TRIUMF
Canada's National Laboratory for Particle and Nuclear Physics
Laboratoire national canadien pour la recherche en physique nucléaire et en physique des particules

Briefing Note
Submitted to Standing Committee on Natural Resources

By **Nigel S. Lockyer, Director, on behalf of TRIUMF**

Summary

Canada is facing a crisis in the supply of the world's chief medical isotope—Molybdenum-99 (Mo-99). The daughter product of this isotope (Tc-99m) is combined with biological molecules and used in more than 85% of the world's nuclear-medicine procedures; Canada has provided the majority of the global supply through its NRU reactor at Chalk River, Ontario, for decades.

This crisis is neither permanent nor untenable: Canada has options—options not only to address the immediate healthcare crisis but also to maintain a medium to long-term economic competitive advantage in this global industry. Two separate but related questions frame all discussions of solutions.

- How else can one produce Mo-99?
- What else can one use besides Mo-99 (in the clinic)?

As a national laboratory with expertise and excellence in accelerators and nuclear medicine, TRIUMF is actively pursuing answers to both questions with partners such as BC Cancer Agency, Terry Fox Institute, Cross Cancer Institute, Advanced Applied Physics Solution, Inc., MDS Nordion, and PAVAC, Inc. Over the past decades, TRIUMF designed many of the cyclotrons presently used in Canada and around the world for isotope production.

Alternative Production Methods. TRIUMF is developing a new "Made in Canada" technology in partnership with MDS Nordion that uses accelerator-driven photo-fission and non-weapons-grade uranium to produce Mo-99 in a manner that easily integrates with the existing supply chain. A technical demonstration is scheduled for 2012 with pilot commercial production by a third-party technology licensee expected by 2015. Such an accelerator system producing sufficient Mo-99 for Canada's domestic needs would cost $50 million to design and build.

TRIUMF is also contributing to the exploration of accelerator-based alternatives that avoid the use of uranium altogether and involve dramatically different supply-chain models. These techniques require new technologies for purifying and creating the target materials as well as new technologies for efficient separation and purification of the Mo-99. One led by National Research Council and Mevex Corp. would irradiate Mo-100 to produce Mo-99, the proposed-chain model obviates the need for the U.S. Mo-99/Tc-99m "generators" manufacturing step by placing an accelerator at each point-of-use. A second option being led by Advanced Applied Physics Solutions, Inc., uses an accelerator to irradiate Mo-98 to produce Mo-99; the key technical challenge is extracting and purifying the Mo-99.

Alternatives to Mo-99. Mo-99 has remained the dominant isotope for medical imaging because the historical legacy of the supply chain has given it economic advantages in production and distribution. The isotope also has chemical properties that make it easy to work with for preparing the final Tc-99m radiopharmaceutical products used in patients. The corresponding imaging technology (called SPECT) is relatively straightforward to purchase, deploy, and operate; as a result, it has dominant market penetration. Using accelerators known as cyclotrons, TRIUMF produces other medical isotopes as part of its ongoing research program (e.g., Ga-67, C-11) and as part of its 30 year manufacturing partnership with MDS Nordion (e.g., Tl-201, I-123, Ge-68). With its partners, TRIUMF is advancing the development of alternative medical-isotope products that require SPECT imaging technology as well those that use next-generation PET imaging technology. Many of the "PET isotopes" would be clinically superior to current Mo-99/Tc-99 products. TRIUMF is also actively involved in the development of next-generation cyclotrons that could be inexpensively sited at every hospital across Canada to meet nearly all clinical needs for medical isotopes.

TRIUMF is Canada's national laboratory for particle and nuclear physics. It is owned and operated as a joint venture by a consortium of Canadian universities via a contribution through the National Research Council Canada with building capital funds provided by the Government of British Columbia. Its mission is:

- To make discoveries that address the most compelling questions in particle physics, nuclear physics, nuclear medicine, and materials science;
- To act as Canada's steward for the advancement of particle accelerators and detection technologies; and
- To transfer knowledge, train highly skilled personnel, and commercialize research for the economic, social, environmental, and health benefit of all Canadians.

