5.6.6 Benefits to Canadians

As with the photo-fission technology, the Mo-100 transmutation technology would be Canadian-born and -based. If successful in serving the domestic market, this technology could be exported and provide the basis for new Canadian businesses.

5.6.7 Pros and Cons

Table 5.8. Pros and Cons for the Accelerator — Mo-100 Transmutation Option

Pros	Cons
Technology: • The accelerator technology already exists and the power required is attainable with some development **Environmental:** • Generates minimal waste • Does not require enriched uranium **Regulatory:** • Licensing requirements for accelerators are significantly lower than for reactors **Benefits:** • A unique Canadian technology • Potential for creation of intellectual property and spin-off businesses	**Technology:** • Considerable R&D required to develop converter and targets to handle high power deposition • Substantial R&D for the target extraction, purification and recycling processes **Business:** • Cost of raw materials is high and could become prohibitive • New and less efficient generators would need to be manufactured; these may not be able to compete with the incumbents in the market, putting the business case at risk **Regulatory:** • Licensing of formulation kits could be onerous if the labelling yield and quality control tests are outside the monograph limits accepted by Health Canada • Licensing of a new type of generator

5.7 Cyclotron Option

5.7.1 Technology Description

Cyclotrons were proposed for direct production and delivery of Tc-99m to radiopharmacies. Cyclotrons are particle accelerators whose path of acceleration is circular.

Cyclotron technology is well established, and a Canadian-based company is a significant exporter of cyclotron technology to the world. Furthermore, medical cyclotrons are well established worldwide for the production of PET isotopes.

The cyclotron option is based on bombarding Mo-100 targets with protons. The concept is to devise an extraction technique that would allow the Tc-99m to be extracted directly from the irradiated product. This would eliminate the need for Mo-99 generators, but would require a much more efficient and decentralized system to overcome the significantly shorter half-life of Tc-99m, which is six hours compared with the 66-hour half-life of Mo-99.

5.7.2 Technical Feasibility

Preliminary studies and tests suggest that the cyclotron production of Tc-99m is technically feasible (Takács et al., 2002). Difficulties with this option include: the long-term availability and cost of the raw material Mo-100; the requirement for some R&D associated with target design and Mo-100 recycling; the low specific activity; and the requirement for additional validation from a Health Canada regulatory perspective.

As well, the very short half-life of Tc-99m presents some real challenges. This option requires daily production of Tc-99m and it would be very difficult to supply Tc-99m for after-hour procedures. Also, the distribution range for Tc-99m is limited to nearby communities; this option is not viable for remote areas. For comparison purposes, a one-hour delay in the process for Mo-99 would cause a loss of product of 1%; while for Tc-99m, the same delay would cause a loss of more than 10%.

Processing

Significant R&D would be required for the processing and recycling of Mo-100, which poses significant risk to the timeline and economic viability of this option.

HEU

This technique of producing Tc-99m does not require any form of uranium. The raw material used is enriched molybdenum. Therefore, HEU is not an issue for the cyclotron option.

5.7.3 Business Implementation

The current operation of cyclotrons to produce other medical isotopes demonstrates that the operating and capital costs associated with the cyclotron option are relatively low. The cost of implementing this option would include approximately $5M for R&D, and approximately $5M to $9M for building any new cyclotron.

The option could begin with the use of existing infrastructure, which could inexpensively be adapted to produce Tc-99m. In addition, if required, new cyclotrons could be purchased, adding to the current infrastructure and providing additional benefits such as an incentive to expand the use of PET and single-photon emission computed tomography (SPECT) technologies.

From a business perspective, the cyclotron option would be insulated from competition within its own radiopharmacy network, which would likely allow it to compete with the well-established incumbents in the generator market. The same would not be true outside of its network, however, where operators would face competition when selling their new form of Tc-99m.

The cyclotron option would also require implementation at a regional level. Different business plans would need to be developed and implemented for different medical cyclotron operators.

While cyclotrons in major urban areas and radiopharmacy networks seem viable, the cyclotron option is not a complete solution. The 6-hour half-life of Tc-99m typically requires “bringing the patient to the centre” and does not lend itself well to shipping the isotope. As a result, rural centres without access to a medical cyclotron and associated radiopharmacy would likely not benefit from this option. In addition, licensing of Tc-99m for use in formulation kits could be challenging if labelling yield and quality tests are outside monograph limits accepted by Health Canada, and may limit the range of its diagnostic uses.

The use of medical cyclotrons to produce Tc-99m could be used with another option, such as a multi-purpose research reactor, to ensure security of supply and 100% of Canadian demand of Tc-99m. Because cyclotrons cannot be a complete solution, care would have to be taken not to produce so much Tc-99m by cyclotrons that the remaining market becomes too small to attract generator suppliers[i].

Because this technology is at an early stage of development, it is difficult to say how much of the Canadian market could be or would be served by cyclotrons; however, even if it were only a small fraction, it is attractive that the cyclotron infrastructure could be in place and used for other purposes, so that in times of need, it would be available to avoid shortages. In this way, if R&D proves successful, the cyclotron option would be an important means by which to ensure security of supply over the long term because it would build in all of the elements needed for security – capacity, redundancy and diversity.

Finally, as the administration and delivery of health care services is the responsibility of the provincial and territorial governments, the cyclotron option and associated radiopharmacies would have provincial and territorial considerations associated with approvals and funding.

Missions / Uses

For a number of years, medical cyclotrons have produced isotopes for use in research. Some isotopes already being produced by medical cyclotrons include: Gallium-67, Thallium-201, Iodine-123 and 124, Indium-111, Carbon-11, Nitrogen-13, Oxygen-15 and Fluoride-18. Many of those isotopes are routinely used as alternatives to Tc-99m during times of shortage.

The cyclotron option could be viable for a number of reasons. First, it is easily testable with minimal expenditure since the proposed cyclotron facilities are already built and available for testing and eventually for production. Second, with successful process demonstration and target development, this option is scalable and the cyclotrons may be used as multi-use facilities since they are primarily qualified for producing PET and other isotopes. Finally, communication and collaboration between medical cyclotron operators could ensure redundancy in supply and avoid single point of failure in the supply chain. Although each cyclotron serves a limited geographical area, the failure of one would have only a limited impact on the overall market.

This solution can be implemented gradually as each cyclotron is intended to serve only a localized market.

Environmental and Waste Management

An important benefit of this option is that it does not produce nuclear waste, which results in economic and environmental benefits over fission-based options.

5.7.4 Timeliness

The cyclotron option is the timeliest solution. Commercial production of Tc-99m could begin between 2011 and 2014. Issues that could affect the timelines of this option include the need for R&D associated with target design and Mo-100 recycling, as well as meeting regulatory requirements from Health Canada.

5.7.5 Regulatory Issues

Nuclear

Particle accelerators, including medical cyclotrons, under 50 MeV energy are Class II nuclear facilities. Licensing a Class II nuclear facility is usually straightforward considering the relatively low risk posed by operating such facilities compared with other nuclear facilities.

Under CNSC nuclear regulatory requirements, each medical cyclotron and radiopharmacy would require a licence. However, the 24-MeV cyclotron type is suitable for Mo-100 bombardment and is the only cyclotron currently available on the market with the optimal current (>500 uA). In addition, the 24-MeV cyclotron is already certified, which means that the licensing for the facility would be simplified since the features of the machine and its safety features are already known to the regulator. The modification of the process and the addition of new targets and target stations to the licence require a relatively simple approval process.

Health

The heavier regulatory requirements would be Health Canada-related. A complete New Drug Submission (NDS) would be required for Tc-99m produced by this alternative method. A full radiation dosimetry study, as well as validation of radiolabelling, would be required, among other things. There is a risk of the impurity being close to the regulatory limits established for reaction fission Mo-99. Therefore, a revised set of requirements taking into account this process may have to be elaborated by the health regulator prior to, or in conjunction with, the review of the NDS.

5.7.6 Benefits to Canadians

The cyclotron option is a “Made in Canada” and “Made for Canada” solution. Added benefits include: the use of Canadian technology and existing infrastructure; the shared-use facility, which allows the production of additional medical isotopes; and possible expansion of PET and SPECT technology.

