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The Shortage of Technetium-99m and Possible Solutions

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Abstract

Following a major shortage of ^{99}Mo in the 2009–2010 period, concern grew that the aging reactor production facilities needed to be replaced. Most producers were using highly enriched ^{235}U (HEU) as the target material. The Organisation for Economic Co-operation and Development and the International Atomic Energy Agency sought to remedy these issues by removing HEU from medical isotope production and implementing full cost recovery to enable new production entities to compete with the existing multipurpose reactor facilities, which were heavily subsidized by their respective governments. This review examines the various approaches to producing ^{99}Mo and/or ^{99m}Tc with a critical eye toward their potential success in (*a*) producing the medical isotopes and (*b*) being able to successfully enter and compete in the market. Because many of the new approaches are adapting existing technologies for commercial businesses, some of the details are of a proprietary nature and not available for in-depth technical review.

Contents

1. INTRODUCTION

Technetium-99m (^{99m}Tc), the most widely used radioisotope in nuclear medicine, is used in more than 80% of all nuclear medicine procedures. The expansive use of this radioisotope derives from the fact that ^{99m}Tc ($t_{1/2}$ = 6 h) is produced via the decay of its parent radionuclide, ^{99}Mo ($t_{1/2}$ = 66 h). This isotope pair is made into a generator, which is supplied to nuclear medicine departments around the world, providing a convenient source for imaging patients throughout the day. Following a major shortage of ^{99}Mo in the 2009–2010 period, concern grew that the aging reactor production facilities needed to be replaced. To understand the origins of the shortage and possible future shortages of ^{99}Mo, one must understand the evolution of the current commercial market for supplying the ^{99}Mo/^{99m}Tc generator system for diagnostic medical imaging.

2. BACKGROUND

Working at the Donner Laboratory at Lawrence Berkeley National Laboratory in the 1950s, Hal Anger developed a γ-ray detector that had a wide field of view, opening the possibility of determining the radioisotopic distribution in a human subject. Initially, the radioisotope available was ^{131}I (1). With the invention of the ^{99}Mo/^{99m}Tc generator at Brookhaven National Laboratory in 1958 by Tucker, Greene, and Richards (2), the possibility of having a readily available source of radioisotopes in a medical center became a reality. Initially, the simple molecule of sodium pertechnetate was used for thyroid scans. Over the next several decades, teams of chemists began creating sophisticated molecules to use in diagnosing many clinical conditions (3). Probably the most widely used tracers included those for monitoring cardiac function (4).

The initial source of ^{99}Mo was the ^{98}Mo(n,γ)^{99}Mo reaction (5). However, with the combined masses of the two molybdenum isotopes, the generator system had to be relatively large to handle the gram quantities of material. With the development of the fission-based source of ^{99}Mo

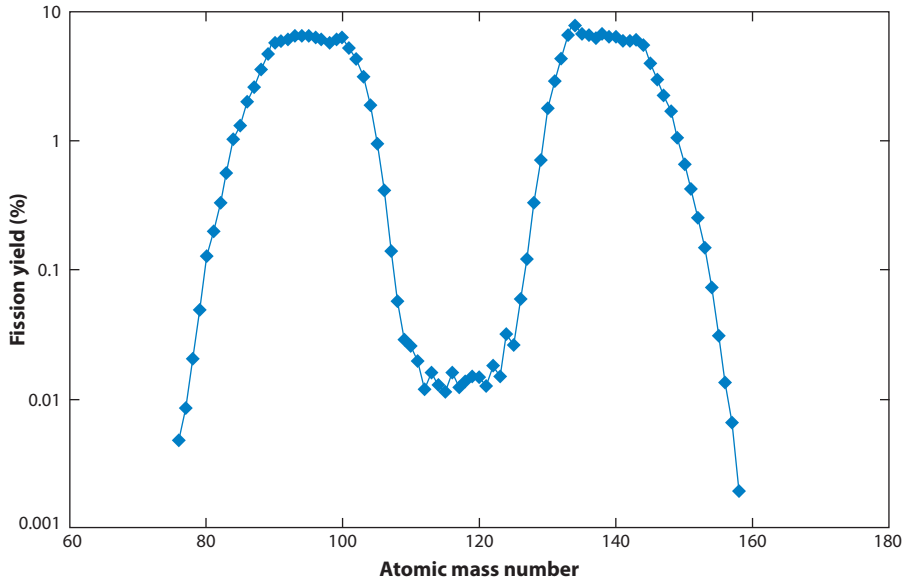


Figure 1

^{235}U thermal neutron fission yield curve illustrating the distribution of isotopes by mass and their respective yields from the fission. Adapted with permission from Reference 7.

(^{235}U(n,f)^{99}Mo) (6), ^{99}Mo could be isolated from the fission product soup of elements at high specific activity (high radioactivity-to-mass ratio). As shown in **Figure 1** (7), in the distribution of fission products, the mass at 99 is near one of the peaks of the bimodal distribution. Thus, approximately 6% of all fissions of ^{235}U result in ^{99}Mo.

