CONTENDING WITH THE ELEMENTS

Isotope supply lines remain tenuous in the U.S., but recent industry and Energy Department moves could secure additional sources for needed radioactive and stable isotopes. Federal funding and a controversial petition are at issue.

NOWHERE IS THE POTENTIAL for medical radioisotope supply problems more vexing than in nuclear medicine's dependence on molybdenum-99 (^{99}Mo). Radiopharmaceutical manufacturers use the isotope to make generators of technetium-99m (^{99m}Tc), which is used in some 80% of all nuclear medicine procedures.

Hospitals in the U.S. obtain ^{99}Mo from a single source in Canada. On January 12, 1991 that source, Nordion International in Kanata, Ontario, was forced to halt production, briefly, following the detection of airborne contamination in a reactor building. Although a back-up reactor was up and running by the end of the following day, the reverberations from the incident continue to rattle the nuclear medicine community.

Glitches in the supply of radioactive and stable isotopes, a mounting concern of researchers and nuclear medicine physicians, are raising urgent questions about the roles of the federal government and industry in ensuring that reliable sources exist for rare elements crucial to science and medicine.

In recent months shortages of isotopes have jeopardized a number of nuclear medicine clinical trials as well as the routine work of nuclear medicine departments. Cancer research on yttrium-90 (^{90}Y) labeled monoclonal antibodies ground to a halt in the spring of 1990 when the Department of Energy's (DOE) Oak Ridge National Laboratory (ORNL) in Tennessee suspended production of the isotope (see *Newsline*, May 1990, p. 18A). More recently, a disruption in the supply of gadolinium- 153 (^{153}Gd), which some hospitals and researchers still use as a source in bone densitometers threatened trials of drugs to treat osteoporosis (see *Newsline*, July 1991, p. 23N).

Stocks of ^{90}Y and ^{153}Gd are again available—after the DOE resumed production distribution of the materials—but the future of at least two segments of the Energy Department's isotope sales appear uncertain: An ambitious plan to outfit a DOE reactor for the production of molybdenum-99 has lost the support of an important industry supplier, and another firm is questioning the Department's right to sell stable isotopes such as oxygen-18 (^{18}O) used in medical cyclotrons.

Molybdenum-99

Nuclear medicine practitioners contend that the molybdenum stoppage last January—a "potentially catastrophic" event, in the words of one physician—demonstrates the peril of dependence on a single source for such a mainstay isotope and reaffirms the need for the DOE to re-enter the molybdenum supply business.

The director of DOE's Office of Isotope Sales and Production in Germantown, Maryland, Donald E. Erb, agrees, but continues to encounter resistance that could sink his plan to produce ^{99}Mo. In September 1990 Mr. Erb proposed to three American radiopharmaceutical distributors a joint study to assess the feasibility of converting a DOE reactor for production of ^{99}Mo and other commercially useful isotopes.

Prospects for the plan looked good in April when DuPont-Merck Pharmaceuticals Co., Medi-Physics Inc., and Mallinckrodt Medical Inc. agreed to contribute a total of about $250,000 for the first phase of the study (see *Newsline*, June 1991, p. 32N). Congress paved the way for work to begin by giving Mr. Erb's office the authority to borrow $8.5 million in fiscal 1992. Phase one of the feasibility plan suggested that it would be economically possible to outfit a DOE reactor for ^{99}Mo production as early as mid 1993—according to an industry source, the study leaned toward the Omega West Reactor at Los Alamos National Laboratory in New Mexico.

The DOE plan, however, was dealt a blow in late October—Mallinckrodt abandoned the DOE initiative to embark on its own feasibility study for the production of ^{99}Mo with the Netherlands Energy Research Foundation (ECN), which runs a nuclear reactor near Mallinckrodt's radiopharmaceutical plant in Petten, Holland. Company spokesperson Roxanna Motchan declined to divulge the cost of the study, but said "we do look at the project as very important."

