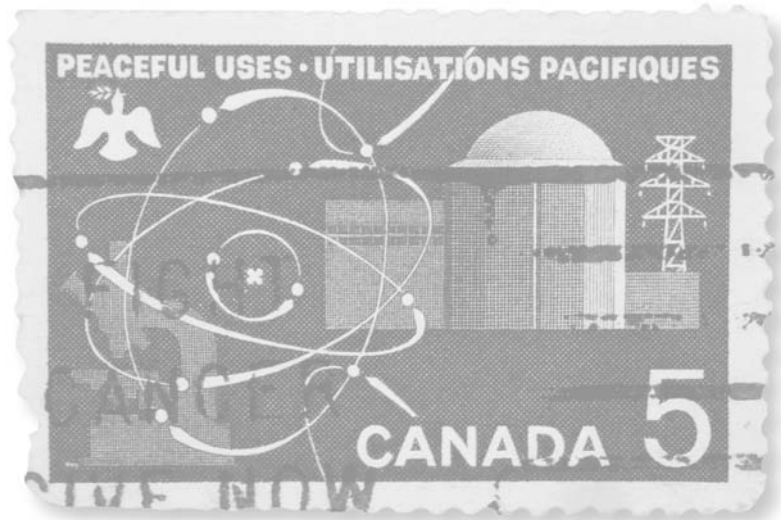


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Lessons learned from the shutdown of the Chalk River reactor



A report submitted to the Minister of Health

**Ad Hoc Health Experts
Working Group on
Medical Isotopes**

May 2008

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Foreword

This discussion paper is based on the Chalk River experience and our participation on Health Canada’s “SWAT team”¹ during and after the crisis. Throughout this period, the ad hoc group’s primary concern was patient care, and it is from this perspective that we present our views. Based on the lessons learned, we recommend measures to minimize the potential for future shortages, to mitigate patient care consequences should shortages occur and to establish a nation-wide plan to coordinate the supply, distribution and management of medical isotopes. The recommendations are broad in scope and, in some cases, may require the cooperation and collaboration of partners outside the formal health care system.

The ad hoc group worked on the premise that when a national shortage of a medically required resource threatens the health of Canadians, the federal government has a responsibility to intervene. The federal government has the tools needed to work with experts, private industry, federal departments and their provincial and territorial counterparts to

- ascertain the nature, scope and extent of the shortage across Canada
- monitor and report the impact on human health and patient care caused by shortages

- act at the national and international levels to secure supplies of scarce medical resources
- create appropriate oversight, including relevant structures within government, such as agencies and advisory bodies
- develop guidelines, protocols and contingency plans
- implement mitigating strategies.

To prepare this document, the members of the ad hoc group analyzed the chronology of events, reviewed testimony presented to the House of Commons Standing Committees on Natural Resources and on Health, sought additional expert information and drew on their experience and expertise in patient care and the provision of nuclear medicine services.

The consequences of the shutdown of the Chalk River reactor are the focus of this paper, but it should be noted that health outcomes can be affected by policies and decisions made outside the health sector. One need only study pandemic planning and the efforts to ensure influenza vaccine readiness to see the complex interplay of medical, social and business interests and the value of planning in advance of a medical crisis.

¹ Health Canada held daily teleconferences with the ad hoc group from 9 to 14 December, then continued calls on a weekly basis. In most recent memory, Health Canada used this “swat team” strategy only once before, during the SARS crisis of 2003.

Executive summary

On 9 December 2007 the federal Minister of Health, the Honourable Tony Clement, called together an ad hoc group of health experts to advise his ministry of the health care consequences of the shutdown of the National Research Universal (NRU) nuclear reactor at Chalk River and the resulting global shortage of the medical isotope, molybdenum-99. Following the resumption of production of medical isotopes, the same ad hoc group was asked to provide a post-event analysis. The ad hoc group would like to commend the minister and his staff for the continuing support they have given and welcomes the minister's initiative to review the events that took place, identify the lessons learned and consider initiatives to minimize the potential for future disruption of medical imaging services.

Our conclusions and recommendations can be summarized as follows:

1. Ensure efficient and effective communication with the medical community and the public.
2. In decision-making, ensure a balance between the health and safety of the public and the health outcomes of individual patients.
3. Assure appropriate physician participation and input into the decision-making process.
4. Minimize the potential for future interruptions in the supply of medically necessary materials and equipment.
5. Mitigate the consequences of unpredicted disruptions.
6. Enhance the capability of suppliers and end users to respond to interruptions in supply.
7. Establish a clear and appropriate alignment of authority and accountability for the management of medical radioisotopes.

Setting the stage

What is nuclear medicine?

Nuclear medicine is the medical specialty concerned with the use of radioactive materials, known as radiopharmaceuticals, for the diagnosis or treatment of diseases. Nuclear medicine specialists are certified by the Royal College of Physicians and Surgeons of Canada (RCPSC) and currently practise in one of Canada's 245 nuclear medicine facilities. They are assisted by certified technologists and usually supported by specially trained physicists and pharmacists.

Radiopharmaceuticals are used routinely in the diagnosis and treatment of disease. Approximately 300 therapeutic doses of medical isotopes and 30 000 diagnostic tests are administered to Canadians each week. A similar number of procedures are completed every day in the United States.

In a nuclear medicine test, small amounts of tracers, called radiopharmaceuticals, are introduced into the body by injection, swallowing or inhalation. Measures are taken to ensure the lowest possible exposure of the patient to radiation. The tracers concentrate in target organs and emit radiation that allows a specialized camera to collect data that are analyzed by a computer. The computer creates images that can be seen on a monitor or made into a photograph.

A nuclear medicine scan differs from radiography, ultrasound or other diagnostic tests because it can detect changes in the functions of an organ, not just its physical characteristics. Nuclear medicine tests are used to

- evaluate heart disease
- study the level of functioning of the brain, heart, lungs, kidneys and other organs
- locate tumours
- monitor the progression of cancer, particularly its spread to bones
- monitor the results of cancer treatments
- diagnose hormonal disorders, in particular thyroid disease.

Nuclear medicine procedures often identify abnormalities at very early stages of disease, before other diagnostic tests. They have particular strength in identifying pulmonary embolism (a potentially fatal disease resulting from

blood clots migrating to the lung), osteomyelitis (infections in the bone) and occult fractures (fractures of bones that are invisible to x-rays).

Most nuclear medicine tests are used for the diagnosis of serious and often life-threatening medical conditions. Although it may be tempting to assume that delays in diagnosis are more acceptable than delays in treatment, that is not the case. Delays in testing often compromise patient care more than delays in treatment. Without proper diagnosis, optimal treatment may be impossible.

