# Making Medical Isotopes

## Report of the Task Force on Alternatives for Medical-Isotope Production

TRIUMF

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TRIUMF
University of British Columbia
Advanced Applied Physics Solutions, Inc.
*with support from Natural Resources Canada*

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UBC

AAPS
Advanced Applied
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ETPP
Exploitation des Techniques
de Pointe en Physique

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# Task Force on Alternatives for Medical-Isotope Production

The Task Force on Alternatives for Medical-Isotope Production was convened by TRIUMF, the University of British Columbia, and Advanced Applied Physics Solutions, Inc., with support from Natural Resources Canada.

Participants attended the workshop and helped write, edit, and prepare the written report. By listing their names here, participants affirm their contribution to the report and their agreement with the consensus of the Task Force based on their individual skills and expertise; these views are independent of and do not necessarily reflect those of their institutional affiliations.

Observers attended the workshop.

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# Acknowledgment of Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the TRIUMF Board of Management. The independent review provides candid and critical comments that assist in making the published report as sound as possible and ensure the report meets institutional standards for objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. Responsibility for the final content of this report rests entirely with the authoring committee.

# Executive Summary

# Executive Summary

In late 2007, North America experienced a critical shortage of the medical-isotope Molybdenum-99 (Mo-99) over a period of several weeks due to an extended shutdown of AECL's NRU reactor. The shortage forced the cancellation and delay of diagnostic testing for life-threatening conditions affecting tens of thousands of patients throughout the U.S. and Canada. The crisis and its effects are well documented in Health Canada's May 2008 report "Lessons learned from the shutdown of the Chalk River reactor."[1]

Presently, 80-85% of all nuclear medicine procedures use Mo-99. There are about 40 million procedures performed worldwide per year, which includes 20 million procedures in North America and about 1.5 million of those procedures in Canada. No facilities in the U.S. manufacture Mo-99.[2] Canada produces about half the world's supply by irradiating highly enriched uranium U-235 (HEU) targets in the NRU reactor (operating since 1957) at Chalk River, Ontario. The supply crisis occurred when the NRU was not returned to operation for several weeks, due to regulatory issues, following a routine maintenance shutdown. Concerns about the long-term supply of medical isotopes have been further exacerbated by the decision, in May 2008, to discontinue development of the MAPLE reactors, two new facilities that were to replace NRU's production of Mo-99, Iodine-125, Iodine-131, and Xenon-133. Europe similarly relies on several aging research reactors: HFR (in The Netherlands, operational since 1961), BR-2 (in Belgium, operational since 1961), OSIRIS (in France, operational since 1966) and SAFARI (in South Africa, operational since 1965). The NRU and HFR reactors produce about 90% of world Mo-99 supply. The shutdown of the HFR since August 2008 has caused Mo-99 shortages in North America and Europe.

No strategy exists to provide a global, long-term reliable supply of Mo-99. In the interests of nuclear security and non-proliferation, the U.S. and other countries are increasing the pressure to migrate all non-military applications (such as research reactor fuel and isotope production targets) to use low-enriched uranium (LEU). Given Canada's historical strengths in nuclear science, technology, and advanced health care, and the rapidly growing demand for nuclear medicine in neurology, cardiology, and cancer world wide, it may be advantageous for Canada to continue to play a central role in this international high-tech field.

With this as a backdrop—and with support from the Ministry of Natural

1 Ad Hoc Health Experts Working Group on Medical Isotopes, *Lessons Learned from the Shutdown of the Chalk River Reactor: A Report Submitted to the Minister of Health*, May 2008.

2 Society of Nuclear Medicine, *Preliminary Draft Report of the SNM Isotope Availability Task Group*, published online June 2008, URL http://admin.triumf.ca/facility/5yp/comm/SNM-Draft-Jul-2008.pdf.

Resources Canada—TRIUMF, the University of British Columbia, and Advanced Applied Physics Solutions (AAPS, Inc.) assembled a task force of North American experts with broad experience to explore the feasibility of using accelerator-driven photo-fission to generate sufficient quantities of Mo-99 to supply a significant fraction of the North American demand. Many cyclotron proton accelerators are used worldwide, including in Canada, to produce many short-lived medical isotopes. However, few are capable of producing Mo-99 and none are suitable for producing more than a small fraction of the required amounts.

The four main commercial producers of Mo-99 in the world use nuclear reactors with HEU targets. The reactors produce neutrons which in turn stimulate fission of U-235, producing Mo-99 about 6% of the time. In comparison, the proposed photo-fission accelerator approach would produce high-energy photons to split natural uranium U-238 with the same fractional production of Mo-99 as produced by neutrons (around 6%). Since the fractional fission yields for Mo-99 (and indeed all of the fission products) from each technique are almost identical, the specific activity of the final Mo-99 product should be identical. The probability of neutron-fission versus that of photo-fission, however, is favoured by a factor of nearly 3,000 and thus a high flux of photons is needed to equal the production rate from neutrons, everything else being equal.

The photo-fission accelerator technique has several key advantages: (1) The targets can be natural or depleted uranium, which (like LEU targets being developed for reactors) eliminates concerns about shipping and handling HEU, obviating questions of security and non-proliferation; (2) The accelerator can be turned on and off at will; (3) At end-of-life, an accelerator is comparatively inexpensive to decommission as major components are less prone to become radioactive over time than occurs in the high neutron environment of an operating reactor; and (4) The technology promises to be scalable. On the down side, an accelerator-based production facility would require substantially more electrical power than a reactor-based facility.

Radioactive waste from the irradiated targets associated with medical-isotope production from any technique is an environmental issue and can be costly to dispose.

The final compound used in the clinic is Technetium-99m (Tc-99m), the medical isotope formed from the decay of Mo-99. Although Canada produces Mo-99, U.S. companies make the final product, called technetium generators, for distribution to North American hospitals and healthcare companies. Because Mo-99 has a 66 hour half life, there are important product losses during the supply chain. The most significant decay losses occur during transport of the material to the U.S. (Boston and St. Louis) to make the Tc-99m generators and then transport them back to Canada for use. Though this process is stream-lined, only about 50% (on average) of the initial Mo-99 reaches the end user.

A “Canada-only solution,” as discussed in the Health Canada report, is not possible without considering Mo-99/Tc-99m generator production in Canada. It is unlikely that the Canadian market will support a fully isolated Canadian supply chain from isotope production through to clinical application, as there is not enough domestic business to support a Canada-only generator manufacturer. A Canadian generator manufacturer would therefore have to break into this robust and competitive world market. The business of producing Mo-99 differs because Canada has a legacy and because the global supply network is

fragile. Moreover, in this context the Government of Canada must carefully consider its planned future role in overseeing, facilitating, and supporting elements of the Mo-99 production process.

# Findings

A summary of the findings of the Task Force is provided here:

## Current Situation

- Although the historical supply from AECL-MDS Nordion has been reliable, the long-term supply of Mo-99 worldwide is at potential risk as it presently relies on two aging reactors that supply 90% of all production. Roughly half comes from Canada.[3]
- The risks can be reduced by having a greater number of reliable Mo-99 producers.
- North America has no replacement reactors under construction or at the advanced planning stage, though modifications to existing research reactors are being explored for isotope production. In Europe, the Jules Horowitz reactor (100 MW, LEU fuel) is being developed primarily for materials studies and could begin operation as early as 2014; it could be used for limited production of medical isotopes.
- A North-American reactor design with LEU core and targets does not exist; LEU targets are not yet used in North America, and no Canadian sites currently process LEU. Commercial success with LEU will require that LEU target processing be demonstrated on a large scale, all the major producers convert, and health regulators approve radiopharmaceuticals using LEU-derived Mo-99.
- National and regional supply of limited Mo-99 using LEU fuel and LEU targets has been demonstrated in Australia, Indonesia, South America, and Korea. Mo-99 recovery and refinement using LEU targets for large-scale commercial supply of Mo-99 is yet to be established, so comparison to that presently achieved with HEU targets is not yet possible.[4]

## Production Using a Photo-Fission Accelerator

- Based on preliminary calculations and numerical simulations, significant quantities of Mo-99 can be produced from natural uranium by photo-fission using accelerators. Several laboratory experiments are needed to establish efficiencies, equivalency of products, reliability of operation, and capacity.
- The technology exists to build an electron accelerator of suitably high

3 There are 4 main producers of Mo-99 worldwide that supply 95% of the global market. Covidien and IRE in Europe both rely on more than one reactor and make use of HFR Petten (Netherlands), OSIRIS (France), and BR-2 (Belgium). Global supply from the 4 main producers actually involves 5 different research reactors if SAFARI-1 and NRU are included in the above list.

4 Chile is probably 2 to 3 years from producing Mo-99 as are Poland, Romania, Libya, and Missouri. B&W LEU MIPS is also in the same time range.

beam power (2-3 MW) to produce a meaningful amount of Mo-99. A single multi-megawatt machine could supply the Canadian market or 5-7% of the North American market.

- A system of several machines would enhance reliability and boost Canada's competitiveness in the North American market.
- The conceptual design of a U-238 target system for efficient photo-fission and dissipation of the generated thermal power is not established, but the worldwide nuclear-physics community is actively developing multi-megawatt target systems.[5]
- The radio-chemistry needed to recover and refine the Mo-99 generated through photo-fission (from natural-uranium targets) most likely resembles that produced by a reactor using HEU targets. The similarity of the initial Mo-99 recovery step will be sensitive to the volume of the target for photo-fission which depends in detail upon optimization of design and performance parameters.
- Because of Mo-99's decay rate, yields from any production method are limited by the transportation times and distances between irradiation facilities, processing facilities, and generator plants. Losses could be reduced by co-locating the activities.
- The photo-fission accelerator option eliminates the security issues of transporting, storing, and disposing of HEU.

## Considerations Going Forward

- Health Canada and the U.S. Food and Drug Administration will need to approve the final Mo-99 product from a photo-fission accelerator for clinical use in North America.
- Licensing procedures must begin during the design stage and are likely to be straightforward for an accelerator. The full facility will likely be regulated as a Class IB Nuclear Facility (*e.g.,* MDS Nordion's facilities in Kanata, Ontario) as defined by Canadian Nuclear Safety Act regulations.
- There are substantial uncertainties in the capital cost and eventual operating costs for a reliable system of accelerator-based isotope production facilities, which require further assessment as experience is acquired from lower power experiments and feasibility tests.
- At present, construction of a photo-fission accelerator would take 3-4 years. Depending on the specific technology chosen for the accelerator, the construction costs, including labour, would be C$50 million, C$80 million, or $C125 million. Power would likely dominate operational costs.
- The total production cycle for medical isotopes includes the manufacture of targets for irradiation, storage of radioactive waste from target processing, and hot-cell facilities to recover and refine Mo-99. These facilities

5 See, for instance, J. Cornell, Ed., "The EURISOL Report," GANIL, Caen, 2003, European Commission contract No. HRPI-CT-1999-50001.

are needed for any new production source of Mo-99 and would cost at least C$50 million.

- Accelerator-based Mo-99 production facilities would be quite focused; they would not allow for production of other non-fission-based medical isotopes and would not provide many of the additional R&D and commercial opportunities associated with present-day research reactors.

## Conclusions

**Accelerator-driven photo-fission of U-238 is an attractive approach for generating Mo-99 without security issues and with lower decommissioning costs at end of life. To ensure high reliability of supply, a half-dozen multi-megawatt machines could be built that would meet about 30%-50% of North American demand.**

The Task Force did not draw a conclusion about which technology (nuclear reactor or photo-fission accelerator) is "better" as this was beyond its scope. Rather, the Task Force analyzed the case for, features of, and development path for photo-fission accelerator technology. The Task Force concluded that this technology has a sufficient number of attractive features that it warrants further attention by public and private enterprises. At the present time, the photo-fission accelerator technology for Mo-99 production is unique in the world and, if developed and validated in the laboratory, would support Canada's continued economic dominance in this world market.

**A strong and focused R&D program is required to validate the use of a photo-fission accelerator for production of significant quantities of high-quality Mo-99.**

The Task Force discussed key scientific, technical, engineering, and operational challenges. An R&D program focusing on the following key work packages is crucial; some of these could proceed in parallel.

1. Produce, over about six months, a short conceptual design report on the optimal design of a high-power electron linear accelerator using photo-fission for production of Mo-99, including:
   a. The configuration and conceptual design of the highest technical risk items: the bremsstrahlung converter, uranium target, and accelerator beam window.
   b. The hot-cell facilities for processing targets and managing the processing waste.
   c. Required validation tests for the design.
   d. Modeling of accelerator uptime for reliability estimates.
2. Calculate capital and operating costs based on the conceptual design report and site considerations.
3. Verify photo-fission accelerator production of Mo-99 equivalency to the present product using laboratory experiments.
   a. Demonstrate Mo-99 yield.

b. Demonstrate Mo-99 recovery and refinement.
c. Demonstrate purity and specific activity.

4. Design a target facility capable of handling 2-3 MW of electron beam power.
   a. Include thermal and structural simulations.
   b. Indicate key validation tests and perform them as possible.

## Recommendation

**The Government of Canada should support a Mo-99 Photo-Fission Accelerator Steering Group of public-private partners who select a project director and provide oversight. The director will be responsible for managing the preparation, coordination, and completion of R&D work packages funded through government and private sources according to an appropriate competitive process of scientific peer review.**

A steering group of public and private partners would bring together the skills, resources, and business sense required to develop the technology, oversee a proof-of-principle demonstration, and then assess and/or pursue commercial viability.

Work packages should follow from the R&D program outlined above. The project director would coordinate formulation of the work packages for submission, consideration, and review by the relevant sponsoring organizations. The completion of these work packages would lead the steering group to present a recommendation on the photo-fission accelerator technology within 3-4 years.

Laboratories around the world such as TRIUMF, Brookhaven National Laboratory and Oak Ridge National Laboratory in the U.S., and IPN-Orsay and GANIL in France have expertise and facilities that can be used immediately. TRIUMF is proposing to build a new accelerator as part of its decadal vision for research in nuclear physics, materials science, and nuclear medicine.[6] A low-power test to generate Mo-99 with a photo-fission accelerator on a timescale of a few years is possible at TRIUMF using this device as it will utilize the same basic technology. Although the total power will be lower (initially 100 kW in 2013 with an upgrade path to 0.5 MW), the device would enable detailed tests at full power density with a target matrix applicable to the Mo-99 photo-fission accelerator. The generated samples could validate beam-power requirements, isotope yields, target performance, chemical recovery, refinement, and purity of Mo-99. The activities at TRIUMF could be expedited.

6 TRIUMF, *Five-Year Plan 2010-2015: Building a Vision for the Future*, Vancouver, B.C.: TRIUMF, 2008.

# Chapter 1
# Introduction

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# Introduction

# 1

# Introduction

Together with the University of British Columbia and Advanced Applied Physics Solutions, Inc., TRIUMF convened the Task Force on Alternatives for Medical-Isotope Production to explore this option and to examine a case for action. Support from Natural Resources Canada was provided to cover costs required to organize, convene, and operate the Task Force.

The Task Force on Alternatives for Medical-Isotope Production was formed in late summer 2008 to discuss, analyze, and evaluate options for using high-power accelerators to generate large quantities of medical isotopes for Canada and its global markets. The group of experts was convened with suggestions for membership from relevant federal agencies and national organizations (see Appendix A). The Task Force met for a 1.5-day in-person meeting. The invitation-only meeting took place October 19-20, 2008, in Vancouver (see Appendix B). A concise written report was prepared within 21 days of the workshop. The report is publicly available for dissemination and the workshop leaders made themselves available for briefings, commentary, and subsequent discussion.

## 1.1 Background

Canada is well known for its production of more than half the global supply of medical isotopes, particularly molybdenum-99 ($^{99}$Mo or Mo-99). The vast majority of these isotopes are presently produced using a research reactor at Chalk River, Ontario, known as the NRU reactor, owned and operated by AECL. About four other reactors around the world provide the balance of global supplies. The age, safety, and reliability of these reactors operations have raised worldwide concerns about potential shortages of medical isotopes.[7] *The Vancouver Sun* reported on 28 August 2008 that "It is impossible for the Chalk River, Ont., nuclear reactor to meet the global demand of medical

7 "IAEA tackles radioisotope supply concerns," MedicalPhysicsWeb.org, published online 06 Nov 2008 at URL http://medicalphysicsweb.org/cws/article/industry/36569, "The global market for medical radioisotopes is at risk of serious supply problems over the coming years, as a limited number of ageing reactors attempt to cope with increasing worldwide demand. The issue recently came to the fore when the simultaneous outages of three European medical isotope production facilities led to a global shortage of technetium-99m (Tc-99m), the radioisotope used in around 80% of all nuclear medicine-procedures. An unexpected shutdown extension of a Canadian reactor resulted in a similar shortage less than a year earlier."

isotopes, even as it ramps up production following warnings of a worldwide shortage, says a spokesperson for Atomic Energy of Canada Ltd."

As Canada's national laboratory for particle and nuclear physics, TRIUMF is the nation's steward of accelerator science and technology. The laboratory is owned and operated as a joint venture by a consortium of Canadian universities. It is operated through a contribution via National Research Council Canada with buildings funds historically provided by the Province of British Columbia. TRIUMF has a 30-year partnership with MDS Nordion in the production of medical isotopes using cyclotron accelerator technologies at its Vancouver site. Traditionally, the isotopes produced with accelerators have been distinct and separate from those produced using a nuclear reactor. TRIUMF has developed world-leading prowess in accelerator production of certain medical isotopes and, with its partners across the country, has cutting-edge expertise in radio-chemistry and medical applications.

