Darrell Fisher: Isotope production in the United States

A dispute over a repair outage at one Canadian reactor, and a decision to cancel two others, have heightened concern over medical isotope supplies. A leader in the field gives his views on whether production can increase in the United States.

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Fisher recently spoke with *NN* Senior Associate Editor E. Michael Blake about the current status and near-term future of radioisotope production and use in the United States.

Fisher: "National policy must include options for low-level waste disposal for medical isotope production and use."

What does your position as scientific director entail?

I provide scientific and technical advice and forward planning, working with federal agencies that have an interest in isotope availability for a broad array of applications in science, medicine, industry, space travel, defense, and oil exploration. My focus is on better alignment of our isotope program with critical national needs, and on ways to channel sufficient federal resources to help the program achieve mission objectives.

What are the main challenges?

In my personal view, key decision-makers in the federal government have come to expect availability of stable and radioactive isotopes without comprehending the resources needed to make them available. Congress doesn't fund isotope production. "Isotopes for peaceful applications" was a founding mission of the Atomic Energy Commission in 1954, but today you won't find this essential mission identified in any current federal agency strategic plan. It has become something of an overlooked or forgotten national priority. The production and processing infrastructure is aging, we lack modern facilities dedicated to isotope production, and our national production capability has not kept pace with advances in molecular nuclear medicine and the needs for isotopes in biomedical research.

For example, the calutrons at Oak Ridge National Laboratory for the electromagnetic separation of stable isotopes were shut down in 1998 at a time of oversupply, but today inventories are depleted for many stable isotopes needed as enriched targets for radioisotope production and scientific research. The proposed National Biomedical Tracer Facility was never built. We have come to rely on foreign imports for a high percentage of the radioisotopes used for nuclear medicine procedures in our hospitals and clinics. With the cancellation of Canada's Maple-1 and -2 reactors [*NN,* June 2008, p. 17], we have become more dependent on the Canadian National Research Universal (NRU) reactor in Ontario for iodine-131 and molybdenum-99 generators to supply technetium-99m.

These and other challenges were highlighted in a recent National Research Council report, "Advancing Nuclear Medicine Through Innovation" (September 2007), which recommended an enhanced federal commitment to isotope production. ANS has long recognized these challenges, and its Special Committee on Isotope Assurance, chaired by David Hill, called for changes in federal policy, new production capabilities, and an appropriated R&D program. Advisory groups have recommended high-level coordination among federal agencies and increased appropriations.

Which federal policies encumber isotope production and use?

Public Law 101-101 (1990) required full-cost recovery, which increased the cost of commercial isotopes and had the unintended effect of nearly eliminating the production of research isotopes. Congress canceled support for research, such as the Advanced Nuclear Medicine Initiative, and education and training programs that help replenish the pipeline of skilled scientists and engineers. The Energy Policy Act of 2005 did little to support medical isotope production, but much to discontinue the use of high-enriched uranium, which is needed for cost-effective medical isotope production with minimal generation of radioactive waste. While it is essential to safeguard radioactive materials against theft or diversion for illicit purposes, eliminating radioisotopes needed for critical applications in medicine, the military, and homeland security seems to make little practical sense.

I think that we have enormous scientific and technical talent in the United States to solve the isotope crisis and find an appropriate balance between safeguards and isotope availability, but we seem to be lacking a well-coordinated federal office that oversees the production and use of radioisotopes for legitimate and beneficial purposes. Other countries have gone forward with incredible vision, innovation, and enthusiasm. For example, the Korean government supports an impressive national strategy that promotes radiation technology and isotope production—including new production reactors and cyclotrons.

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Would it be better to rely on private industry rather than government to meet our isotope needs?

Yes, but the federal government has an important role: strengthening national laboratory R&D capabilities, supporting research, building and operating next-generation facilities for research isotope production, and encouraging federal-private partnerships that encourage companies to invest in isotope production and related products. Some radioisotopes, such as americium-241, which is needed for oil exploration, can be provided only from materials left over from the government's plutonium production and separation activities.

What can we do to provide domestic sources of molybdenum-99?

When the two Maple reactors were under construction in Canada, it seemed unwise to try to compete. The situation has changed substantially, and we may be compelled to rethink the policy of foreign dependency. It will take years to establish a new national isotope production capability infrastructure. Encouraging are private initiatives by the University of Missouri at Columbia's research reactor (MURR) and some major nuclear technology companies to establish that capability in the United States.

So none of the U.S. national labs has stepped forward to be the focus of isotope production?

The national laboratories want to do this, but we don't have a fully dedicated production facility. The High Flux Isotope Reactor (HFIR) at Oak Ridge National Laboratory and the Advanced Test Reactor (ATR) at Idaho National Laboratory were built and are operated mainly for other purposes. They weren't designed for continuous production of short-lived radioisotopes, and they have substantial down times. We need to make new investments in nuclear technology.

