

The campaign to resume domestic production of molybdenum-99

By E. Michael Blake

What may be the country's most energetic new nuclear development effort is entering the licensing phase.

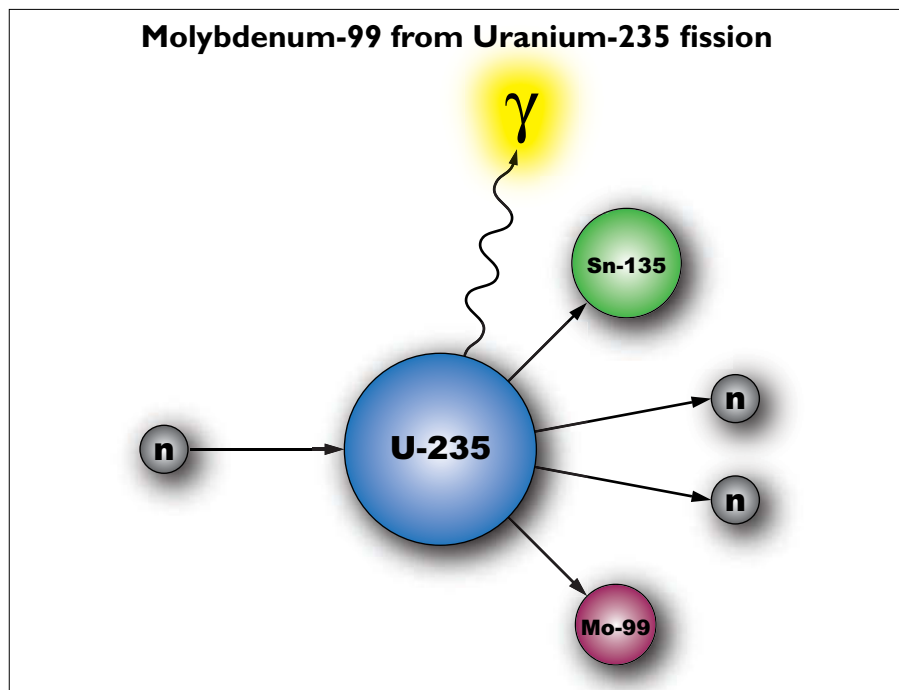
For many years, technetium-99m has been the most widely used radioisotope in nuclear medicine procedures. As the most populous developed country in the world, the United States uses nuclear medicine to a greater extent than any other country. (As of 2009, half of the nuclear medicine procedures in the world were performed here.) For many years, however, the United States has depended on facilities in other countries to provide Tc-99m, and a combination of the dwindling reliability of

these suppliers and the short duration of the isotope's usefulness has forced health care providers to wait for availability, seek other sources, or put some patients' procedures on long-term deferral. With the federal government pursuing a dual mission to restore production capability and decouple it from the use of high-enriched uranium (HEU), several organizations have begun initiatives to create new production facilities for the