Mallinckrodt's withdrawal will make it tough for the DOE to finance production of the isotope by taking a chunk out of the potential market. Mallinckrodt accounts for about 30% of U.S. demand for ^{99}Mo, according to Mr. Erb. Mallinckrodt officials declined to confirm that figure, but Ms. Motchan says that Mallinckrodt is the market leader in sales of ^{99m}Tc generators in Europe, the U.S., and Central and South America. Says Mr. Erb: "We're looking at a loss of some of the economy of scale anticipated, but we're soldiering on." At this writing, Mallinckrodt executives hadn't responded to requests from *Newsline* for comment.

The continuation of the DOE plan depends on commitments from Medi-

Physics and DuPont-Merck, which at this writing neither had made. Mr. Erb asked each company for some $40,000 to fund phase two of the feasibility study and a promise to buy a certain proportion of their ^{99}Mo from the DOE for five years, contingent on the price and delivery date guarantees.

To comply with these terms, industry executives say they need to be convinced that a DOE product will be cost-effective. "We're still in support of what Don Erb is trying to do, and we want to move quicker," says Alan F. Herbert, president of Medi-Physics.

DuPont-Merck's Roger Heiser, executive director of operations, says the DOE stipulations call for a commitment to buy a "significant" proportion of ^{99}Mo. "That could be a hurdle," he says. "I am concerned that DOE will not be able to supply molybdenum at a price comparable to Nordion—DOE prices on other isotopes have not been cost-effective."

An Important Crossroads

The entrance of a second supplier in the ^{99}Mo market could drive prices up. The dollars spent on ^{99}Mo now would have to be split between two suppliers, each with operating costs that would remain fixed despite volume of sales. The uncertainty ahead leads Mr. Heiser of DuPont to conclude that the radiopharmaceutical industry has reached "a very important crossroads."

"I am concerned about the price, not the supply, of this very precious raw material [^{99}Mo]," he says. Nordion will have more than enough capacity and back-up, he predicts, with two operating reactors. Mr. Heiser says that he has talked to Nordion executives about negotiating a long-term contract to set prices for ^{99}Mo over the next decade or so. If such an agreement could be struck, then the DOE plan would be pointless, he says.

Other sources agree that Nordion is a dependable supplier that has been able to maintain production with the back-up NRX reactor despite the emergency shut-down, and more recently a strike that required managers to roll up their sleeves to maintain production of key isotopes. "Ever since January 12 we haven't had a shortage [of ^{99}Mo]," says Nordion's Iain C. Trevena, PhD, vice-president of isotope products. Nordion's NRU reactor, put out of commission due to a leaky coolant pipe, is scheduled to be fired-up by January 1992 and a new reactor is expected in 1993.

Mr. Herbert of Medi-Physics praises Nordion's handling of the "responsibility of being the sole supplier of molybdenum," but says, "I'd feel more comfortable if there were another good source of molybdenum, and a domestic source would be good."

The desire for domestic sources for radioisotopes is common among nuclear medicine physicians, and biomedical and physical scientists, some of whom speak longingly of the years immediately following WWII when isotopes, no matter how rare, always seemed to be at hand from the catalogs of federally run facilities.

"Nowadays, it seems availability of isotopes is a big factor in deciding the course of research. It used to be that wasn't a factor—it was like a golden age, materials were always available," says radiochemist Richard Hahn, PhD, director of the department of solar neutrino chemistry at Brookhaven National Lab in Upton, New York.

Since the 1950s, the DOE has withdrawn from the production of dozens of products. In the last few years researchers and physicians have found themselves increasingly dependent on private-sector and foreign suppliers. The trend is viewed by some as an example of the eroding stature of the United States as a leader in science and medicine. "Why should the U.S. be put in this position of total dependence on foreign suppliers?" asks Gopal Subramanian, PhD, professor of radiology at the Upstate Medical Center in Syracuse, New York, and president of the radiopharmaceutical science council of The Society of Nuclear Medicine (SNM). "Some areas [of industry] are sacred for science and research."

