ENSURING RELIABLE MEDICAL ISOTOPE SUPPLY

Hedges, K.¹, and Malkoske G.²
¹Atomic Energy of Canada Limited, Mississauga, Ontario, Canada
²MDS Nordion, Ottawa, Ontario, Canada

1. Introduction

This paper describes the role of MDS Nordion and AECL in ensuring a reliable global supply of medical isotopes. The first part of the paper discusses the uses of medical isotopes, their importance to the medical community, and the benefits to patients of a secure supply of medical isotopes. The second part describes the role of the NRU reactor and the future role of the MAPLE reactors and New Processing Facility being commissioned at AECL’s Chalk River Laboratories for production of medical isotopes to meet the world market demand for the next 40 years.

MDS Nordion is the world’s leading supplier of medical isotopes. These isotopes are used to conduct some 34,000 nuclear medicine procedures performed every day around the world, such as determining the severity of heart disease, the spread of cancer, and diagnosing brain disorders. These medical isotopes are currently produced primarily by AECL in the NRU reactor at Chalk River, Ontario, Canada.

2. Maintaining an Essential Source of Global Supply

Every day more than 34,000 nuclear medicine procedures take place using medical isotopes supplied by MDS Nordion and produced in reactors owned by Atomic Energy of Canada Limited (AECL). Sustaining this daily supply stream of medical isotopes requires a commitment to patients around the world to meet their healthcare needs. Essential criteria for the supply of medical isotopes includes reliable and continuous supply, proven product quality and timely delivery for patient use (Table 1). These factors drive the safe, production, processing, and timely delivery of medical isotopes from AECL’s reactor facilities and MDS Nordion’s processing operations.

<table>
<thead>
<tr>
<th>Essential Criteria for Medical Isotope Supply</th>
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<tr>
<td>Reliable and continuous product supply</td>
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<tr>
<td>Proven quality and product characteristics</td>
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<td>Predictable and consistent product yields</td>
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<tr>
<td>Economical supply and timely delivery</td>
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<td>Meets all regulatory requirements</td>
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⇒ patient healthcare needs must be met, every time, all the time

Table 1: Essential Criteria for Medical Isotope Supply

The NRU reactor located at Atomic Energy of Canada’s (AECL’s) Chalk River site in Ontario, Canada has been, for many years, the world’s largest supplier of Molybdenum-99, and several other medical isotopes. Over the last decade, supply reliability has been excellent. NRU, which started operation in 1957, has been upgraded with a number of significant safety enhancements and a remaining life assessment is well advanced. Based on these factors it is anticipated that NRU will continue to reliably operate until at least 2012.

2.1 Importance of nuclear medicine

For physicians and patients, molybdenum-99 is the world’s most important medical isotope. Eight out of ten nuclear medicine diagnostic procedures depend on this isotope. It has particular significance in diagnosing cancer and heart conditions.
Other isotopes produced in the NRU reactor are iodine-131 used for a variety of treatment applications including thyroid cancer therapy and diagnostic imaging, iodine-125 used for treating prostate cancer and xenon-133 used for lung ventilation studies. The MAPLE facilities will be dedicated to the production of these key isotopes (Figure 1).

There are some 100 applications of medical isotope scans used in today’s medical procedures. More than 34,000 patient procedures are performed daily worldwide using medical isotopes supplied by MDS Nordion (over 12 million procedures annually). Overall, some 60 countries globally rely on Canada for a substantial portion of their reactor-produced isotope needs.

Some of these procedures are performed using medical isotopes that have left the NRU reactor only 41 hours earlier. This is truly a just-in-time business and a global endeavour (Figure 2). As the radioisotope decays, MDS Nordion must deliver the product to the customer as quickly as possible. Over 5000 hospitals in North America depend on this supply each week. Other examples of hospitals around the world that rely on the supply of medical isotopes currently produced at AECL’s NRU reactor include 850 hospitals in Germany, more than 1000 hospitals in Japan, and 250 hospitals in Argentina.

MDS Nordion’s medical isotope supply and isotope technology continues to be the foundation for the discovery of new ways to diagnose and treat disease. Today, molybdenum-99 is the most extensively used isotope. However, new medical techniques are providing opportunities for iodine-131, iodine-125 and xenon-133. Radioisotope technology is being applied to develop new ways to target and treat cancer. It is now possible to deliver the radiation right at the cellular level from within the body. Known as radioimmunotherapy, monoclonal antibodies are used to carry the radioisotope to the cancer cell where...
radiation destroys the individual cell and largely spares healthy cells. The treatment is offering new hope for conditions like non-Hodgkin’s lymphoma. MDS Nordion is a supplier of the medical isotope, iodine-131, being used in this product. Canadian enterprise has become an essential partner for biotechnology companies to develop their leading-edge treatments by radiolabelling molecules.

Medical isotope innovation continues to unfold. Recently the USFDA has unveiled their Critical Path Opportunities List to advance innovation in medical products as part of the USFDA Critical Path Initiative. The importance of bringing new drugs to market faster will have a direct application to the use of nuclear science to support public health needs. “Molecular imaging” is leading to new ways to develop drugs. Molecular imaging is the term used for an emerging set of drug development tools that are based on nuclear technologies and are anticipated to help bring drugs to market faster, more economically and with a greater probability of success.