Nuclear medicine plays a growing role in diagnosis and therapy in Canada and has done so since the mid 1950s. Newer technologies, such as computed tomography and magnetic resonance imaging, (MRI) are adding to the diagnostic armamentarium, but cannot replace nuclear medicine. Radioisotopes remain the primary and, frequently, sole means to assess many diseases.

How are radiopharmaceuticals supplied?

The supply chain in nuclear medicine is complex (Fig. 1). A publicly owned crown corporation (Atomic Energy of Canada Limited (AECL), which is overseen by a federal safety commission (the Canadian Nuclear Safety Commission (CNSC)), produces the raw material for most tests performed in nuclear medicine imaging facilities. The product of the nuclear reactor is transferred to a private company (MDS Nordion in Kanata, Ontario), where the raw materials are refined. MDS Nordion supplies over 50% of the world's needs. The refined material is provided to a second series of manufacturers where it is incorporated into a "generator," a format uniquely suitable for providing radioisotopes for medical use. Two private companies — Covidien and Bristol-Myers-Squibb (BMS)² — are the exclusive suppliers of generators in Canada.³ Worldwide, there are approximately a dozen manufacturers, some of whom are geographically close enough to provide support to Canada in the event of a shortage, if they had a surplus.

Once manufactured, the generator can be safely transported to, and used in, a health facility's radiopharmacy. Radiopharmacies purchase the generators and undertake the final steps necessary to provide Canadian imaging facil-

² BMS has recently been purchased by Avis Capital Partners and is now known as Lantheus Medical Imaging. In this document, we will continue to refer to BMS for historical relevancy.

³ Canada and the United States have agreements that permit the movement of medical isotopes across the border.

ities and hospitals with the specifically formulated treatments and diagnostic radiopharmaceuticals that they need. Each facility is independent and uses its own budget (provided by the publicly funded health care systems in the provinces and territories) and its own contracting system to purchase generators or radiopharmaceuticals.

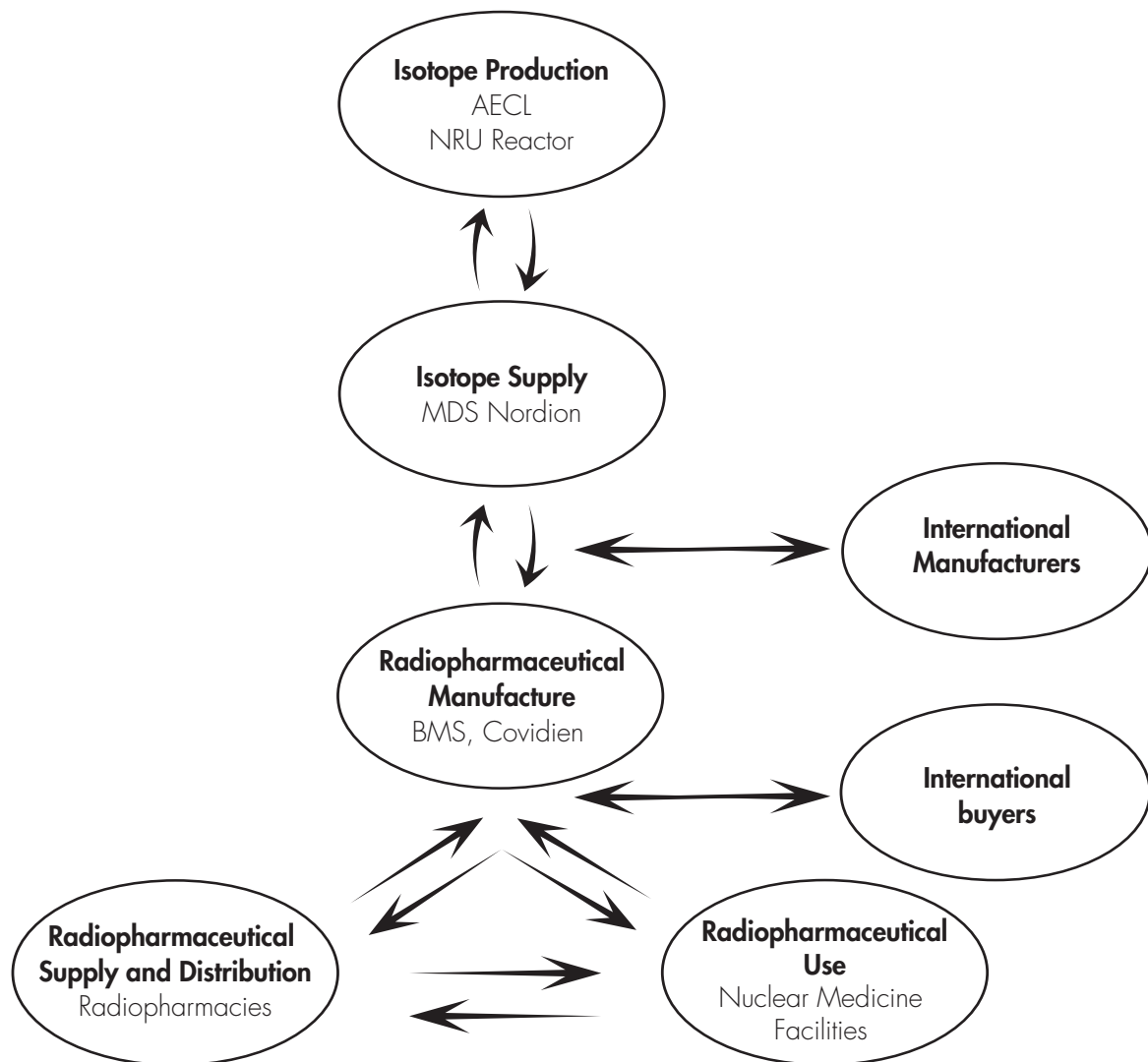
Like other pharmaceutical products, radioisotopes have a “shelf-life,” similar to a “best-before” date. However, unlike many other products, there is no date at which the product transforms from “good-to-go” to garbage. Instead, radioisotopes degrade in a predictable manner that is measured by the isotope’s half-life profile. The half-life is the time it takes for half the product to lose its radioactivity. Because most medically useful isotopes have short half-lives, they can’t be stockpiled like other more stable products, such as vaccines. Therefore, radioisotopes must be

used in a timely manner to be effective treatments or to produce a high-quality nuclear medicine image.

The most important medical radioisotopes produced by the NRU reactor at Chalk River are molybdenum-99 (⁹⁹Mo), iodine-131 (¹³¹I) and iodine-125 (¹²⁵I). Iodine radioisotopes are used mainly for therapeutic purposes. ⁹⁹Mo and its radioactive daughter, technetium-99m (^{99m}Tc), are the raw material used for over 85% of all nuclear medicine procedures.