5.7.7 Pros and Cons

Table 5.9. Pros and Cons for the Cyclotron Option

Pros	Cons
Technical: • Existing infrastructure **Business:** • Shared-use facility • Distributed supply chain • Easily adaptable to changing demand and technology • Scalable solution • No additional cost linked to a stop in production of Tc-99m • Redundancy of supply • No single point failure • Multi-use infrastructure **Regulatory:** • Straightforward nuclear licensing of facility **Environmental:** • Clean solution: no waste stream **Benefits:** • Tc-99m is simply one more medical isotope for a cyclotron; therefore infrastructure could remain useful for PET even if demand for Tc-99m drops • Infrastructure is same as used for PET; therefore can produce broad spectrum of medical isotopes	**Technical:** • R&D required to design optimal target, target station, processing and recycling • Need to evaluate Tc-99m impurities **Business:** • Not a stand-alone solution — not ideal for rural centres • Price of Mo-100 could be prohibitively high • 6-hour half-life means that product must be used quickly and cannot be shipped or held very long • Difficulty in shipping and transport **Regulatory:** • Significant health regulatory requirements • Licensing of Tc-99m for use in formulation kits could be challenging if labelling yield and quality tests are outside monograph limits accepted by Health Canada and may limit range of diagnostic uses **Other:** • Loss of production of other reactor isotopes such as I-131

Chapter 6

Recommendations

Given the complexity of the medical isotope issue, and the ongoing fragilities in the isotope supply chain, we are convinced that there is no quick fix solution, and that the path to security of isotope supply lies in diversification. Having said that, it is not practical to pursue all possible options, and our recommendations attempt to prioritize among the various possibilities.

6.1 General Recommendations

1. Strive for diversity and redundancy throughout the supply chain.

We recommend that the supply strategy create redundancy at every step in the supply chain. Redundancy is naturally achieved through a distributed supply chain with more players. The linear accelerator and cyclotron options lend themselves to this supply chain model.

Technetium-99m (Tc-99m) is a perishable product and, as such, cannot be stockpiled. This imposes a just-in-time supply chain that does not enjoy the buffering effect that comes with inventory. Because security of supply cannot be assured through a well-stocked inventory, it must be sought through excess capacity, redundancy and diversity.

Technological diversity in the supply chain would improve security in that it would naturally lead to a more distributed and redundant system overall, and it would help avoid collapse of the supply chain if one technology became obsolete or unviable for technical or economic reasons.

2. Leverage multi-use infrastructure.

We recommend leveraging multi-use infrastructure when possible. Infrastructure that is designed for multiple uses is more likely to remain useful over the long term, regardless of how the use of medical isotopes evolves. The National Research Universal (NRU) reactor is a good example of how a multi-use facility can be adapted over time to remain useful for 50 years or more. Shared

infrastructure has the added benefit of costs being shared over a larger base of activities. Because the market for Tc-99m is relatively small, multi-use infrastructure makes both business and economic sense because it creates an opportunity for other missions to make the overall venture commercially viable or a sound investment of public monies.

The nuclear medicine landscape is evolving and new technologies and tracers are emerging, which makes the level of demand for Tc-99m in the long term uncertain. We are convinced that those options that will remain attractive over the long term will be those that have the flexibility and adaptability to serve multiple purposes.

3. Continue with international coordination and seek processing standardization within North America.

We recommend that the government continue to inform itself of all international isotope initiatives, and work with other countries to better coordinate worldwide efforts related to isotope production and distribution.

We encourage the government to start laying the groundwork now for establishing target and target processing compatibility, especially for any new reactor sources developed in North America.

4. Highly enriched uranium (HEU) options are only viable in the short to medium term.

We recommend that any option reliant on HEU be dismissed as a long-term solution. As a proponent of non-proliferation, Canada must work to eliminate HEU from civilian use. Further, legislation currently under consideration in the United States would end supply of HEU within 7 to 10 years.

However, HEU will continue to dominate supply in the short to medium term. Recognizing that HEU is not compatible with long-term strategies does not preclude continued use of HEU in the NRU reactor or in any short-term or bridging options. Because most options associated with existing reactors are based on using HEU targets, they should only be considered within a short-term context.

6.2 Technology-specific Recommendations

1. Make policy decisions on the requirement for a new research reactor.

We recommend that the government expeditiously engage in the replacement of the NRU reactor as we believe a multi-purpose research reactor represents the best primary option to create a sustainable source of Mo-99, recognizing that the

reactor's other missions would also play a role in justifying the costs. With the NRU approaching the end of its life cycle, a decision on a new research reactor is needed quickly to minimize any gap between the start-up of a new reactor and the end of life of the NRU.

The only proven means of supplying commercial quantities of molybdenum-99 (Mo-99) and Tc-99m is a nuclear research reactor. From this perspective, the lowest-risk strategies for ensuring adequate supply of isotopes in the future would include a new multi-purpose research reactor. However, the significant costs associated with this option likely cannot be borne by the isotope mission alone, and as a Panel we do not recommend a dedicated isotope reactor. The revenue from isotope production would offset only a small fraction of the costs of a new research reactor, and therefore, any new reactor would have to be justified largely based on its other missions. Although a new research reactor cannot be justified by isotopes alone, isotope production should be included as a mission in any new multi-purpose research reactor.

If a new reactor is to be built, we see a need for a deliberate process, with detailed consideration of site selection, functionality, missions, cost, timeline and partners. We suggest a careful weighing of the risk–benefit tradeoff of incorporating a wide variety of missions versus a more narrow focus.

An integral part of the planning should examine the cost of processing facilities and waste management, which should not be underestimated. Moreover, because processing facilities can represent a bottleneck in isotope production, careful attention should be paid to the design and construction of these facilities. As outlined in the report, LEU processing should be made compatible with other North American facilities to improve redundancy by enabling supply chains to be interconnected.

2. Support a research and development (R&D) program for cyclotron-based Tc-99m production.

We recommend that the cyclotron option for direct production of Tc-99m be explored further. Although this option requires significant R&D, the infrastructure and know-how to undertake that work is readily available in Canada; costs associated with the R&D remain relatively low. Assuming technical viability, the infrastructure necessary to demonstrate this approach in selected centres across Canada is already in place.

A significant advantage of this option is that any new cyclotron infrastructure would also be available for isotope R&D and production of PET isotopes. Therefore, this would be multi-use infrastructure that would likely remain useful even if there were a significant shift away from SPECT toward PET technology.

The cyclotron option would introduce a supply of Tc-99m that is independent of existing producers or distributors, and thereby significantly improve the overall security of supply for Canada.

This cannot be a complete solution. The cyclotron option would produce Tc-99m directly, and because of Tc-99m's very short half-life, this option is suitable only for large centres and surrounding hospitals. The cyclotron option would necessarily have to co-exist with and rely upon other supply options for Tc-99m, domestic or global, to satisfy demand in smaller, more remote locations, and also service the after-hours needs of hospitals everywhere.

The necessary R&D for this option should be pursued, regardless of what other options are considered. Ideally, this R&D would be funded using existing competitive government processes, but with a more aggressive strategy to resolve the remaining issues on target design, target processing, Mo-100 recycling and Tc-99m purity.

Should the R&D results be promising, a demonstration project should be undertaken at one of the existing cyclotron centres in Canada. Should that demonstration prove successful, work should be done to evaluate the optimal number of sites to serve Canadian needs, both during normal market conditions and during times of market shortage. The optimal number of sites should be determined taking into account the need to maintain the viability of the Canadian market for generator manufacturers, since this option would require a balanced supply of generators from other sources.

Despite its attractiveness, this option is still an R&D activity at this stage. It is important, therefore, to evaluate progress so that in the case of a roadblock, R&D efforts can be shifted to other accelerator options.

3. Achieve better use of Tc-99m supply through advanced medical imaging technologies.

We recommend programs to encourage the replacement of older equipment with more efficient scanners using solid state crystal detectors and resolution-recovery software. These new and clinically available technologies reduce the amount of Tc-99m needed to perform nuclear medicine procedures, and patients and nuclear medicine workers benefit from reduced radiation exposure.

Short-term efforts to address the recent supply shortages of Tc-99m have centred on managing the demand side of the market. Demand has been moderated by avoiding waste and making efficient use of the product. We believe that demand-side strategies also have a place in ensuring security of supply in the medium to long term, and that action can begin now to put them in place.

In addition to the deployment of newer single-photon emission computed tomography (SPECT) technology, we suggest appropriate investment in positron emission tomography (PET) technology. By improving access to PET across Canada, not only would patients benefit from the most advanced technology, but dependency on reactor-produced isotopes would also be gradually reduced.

6.3 Other Considerations

1. Linear accelerator options

The two linear accelerator options (photo-fission and Mo-100 transmutation) have limited prospects for multiple uses, and do not appear to have significant cost advantages over reactor technologies. On this basis, they rated less favourably than the cyclotron option. We wish to emphasize that they may be technically viable, but require further R&D to develop targets and prove yields.

The economics of the photo-fission option is poor because production of commercial quantities of Mo-99 would require building dedicated accelerator facilities. This would introduce all the disadvantages associated with single-use facilities discussed in the report. Nonetheless, a modest R&D investment could be a way to hedge against the risk of failure of other options. Of the two linear accelerator options, we prefer the technology based on Mo-100 transmutation since the projected economics appear better, and it largely avoids nuclear waste management issues.