Over the last several decades, ^{99}Mo was produced from the fission of HEU (>90% ^{235}U) in multipurpose research reactors built for diverse nuclear programs in their respective countries. In the early 2000s, the world market for ^{99}Mo was supplied by research reactors that used HEU targets. These reactors included the National Research Universal (NRU) in Canada, the High Flux Reactor (HFR) in the Netherlands, the Belgian Reactor 2 (BR2) in Belgium, SAFARI-1 in South Africa, and OSIRIS in France. The Australian Nuclear Science and Technology Organisation (ANSTO) in Australia and the RA-3 reactor in Argentina supplied regional markets using low enriched ^{235}U (LEU; <20% ^{235}U) targets (8).

2.1. Overview of Production and Processing of ^{99}Mo

The steps required at each of these sites involve target preparation and irradiation for about 6 days at their respective reactors. At the end of bombardment, there is a short cooling-off period to allow short-lived radioactivity to decay (<1 day) before the target(s) is transferred to the site's processing facilities. Depending on the target construction used, there will be different chemistries involved—primarily dissolutions and solvent extraction followed by ion column separation and isolation. Each irradiating facility uses a separate process facility; some are colocated with the irradiation facility, while others send their irradiated targets to a separate location.

The NRU in Canada uses chemistry laboratories within their complex (actually, the same building) for dissolution of the targets and removal of the uranium target material and isolation of the volatiles. Then the fission products are sent to MDS Nordion (~30 km away) for final

purification. The HFR has labs in a separate building in Petten, the Netherlands, a short truck drive away, as does the BR2 in Belgium, which sends its targets for processing to the Institut National des Radioéléments (IRE). The SAFARI-1 reactor in South Africa uses the laboratories at Nuclear Technology Products (NTP), and the Open Pool Australian Lightwater (OPAL) reactor uses the labs at ANSTO.

Once the ^{99}Mo is separated and purified, it is sent to generator manufacturers. From there, the generator manufacturers sell the packaged generators in different quantities (1–20 Ci) to large hospitals and centralized radiopharmacies, where individual doses are dispensed in syringes for single patient injections.

All of the HEU material used in the production of medical isotopes is purchased from the US Department of Energy (DOE) and sent to CERCA (Compagnie pour l'étude et la réalisation de combustibles atomiques, the French Government company that prepares uranium targets to the producers' specifications), where the HEU is made into targets, either as aluminum alloy plates with the HEU in the middle or as rolled tubes. Each company owns its respective HEU supply. The DOE controls how much HEU is needed based on its production schedule for each year (8).

The purified ^{99}Mo is shipped to the manufacturers. In some cases, shipment is within their respective facilities, while in other cases it can be to generator manufacturers at great distances. For example, Curium, which is collocated at the HFR, prepares generators there and ships some to their facility in Missouri, where generators are prepared for the North American market. Lantheus (Massachusetts) receives shipments from a number of ^{99}Mo producers, such as NTP (South Africa), IRE (Belgium) and OPAL (Australia).

The industry uses the term six-day curie: a unit of measure that takes the ^{99}Mo decay rate into account and represents an average amount of ^{99}Mo that would be available for use after six days. Some have suggested dropping this approach to the measurement of the amount of ^{99}Mo in a generator (9). According to Paterson et al. (10), the use of the term six-day curie is applied inconsistently: The calibration time is given variously as time since end of production, time since leaving production facility, or time since arrival at the technetium generator manufacturer (9, 10).

2.2. Production Status Through the 1990s

As indicated above, at the turn of this century, fission-produced ^{99}Mo was handled by the NRU in Canada (which started operation in 1957), the HFR in the Netherlands (1961), the BR2 in Belgium (1961), SAFARI-1 in South Africa (1965), and OSIRIS in France (1966). All of these reactors were multipurpose and had been built by their home countries' respective governments for various neutron-based research. The production of ^{99}Mo became an added use.

2.3. MAPLE Project

In the late 1990s, MDS Nordion contracted with AECL (Atomic Energy of Canada, Limited), the operator of the NRU reactor, to build two 10-MW reactors for the sole purpose of producing fission ^{99}Mo. This venture was called the MAPLE (Multipurpose Applied Physics Lattice Experiment) project. The targets were designed to be HEU with each reactor capable of producing the world's demand. The Canadian Nuclear Safety Commission would not give permission to operate because of an unexpected positive reactivity coefficient: As the reactor power increased, the neutron flux would continue to rise. The reactors had been designed to have a negative reactivity coefficient, meaning the neutron fluxes would decrease. In that sense, the reactor design would control itself and not "run away." After numerous design reviews that did not reveal any flaws in the design, AECL canceled the project in 2010 (9).