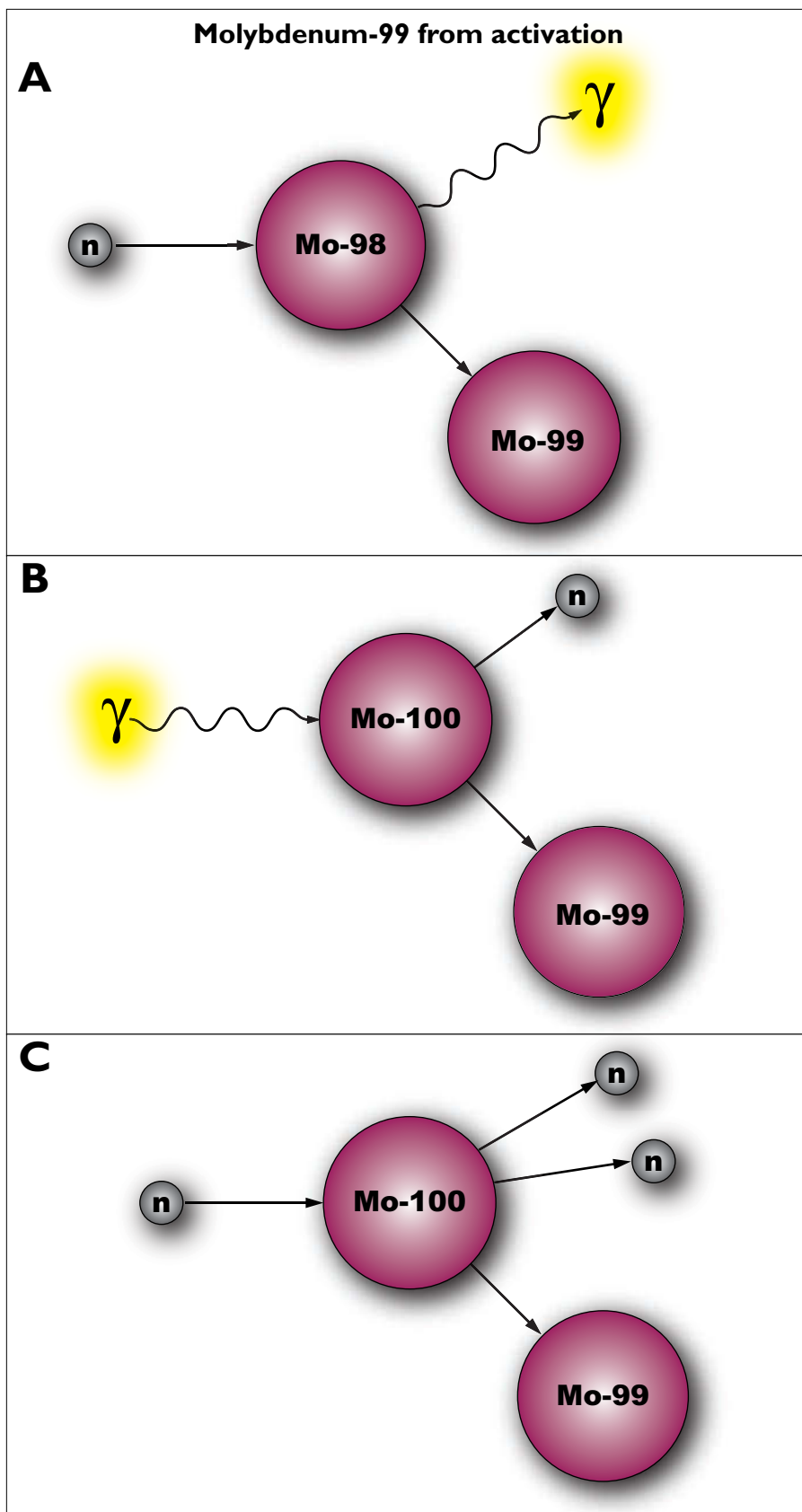
precursor to Tc-99m, molybdenum-99. As part of that effort, they have also explored new ways to produce the material and to control the environmental impact of its production.

If one were to take the goals of all of the proposed new Mo-99 producers and add them together, the United States could go from making none of the stuff to making about five times as much as is now used. Upon closer examination, however, it becomes apparent that some of the proposed facilities could stop short of their theoretical maximum productivity, and some would be capable of producing a variety of radioisotopes in addition to Mo-99. One thing that all of the approaches have in common is the absence of HEU (in part because of the National Nuclear Security Administration's offers of cost-shared funding for systems that don't use it), although some ventures try to get as much fissionable material involved as would be acceptable. With the definition of low-enriched uranium (LEU) set at anything below 20 percent U-235, the candidates' targets are usually referred to as enriched in the range of 19.5 to 19.75 percent. The NNSA seeks to minimize HEU production and use worldwide, including in the United States, in the hope of minimizing the availability of weapons-grade material.

The NNSA also considers the availability of Tc-99m a national priority, and a quarter-century of dependence on sources from abroad has become especially dire in about the past five years. The National Research Universal (NRU) reactor at Canada's Chalk River Laboratories in Ontario was found to be unqualified for continued operation by Canada's erstwhile regulatory agency, the Atomic Energy Control Board, but the regulator was overridden by Parliament and



The uranium-235 fissions that produce this result are common enough that it is worthwhile to extract Mo-99 from irradiated targets, but the vast majority of the fission products are not the ones shown above. Tin-135 is cited in the scientific literature as the other product in this fission; it is extremely unstable, with three beta-decays with half-lives shorter than 20 seconds, then further beta decays from iodine (half-life 6.585 hours) to xenon (9.1 hours) to cesium (3 million years) to stable barium-135.