Depending on factors such as life extension of the NRU reactor and the urgency of the need for new sources of supply, it may be appropriate to consider investing limited amounts in R&D for the linear accelerator option in parallel with investment in cyclotrons. If the timing is not urgent, decisions regarding investment in R&D for this option could be delayed until the results of the cyclotron R&D were known.

2. Dedicated Isotope Facility (DIF)

Cost and timeline estimates associated with the commissioning and licensing of the DIF varied widely. Although it may be possible to bring the facility into operation, the business case is such that even if it could be licensed immediately at no cost, ongoing revenues from isotope sales would be insufficient to cover the ongoing operating expenses, particularly with the reduced throughput from future conversion to LEU targets and decreased market share.

While we recognize that some situations warrant federal subsidies for activities important for the health of Canadians, in this situation, subsidies would be questionable. There is a high level of risk associated with this option and, based

on current prices and expected sales volume, other options alone or in combination present better economics and timelines that are not significantly different from the DIF when risk and uncertainties are taken into account.

Although we can see the merits, to some level, of federal support for the production of isotopes for Canadians, we do not believe that Canada should be underwriting Mo-99 production for what becomes a for-profit global supply chain that includes non-Canadian private companies where the bulk of the benefit is realized outside of Canada.

A dedicated facility purely based on a private sector cost-recovery model would be a good solution assuming a private sector organization would be willing to accept the full commercial risk associated with this model.

A dedicated isotope infrastructure requires a leading global market share to make the economics work; this may be at odds with the goal of achieving diversity of supply in Canada. Shared-use facilities can run at low output for isotopes and concentrate on other missions while retaining excess capacity for times of need. As a single-use facility, the DIF cannot rely on other missions to offset costs and does not offer concomitant benefits to Canadians.

6.4 Closing Remarks

We brought forward those technology options that meet our general recommendations; the exact combination and sequence of choices would depend on how the R&D evolves, and what government policy decisions are made.

Chapter 7

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Chapter 8

Glossary

Accelerator	A device that uses electric fields to propel ions or charged subatomic particles to high speeds and that contains them in well-defined beams. An ordinary CRT television set is a simple form of accelerator. There are two basic types: linear accelerators and circular accelerators or cyclotrons.
AECL	Atomic Energy of Canada Limited is a crown corporation that develops and markets CANDU nuclear reactor technology and is Canada's leading provider of nuclear research and development. AECL also operates the NRU reactor, which supplies 30 to 40% of world demand for Tc-99m, as well as other medical isotopes.
AIPES	Association of Imaging Producers and Equipment Suppliers
ANL	Argonne National Laboratory
ANSTO	Australian Nuclear Science and Technology Organisation
ARI	ANSTO Radiopharmaceuticals and Industrials
ATR	Advanced Test Reactor
B&W	The Babcock & Wilcox Company
BMS	Bristol-Myers Squibb
BR2	Belgian Reactor II
Breakthrough	Breakthrough is excessive Mo-99 contamination in the Tc-99m eluted from a generator. Regulatory limits in Canada specify that the maximum acceptable limit beyond which the generator fails the breakthrough test is 0.15 µCi of Mo-99 per mCi of Tc-99m.

CEAA	*Canadian Environmental Assessment Act*
CERCA	Compagnie pour l'étude et la réalisation de combustibles atomiques
CNEA	Comisión Nacional de Energía Atómica
CNSC	The Canadian Nuclear Safety Commission regulates the nuclear sector in Canada. It protects the health, safety and security of Canadians as well as the environment, and respects Canada's international commitments on the peaceful use of nuclear energy.
CRL	Chalk River Laboratories
CT	Computed tomography
Curie (Ci)	A unit of radioactivity, defined as 1 Ci = 3.7x 1010 radioactive decay per second.
Cyclotron	A circular particle accelerator that accelerates charged atomic or subatomic particles in a constant magnetic field. It consists of two hollow semicircular electrodes, called dees, in a large evacuated cylindrical box. An alternating electric field between the dees continuously accelerates the particles from one dee to the other, while the magnetic field guides them in a circular path. As the speed of the particles increases, so does the radius of their path and the accelerated particles spiral outward.
Daughter isotope	The product of the decay of a radioactive isotope
Decay (or radioactive decay)	The process in which an unstable atomic nucleus spontaneously loses energy by emitting ionizing particles and radiation. This decay, or loss of energy, results in an atom of one type, called the parent nuclide, transforming to an atom of a different type, named the daughter nuclide.
DIF	Dedicated Isotope Facility located at AECL's Chalk River Laboratories. Included in the DIF are the two Multipurpose Applied Physics Lattice Experiments reactors, the New Processing Facility (NPF) and associated waste management structure, all of which are currently in an extended shutdown state.

DMF	A Drug Master File is a reference that provides information about specific processes or components used in the manufacturing, processing, and packaging of a drug. The DMF is a useful vehicle for providing information to Health Canada, and can be referenced by drug manufacturers in support of their New Drug Submission or other submission.
Eluting	Recovering an isotope (Tc-99m) by passing a saline solution through the alumina column of the generator.
Enriched uranium	Uranium with a higher concentration of the U-235 isotope than found naturally.
Enrichment isotope separation	The process of concentrating specific isotopes of a chemical element by removing other isotopes from it. For example, separating natural uranium into enriched uranium and depleted uranium.
EOI	Expression of Interest
FDG 2-deoxy-2-[18F]	Fluoro-D-glucose (also called fluordeoxyglucose)
Fission	Process whereby a large atomic nucleus (such as uranium) is split into two (and sometimes three) smaller nuclei, resulting in new isotopes.
FISST	Fissile solution storage tank
Flux	(see Neutron flux)
FRM-II Forschungsneutronenquelle Heinz Maier-Leibnitz	German: Research Reactor Munich II
FRRSNF	Foreign Research Reactor Spent Nuclear Fuel
Gamma camera	Nuclear medicine imaging device optimized to image single photon emission tracers. This camera can perform images acquisition in 2D (planar imaging) or 3D (SPECT).
GE	General Electric

Half-life	The time required for a quantity of radioactive material to decay to half of its initial value.
HEU	Highly enriched uranium (>20% U-235). Uranium enriched to concentrations greater than or equal to 20 percent by weight of U-235.
HFIR	High Flux Isotope Reactor
HFR	High Flux Reactor
HIFAR	High Flux Australian Reactor
High-level waste (HLW):	Highly radioactive materials containing fission products and transuranic elements produced as a by-product of the reactions that occur inside a nuclear reactor.
Hot cell	Shielded workspace for working with highly radioactive materials
IAEA	International Atomic Energy Agency
INL	Idaho National Laboratory
INVAP	Investigaciones Aplicadas Sociedad del Estado
IRE	Institut National des Radioéléments
Isotope	Atoms having the same number of protons but different number of neutrons. Isotopes can be stable (non-radioactive) or unstable (radioactive).
KAERI	Korea Atomic Energy Research Institute
LEU	Low enriched uranium (5% < U-235 <20%) Uranium enriched to concentrations less than 20 percent by weight of U-235.

LINAC	A linear particle accelerator (often shortened to linac) is a type of particle accelerator that greatly increases the velocity of charged subatomic particles (e.g., electrons) or ions by subjecting them to a series of oscillating electric potentials along a linear beamline. It uses alternating voltages of high magnitude to timely push particles along in a straight line. Particles pass through a line of hollow metal tubes enclosed in an evacuated cylinder. Linacs have many applications, from the generation of X-rays for radiotherapy, to being an injector for higher-energy accelerators, to the investigation of the properties of subatomic particles.
LLW	Low-level waste
MAPLE	The Multipurpose Applied Physics Lattice Experiment (MAPLE) dedicated isotope-production facility was a project jointly undertaken by AECL and MDS Nordion. It was intended to include two identical 10 MW reactors, as well as the isotope-processing facilities necessary to produce a large portion of the world's medical isotopes, especially Molybdenum-99, medical Cobalt-60, Xenon-133, Iodine-131 and Iodine-125.
Medical isotopes	A medical isotope is a very small quantity of radioactive substance used in safe, cost-effective medical imaging and treatment of disease. This is different from external beam radiation treatment where radiation is directed from outside of the body.
Mo-99	Molybdenum-99 is a radioactive isotope, currently produced in commercial quantities through neutron irradiation of Uranium-235 in nuclear reactors. It is the parent isotope of Tc-99m, which is a key isotope used in nuclear medicine.
MPF	The Molybdenum-99 Production Facility is the facility currently used for processing Mo-99 targets irradiated in the NRU reactor at AECL’s Chalk River Laboratories.
MRI	Magnetic Resonance Imaging
MTR	Materials Test Reactor
Multipurpose research reactor	A nuclear fission reactor that is not used for producing energy but has several missions and uses such as neutron beam research, activation analyses, radioisotope production for medical and industrial uses, materials testing for nuclear power reactor components and other materials, and neutron radiography.