Like all radioactive materials, ⁹⁹Mo begins to decay immediately after production. The conversion of ⁹⁹Mo to ^{99m}Tc is a natural physical process that occurs rapidly (⁹⁹Mo’s half-life is 66 hours) and cannot be altered. From the moment that ⁹⁹Mo leaves Chalk River en route to MDS Nordion, the clock is ticking. To make medical use of the ^{99m}Tc generated as ⁹⁹Mo decays, the ⁹⁹Mo must be

Figure 1: Canadian radioisotope supply chain



Note: AECL = Atomic Energy of Canada Ltd., BMS = Bristol-Myers-Squibb, NRU = National Research Universal.

processed into a sterile “radioisotope generator system” to facilitate separation of the daughter from the parent.

The first steps take place at MDS Nordion, where the raw ^{99}Mo is refined into a form suitable for incorporation into generators. From MDS Nordion, the ^{99}Mo is sent to the companies that make generators (BMS and Covidien, located in the United States).

Generators are the assemblies that allow technologists in radiopharmacies to separate ^{99}Mo from $^{99\text{m}}\text{Tc}$ in a very clever manner. Inside each generator is a small glass column filled with alumina, a substance that strongly adheres ^{99}Mo to its surface. $^{99\text{m}}\text{Tc}$ does not bind as strongly. To separate $^{99\text{m}}\text{Tc}$ from ^{99}Mo , one need only wash (elute) the column with sterile saline and collect the $^{99\text{m}}\text{Tc}$ that comes out with the saline.

Immediately following manufacture, the generators are delivered to one of three types of centres: imaging facilities, hospitals or radiopharmacies. Nuclear medicine facilities must carefully manage their processes and procedures to maximize their use of $^{99\text{m}}\text{Tc}$, because the amount of $^{99\text{m}}\text{Tc}$ in each generator decreases by approximately 20% each day. Careful consideration must be given to the time required for the processing and preparation of the radiopharmaceuticals, the list of treatments and procedures required and the timing of scheduled appointments. The clock is ticking faster now — $^{99\text{m}}\text{Tc}$'s half-life is only 6 hours. Logistically, this is one of the most complex undertakings in a hospital.

The most efficient distribution of $^{99\text{m}}\text{Tc}$ radiopharmaceuticals happens in centralized radiopharmacies because they can most efficiently match the timing of generator delivery to radiopharmaceutical demand. Large, centralized facilities receive a number of generator deliveries staggered throughout the week and have a large staff to process materials and manage operations. This allows them to produce and distribute radiopharmaceuticals in either multidose vials or as single doses to multiple imaging centres and hospitals. Unfortunately, most imaging facilities and hospitals in smaller centres do not have access to a central radiopharmacy and, by necessity, prepare their own radiopharmaceuticals. Smaller and more rural nuclear medicine departments receive only a single generator from a single source weekly. As a result, smaller facilities are far more vulnerable to a disruption in supply.

What happened?

The physician's perspective

Between 27 and 30 November 2007, nuclear medicine specialists, technologists, physicists and radiopharmacists working in hospitals or clinics began to receive notices from their immediate suppliers that there was a problem with the supply of medical isotopes. Quickly, and on an

ad hoc basis, bookings for procedures were adjusted to deal with what was presumed to be a temporary shortage.

However, by 3 December, it had become clear that the problem was not temporary and the shortages were worse than anticipated. Access to nuclear medicine procedures was increasingly compromised and rationing became necessary throughout Canada. On 5 December, an emergency teleconference of the Board of the Canadian Society of Nuclear Medicine (CSNM) was held. At the time, there were no lines of communication with AECL, CNSC or the federal government. With no means by which the medical community could raise the alarm, the CSNM board prepared a press release describing the desperate situation that many patients were facing. The next day, the shutdown of the NRU reactor at Chalk River was front page news. As the days passed, successive worrisome press releases hinted that supplies of isotopes might not return to normal until January 2008 or even February 2008.

Over the weekend of 8–9 December, Health Canada stepped in and established an ad hoc medical advisory group. From the physician's perspective, this was a major leap forward. Health Canada information was more reliable than media reports, even though federal departments seemed to be working on a day-to-day basis, just as we were.

For patients with serious and often life-threatening conditions, the lack of certainty was chilling. People scheduled for diagnostic tests received little or no information about how long they would have to wait or whether they would have the prescribed test at all. In some circumstances, patients and their health care providers had to decide whether they would resort to procedures known to have higher risks or to be less accurate. Others faced being placed on long waiting lists for alternative procedures or risked being managed with less than ideal diagnostic information.

Dealing on a daily basis with the distress of suffering patients who must endure long waits for critical imaging procedures created emotional stress and tension at every level of the health care system. Unless one has had this experience, it is difficult to appreciate the extremely deleterious effect of this type of uncertainty on individual patients, their families and their health care providers.

There appeared to be no end in sight, as the availability of medical isotopes decreased each day. Departments were forced to close and, by 12 December, emergency services in some regions were compromised.

There were enormous variations in how well or poorly Canada's nuclear medicine facilities fared during the shutdown of the reactor. Some were actually unaware of the radioisotope shortage until they read about it in the newspapers. Some large centres continued to operate at close to full capacity because of the nature of their supply contracts. Every patient in those centres, regardless of the level of urgency, received the prescribed treatment or diagnostic

test. At the same time, some small facilities received virtually nothing, and their patients were denied nuclear medicine imaging regardless of the acuity of their situation or level of need. In Saskatchewan, for example, virtually no medical isotopes were available.

The most disconcerting issue for all concerned was the fact that the nuclear medicine community could not properly plan an appropriate response to the crisis. No process or mechanism was in place to facilitate effective communication. The nature and full extent of the crisis was simply not known. The nuclear medicine community found itself working on a day-by-day basis, guided by information gleaned from the newspapers. Each morning brought more bad news: enough isotope for 6 patients, and 14 people booked. Who would get their diagnosis? Their treatment? What about tomorrow? Rebook? Try another facility? Who can make do? Who must be treated? Should we use another method? Wait? Act? Wait? Act?

Simply put, the ability to provide service was teetering on the brink of disaster when the reactor was finally restarted. When the isotope supply began to flow again, one technologist spoke for all by saying, “It was as if a weight was taken off my shoulders.”

The international perspective

⁹⁹Mo from Chalk River is used around the world, but the largest user is the United States. According to a market study of radiopharmaceuticals conducted by Frost & Sullivan in 2000, 80%–90% of the 40 000 diagnostic procedures performed daily in the United States use ^{99m}Tc; 90% of the US supply of isotopes is imported; 75% is obtained from MDS Nordion in Canada.