The diagrams may make these processes look simple and straightforward; in fact, the processes work only under very limited conditions, and even then do not always produce Mo-99 in very much quantity. In the first case, a nucleus of Mo-98 absorbs a neutron, becoming Mo-99 and emitting a gamma ray. In the second case, Mo-100 receives enough energy from an input gamma to lose a neutron and become Mo-99. In the third case, neutron bombardment of Mo-100 can free two neutrons, leaving behind Mo-99. Not shown: the theoretical, but not yet dependable, bombardment of zirconium-96 by an alpha particle (helium-4 nucleus), to release Mo-99 and a neutron.

was kept operable. The NRU is scheduled to close for good next year, however, and the MAPLE-X reactors that were to replace it were canceled. Another source—the High Flux Reactor at the European Community’s Joint Research Center in the Netherlands—is, like the NRU, an old facility prone to unplanned outages. The IER complex in Belgium has production capability, but in limited quantities. Some new capacity or productivity is expected soon in Australia and South Africa, but probably in smaller quantities than the United States usually needs, and this additional capacity would be available to both the host countries’ domestic markets and other customers worldwide.

As knowledgeable as the readers of *Nuclear News* are in the science and technology of the atomic nucleus, the day-to-day work of most readers relates to nuclear power rather than to nuclear medicine. For this reason, we now present a summary of the Mo-99/Tc-99m production process.

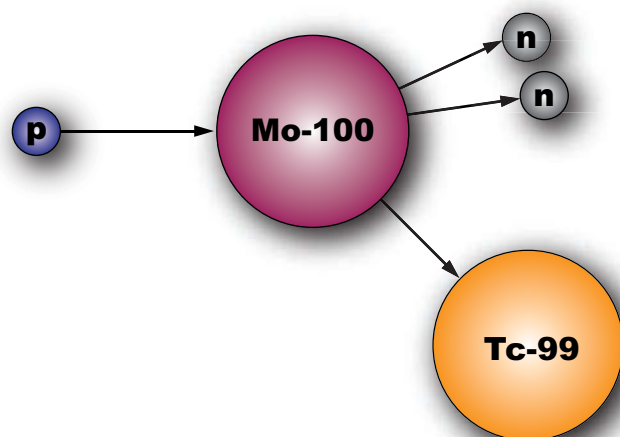
Getting the gamma rays

Traditionally, HEU has been the source for medical Mo-99 through the placement of small, readily removable amounts of U-235 in a neutron-rich environment, such as the core region of an operating reactor or the path of neutrons generated from a target impacted by accelerator particles. Mo-99 is an unstable isotope, and from a nuclear physics standpoint, what ultimately happens to this nucleus is two decays by emission of an electron (still known as a “beta particle,” from the era in which there was neither theory nor detection and analysis equipment to determine what in fact it was). This leaves a nucleus of ruthenium-99, which is a stable isotope. It is what happens during the decay process that gives Tc-99m, one of the stages between Mo-99 and Ru-99, its value in nuclear medicine.

The Mo-99 decay process involves the emission of not only beta particles, but also a gamma ray (photon) with an energy of 140,510 electron-volts. Gamma rays of this energy provide especially useful images of conditions inside the human body, in regions such as the heart, brain, and kidneys. Sometimes the gamma emission occurs before the first beta emission, and then the beta emission produces Tc-99, which is not able to provide worthwhile imagery. When the first beta emission occurs before the gamma emission, the result is Tc-99m, with the suffix “m” indicating that it is still capable of emitting a gamma.

While decades of study have made it possible to identify radionuclides and predict (in quantities of at least several atoms) what they will do, and when, it is not yet possible to control any of the decay process. The Mo-99 nuclei that emit their gammas before their betas cannot be prevented from doing so, any more than post-gamma Tc-99 nuclei

Technetium-99 from activation



Proton bombardment of Mo-100 can yield two neutrons and Tc-99m. This might seem like a more efficient way to get to the isotope that will actually provide gamma images, but it makes the process even more time-critical. Mo-99 has a 66-hour half-life to allow for extraction and delivery. Tc-99m starts on its six-hour half-life as soon as it is emitted, leaving very little time for the radioisotope to be extracted, bonded to a drug, and positioned inside a patient. This is why, in some extraction systems, the technetium is actually discarded in favor of the molybdenum.

can be encouraged to become Ru-99 more quickly than at their existing pace, with a half-life of 213,000 years. It has been possible to work effectively with the characteristics of Mo-99 and Tc-99m, however, in part because essentially all of the gammas will be emitted fairly quickly. (Mo-99 has a half-life of 66 hours, and the half-life of Tc-99m is six hours, so one month after a sample of Mo-99 comes into existence, about 99.9 percent of its gamma activity has been spent.)