MURR	Missouri University Research Reactor
NECSA	Nuclear Energy Corporation of South Africa
Neutron capture	Process involving the capture of neutrons by an atomic nucleus to form a heavier nucleus.
Neutron flux	Measure of the intensity of neutron radiation, defined as the number of neutrons crossing a unit area of a square centimetre in one second (neutrons/cm^2-sec).
NDA	A New Drug Application is a written application seeking approval to sell a pharmaceutical in the United States.
NDS	A New Drug Submission is an application to Health Canada for authorization to market a drug in Canada. An NDS contains information and data about a drug's safety, effectiveness and quality. It includes the results of preclinical and clinical studies, details regarding the production of a drug, packaging and labelling details, and information regarding therapeutic claims and side effects.
NPF	New Processing Facility that, together with the two MAPLE reactors, forms part of the Dedicated Isotope Facility at AECL's Chalk River Laboratories. The DIF is currently in an extended shutdown state.
NRCan	Natural Resources Canada is the Federal department responsible for nuclear energy policy and AECL.
NRG	Nuclear Research and Consultancy Group
NRU	The National Research Universal reactor is located in Chalk River, Ontario, Canada and is operated by AECL.
NRX	The National Research Experimental reactor, located in Chalk, River, Ontario, Canada, was operated from 1947 to 1992.
NTP	Nuclear Technology Products
Nuclear reaction	The process in which two nuclei or nuclear particles collide to produce products different from the initial particles. While the transformation is spontaneous in the case of radioactive decay, it is initiated by a particle in the case of a nuclear reaction.

NSCA	*Nuclear Safety and Control Act*
Nuclear transmutation	The conversion of one chemical element or isotope into another, which occurs through nuclear reactions. Natural transmutation occurs when radioactive elements spontaneously decay over a long period of time and transform into other more stable elements. Artificial transmutation occurs in machinery that has enough energy to cause changes in the nuclear structure of the elements. Machines that can cause artificial transmutation include particle accelerators and nuclear reactors
OPAL	Open Pool Australian Light water (reactor).
Parent isotope	An isotope that decays to form a new isotope, which is referred to as the daughter isotope.
PET isotope (or Positron emission tracer)	Radioactive isotope emitting a positron (Beta+) while decaying e.g. F-18, C-11, N-13, O-15
PET technology (Positron Emission Tomography)	Nuclear medicine imaging technology optimized to image positron emission tracers.
R&D	Research and development
Radio-pharmaceutical	A radioactive compound used in radiotherapy or diagnosis.
Reactor or nuclear reactor	A device in which nuclear chain reactions are initiated, controlled, and sustained at a steady rate.
Single photon emission isotope	Radioactive isotope emitting a photon (Gamma or X-rays) while decaying. E.g., Tc-99m, Tl-201, In-111, I-131
Specific activity	The activity of a particular radioactive element (i.e., the number of decays per unit of time) divided by the mass of material in which it exists. The specific activity defines the relationship between the activity and the mass of material. Units for specific activity include the curie per gram (Ci/g).
SPECT	Single photon emission computed tomography refers to an acquisition mode of single photon emission by tomography

	(multiple images around the body at different angles).
Target	Material that is designed to be irradiated in a nuclear reactor or particle accelerator.
Tc-99m	Technetium-99m is a radioactive isotope having a half-life of six hours. It is the daughter of Mo-99. It is used in 80% of nuclear medicine procedures.
Technetium generator curies	Calibrated quantity of Mo-99 based on the number of curies that are contained in the generator on the day of or day after its delivery to the radiopharmacy, hospital, or clinic.
Technetium generator	Device used to store Mo-99 and extract its decay product Tc-99m.
Tracer	An identifiable substance, such as a dye or a radioactive isotope, that is introduced into a biological or mechanical system and can be followed through the course of a process, providing information on the pattern of events in the process or on the redistribution of the parts or elements involved. Also called label.
U.S. DOE	U.S. Department of Energy
U.S. FDA	U.S. Food and Drug Administration
USNRC	U.S. Nuclear Regulatory Commission
USP	United States Pharmacopeia
Yield	The amount of product obtained in a reaction.

Appendix 1

Expert Review Panel on Medical Isotopes Production

Biographies

Richard Drouin

Counsel in the law firm of McCarthy Tétrault, Richard Drouin is the former Chairman of the North American Electric Reliability Corporation. He previously served as Chairman and CEO of Hydro-Québec and, until recently, as Chairman of Abitibi-Consolidated. Mr. Drouin sits on the boards of American Superconductor Corporation, BAA ltd (British Airports), Gesca (French daily newspapers) and President's Choice Financial, and he is a Fellow of the Royal Canadian Geographical Society.

Mr. Drouin received his undergraduate degree from the Université de Montréal and his law degree from l'Université Laval in Quebec City, and he holds an honorary degree from l'Université Lumière in Lyon, France. Mr. Drouin is a Companion of the Order of Canada, an Officer of l'Ordre national du Québec and an Honorary Consul for Great Britain in Quebec City. In 2001, he was nominated the Energy Person of the year by the Energy Council of Canada.

Peter Goodhand

President and CEO of the Canadian Cancer Society (CCS), Peter Goodhand joined the CCS in 2004 as the Chief Executive Officer of the Ontario Division. Since that time, Mr. Goodhand has championed greater urgency and intensity in the fight against cancer.

Mr. Goodhand brings with him more than 20 years of international experience in the health care industry. Before joining the Canadian Cancer Society, he was the President and CEO of MEDEC, a national association of Canada's medical

technology industry. In this role, he represented the industry to the Senate Committee and Romanow Commission on health care reform and at Canada's Innovation Summit. In the private sector, his career included roles as vice-president of sales and marketing and vice-president of global marketing with leading health care companies. Mr. Goodhand has also worked with several not-for-profit organizations towards the goal of enhancing the overall performance of the health care system and ultimately improving the quality of patient care.

Mr. Goodhand currently chairs the Board of the Health Technology Exchange and serves on: the Board of the Canadian Partnership Against Cancer, the Board of the Canadian Association of Provincial Cancer Agencies, the Advisory Committee on Oncology for Princess Margaret Hospital, and the Editorial Advisory Board of Healthcare*Papers*.

Dr. Thom Mason

Laboratory Director at the Oak Ridge National Laboratory in Tennessee, the largest U.S. Department of Energy science and energy laboratory, Dr. Mason is a condensed matter physicist with a background in studies of the structure and dynamics of materials using research reactors and accelerators around the world. He has been responsible for the High Flux Isotope Reactor and the construction of the $1.4 B Spallation Neutron Source. Prior to joining Oak Ridge he held academic appointments in the Department of Physics at the University of Toronto and he has served on a variety of advisory panels and review committees.

Dr. Mason received a B.Sc. in physics from Dalhousie University in Halifax, Nova Scotia, and a Ph.D. in physics from McMaster University in Hamilton, Ontario. He conducted research at AT&T Bell Laboratories in Murray Hill, New Jersey, and at Risø National Laboratory in Denmark, and was an Alfred P. Sloan Research Fellow from 1997 to 1999. Dr. Mason has been an Associate of the Quantum Materials Program of the Canadian Institute for Advanced Research, a Fellow of the American Association for the Advancement of Science in 2001, a Fellow of the Institute of Physics in 2004, and a Fellow of the American Physical Society in 2007.

Dr. Éric Turcotte

A nuclear medicine specialist at the Centre Hospitalier Universitaire de Sherbrooke (CHUS), Dr. Éric Turcotte is the clinical head of the Molecular Imaging Centre of Sherbrooke. He holds an establishment licence from Health Canada to operate one of the most advanced PET radiotracer synthesis facilities in Canada.

Dr. Turcotte is an Associate Professor at the University of Sherbrooke, where he teaches nuclear medicine to students from Canada and around the world, as well as to many Canadian nuclear medicine specialists seeking special training in PET. He holds a degree in nuclear medicine from Université de Sherbrooke and recently returned to Sherbrooke following a two-year Fellowship in Positron Emission Tomography with Novel Radiotracers at the University of Washington Medical Center in Seattle.