It is not surprising that the shutdown of the NRU

reactor had a severe impact south of the border. Over 1000 members of the American Society of Nuclear Medicine responded to a survey conducted by the US-based Society of Nuclear Medicine during the shutdown:

- 84% said their facility was affected
- 9% were functioning at less than 10% capacity, 14% at 10%–25%, 18% at 26%–50%, 18% at 51%–75%. The remaining 40% were at better than 75% or full capacity.
- Only 31% of facilities had been able to identify an alternative source of ^{99m}Tc generators.

The Chalk River shutdown has renewed calls in the United States to secure a domestic supply of medical isotopes. The *Globe and Mail* recently reported that researchers in the US are mobilizing hundreds of millions of dollars to upgrade facilities and develop independent capacity for the US medical community.

It is noteworthy that recently Australia reported that its reactor was shutting down for upgrades and they expect to face shortages. Fewer than 10 reactors in the world are capable of making medical isotopes⁴; approximately 50% of the world’s supply of raw material comes from Chalk River. Many of these, like the NRU reactor, are old and aging. No one reactor, and probably not even all of them in combination, can replace the production of Chalk River. Clearly, seeking international sources and cooperation may mitigate supply disruptions but, overall, the global market is limited and cannot compensate for the loss of the NRU reactor. In addition, any new replacement options will require significant lead time and financing to implement.

⁴ Institut National des Radioelements in Brussels (15%–25%); Tyco Healthcare in the US (20%); Nuclear Energy Corporation of South Africa (10%); the remainder account for 5%–10%.

Lessons learned and recommendations

Lesson 1: Risk-based communication

The rapid dissemination of relevant, consistent, accurate and timely information is crucial to an effective medical response during a supply crisis and is an essential component of any contingency plan. Early statements from MDS Nordion and AECL gave no indication of how long it would take to re-establish the medical isotope supply. Although it is now recognized that the time needed to restart the reactor was unknown to all parties, even this aspect of the timetable was not made public. During the recent crisis, it was apparent that the absence of communications planning had a detrimental impact on patient care. Information provided to the end user (physicians, hospitals, imaging facilities and radiopharmacies)

- did not occur until shortages were imminent
- did not include complete information
- did not indicate the severity of the shortages
- did not indicate the probable duration of the shortages.

Although prompt notification would not have solved every problem that arose during the shortage, it would have enabled the best use of scarce resources and allowed physicians to provide the best available treatment or use the best diagnostic tool for the most appropriate patients. In particular, timely and accurate information would have reduced the sometimes overwhelming stress and worry felt by patients and their caregivers.

Recommendations

- 1.1 While recognizing that there are expected (and temporary) interruptions to the flow of radioisotopes, it is essential that the relevant Canadian authorities establish a comprehensive series of processes and mechanisms to
 - evaluate the risk from exceptional stoppages in terms of the adequate supply of isotopes for medical procedures
 - ensure timely disclosure of any potential extended interruption at any point along the supply chain from the production of the raw materials to the intermediaries, through to the manufacturers of generators
 - evaluate, then report serious threats to the supply of generators to nuclear medicine facilities, both national and international
- 1.2 Relevant Canadian authorities and organizations must work with nuclear medicine facilities to ensure accurate communications and the equitable distribution of generators during shortages.
 - Communications must include rapid dissemination of relevant information to the generator producers (BMS and Covidien). These suppliers have the most complete and current knowledge of who will be affected and how.
 - Generator producers must provide ongoing, up-to-date information to their customers.
- 1.3 Health Canada should work with the CSNM, the CANM, the CMA and others, particularly provincial and territorial authorities, to develop a real-time communications protocol and maintain a network to ensure that when supply events occur, current and relevant information is distributed to all nuclear medicine facilities.
- 1.4 With support from Health Canada, the CANM and the CSNM must develop the capacity to provide real-time notifications to the nuclear medicine community.

Lesson 2: Physician engagement in decision-making

Nuclear medicine specialists undergo training that emphasizes radiation protection and safety. As such, they bring to the table not just knowledge of medicine and patient care, but also expertise concerning the safe handling and use of medical isotopes. Nuclear medicine specialists are an integral part of a larger nuclear medicine community that includes technologists, physicists and radiopharmacists. As a result, nuclear medicine specialists are uniquely able to balance the health of patients, the safe handling of medical isotopes and overall patient management.

Until 2001, the CNSC maintained a number of external advisory councils, including a medical advisory council, that facilitated communication between the medical community and the commission. Members of the council pro-

vided CNSC staff with insight into how operational and policy decisions would affect patient care across the country. In 2001, the councils were disbanded, effectively isolating CNSC from physician input and marginalizing an important source of knowledge concerning radiation safety and patient care. In our opinion, this knowledge was, and remains, critical to appropriate decision-making.

In 2001, the CNSC also removed the requirement that the physician responsible for the nuclear medicine laboratory in a clinical setting be an RCPSC-certified nuclear medicine specialist, thereby discounting the important role of the nuclear medicine specialist and potentially compromising the standard of care provided to Canadians who require diagnostic and treatment services utilizing radio-pharmaceuticals.

In our opinion, the lack of input from qualified nuclear medicine specialists and inadequate consideration of the health needs of Canadians in the assessment and decision-making processes exacerbated the situation caused by the extended shutdown of the Chalk River reactor. In addition, the absence of physician input into the decision-making processes at multiple levels compromised the ability of physicians to respond to the extended shutdown.

Recommendations

- 2.1 The impact on individual patient care must be considered and factored into any decisions that might result in disruptions of the supply of medical isotopes.
- 2.2 The federal government, through Health Canada, should work with national nuclear medicine organizations and the CMA to ensure that nuclear medicine specialists are actively involved in the decision-making processes at all levels of the supply chain and in all decisions regarding the
 - supply, distribution and use of medical isotopes across Canada and
 - the management of medically significant shortages of isotopes.
- 2.3 A process to ensure early, ongoing and meaningful physician input and involvement in decision-making should be established by the federal government.
- 2.4 The requirement that the monitoring physician at nuclear medicine sites be an RCPSC-certified nuclear medicine specialist should be restored.

Lesson 3: Planning for disruptions

The recent experience of a disruption in the supply of ^{99}Mo from Chalk River highlighted the complexity and potential weakness of the supply chain. This incident was not the first, nor will it be the last, interruption in the supply of medical isotopes.

Improving Canada's capability to prevent and manage shortages can be considered at three stages along the isotope supply chain.