As a laboratory serving Canada, TRIUMF is a national resource for science and technology. Recently, the laboratory and its research community have identified a technology that may provide alternatives to the present scheme for production of medical isotopes, especially Mo-99. Traditionally, accelerators and nuclear reactors make different isotopes; a new concept being developed at TRIUMF could change this. Rather than using nuclear-reactor generated neutrons to split uranium atoms to make medical isotopes, photons produced from a high-power electron accelerator would be employed.

## 1.2 Charge to the Task Force

- Briefly characterize Canada's present production capabilities for medical isotopes. Comment on global supplies and demands.
- Analyze and validate options for using accelerator-based photo-fission techniques to produce medical isotopes. Identify trade-offs with existing nuclear-reactor technologies, make comparisons between the two approaches, and make projections about full-scale production capabilities of an accelerator option.
- Develop a realistic option for accelerator-based production of medical isotopes, particularly Mo-99, providing design and performance parameters, and, as much as possible, a basis for computing total project cost. Comment on schedule and how such a device would reinforce Canada's supply of isotopes and secure the health of Canadian citizens.
- Identify steps for moving forward and define any laboratory benchmarks that will validate the design. Examine opportunities for enhancing

Canada's economic competitiveness in this regard.

The Task Force used advance homework assignments, a 1.5-day workshop, and subsequent discussions by e-mail and telephone to prepare this report. Some experts attended the workshop as observers. Despite an aggressive schedule, the Task Force did not have time to fully consider the economic competitiveness of an accelerator option. This was in part hampered by the effort needed to understand the complex network of agreements that support the present system.

# Chapter 2

# Production and Use of Medical Isotopes

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# 2

# Production and Use of Medical Isotopes

Modern healthcare routinely requires examining a patient with more than the unaided eye. Molecular imaging—the imaging of molecules, biochemical processes, and physiological activity within the human body—is rapidly becoming one of the most powerful tools for diagnosis and staging of disease. The main tools for molecular imaging are the SPECT and PET scans that tag specific biologically active molecules (biomolecules) with medical isotopes.[8] A medical isotope is an unstable (*i.e.,* radioactive) atom derived from a stable one. When the unstable atom decays, it emits a particle that can be detected and used to pinpoint its location.

By chemically connecting the medical isotope to a biomolecule and introducing the compound into the human body, one can then "see" where the body is using the biomolecule. For instance, the compound teboroxime labelled with Tc-99m is used in myocardial perfusion imaging to distinguish normal from abnormal myocardium in patients with suspected coronary artery disease (CAD) using rest and stress techniques. When the Tc-99m medical isotope decays, a SPECT camera (or scanner) can locate the teboroxime. By following the uptake and clearance of radioactivity in the heart muscle, the physician can tell whether the patient had a heart attack (see Figure 2.1).

8 For background on Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET), please see P.J. Cassidy and G.K. Radda, "Molecular imaging perspectives," *J. R. Soc. Interface,* 2005, published online.

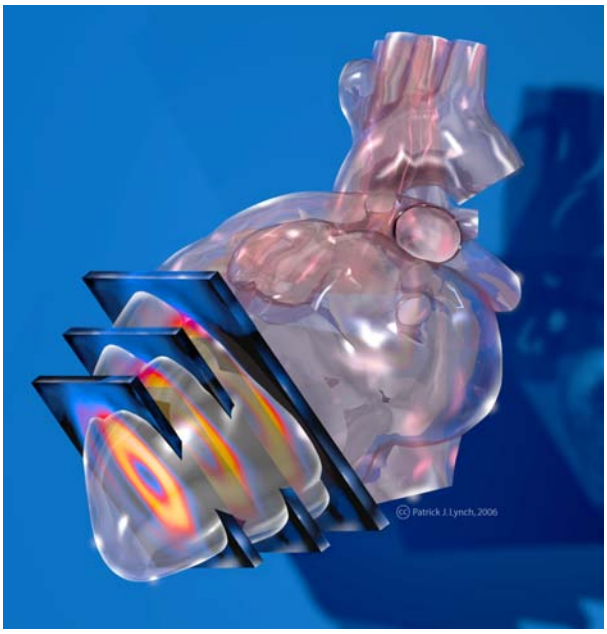


**Figure 2.1**: Short-axis views of the heart showing SPECT nuclear imaging. Credit: Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist.

# 2.1 Setting the Stage

The production and use of medical isotopes relies on research from several fields of science, notably nuclear medicine, radiochemistry, and nuclear science and engineering.

Medical isotopes are produced using nuclear reactions at either nuclear reactors or accelerator facilities. The basic setup involves using a *beam* of particles (from the reactor core or the accelerator) to strike a *target*. Nuclear (as opposed to chemical) reactions within the target then create the medical-isotope atoms from the atoms of the target material. After irradiation by the beam, the target is then removed to *recover* the medical isotopes of interest using mechanical and chemical procedures. A *refinement* step then isolates and purifies the medical isotope so that it is ready for transport. It can then be combined with the relevant biomolecules to form the specific *radiopharmaceutical* for administration to a patient.

Since its humble beginnings in 1958, Technetium-99m ($^{99m}$Tc or Tc-99m) has become the most widely used radioisotope for diagnosing diseased organs. Derived from the man-made element technetium, Tc-99m emits radiation

without causing damage, and its six-hour half-life is long enough for a medical examination and short enough to allow a patient to leave the hospital soon afterwards. More importantly, Tc-99m is generated from molybdenum-99 (Mo-99), whose half-life of 66 hours allows for transport over long distances. Mo-99 is produced at nuclear reactors where the beam is the neutrons from the fission reaction in uranium; the targets also contain uranium, predominantly U-235. In principle, the entire process from removal of irradiated HEU targets from the reactor to patient injections of Tc-99m radiopharmaceuticals can be accomplished in as little as 36 to 48 hours.

The journey for Tc-99m begins at a nuclear reactor (see Figure 2.2). The raw irradiated target material from the reactor, containing a variety of radioisotopes, then travels to a separate facility to be separated and purified. Chromatography and precipitation procedures are used to yield Sodium Molybdate ($Na_2MoO_4$). This highly radioactive solution is then packaged for transport to the generator-manufacturing facility. International customs, lim-

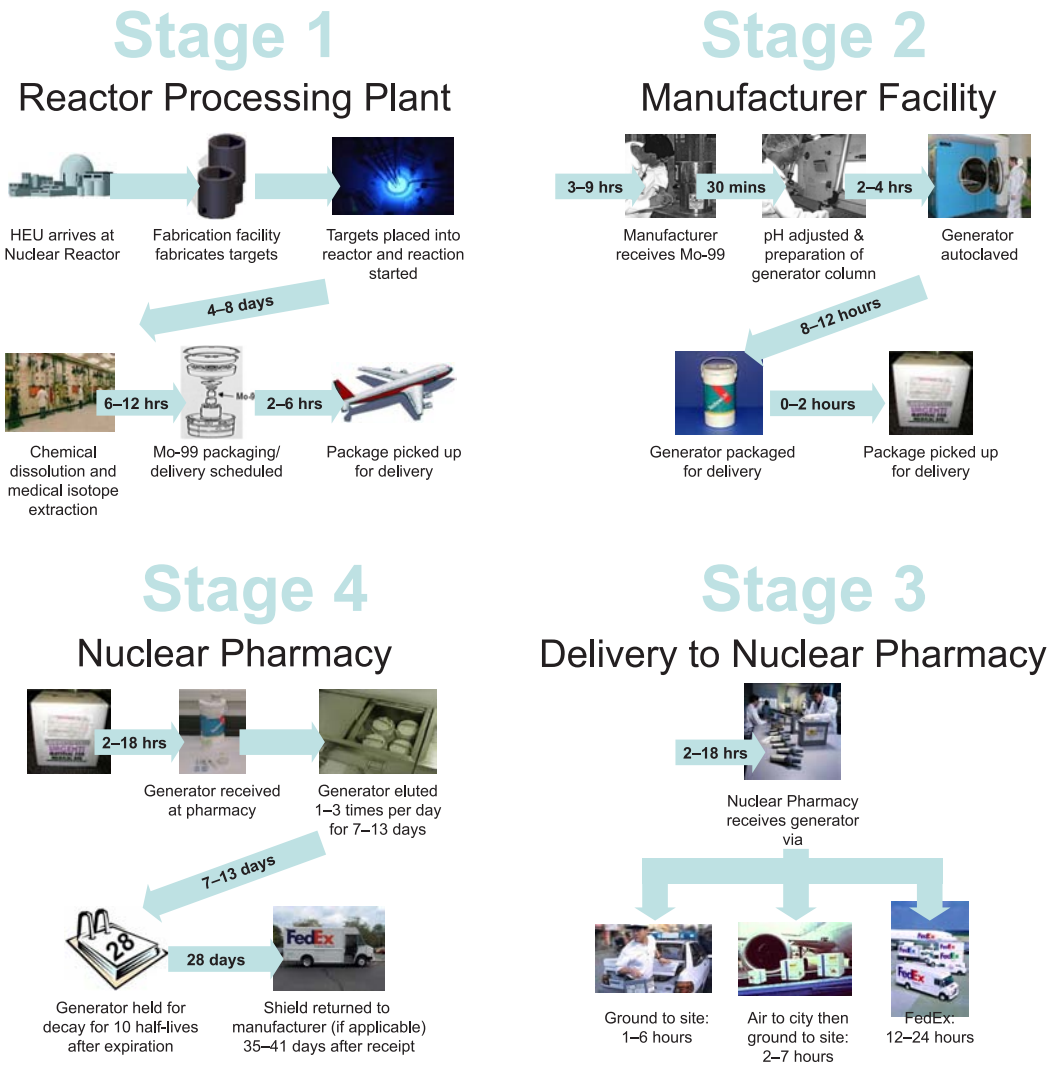


**Figure 2.2:** Overview of the present production process for Mo-99.

ited flight schedules, and unpredictable weather can all be obstacles to this raw material arriving at one of a limited number of manufacturing facilities. Typically, the Mo-99 solution is first diluted to a useable concentration and then absorbed onto generators in alumina columns. The columns are then sterilized in an autoclave. The components of the generator and its shielding are then assembled under aseptic conditions using remote manipulators.

Each final product is tested for proper function prior to being released. The Mo-99 generator has a shelf life of almost two weeks. It is typically received via courier at the radiopharmacy the day before it is needed. The first elution of the generator is made in the early morning. Quality control tests on the elution include radiochemical purity for Tc-99m pertechnetate, Mo-99 breakthrough, and chemical purity for aluminum. Upon successful completion of all quality control tests, Tc-99m pertechnetate is added to multidose vial "kits" containing the nonradioactive components of the radiopharmaceutical. Quality control tests are also performed on each radiopharmaceutical kit prepared.

Most of the Tc-99m-based radiopharmaceuticals have a shelf-life between six and twelve hours. The radiopharmaceutical is then dispensed in patient-specific unit doses and placed in a lead shield and delivery case for transport. Once received at the nuclear medicine department, the package is surveyed for contamination and each dose is then prepared for administration to the patient.

## 2.2 Current Demand

Within the United States, about 80,000 procedures are performed daily using medical isotopes; 80-90% of these useTc-99m. Canada's use of this medical isotope is about 7% of that of the U.S. In terms of demand for the Mo-99 raw ingredient, North America uses about 6,000-7,000 six-day curies per week. Because Mo-99 has a half-life of about 66 hours, 20% decays away each day. The "six-day curie" is a unit of measure that takes this decay rate into account and represents an average amount of Mo-99 that would be available for use after six days. World demand for Mo-99 is estimated at 10,000 to 12,000 six-day curies per week, not including some countries' domestic Mo-99 production for domestic needs.

# 2.3 Current Supplies

The two dominant producers of Mo-99 for North America are AECL for MDS Nordion with the NRU reactor and Covidien with the HFR reactor in Petten, the Netherlands (see Figure 2.3).

McMaster University also has a research nuclear reactor that is involved in medical isotope production (mainly I-125). Its production capability for Mo-99 was not discussed at this workshop.

The Mo-99 raw material is transported to manufacturers of technetium generators. Within North America there are only two such companies: Covidien, which uses Mo-99 from Canada and Europe, and Lantheus Medical Imaging (formerly Bristol-Myers Squibb), which relies predominantly on Mo-99 from Canada.

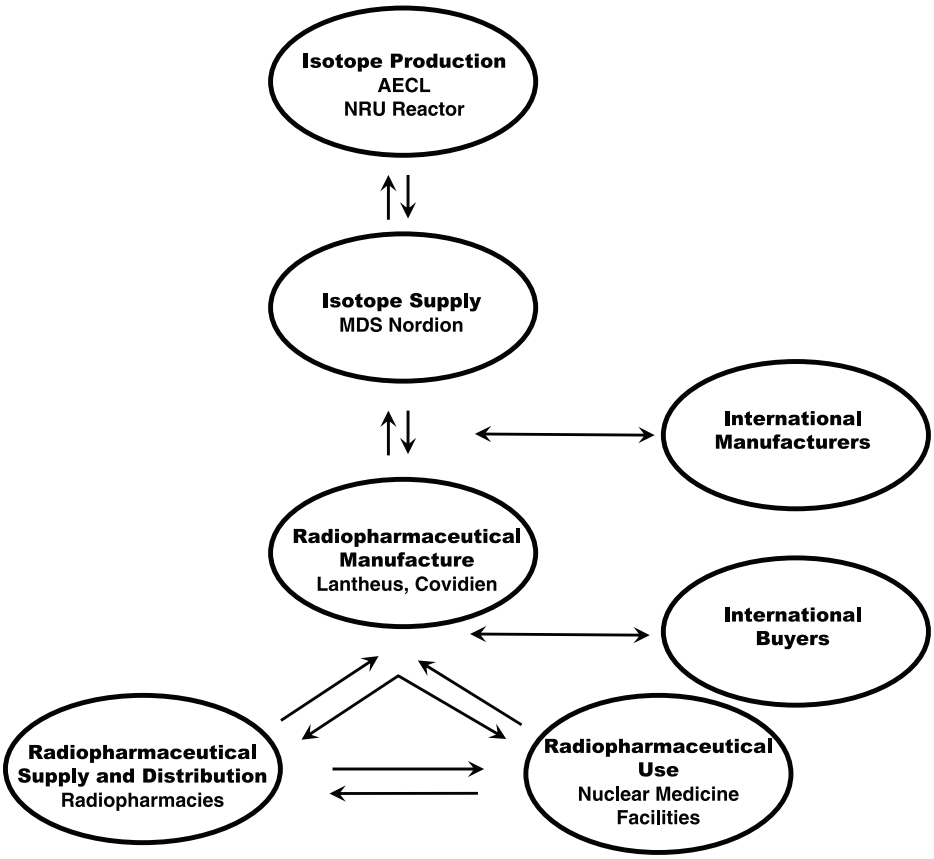


**Figure 2.3**: Supply chain for Mo-99/Tc-99m radiopharmaceuticals in Canada. Courtesy Ad Hoc Health Experts Working Group on Medical Isotopes.

# 2.4 Need for Action

The present system for Mo-99 production, recovery, refinement, and distribution is under some strain primarily because it relies on such few, aging sources of Mo-99. As indicated, the nuclear reactors producing Mo-99 have experienced interruptions in operation.

- NRU (commissioned in 1957) was shut down for three weeks late 2007. The present operating license of the NRU expires in 2011 with anticipated extension to 2016.
- HFR (commissioned in 1961) was shut down in August 2008 with technical problems and will not be operational until February 2009. The HFR is scheduled to be replaced but the site has not been finalized and the probable completion date is beyond 2015.
- BR2 (commissioned in 1961) was shut down for an unplanned radioactive-chemical release in Fall 2008 for the duration of its normal refuelling cycle. The processing facility at Institut national des Radioelements (IRE) has been shutdown since September 2008 for I-131 release. IRE extracts Mo-99, I-131, and other isotopes from targets that have been irradiated at the BR2 reactor, HFR reactor, and OSIRIS reactor.
- OPAL (at Australia's ANSTO facility and commissioned in 2008) start-up was delayed due to technical problems but is now scheduled for the end of 2008.

Worldwide clinical use of technetium-based imaging procedures is expected to remain strong (with modest growth) for at least another decade. The predominance of these procedures is expected to be challenged over the next 8-10 years by the emergence of PET (positron-emission tomography) based procedures.

Nuclear non-proliferation and security concerns have led to advanced discussions around the world about moving away from the use of HEU as reactor fuel and in targets for producing Mo-99. Transition to LEU for reactor fuels has made significant progress, but large-scale viability of LEU targetry is still under development.

Based on the incidents of late 2007 and these considerations, an ad hoc working group of experts recommended the following actions to the Government of Canada to minimize the potential for future interruptions:

- Develop a robust "Made in Canada Solution" (timely replacement of NRU)
- Formal cooperation agreements (international partnerships)
- Diversify generator supply sources
- Fast-track generator approvals in emergencies
- Maximize expired generator use, especially in emergencies

# Chapter 3

# An Alternative Method

# Chapter 3

# An Alternative Method

# 3

# An Alternative Method

The present technology for producing Mo-99 uses neutrons generated from a nuclear reactor to irradiate targets almost universally composed of HEU. Argentina currently produces Mo-99 commercially using LEU targets and an associated extraction process. Only the Australian OPAL reactor uses LEU target material at a level capable of significant production, but the processing and licensing of that approach has not been completed.