For example, at the developmental stage, it allows researchers to track the bio-distribution of a drug in animals and therefore, to better translate the results into humans. Molecular imaging could also be used at the clinical and commercial stages of drug development to identify which patients could benefit from a particular drug before they take it and then monitor how well it performs. This can be used for diagnosing or treating heart disease, cancer and neurological disorders. MDS Nordion is positioning itself as a leader in this area because of its expertise in radiation technology and access to radioisotope supplies.

Some other recent examples of innovative developments include the development of iodine-131 labeled antibody for a severe form of brain cancer and an iodine-131 labeled fatty acid for neuroblastoma, an often fatal childhood cancer.

2.2 Canada’s important role in ensuring isotope supply

MDS Nordion’s distribution to top export destinations (Table 2) reveals an interesting picture of the relative importance to Canada of this global supply chain, which starts at Chalk River Laboratories and Ottawa and extends to many locations around the world.

<table>
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<tr>
<th>MDS Nordion’s Distribution of Exports</th>
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<tr>
<td>Europe 17%</td>
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<td>United States 50%</td>
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<tr>
<td>South America 80%</td>
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<tr>
<td>Japan 85%</td>
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(Source: figures are estimated; MDS Nordion data for medical isotopes, 2005.)

If today for whatever reason, the Chalk River Site and NRU reactor were not available for isotope production, there would be a shortage in global supply of medical isotopes. Collectively, all other reactor producers of isotopes in the world cannot fill the supply gap that would be created by the unavailability from NRU. MDS Nordion does maintain supply agreements to back up short-term isotope requirements from the handful of reactors in other countries that produce reactor-isotopes. But, if NRU is unable to supply isotopes for an extended period, beyond a routine maintenance shut down, there is not enough global capacity to supply the world’s demand for reactor-produced medical isotopes.

3. The role of the NRU reactor

NRU, which has played a key role in supplying medical isotopes to date, has been in operation for a period of time approaching 50 years. AECL continues to invest in safety system upgrades, plant life extension programs, and performance improvement initiatives for the NRU reactor. AECL has spent more than $30 million Canadian over the past 15 years upgrading the reactor’s safety systems to current standards and has increased the spending rate for reactor operations by about 25% to improve safety and performance.
These increases are in the areas of staffing level, training, spare parts, life cycle management work, safety assessments, and improvement plans.

AECL has proactively undertaken the NRU reactor Improvement Initiative Program Plan to industry best practices. The Program was developed from peer review and is presently focused on eight areas for improvement:

- Human Performance,
- Operational Decision Making,
- Plant Status Control,
- Housekeeping,
- Learning Organization,
- Foreign Material Exclusion,
- Conduct of Maintenance, and
- Management Effectiveness.

The reactor continues to operate with a high degree of assurance of safety and reliability. AECL has requested, and the Canadian Nuclear Safety Commission (CNSC) staff have recommended at Commission Hearings on April 26, 2006 and June 28, 2006, that the Commission extend the Chalk River site licence, which include the operation of the NRU reactor for a time period of 63 months, to October 31, 2011. A Commission decision on the Chalk River site licence is expected in July 2006.

Over the past five years, the performance of the NRU reactor to meet market demand for Mo-99 has exceeded 97%. This performance was measured over 1700 shipments from AECL to MDS Nordion and is calculated as follows:

\[
\text{Performance} \% = \left(1 - \frac{\text{number of short or late shipments}}{\text{total number of shipment}}\right) \times 100
\]

However, replacing isotope production in this aging reactor with production in the MAPLE facilities continues to be a priority for AECL and MDS Nordion in order to assure the global nuclear medicine community that Canada can continue to be a dependable supplier of medical isotopes for the world. From radiopharmaceutical companies, who are MDS Nordion’s customers, to nuclear medicine physicians, the health care system depends on Canada to supply medical isotopes reliably and routinely.

4. The new Dedicated Isotope Facilities

To ensure a reliable, continuous supply of medical isotopes, two MAPLE reactors and a New Processing Facility are being built at Chalk River. In August 1996, MDS Nordion contracted AECL to build these facilities and the project was initiated in September 1996. The objectives of the project were to design, build, and commission two identical 10 MW MAPLE reactors and a processing facility that would start commercial production of medical isotopes in calendar year 2000.

The environmental assessment for the project was approved in April 1997, construction approvals were granted in December 1997, and all construction work was completed in 29 months by May 2000. Figure 1 shows the MAPLE reactor and the isotope processing facility buildings (these are the buildings with beige siding). The photograph also shows the NRU reactor in the background and the NRX reactor, which was shut down in 1992, to the right in the photograph.
Today, the two MAPLE reactors and New Processing Facility are collectively referred to as the Dedicated Isotope Facilities (DIF). This is the only worldwide large-scale facility dedicated to isotope production.

Medical isotope supply will continue from NRU until the Dedicated Isotope Facilities (DIF) are brought into operation.