TRIUMF was opened forty years ago by Simon Fraser University, the University of British Columbia (UBC), and the University of Victoria to meet research needs that no single university could provide. The University of Alberta joined the TRIUMF consortium almost immediately. There are currently eight full members and six associate members from across Canada in the consortium that governs TRIUMF.

Since its inception as a local university facility, TRIUMF has evolved into an internationally renowned laboratory while strengthening ties to the research programs of the Canadian universities. The science program has expanded from nuclear physics to include particle physics, molecular and materials science, and nuclear medicine. TRIUMF provides research infrastructure and tools that are too large and complex for a single university to build, operate, or maintain. There are over 350 scientists, engineers, and staff performing research on the TRIUMF site. It attracts over 500 national and international researchers every year and provides advanced research facilities and opportunities to 150 students and post-doctoral fellows each year.

TRIUMF's operations are primarily supported by five-year contributions from the Government of Canada, enhanced by research grants and awards from NSERC, CFI, CIHR, and other agencies. The present cycle of funding completes in 2010. Working together with the scientific community and its patrons, TRIUMF has proposed a new five-year plan for 2010-2015. The new plan requests an enhanced level of investment of $328 million over the five-year period coupled with a capital infrastructure project of $60.7 million.

TRIUMF's new vision brings together university, industrial, and international partners in three priority areas with the promise of true competitive advantage. For the next decade, TRIUMF is focusing on the development and deployment of two platform technologies: radiochemistry & bio-markers for nuclear medicine and superconducting radio-frequency cavities (SRF) for next-generation accelerators. Nuclear medicine is undergoing a revolution and has great potential for dramatically improving health care for all Canadians while trimming costs. Using nuclear medicine, doctors are able to image detailed disease metabolism within the body, before, during, and after treatment, dramatically improving success rates. SRF technology has widespread applications, ranging from next-generation accelerators for research in materials, nuclear and particle physics, production of medical isotopes, and environmental remediation through "scrubbing" of flue gases. TRIUMF has partnered with PAVAC Industries, Inc., in Richmond to develop the first "Made in Canada" SRF device—one of only 5 teams in the world with this capability.

Background

Medical isotopes allow clinicians to see what is happening inside the body non-invasively and at a molecular level. Canada has a dominant position in the roughly $4 billion global business of medical isotopes contributing more than 50% of the world's "raw material" isotope supply. Canada has the potential to be a leader not only in the next generation of raw material medical isotopes, but also in developing added-value isotopes that will drive market growth with substantially enhanced capabilities. If Canada does not aggressively maintain its market position, this growing business (and its direct impact on health and wellness) will slip away from Canada.

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. 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 external to the body and used to pinpoint its location. By chemically connecting the medical isotope to a biomolecule and injecting the compound into the human body, one can then "see" where the body is using that biomolecule. The main tools for molecular imaging are the SPECT and PET scans that image the decay particles from the medical isotopes.

Molecular imaging allows the physician to understand what is happening inside the body at a biochemical level. An MRI or CT scan cannot, for instance, tell if a patient is dead or alive because it only shows anatomy and structure. A PET or SPECT scan indicates what is happening chemically and biologically inside the body.

Canada is a world leader in the production of medical isotopes. Nearly 30 million nuclear medical procedures are performed annually around the world, half in North America. Over 80% of these procedures use Mo-99, the most widely used medical isotope. The long term supply of Mo-99 has become unreliable due to the fact that most production derives from two aging research reactors, one in Canada (NRU) and one in the Netherlands (Petten). Furthermore, these reactors must use weapons-grade (92% pure U-235) highly enriched uranium (HEU) targets to produce Mo-99, raising concerns by the world community about proliferation. Consequently, any new reactor solutions have been strongly encouraged to use low enriched uranium (LEU) targets. At present, no large-scale demonstration of using LEU to produce Mo-99 exists.