- Enhancing our production and handling of raw materials
 - in a timely manner
 - in sufficient quantity.
- Enhancing our capacity to produce and deliver generators to clinical settings
 - in a timely manner
 - in sufficient quantity.
- Enhancing our ability to respond in clinical settings
 - by finding suitable alternatives to radioisotopes when there are shortages
 - by maximizing the productivity of generators
 - by triage and managing the throughput of patients.

Raw materials

It is clear to the ad hoc group that further study must be undertaken on issues related to the security of supply and distribution of medical isotopes. It is important to have a reserve (surplus) available, and Canada needs reactors that are designed to expand their production capabilities quickly in response to an emergency.

Recent events have shown that the industry's current dependence on an approximately 50-year-old NRU reactor at Chalk River is less than optimal, particularly when maintenance regimes can lead to extended shutdowns. Built in the middle of the last century, the Chalk River reactor is old, and it is not alone. It and many other aging facilities will soon have to be replaced.

Are there reasonable alternatives in Canada? The Maple I and II reactors were expected to be able to satisfy national and probably international supply demands; however, their commissioning has been delayed and there appears to be a risk that they will never be put into operation.⁵ McMaster University has operated a 5-MW research nuclear reactor for nearly 50 years at its main campus in Hamilton, Ontario. It currently supplies a range of radioisotopes including ^{125}I , for treating more than 60 000 prostate cancer patients each year. Other university centres may have additional capacity.

In the opinion of the ad hoc group, a made-in-Canada solution that assures a secure domestic supply of raw material is the preferred option. The production of medical isotopes is, in fact, a growing business opportunity. Canada should continue its predominance in medical isotopes — it is in keeping with Canada's philosophy on the peaceful use of nuclear energy.

⁵ On 16 May 2008, AECL announced they would discontinue efforts to bring the MAPLE reactors on-line.

Recommendations

- 3.1 A made-in-Canada solution is the preferred option for addressing Canadian shortages. To this end, the federal government should
 - undertake a review of the risks and benefits of sourcing raw materials from outside Canada
 - plan for the timely replacement of the NRU reactor and consider expeditious commissioning of Maple I and II reactors⁴.
- 3.2 CNSC and other relevant agencies should
 - plan for the timely replacement of the NRU reactor for ⁹⁹Mo production
 - extend the license of the NRU reactor to operate until other supply sources are online
 - ensure the collaboration of Health Canada and others to ensure that the health care needs of Canadians are addressed.
- 3.3 The federal government should explore opportunities to use other nuclear reactors in Canada. To this end
 - a survey should be conducted to evaluate the feasibility of other Canadian reactor facilities producing ⁹⁹Mo
 - if other facilities are capable, evaluate the feasibility of providing the necessary enhancements to their infrastructure.
- 3.4 Canada should promote formal cooperation agreements within Canada among the current reactor facilities to
 - supply key medical isotopes (including ⁹⁹Mo, ¹³¹I and ¹²⁵I) in the event of an emergency
 - secure a domestic supply against future shortages of medical isotopes
 - actively engage in developing new production methods and medical applications for emerging isotopes as a means of strengthening the industry in Canada
 - offer a program for training scientists, engineers and regulatory officers in isotope production and safety.
- 3.5 Canada should work with its international partners to review global capacity to produce medical isotopes, encourage the development of international protocols, remove current barriers or obstacles to international movement of radioisotopes during periods of shortages.

Generators

It is not uncommon for larger hospitals and independent radiopharmacies to have contracts with both generator manufacturers. However, smaller hospitals and facilities have little choice but to contract with one manufacturer to control costs.

During the shutdown of the NRU reactor, nuclear medicine facilities and radiopharmacies who had contracts with Covidien continued to receive generators, but those relying on BMS did not. This is not intended as criticism. In November 2005, for example, Covidien experienced manufacturing problems, and the facilities relying on them did not receive generators, while BMS supplied facilities did.⁶ At the time of that incident, Covidien supplied only 20% of the Canadian market and BMS was able to step in to fill the gaps. Although the most recent shortage was triggered by a maintenance issue and the 2005 event was caused by failure to maintain sterility, any one of a number of events including regulatory problems (such as out-of-specification product) or catastrophe (such as flood or fire) could have been just as chaotic.

Radiopharmaceuticals are well recognized as a growing diagnostic and treatment modality in medicine and represent an important business line for the United States. In keeping with our focus on made-in-Canada solutions and international leadership, creating a capacity to produce generators in Canada should be seen as a win-win opportunity for Canadians.

Recommendations

- 3.6 Explore options and opportunities to diversify generator supply sources within Canada.
- 3.7 Evaluate mechanisms that would allow Health Canada to “fast track” generator products that are currently not approved by Health Canada but may be of use in emergency situations should be evaluated.
- 3.8 Hospitals and radiopharmacies should secure generators from more than one supplier. This may require facilities in smaller centres to develop regional purchasing strategies. Nuclear medicine facilities contracting for supply with central radiopharmacies should stipulate that the radiopharmacy will obtain generators from more than one supplier.
- 3.9 Health Canada, as the regulatory authority that ensures generators are safe for transfer between facilities, and the provincial and territorial governments, as the bodies responsible for health care delivery, should develop a strategy to maximize generator productivity including
 - shipping partly spent generators to more remote regions from central large facilities (as was done in Alberta during the recent crisis) for use in the event of a supply disruption
 - developing a plan to monitor and use generators past their expiry dates.

⁶ On 18 November 2005, Mallinckrodt (currently Covidien in Canada) issued a recall of their generators due to a breach in sterility control processes. The shutdown of their facility lasted until 5 April 2006. Fortunately, in Canada, BMS was able to offset the shortage and the worst of the shortfall was contained after only one week of critical shortages.

Clinical practice settings

The ad hoc group has come to realize that, during the recent isotope shortages, nuclear medicine facilities individually and collectively carried out initiatives to ration isotopes and to identify potential alternative isotopes to fill the gaps. Although many in the nuclear medicine community had, or quickly made, contingency plans, some nuclear medicine laboratories in Canada were caught off guard and had to scramble.

The nature of radioisotope generators is such that approximately 20% of their capacity is lost every day. The very limited supply of ^{99m}Tc would be better used if facilities had the capacity to keep working beyond usual work hours.

Recommendations

3.10 The nuclear medicine community, including technologists, physicists, radiopharmacists and other stakeholders, should develop guidelines and best practice protocols for

- triage of patients during an isotope shortage
- the use of radiopharmaceuticals labeled with alternative isotopes
- alternative procedures to be used in patient assessment during isotope shortages
- increasing the availability of diagnostic and therapeutic slots and extending the workday during the early stages of a shortage when the ^{99}Mo generators are still robust
- addressing the backlog once the supply of isotopes resumes.