Decreasing funding for isotope production and research is a factor. And each year the department expends more money cleaning up nuclear weapons sites in the aftermath of decades of escalating arms production. This year, the DOE allotted $4 billion for waste management and restoration work. Predictions for the total cost to clean up the weapons production complex have shot up from $29.9 billion to $37.7 billion to be spent over the next five years.

The clean-up expenses are draining resources for isotope production and research. Since DOE established the Office of Isotope Production and Distribution in 1989, isotope manufacturing costs have to be paid through a revolving fund that is replenished only by isotope sales. "We're almost forced to make a profit because this revolving fund has to pay for capital improvements and to meet new environmental requirements," says Robert W. Atcher, PhD, group leader for nuclear medicine research at the DOE's Argonne National Laboratory in Argonne, Illinois. "We are being held to a higher standard environmentally, and some of the money to pay for that compliance comes out of the revolving fund," he says.

The nuclear waste burden poses another problem. Fission of uranium-235 yields less than 10% of ^{99}Mo. Although the process yields small amounts of other commercially important isotopes, the majority of the fission products are waste. "Starting up a situation like that is not something a lot of the labs would welcome," says Dr. Atcher. "We had looked at [^{99}Mo production] at Argonne and the lab management decided not to take it on because of the waste." With the public outcry against radioactive waste siting and increasingly stringent government regulations in the U.S., it's no surprise that foreign sources for isotopes are gaining prominence.

For materials like ^{99}Mo in which there is a profit to be made, lack of DOE involvement, or a domestic supplier may not end up threatening nuclear medicine—if major corporations like Mallinckrodt and DuPont-Merck judge that arrangements with foreign suppliers will

keep them in business. But a more substantial threat lurks behind the shrinking role of the DOE.

If the DOE isotope production office exempts itself from markets for profitable materials, such as ^{99}Mo, can it stay in business producing experimental oddities such as calcium-46 or tin-117m, which hold promise for studying and treating disease?

Controversial Petition

The question touches a raw nerve among researchers dependent on isotopes, and it was laid bare by a petition filed with the DOE by Isotec, Inc. on July 27, 1990. The market supplier of stable isotopes based in Miamisburg, Ohio, asked the DOE to stop selling several noble gas stable isotopes, stable carbon, nitrogen, and oxygen isotopes, and enriched helium-3 (^{3}He), citing a 1965 Atomic Energy Commission policy statement refraining the government from competing with the private sector.

The DOE was flooded with letters protesting the Isotec petition after the requests for comment were printed in the Federal Register in September. Many of those who object to the petition question Isotec's ability to maintain stocks of stable isotopes. Others express alarm that Isotec bought some of its bulk material from the Soviet Union, and that the company is a subsidiary of a Japanese corporation.

When these concerns were posed to officials at Isotec's executive offices in Miamisburg, the company's Washington, D.C. law firm responded, in writing, saying that "Isotec will gladly match its record as a reliable supplier of stable isotopes against that of the DOE."

The letter from Charles L. Marinaccio of Kelley, Drye & Warren, goes on to say that Isotec obtains the raw materials for the noble gases and life science isotopes from domestic sources or manufactures them at its own facilities, which are all located in the United States. The company acknowledges that "several years ago, for approximately two years, Isotec obtained He-3 from the U.S.S.R. but no longer does so." The DOE now supplies the ^{3}He that Isotec refines and sells to end users.

The letter says criticism that Isotec is a wholly owned subsidiary of Matheson Gas Products, Inc., in turn owned by Nippon Sanso KK of Japan, carries a "strikingly protectionist and 'Japan bashing' ring..."