Where do medical isotopes presently come from?

Generally speaking, medical isotopes come either from nuclear reactors or special particle accelerators known as cyclotrons. TRIUMF is a world leader in the design and development of cyclotrons; many of the cyclotrons presently in use in Canada and around the world are based on TRIUMF technology.

Tc-99m comes from the parent atom Molybdenum-99 or simply Mo-99. Mo-99 is produced in nuclear reactors (such as Canada's NRU reactor at Chalk River) by irradiating highly enriched "weapons-grade" uranium which is then processed and shipped to hospitals and clinics all over North America. The Mo-99 has a fairly long half-life (it takes on average 66 hours for half of a sample of Mo-99 to decay to Tc-99m). The Tc-99m is used at the hospitals and clinics to create the radiopharmaceuticals used in patients.

Cyclotrons generally produce a very different set of isotopes, typically shorter-lived PET isotopes. MDS Nordion Vancouver Operations (based at TRIUMF) currently operates three cyclotrons 24/7 365 days a year to produce non-Mo-99 medical isotopes primarily for export. Total production exceeds 2.5 million patient doses per year.

What is the future of medical isotopes?

Two categories of development are driving the future business of medical isotopes. Canada has a strong position in both.

- The emerging technology of PET which will eventually supplant the current SPECT technology.

- The development of more and more advanced "radiotracers" (medical isotopes with the added-value of sophisticated biomolecules) which will allow clinicians to quickly and precisely identify—and eventually treat—cancer and neurodegenerative disease in patients.

SPECT technology stands for Single Photon Emission Computed Tomography and uses a particular set of medical isotopes (*e.g.*, Tc-99m) and a particular type of camera. PET technology stands for Positron Emission Tomography and uses different medical isotopes (*e.g.*, F-18) and a different camera. There are several medical isotopes, and the number is growing, that are imaged with a PET camera. At present, SPECT is lower resolution but cheaper than PET. As a result, nearly every hospital in North America has a SPECT system.

PET and SPECT scans differ by the type of decay of the isotope and therefore use different "cameras" to image or "scan" the patient. SPECT is the better established modality and is prevalent in every hospital and is presently cheaper than PET. PET offers higher resolution scans and access to more sophisticated biology in the body. PET isotopes produce two decay products instead of one for SPECT isotopes, meaning they produce a stronger signal that can more easily be detected using medical imagers. It's this improved imaging, and not the isotope shortage, that is behind a recent move towards in-hospital cyclotron facilities across the country.

It turns out that PET isotopes are easier to work with than Tc-99m, and so more molecules are available for PET than SPECT with Tc-99m. As the number of these special molecules increases, hospitals are increasingly buying PET cameras rather than SPECT. Last year in the U.S., sales of PET were greater than SPECT for the first time. The number of installed SPECT cameras is about 10 times greater than PET, but the gap is closing rapidly.

The half life of PET isotopes is usually quite short. The most widely used PET radiotracer is FDG (F-18-fluro-deoxyglucose, with a roughly two-hour half-life), an isotope-labeled sugar, however there are several other "radiotracers" that are emerging for use in cancer diagnosis, staging, and therapy. For example, FES (fluoroestrodiol) is a PET radiotracer and determines whether a breast cancer tumour has estrogen receptors. If this is the case, then the doctor orders a particular therapy: hormone therapy, benefitting the patient and saving the cost of an incorrect and ineffective therapy.

Alternative Methods for Producing Mo-99

The present-day Mo-99 supply chain can be described as shown in Figure 1.