The key physical process is the fission of a uranium nucleus; the most frequent decay products include Mo-99. The present-day technique uses a neutron to split the uranium. The alternative solution examined in this report uses a photon instead to fission the uranium nucleus. Before addressing that option in detail, several different techniques employing accelerators are surveyed.

## 3.1

## Survey of Selected Alternative Methods

Any student of nuclear physics can outline a good number of different techniques to produce Mo-99 (see Figure 3.1). The challenge is to identify those techniques which have high yields and high specific activity. The yield measures the production rate of Mo-99 for a given target material. The specific activity measures the "concentration" of Mo-99 per unit mass in the reaction products. A competitive Mo-99 production process requires high yield and high specific activity.

This section examines three different processes:

- The neutron-capture process. An intense neutron beam generated by a nuclear reactor adds one neutron to a Mo-98 target to produce Mo-99.
- The photo-neutron process. An intense photon beam generated by an electron accelerator removes a neutron from a Mo-100 target to produce Mo-99.

- The photo-fission process. A very intense photon beam generated by an electron accelerator causes a uranium target to fission to produce Mo-99.

Present production of Mo-99 employs a fourth process, neutron-fission: an intense neutron beam generated from a nuclear reactor strikes highly enriched uranium (U-235), producing Mo-99 for 6% of the fission reactions.

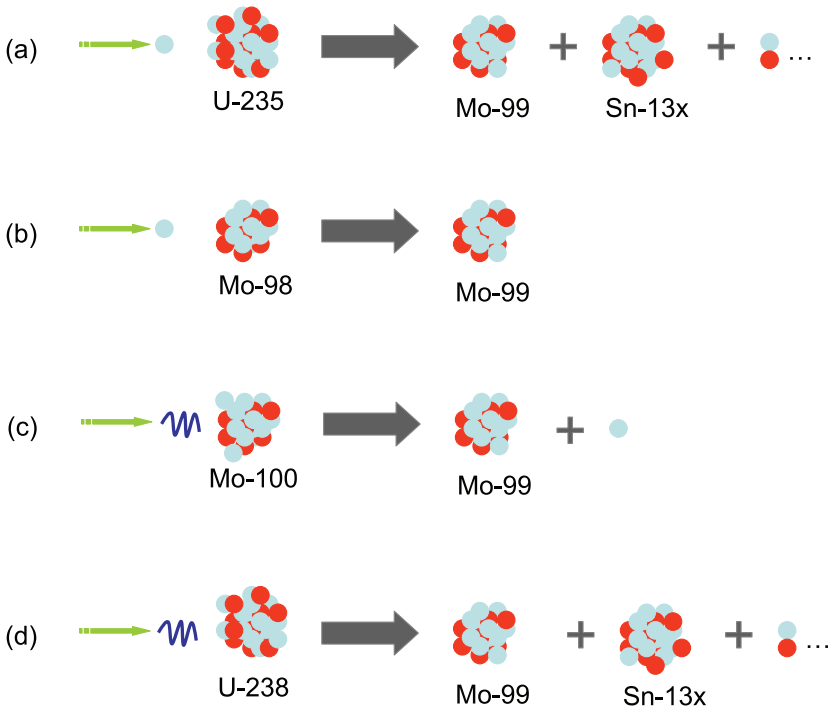


**Figure 3.1**: Different nuclear processes for producing Mo-99. (a) Neutron-fission of U-235 (present technique). (b) Neutron-capture process. (c) Photo-neutron process. (d) Photo-fission of U-238 (technique proposed in this report).

## 3.1.1 Neutron capture $^{98}Mo(n,\gamma)^{99}Mo$

The neutron-capture reaction on a $^{98}Mo$ target is given by $^{98}Mo(n,\gamma)^{99}Mo$. The target material would be separated isotope Mo-98, a 24% naturally occurring isotope of molybdenum. The target material would likely be irradiated in a nuclear reactor with an approximate flux of $3 \times 10^{14}$ n/s/cm$^2$.

As a starting point, the rate of production of Mo-99 from a one-gram separated-isotope target in a thermal flux of $3 \times 10^{14}$ n/s/cm$^2$ is calculated. This is given by:

$$Y = N \times \sigma \times \phi$$

Where $N$ = number of target atoms in one gram = $1/98 \times 6 \times 10^{23} = 6.1 \times 10^{21}$; $\sigma$

= 0.13 barns = 0.13 x $10^{-24}$ $cm^2$ and $\phi$ = 3 x $10^{14}$ n/s/$cm^2$. Combining these quantities gives a yield $Y$ = 2.4 x $10^{11}$ atoms of Mo-99 per second per gram of target material.

If the target is left in the reactor for about five half-lives (*i.e.*, 5 x 66 hours = 13.75 days), it will reach secular equilibrium with a rate of decay equal to the rate of production, *i.e.*, Y = 2.4 x $10^{11}$ decays per second or Bq. This is equivalent to (2.4 x $10^{11}$ Bq/g)/(3.7 x $10^{10}$ Bq/Ci) or 6.6 Ci/g of separated target material. Significant epithermal capture that tends to enhance the yield by at least a factor of 2, leading to about 12 Ci/g of separated target.[9]

**This is equivalent to 12 x 0.22 = 2.6 six-day curies per gram of separated isotope at saturation (about 2 weeks). In a one-week irradiation this would produce (1 – $e^{-\lambda t}$) x 2.6 = 2.2 six-day curies.**

The approximate Canadian demand was identified to be perhaps 7% of the estimated U.S. demand, roughly 420-600 six-day curies per week. Using 500 six-day curies as a working number, this would lead to a requirement of roughly 500 six-day Ci/week/2.2 Ci/g ~ 227 g/week of enriched target or four times that amount of natural molybdenum to meet the demand.

## Potential Advantages and Disadvantages of This Approach

The main advantage of this approach is:

- There would be nearly no waste stream.

The significant disadvantages of this approach are:

- A major change in the generator technology would be needed because of the very low specific activity product and need to separate Mo-98 from Mo-99.
- Viability of separation techniques. There are a variety of techniques proposed to separate the Tc-99m from the parent Mo-99 that will need to be proven to work in a high-volume application.[10]
- A nuclear reactor would still be required to provide the intense flux of neutrons.

9 Radionuclides Production, Volume 2, by Frank Helus, Chapter 4, CRC Series in Radiotracers in Biology and Medicine, 1983.

10 A generator using gel is being produced in India and is being developed in Brazil, Romania, and Kazakhstan. In this generator, a hydrated zirconium molybdate powder is precipitated in a sol-gel process. These particles are loaded into a generator. Depending on the reactor flux and other variables, the elution volume is 4-20 x that for fission generators of Mo-99.

## 3.1.2 Photo-neutron process $^{100}Mo(\gamma,n)^{99}Mo$

The photo-neutron process uses a high-powered electron accelerator to irradiate a high-*Z* converter target such as liquid mercury or water-cooled tungsten. High-energy photons known as bremsstrahlung radiation are produced by the electron beam as it interacts and loses energy in the converter target. The photons can then be used to irradiate another target material placed just behind the convertor, in this case Mo-100, to produce Mo-99 via the reaction $^{100}Mo(\gamma,n)^{99}Mo$.

For this process, the calculation of the Mo-99 yields in curies per gram of enriched target material is more difficult because it is necessary to use a semi-realistic target configuration to account for the absorption of the high-energy photons. The radiation length of photons striking a molybdenum target is 9.8 g/cm$^2$ or 0.96 cm. The ($\gamma$,*n*) yield from a mid-mass target is about $10^{12}$ n/s/kW of electron-beam power for a thick target and electron energies of greater than about 30 MeV. A thick target corresponds to about five radiation lengths in thickness or nearly 5 cm of molybdenum. A yield of about 30% of the thick-target yield is produced in the first radiation length and 50% in two radiation lengths.

Because the cost of preparing the target composed of separated isotope (Mo-100) is high, an initial target concept is to use a 2 cm diameter by 2 cm thick (*i.e.*, two radiation lengths) of separated Mo-100 for irradiation by the bremsstrahlung of a 100 kW beam of electrons. There would be approximately 50% x 1 x $10^{12}$ n/s/kW x 100 kW = 5 x $10^{13}$ n/s in that target volume of 6 cm$^3$ at a density of about 10 g/cm$^3$ or a total target weight of 60 g. About 60% of the neutrons produced come from the ($\gamma$,*n*) reaction leading to Mo-99 and the rest come from ($\gamma$,2*n*) and ($\gamma$,3*n*) reactions leading to other stable molybdenum isotopes. The total amount of Mo-99 produced would be roughly 5 x $10^{13}$ x 0.6 = 3 x $10^{13}$ atoms/s. At equilibrium the activity is 3 x $10^{13}$/3.7 x $10^{10}$ = 810 Ci.

There is good agreement between this estimate and a more detailed calculation done using the Monte Carlo code GEANT 3.[11] Those calculations, shown in Table 1, also provide the power in the molybdenum target for the proposed beam conditions. For the estimate shown here, about 30% of the 100 kW of electron-beam power would be deposited in the target or less than 0.5 kW/g. The aggressive thermal designs used for the production of Mo-100 from fission of HEU deal with target power densities of 5 to 10 kW/g of uranium. Molybdenum should be capable of similar power densities although bremsstrahlung tends to produce its peak power near the entrance to the target while fission will produce near uniform power densities through the volume of the material.

Using the calculations in Table 3.1 and power densities of 3 to 5 kW/g of target as a guideline, one can make a reasonable estimate of target yield for a higher-power electron accelerator such as 500 kW (*i.e.*, equivalent to the device proposed for research at TRIUMF). A 30 gram target should yield on the order of 700 curies/100 kW at saturation and about 25 kW in the target (less than 1 kW/g). Scaling to a 500 kW electron accelerator, it should be possible to pro-

11 Monte Carlo Calculations done by Dr. J.R. Beene, Director, Holifield Laboratory, Oak Ridge National Laboratory, USA, *Used with permission.*

duce about 3,500 curies at saturation or 2,900 in one week from the same 30-gram target at power densities of less than 5 kW/g. The thermal design of the target will be challenging but the proof-of-principle designs already in use for HEU fission targets provide some confidence that such a target can be produced.

**This would be equivalent to 2,900 x 0.22 = 640 six-day curies per week with a usage of just 30 grams of separated isotope target at an average activity of 21 six-day curies/g.**

This is a much higher specific activity in the separated isotope target than can be produced via neutron capture and would meet the Canadian domestic demand.

## Potential Advantages and Disadvantages of This Approach

The main advantages of this approach are:

- There would be nearly no waste stream.
- The facility would (likely) be a Class II nuclear facility per CNSC licensing consideration and could be sited in a "green-field" location.
- Higher predictability of schedule, cost, and licensing than for a reactor. The main facility costs and licensing issues should be reasonably low in risk.
- Scalable—can be built as a small (low power) facility or large facility. Technology is equally useful over a wide range of powers.

The significant disadvantages of this approach are:

- A major change in the generator technology would be needed because of the different target.
- Health Canada/FDA approvals would be needed for new product.

| Target mass (g of Mo-100) | Ci/100kW at saturation | Spec. Activity (Ci Mo-99/g of Mo) | Power deposited in target (kW) |
|---|---|---|---|
| 0.29 | 100. | 360. | 2.2 |
| 1.0 | 210. | 208. | 4.8 |
| 2.3 | 300. | 147. | 11.4 |
| 9.1 | 518. | 57. | 16.4 |
| 70.6 | 900. | 12.8 | 29.0 |

**Table 3.1**: Production of Mo-99 by a 50 MeV electron beam. This table shows the saturated yield of Mo-99 for Mo-100 targets of various sizes irradiated by a 100 kW electron beam incident on a converter target. The columns provide the total activity, the specific activity, and the actual power that is deposited in the production target.

- The cost of manufacturing Mo-100 targets and the cost of separating Mo-100 from Mo-99 would likely be quite high. Mo-100 comprises less than 10% of naturally occurring molybdenum and separated isotope presently costs dollars per milligram.

Some research and development work to examine the Mo-100 target chemistry for direct extraction of Tc-99m could be considered. If successful, it could make the possibility of very small, self-contained generator systems being possible for central radio-pharmaceutical labs for a group of hospitals, very similar to PET cyclotrons.

### 3.1.3 Photo-fission process $^{238}U(\gamma,F)^{99}Mo$

The photo-fission process is similar to the photo-neutron process. Fission of natural uranium is produced via the reaction $^{238}U(\gamma,F$ where one of the common fission products is Mo-99.

The cross section for photo-fission of U-238 is about the same as it is for the photo-neutron process using Mo-100, and it is about 60 to 70 percent of the photo-fission cross section for a HEU target (see Figure 3.2). Therefore, this small advantage in cross section does not justify the extra challenges of using enriched uranium.

Some assumptions about the target are necessary to compute the Mo-99 yield. Conservative estimates are provided here (for instance, more advanced geometries or scanning of the beam across a matrix of targets would allow higher beam powers to be used for the same target mass and lower power densities).

The radiation length of uranium is about 0.33 cm, so a two-radiation length target is about 0.66 cm thick and a thick target is about 2 cm thick. The fission yield per 100 kW of electron beam power has been calculated using analytical procedures[12] and in detail using Monte Carlo techniques.[13] Depending on the details of the target and converter designs, it is reasonable to expect fission yields of about $5 \times 10^{11}$ f/s/kW of electron-beam power for a thick target and electron energies of greater than about 30 MeV. A thick target can be used because the cost of the target material is not a significant cost of the process. The fission yield is $5 \times 10^{11}$ f/s/kW x 100 kW = $5 \times 10^{13}$ f/s in that target volume. Realistic yields might be somewhat lower (tens of percent).

Six percent of the fission yield will be Mo-99. At saturation (equilibrium), about 14 days of irradiation, there will be $0.06 \times 5 \times 10^{13}$ Bq of Mo-99 produced by a 100 kW electron beam. This is equal to $3 \times 10^{12}/3.7 \times 10^{10} = 81$ Ci.

12 A Radioactive Ion Beam Facility Using Photo-fission, William T. Diamond, Nucl. Inst. And Meth. In Physics Research A, 432 (1999) 471.

13 Monte Carlo Calculations done by Dr. J.R. Beene, Director, Holifield Laboratory, Oak Ridge National Laboratory, USA, *Used with permission.*

**This would produce about 81 x 0.22 = 18 six-day curies in a two-week irradiation. A one-week irradiation will produce about 83% of saturated yield or 15 six-day curies per week. Some present-day reactors choose the shorter irradiation period for economic reasons.**

Producing 500 six-day curies requires about 500/15 = 33 x 100 kW of electron beam power, or just over 3 MW.

Both photo-neutron reactions on a separated-isotope target of Mo-100 and neutron-fission of HEU or LEU targets require expensive target material that represents a significant fraction of the cost of the end product. The irradiation is generally extended to between three and five half-lives to obtain the highest yield from the expensive target material. The natural uranium used for a photo-fission target is much less expensive than the separated-isotope targets and would not be a significant fraction of the isotope cost. Therefore, it is not an unreasonable approach to use shorter irradiations to obtain a higher amount of total isotope production. Irradiation to one half-life (2.75 days) of Mo-99 yields 50% of the saturation yield but will produce five separate irradiations in a two-week period (2.5 x saturation yield) or 22.5 six-day curies per week. The down side of this approach is that reduced irradiation cycle might significantly affect present hospital and radiopharmacy routines.

**This approach reduces the size of the accelerator to about 2.2 MW, with a modest increase in waste handling. 2.2 MW is a reasonable scale for a single electron linear accelerator (linac).**

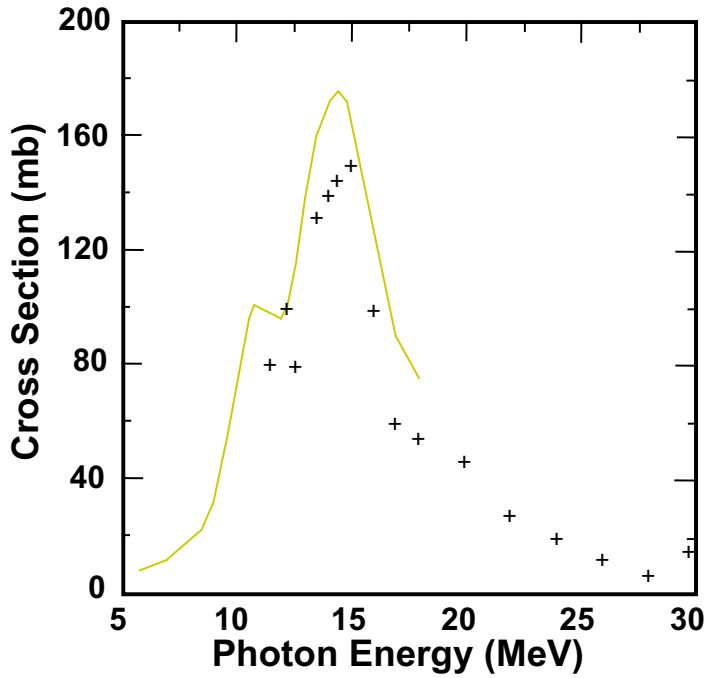


**Figure 3.2:** Experimentally measured cross-sections for photo-fission of U-238 for photon energies up to 30 MeV. The solid-line is a fit to data and the plus signs are data from another laboratory. Inspired from Figure 3, Diamond NIM article.