The process for making an imaging agent involves the use of properties at a more macroscopic level than the nuclear one. All isotopes of technetium have the same chemical behavior, which is also similar to that of other elements in technetium's column in the periodic table (such as manganese). First, the post-fission sample of what had been U-235 is passed through a column of acid alumina, which preferentially adsorbs Mo-99 from the other substances. When a normal saline solution is then passed through the column of immobilized Mo-99, the Tc-99 is eluted as TcO_4^- ions. The TcO_4^- can then be bonded chemically to substances that will take the technetium (with enough of it being Tc-99m and able to emit gammas) where it is needed in the human body—lipids to reach the heart, for instance.

The very long half-life of Tc-99 is a concern where fission product quantities are large (such as in the nuclear fuel cycle), but the consensus belief is that in the quantity used for a single patient in nuclear medicine, there is little safety or environmental concern from the Tc-99 beta decay to Ru-99, and this material is not retained for long in the human body. In general, the dose needed to provide useful images is

considered acceptable, and, as noted above, the gamma activity dwindles quickly.

The short half-lives of the gamma emitters may be beneficial, but they also pose challenges—especially if the material has to travel for thousands of miles, in addition to going through the separation, elution, and bonding processes (which are generally taken together to make an Mo-99/Tc-99m “generator”). The short shelf-life of Tc-99m has given rise to a specialized quantity to describe what one gets from the generator, the “six-day curie”—the dose that can be delivered six days after the Mo-99 has come into existence. After six days, Mo-99 has already entered its third half-life (leaving less than a quarter of the original substance undecayed) and its Tc-99m will have dwindled even more rapidly. The processing steps of elution, bonding to an imaging agent, and delivery to the patient lead to inherent inefficiency (very few of the Tc-99m gammas will ever produce images), which could be alleviated somewhat for patients in this country if the Mo-99 source were within three or four hours of air travel time.

Why production stopped

What follows is not a tale of woe. Anyone who wants to attribute the end of Mo-99 production in the United States to a presumed decline in American initiative, ingenuity, science education, or gumption will have to look elsewhere. Given the events and the circumstances, the decisions that were made do not appear to have been unreasonable. The fact that production depended on a single private company, rather than on a broader range of suppliers or facilities at national laboratories, might indicate a lack of

vision among decision-makers, but speculations along those lines would have to take into account whether gamma imaging would remain as it was, and whether Tc-99m was expected to remain such a widely used gamma source. It appears that the path of least resistance was followed, and for several years there was no reason to second-guess this choice.

Until the late 1980s, Mo-99 was produced in the United States by Cintichem, a division of the research firm Hoffman-LaRoche that is now no longer in the pharmaceutical business. The company operated a 5-MWt research reactor in Tuxedo, N.Y. By 1989, it was determined that tritium from the reactor had contaminated surface water near the site. Operation was halted, and a later risk-benefit study led to the conclusion that continued operation could not be justified. This led to the decision to decommission the reactor.