Is the evolution of diagnosis and treatment likely to alter the demand for specific radioisotopes?

Yes, of course. Progress in molecular biology has fundamentally changed the dynamics of isotope use. Molecular nuclear medicine has made it possible to target single cells with unique isotopes, either for imaging or for treatment. Recently, this approach has evolved to the use of nanoparticle technologies for the delivery of isotopes in new ways. As technology drives the need for isotopes, we recognize that isotopes need to be carefully tailored for specific applications, and in many cases the most desirable isotope may not be available.

A radioisotope with ideal properties for treating cancer cells may be very difficult to find because it's not being produced or it can't be produced cost-effectively. We are struggling with the issue of actinium-225 supply to meet growing needs for bismuth-213 for cell-targeted radioimmunotherapy. And with new technology comes the new challenge to produce what we might consider to be more appropriate isotopes for specific applications. The best example is the increasing use of positron emitters for diagnosing disease—and not just cancer, but brain disorders, heart and circulatory disorders, infections, and other diseases. The high resolution provided by positron emitters has opened up a whole new class of potential pharmaceuticals.

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As a rule, positron emitters have extremely short half-lives.

That's correct. And because of this, private industry has found ways to produce and distribute positron emitters such as fluorine-18 for clinical diagnostics. Our isotope program helps by producing strontium-82/rubidium-82 and germanium-68/gallium-68, which are produced by accelerators at Los Alamos National Laboratory and Brookhaven National Laboratory and sold by the isotope program to major health care suppliers.

You mentioned molecular biology. Does it become an even more elaborate process to bond a radioisotope to a molecule with a geometry that's appropriate for attachment to a specific cell? Does this also factor into the shelf-life issue?

This question involves labeling chemistry and radiation effects on protein delivery vehicles. The short half-life of many ideal radioisotopes precludes a long shelf life. One generally tries to administer a radiolabeled compound as soon as possible after radiolabeling to minimize dose to the carrier protein and to maximize the specificity of the carrier to a population of cancer cells expressing the receptors.

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You mentioned the decline in federal support for teaching programs in radiochemistry and nuclear technology. Is that more of a problem specifically in the United States, or is it happening pretty much worldwide?

We've seen a number of training programs reduced in the United States, while elsewhere these programs are becoming increasingly sophisticated. The result is a graying of our nuclear workforce, as has been experienced in other nuclear technology sectors. With reduced focus on radioisotope technology R&D, the amount of grant money for graduate and undergraduate students has been reduced. At PNNL, we see a lot of expertise retiring or leaving, and that expertise is hard to replace.

There's been a long-standing policy across several administrations to convert reactors from high- to low-enriched uranium. Does this affect the extent to which medical isotopes can be produced?

I think it represents a major challenge for the isotope industry. As I mentioned earlier, the technology is available, but the costs will be higher and the amount of radioactive waste generated will be greater. It may not be practical on a large commercial scale, and some reactors could not be converted. For example, one would not expect this conversion to take place in our nuclear navy.

In the United States, how many administrations of radioisotopes are there for medical purposes?

About 35 million per year, including imaging and treatment. Diagnostic uses of positron emission tomography (PET) radioisotopes are increasing at a rate of about 20 percent per year.

And about how often are the at-risk isotopes from Canadian sources used in the United States?

Technetium-99m is used in about 30 different radiopharmaceuticals for bone scans, liver scans, and kidney function tests, among others. Iodine-131 is commonly used for diagnosing thyroid disease or treating thyroid carcinoma. Something like 80 percent of nuclear medicine procedures involve Tc-99m, and 5 percent involve I-131. They are important to our health care system.

In your view, have the problems at the NRU reactor and the cancellation of Maple-1 and -2 spurred any action in the United States?

Yes. We have a new opportunity to plan modern facilities that will be needed well into the 21st century. Congress will need to understand that we should not be dependent on foreign supplies of stable and radioactive isotopes, including americium-241, californium-252, iodine-125, gadolinium-153, and others.

A fair number of the medical isotopes have short half-lives, but some of them don't. Many of them have half-lives up to 30 years. Is the closure of the Barnwell low-level waste facility going to affect what isotopes are likely to be used?

National policy must include options for low-level waste disposal for medical isotope production and use. However, our situation is not as serious as it is for the nuclear power industry.

What new technologies may be available in the future for isotope production?

Alternatives to large and expensive reactors and cyclotrons may include compact systems. Compact accelerators and neutron generators may provide more versatile and less expensive ways to produce a wider variety of research isotopes needed in small quantities. Federal programs should be looking toward compact systems to help solve a number of needs for both stable and radioactive isotopes. One such system is the PULSAR compact linear proton accelerator built by AccSys Technology and Hitachi. As this and other compact systems are developed and tested, I think we will see new opportunities to improve the isotope supply in the United States. NN