Oxygen-18 Shortage

Further concerns have risen among researchers at PET centers because Isotec is the main supplier of ^{18}O water and the material has been scarce for several months. "There are two problems: One, the price has doubled, and two, you can't get any of it," says Michael J. Welch, PhD, director of the division of radiation sciences at the Mallinckrodt Institute of Radiology of Washington University Medical School in St. Louis, Missouri and past-president of SNM.

The problems surfaced following the DOE's decision to cease production of ^{18}O water at the end of 1989. PET centers around the country are now reporting delays of six months to a year for new stocks of ^{18}O water. Researchers complain that the price has leaped from around $70 per gram to over $130 per gram in little over a year. For institutions, such as Dr. Welch's, that submitted budgets to granting agencies two years ago, the soaring prices threaten to soak up precious research dollars.

The surging demand for ^{18}O with the opening of new PET facilities in the U.S. and abroad is one cause for the scarcity. Isotec's lawyers told *Newsline* that the DOE withdrawal came "without any notice or warning [that] would have allowed other producers such as Isotec to increase production to meet the increased demand" and "was a prime cause of the delays in meeting demand for O-18." The company says it began building a new cryogenic distillation plant in January 1990 to boost its production of ^{18}O. The plant is scheduled to open this month. The only other source of ^{18}O water, the Yeda facility in Israel, hasn't sold the 97% enriched material in North America since 1989, placing "the major burden" on Isotec to supply nuclear medicine facilities, company officials say.

The DOE Office of Isotope Production and Distribution declined to comment on any aspect of Isotec's request, citing legal concerns about the pending petition.

The DOE is, however, negotiating with private sector companies to lease the cryogenic distillation columns at Los Alamos National Laboratory in New Mexico for production of ^{18}O. The Isotec petition calls for the DOE to cease distributing ^{18}O water. According to company lawyers, "Isotec strongly objects to the DOE's reported re-entry into the ^{18}O market... DOE has a record as an unreliable supplier, its selling prices are subsidized by the taxpayer and sufficient production capacity of Isotec and Yeda to meet world demand will soon be operational."

Isotec maintains that current prices for ^{18}O water are only marginally higher than they were in March of 1988, reflecting inflation and the costs of capital investments to increase isotope production capacity. For PET researchers with DOE grants, however, prices jumped when special reduced rates for those researchers were discontinued in 1989, the company says.

Isotec has petitioned the DOE before. The Energy Department discontinued sales of carbon-13 following a petition from Isotec. The EG&G Mound Applied Technologies facility in Miamisburg, Ohio, is a DOE outlet for stable isotopes and stands to lose further business because of the current Isotec petition. The Department's action soliciting comments on the stable isotope petition—a break from past responses—is a sign of opposition to the petition within the DOE. The Department is expected to render a decision on the matter this month.

Helium-3

The petition would wrench from DOE's Mound facility the profitable sales of the stable isotope ^{3}He. A decay product of tritium produced for nuclear weapons, ^{3}He is available for sale in bulk only from the DOE and the Soviet

Union. Thousands of liters of commercially enriched ^{3}He, worth about $1 million, produced by DOE are sold each year. Isotec buys the material in bulk from DOE and sells enriched quantities to a variety of industries. The ^{3}He is used in neutron detectors, and has applications in nuclear power plants, well drilling, laser manufacturing, and physics and chemistry research.

Some isotope researchers argue that shrinking the DOE line of money-making products, such as ^{3}He, indirectly threatens support for research.

Leonard F. Mausner, PhD, director of the isotope distribution office of Brookhaven National Laboratory, sums up the concern of many researchers: "We need relatively exotic isotopes in small quantities and only intermittently, so even a compromise situation in which the DOE may not compete with private industry is a problem," he says. Eliminating the DOE market for profitable isotopes would leave the department even more strapped for funds and undermine research on rare materials, Dr. Mausner contends.