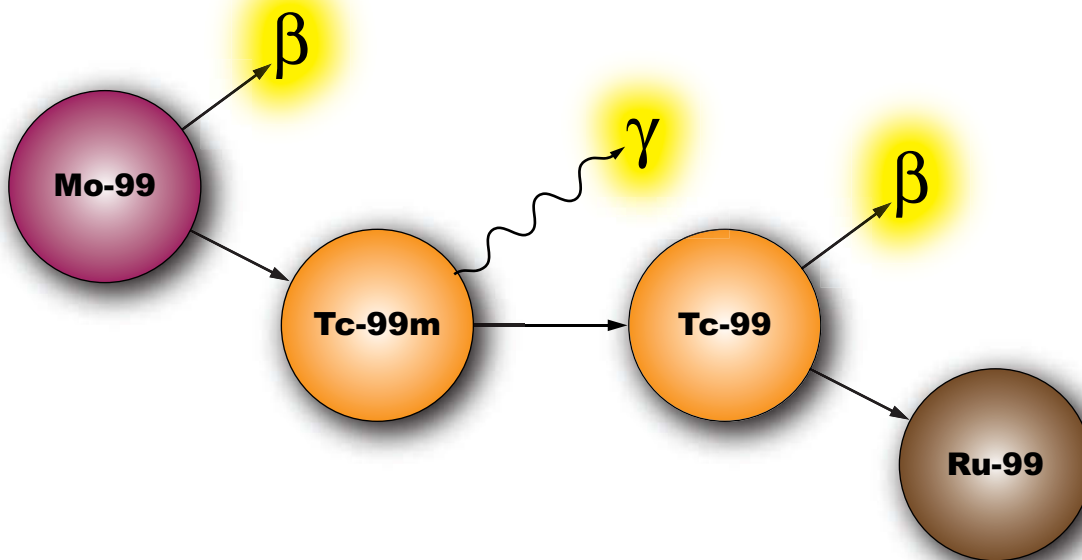
At the time that the Tuxedo reactor was closed, the techniques for Mo-99 production were limited. Cyclotrons could be used to make small amounts at a high cost, while reactors could deliver the product at less expense, but without the reckoning of substantial externalities: HEU at the front end, and a slew of fission products at the other. Mo-99 was just one of many of those fission products. Several of the other fission products from reactor-based production either had scant commercial value or presented management and disposal issues. With the NRU in its prime, able to turn out large quantities of Mo-99 dependably (and with it being possible to think of all environmental considerations as Canada's problem), nuclear medicine providers in the United States generally had little difficulty scheduling Tc-99m procedures.

This doesn't mean that the situation was just accepted with a shrug. Congress established the Isotope Production and Distribution Program in 1991, and the Department of Energy tried a number of times during the 1990s to reestablish domestic production (including through purchase of the Cintichem process). One attempt ended after a tritium leak at Los Alamos National Laboratory, and the effort to produce Mo-99 essentially ended when it was concluded that what could be done through a DOE-supported project at Sandia National Laboratories would not be economically competitive with existing sources, including the NRU.

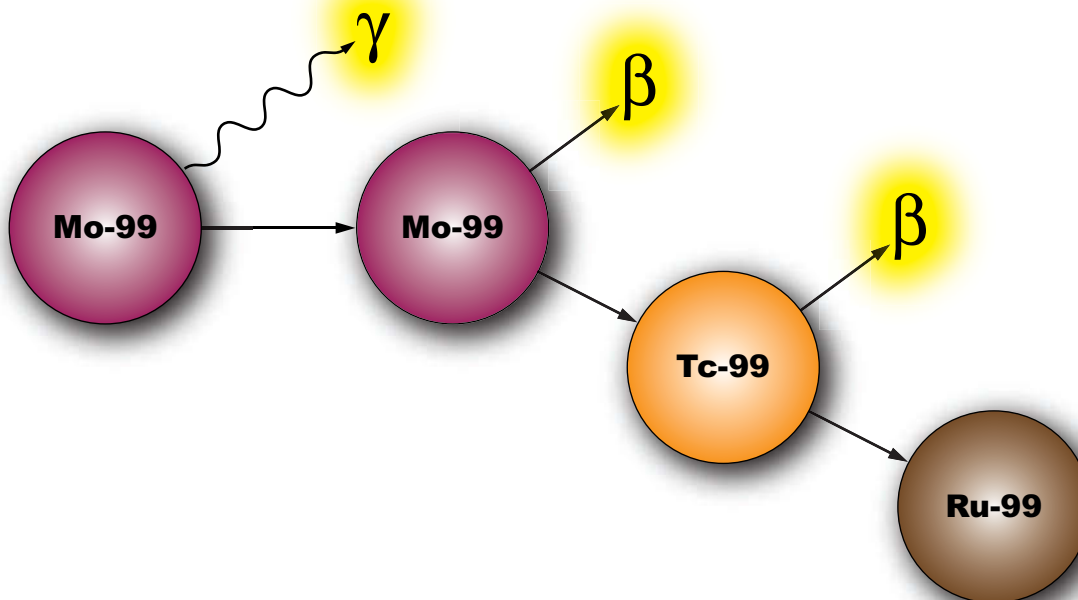
It also appeared that Canada would have no trouble maintaining the supply. In 1986, design work had begun on the MAPLE project, which ultimately included two reactors intended specifically for isotope production. At that time there was no reason to expect what actually came to pass: Atomic Energy of Canada Limited and its pharmaceutical partner, MDS-Nordion, abandoned the project in 2008, before either new reactor