Appendix 2

Chronology of Panel Activities and Processes

May 28, 2009	The Honourable Lisa Raitt, Minister of Natural Resources, and the Honourable Leona Aglukkaq, Minister of Health, announced that the Government of Canada would establish an expert panel to review submissions from the private and public sectors for the alternative production of the key medical isotope molybdenum-99/ technetium-99m for Canada.
June 19, 2009	The Minister of Natural Resources announced the members of the Expert Review Panel on Medical Isotope Production (the Panel) and launched the process to solicit Expressions of Interest (EOIs) from private and public sector organizations for the alternative production of molybdenum-99/technetium-99m, over the medium and long term.
July 16, 2009	The Panel held its inaugural meeting in Toronto to discuss its Terms of Reference and initiate its processes and work.
July 31, 2009	The deadline for submitting EOIs to the Panel was July 31, 2009. In total, 22 EOIs were submitted to the Panel from a range of private and public sector organizations.
August 5, 2009	A Request for Proposal (RFP) was posted on MERX to award a contract for additional technical and business analysis of EOIs.
August 31, 2009	The Panel held an in-person meeting in Montreal to begin the assessment of the EOIs.
Sept. 8, 2009	The Panel visited Atomic Energy of Canada Limited's Chalk River Laboratories in order to obtain a better understanding of all aspects of the Dedicated Isotope Facility.

	As well, the Panel toured the National Research Universal (NRU) reactor and received a presentation/debrief on the status of the NRU, including its return to service and licence extensions.
Sept. 9, 2009	The Panel held an in-person meeting with the technical and business experts to discuss the requirements for additional analysis of EOIs. As well, the Panel held an in-person meeting in Ottawa with the Health Canada Ad Hoc Health Experts Working Group on Medical Isotopes[8] as well as with Dr. Alexander (Sandy) McEwan, Special Advisor to the Minister of Health on Medical Isotopes.
Sept. 17, 2009	The Panel's Secretariat forwarded EOIs to the Canadian Nuclear Safety Commission for nuclear regulatory feasibility review.
Sept. 23, 2009	The Panel held a teleconference to discuss the preliminary report from the technical and business experts.
Sept. 30, 2009	The Panel sent a letter to all proponents thanking them for their EOIs and confirming the Panel's ongoing review and assessment of the submissions.
Oct. 2, 2009	The Panel received a report from the technical and business experts providing additional analysis of the EOIs.
Oct. 5, 2009	The Panel received a CNSC staff assessment report on the nuclear regulatory feasibility of EOIs.

[8] The Ad Hoc Health Experts Working Group on Medical Isotopes of Health Canada includes representatives from the Canadian Association of Medical Radiation Technologists, the Canadian Association of Nuclear Medicine, the Canadian Association of Radiologists, the Canadian Medical Association, the Canadian Society of Nuclear Medicine, and the Ontario Association of Nuclear Medicine. The Ad Hoc Health Experts Working Group also includes representation by individual nuclear medicine specialists not always representing a specific medical association.

Oct. 6, 2009	The Panel received a report from the Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics of Health Canada on the pharmaceutical regulatory feasibility of EOIs.
Oct. 8-9, 2009	The Panel held a two-day in-person meeting in Ottawa during which the Panel further deliberated on the merits of the EOIs. Also, the Panel held a second teleconference with representatives of the medical community and AECL as well as a teleconference with the Canadian Institutes of Health Research.
Oct. 28, 2009	The Panel held a teleconference to deliberate on its findings and to discuss its draft final report.
Nov. 2, 2009	The Panel held a teleconference to deliberate on its findings and to discuss its draft final report.
Nov. 6, 2009	The Panel held a teleconference to deliberate on its findings and to discuss its draft final report.
Nov. 12, 2009	The Panel held a teleconference to discuss its draft final report.
Nov. 30, 2009	The Panel's Final Report was submitted to the Minister of Natural Resources

Appendix 3

Expert Review Panel on Medical Isotope Production Terms of Reference

Mandate

The Expert Review Panel on Medical Isotope Production (the Panel) will report to the Minister of Natural Resources Canada on its assessment of the most viable options for securing supplies of technetium-99m to the Canadian health system over the medium and long term, and the actions that may be required by governments and others to facilitate realization of the options.

The Panel will receive and review submissions from public or private-sector organizations in response to a Call for Expressions of Interest (EOI) for alternative production of molybdenum-99/technetium-99m. The Panel will assess the EOIs, in a fair and transparent manner, against specified criteria.

Context

Technetium-99m (Tc-99m) is widely used in medical imaging and accounts for the largest proportion of nuclear medicine diagnostic procedures. Canada's supply of Tc-99m generators is largely met by two U.S.-based manufacturers that, in turn, source the parent isotope, molybdenum-99 (moly-99), principally from five research reactors, including Atomic Energy of Canada Limited's (AECL) National Research Universal (NRU) reactor in Chalk River, and four other reactors located in Europe and South Africa. Production of moly-99 at AECL's Chalk River facility is part of a complex supply chain that originates with the import of highly-enriched uranium (HEU) "targets" that are irradiated in the NRU reactor and processed on site for moly-99 extraction. Moly-99 is then shipped to the facilities of MDS Nordion in Kanata, Ontario, for purification, before being exported to Tc-99m manufacturers in the U.S. and offshore. All steps in this process are overseen by national and foreign nuclear and medical regulatory authorities to ensure health, safety, and security.

Since the November 2007 outage of AECL's National Research Universal (NRU) reactor, a number of proposals have been advanced by private and public sector organizations for alternative production sources of molybdenum-99/technetium-99m. With a view to understanding the options available and how they may be integrated into the existing supply chain for medical isotopes, the Minister of

Natural Resources announced on May 28 that the Government would establish an Expert Review Panel on Medical Isotope Production to review alternative supply options and provide advice to the Minister on the most promising options for further development.

Composition of Panel

The Panel will be composed of four individuals with health sciences, technology and public policy background and experience. One of the members will be designated as Chair.

Assessment Criteria

The Panel will assess options for long-term security of supply of medical isotopes according to the following criteria:

Technical Feasibility: The Panel will assess the scientific and technical merits of projects taking into account risks associated with the introduction of new technologies and the likelihood that technologies could be realized on a commercial scale.

Business Implementation: The Panel will assess the business merits of the projects, taking into account the partnerships established by the proponents; funding requirements and secured resources; access to existing or new physical infrastructure required; the ability of the proponents to integrate their proposal within a supply chain; and cost structure and required revenue from market or other sources. The Panel will take into account business risks associated with these elements.

Timeliness of Proposal: The Panel will assess the schedule for implementing proposed options, including the risks of delays.

Regulatory Issues: The Panel will assess EOIs with regard to the capacity of proponents and the project to meet nuclear and medical safety standards and provide an assessment of potential issues, including nuclear and medical regulatory issues that could affect implementation. The EOI should provide information about how facilities would be sited, how controlled nuclear materials

would be handled, facility safety and security would be ensured, and waste management or transportation issues would be addressed.

Benefits to Canadians: The Panel will provide an assessment of the benefits of implementation to Canadians. While this assessment will focus on the overall ability of the project to assure supplies of technetium-99m generators to the Canadian health care system, it will also consider concomitant scientific and technological benefits, economic benefits, or any other benefits to Canadians.

Soliciting Expert Review and Advice

In the pursuit of its work, the Panel will consult and engage actively with domestic and international experts, including the Canadian nuclear medicine and broader medical community and their national associations, to better understand the many considerations that have bearing on the determination of a long-term strategy for Canada given its position in the North American and global markets for medical isotopes. Additional resources may also be engaged to review Expression of Interests, or parts thereof.

Secretariat Resources and Budget

In order to provide support to the Panel members and to assist with preparation of a final report, a secretariat will be constituted with personnel seconded from Natural Resources Canada and Health Canada, and will be housed in Natural Resources Canada.

In addition to seconded personnel, the secretariat will manage a budget of approximately $1 million, which will be used to fund Panel members' per diems and expenses, to cover costs of ancillary research ordered by the Panel, and to support the operations of the secretariat and the production of a final report to the Minister.

Schedule

By June 19, 2009, the secretariat will finalize a public call for expressions of interest. This call will be posted on the Natural Resources Canada website and communications efforts will be undertaken to ensure appropriate dissemination of the information for potential proponents.

The proposals will be submitted to Natural Resources Canada by July 31, 2009. The Panel will have the opportunity to engage with proponents and solicit additional information in a manner and form to be established by the Panel. The Panel will submit a final report to the Minister of Natural Resources Canada by November 30, 2009.

Appendix 4

Department of Natural Resources Canada

Expert Review Panel on Medical Isotope Production

Call for Expressions of Interest
Proponent's Guide

Ce document est aussi disponible en français. Veuillez envoyer un courriel à isotopeERP@nrcan-rncan.gc.ca en indiquant à la ligne Objet « Guide » (sans les guillemets).