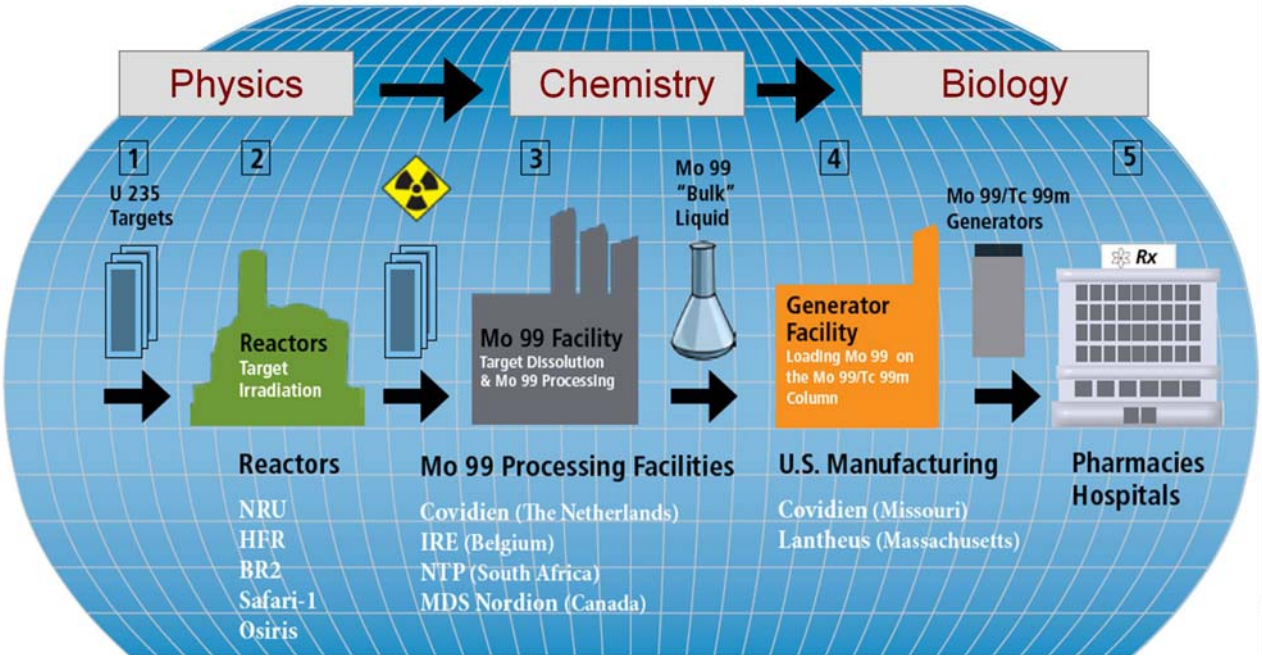

Figure 1. Present-day supply chain for Mo-99. The process can be separated into three steps: "physics" to produce Mo-99, "chemistry" to separate and purify the Mo-99 (and manufacture the generators) and "biology" which uses Mo-99 to create the Tc-99m radiopharmaceutical for use in the clinic with patients.

As Canada's national accelerator laboratory, TRIUMF is examining alternatives to the "physics" step that involve accelerators instead of nuclear reactors (see Figure 2). Some of these alternatives have dramatic implications for the "chemistry" steps as well as the present-day networks for distribution and transport. Accelerators have 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.
- Accelerators can employ different "physics" and achieve useful Mo-99 yields without using weapons-grade uranium.
- The technology is scalable: additional accelerators can be built or turned on and off as needed.
- The licensing and decommissioning processes are straightforward, a few months or less compared to years.