Molybdenum-99 to Ruthenium-99

A



B



If the Mo-99 emits the beta without emitting the gamma, the result is the Tc-99m that medical professionals (and patients) want. If the Mo-99 emits the gamma before emitting the beta, the result is the lower-energy Tc-99, which serves no medical purpose. With enough technetium atoms in a sample, it is generally assumed that enough of them will be Tc-99m to provide a worthwhile gamma supply. As for the final stage in the decay, Tc-99 has a half-life of 213,000 years. Technetium is not found in nature, and nuclear technology first produced it in 1936. In the 78 years that technetium has been produced, therefore, almost none of it has settled into the stability of ruthenium-99.

could begin production, because of nuclear safety concerns. By this time, the NRU had become much less reliable, and even the Parliamentary edict for its continued operation cannot make the NRU what it was before.

Making it where it's needed

And so, we have entered an era in which the development of new capacity is encouraged, some ventures have started work (one of which has made it to the point of a license application), new techniques may make production more environmentally benign, and, despite the fact that it has remained a

staple of gamma imaging, Tc-99m has recently come to be used less often than it had been. Still, it is estimated that Tc-99m is used in roughly 80 percent of nuclear medicine procedures, whereas that share was once around 90 percent. Contributing to the decline in the use of Tc-99m are delayed or canceled procedures because of supply outages, the use of some alternatives (such as thallium-201, which emits gamma rays in the range of those from Tc-99m, has a half-life of 73 hours, and decays by electron capture to stable mercury-201), and the development of new techniques—or, as medical

professionals call them, “modalities”—that have increased the range of work that can be done in nuclear medicine.

What follows is probably not a comprehensive summary of every prospect for Mo-99 production in the United States, because we have chosen to exercise some judgment as to how feasible some of those prospects are. Ventures that exist only as declared intentions on websites, with no indication of broad expertise, substantial funding, or involvement with an established pharmaceutical firm, are not included here. (Not every venture included here has all of

the above in place, but they all have at least one of them.)

We must first acknowledge what may have been the first project of the new era, although it is not currently on track for licensing. The **Babcock & Wilcox Company** announced in 2009 that it had formed a partnership with the pharmaceutical firm **Covidien**, aimed at the licensing, construction, and operation of an aqueous reactor for the production of Mo-99. In 2011, B&W presented a paper at the 1st Annual Molybdenum-99 Topical Meeting, held in Santa Fe, N.M., declaring the successful demonstration of a proof-of-principle test loop. B&W has held meetings with the Nuclear Regulatory Commission staff to prepare for the submittal of a license application. There has been no such submittal yet, however, and since 2012, there have been no further discussions. B&W has informed *NN* that the project is “suspended on most technical aspects, but we are continuing ongoing analysis and discussions with the marketplace.” The aqueous reactor would be based on a B&W 1950s version of the original concept, which involves fission through uranium salts dissolved in water.

SHINE Medical Technologies has gone the farthest in the NRC licensing process. The company submitted a construction permit application in two parts, and both parts had completed the acceptance review process last December. SHINE’s project has also been defined by the NRC as a production and utilization facility, allowing for two-step licensing, with an application for an operating license to follow the decision on the construction permit application. The company intends to operate a facility in Janesville, Wis., and to produce iodine-125 and -131 and xenon-133, in addition to Mo-99.

SHINE’s approach shows how innovation has been proposed to alter the traditional production process. Fission-product Mo-99 would be generated, but in an accelerator-based system. SHINE’s partner, **Phoenix Nuclear Labs**, has developed a system to accelerate deuterons into tritium in a gas target, and the resulting fusion neutrons irradiate an LEU sulfate solution. According to SHINE, this allows for Mo-99 extraction without the acid-column step and for the reuse of the target solution.

On September 19, more than nine months after docketing, the NRC staff took SHINE to the next step of the process by issuing a request for additional information (RAI) on the company’s application. The RAI is 106 pages long, and the NRC requested a response within 30 days. Welcome to nuclear licensing, SHINE. (There had been some earlier discussion of a draft RAI, so SHINE had some advance knowledge of the content.)