However, another solution might be to build several 1.1 MW photo-fission accelerators that provide backup to each other. Targeting issues at about 1 MW become more easily managed.

## Potential Advantages and Disadvantages of This Approach

The main advantages of this approach are:

- Would use natural uranium targets which have lower cost, no criticality issues, and would reduce security required for waste-storage site.
- Could use existing processing techniques, although the volume of the dissolved uranium solution used for Mo-99 recovery could be larger than present (depending on the target designs). Once recovered, the Mo-99 refinement and purification steps should be identical.
- Could continue to use existing generator technologies.
- Higher predictability of schedule, cost and licensing than for a reactor. The main facility costs and licensing issues should be reasonably low in risk.

The significant disadvantages of this approach are:

- Could result in higher waste volume than HEU reactor target technology because of low concentration of the product per gram of target material used (depending on the target design). The specific activity of the actual Mo-99 product should be similar to the value obtained from neutron-fission of HEU, but the total target volume may be significantly higher because of thermal or mechanical issues associated with handling beam power.
- Higher operating and capital costs for the accelerator than the photo-neutron process because of higher beam-power requirements.
- The facility would likely be a Class IB facility similar to existing hot-cell facilities used in Mo-99 recovery and refinement.

# 3.2 Accelerator-driven Photo-fission of Uranium

After considering the three accelerator-based methods listed above, the Task Force examined the photo-fission option more carefully. It was judged that much of this technology was readily available and could be deployed in a straightforward fashion.

The possibility of using an accelerator—as opposed to a reactor—to generate high intensities of thermal-energy neutrons (neutrons of energy ~0.02 eV, relevant for stimulating fission) was not seriously considered by the Task Force primarily because of the projected costs. The U.S. Spallation Neutron Source and the Japan Proton Accelerator Research Complex will be capable of producing approximate time-averaged neutron intensities of perhaps $10^{16-18}$ neutrons/sec. These machines use high-intensity proton beams of a few GeV to strike liquid-metal targets capable of handling megawatts of beam power. However, each project exceeded US$1 billion in construction and took more than a decade to design and build. Other schemes for producing intense beams of low-energy neutrons are possible but have not been as rigorously developed by the research community.

A qualitative comparison of neutron and photo-fission is presented here.

## 3.2.1 Neutron-fission

One gram of U-235 in the rough thermal-neutron flux of a nuclear reactor of 3 x $10^{14}$ n/cm$^2$/s produces:

$$Y = N \times \sigma \times \phi$$

Where $N$ = number of target atoms in one gram = 1/235 x 6 x $10^{23}$ = 2.6 x $10^{21}$; $\sigma$ = 600 barns = 600 x $10^{-24}$ cm$^2$ and $\phi$ = 3 x $10^{14}$ n/s/cm$^2$. Hence, $Y$ = 4.6 x $10^{14}$ f/s/g.

One watt of fission energy is produced by 3.1 x $10^{10}$ f/s so this would correspond to 4.6 x $10^{14}$/3.1 x $10^{10}$ = nearly 15 kW/g of U-235. In the neutron-fission technique, the actual target contains a large fraction of aluminum to handle the extreme power density.

About 6% of the fission yield is Mo-99 or about 2.8 x $10^{13}$ atoms of Mo-99/s/g of U-235. If the target is left in the reactor for about five half-lives, it will reach secular equilibrium with a rate of decay equal to the rate of production, *i.e.,* $Y$ = 2.8 x $10^{13}$ decays per second or Bq. This is equivalent to 2.8 x $10^{13}$/3.7

x $10^{10}$ Bq/Ci or 760 Ci/g of separated HEU. This would be reduced to 93% x 760 = 700 Ci/g of target material for a HEU target at 93% enrichment.

This is equivalent to 700 x 0.22 = 150 six-day curies per gram of HEU. This is at the very high end of production and a yield of about 50% to 70% is more typical. Using a yield of 100 six-day curies per gram of HEU leads to only 5 grams of HEU in the waste stream to make 500 six-day curies.

## 3.2.2 Photo-fission

An analysis comparable to the one above is presented here for comparison for an estimate of power per gram of target. One can calculate the yield using the same basic formula that was used for neutron fission but using some estimates of useful photon flux and an average cross section.

$$Y = N \times \sigma \times \phi$$

Where $N$ = numbers of target atoms in one gram = ½38 x 6 x $10^{23}$ = 2.5 x $10^{21}$; $\sigma$ = 0.2 barns = 2 x $10^{-25}$ $cm^2$. An estimate of the photon flux is needed.

About 50% of the energy of a 50 MeV electron beam will be converted into bremsstrahlung with an energy spectrum from near zero up to 50 MeV. Perhaps 45% of that spectrum will overlap the giant dipole resonance of the uranium nucleus between about 10 and 20 MeV. Assuming that the 45% overlap is all at 15 MeV, then the total number of photons per mA of beam current (assuming 50 kW of beam power) is given by:

50 kW x 0.5 x 0.45 = 11.25 kW of photons of 15 MeV

11.25 kW = 11.25 kJ/s = 7 x $10^{16}$ MeV/s

7 x $10^{16}$ MeV/s/(15 MeV per photon) = 4.7 x $10^{15}$ 15-MeV photons/s

and $Y$ = 2.4 x $10^{12}$ f/s/g. Recall that the neutron fission rate was 4.6 x $10^{14}$ f/s per gram of U-235 in a typical reactor flux. The photo-fission rate per gram of U-238 in a modest 50 kW beam is lower by about a factor of 200. This estimate employs a conservative, unoptimized target design.

Using a 6% production of Mo-99 produces 1.44 x $10^{11}$ atoms of Mo-99 at saturation or 3.9 production curies per gram of uranium or 0.86 six-day curies per gram.

One watt of fission energy is produced by 3.1 x $10^{10}$ f/s which corresponds to 2.4 x $10^{12}$/3.1 x $10^{10}$ = 78W/g of U-235. Creating 150 six-day curies (equivalent to estimates for one gram of HEU material via neutron fission) would need 200 grams of photo-fission target material at the high power density. However, there would be 11.25 kW of photons on that same gram of material. This power density is rather high and stretches present-day experience; there is room for substantial improvement in the photo-fission target design.

## 3.2.3 Survey of Yield Projections

The cumulative yields of Mo-99 from photo-fission of U-238 are about the same as those from thermal neutron fission of U-235 when considered on a "per fission" basis. Reported $^{235}U(n_{thermal},F)$ yields are of the order of 6%.[14,15,16] Cumulative $^{99}Mo$ yields from $^{238}U(\gamma,F)$ have been reported by several studies with some comparisons to $^{235}U(n_{thermal},F)$.[17,18]

Schmitt and Sugarman measured $^{natural}U(\gamma,F)$ mass yield curves with 48 MeV photons and determined peak and trough fission product distributions at 7, 10, 16, 21, 48, 100 and 300 MeV photon energies.[19] They normalize their measured yields to a 6.6% cumulative yield of Mo-99 at all photon energies and compare to a 6.8% yield from $^{235}U(n_{thermal},F)$. The authors state, "The observed photo-fission yield curves are interpreted as a superposition of two components, a low energy (double- humped) curve and a high energy single-humped curve, produced by the absorption of high-energy photons." Since

| Product | $^{235}U(n_{th},F)$ Yield | $^{238}U(\gamma,F)$ Yield | $E_\gamma$ (MeV) | Ref. |
|---|---|---|---|---|
| Mo-99 | 6.2 | | | Turkevich & Niday |
| Mo-99 | 6.8 | 6.6 | 7-300 | Schmitt & Sugarman |
| Mo-99 | 6.06 | 5.30 | ≤ 23 | Cuninghame & Edwards |
| Mo-99 | | 4.94 | ≤ 10 | Richter & Corell |
| Mo-99 | | 6.06± 0.16 | ≤ 16 | Richter & Corell |
| Mo-99 | | 5.6 ± 1.0 | ≤ 17.5 | Meason & Kuroda |
| *A* = 99 | | 6.48 ± 0.28 | ≤ 25 | Thierens *et al.* |
| *A* = 99 | | 6.76 ± 0.28 | ≤ 12 | Jacobs *et al.* |
| *A* = 99 | | 6.13 ± 0.26 | ≤ 15 | Jacobs *et al.* |
| *A* = 99 | | 6.17 ± 0.26 | ≤ 20 | Jacobs *et al.* |
| *A* = 99 | | 6.09 ± 0.25 | ≤ 30 | Jacobs *et al.* |
| *A* = 99 | | 5.90 ± 0.25 | ≤ 70 | Jacobs *et al.* |

**Table 3.2**: Comparison of reported Mo-99 cumulative yields in terms of percentage of total fission yield.

14 A. Turkevich and J.B. Niday, Phys. Rev. 84(1) (1951) 52

15 R.A. Schmitt and N. Sugarman, Phys. Rev. 95(5) (1954) 1260

16 J.G. Cuninghame, M.P. Edwards, G.P. Kitt and K.H. Lokan, Nucl. Phys. 44 (1963) 588

17 H.G. Richter and C.D. Corell, Phys. Rev. 95(6) (1954) 1550

18 J.L. Meason and P.K. Kuroda, Phys. Rev. 142(3) (1966) 691; H. Thierens, D. De Frenne, E. Jacobs, A. De Clerq, P. D'hondt and A.J. Deruytter, Phys. Rev. C 14(3) (1976) 1058; E. Jacobs, H. Thierens, D. De Frenne, A. De Clerq, P. D'hondt and A.J. Deruytter, Phys. Rev. C 19(2) (1979) 422

19 See Schmitt and Sugarman.

Mo-99 falls at the peak of the lower mass double-humped curve, increasing photon energy has little effect on its cumulative yield. Photo-fission mass yield curves for natural uranium at 7-300 MeV photon energies are compared to the yield curve from $^{235}U(n_{thermal},F)$ in Figure 2 of Schmitt and Sugarman.

In their study of independent fission yields from U-238 photo-fission with ≤ 23 MeV bremsstrahlung, Cuninghame *et al.* normalized production of Br, Nb, Cs and La nuclides to an assumed $^{99}$Mo yield of 5.30% compared to 6.06% for $^{235}U(n_{thermal},F)$.

Richter and Corell compared the fission mass yield curves from $^{natural}U(\gamma,F)$ ($\gamma \leq 16$ MeV) with those from $^{235}U(n_{thermal},F)$. While no numerical comparison of cumulative Mo-99 yields is given, a graphical comparison of yield curves (Figure 1 of Richter and Corell) shows essentially equal yields at $A$=99. The reported Mo-99 cumulative yields were 4.94% for $\gamma \leq 10$ MeV and (6.06 ± 0.16)% for $\gamma \leq 16$ MeV.

A (5.6 ± 1.0)% $^{99}$Mo cumulative yield was reported for $^{238}U(\gamma,F)$ ($\gamma \leq 17.5$ MeV) by Meason and Kuroda.

The above values are summarized in Table 3.2 along with total cumulative $A$=99 mass chain yields. While the independent fission yield of Mo-99 may be small, the cumulative yield is enhanced by feeding the relatively long-lived Mo-99 from short-lived $A$=99 progenitors produced in higher quantities. This is clearly demonstrated by comparing cumulative Mo-99 yields with $A$=99 yields.

### 3.2.4 Relative Advantages of an Accelerator Solution

The photo-fission accelerator solution has several attractive features.

- The accelerator can be turned on and off at will and without consequence.
- The accelerator does not produce radioactive waste from its operation although waste from chemical processing of irradiated targets to recover and extract the Mo-99 would be similar to a reactor-based approach.
- The proposed technology can achieve similar yields from natural uranium, LEU, or HEU targets because the photo-fission process is not very sensitive to the neutron number of uranium.
- The technology is scalable: additional accelerators can be built or turned on and off as needed.
- The licensing and decommissioning processes are straightforward.

The proposed technology has several disadvantages.

- As a new technology, it is intrinsically unproven. There are key elements of the process that require substantial R&D (*e.g.,* optimal design of high-

power target). The accelerator systems will need to be optimized for maximum uptime and reliability.

- There are no current LEU-target processing or generator-manufacturing capabilities within Canada; this may change as new options for nuclear-reactor production of Mo-99 are explored. The irradiated target material produced at an accelerator may not be compatible with either the existing HEU recovery and refinement facilities or proposed new ones that focus on reactor-based LEU targets.
- The technology requires full performance validation and product verification before it can compete.
- Although the full operating and maintenance costs could be borne by an independent manufacturer, it is not clear that the final product price will be competitive with present-day reactor-produced Mo-99 (whose present market price does not fully recover costs, such as those associated with the procurement of HEU).

# 3.3 Designing an Alternative Production Capability and Integrating with Existing Systems

This section takes the above intriguing premise one step further: What would it take to design, build, and operate a facility that uses accelerator-driven photofission to produce Mo-99? Such an accelerator facility would be viewed as a single-purpose facility operating strictly for business. Applications of the basic technology for research purposes would take place elsewhere as part of other institutional research programs.

## 3.3.1 Accelerator

The above discussions led to consideration of building and operating an electron linear accelerator, or e-linac, for the production of Mo-99 via photo-fission of a (natural) uranium target. Based on the production of sufficient six-day curies to satisfy the clinical demand for Mo-99 in Canada, it is estimated that several megawatts of electron-beam power at 100% duty factor is required. The nominal e-linac parameters are 50 MeV electron energy and 100 mA beam current. The adoption of superconducting radio frequency (SCRF) accelerating structures for the e-linac provides a cost effective approach to a MW-class fission driver because of the intrinsic power efficiency, compactness and high accelerating gradient they offer. Presently available technology offers a choice of frequencies of the accelerating structures ranging from 500 MHz to 1.3 GHz. Two possible frequencies, 704 MHz and 1.3 GHz, are discussed to illustrate technically feasible conceptual designs. However, based on a preliminary analysis, the lower frequency option will probably result in lower capital cost. The operations costs are similar, as they are dominated by the high-power microwave generators driving the structures.

Other considerations, such as overlap with other applications of SCRF technology, may influence a final decision. For the purposes of benchmarking, a 5 MW photo-fission accelerator is discussed here.

### 704 MHz Option

U.S. Brookhaven National Laboratory (BNL) is constructing a 20 MeV R&D Energy Recovery Linac (ERL) facility based on SCRF 5-cell cavities operating at 704 MHz, and designed to accelerate up to 0.5 A of average current. A single 1 MW CW klystron with a 2 MW IGBT power supply will power the 2.5 MeV SCRF injector cavity. The 500 kW input couplers for this injector are presently under construction and will be tested in a conditioning box at BNL in 2009. The

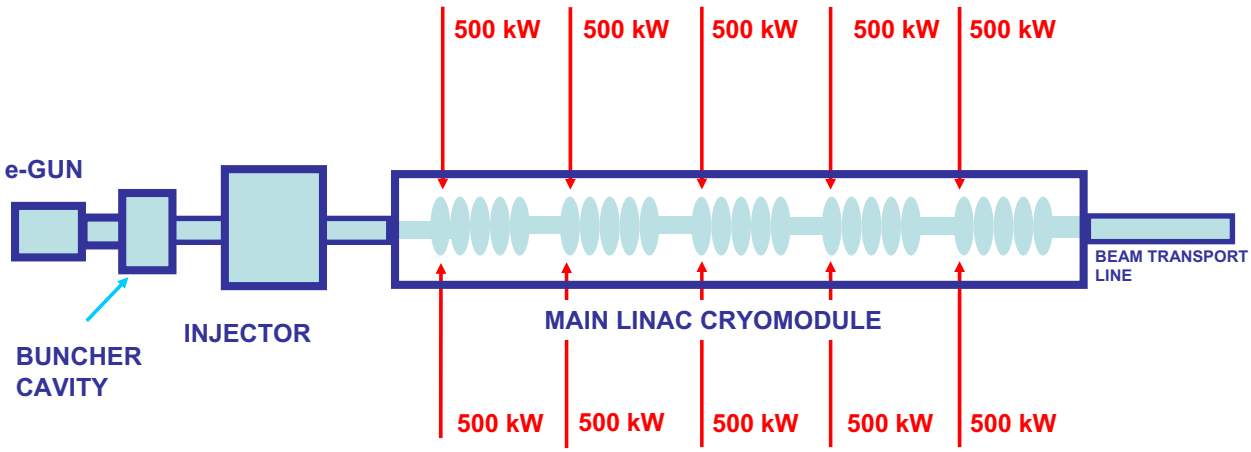


**Figure 3.3:** Schematic layout of 5 MW e-linac based on 704 MHz SCRF technology.

5-cell SCRF linac cavity has been successfully tested in the vertical test facility at the U.S. Thomas Jefferson National Accelerator Facility (JLab), demonstrating a quality factor in excess of $10^{10}$ at an accelerating gradient in excess of 20 MV/m. Since the cavity design has been developed for high current applications, its longitudinal loss factor is exceedingly small (less than 1 V/pC) resulting in relatively low power dissipation in the higher order modes. Based on the availability and demonstrated performance of these components, a 5 MW photo-fission driver for the production of Mo-99 can be configured as follows: a thermionic injector can be used to supply 100 mA average current at a bunch repetition rate of 704 MHz and charge per bunch of 140 pC. The main accelerator (see Figure 3.3) consists of a single cryomodule housing five 5-cell cavities, each providing an energy gain of approximately 10 MeV. For 100 mA of average current, the required RF power per cavity is 1 MW, supplied by a 1 MW klystron via two 500 kW input couplers. As the IGBT technology is scalable, a single power supply can be used for several klystrons, although the exact number will be determined by the manufacturer. The wall-plug to beam efficiency for this design concept is estimated to be greater than 40%, dominated by the klystron efficiency at 60%. The total wall plug power consumption is about 12 MW, assuming 2 K operation of the cryogenic plant. The frequency choice of 704 MHz in principle allows the option of 4 K cryogenic operation. This option has several advantages, including ease and robustness of operation, reduced system complexity, and lower operating and capital costs. For an industrial-scale application, such as the production of Mo-99, this option should be explored. The estimated capital cost of the accelerator, including ancillaries and conventional services, is C$50-60 million.