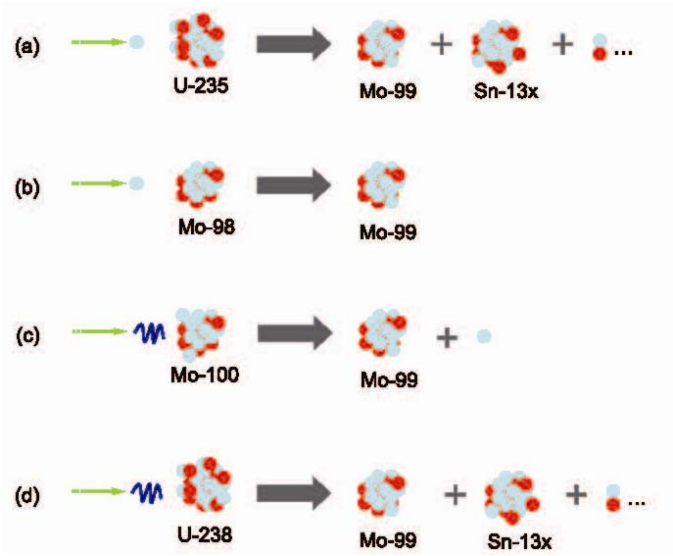

Figure 2. Physics mechanisms for producing Mo-99. (a) Neutron fission of U-235 (present-day reactor technique). (b) Neutron-capture process on Mo-98. (c) Photo-neutron process on Mo-100. (d) Photo-fission of U-238.

ZEUM Technology (Photo-fission using Accelerators)

In partnership with MDS Nordion, TRIUMF is developing a new technology using photo-fission and accelerators called ZEUM (Zero-Enriched Uranium Mo-99) technology that would replace the "physics" step of the supply chain without disrupting the downstream "chemistry" and "biology" steps. The technology uses a high-power electron accelerator and non-weapons-grade uranium. The key breakthrough has been the development of superconducting RF (SRF) accelerators by TRIUMF and Canadian industry which make tenable the private-sector construction and operation of 1-2 small machines (fitting in a mid-size room) to meet Canada's domestic needs.

A demonstration of ZEUM technology (in terms of overall yield, purity, and specific activity) is planned for 2012. The demonstration will use a U-238 target at TRIUMF using a prototype high-power electron accelerator. The target chemistry and analysis will be performed by MDS Nordion. The demonstration builds upon the expertise and resources of the partners and the results will be made public. The ZEUM technology was validated by an

international task force in autumn 2008 with support from Natural Resources Canada that examined all three accelerator-based techniques shown in Figure 2. [1]

Major advances in accelerator technology in the last decade allow an innovative method using photo-fission to be considered. Zero-Enriched Uranium Molybdenum (ZEUM) technology offers an alternate option for supplementing the production capacity of Mo-99. In this accelerator driven method, a high intensity beam of electrons (0.5-2 MW) impinge on a converter target producing photons. These photons are used to fission natural uranium, producing Mo-99 atoms 6% of the time, the same ratio as in the NRU and Petten reactors when using HEU. The chemical processing of the irradiated targets will be similar to the present processing method used for HEU targets. State-of-the-art technology to build high power electron accelerators is available in Canada. It is estimated that a 5 MW photo-fission driver would satisfy the Canadian market, which is certainly feasible based on available technology. The optimal design of the high power converter and uranium targets need to be developed. The technology is scalable and modular in that multiple streams can be pooled to stabilize and supplement the current Mo-99 supply.

If the demonstration confirms that the ZEUM technology is a viable option, a commercial system of the scale of the Canadian Mo-99 market could be online by the end of 2015. The project will be an opportunity for Canada to offer the world an innovative solution for producing Mo-99 while creating jobs, protecting existing global markets, and securing a stable source of medical isotopes critical to the health of Canadians.

Mo-100 Technology

TRIUMF is evaluating contributions to an exploratory project led by National Research Council (NRC) and Mevex Corporation that proposes a whole new supply chain for Tc-99m in the clinic. An electron accelerator is used to irradiate a special target made of purified Mo-100 to produce Mo-99 using the photo-neutron reaction. This technology uses high-energy x-rays produced by a 30-35 MeV, 100 kW electron beam to irradiate a Mo-100 target. The x-rays transmute the Mo-100 into Mo-99. The optimal "chemistry" to separate out and purify the Mo-99 is under development. This approach is also being investigated in the U.S.