Natural Resources Canada | Ressources naturelles Canada

Preface – Expert Review Process

This Proponent's Guide outlines the Call for Expressions of Interest (EOI) process for the Expert Review Panel (the Panel) on Medical Isotope Production. It explains how the Panel will review, in a consistent, fair, and transparent manner, EOIs submitted in response to the Call.

The Panel's opinions and advice will only be provided for consideration and will not bind the Government of Canada. Further, the Government of Canada makes no commitment nor will it have any obligation to provide a financial contribution to any project, including any costs incurred or paid in the preparation of the said EOI.

1. Introduction and Objectives

Technetium-99m (Tc-99m) is widely used in medical imaging and accounts for the largest proportion of nuclear medicine diagnostic procedures. Canada's supply of Tc-99m generators is largely met by two U.S.-based manufacturers that, in turn, source the parent isotope, molybdenum-99 (moly-99), principally from five research reactors, including Atomic Energy of Canada Limited's (AECL) National Research Universal (NRU) reactor in Chalk River, and four other reactors located in Europe and South Africa. Production of moly-99 at AECL's Chalk River facility is part of a complex supply chain that originates with the import of highly-enriched uranium (HEU) "targets" that are irradiated in the NRU reactor and processed on site for moly-99 extraction. Moly-99 is then shipped to the facilities of MDS Nordion in Kanata, Ontario, for purification, before being exported to Tc-99m manufacturers in the U.S. and offshore. Steps in this process are overseen by national and foreign nuclear and medical regulatory authorities to ensure health, safety, and security.

Given the relatively short half-life of molybdenum-99 (66 hours) and the shorter half-life of technetium-99m (6 hours), it cannot be stockpiled for later use. The production of molybdenum-99 must be done on a frequent basis to assure continuous availability, which adds to the complexity of ensuring security of supply.

While Canada accounts for less than ten per cent of the global demand for Tc-99m generators, AECL's NRU typically has represented 30 to 40 per cent of the global supply of moly-99. Correspondingly, domestic production of moly-99 has far exceeded domestic requirements and served an important export market. Tc-99m sourced from moly-99 produced at the NRU has typically represented 85 per cent of the Canadian market and about 50 per cent of the U.S. market. There are currently no sources of moly-99 in the U.S., and hence, the North American market has been very dependent on the NRU.

Over the long term, the supply chain to meet Canada's needs of Tc-99m could take many forms. Solutions must be integrated in a supply chain that will be situated in a North American and global market and that will assure enhanced security of supply. This may entail a domestic source of moly-99 that may be reactor or non-reactor based, as well as processing capabilities and facilities or arrangements for the manufacture of Tc-99m generators in Canada or abroad.

The nuclear and medical isotope industries are highly sophisticated, technology intensive industries and new sources of medical isotopes, from existing or new facilities, will require expert capabilities, deliberate planning, research and/or development, and significant investment, as well as close oversight on the part of regulatory authorities. The process of bringing new sources of supply on stream is expected to take a number of years. Correspondingly, as an interim solution, the Government of Canada has confirmed

the intention to pursue an extension of the operating licence of the NRU past the current licence expiry date of October 2011.

The Government of Canada has established an Expert Review Panel (the Panel) to report on new options for secure medium to long-term supply of medical isotopes for the Canadian health care system, specifically, Tc-99m and its generators.

The Expert Review Panel solicits and will review confidential expressions of interest, supported by a secretariat staffed by Natural Resources Canada (NRCan) and Health Canada employees. It may also engage resources to assist in its assessment of the submissions. In that event, proponents will be asked for permission to release EOIs to expert reviewers, and appropriate confidentiality agreements will be discussed and negotiated as and when required.

In the pursuit of its work, the Panel may request information from any source, including the nuclear medicine community, to better understand the many considerations that have bearing on the determination of a long-term strategy for Canada given its position in the North American and global markets for medical isotopes.

The output of this process will be a report documenting the Panel's assessment of the most viable options for securing supplies of technetium-99m to the Canadian health system over the medium and long term, and the actions that may be required by governments and others to facilitate realization of the options.

2. EOI Structure and Content

The Expressions of Interest must include the following:

a) The completed covering forms given in Appendix 1 with the signature of a duly authorized officer for the proponent;
b) Detailed information structured and organized according to the headings given below. Proponents must include information related to each of the headings, in the order given, providing supporting documentation for all assertions; and
c) All other information considered necessary by the proponent for the fair evaluation of its proposal.

2.1 Project Details

The information provided in this section should be concise, but sufficient to provide reviewers with a sound understanding of the proposal. Please take into account the selection criteria outlined in Appendix 4 of the Proponent's Guide.

2.1.1 Project Description and Technology Identification

This section should provide a general overview of the project and provide information on the ability of the project to contribute to a significant and reliable quantity of technetium-99m to the Canadian health care system at a specified time in the future.

- Explain the reasons for undertaking the proposed project, including why the various parties are involved in its implementation.
- Describe in detail the technological basis for the proposal.
- Identify all technologies that would be required to implement the proposal, including detailed information on the stage of development and the commercial readiness of the technologies. If the proposal can be implemented using commercially available technology, this should be highlighted.
- If additional scientific or technological investigations are required, a plan must be specified and an estimated timeframe provided. This should be included as part of the Project Statement of Work described in Section 2.2.1. Where possible, scientific and technological support for the plan (for instance in the form of peer reviews) should be provided to substantiate the plan.
- Developed plans to bring the technology to a commercial scale should be provided and substantiated with evidence that such scale is possible.
- Describe past work upon which the proposal builds. Provide references to the results of that past work that have been used in developing this EOI. If applicable, also include description of previous regulatory approvals or engagement with regulatory authorities in other jurisdictions or other countries.

2.1.2 Partners and Collaborators

List all partners and collaborators, including the proponent, and explain the nature of their role in, and contribution to, the project. Why are these other stakeholders and collaborators involved, what value do they bring to the project, and how might they be involved in further deployment of the project concept? How will they interact with each other, and what legal understandings are expected?

For all organizations involved, provide evidence that they would have the financial and technical means to deliver their proposed contribution to the project.

2.2 Methodology and Risk Mitigation

This section is the statement of work for the proposal and how project risks might be mitigated.

2.2.1 Statement of Work

Describe in detail the “what and how” of the project proposal: what work would be

carried out, and how it would be done. Describe the different phases (if appropriate) and activities. Identify and explain the key stage gating "go / no go" decision points. Explain clearly how the project would be managed and coordinated. Refer to the tables in Section 2.2.3 to avoid duplication.

2.2.2 Milestones and Outputs

Complete Table A1 (see example in Appendix 2) summarizing the principal phases / activities to be undertaken (identified under 2.2.1) on a year-by-year basis, with expected completion dates. Include principal milestones and outputs. The proponent should identify the timeframes required for each stage of project development, including uncertainties that could result in delays. Timeframes should be provided for: research and development, construction of facilities, testing, regulatory approvals from nuclear safety and medical authorities, and production and processing of isotopes for supply to the market.

2.2.3 Financial Structure & Business Case

Provide a business case justifying the pursuit of this proposal. This should include cost estimates for the overall proposal from today through to the first use of technetium-99m by a health care institution. Include as much detail as possible at this time.

The proponent should provide an assessment of the cost of new infrastructure required and/or costs for using existing infrastructure. Operating costs for facilities proposed should be estimated and the access of the proponents to required existing facilities should be described. A list of resources secured by the proponent and its partners should be identified.

A projection of the revenues required for project viability should also be given. Revenues should be specified as originating from the market, and if necessary, public sources.

The proponent should describe how the project will be integrated into the existing supply chain and should describe any existing or proposed partnerships with current supply chain participants.

Identify the financial risks and the mitigation plan. Proponents are advised that NRCan may carry out financial due diligence on the proponent as part of the review process.

2.2.4 Expectations of Government

Discuss any actions that would be required on the part of the Government of Canada or any other government to realize the option.

2.2.5 Risks and Risk Mitigation Strategy

Provide a review of the project risks in terms of technical risk, business risk, and other risks (environmental review, permitting etc). Note that regulatory issues and risks are to be discussed in Section 2.2.6. The project will be evaluated based on how well the risks have been identified and on the risk mitigation strategy. It is understood that all proposals will carry risk. What is needed is for the proponent to demonstrate that they understand the risks at various stages of the project development and that there is a well thought out plan to execute the project in such a manner that risk is mitigated.

2.2.6 Regulatory Issues

The proponent must identify nuclear and medical regulatory issues that could impact the EOI and identify a strategy for obtaining approvals from the Canadian Nuclear Safety Commission and Health Canada, respectively. Any special requirements, including those associated with the siting of facilities, handling controlled materials, highly-enriched uranium (HEU) or low-enriched uranium (LEU), nuclear waste management, and approval of new medical products, should be highlighted.