To some extent, new production ventures branch off from existing infrastruc-

ture, notably universities with research reactors or nuclear engineering programs. One such starting point for Mo-99 ventures has been the University of Wisconsin at Madison, not far to the north of Janesville. Also nearby, south of Janesville in Beloit, **NorthStar Medical Radioisotopes LLC** broke ground in July for a facility that would support its work at the University of Missouri Research Reactor (MURR) in Columbia, Mo., where the company is developing a neutron capture process to generate Mo-99, but could also include a linear accelerator intended to use one or both of the most likely approaches for production without fission: gamma-ray bombardment of Mo-100, spurring neutron emission and leaving Mo-99 behind, and neutron capture of Mo-98, yielding Mo-99. The linac could also produce other isotopes for which a demand exists, such as actinium-225.

Mo-98 and Mo-100 are both stable isotopes, and while both processes involve neutron emission, NorthStar expects that they can be licensed entirely through Wisconsin’s agreement state program, rather than through the NRC. The reactor/fission approach, however, would be NRC-regulated. NorthStar has received cost-shared funding from the NNSA for both of its approaches.

Taking on what may be the biggest regulatory challenge is **Coquí Pharmaceuticals**, a Puerto Rico-based venture that would not only produce reactor-based fission-product Mo-99, but would do so in reactors that do not yet exist, and therefore must be permitted and licensed through the NRC. The company has an arrangement with the University of Florida to use college-owned land in Alachua, Fla., to build a complex that would include two open-pool reactors from the Argentine company **INAVAP** for the production of Mo-99 and various other radioisotopes.

Perhaps because this project needs its own reactors, Coquí has already had to defer some of its licensing target dates. Originally aiming for the submittal of both construction permit and operating license applications in March 2014, the company now plans to deliver a preliminary safety analysis report and environmental report to the NRC in mid- to late 2015.

A recent entry comes from **Niowave Inc.**, based in Lansing, Mich., which produces superconducting electron accelerators. The process is another that would send neutrons into a U-235 target to yield fission-product Mo-99, but in this one, it is an electron accelerator that is directed at the targets. Niowave has stated an intention to submit an application to the NRC by the end of this year to begin the first phase of the licensing process, which would be limited to the irradiation of uranium metal targets and would not extend to chemical separation or dissolution of the targets.

Perma-Fix Medical Corporation has declared that it has demonstrated portions of a proprietary process to make nonfission production (neutrons into Mo-98) practical. The company has not announced a schedule for production, and the lack of fission may allow it to forgo NRC licensing. At the 8th International Conference on Isotopes, held August 24–28 in Chicago, Ill., the company’s chairman, Lou Centofanti, stated his plans to apply to the Food and Drug Administration in the fourth quarter of this year. He also stated that Perma-Fix has set up a subsidiary in Europe; some of the demonstration work has been done in Poland.

In Centofanti’s view, the problem with production from Mo-98 has been the adsorption of molybdenum. He said that Perma-Fix has developed a micro-porous composite resin that can adsorb up to 70 percent of the molybdenum in a sample, compared to about 2 percent from an acid-alumina column.

Northwest Medical Isotopes (NWMI) began as a venture of the Samaritan Health Services hospital system in Oregon, spurred by the hospitals’ difficulty in obtaining Mo-99/Tc-99m five years ago. (A similar motivation led to the establishment of **Coquí**.) In another connection to an academic program, NWMI would develop a facility in Corvallis, Ore., that would make use of a production process developed by, and to be employed in the reactor of, Oregon State University. The company has had meetings with the NRC in preparation for the submittal of a construction permit application.

Those appear to be the main players at this stage, although the NRC has also received letters of intent from **GE Hitachi Nuclear Energy**, **Eden Radioisotopes**, **Flibe Energy**, and **Precision Engineering Consultants**. If there are other major contenders that would operate in the United States that we have not listed here, we will surely be notified. While many of the ventures above have set target dates for the startup of Mo-99/Tc-99m deliveries, we have chosen not to mention these dates because, in a fairly untested environment for licensing, the companies should perhaps not be held to them.

Also, while the prospects for Mo-99 production that departs from reactors and uranium may ultimately offer even more environmental and nonproliferation benefits than the switch from HEU to LEU, they may not provide the kind of made-in-the-USA assurance that is also sought in the current campaign for new production. Molybdenum has seven stable isotopes, and while Mo-98 is the most abundant, it accounts for less than a quarter of all natural molybdenum. For the Mo-98 and Mo-100 processes to be worthwhile, the target material needs to be enriched in those isotopes. And at the moment, enriched Mo-98 and Mo-100 are available from only one source: Russia. **NN**