The Future Supply of Molybdenum-99

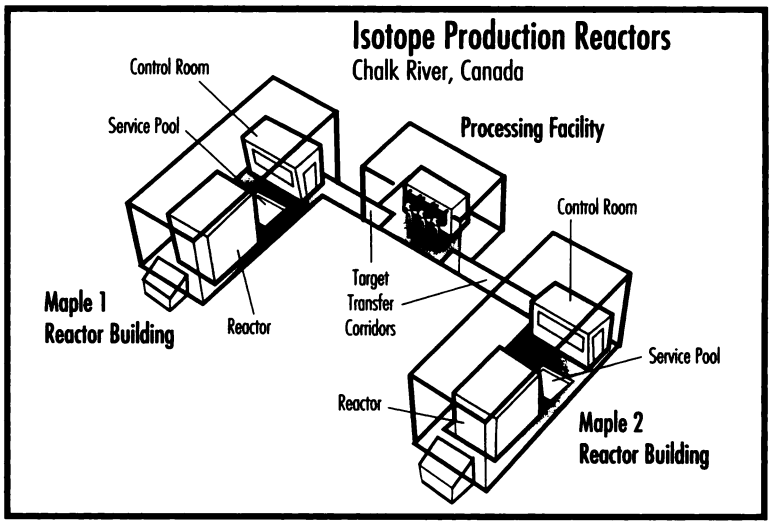
Since 1991, nuclear medicine physicians across the United States and much of the world have relied entirely on one 38-year-old nuclear reactor in Canada for the production of ^{99}Mo, the isotope used in ^{99m}Tc generators. This situation came about quietly in the 1980s as alternate suppliers dropped out of the market, leaving Nordion International Inc. in Kanata, Ontario as the major supplier in the world. While Nordion has managed to maintain a steady supply of the essential material to radiopharmaceutical makers, a series of reactor failures and labor disputes have come close to halting production several times at the facilities that produce isotopes for Nordion in Chalk River, Ontario.

After four years during which nuclear medicine professionals had concerns about the reliability of ^{99}Mo supplies, several major initiatives to bring new production reactors on-line are finally getting off the ground. Nordion officials say they will soon resume construction on two new 10 megawatt reactors that will be dedicated entirely to isotope production. Pharmaceutical giant Mallinckrodt Medical recently obtained a license in The Netherlands to begin upgrading a reactor for ^{99}Mo production for their own supply. Moreover, the U.S. Department of Energy (DOE)—despite severe budget-cutting pressures from Congress and the Clinton Administration—has sustained efforts to convert a reactor formerly used for weapons research into a back-up supplier for ^{99}Mo.

"For now, we're still vulnerable if anything catastrophic happens to Nordion's NRU reactor. But at least there seems to be definite plans on the table," said Wynn Volkert, PhD, chairman of the Society of Nuclear Medicine's committee on radioisotope supply and professor of radiology at the University of Missouri. "There are options now that we didn't have a few years ago."

Representatives from radiopharmaceutical companies are expressing similar optimism tinged with some reservations. They say all of the new initiatives will require at least a year or more before they will result in facilities capable of producing ^{99}Mo. "That means there is still a very significant period of risk for the next couple of years," said William Ehmig, a vice-president with Medi-Physics Inc., a unit of Amersham. Other industry executives point out that the building of any new facility is bound to bring increases in the price of molybdenum. The exact amount of the increase that will come from the proposed plans as well as the pass along increase in cost for technetium generators remains unclear.

Regardless of the current concerns, both radiopharmaceutical manufacturers and nuclear physicians recognize the need for a reliable back-up supply of ^{99}Mo. They know that a steady supply of ^{99}Mo is crucial to the practice of nuclear medicine. In fact, ^{99}Mo/^{99m}Tc generators are used in more than 80 % of clinical nuclear imaging procedures. Moreover, the parent isotope has a 67-hour half-life, so it cannot be stockpiled. This is why the nuclear medicine community has for years been pushing for an alternative source of ^{99}Mo in the event that Nordion's supply was ever halted. What follows are updates on the three biggest ^{99}Mo production ventures.



This diagram illustrates Nordion's proposed plans to build a new reactor facility for the production of ^{99}Mo. The site will have two identical reactors and a processing facility.