## 1.3 GHz Option

Cornell University has a 1.3 GHz Injector Linac designed to provide 0.5 MW beam power. This linac is built from building blocks composed of a 100 kW klystron, two 50 kW input couplers and a 2-cell RF cavity driven at up to 10 MV/m gradient. The five SCRF cavities are housed in a single cryostat. The energy gain is 1 MeV per cavity at 100 mA. The high-power coupler and klystron designs were demonstrated in 2007. Systems integration tests started in May 2008 and beam tests are expected to start in December 2008. To first order, this design is directly scalable: 50 cavities driven by 50 klystrons (see

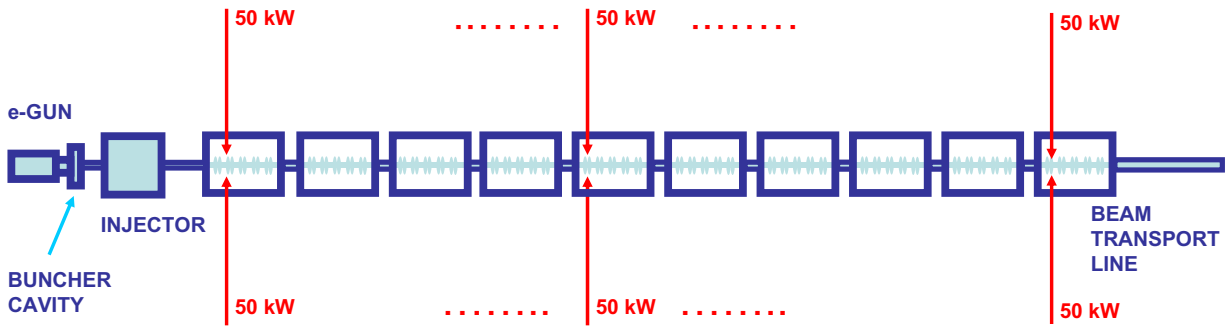


**Figure 3.4**: Schematic layout of 5 MW e-linac based on 1.3 GHz SCRF technology.

Figure 3.4) provide the desired 5 MW electron beam power. The cavities would be divided among five cryostats with focusing elements between each cryomodule. Simple scaling of the equipment cost for the 0.5 MW machine leads to a rough estimate of C$150 million for the 5 MW version. However, the R&D cost is eliminated and some economy of scale should result from large-scale production. A capital cost around C$125 million could be expected for the entire machine including ancillaries and conventional services.

The coaxial-type input couplers, and to a lesser extent the klystrons, form a bottleneck in the design. ERL prototypes at 1.3 GHz presently under development around the world drive the development of high power couplers and CW klystrons for their injectors, so it is safe to assume that 100 kW couplers and 200 kW klystrons will be successfully tested and operated in the near future. Doubling the power handling would allow the number of high-power RF building blocks to be halved: 25 cavities and 200 kW beam power per cavity. An existing 250 kW 60% duty factor klystron could be modified to CW operation. The multi-purpose input coupler design could be simplified, consistent with its narrower purpose in the fission driver application, and additional means of cooling introduced. These measures might reduce the capital cost by one third, to roughly C$80 million.

## Conclusion

A 5 MW photo-fission accelerator is feasible based on available technology. The frequency choice of 704 MHz has several advantages:

- This frequency lies in the traditional television-broadcast range, so the klystron design is less specialized than at 1.3 GHz;
- The structures have larger apertures, which is beneficial to wakefield generation and halo losses;
- Input couplers can operate at significantly greater power levels than at higher frequencies, resulting in a simpler design with fewer components, which means lower capital costs and higher availability; and
- Cryoplant operation at 4 K is a possibility worth studying.

High machine reliability and availability are important for this application and can be achieved. However, this requirement should be integrated in the initial design stages. The construction can take up to 3-4 years.

## Compton Backscattering Concept for Production of Molybdenum-99

There is an alternate accelerator approach for photo fission production of Mo-99 that requires significant R&D but promises to substantially reduce the operating costs of the facility. This technique uses uranium photo-fission from quasi monochromatic gamma-rays produced by Compton backscattering of laser photons from relativistic electrons.

Compton backscattering has been used to generate high energy gamma-rays for decades. Low-energy photons colliding head-on with high-energy electrons with relativistic factor $\gamma$ create a pencil-like beam of gamma rays in the

direction of the initial electron beam, and with energy up-shifted by $4\gamma^2$. The wavelength of the backscattered radiation depends on the angle θ between the incident electrons and the gamma rays:

$$\lambda\gamma = \lambda_L (1 + \gamma^2 \theta^2) .$$

For gamma rays with maximum energy of 14 MeV, the required electron beam energy is 485 MeV for a laser wavelength of 330 nm. To generate significant gamma-ray flux, a short-pulse laser operating with very high average power is required. The concept used here assumes that an optical enhancement cavity with Q of 1000 is driven by a 5kW average power laser to generate 5 MW of intracavity laser power colliding with the electron beam. Assuming the performance of the MIT high average power laser,[20] a 5 MW intracavity laser beam, at 330 nm wavelength, can be focused to a 3 μm spot size. For a bunch repetition rate of 100 MHz and 10 mA average electron beam current, the possible gamma flux from the Compton source is $N_\gamma \sim 9.3 \times 10^{15}$ gamma rays per second. Because the induced energy spread on the electron beam is below 3%, one may recover most of the electron beam energy, which substantially increases the efficiency of the system.

A possible accelerator concept would employ a DC photoinjector delivering 10 mA average current at 1.3 GHz and 80 pC per bunch, followed by a room-temperature buncher cavity and a SCRF 5 MeV injector. The beam is then injected into the main linac which comprises one cryomodule with eight cavities operating at 20 MV/m, for a single-pass energy gain of 160 MeV. A three-pass recirculation system will result in final beam energy of about 485 MeV. The laser-beam interaction happens during the last recirculation, generating gamma rays, and the spent electron beam is sent back through the linac for three passes, 180o out of phase for deceleration and energy recovery. The beam is dumped at the final energy of 5 MeV. A rough estimate of the total wall plug power consumption of this facility is 800 kW, more than an order of magnitude below the concept of bremsstrahlung-induced photons. Several free-electron laser groups around the world have reported the production of MeV-scale gamma rays via Compton backscattering inside a free-electron laser optical cavity.[21]

## 3.3.2 Convertor and Target

The photo-fission of U-238 comes from the excitation of the giant dipole resonance, which is around 15 MeV. Photons of 15 MeV energy can be produced using the braking radiation ("bremsstrahlung") spectrum of an electron beam impinged on a high *Z* material such as tungsten or lead. The beam energy should be at least 40 MeV to optimize photon production in the 13-18 MeV region.

A beam power of 2-5 MW can satisfy the Mo-99 production requirements.

20 MIT Compact X-ray Source," D. Moncton, W. Brown, T. Y. Fan. W. Graves, F. Kaertner, January 2008.

21 See, for example, "Gamma-ray production in a storage ring free electron laser," V. Litvinenko, et al., PRL Vol. 78. Number 24, June 1997.

This power level presents a key technical challenge that could be met with a systematic and focused R&D program. High-power targets are in demand for many applications, particularly rare-isotope beam facilities for nuclear physics. Such power can be handled by splitting the electron beam onto 5 converters that are followed by 10 targets each. The electron beam power could be dissipated in the converter that would be cooled using water and/or liquid metal. The combined photon power and the fission power represent about 750 kW. Each target would dissipate approximately 15 kW. The target can be water-cooled using 10 l/min flow. The design of the target would have to be optimized to dissipate excess thermal power and to minimize overall volume to ensure economy of Mo-99 recovery and refinement. Preliminary novel concepts for targets in a 2.5 MW beam could increase the fission rate to 1.2 x $10^{14}$ f/s/g, rivalling the rate achieved by neutrons to within a factor of 4.

The converter for such power requirement could be lead or mercury. The production of activity from the converter can be estimated: ($\gamma$,*n*) is the main process for producing radioactive nuclei. Lead has two long-lived isotopes Pb-205 and Pb-203 with half lives of 2.0 x $10^{7}$ years and 52 hours, respectively.

Mercury has three long-lived isotopes that can be produced with ($\gamma$,*n*) process: Hg-195,197 and 203, which have the following half-lives, 9.5 h, 63 h and 47 d, respectively. The cross-section for this process is about 50 mb at 15 MeV. The other processes, ($\gamma$,2*n*) and ($\gamma$,*p*) have much smaller cross-sections.

Some preliminary testing can validate these concepts. A U-238 foil backed onto an Al disk can be bombarded with photons from bremsstrahlung. The discs would then be treated using the same chemical process used for Mo-99 production from reactors. Once the Mo-99 is separated from the uranium target, the production yields can be assessed.

## 3.3.3 Mo-99 Recovery, Processing, and Generator Manufacture

During the past 40 years, various versions of the chemical process for separation of Mo-99 from neutron-irradiated U-235 (first described by researchers at BNL and described below) were used on both HEU and LEU targets, either in the form of uranium metal or oxide (see Figure 3.5). It is believed that this process (with some modifications) was also used for many years by Cintichem, and is currently used by the Australians and perhaps by AECL of Canada.

The BNL process described a method to extract curie amounts of Mo-99 from an irradiated uranium target by column chromatography.[22,23] In brief, the U target (93% enriched U-235 metal as an alloy with Al) was dissolved in 6 M $HNO_3$ catalyzed by $Hg(NO_3)_2$. After adding 0.5 mg of Te carrier, the target solution (U plus all the fission products, including Mo) was loaded on an alu-

mina column which selectively retained Mo and Te. The bulk of U and the fission products (including all the rare earth and Ru isotopes) was removed from the alumina column by serial washing of the column with 1 M $HNO_3$, $H_2O$, and 0.01 M $NH_4OH$. The Mo-99 was then eluted from the column with 1 M $NH_4OH$. The reported Mo recovery was ~70% with a purity of 99.99%. In a subsequent purification step, Mo was re-absorbed on a strong anion-exchange resin washed to remove the trace impurities, then eluted with 12 M HCl and evaporated to dryness. Later, silver-coated alumina was shown to be superior in removing Mo from very high concentration of U (>100 $g.L^{-1}$) in 1 M $HNO_3$.[24] Again, Mo is eluted from silver-coated alumina with 1 M $NH_4OH$. The efficiency of Mo recovery was reported to be 70-80% with very high purity especially from Te-132 radioisotope, which is typically the major impurity in Mo-99.

Whatever target is developed should not use aluminum cladding. The use of aluminum usually requires some mercury in the processing as noted above, but the overall production of Mo-99 improves significantly when mercury is not involved.

Alternatively, a process based on extraction of Mo from acidic solution by di-(2-ethyhexyl) ortho-phosphoric acid (HDEHP) dissolved in an organic solvent was reported by the Oak Ridge group.[25] After separating the organic layer

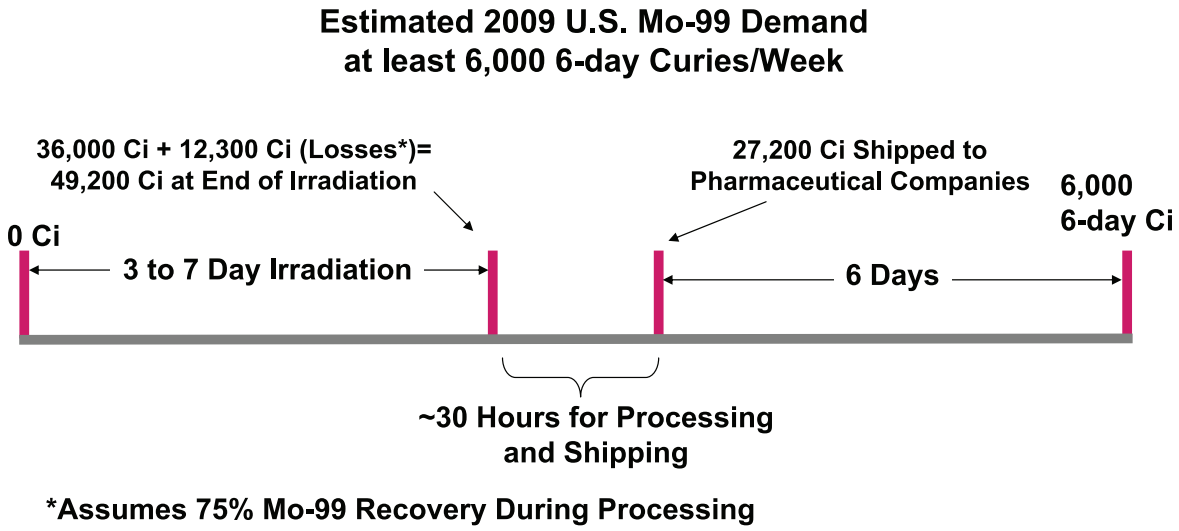


**Figure 3.5:** Overview of the timeline for irradiation, recovery, and refinement to produce Mo-99. Courtesy of G. Vandegrift, U.S. Argonne National Laboratory.

containing Mo isotopes (U and other fission products remain in the aqueous phase), and washing it with 1 M HCl, the Mo-99 was back-extracted into a

22 Stang, Jr. (Coordinator), 1964, in Manual of Isotope Production Processes in Use at Brookhaven National Laboratory, BNL864 (T-347).

23 Richards, P., 1966, in Radioactive Pharmaceuticals, Proceedings of a Symposium held at the Oak ridge Institute of Nuclear Studies, Nov. 1965. Published by USAEC/Division of Technical Information, PP. 323 - 334.

24 Barnes, R. K. un-published.

25 Ottinger, C. L., 1970, "Short-Lived Fission Products Program," in CONF700646, Radioisotope Production Technology Development Meeting, ORNL, pp.34-43 (June 1970).

mixture of 0.1 M HCl and 2% $H_2O_2$. After destroying the residual peroxide by adding $NaNO_2$, the Mo-99 solution was adjusted to 1 M HCl, and the extraction process was repeated to produce very high purity Mo-99. In a variation of the above method, after two extraction processes, Mo-99 was further purified on a very small alumina column as described earlier. With the advent of modern and compact centrifugal contactors, perhaps the extraction techniques should be re-evaluated for routine and continuous processing of Mo targets.

A precipitation method can also serve as the preliminarily step to separate Mo from the bulk of U and other fission products.[26] In this process, Mo was precipitated as sulfide from 1 M $HNO_3$, where U and the majority of the fission products remain in solution. The recovery of Mo is about 80%, and main impurities are Te and Ru isotopes. The Mo sulfide is then dissolved in 7 M NH4OH, evaporated to dryness, and further purified on a small alumina column as before. The precipitation method is more common because of the ease of recovering the uranium from fissile solution by filtration. This point may affect which process is chosen to manage the waste from processing a photofission uranium target.

The processes outlined above are equally feasible for processing a U-238 target. Regardless of the method for processing Mo, the capital investment will be very high, as a special facility is required to deal with the emissions and disposal of highly radioactive fission products. Note that in the fission process, for each Ci of Mo-99, 100 Ci of other radioisotopes are produced, including a number of Xe and I radioisotopes which must be removed from off-gas prior to being discharged to the environment. An advantage of using a U-238 target is that the waste generated from the process may not be trans-uranic (TRU) waste, which greatly simplifies the safeguard, accountability, criticality, and waste disposal issues. But, in a complicating factor, depending on the design of the target and flux of the secondary thermal neutrons, some $^{239}Pu$ may be produced by $^{238}U(n,\gamma)^{239}U\ [\beta] \rightarrow {}^{239}Np\ [\beta] \rightarrow {}^{239}Pu$ nuclear reaction.

## 3.3.4 Drug Licensing, Distribution, and Clinical Use

There are important considerations for proposing a new source of Mo-99, independent of the specific technical details. Both Health Canada and the US Food and Drug Administration would need to be involved. Because the present system of Mo-99 recovery and refinement is optimized for the present nuclear-reactor producers, any perturbations introduced to accommodate additional production facilities will need careful consideration and involvement of the drug regulators.

The proposed means for the production of Mo-99 uses a different target

26 Tanase, M., Kase, T., Shikata, E., 1976," Separation of Molybdenum-99 from Neutron-Irradiation Uranium-235 with Sulfur as collector," J. Nucl. Sci. Tech. 13 (10), pp. 591 -595.

material than present thermal neutron fission process, U-238 versus U-235, respectively. Although the fission yield from both processes ($^{235}U(n,F)$ and $^{238}U(\gamma,F)$) are nearly identical in terms of elemental and isotopic distribution, the regulatory bodies will require proof that the Mo-99 available for preparing the Mo-99/Tc-99m generators meet or exceed the existing specifications for purity and specific activity.