3.11 Nuclear medicine facilities should prepare guidelines and implementation plans to mitigate shortfalls in supply, including protocols and practice guidelines for the use of alternative radiopharmaceuticals and the use of positron emitting radiopharmaceuticals.

3.12 Canada's cyclotron facilities should be encouraged to develop clinical trial agreements with Health Canada for positron emitting radiopharmaceuticals that will be able to substitute for analogous technetium-labeled materials (e.g., Na-F-18 instead of ^{99m}Tc ; methylene-diphosphonate, N-13 ammonia or rubidium-82 instead of ^{99m}Tc -sestamibi or ^{99m}Tc -tetrafosmin) during shortage periods.

Lesson 4: Federal, provincial and territorial responsibilities

As the ad hoc group sees it, triage of the radioisotope supply within and between provinces and nuclear medicine facilities to ensure an equitable distribution across the country is essential. In situations where national security is compromised, federal coordination is required and can be accomplished through bodies such as Public Security and

Emergency Planning. Certain health emergencies can activate the Emergency Operations Centre within the Public Health Agency of Canada. The supply of medical isotopes may not be an issue of national security, but it still requires a coordinated and integrated national response involving federal, provincial, territorial and regional authorities.

It is notable that facilities whose provincial government had a collaborative contingency plan for coordinated management of shortages fared much better than those that did not. For example, British Columbia activated its Emergency Operating Centre and used an existing imaging council to support its goal: equitable distribution of generators.

The ad hoc group applauds the work that Health Canada has undertaken to establish a protocol for notification and information-sharing with and between AECL and the Natural Resources Canada (NRCAN) concerning shortages of medical isotopes. We are encouraged that a section specifically related to information-sharing between Health Canada and the medical community is included. Very early in the crisis, Health Canada decided that it would not undertake action without consulting nuclear medicine specialists; the ad hoc group agrees that that decision was pivotal.

Recommendations

A number of federal departments and agencies are involved in nuclear safety. Without prejudice as to the obligations of any particular arm of the federal government and acknowledging that the ad hoc group may not have identified all responsible organizations, we recommend the following.

4.1 Key federal organizations such as Health Canada, CNSC and AECL should collaborate on the development of best practices for the management of medical shortages of radioisotopes and should develop these in collaboration with

- nuclear medicine specialists
- provincial and territorial partners.

4.2 Governments should work with nuclear medicine facilities to assure that each has a contingency plan that would enable it to respond to a health emergency such as the one triggered by the shutdown of the NRU reactor. The standard for such a plan should be developed with the nuclear medicine community.

4.3 A Canada-wide effort to create a systematic and sustainable mechanism to ensure a fair and just distribution of medical isotopes during national shortages is required.

- The nuclear medicine community must be involved.
- A larger stakeholder community should be involved, in particular, patients.
- Respecting the responsibility of the provinces and territories in the provision of health care, the ad hoc group recommends that the provinces and territories be prepared to undertake coordinated distribution

- of scarce medical resources, such as radioisotope generators, during emergency situations.
- 4.4 The ad hoc group recommends that the nuclear medicine community work with Health Canada to accelerate the development of alternatives to commonly used radioisotopes, such as pre-approving clinical trial applications, more rapid reviews of licensing of new products or uses of established products and other similar legislatively bounded actions. It is recognized that Health Canada's capacity to accelerate these processes should be enhanced.
- 4.5 A national contingency plan must be prepared to ensure that the supply of medical isotopes can be returned to pre-interruption levels as soon as possible after an interruption and to ensure that appropriate protocols are implemented during the transition period.
- 4.6 As the implications of shortages are international, facilitation of the participation of international stakeholders should be undertaken.

Conclusions and summary of recommendations

The ad hoc group recognizes the role of Health Canada as a regulator in setting standards, establishing guidelines and supporting research and as a leader in protecting the health of Canadians. The minister and his staff demonstrated that Health Canada was a valued partner to the nuclear medicine community and to the patients and their families who suffered during the crisis. The ad hoc group believes that it is essential to use the momentum from the crisis to create a robust, integrated and effective system for the management of medical isotopes in Canada and internationally.

To this end, we are confident that the recommendations contained in this paper, when taken together, will address seven critical areas requiring both immediate and long-term action.

1. Ensure efficient and effective communication with the medical community and the public.

- 1.1 Implement a process to ensure timely disclosure of potentially extended interruption at any point along the supply chain; report serious threats to nuclear medicine facilities.
- 1.2 Work with nuclear medicine facilities to ensure accurate communications and the equitable distribution of generators during shortages.
- 1.3 Health Canada should work with the CSNM, the CANM and the CMA to develop a real-time communications protocol to ensure that relevant information is distributed to all nuclear medicine facilities.
- 1.4 With support from Health Canada, the CANM and the CSNM should develop the capacity to provide real-time notifications to the nuclear medicine community.

2. In decision-making, ensure a balance between the health and safety of the public and the health outcomes of individual patients.

- 2.1 The impact on individual patient care must be considered and factored into any decisions that might result in disruptions of the supply of medical isotopes.

3. Assure appropriate physician participation and input into the decision-making process.

- 2.2 Ensure that nuclear medicine specialists are actively involved in the decision-making processes at all stages

in the supply chain and in all decisions regarding the supply, distribution and use of medical isotopes across Canada and the management of medically significant shortages of isotopes.

- 2.3 The federal government should establish a process to ensure early, ongoing and meaningful physician input and involvement in decision-making.
- 2.4 The requirement that the monitoring physician at nuclear medicine sites be an RCPSC-certified nuclear medicine specialist should be restored.

4. Minimize the potential for future interruptions in the supply of medically necessary materials and equipment.

- 3.1 Strive for a made-in-Canada solution.
- 3.2 Plan for the timely replacement of the NRU reactor as a supply of ^{99}Mo .
- 3.3 Explore potential opportunities to bring new nuclear reactors on line to produce medical isotopes.
- 3.4 Create formal cooperation agreements among the current reactor facilities in Canada.
- 3.5 Work with international partners to review global capacity and remove current barriers or obstacles to the international movement of radioisotopes during periods of shortage.
- 3.6 Diversify generator supply sources, preferably within Canada.
- 3.7 Secure generators from more than one supplier. This may require that facilities in smaller centres develop regional purchasing strategies.

5. Mitigate the consequences of unpredicted disruptions.

- 3.8 “Fast track” approval of generator products that may be of use in emergency situations.
- 3.9 Develop a regulatory and procedural strategy to maximize expired generator productivity.