Nordion's Plans for Maple-X

With plans drawn up to build a new reactor facility, Nordion executives may have felt even more compelled to get their plans off the ground after a glitch occurred in the aging NRU reactor at Chalk River last April. Production was halted for five days when a fuel rod became stuck and could not be readily withdrawn from the reactor. Nordion managed to maintain shipments to generator manufacturers by calling on a back-up agreement with the Institute National des Radioelements (IRE) in Belgium. IRE provided material for use in Europe and supplies were ready for emergency approval

POTENTIAL NEW SUPPLIERS OF MOLYBDENUM-99 IN THE FUTURE

Supplier	Reactor	Power	Target date	Project cost	Production capacity
Nordion/AECL *Chalk River, Ontario*	Maple-X (new)	10 MW	~1998	$140 million	Up to 100% world demand
U.S. DOE Sandia National Lab *New Mexico*	ACR (upgrade)	4 MW	mid-1996	>$11.4 million	Up to 70% U.S. demand
Mallinckrodt Medical *The Netherlands*	HFR	45 MW	1996	N/A	About 25% world demand and more if needed

The chart above outlines the three biggest initiatives world wide concerning the production of ^{99}Mo. All aim to ensure a reliable supply.

by the Food and Drug Administration in the U.S., but the NRU became functional before this was necessary.

Nordion officials now say they have secured an "agreement in principle" with Atomic Energy of Canada, Ltd. (AECL) and the government of Canada to resume construction of two new reactors at Chalk River. Back in 1993, AECL tried to cancel the Maple-X project and halted construction after spending $40 million on planning and other work. Nordion and its parent company MDS Health Group Ltd. filed a breach of contract lawsuit against AECL. The suit has not gone to court yet, but the parties have been engaged in arbitration hearings where they have forged a tentative agreement. "There are some outstanding details to be worked out," said Nordion spokesman Ian Mumford.

The latest plan, calls for building two, 10 megawatt reactors and a new processing plant committed entirely to isotope production at a projected cost of $140 million.

Constructing and getting the first Maple reactor up to full power will take three years, and no start date has been set for the construction. The second Maple-X reactor will be completed a year later. To finance the project, Nordion officials originally said they would have to raise the price of molybdenum by 40% in October 1995. In September, they announced that the increase would be "something less than 40%" and that the company would delay the increase until January of next year when the agreement with the Canadian government should be finalized. (See *Newsline*, October 1995, p. 32N)

Without firm figures, radiopharmaceutical makers are reluctant to estimate how the increase would affect the cost of generators. Molybdenum accounts for about 30% to 60% of the cost of manufacturing a generator. This will mean an increase in hospital budgets at a time when administrators are being pressured by managed care consultants to cut costs. Nordion's three biggest U.S. customers, Dupont Merck, Amersham and Mallinckrodt, have recently informed their own customers about the possibility of a future increase in the cost of ^{99}Mo/^{99m}Tc generators and ^{99m}Tc unit doses and are awaiting their feedback. Ehmig acknowledges that the price increase may be a cause for con-

(Continued on page 35N)

The Birth of Technetium—By Mail Order

The reference to ^{99}Mo as the "parent" of ^{99m}Tc makes complete sense, since ^{99m}Tc was literally born from ^{99}Mo. In 1937, Emile Segre and C. Perrier received a small package sent to their Italian laboratory from the Lawrence cyclotron at Berkeley, CA, which contained ^{99}Mo targets that the two scientists had previously sent there to be bombarded with deuterons. Segre and Perrier dissolved the target in a solution of one part nitric acid and three parts hydrochloric acid. They then added manganese salts and allowed the resulting metals to precipitate. The result was a new element with a half-life of 6 hours. Since the element had to be manufactured in the laboratory, its creators dubbed it "technetium," which derives from the Greek word technetos, meaning artificial.

Perhaps a more fitting name for ^{99m}Tc would have been "freedomium", since Segre was able to use his discovery as a ticket out of facist Italy to gain entrance into the U.S. Segre persuaded Italian officials to allow him to travel to Berkeley to manufacture vast quantities of the element—which he emphasized was bringing scientific fame to Italian soil. The officials were not aware that Segre was indeed able to produce ^{99m}Tc in his Italian lab by sending shipments back and forth to the Lawrence cyclotron. It was this duplicity that allowed Segre to emigrate in 1938 and enabled him to join his mentor, the Nobel prize winning physicist Enrico Fermi. Fermi had left Italy for the U.S. the previous year, after he convinced the Italian government to allow his family to travel to Stockholm with him as he accepted the Nobel prize.

—Adapated from Marshall Brucer's A Chronology of Nuclear Medicine (St. Louis; Heritage: 1990).