Commissioning of the facilities has been on-going and over the last year significant progress has been made in resolving technical issues. Once commissioning of the DIF facilities is complete in 2008, there will be a gradual transition from the current NRU stream to the DIF stream. The capacity of DIF is significantly greater than the current NRU stream and this capacity supports the expected growth in isotope demand.

The MAPLE 1 reactor has been commissioned to a power of 8 MW. Commissioning was interrupted in June 2003 after the measured power coefficient of reactivity was found to be of a small positive value and different from the predicted negative value of about –0.1 mk/MW for the reactor’s initial core. This difference has consequences on the assumptions made in the safety case supporting the operation of the MAPLE reactors.

AECL has deployed significant efforts to analyze the cause for the difference between the measured and predicted values for the power coefficient of reactivity. External organizations such as Idaho National Laboratory, Brookhaven National Laboratory and INVAP are engaged in studies to arrive at causes for the difference. The CNSC has recently authorized AECL to resume low-power operation of the MAPLE 1 reactor. The reactor resumed low-power operation in June 2006. AECL has requested CNSC approval to increase the reactor power to 5 MW and conduct tests to resolve the positive power coefficient of reactivity issue. These tests are scheduled to be completed in 2007 after which the commissioning of the DIF facilities will be completed in 2008.

In support of the international efforts to minimize civilian commerce in Highly Enriched Uranium (HEU), AECL and MDS Nordion are engaged in a stakeholder review to determine the feasibility of converting their large-scale, commercial molybdenum-99 production process to Low Enriched Uranium (LEU) targets in a dedicated LEU processing facility. At this time, only approximately 2-4% of the world’s molybdenum-99 production is based on LEU targets. While significant progress has been made in developing LEU target technology for molybdenum-99 production, the transferability from low volume to high volume production processes and facilities is yet to be developed and realized. AECL and MDS Nordion remain committed to convert isotope production from HEU targets once a large-scale, commercial LEU target technology has
been developed that can be implemented in a technically and economically feasible manner, while meeting the Essential Criteria for Medical Isotope supply as set out in Table 1.

5. The MDS Nordion/AECL business relationship

MDS Nordion and AECL entered into an agreement in 1996 to construct, license, and commission new medical isotope production facilities at AECL’s Chalk River Laboratories. This project, comprised of two 10 MW MAPLE Reactors and a New Processing Facility, were to be owned by MDS Nordion. The operation and licensing of the facilities would be done by AECL on behalf of MDS Nordion. The facilities would be dedicated solely for isotope production for MDS Nordion. Originally, these Dedicated Isotope Facilities were to start commercial production of medical isotopes in the year 2000.

As noted previously in the paper, the project was substantially delayed to resolve certain technical issues. To resolve the mounting costs and ongoing operation obligation, MDS Nordion and AECL entered into a comprehensive mediation process. The mediation reached a successful conclusion on February 21, 2006 and MDS Nordion and AECL entered into a new agreement related to completion of the project and supply of isotopes. Under the new agreement AECL will assume complete ownership of the MAPLE facilities and be responsible for all costs associated with completing the project and the production of medical isotopes. MDS Nordion will continue to provide the medical isotopes for medical imaging for patients around the world.

The press releases issued by MDS Inc. and AECL are an excellent testimony to the willingness of the parties to move forward together in this important initiative.

“I am very pleased with the outcome of this process. This new agreement provides a solid basis for both parties to move forward and successfully complete this project. It protects MDS shareholders from further capital costs related to the commissioning of MAPLE and creates a more economically viable relationship going forward that allow us to continue to provide these important medical imaging products to patients around the world,” said Stephen P. DeFalco, President and Chief Executive Officer, MDS Inc.

“This is obviously a very positive outcome that strategically aligns the interests of both companies and allows each of us to focus on our core competencies while creating a stronger commercial arrangement,” AECL chief executive Robert Van Adel said in a release.

Under the new agreement, AECL will complete commissioning of the MAPLE 1 reactor and New Processing Facility by October 31, 2008. MAPLE 2 is to be commissioned and in-service by October 31, 2009. Also, MDS Nordion and AECL have entered into a 40 year supply agreement on terms similar to the NRU supply agreement. This important development will further ensure the global nuclear medicine community of Canada’s role in ensuring a reliable supply of medical isotopes.

6. Conclusion

Operation of the Chalk River Site is vital to support Canada’s role as an essential link in global medical isotope supply. The NRU reactor continues to play a key role in producing medical isotopes. At times, when NRU’s operation is disrupted beyond what is planned, our customers have temporarily been short of key products. This underscores the importance of an Operating License Renewal. This renewal will ensure NRU’s place as the pre-eminent global producer of medical isotopes until such time as the MAPLE facilities assume this role.

MDS Nordion expects that AECL, as the licensed operator of the Chalk River Site and the NRU reactor, will operate these facilities with paramount consideration to safe and reliable production of medical isotopes. Safety, quality and reliability of operation will enable Canada to remain as a premier supplier of medical isotopes for the international health care community. These hallmarks will ensure the global nuclear medicine community that MDS Nordion and AECL will continue with a reliable supply of medical isotopes.