2.3 Impact and Expected Outcomes (Benefits to Canadians)

Describe the potential impact of the project if it were implemented. The EOI should include an estimate of its potential contribution to the security of supply of moly-99 and/or Tc-99 to serve the Canadian, North American and/or global markets for Tc-99m. Export capacity may represent a benefit for the domestic health care system if contributing to enhanced, more resilient North American or global supply. The EOI should also identify other medical isotopes that may be supplied, if any, to serve wider health care needs in Canada, North America or globally.

Investment in facilities for the production and potential export of medical isotopes may also represent an opportunity for research and development, application of science, and employment that would have broader benefits for Canada. These benefits would be facility and technology specific and ought to be identified and quantified to the extent possible.

Investment in facilities may also create broader opportunities for Canada's nuclear industry, Canada's medical industry, or Canada's research community. Again, such benefits should to be identified and quantified to the extent possible.

Appendix 1: Expression of Interest Cover Form

CONFIDENTIAL WHEN COMPLETED[9]

Section 1 General Information and Proponent's Attestations

Please note that the proponent's name, project partners' names, project title, non-confidential overview, and expected benefits, will be released publicly, unless expressly requested otherwise by the proponent.

1. Project Title		
2. Project proponent(s) (legal names of companies)		
3. Project partners (legal names of companies, utilities, provinces)		
4. Project Start Date: (year/month)	5. Project Completion Date: (year/month)	
6. Project Location(s) (i.e. location(s) where isotopes would be produced and processed)		
7. Project Summary (max.1 page) (**non-confidential**)		
8. Expected Benefits (**non-confidential**)		

[9] Except the information identified as public in Section 1 of this form.

Attestations

By submitting this EOI, the project proponent attests that:

- It is acting on behalf of all partners and collaborators and has received written permission from them to do so.
- It agrees with the terms and conditions of the Panel Call for Expressions of Interest process as described in the Proponent's Guide.
- Any proprietary or confidential information provided as part of the submission, by any party, is provided with the authorization of that party. Reviewers are bound by the requirements of the Access to Information Act and the Privacy Act regarding the treatment of confidential information.
- It understands and acknowledges that no liability and no commitment or obligation exists on the part of NRCan to make a financial contribution to the project, and, furthermore, that any costs or expenses incurred or paid by the proponent in the preparation of the Expression of Interest are the sole responsibility of the proponent, and no liability exists on the part of NRCan.
- It understands and acknowledges that NRCan reserves the right to alter or cancel the currently envisaged process at its sole discretion.
- The individual signing below attests that he/she has authority to sign on behalf of the proponent.

Please sign below to confirm these attestations:	
_____ Name of Duly Authorized Officer for Proponent: Title:	_____ Date

Appendix 2: Example of Table for Section 2.2.2

The following is an example of a table summarizing the principal phases / activities and completion dates for the proposal.

Table A1

Activities	Year	Principal Milestones	Completion date	Outputs
Phase 1 – R&D				
Phase 2 – Design				
Phase 3 – Construction				

Phase 4 – Commissioning and Operation				

Appendix 3: Submission Process

A submission must include a completed Expression of Interest having the structure and content requested in Section 2 of this Guide. The evaluation criteria are detailed in Appendix 4. Confidentiality considerations are outlined in Appendix 5. Other terms and conditions are given in Appendix 6.

A proponent may provide supporting material for any aspect of the EOI. Proponents are required to submit all of the required documents **by 11:59 p.m. EDT, July 31, 2009**. It is the proponent's responsibility to retain proof of time the documentation package was sent to NRCan. This may be required in the event that NRCan does not receive the documentation package by the deadline for reasons that are beyond the control of the sender.

As per Appendix 5, NRCan recognizes that e-mail is not a secure means of communication, and NRCan cannot guarantee the security of confidential information sent via email while it is in transit. Nonetheless, proponents who regularly use email to communicate confidential information within their own organizations may choose to submit their documentation packages by e-mail to: isotopeERP@nrcan-rncan.gc.ca.

Proponents may also submit their documentation by courier or registered mail to:

Expert Review Panel on Medical Isotope Supply
Natural Resources Canada
580 Booth St., 17th floor
Ottawa, ON K1A 0E4

Where proponents submit by courier or registered mail, we request that an electronic version on a memory stick or CD-ROM be included in the package, clearly marked with the name of the organization and the title of the EOI.

Submission of an EOI and other required information does not imply that the EOI will be approved or funded by the Government of Canada. Failure to provide all of the requested information may lead to the rejection of the EOI.

The Panel's opinions and advice will only be provided for consideration and will not bind the Government of Canada in any way whatsoever. Further, the Government of Canada makes no commitment nor will it have any obligation to provide a financial contribution to any project, including any costs incurred or paid in the preparation of the said EOI.

NRCan reserves the right to alter the process and deadlines. Any changes will be communicated via the website. Proponents are asked to check the site regularly for new information.

Appendix 4: Selection Criteria

Proponents are asked to address all of the criteria below in their Expression of Interests, providing supporting documentation for all assertions. Note that the description of the individual criteria below are indicative of the factors considered by reviewers, but are not meant to be all inclusive. Proponents are urged to submit all information they feel would be relevant in addressing the criteria in their EOIs. Project EOIs will be rated and ranked on a comparative basis, against other EOIs being reviewed, based on the following criteria and on an overall assessment of individual Expression of Interests.

Evaluation Criteria

Assessment criteria used by the Panel will include:

- Technical Feasibility: The Panel will assess the scientific and technical merits of projects taking into account risks associated with the introduction of new technologies and the likelihood that technologies could be realized on a commercial scale.

- Business Implementation: The Panel will assess the business merits of the EOIs, taking into account the partnerships established by the proponents; funding requirements and secured resources; access to existing or new physical infrastructure required; the ability of the proponents to integrate their proposal within a supply chain; and cost structure and required revenue. The Panel will take into account business risks associated with these elements.

- Timeliness of Proposal: The Panel will assess the schedule for implementing proposed options, including the risks of delays.

- Regulatory Issues: The Panel will assess EOIs with regard to the capacity of proponents and the project to meet nuclear and medical safety standards and provide an assessment of potential issues, including nuclear and medical regulatory issues that could affect implementation. The EOI should provide information about how facilities would be sited, how controlled nuclear materials would be handled, facility safety and security would be ensured, and waste management or transportation issues would be addressed.

- Benefits to Canadians: The Panel will provide an assessment of the benefits of implementation to Canadians. While this assessment will focus on the overall ability of the project to assure supplies of technetium-99m generators to the Canadian health care system, it will also consider concomitant scientific and technological benefits, economic benefits, or any other benefits to Canadians.

Appendix 5: Confidentiality and Security of Information

The *Access to Information Act*, (the "Act") governs the protection and disclosure of information, confidential or otherwise, supplied to a federal government institution. This Act is a law of public order which means that the government of Canada, including NRCan, can not contract out of it.

Paragraph 20(1) (b) of the Act states that:

> a government institution [such as NRCan] shall refuse to disclose any record requested under the Act that contains financial, commercial, scientific or technical information that is confidential information supplied to a government institution by a third party and is treated consistently in a confidential manner by the third party.

Paragraph 20(1) (b) of the Act sets out two mandatory criteria in order to protect proponent's confidential information supplied to NRCan from disclosure. First, the proponent's documents supplied to NRCan must contain financial, commercial, scientific or technical information. Second, the proponent must consistently treat such information in a confidential manner.

In other words, NRCan will protect the proponent's confidential information in its possession as much as the proponent protects said confidential information in its own establishment: if the proponent chooses to send the EOI or other confidential information to NRCan by e-mail, NRCan will respond by e-mail. Similarly, if the proponent's correspondence is through regular mail, NRCan's response will be in like manner. However, in all cases, NRCan will use e-mail correspondence to the proponents for all non-confidential matters.

For more information on this subject, a careful reading of the entire section 20 of the *Access to Information Act* is recommended.

Note that the Panel may engage non-governmental experts to review the Expression of Interests, or parts thereof. If and when required, proponents will be asked to authorize the release of their Expression of Interests to specific individuals or organizations outside of NRCan for the purposes of expert review. Non-disclosure agreements or other confidentiality agreements may be negotiated if and when required.

Appendix 6: Terms and Conditions

The Government of Canada has established an expert panel (the Panel) to report on new options for secure supply of medical isotopes for the Canadian health care system, specifically, technetium-99m and its generators. The Panel will consult broadly across the public and private sectors to better understand the many considerations that factor into a determination of a long-term strategy.