Because the distribution of elements is almost identical in both processes, the validation of the chemical process should be fairly straightforward. One caveat is the contamination level from the production of Pu-239 from the neutron capture on U-238 and the subsequent decay of U-239 to Pu-239. The chemistry for removing Pu-239 has been worked out for LEU targets where the abundance of U-238 is >80%. The U-238 targets for photo-fission will probably be larger but the thermal neutron flux will be lower. In any case, the chemical and isotopic purity of the Mo-99 generated from photo-fission of U-238 must be demonstrated. If an existing generator manufacturer is to use this, then a modification to the Drug Master File for Mo-99 may suffice. But new manufacturers would require an entirely new submission to the FDA and HC.

Ideally, chemical and other analyses used to confirm the equivalence of Mo-99 recovered and refined from different sources (*e.g.*, nuclear reactors using neutron fission and accelerators using photo-fission) will satisfy the regulatory bodies. Ultimately, the labelling equivalence and performance of the radiopharmaceutical in the clinic will be the determining factors.

A production stream from accelerator to Mo-99 distributors such as MDS Nordion will effectively be a new product. Therefore, it would likely require at least an amended drug master file that includes validation of:

- Target viability;
- Recovery process;
- Impurities and refinement process; and
- Equivalence of Mo-99.

## 3.3.5 Operations

The Task Force focused on the operational issues associated with the photo-fission accelerator system. At this preliminary stage, only general considerations of facility operation can be sketched. Clearly, the operating cost will be a key determinant of the overall unit-cost of the final Mo-99 radiopharmaceutical used in healthcare delivery. The present business model relying on nuclear reactors does not explicitly include capital or amortization costs for the irradiation facilities.

Power consumption will likely dominate the operating costs of the proposed photo-fission accelerator. The power demands for the concepts listed above are roughly 12 MW for the two SRF e-linacs and 8 MW for the Compton-backscattered concept. The operating costs for the accelerator are more difficult to estimate; typically, about 10% of the capital investment is required to operate and maintain such an accelerator, although this depends on how

labour is included.

Considerations for operating costs of a photo-fission accelerator must include:

- Procurement of raw target materials and manufacture of targets;
- Accelerator operation including electrical power and/or power-plant construction and operation;
- Licensing costs;
- Waste disposal costs; and
- Decommissioning costs.

For any given new source of Mo-99, a commercial enterprise would also need to recover changes in costs associated with the downstream recovery, refinement, and distribution systems if they are adversely affected by the new source.

Too many elements are missing at this stage to provide a realistic operational cost or an effective cost-per-dose estimate for the photo-fission accelerator technology. Similarly, the Task Force was not able to prepare an estimate for a hypothetical LEU reactor solution. An economic-competitiveness analysis could not be completed.

Reliability and availability also matter in considering the proposed technology. Accelerators generally have high reliability when used in research laboratories. Sophisticated techniques have been developed to consider reliability issues in the design stage, and these can be quite effective. Depending on the specific model for supplying Mo-99 to Canada or to the world, another option is to develop several such accelerators to not only improve reliability but also to improve scalability and flexibility of operation.[27] The Mo-99 accelerator centres could be centrally located or distributed geographically as a coordinated production network.

### 3.3.6 Nuclear Regulatory Aspects

Licensing for an accelerator-based photo-fission facility should include all aspects of the production and recovery of Mo-99. That is, it would include the accelerator facility, the Mo-99 recovery facility, and the waste handling facility.

The weekly quantity of Mo-99 at end of irradiation sufficient for 30-50% of the North American market is 25 kilo Curies, before allowing for any decay. A facility that handles this much activity and its irradiation by-products would be a Class IB facility according to CNSC regulations. The regulatory requirements for such a facility include a Safety Analysis Report (SAR) outlining: the site lay-

27 Two accelerators operating each with 80% reliability together provide a reliability of 96% for having one fully operational.

out, building location, and exclusion zones; a description of the radiological hazards and the proposed mitigation measures to limit the associated risks of these; a quality management system which would include a QA program; an environmental protection program and occupational health and safety for facility staff; a description of proposed effluent and environmental monitoring programs; compliance with NPA-801 fire protection standard for Class IB facilities; a public-information program; and lastly a preliminary decommissioning plan (PDP). The PDP would need to include a fairly detailed level of costing for dismantling the facility and would require separate regulatory approval. A review of the SAR and PDP would take six months to one year.

After submitting the SAR, a licensing process would proceed with an environmental screening carried out by the regulator to document the environmental effects of the project and determine any required additional environmental assessment. The expected environmental considerations for this facility would be low levels of airborne radioactivity from the irradiation of the shielded high flux e-linac targets and the contained airborne volatile activity when irradiating and processing the target. Neither of these is expected to pose an environmental hazard, especially if the facility is located on the order of one kilometre from its nearest neighbour (such as the present facilities at Chalk River). The complexity of the project likely means an allowance of about three months for the screening report and another several months to complete environmental sampling and measurements.

Once the environmental assessment requirements have been satisfied, the regulators would consider giving the approval to proceed. Licensing would proceed to a site preparation license, followed by a license to construct, and ultimately a license to operate. Assuming much of the legwork is done to a sufficient level of detail with the Safety Analysis report, the regulatory activities leading up to an operation license should not take more than a few months.

The issue of safeguards and operation of the facility within the CNSC security regulations in order to adhere to Canada's commitments to the IAEA will also need to be addressed. A barrier analysis would need to be performed to determine the level of security measures required at the facility. Because of the sensitive nature of this information it is best included in a separate document from the SAR. It will need to be reviewed separately. Additionally, cross-border shipping and receiving of radioactive materials would need to comply with regulations established by relevant agencies including the U.S. Nuclear Regulatory Commission.

# 3.4 Findings

A summary of the findings of the Task Force is provided here:

## Current Situation

- Although the historical supply from AECL-MDS Nordion has been reliable, the long-term supply of Mo-99 worldwide is at potential risk as it presently relies on two aging reactors that supply 90% of all production. Roughly half comes from Canada.[28]
- The risks can be reduced by having a greater number of reliable Mo-99 producers.
- North America has no replacement reactors under construction or at the advanced planning stage, though modifications to existing research reactors are being explored for isotope production. In Europe, the Jules Horowitz reactor (100 MW, LEU fuel) is being developed primarily for materials studies and could begin operation as early as 2014; it could be used for limited production of medical isotopes.
- A North-American reactor design with LEU core and targets does not exist; LEU targets are not yet used in North America, and no Canadian sites currently process LEU. Commercial success with LEU will require that LEU target processing be demonstrated on a large scale, all the major producers convert, and health regulators approve radiopharmaceuticals using LEU-derived Mo-99.
- National and regional supply of limited Mo-99 using LEU fuel and LEU targets has been demonstrated in Australia, Indonesia, South America, and Korea. Mo-99 recovery and refinement using LEU targets for large-scale commercial supply of Mo-99 is yet to be established, so comparison to that presently achieved with HEU targets is not yet possible.[29]

## Production Using a Photo-Fission Accelerator

- Based on preliminary calculations and numerical simulations, significant quantities of Mo-99 can be produced from natural uranium by photo-fission using accelerators. Several laboratory experiments are needed to establish efficiencies, equivalency of products, reliability of operation, and capacity.

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28 There are 4 main producers of Mo-99 worldwide that supply 95% of the global market. Covidien and IRE in Europe both rely on more than one reactor and make use of HFR Petten (Netherlands), OSIRIS (France), and BR-2 (Belgium). Global supply from the 4 main producers actually involves 5 different research reactors if SAFARI-1 and NRU are included in the above list.

29 Chile is probably 2 to 3 years from producing Mo-99 as are Poland, Romania, Libya, and Missouri. B&W LEU MIPS is also in the same time range.

- The technology exists to build an electron accelerator of suitably high beam power (2-3 MW) to produce a meaningful amount of Mo-99. A single multi-megawatt machine could supply the Canadian market or 5-7% of the North American market.
- A system of several machines would enhance reliability and boost Canada's competitiveness in the North American market.
- The conceptual design of a U-238 target system for efficient photo-fission and dissipation of the generated thermal power is not established, but the worldwide nuclear-physics community is actively developing multi-megawatt target systems.[30]
- The radio-chemistry needed to recover and refine the Mo-99 generated through photo-fission (from natural-uranium targets) most likely resembles that produced by a reactor using HEU targets. The similarity of the initial Mo-99 recovery step will be sensitive to the volume of the target for photo-fission which depends in detail upon optimization of design and performance parameters.
- Because of Mo-99's decay rate, yields from any production method are limited by the transportation times and distances between irradiation facilities, processing facilities, and generator plants. Losses could be reduced by co-locating the activities.
- The photo-fission accelerator option eliminates the security issues of transporting, storing, and disposing of HEU.

## Considerations Going Forward

- Health Canada and the U.S. Food and Drug Administration will need to approve the final Mo-99 product from a photo-fission accelerator for clinical use in North America.
- Licensing procedures must begin during the design stage and are likely to be straightforward for an accelerator. The full facility will likely be regulated as a Class IB Nuclear Facility (*e.g.,* MDS Nordion's facilities in Kanata, Ontario) as defined by Canadian Nuclear Safety Act regulations.
- There are substantial uncertainties in the capital cost and eventual operating costs for a reliable system of accelerator-based isotope production facilities, which require further assessment as experience is acquired from lower power experiments and feasibility tests.
- At present, construction of a photo-fission accelerator would take 3-4 years. Depending on the specific technology chosen for the accelerator, the construction costs, including labour, would be C$50 million, C$80 million, or $C125 million. Power would likely dominate operational costs.
- The total production cycle for medical isotopes includes the manufacture of targets for irradiation, storage of radioactive waste from target process-

30 See, for instance, J. Cornell, Ed., "The EURISOL Report," GANIL, Caen, 2003, European Commission-contract No. HRPI-CT-1999-50001.

ing, and hot-cell facilities to recover and refine Mo-99. These facilities are needed for any new production source of Mo-99 and would cost at least C$50 million.

- Accelerator-based Mo-99 production facilities would be quite focused; they would not allow for production of other non-fission-based medical isotopes and would not provide many of the additional R&D and commercial opportunities associated with present-day research reactors.

## 3.5 First Conclusion

**Accelerator-driven photo-fission of U-238 is an attractive approach for generating Mo-99 without security issues and with lower decommissioning costs at end of life. To ensure high reliability of supply, a half-dozen multi-megawatt machines could be built that would meet about 30%-50% of North American demand.**

The Task Force did not draw a conclusion about which technology (nuclear reactor or photo-fission accelerator) is "better" as this was beyond its scope. Rather, the Task Force analyzed the case for, features of, and development path for photo-fission accelerator technology. The Task Force concluded that this technology has a sufficient number of attractive features that it warrants further attention by public and private enterprises.

Canada has invested in the R&D capacity for exploring alternatives for producing Mo-99. The time is ripe to leverage these investments and support proof-of-principle demonstrations. Accelerator-driven photo-fission is a uniquely Canadian solution and offers much potential. If the Task Force estimates are borne out in the laboratory, several such machines could provide a combination of reliability and supply security. If developed and validated in the laboratory, this technology would support Canada's continued economic dominance in this world market.

# Chapter 4
# The Path Forward

4

# Chapter 4

# The Path Forward

# 4

# The Path Forward

The Task Force considered the initial steps necessary to develop the proposed technical solution into a production-ready technology. Laboratory measurements are required to verify proof-of-principles, to validate the technology, and to identify challenges to scalability.

## 4.1

## Benchmarks and Laboratory Validation

The Task Force examined existing laboratories, machines, and research activities to determine an effective strategy for moving forward. The electron linear-accelerator project proposed at TRIUMF (construction to begin in 2010 with operations beginning in 2013) offers a powerful laboratory to validate crucial aspects of the technology.

The most important validations of the proposed technology are (1) Completion of a full technical and engineering design of a full-scale machine, and (2) proof-of-principle demonstration of the accelerator and target system for producing Mo-99. Progress on both items can take substantial advantage of present ongoing efforts around the world.

Risks were ranked according to their potential impact on the project's key objective—a reliable source of medical isotopes, particularly Mo-99—and the estimated probability that such risk would occur. Above and beyond the need for developing a proof-of-principle demonstration in the laboratory, this technology would face additional hurdles before being viable.

The following three technical risks were discussed:

- Radionuclide purity of the medical isotope product;
- Supply reliability; and
- Isotope extraction efficiency.

The assessment of these risks is summarized in Table 4.1. The highest technical risk is in achieving high isotope supply reliability. The most significant technical risks were identified in the area of the bremsstrahlung converter and uranium target, where significant effort is needed in modelling and experimen-

tal verifications to minimize the potential impact of these risks on isotope supply reliability.

| Risk | Impact | Probability | Rank |
|---|---|---|---|
| Radionuclide purity | High | Low | Medium |
| Supply reliability | High | High | High |
| Extraction Efficiency | Medium | Medium | Medium |

**Table 4.1**: Technical risks.

### 4.1.1 Radionuclide Purity

The main medical isotopes produced in research reactors by fission of Uranium-235 (U-235) and used in nuclear medicine procedures are Molybdenum-99 (Mo-99), Iodine-131 (I-131), and Xenon-133 (Xe-133).

Fission fragment yield for thermal-neutron induced fission of U-235 has two peaks. One peak is for nuclei with mass between 90 and 100. The other peak is for nuclei with mass between 130 and 145. Fission fragment yield for photonuclear fission of Uranium-238 (U-238) will have a mass distribution similar to that of thermal-neutron induced fission of U-235. Chemical extraction processes currently used to extract Mo-99, I-131, and Xe-133 from uranium targets irradiated in research reactors will yield similar radionuclide purity with uranium targets that have been irradiated with bremsstrahlung from a 50 MeV electron beam. This conclusion, however, needs to be verified by computer simulations for the selected target geometry and validated with results from experimental verifications at low electron beam power to confirm the fission mass distribution, and possible contaminations due to a much larger mass of U-238 target.

The impact that would come from radionuclide impurities beyond the specifications for current medical products is high: the product is rejected for use. This issue could be resolved by adding chemical purification steps, but would require a development program be undertaken in advance to avoid potential delays in introducing the product to the market.

The estimated probability of impurities in a photo-fission-derived medical product is low, and whether a development program is required to add processing steps to remove impurities not encountered in thermal neutron induced fission, is qualified as medium.

Concerns were raised about production of Plutonium-239 (Pu-239) in the U-238 target and the associated accountancy requirements. The larger target volume and associated cooling fluid could provide a larger moderator body for fast secondary neutrons produced in the fission process. This could lead to the production of additional plutonium. These concerns could also be examined by computer simulations and chemical analysis of targets irradiated with a low power electron beam. At the present, due to the short irradiation times and the expected energies and flux of the associated secondary neutrons, the amount of

Pu-239 should not present a significant problem to solve. This challenge also arises in the use of LEU targets in a reactor.

In addition, results from experimental verifications at low electron beam power would address isotope yield and specific activities. At electron beam energies above 30 MeV, power scaling will be nearly linear.

### 4.1.2 Supply Reliability

The market expects on-time delivery of requested quantities of Mo-99. This expectation is driven by the short half-life of 66 hours for Mo-99 and requires the timely mobilization of several organizations between the production facilities to eventual delivery of a procedure to a patient.

The reliability target for the production facility should be greater than 98% on-time delivery of Mo-99 demanded by organizations preparing Technetium-99m (Tc-99m) generators. The 98% reliability target needs to be incorporated as a design requirement for the combination of the accelerator, accelerator window, bremsstrahlung converter, uranium target, and Mo-99 extraction processing equipment in the uranium target processing hot-cell facility and shipment of Mo-99 product to Tc-99m generator manufacturing facilities.

Accelerators used for research have availabilities greater than 80% (although notable exceptions are the new lights sources; for instance, the Advanced Photon source at Argonne operates with better than 95% availability), but the causes of downtime are broadly distributed and often involve activities related to research and development. Reliability analysis of accelerator components would identify areas where redundancy would increase accelerator reliability. Because the accelerator can be easily turned off and restarted, downtime events would likely have significantly less impact than that for a reactor.

A lower than expected reliability of Mo-99 supply would greatly affect the success of the proposed technology. The heat removal and thermal hydraulic behaviour of the accelerator window, bremsstrahlung convertor, and uranium target have high probability of affecting reliability. Engineering studies of the target and convertor configuration—including experimental verifications of target geometry at operating accelerator facilities—are needed to assess the merits of designs and of their expected reliabilities. The proposed converter target assemblies for the TRIUMF e-linac accelerator project, which will be designed to handle 0.5 MW power, will pave the way towards higher beam power assembly concepts.

The design of the hot-cell processing facility systems to extract radioisotopes and manage the highly radioactive waste from the chemical extraction process needs to incorporate the isotope supply reliability target. Reliability analysis of these systems would identify areas where redundancy is required to meet the Mo-99 supply reliability target.

The design of the target system and operation of the facility will need to consider the inconsistent demand for Tc-99m generators. The demand is usually greater at the start of the week. Because the Mo-99 inventory in a target will reach its maximum after about 13 days' irradiation and then decrease, the question of a single or multiple targets will need to be considered.

### 4.1.3 Extraction Efficiency

A uranium target used for photo-fission production of medical isotopes would require a mass of at least 200 g of depleted U-238 for thick target yield, depending upon the geometry of the target. The volume of the uranium target assembly may need to be large to address heat dissipation concerns.