Dr. Mausner is involved in an effort at Brookhaven to develop tin-117m complexes, which he says show promise for treating chronic bone pain caused by cancer metastases. For some research isotopes, they and other researchers depend on a bank of aging calutrons at Oak Ridge National Laboratory in Tennessee left over from the WWII effort to build atomic bombs.

Investigators at Mound are developing methods to separate and enrich calcium-48 (^{48}Ca) and calcium-46 (^{46}Ca), which may prove useful for assessing bone metabolism and studying osteoporosis. The mammoth expense of the isotopes—$3.5 million per gram for ^{46}Ca—presents an investment risk that few private companies would likely hazard if profit is the bottom line. Chemists at Mound are experimenting with less expensive ways to separate the isotopes and William R. Wilkes, PhD, isotope separation manager at Mound, believes the effort is worthwhile. "Nobody out there in the private sector is likely to take the risks to develop new uses of isotopes," he says.

Critics of the DOE isotope production effort say that some petitions have benefitted the nuclear medicine community. "Molybdenum, cyclotron products, a number of isotopes have been petitioned out of production by the DOE, and that's both good and bad," says independent consultant Henry H. Kramer, PhD, who has worked with industry and the DOE. It's bad if petitioners fail to meet market demand for isotopes. But often the private sector is able to produce isotopes at a lower cost, says Dr. Kramer, since they aren't strapped with the heavy overhead of the national labs or the dense bureaucracy of the federal government.

"They [DOE] have to learn how to be competitive," concurs Carl Seidel, manager of radiopharmaceuticals and radioactive source products at Dupont-Merck. Considering developments such as Mallinckrodt's commitment to study ^{99}Mo production in Holland, the private sector seems less than convinced that DOE involvement is the only way to make isotope supply lines less tenuous.

From the perspective of researchers who use isotopes, Dr. Hahn of Brookhaven says that "the Isotec petition has helped focus people's attention on the issue of isotope supply, but it's not clear what the answers to all the questions are—if you had all of these programs under private ownership, would you find that it's only the profitable isotopes that get accentuated? Would companies only produce the important [or profitable] isotopes?"

Dr. Hahn heads the National Academy of Sciences committee on nuclear and radiochemistry, which expects funding soon to study the availability of research isotopes. The committee plans to identify the needs for specific isotopes and to try to convince federal funding agencies that isotope production facilities should be maintained. The group will study the effects of the reorganization of the DOE's isotope production effort.

"After the revolving fund was set up in 1989, for example, the costs of some of the materials went up considerably," Dr. Hahn says. "We need to ask how these changes have affected the scientific community."

Accelerator-Produced Isotopes

U.S. scientists already view with envy colleagues in Canada, Japan, and parts of Europe where a continuous supply of accelerator-produced isotopes is available for medical research. In the U.S., many research isotopes are produced in particle accelerators at national labs primarily used for physics research. These machines operate only intermittently, reducing access to isotopes and preventing the progress of some long-term clinical trials.

For this reason, nuclear medicine researchers are lining up behind the proposed National Biomedical Tracer Facility (NBTF), for which The Society of Nuclear Medicine produced a feasibility study with funding from the DOE. The Society leaders and government relations staff are meeting with White House officials this month to seek support for the NBTF.

As described in the feasibility study, the NBTF would be equipped with a 100 million electron volt cyclotron capable of producing most of the radioisotopes used currently or envisioned for biomedical application. The NBTF would augment the isotope production work at the Brookhaven National Laboratory and at the Los Alamos National Laboratory, though the study notes the uncertain future of these accelerators due to larger machines planned and under construction for high-energy physics research.

With the widespread sense of urgency among researchers and nuclear medicine physicians, government officials face some pressing questions. If Congress decides to step in to ensure the availability of research and medical isotopes by funding the NBTF, will government funding also be available to maintain the isotope enrichment machinery at DOE sites? Says one frustrated DOE official: "There are medical isotopes now limited in supply that need not be—we could be producing them."

J. Rojas-Burke