To ensure that the broadest range of ideas and concepts are considered by the Panel, the Call for Expressions of Interest process has been launched to encourage organizations to submit proposals they may have.

1. General Features

The Call for Expressions of Interest process will accept EOIs until July 31, 2009. All EOIs will be reviewed against the mandatory criteria identified in Appendix 4. Those EOIs that meet the mandatory criteria will be assessed against the evaluation criteria given in Appendix 4. Only the most promising EOIs, as determined by the Panel, will be further scrutinized through due diligence research, external reviews and requests for supplementary information from proponents. The Panel may, at its sole discretion, determine which EOIs will be discussed in the final report.

A proponent may withdraw its EOI without penalty at any stage of the assessment process.

All non-confidential communications in relation to this process should be in writing via e-mail to isotopeERP@nrcan-rncan.gc.ca.

2. Timeframe

Expression of Interests must be submitted by July 31, 2009. The Panel will issue a final report by November 30, 2009.

3. Eligible Proponents

To ensure that the broadest range of ideas and concepts are advanced, the process will be open to public sector and private sector organizations, including: for-profit and non-profit organizations, industry associations and research associations; academic institutions; federal, provincial, territorial and regional and municipal governments and their departments and agencies, and non-Canadian organizations.

4. Requests for Information

The Panel may contact proponents as required to request additional information and clarifications as necessary to perform a thorough assessment of EOIs. Proponents are

asked to expect such requests for information and to be prepared to respond to such requests in a timely manner. The Panel may ask proponents to provide written materials, written correspondence, and/or to be available for telephone or in-person meetings. Proponents may be asked to make one or more presentations to the Panel.

5. Sharing of Information

EOIs submitted on July 31, 2009 should be based on information available to the proponent through its own means. Sufficient detail should be included to allow for measurement against assessment criteria so as to inform the Panel in identifying the most promising options. As the Panel investigates further the short list of options, it may solicit additional information that may, in turn, require that proponents of short-listed projects have access, on a confidential basis, to a virtual data room. The timelines for the submission of additional information and the details of the data room, should it be necessary, will be provided under the instructions of the Panel.

6. Other Terms and Conditions

No commitment or obligation exists on the part of NRCan to make a financial contribution to any Expression of Interest.

SUMMARY OF TECHNICAL ASSESSMENTS

APPENDIX 5

Summary of Technical Assessments				New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Raw Materials	Type	Uranium based (HEU, LEU, Natural U) or Molybdenum based (enriched Mo-100)		LEU	Most proposals were HEU based	Phase 1 HEU, phase 2 LEU	Enriched Mo-100	Enriched Mo-100	Natural uranium
	Cost / Availability			Available	HEU continuous supply not guaranteed	HEU continuous supply not guaranteed	Limited availability but high price, increases with purity	Limited availability but high price, increases with purity	Cheap and abundant materials
	Recycling required			Not required	Not required	Not required	Required	Required	Not required
Irradiation	Technology	Reactor based or Accelerator based		Reactor based	Reactor based	Reactor based	Accelerator based	Accelerator based	Accelerator based
	Facility	Commercial scale	Available, does not exist, requires major modification/ upgrade	Does not exist	Facilities are in place	Requires sorting out licensing issues	Commercially available	Design parameters technically achievable; no off the shelf unit	Not available
		Demonstration	Available or does not exist	Not needed since proven technology	Available	Available	Tests are available on at least two existing facilities	Proposed facility to test principle available	A facility to test the concept is not available but will be built in 2 years under a research project not related to isotope

Summary of Technical Assessments			New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Targetry	**Target Design**	Available/validated or requires R&D	Not available but there exists several proven models around the world	Most proposals were for current design of HEU targets or HEU fuel	Available, unique design, never tested for production	Not available, several techniques will be explored, requires R&D	Not available, requires R&D to optimize the yield without compromising the specific activity	Not available
	Target station	Design available or requires R&D	n/a	n/a	n/a	Not available, advanced designs for solid target stations for other isotopes are available in Canada	Not available, heat transfer and convertor design require R&D	Not available, heat transfer and convertor design require considerable R&D

Summary of Technical Assessments			New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Processing	Technology	Proven or requires R&D	Many laboratory testings useful, commercial scale production is currently being tested with the Australian project	HEU based solutions would be essentially similar to the proven technology at Chalk River	Original design uses extraction technique similar to waste processing in France, unique among Moly producer. OPAL style modification should benefit from their LEU experience	Requires R&D although other solid target processing experience exists	Researches in Idaho labs patented extraction techniques. Dry gel Moly technology used on commercial scale for reactor Mo-98 activation. Requires R&D	Never tested before but the reactor fission processing experience could be transferrable
		Uranium based or Molybdenum based	Uranium based	Uranium based	Uranium based	Molybdenum based	Molybdenum based	Uranium based
	Facility requirement	Elaborate or simple	Elaborate, shielding nuclear ventilation and confinement, radiation protection	Elaborate, shielding nuclear ventilation and confinement, radiation protection	Elaborate, shielding nuclear ventilation and confinement, radiation protection	simple, moderate radiation protection provisions	simple, moderate radiation protection provisions	Elaborate, shielding nuclear ventilation and confinement, radiation protection
	Facility availability	Available, requires minor modifications, requires major modifications, or new facility required	Not available; needs to be built in conjunction with the reactor	If same NRU target used, ageing MPF processing facility requires replacement or upgrade; use of NPF requires major modification	Available pending completion of commissioning but not converted to LEU: requires major modification	Not a challenge	Not a challenge	Not available

Summary of Technical Assessments			New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Radioactive Waste	Type	Whether it contains fissile waste, nuclear fission products, or both	Nuclear waste	Nuclear waste and, if HEU is used, safeguardable materials	Nuclear waste and, if HEU is used, safeguardable materials; dedicated facility for interim storage is in place	No nuclear waste	No nuclear waste	Nuclear waste but without safeguard concerns
Technetium Extraction	Generator Technology	Proven or requires R&D	Proven	Proven	Proven	Requires R&D	Requires R&D	Requires R&D
		Standard Mo/Tc generators, new generator design, or direct extraction (no generator required)	Standard Mo/Tc generators	Standard Mo/Tc generators	Standard Mo/Tc generators	No generator required; extraction techniques available for other isotopes or other technology but need R&D to validate this method	Dry gel (used for reactor Moly) needs validation on accelerator; patented concepts available for goat system, need R&D	Standard Mo/Tc generators

Summary of Technical Assessments			New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Product	Yield	Estimated capacity sufficient	Expected to easily supply Canada's need and beyond	Existing Canadian research reactors capacity questionable; could barely cover Canada's needs	With HEU the plan was to surpass NRU capacity by 50%; capacity with LEU not established but would not be less than 1/5 HEU	17 mCi of Tc99m/µAh estimated at end of irradiation; several 500µA cyclotrons may be sufficient pending efficient extraction and delivery	Optimal yield not established but studies suggest 2 units to cover Canada's needs	Estimated one super (5 MW) unit or several smaller power units to supply Canada's needs
		R&D required to confirm capacity	Partially confirmed, can benefit from experience with other international LEU processing projects	If HEU used, capacity would be similar to standard production method	The theoretical capacity established but pending successful processing	Proof of cross section limited (Takacs); more principle validation required; processing, efficiency, and delivery are crucial to convert EOB yield into product	Very limited studies (Bennett, Nelson) suggest a feasible system. Bombardment yield can not be increased significantly: affects specific activity; R&D required for target optimization and processing as well	Unique concept to TRIUMF; cross section data are not a challenge but target design, geometry and conversion system would define the EOB yield
	Pharmaceutical Quality	Specific activity	Not a concern	Not a concern	Not a concern	Inherently limited	Limited; decreases with target size	Not a concern
		Purity	Reactor LEU Moly purity practically proven	Reactor LEU Moly purity practically proven	Reactor LEU Moly purity practically proven	Issues of high dose Tc isotopes, along with raw material purity requires studies	Issues of secondary neutrons impact on purity of irradiated targets requires studies	Requires R&D to confirm limited contamination with alpha emitters

Summary of Technical Assessments		New Reactor	Existing Reactor	DIF Project	Cyclotron	Linear Accelerator with Molybdenum	Linear Accelerator with Uranium
Logistics	**Processing time**	Not a challenge	Challenging due to geographical distance between irradiation and processing facilities	Not a concern	Critical to success of model	Important but not critical	Not a concern; assuming processing facility is nearby
	Delivery time & distribution range	Same constraints as the standard model	Same constraints as the standard model	Same constraints as the standard model	Daily production instead of weekly, difficulty to supply after hour procedures; small distance delivery due to short half life of product	Requires a stringent schedule of processing; in the case of goat system, milking several times a day	Same constraints as the standard model