The scalability and efficiency of current extraction process, with respect to Mo-99, I-131, and Xe-133 yield and radioisotope purity with 200 g uranium targets, require confirmation by tracer chemistry measurements. The concern is for Mo-99 breakthrough in the recovery columns at high uranium concentration in the chemically dissolved or digested target solutions. Argonne National Laboratory has worked on using LEU targets, which present similar challenges, and the chemistry developed can be a starting point for assessing these larger targets.

The impact and probability of difficulties with scaling existing extraction systems used for HEU and LEU targets and the extraction efficiency are estimated medium.

## 4.2 Second Conclusion

**A strong and focused R&D program is required to validate the use of a photo-fission accelerator for production of significant quantities of high-quality Mo-99.**

The Task Force discussed key scientific, technical, engineering, and operational challenges. An R&D program focusing on the following key work packages is crucial; some of these could proceed in parallel.

1. Produce, over about six months, a short conceptual design report on the optimal design of a high-power electron linear accelerator using photo-fission for production of Mo-99, including:
   a. The configuration and conceptual design of the highest technical risk items: the bremsstrahlung converter, uranium target, and accelerator beam window.
   b. The hot-cell facilities for processing targets and managing the processing waste.
   c. Required validation tests for the design.
   d. Modeling of accelerator uptime for reliability estimates.
2. Calculate capital and operating costs based on the conceptual design report and site considerations.
3. Verify photo-fission accelerator production of Mo-99 equivalency to

the present product using laboratory experiments.

a. Demonstrate Mo-99 yield.
b. Demonstrate Mo-99 recovery and refinement.
c. Demonstrate purity and specific activity.

4. Design a target facility capable of handling 2-3 MW of electron beam power.
   a. Include thermal and structural simulations.
   b. Indicate key validation tests and perform them as possible.

# 4.3 Recommendation

**The Government of Canada should support a Mo-99 Photo-Fission Accelerator Steering Group of public-private partners who select a project director and provide oversight. The director will be responsible for managing the preparation, coordination, and completion of R&D work packages funded through government and private sources according to an appropriate competitive process of scientific peer review.**

A steering group of public and private partners would bring together the skills, resources, and business sense required to develop the technology, oversee a proof-of-principle demonstration, and then assess and/or pursue commercial viability.

Work packages should follow from the R&D program outlined above. The project director would coordinate formulation of the work packages for submission, consideration, and review by the relevant sponsoring organizations. The completion of these work packages would lead the steering group to present a recommendation on the photo-fission accelerator technology within 3-4 years.

Laboratories around the world such as TRIUMF, Brookhaven National Laboratory and Oak Ridge National Laboratory in the U.S., and IPN-Orsay and GANIL in France have expertise and facilities that can be used immediately. TRIUMF is proposing to build a new accelerator as part of its decadal vision for research in nuclear physics, materials science, and nuclear medicine.[31] A low-power test to generate Mo-99 with a photo-fission accelerator on a timescale of a few years is possible at TRIUMF using this device as it will utilize the same basic technology. Although the total power will be lower (initially 100 kW in 2013 with an upgrade path to 0.5 MW), the device would enable detailed tests at full power density with a target matrix applicable to the Mo-99 photo-fission accelerator. The generated samples could validate beam-power requirements, isotope yields, target performance, chemical recovery, refinement, and purity of Mo-99. The activities at TRIUMF could be expedited.

31 TRIUMF, *Five-Year Plan 2010-2015: Building a Vision for the Future*, Vancouver, B.C.: TRIUMF, 2008.

# Appendix A

# Biographical Sketches of Task Force Members

# Appendix A

# Biographical Sketches of Task Force Members

**Nigel Lockyer (Co-convener), Director, TRIUMF and Professor, University of British Columbia**

Nigel S. Lockyer earned his B.S. from York University (Toronto) in 1975 and his Ph.D. in 1980 from Ohio State University. From 1980 to 1984, Dr. Lockyer was a postdoctoral fellow at the Stanford Linear Accelerator Center. Dr. Lockyer was an assistant professor of physics at the University of Pennsylvania from 1984 to 1990 and associate professor from 1990 to 1997. He was a visiting scientist at the SSC Laboratory from 1989 to 1990. From 1997 to 1998, Dr. Lockyer served as the Associate Chair for Graduate Affairs, and from 1997 to 2007, he was a professor of physics at the University of Pennsylvania. Since 2007, Dr. Lockyer has been the director of TRIUMF and a professor of physics at the University of British Columbia. Dr. Lockyer has also been spokesperson for the Mark-II Collaboration (1983-1984), the BCD Collaboration (1987-1993), co-spokesperson for the CDF Collaboration (2002-2004) and co-spokesperson for the SMTF Collaboration since 2005. Dr. Lockyer's research has focused on high-energy particle experiments, at the energy frontier, with an interest in testing symmetries and studying bottom and top quarks. More recently, his interest has been in lepton number violating and R-Parity violating supersymmetry searches. He has collaborated on proton therapy applications and medical physics detectors with colleagues at Brookhaven National Laboratory and the Hospital of the University of Pennsylvania. His research plans include participating in accelerator advances, including the Linear Collider. Dr. Lockyer's has chaired committees including the Nuclear Science Symposium in 2002, the NSERC Grant Selection Committee, the Canada Foundation for Innovation Review in 2006, and was Co-Chair of ICHEP2008. He has served on numerous grant-selection committees, laboratory advisory committees, and panels providing advice on public policy for the United States government. Nigel S. Lockyer is a Fellow of The American Physical Society and was awarded the American Physical Society W.K.H. Panofsky Prize in 2006.

**Thomas J. Ruth (Co-convener), Senior Research Scientist, TRIUMF and Senior Scientist, British Columbia Cancer Agency**

Tom Ruth graduated from St. Francis College in 1964 with a B.Sc. in Chemistry. In 1967, he earned his M.A. in Nuclear Chemistry at the College of William and Mary. At Clark University, he earned an M.A. in Chemistry and a

Ph.D. in Nuclear Spectroscopy, both in 1973. From 1989 to 2008, Dr. Ruth was the director of the PET Program at TRIUMF, and from 1996 to 2008 he was head of the Life Science Program. He has been a senior research scientist at TRIUMF since 1980; an adjunct professor at the University of British Columbia since 1984, Simon Fraser University since 1989, and the University of Victoria since 2002; and a research professor at Vancouver General Hospital since 1990. He teaches pharmaceutical sciences, chemistry, medicine, and physics and astronomy. He was an affiliated scientist with the B.C. Cancer Research Centre from 2005 to 2007, and he became a senior scientist in 2008. As PET director, Dr. Ruth had the responsibility of pulling together the varied technologies associated with the PET technique to perform *in vivo* biochemistry. Along with his colleagues, he has proposed a new method of producing large quantities of 18F-fluoirde; developed a method to perform the equivalent of an *in vivo* Scatchard analysis of PET data; demonstrated changes in turnover of fluorodopa; measured binding potentials (BP) associated the dopamine transporter; demonstrated that the placebo effect is associated with expectation resulting in dopamine release in Parkinson's patients; and described a method for inserting F-18 into large molecules for a more efficient approach to radiolabeling. Dr. Ruth is currently a member of the National Academy Sciences (NAS) Committee on the Production of Medical Isotopes without Highly Enriched Uranium. He was previously a member of the NAS Committee on the Status of Nuclear Medicine and a member of the Canadian Society of Nuclear Medicine's committee on the Regulation of PET Radiopharmaceuticals.

**Pierre Bricault, Group Leader, Ion Source Targets & Target Development, TRIUMF**

Pierre Bricault graduated from the Université Laval with a B.Sc. in physics in 1979. He received his M.Sc. and Ph.D. in physics from Université Laval in 1981 and 1986 respectively. From 1987 to 1988, Dr, Bricault was a research associate for the Commissariat à l'Énergie Atomique (CEA), in France. From 1988 to 1989, he was a research scientist at CNRS, and then from 1989 to 1993 he was a research scientist at CAE – GANIL in France. In 1993 he was a visiting research scientist at TRIUMF, then from 1993 to 2008, he became a TRIUMF research scientist. Since 2005 he has been an adjunct professor with Université Laval, and since 2008 he has been the TRIUMF Target/Ion Source Development Group Leader. Dr. Bricault is currently in charge of Research and Development for Radioactive Ion Beam (RIB) production and in charge of the system integration regarding the target station, mass separator and related systems at TRIUMF. Dr. Bricault is leading the design of the ISAC Drift-Tube-LINAC accelerator structures and the design of the ISAC mass separator and installation. He has collaborated with the 8,9,11Li charge radius measurement and the Superallowed beta decay studies at TRIUMF as well as mass measurements on highly charged radioactive ions with TITAN. In 1995, Dr. Bricault chaired the workshop on Ion Sources for Radioactive Ion Beams, and in 2000 he chaired the workshop on Laser Ion Sources for Radioactive Ion Beams. Dr. Bricault chaired the review committee for SPIRAL-II front end and mass separator in 2005, and he was a member of the CARIBU mass separator review committee. Since 2006 he has been a member of the Committee on International conference on Electromagnetic Isotope Separators and Techniques Related to their Applications.

**Mark de Jong, Director of Operations, Canadian Light Source Inc.**

Mark de Jong graduated from the University of Manitoba with a B.Sc. in Physics (Hon.) in 1974 and a Ph.D. in Accelerator Physics in 1981. From 1981 to 1999, Dr. de Jong was a staff scientist at the AECL Chalk River Laboratories in Ontario. As Acting Branch Manager of the Instrumentation and Control Branch from January 1997 to April 1998 and of the Control and Operations Technology Branch from April to August 1999, he managed the development programs in control and safety computer systems and instrumentation for existing and future CANDU nuclear power stations. Dr. de Jong was a project leader at the Canadian Light Source Inc. from September 1999 to December 2003, where he managed the technical development and construction of a 2.9 GeV electron synchrotron, storage ring and synchrotron light beam lines. Dr. de Jong is currently the Director of Operations at the Canadian Light Source Inc. He manages the operations of the 2.9 GeV electron storage ring, which includes oversight of the departments of Accelerator Operations and Development, Engineering and Technical Services, Controls and Instrumentation Development, and Information and Communication Technology.

**William Diamond, Senior Researcher, Chalk River Laboratories, AECL**

Bill Diamond earned his B.Sc. in Applied Physics from the University of Waterloo in 1969 and his Ph.D. in Nuclear Physics from the University of Toronto in 1974. From 1974 to 1975, Dr. Diamond was a National Research Council Postdoctoral Fellow at the Chalk River Nuclear Laboratories. From 1976 to 1978, he was a cyclotron physicist at the Nevis Laboratories at Columbia University. From 1978 to 1984, he was a member of the professional staff at Schlumberger-Doll Research. From 1984 to 1989, he was a senior accelerator physicist at CEBAF, now Thomas Jefferson National Accelerator Facility. From 1989 to April 1997, Dr. Diamond was a senior accelerator physicist at the Chalk River Tandem Accelerator SuperConducting Cyclotron Facility (TASCC). Since April 1997, he has been a senior researcher at the Mechanical Equipment and Seal Development Branch at Chalk River Laboratories. Dr. Diamond's research focuses on plasma physics of ion sources and he is an expert in vacuum high-voltage insulation. He has been involved in many projects including cyclotron ion source development; electron gun design and construction; R&D on miniature deuterium-tritium neutron generators for use in an oil well; R&D on the use of a 3.5 MeV-electron linac in oil-well logging applications; the design, prototyping and commissioning of the injector of the superconducting electron accelerator at the Thomas Jefferson Laboratory; negative heavy-ion source development at Chalk River Laboratories; and R&D on the electrostatic deflector of the Chalk River Superconducting Cyclotron. He conceived the idea of using photo-fission to produce Radioactive Ion Beams for the TASCC facility and proposed the use of photo-neutrons for Mo-99 production. Dr. Diamond has recently focused on the conceptual engineering and prototyping of components for the robotic fuel handling required for on-power operation of a CANDU reactor. He has also acted as Branch Manager for several periods. In addition to research, Dr. Diamond has served as Radiation Safety Officer at Nevis Laboratories and Schlumberger-Doll, and on the safety committees at Thomas Jefferson and Chalk River Laboratories.

**Marik Dombsky, Group Leader, ISAC Targets, TRIUMF**

Marik Dombsky graduated from Simon Fraser University with a B.Sc. in 1979 and a Ph.D. in Chemistry in 1990. Since 1996, Dr. Dombsky has been a research scientist in TRIUMF's ISAC Beam Development Group. He is an expert in the development of intense beams of radioactive nuclei. While at TRIUMF, he has developed the world's most intense on-line beams of both very short-lived (e.g. 11Li, $t_{1/2}$ = 8.4 ms) and long-lived (26gAl, $t_{1/2} = 7.1 \times 105$ y) radionuclides. He works on experimental programs on fundamental symmetries, precision mass measurements and fusion reactions with light neutron-rich nuclei. Dr. Dombsky is involved with external collaborations, including those with the ISOLDE Targets & Ion Sources Group at CERN, Geneva; the European Isotope Separation On-Line Radioactive Ion Beam Facility (EURISOL) Direct Target Task Force 3; and the RIB Targets Group at the Holifield Radioactive Ion Beam Facility, Oak Ridge National Laboratory. Dr. Dombsky's studies include the topics of refractory elements and compounds, surface interactions at high temperature, radiation enhanced diffusion, solid-gas phase equilibria and formation of both stoichiometric and sub-stoichiometric molecular species under intense irradiation conditions. He was a consultant to the OECD Megascience Forum Working Group on Nuclear Physics' Study Group on Radioactive Nuclear Beams at both the Rutherford-Appleton Laboratory, Didcot, UK and at TRIUMF. He was also a consultant to the DOE/NSF Nuclear Science Advisory Committee (NSAC) Rare Isotope Accelerator (RIA) ISOL Task Force. Dr. Dombsky has published more than 100 papers and given invited talks in Canada and around the world.

**Phil Gardner, Director, President and Chief Executive Officer, Advanced Applied Physics Solutions (AAPS), Inc.**

Philip L. Gardner earned his B.A. and M.A. in British Columbia, a Diploma in Finance from the University of Calgary, and a Diploma in Business from Michigan State University. For the past 12 years, Mr. Gardner was the Head of the Technology Transfer Division at TRIUMF, and was responsible for the daily production of medical isotopes for delivery throughout North America and to international locations. Mr. Gardner has more than 30 years experience in the private, public, and research technology sectors of the economies of Europe and Canada. He has served on many national and international Boards of Directors, committees, awards committees, corporate advisory boards, and community organizations. He has published over 50 academic articles, several of which have received international awards, and has taught at universities in Canada and overseas, and presented a report on technology to the OECD in Paris. He is and has been a member of numerous professional and community organizations.

**Shane Koscielniak, Senior Research Scientist, TRIUMF**

Shane Koscielniak graduated from Cambridge University with a B.A. in Natural Science in 1983. In 1987, he earned his Ph.D. from Oxford University. From 1987 to 1991, Dr. Koscielniak was a research associate at TRIUMF. Since 1992, he has been a TRIUMF research scientist. In 2008, he became an adjunct professor at the University of Victoria. Dr. Koscielniak's research interests have led him to contribute to the stability of heavily particle-beam-loaded RF systems by formulating Robinson stability criteria, introducing the concept of coherent RF bucket, formulating stability criteria in the presence of

multiple layer control loops, and influencing delays in direct vector-type feedback employed to reduce the apparent impedance of the cavity. He has been invited repeatedly to CERN and KEK as an expert. He was also the principal in the beam dynamics and vane design of the TRIUMF ISAC RFQ, contributing many ideas to the electromagnetic design. In addition, he has observed and analyzed space-charge induced solitons at the CERN PS Booster, and he was an important contributor to FFAG accelerators by formulating a general principle for accelerating over a range spanning multiple fixed points. FFAGs are proposed for muon acceleration in high-energy physics and hadron acceleration in medical applications for cancer therapy. Dr. Koscielniak has been a member of the CONFORM Board of management since 2007; the International Linear Collider Global Design Effort since 2005; and Chair of the Scientific Program Committee of 2009 Particle Accelerator Conference since 2008. He chaired the North American Meeting on FFAG Accelerators in 2004.

**Jean-Pierre Labrie, Director, Special Projects, Commercial, Client Interface, Atomic Energy of Canada Limited**

Jean-Pierre Labrie earned his Ph.D. in Nuclear Physics from l'Université de Montréal in 1979. He has 27 years experience in the nuclear industry, including having led research and development programs, restructured and managed medical isotopes production, and negotiated contracts for major nuclear projects. The projects he manages include all phases of licensing, design, procurement, construction, commissioning and operation of particle accelerators, research reactors and hot-cell facilities. Dr. Labrie has both Canadian and international experience.

**Sandy McEwan, Department of Oncologic Imaging, Cross Cancer Institute, and University of Alberta**

Dr. Alexander (Sandy) McEwan, MBBS, FRCPC, is the Chair of the Department of Oncology at the University of Alberta and Associate Director (Research) at the Cross Cancer Institute, where he is also Professor and Director of the Department of Oncologic Imaging. He has published widely in the field of nuclear medicine. Dr. McEwan was the recipient of a McCalla Professorship at the University of Alberta in 2001, a former President of the Canadian Association of Nuclear Medicine and is past President of the Society of Nuclear Medicine. He graduated from Middlesex Hospital Medical School, London University, England, in 1975, and earned his M.Sc. there in Nuclear Medicine in 1981, and became an FRCPC in Nuclear Medicine in 1986. After serving as Medical Officer in the Royal Navy and as Registrar in Oncology in Auckland, New Zealand and senior registrar in Nuclear Medicine at Southampton General Hospital, U.K., he emigrated to Canada in 1986. In addition to his leadership duties as Chair and his administrative, teaching and clinical activities, Dr. McEwan is active on many committees. His research interests include radioisotope therapy and very low dose rate radiation effects, novel radiopharmaceuticals, clinical trial development of novel molecular imaging agents and imaging biomarkers. Dr. McEwan has been instrumental in the development of the Positron Emission Tomography (PET) Programme at the Cross Cancer Institute.