Diatech Receives $10 Million for Peptide Research

In a deal that may signal the beginning of a new trend for radiopharmaceutical start-up companies, Diatech, Inc. in Londonderry, NH, recently announced that it had received a $10 million investment from Hafslund Nycomed, a large company based in Oslo, Norway that makes contrast media products. Under a five-year cooperation pact with an estimated potential value of $50 million to Diatech, Nycomed's initial investment will ensure a 17% stake in Diatech's peptide imaging drugs market.

Diatech currently has six peptide products that are in various stages of clinical trials, including P-280 which is in Phase III trials for the detection of deep vein thrombosis. The other peptides are in Phase I and II stages and are being tested as diagnostic agents for pulmonary embolism, somatostatin receptors in endocrine tumors, atherosclerortic plaque and infections of unknown origin. Diatech has not yet submitted any of its peptide products to the FDA for approval. "Nycomed's investment will significantly underwrite the cost of conducting studies for FDA approval," said Brad Miles, a spokesperson for Diatech.

He said Nycomed will make additional payments if Diatech's products win regulatory approval. "This is a giant company that was never involved in nuclear medicine, and this is their first leap into this area," said Miles. Nycomed executives recognize the promise of an imaging tool that could pinpoint diseases at an earlier stage and illustrate disease progression at a cellular level with greater sophistication than existing technology, including contrast media agents that Nycomed markets for x-rays and ultrasound. ■

Supply of Molybdenum-99
(Continued from page 22N)

cern among nuclear physicians, but he feels the new facility will be worth the extra cost. "My gut feeling is for people using unit doses out of a radiopharmacy the cost increases won't add more than a couple or three percent to their budget," said Ehmig. "And I can't think of a better way to assure a more secure supply."

The DOE's Proposal to Convert Sandia

For years, SNM leaders and other nuclear medicine leaders have been urging the DOE to build a reliable back-up facility for the production of ^{99}Mo. The DOE is currently preparing an environmental impact statement (EIS) on the production of ^{99}Mo. The department's preferred alternative is the annular core research reactor (ARR), a 2-megawatt reactor at Sandia National Laboratories in Albuquerque, New Mexico. By upgrading the Sandia reactor to 4 megawatts and adding processing equipment, Wade Carroll, the EIS Project Manager at DOE, said the DOE could provide 100% of the U.S. demand for molybdenum on a short-term basis. Carroll said the department is not planning to re-enter the market as a competitive supplier. "It would strictly be a back-up at this point," he said.

Given Nordion's plans to build a Maple-X reactor to be used solely as a back-up, the DOE's current plans to ensure a back-up supply may seem duplicative. DOE officials say they are acting on a need expressed in the nuclear medicine community and that the U.S. cannot rely on the Nordion proposal to build the two reactors to assure an adequate U.S. supply in the future. Carroll said that a decision by the DOE is expected early next year on whether or not the department will produce ^{99}Mo and, if so, at what facility. "If Sandia is selected, production of moly could occur by October of next year at the earliest," he said.

Some industry observers remain skeptical of the DOE's effort. They say the project is bound to be delayed for months, if not longer, by the DOE's decision to put together a full-blown EIS. More than a few observers have expressed dismay at what they consider a lack of responsiveness from the federal agency. "We don't feel like they are listening to their customers," said Ehmig. The major concern is that DOE has moved too sluggishly to be of much help. "The DOE has great plans, and I have no doubts about their good intentions, but I do have doubts about their budget," said Peter Vermeeren, general manager of Mallinckrodt's nuclear medicine division.

Mallinckrodt: A New Producer of Moly?

In August, Mallinckrodt received a license from the Dutch nuclear regulatory agency to begin work on medical isotope production at facilities in Petten owned by the Joint Research Center of the European Community, according to Vermeeren. The company started a trial production run in September as a step in gaining approval from the FDA to provide ^{99}Mo for generators marketed in the U.S.

"We expect to produce moly by the beginning of 1996," Vermeeren said. "We will then be able to use our own moly in Europe and in the U.S. when the FDA approves it." Mallinckrodt launched their plans about three years ago in an effort to create a secure supply of ^{99}Mo to ship generators to their customers. Vermeeren said Mallinckrodt is planning to produce only enough molybdenum to supply the company's own needs. Mallinckrodt supplies about 25% of the global market for ^{99m}Tc generators, he said, and about 20% of the U.S. market. "We are not out to conquer the world market for moly production," he said. "We're just trying to create a more stable situation and a more acceptable situation for our customers worldwide." In the event of a sudden shutdown of the NRU reactor in Canada, Vermeeren said, "it would be possible for IRE and Mallinckrodt to crank up production to supply the world."

J. Rojas-Burke