6. Enhance the capability of suppliers and end users to respond to interruptions in supply.

- 3.10 Develop guidelines and best practice protocols for
 - triage
 - use of radiopharmaceuticals labeled with alternative isotopes
 - alternative procedures for patient assessment

- increasing diagnostic and therapeutic slots and extending the workday
 - addressing the backlog.
- 3.11 Prepare guidelines and implementation plans to mitigate shortfalls, including protocols for the use of alternative radiopharmaceuticals and the use of positron emitting radiopharmaceuticals.
- 3.12 Develop clinical trial agreements with Health Canada for positron emitting radiopharmaceuticals.

7. Establish a clear and appropriate alignment of authority and accountability for the management of medical radioisotopes.

Recognizing that a number of federal departments and agencies are involved in nuclear safety, the ad hoc group recommends that

- 4.1 Health Canada, CNSC and AECL collaborate on the

development of best practices for the management of medical shortages in collaboration with provincial and territorial partners

- 4.2 All nuclear medicine facilities require a response plan in case of shortages of medical isotopes
- 4.3 A systematic and sustainable mechanism to ensure fair and just distribution of medical isotopes during national shortages be created
- 4.4 Development of alternatives to commonly used radioisotopes be accelerated, i.e., by pre-approving clinical trial applications
- 4.5 A national contingency plan be developed to ensure that the supply of medical isotopes can be returned to pre-interruption levels as soon as possible after an interruption
- 4.6 The participation of international stakeholders be facilitated.

Appendix 1: Medical notes on risk-mitigation strategies

1. Extended use of generators

Central facilities may receive generators from one or more manufacturers, depending on their business practices. Although generators are labeled with an expiry date, they can continue to supply useful, but diminishing, quantities of technetium beyond their expiry date provided that stringent quality assurance measures are in place. As well, the generators can be eluted more frequently, albeit at reduced efficiency, to provide technetium that is urgently required.

2. Alternative radiopharmaceuticals

Thallium-201

This cyclotron-produced product can be used to image heart blood flow. The images produced are of lesser quality than those produced with ^{99m}Tc sestamibi or tetrofosmin and expose the patient to higher radiation levels.

I-123 hippuran

This radiopharmaceutical, which can be used for renal imaging, is labeled with cyclotron-produced isotope and is expensive and difficult to obtain. Broader availability would require significant investment and the establishment of transportation mechanisms.

Gallium-67 citrate/In-111

These materials can be used in place of ^{99m}Tc to image infection by labeling white blood cells.

Fluorine-18 fluorodeoxyglucose

This material is used for detection of malignancy, the staging of cancer and monitoring cancer therapy. Some limited information indicates that staging with FDG positron emission tomography (PET) might supplant some of the need for bone scanning. The material is produced in a medical cyclotron facility and imaged with a camera designed for PET. Outside Quebec, there is limited capacity for PET imaging.

Sodium fluoride-18

This material can be used for bone imaging as a direct replacement for the ^{99m}Tc labeled compound. It must be locally produced at a medical cyclotron and imaged with a PET camera. PET imaging facilities are in limited supply in Canada. The regulatory requirements for the introduction of each radiopharmaceutical are substantial and at the

time of closure of the NRU reactor, no facility had an established clinical trials agreement with Health Canada for the use of this material.

Nitrogen-13 ammonia

This material must be produced at a medical cyclotron and imaged with a PET camera. This procedure is available at a number of PET centres in Canada (e.g., Hamilton and Ottawa). For technical reasons, this imaging technique cannot be used for exercise stress testing and could only be made available to a small number of patients. It would not be possible to handle the volume of urgent myocardial perfusion studies performed on a daily basis across the country.

Rubidium-82

This positron-emitting radiopharmaceutical is produced using specialized generators that are available in only three centres in Canada. This imaging technique could only be made available to a small number of patients. It would not be possible to handle the volume of urgent myocardial perfusion studies performed on a daily basis across the country.

3. Alternative imaging

In view of the potential negative impact of closure of the NRU reactor, it is indeed fortunate that other high-technology imaging modalities have evolved over the past decade to provide alternatives, in some circumstances, to nuclear medicine procedures. However, as evidenced by the documented wait lists for computed tomography and MRI, there is no capacity in the Canadian health care system to absorb any more than a small fraction of the procedures currently performed by nuclear medicine techniques by using these alternatives.

Pulmonary embolism by computed tomography

Computed tomography with contrast administration is used to image the pulmonary arterial system and diagnose pulmonary embolism. This technique cannot be used in patients with significant renal impairment or allergy to contrast agents and can be technically challenging in acutely ill patients. The radiation dose to the breast in young females is of concern. For these reasons, ventilation-perfusion imaging with ^{99m}Tc -labeled radiopharmaceuticals remains an important test to diagnose this life-threatening condition.

Bone metastases by magnetic resonance imaging

Whole-body MRI would allow for the accurate evaluation of bone metastases. There are insufficient MRI instruments to image the large number of patients being staged and followed for cancer. Furthermore, a significant number of patients cannot tolerate this procedure because of claustrophobia and the inability to tolerate prolonged imaging procedures because of pain.

Diagnosis of coronary artery disease by computed tomography–angiography

This test requires multi-detector computed tomography, which is not available in all Canadian centres, and administration of contrast agents (contraindicated in patients with renal impairment or allergy to contrast agents). The test is technically challenging to interpret and few radiologists or cardiologists are sufficiently experienced. The test is still under evaluation. The high negative predictive value indicates that the test could have replaced myocardial perfusion imaging to exclude coronary artery disease, but in

widespread use this test with its relatively low positive predictive value would have increased the need for invasive cardiac catheterization and the attendant risks.

Cardiac risk assessment by stress echocardiography, dobutamine stress MRI, computed tomography perfusion

These techniques are not available in most Canadian centres. The large validated database supporting the use of myocardial perfusion imaging for this application is not available for these alternative techniques.

4. Alternative therapy

There are no alternatives to therapy with ^{131}I for benign and malignant thyroid disease. These treatments are not usually considered to be urgent. However, a prolonged disruption in isotope supply could result in a substantial backlog of patients, which might take a significant time to absorb, particularly in the case of hospital inpatient therapy for cancer.