**Lia Merminga, Head, Accelerator Division, TRIUMF**

Dr. Merminga earned a B.Sc. in physics from the University of Athens, Greece in 1983, and a Ph.D. in physics from the University of Michigan physics in 1989. She worked at the Stanford Linear Accelerator Center from 1989 to 1992, and joined Jefferson Lab in 1992, first as a staff scientist and later as the Director of the Center for Advanced Studies of Accelerators. Her research interests include advanced accelerator systems and nonlinear dynamics, with a recent focus on the design and development of energy recovery superconducting radio-frequency linear accelerators and their applications to high-power free-electron lasers, synchrotron radiation sources, and electron-ion colliders for nuclear and particle physics. She has served on two U.S. National Academy of Sciences (NAS) committees (Plasma 2010 and Scientific Assessment of Free Electron Laser Technology for Naval Applications) and was a member of the NSAC 2007 Long Range Plan writing group. She is currently serving on several machine advisory committees and on the editorial board for "Physical Review Special Topics – Accelerators and Beams" (PRST-AB). Dr. Merminga is a Fellow of the American Physical Society.

**Saed Mirzadeh, Isotope Development Group, Nuclear Science and Technology Division, U.S. Oak Ridge National Laboratory**

Saed Mirzadeh joined the ORNL Nuclear Medicine Program in 1989, and in 2006 he was promoted to Distinguished Staff Scientist. Mirzadeh earned his B.Sc. in chemistry from the National University of Iran in 1969, and his Ph.D. in Physical Chemistry (Radiochemistry) from the University of New Mexico in 1978. After a short postdoctoral position at Los Alamos National Laboratory (LANL), Medical Radioisotope Program and a two-year research associate position at Brookhaven National Laboratory (BNL), Chemistry Department, he joined the BNL Medical Department, where he developed methods of producing medical radioisotopes at BNL 200 MeV proton LINAC (1982-1987). During 1985–1987, he held an adjunct associate professorship in the Chemistry Department, Natural Sciences Division, Long Island University. During 1987-1989, he joined Radiation Oncology, National Cancer Institute, National Institutes of Health (NIH). In 1993, Mirzadeh was a visiting scientist at the Australian Nuclear Science and Technology. Mirzadeh's main interest is in the use of alpha particles in radioimmunotherapy of micrometastases. Other interests include: encapsulation of radioactive metal ions in chelating ligands, hot atom chemistry of endohedral-fullerenes containing radioactive metal ions; applications of radio-metallo-fullerenes and nano-particles in medicine, and as a potential nano-power source. Mirzadeh is a member of the editorial board of the Journal of Applied Radiation and Isotopes. He is also a member of Divisions of Nuclear Chemistry and Technology (DNCT), and Physical Chemistry (1979-present), of the American Chemical Society (ACS), and a member of American Nuclear Society (2000-present). His awards include: 2007 ANS Glen Seaborg, 2005-06 co-recipient ORNL LDRD, 1999 co-recipient Scientific Achievement (ORNL Life Sciences Division), 1998 co-recipient R&D-100, 1996-97 co-recipient ORNL LDRD, 1994 Lockheed Martin R&D Achievement, and 1984-85 co-recipient BNL Director R&D.

**Herb Moore, Senior Research Scientist, Dupont (retired)**

Herbert Moore is a professional nuclear/ radiochemist with extensive experience related to nuclear weapons, naval power reactors and radiopharmaceuticals. He was a senior research scientist in radiopharmaceuticals for Hoffmann La Roche and Du Pont. In that capacity he developed processes for accelerator medical isotope production, i.e., Tl-201, Ga-67, Ge-68, etc. He also helped develop several Tc-99m-based radiopharmaceuticals including Cardiolite and Neurolite. At Hoffmann La Roche he helped develop the low specific activity neutron Mo-99 extraction method for preparing Tc-99m Insta-Tc. At Du Pont he acquired, examined and evaluated every commercially available Tc-99m generator, contributed to redesigning Du Pont's fission Mo-99 generator, and generator production facilities, and evaluated the new generator's performance with their end-users. He served as Du Pont's senior scientific liaison to Chalk River and Kanata on issues associated with Mo-99 supply and quality and to the Missouri University Research Reactor for other isotopes produced with the MIT reactor. Since retiring, he has focused on photonuclear production of radionuclides with potential for targeted radiotherapy of cancer, and development of a labelled-peptide-based targeted treatment for melanoma. Aspects of those efforts have been funded through NCI, and DOE grants. He continues to consult with several private companies, universities, U.S. national laboratories and foreign organizations.

**Jean-Michel Poutissou, Associate Director, TRIUMF**

Jean-Michel Poutissou graduated from the Institut National des Sciences Appliquées (INSA) in Lyon with an Engineering Physics degree in 1965. He earned his M.Sc. and Ph.D in Nuclear Physics from l'Université de Montréal in 1968 and 1972, respectively. Dr. Poutissou was a postdoctoral fellow at l'Université de Montréal in residence at TRIUMF from 1972 to 1978. Since 1978 he has been a research scientist at TRIUMF, and since 1988 he has been the associate director and science division head at TRIUMF. Poutissou helped found the collaboration and the Canadian group for the T2K-ND280 experiment, and serves as a member of the T2K's Executive Committee. He is a founding member of the international collaboration of TWIST, and developed the trigger system and special fine degrader for the experiment. He participated in the E787 experiment, providing the initial end cap photon detectors, and helped develop the "Long Baseline Neutrino Oscillation at the AGS, E889" proposal at TRIUMF. Poutissou has served on the RIKEN International Advisory Committee in Japan since 2007 and the J-PARC International Advisory Committee in Japan since 2002. He has been chair of the KEK – Muon Science Advisory Committee since 2003. He chaired the KEK – IMMS International Review Committee in 2004 and 2008, the KEK – Muon Technical Advisory Committee from 2004 to 2006, and the Weak Interaction Committee for LAMPF from 1992 to 1995. In 2006, Poutissou was conferred the French Chevalier de la Légion d'honneur.

**John Root, Director, NRC Canadian Neutron Beam Centre**

Dr. John Root graduated with a Ph.D. in condensed matter physics from the University of Guelph in 1986, having elucidated some of the quantum effects on the structure of water. He joined Atomic Energy of Canada Limited, working with the Neutron and Solid State Physics branch on the then-new program called Applied Neutron Diffraction for Industry (ANDI). In 1998, Dr. Root was made a Program Leader, responsible for the neutron beam facility at Chalk River, which had been transferred to the NRC in 1997. In 2003, he was appointed Director of the facility, which is now called the Canadian Neutron Beam Centre. Some of Dr. Root's contributions to science and technology have included *in-situ* investigations of hydride precipitation and dissolution in zirconium alloys, investigations of solid-state reactions during sintering of metal-matrix composites, new insights about the phase transitions in steel, and application of neutron diffraction methods to evaluate fitness-for-service of components in nuclear reactors. Along with his responsibilities of managing the CNBC as an international user facility for materials research, Dr. Root is currently coordinating an NRC discussion among stakeholders and users of a possible future Canadian Neutron Centre to take over the three missions of the NRU reactor.

**Dave Tucker, Senior Health Physicist, McMaster University**

David Tucker has over 20 years of research in reactor health physics and licensing experience, gained at the NRU and NRX reactors at Chalk River and at the McMaster Nuclear Reactor. For the past ten years, David has been employed at McMaster University as the Senior Health Physicist, responsible for managing the radiation safety program for the University's reactor, accelerators and laboratories. He is also responsible for teaching graduate health physics courses in the Faculties of Science and Engineering and for providing services and consultation to industry and government through the McMaster Institute of Applied Radiation Sciences. Dave has a B.Sc. in Health and Radiation Physics and an M.Sc. in Medical Physics from McMaster University. He is an American Board of Health Physics (ABHP) Certified Health Physicist and holds Registration with the Canadian Radiation Protection Association (CRPA) and the National Registry of Radiation Protection Technologists (NRRPT). Dave is currently the President-Elect of the CRPA, a member of the ABHP Panel of Examiners and a member of the Board of the NRRPT.

**Anne Trudel, Head, Environment, Health and Safety, TRIUMF**

Anne Trudel has extensive experience with radiation protection and low- and high-energy physics. She is the liaison for TRIUMF with the Canadian Nuclear Safety Commission, which monitors and audits every aspect of TRIUMF's many activities. In addition she is accountable to WorkSafe BC for the health, safety and welfare of the TRIUMF staff. Anne and her team ensure both industrial and radiation safety for employees, while maintaining environmental protection requirements and providing technical expertise to the TRIUMF scientists.

**John Valliant, McMaster Institute of Applied Radiation Sciences and Centre for Probe Development and Commercialization**

John Valliant is an Associate Professor of Chemistry and Medical Physics, the Acting Director of the McMaster Institute of Applied Radiation Sciences, and the Scientific Director of the Centre for Probe Development and Commercialization. The Valliant research group specializes in R&D of new radiopharmaceuticals, including developing new methods for the expedient discovery of targeted probes and preparing agents in high yield and purity for clinical use.

**George Vandegrift, Distinguished Fellow, U.S. Argonne National Laboratory**

Dr. Vandegrift is an Argonne Distinguished Fellow in the Chemical Sciences and Engineering Division of Argonne National Laboratory, where he has been for 35 years. Over that period, he has served as group leader, section head, department head, and associate division director. He is considered a world expert in the areas of (1) separation processes for radioisotope production, radioactive waste treatment, and industrial applications; (2) development of technology to convert Mo-99 production from high-enriched uranium to low-enriched uranium as part of the Global Threat Reduction—Conversion Program; and (3) development of processes for treating spent nuclear fuel in support of the Global Nuclear Energy Partnership. He has almost 200 journal articles, book chapters, reports, and patents in basic chemistry and applied topics associated with these areas. He has helped develop processes to convert fission-product Mo-99 production from high-enriched to low-enriched uranium since 1986 and has led this program since 1994.

**Dennis Wester, Director, Applied Research, MDS Nordion**

Dennis Wester is currently Director, Applied Research, at MDS Nordion's Vancouver Operations. Prior to this position, Dr. Wester was employed at the U.S. Department of Energy's (DOE) Pacific Northwest National Laboratory, where he was the site representative for the National Isotope Program and played key roles the development and commercialization of a process for Y-90 production, manufacture of Pb-212 generators, and purification of kilocurie quantities of Sr-90, among other projects. In addition, Dennis has worked at NeoRx Corp. on the radiolabeling of monoclonal antibodies, Mallinckrodt Medical on the design and synthesis of Tc complexes for myocardial imaging, and the DOE's Argonne National Laboratory on the fundamental chemistry of actinides and lanthanides. He holds a Ph.D. in Inorganic Chemistry with a minor in Russian from the University of Florida and a B.Sc. in Chemistry from the University of Missouri-St. Louis.

**Ann Fong (Executive Staff), Corporate Secretary, AAPS, Inc.**

Ann Fong has been involved with Technology Transfer at TRIUMF for the past 12 years. She was most recently the Manager of Intellectual Property and Technology Commercialization. She was responsible for the management of TRIUMF's patent portfolio and commercial contracts. She also has experience assisting start-ups/spin-offs with patent protection, company formation, identification of management needs and business plan writing. Mrs. Fong has a B.A. from the University of British Columbia and an M.B.A. from Queen's University. She has served on a number of TRIUMF internal committees, including an employee representative committee, the TRIUMF Board of Man-

agement Technology Transfer Sub-committee, a TRIUMF Re-Organization Task Group, and the 2010-2015 Five-Year Plan Steering Committee.

**Timothy I. Meyer (Executive Staff), Head, Strategic Planning and Communications, TRIUMF**

Dr. Meyer earned a B.A. in Physics and Mathematics from Johns Hopkins University in 1996 and finished his graduate work with Stanford University in 2002. Before joining TRIUMF in 2007 as head of its Strategic Planning and Communications Division, Meyer was a senior program officer at the National Academies (2002-2007). He received a Notable Achievement Award from the Division on Engineering and Physical Sciences in 2003 and a Distinguished Service Award from the National Academies in 2004. His portfolio included projects such as EPP2010, the Rare Isotope Science Assessment Committee, Plasma 2010, and the MRSEC Impact Assessment Committee. From 1996 to 2002, Dr. Meyer was a research associate at the Stanford Linear Accelerator Center. His doctoral thesis concerned the time evolution of the B meson in SLAC's BaBar experiment. His work also focused on radiation monitoring and protection of silicon-based particle detectors. During his time at Stanford, Dr. Meyer received both the Paul Kirkpatrick and the Centennial Teaching awards for his work as an instructor of undergraduates. Dr. Meyer's work involves assisting public policymakers in understanding the choices they face for supporting scientific research as well as working with scientists and research institutions to articulate their future strategies.

# Appendix B

# Agenda of the Workshop

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## Task Force Workshop
## October 19–20, 2008
## TRIUMF, 4004 Wesbrook Mall, Vancouver, BC

### Sunday, October 19, 2008

18:45 Convene at TRIUMF, Hot Spot Café
19:00 Working dinner
Opening Remarks and Welcome
—Stephen Owen, VP External, Legal, and Community Relations, UBC
20:30 After-dinner speaker (adjourn to Auditorium)
Introductions, including statement of expertise (~2 min each)
Overview of Health Canada Report
—Sandy McEwan
21:30 Adjourn (Transport to hotels via carpool and TRIUMF shuttle)

### Monday, October 20, 2008

07:00 Depart for TRIUMF (via carpools and TRIUMF shuttle)
07:30 Breakfast (Auditorium)
08:00 Logistics for the Day and Charge to the Task Force
—Tim Meyer, Ann Fong
08:15 Issues with existing Mo-99 production, including HEU, aging reactors, licensing,
—Tom Ruth
08:30 How much Mo-99 is produced in NRG & NRU from U-235 fission? What is Canada's need and 50% of world (North America)?
—Chris Heysel, George Vandegrift
08:45 Yields from alternative modes of production – photofission of U233/U235/U238 (yield per photon). Also photoproduction via Mo-100 ($\gamma$,$n$).
—Bill Diamond, Herb Moore, Marik Dombsky, Pierre Bricault
09:30 Discussion
09:45 Coffee break

10:15 Efficiency factor associated with Chemistry including chemical yield, waste from various targets U233/U235/U-238/Mo-100 (result is Mo-99/photon after separation). How many photons are required to match the output for Canada and 50% of the world (North America)?
—George Vandegrift, Saed Mirzadeh

10:45 Discussion

11:00 Break out sessions

A: Design. What are the design specifications of an e-linac and number of e-linacs that meets the no. of photons needed? What is the expected cost of machine, including capital costs, tunnel, enclosures, and operating costs? Time scale for building? Years to amortize? Calculate the total cost of producing one 6-day Curie of Mo-99.
—Mark de Jong, Lia Merminga (leads), Pierre Bricault, Shane Koscielniak, Bill Diamond, Dennis Wester, John Valliant, John Root, Nigel Lockyer

B: Demonstration. Provided the TRIUMF e-linac will be operational by 2013 as a demonstration machine, what experiments would be required as proof-of-principle? Yields, specific activities, power scaling issues, other issues, etc. What other labs and devices around the world could provide needed benchmarks?
—Jean-Pierre Labrie (lead), Jean-Michel Poutissou, Saed Mirzadeh, Chris Heysel, Herb Moore

C: Regulation. Citing of facility – location, licensing, HC and FDA concerns—what is needed beyond a Drug Master File?
—Sandy McEwan (lead), George Vandegrift, Anne Trudel, Abdul Alwani, Rod Huggins, Dave Tucker

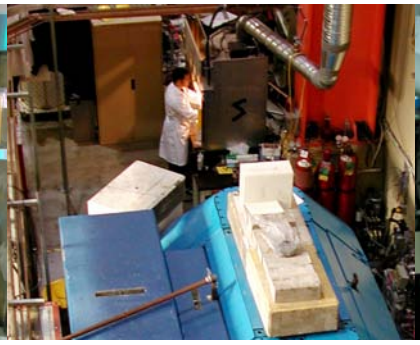
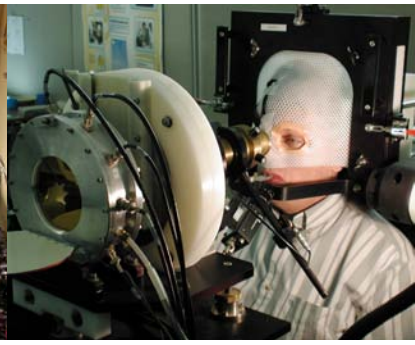
12:30 Working lunch — 15-min reports from breakout sessions

13:30 Round-table discussion
What model do we use to move forward?
— John Valliant (lead), Phil Gardner, Sandy McEwan, Lia Merminga, Dennis Wester, Tom Ruth

14:15 Writing the report: structure of report, draft conclusions, writing assignments
—Tim Meyer, Ann Fong

14:30 Adjourn (Transport to hotels, airport via carpool, taxi)



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