The extracted Mo-99 is then used to immediately manufacture Tc-99m on site. This model for supply chain and distribution replaces the "physics" step and would redesign the "chemistry" step while eliminating the U.S. manufacturing step. The model places an accelerator and Mo-100 target complex at each major point-of-use for Tc-99m. The Mo-99 is not shipped anywhere; it is used where it is produced, at the point-of-use for the Tc-99m radiopharmaceutical. It could be shipped within the hospital housing the production facility, within the city, or a geographic area compatible with the 6 hour lifetime of Tc-99m, analogous to those hospital-based nuclear medicine departments which have in-house cyclotrons to support their PET imaging programs with isotopes.

Mo-99 Technology

TRIUMF is evaluating contributions to an approach led by Advanced Applied Physics Solutions, Inc., that would use an accelerator to irradiate Mo-98 targets to produce Mo-99 through the neutron-capture process. The key technical challenge is the isotope-separation process for extracting the Mo-99 with high efficiency and yield. In terms of the supply-chain model, this approach proposes new "physics" and new "chemistry" and would use the existing infrastructure and networks for distribution of the Mo-99 product.

Alternatives to Using Mo-99

TRIUMF is one of Canada's centres of excellence in nuclear medicine. For instance, a TRIUMF scientist is co-chair of the Canadian Medical Imaging Network which is supported by GE Healthcare. TRIUMF partners with the Pacific Parkinson's Research Centre and the BC Cancer Agency to research, develop, and supply medical isotopes (and advanced PET-imaging technologies). The primary isotopes used in these programs are the PET isotopes Fluorine-18 and Carbon-11.

[1] See *Making Medical Isotopes: Final Report for the Task Force on Alternatives for Medical-Isotope Production*, TRIUMF (2008).

Because of TRIUMF's technical skills and abilities, MDS Nordion has a manufacturing plant in Vancouver that produces and sells a variety of medical isotopes to the world. This partnership is more than 30 years old. The current isotopes commercially produced include:

- Iodine-123, used in medical imaging of the thyroid, brain, heart, neuroblastoma
- Thallium-201, used in medical imaging of the heart
- Gallium-67, used in medical imaging of soft tissue, abscesses, lymphoma)
- Indium-111, used in medical imaging of tumours
- Palladium-103, used in preparing therapeutical "seeds" (prostate cancer)
- Strontium-82, used in generators for Rubidium-82 and in medical imaging of the heart (PET)
- Copper-64, used in medical imaging for hypoxia; labeled antibodies, proteins (PET)
- Germanium-68, used in generators for Gallium-68; medical imaging (PET) (in progress)

The fastest-growing part of TRIUMF's Five-Year Plan is in nuclear medicine and includes developing next-generation cyclotrons to dramatically expand the production of PET isotopes around the world and developing new PET isotopes in combination with novel radiochemistries for new types of disease diagnosis and treatment.

The future of nuclear medicine is in PET isotopes. They offer superior "chemistry" meaning that they can be combined with more sophisticated biomolecules to selectively target, identify, or destroy specific aspects of neurological disease and cancer. The intrinsic precision and resolution of PET isotopes is also superior to that of SPECT isotopes. The main barriers for PET imaging technology to overcome are the initial capital cost of the imaging cameras and a distribution model built around regional cyclotron accelerator networks rather than international centres of production.

Contacts

Nigel S. Lockyer
Director
4004 Wesbrook Mall
Vancouver, BC V6T 2A3
Tel: 604-222-7490
Web: http://www.triumf.ca

Timothy I. Meyer
Head, Strategic Planning & Communications
Tel: 604-222-7674
Fax: 604-222-3791
Cell: 650-464-8955
E-mail: tmeyer@triumf.ca