Appendix 2: The course of events

2007	
30 November	Hospitals learn from commercial radiopharmacies that a shutdown of the NRU reactor has occurred and is expected to be prolonged. Rationing of technetium-based products will be necessary.
5 December	Bilateral discussions among nuclear medicine specialists at CSNM and CANM take place.
6 December	<p>The CSNM issues a press release commenting on the negative impact of the extended shutdown of the NRU reactor on patient care and access to vital diagnostic procedures. Noting that the nuclear medicine community is frustrated in that there does not appear to have been a contingency plan in place to address this situation adequately, the society states that it is looking forward to working with the federal government and its regulatory agencies.</p> <p>Health Canada sends questions via email to 773 health care facilities, including 245 nuclear medicine facilities.</p> <p>Work begins at Health Canada to establish an ad hoc group of external health experts to provide on-the-ground intelligence and advice.</p> <p>Continued bilateral discussions between Health Canada and nuclear medicine specialists take place.</p>
7 December	<p>The CSNM issues a second press release saying that it is concerned that the impact of the extended shutdown of the NRU reactor is being diluted by discussions not directly related to patient care.</p> <p>CSNM notes that the loss of scanning capability affects all areas of medicine, especially patients with cancer and heart, lung and kidney disease. The society urges that reinstatement be expedited as quickly as possible so that patient care is maintained.</p> <p>Preliminary responses from the nuclear medicine facilities to Health Canada's survey indicate variable impacts across the country. Eastern provinces and northern Ontario appear to be the hardest hit, while Alberta has an alternative supplier and Manitoba is maximizing limited supplies. This information is shared with the ad hoc group.</p>
8 December	<p>Health Canada continues call to nuclear medicine specialists to identify appropriate people to participate in the ad hoc group.</p> <p>Nuclear medicine facilities provide further responses to Health Canada's survey, confirming shortages in other parts of the country.</p>
9 December	<p>Minister Clement calls Dr. A.J.B. McEwan, Chief of Oncologic Imaging, Cross Cancer Institute, Alberta (Past-President of the CSNM and current President of the American Society of Nuclear Medicine) to get a first-hand account of the health consequences of the shortage.</p> <p>Deputy Minister of Health contacts the Secretary General and CEO of the CMA to help identify members for the ad hoc group.</p> <p>Health Canada contacts nuclear medicine specialists (including representatives from the CSNM and the CMA) to formalize the ad hoc group that would assist Health Canada in ascertaining the nature, scope and extent of the shortage across the country, monitor the shortage, provide advice on the medical and clinical consequences and impact of the shortage on patient care and identify mitigating strategies and contingency plans (e.g., alternative diagnostic procedures) during the shortage.</p>
10 December	<p>Health Canada conducts its first teleconference with the ad hoc group. Their findings are as follows. The situation is variable across the country, with the eastern provinces and remote areas being most affected, confirming responses to Health Canada survey.</p> <p>On average, there is a 40%–60% reduction in capacity across the country.</p> <p>Approximately 10% of affected patients are critical (i.e., life–death situation); in 30%–40% of cases there is a risk of physicians making less than ideal diagnostic and treatment decisions; and the remainder of delays in scheduling elective procedures are affecting patients' quality of life.</p>

10 December <i>(cont'd)</i>	<p>Use of alternative radioisotopes or procedures is being explored (e.g., expediting clinical trials for use of sodium fluoride-18) but there are challenges:</p> <ul style="list-style-type: none"> • Alternative diagnostic procedures for one of the preferred alternatives requires a PET scan, which is not widely available, and not available in most affected, smaller institutions. • Other diagnostic tools such as MRI and computed tomography do not, in some cases (e.g., bone and lung scans), provide sufficiently detailed diagnosis. Regardless there are already waiting lists for MRI and computed tomography across the country <p>CMA president Dr. Brian Day writes to the presidents of the CNSC and AECL to express concern about the impact the shortage of isotopes is having on patient care. Dr. Day urges both to resolve the issue by determining a safe means of restarting the NRU reactor. The letter is copied to the Minister of Health and opposition health critics.</p>
11 December	<p>Health Canada holds a teleconference with an expanded ad hoc group (including oncologist, cardiologist, CSNM and CMA representatives) to discuss the shortage situation, the feasibility of alternatives and the clinical consequences of the shortage.</p> <p>The CSNM initiates its own survey via email to over 1000 facilities in Canada. The Society for Nuclear Medicine (US) surveyed the United States.</p> <p>Department officials indicate that the government is preparing to resort to legislative action to restart the NRU reactor (<i>Bill 38 An Act to permit the resumption and continuation of the operation of the National Research Universal reactor at Chalk River</i>)</p>
12 December	<p>Daily teleconference with ad hoc group continues to assess situation.</p> <p>CSNM survey results confirm Health Canada's survey results.</p> <p>Health Canada holds teleconference with the Food and Drug Administration (FDA) in the United States to discuss shortage of medical isotopes and general issues on shortages of critical health products. The FDA indicates that it continues to monitor the situation, but a prolonged shortage would pose a problem.</p>
13 December	<p>Daily teleconference with ad hoc group continues to assess situation</p> <p>The CSNM issues a press release.</p>
14 December	<p>Daily teleconference with ad hoc group continues to assess situation.</p> <p>Letter to the editors appears in the <i>Ottawa Citizen</i> congratulating parliamentarians for coming together in the best interests of patients and passing Bill C-38.</p>
15 December	<p>CSNM and CMA place an ad in the <i>Globe and Mail</i> recognizing the actions of all members of Parliament in moving beyond politics and considering the best interests of patients by passing Bill C-38.</p>
17 December	<p>Decision is made by Health Canada and members of the ad hoc group that teleconferences will continue weekly.</p> <p>Members of the ad hoc group and Health Canada continue to monitor the situation and the ad hoc group continues to meet to examine contingency plans should this happen in the future.¹</p>
19 December	<p>Isotope production is restored to pre-shutdown levels and supply across Canada is restored.</p>
2008	
5 February	<p>Dr. Karen Gulenchyn, a member of the ad hoc group, appears before the House of Commons Standing Committee on Natural Resources during hearings on nuclear safety in Canada.</p>
7 February	<p>Dr. Christopher O'Brien, a member of the ad hoc group, appears before the House of Commons Standing Committee on Natural Resources during hearings on nuclear safety in Canada.</p>
12 February	<p>Dr. Doug Abrams, member of the ad hoc group, appears before the House of Commons Standing Committee on Health during hearings on nuclear safety in Canada.</p>
5 March	<p>Ad hoc group meets with the Honourable Tony Clement, Minister of Health, to present the discussion paper <i>Lessons learned from the shutdown of the Chalk River reactor</i>.</p>
<p>¹ Health Canada held daily teleconferences with the ad hoc group from 9 to 14 December, then continued calls on a weekly basis. In most recent memory, Health Canada used this "swat team" strategy only once before, during the SARS crisis of 2003.</p>	

Appendix 3: Authors and advisors

The Ad Hoc Working Group on Medical Isotopes included

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