In some respects, the initiation of the MAPLE project hindered any competitive projects because the market is so narrow and profit margins at the production stage are so small (8). Thus, any plans to replace the aging reactor fleet worldwide were delayed for a decade or more (9).

2.4. Supply Disruption

Following the tumultuous years of 2009–2010, which saw shortages of ^{99}Mo due to several major producers going offline, a number of alternative approaches to producing this important radionuclide have been developed along with the securement of supplies from existing facilities and plans to replace some of the aging facilities.

2.5. Removal of Highly Enriched ^{235}U

For the last two decades, beginning shortly after the terrorist attacks in the United States in 2001, the International Atomic Energy Agency and the US National Nuclear Security Administration (NNSA) have been trying to eliminate the use of HEU for civilian purposes. Previously, efforts were focused on converting research reactors from using HEU fuel to LEU fuel whenever possible.

A relatively small amount of HEU can be used to prepare a fissile device, while ^{235}U of less than 20% does not have sufficient ^{235}U to do so. The more recent efforts were to move away from HEU-based targets to LEU targets (8). To have the same amount of ^{235}U as target material, four to five times more uranium would be required (HEU $\approx$ 93% ^{235}U, while LEU $\approx$ 19% ^{235}U). Because the US DOE supplies the ^{235}U used in the preparation of the targets, it has major control of the supply chain. This explains the interest from the NNSA, a division within the DOE (8).

In South Africa, the SAFARI-1 reactor used HEU of approximately 50% enrichment sourced from within South Africa (8). In 2010, SAFARI-1 began conversion to LEU targets, and by 2015, 95% of the targets were of LEU construction. The ANSTO-OPAL reactor has been built from the start to operate with LEU targets, and the HFR in Petten, the Netherlands, has converted as of 2018. In the meantime, the OSIRIS reactor in France stopped ^{99}Mo production in 2015. Also, the NRU reactor at Chalk River in Canada ceased production in 2018 without having converted to LEU targets, and the BR2 reactor in Belgium has not completed conversion (9). Two other reactors in Europe supply irradiated targets to the processors in the Netherlands and Belgium (the Maria reactor in Poland and the LVR-15 in the Czech Republic). Each has recently converted to LEU targets.

3. ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT/NUCLEAR ENERGY AGENCY

The Nuclear Energy Agency (NEA), a division of the Organisation for Economic Co-operation and Development (OECD), convened after the shortages to address the problem (9). Steps included establishing coordinating schedules, which would ensure sufficient production capability during regular scheduled outages for routine maintenance, and building in an outage reserve capacity to provide sufficient capacity from operating reactors during unscheduled outages of other reactors.

The NEA also publishes a yearly report showing the ^{99}Mo demand plus projected production and processing capacity. These projections, which cover the existing year and look forward 5 years, include the existing reactor facilities plus the proposed new facilities using their respective estimates for capacity and start-up times (11). Because the data are self-reported and difficult to assess, there is a resulting level of uncertainty.

In addition, the NEA Working Group instituted the concept of full cost recovery (FCR) (11). FCR was established to recognize that, historically, all of the major producers had used multipurpose research reactors constructed by their respective governments and that, if new independent entities were to compete, there had to be a level playing field in terms of recovery of the costs of construction and start-up because government-subsidized facilities could undercut the costs of production.

4. NORTH AMERICAN RESPONSE TO ^{99}Mo SHORTAGE

In the United States, the NNSA, in response to the American Medical Isotopes Production Act of 2012 (9), supported projects that made use of the ^{98}Mo(n,γ)^{99}Mo reaction to produce the desired product and the ^{100}Mo(γ,n)^{99}Mo reaction. For ^{99}Mo production, a reactor or neutron source is required, while a powerful electron beam that produces high-energy photons through the Bremsstrahlung process is required to produce the ^{100}Mo(γ,n)^{99}Mo reaction. Other approaches included using power reactors as the source of neutrons and developing new alternative sources of neutrons, such as accelerator-based methods.

Some privately funded projects have pursued the construction of new reactors dedicated to the production of radioisotopes, principally ^{99}Mo. In Canada, there were basically two approaches pursued: One used the (γ,n) approach, while the other made use of the ^{100}Mo(p,2n)^{99m}Tc reaction to produce the 6-h product directly, bypassing several steps including the need for the generator. In the following sections, the advantages and disadvantages of each approach are discussed along with their respective statuses at the start of 2020.

5. PROPOSED NEW APPROACHES IN THE UNITED STATES

The NNSA has funded four companies in a cost-sharing approach ($30 million in matching funds from each awardee). As of the end of 2019, the awardees are NorthStar (two projects), Shine, Niowave, and Northwest Medical Isotopes (NWMI) (12). There are several other projects, some with brief descriptions (others are not described because of a lack of available information). These include the following (along with the proponents' anticipated starting dates):

- BWXT: 2021 (15)
- Coquí RadioPharmaceuticals: 2022 (14)
- Eden Radioisotopes: 2023 (13)
- Global Medical Isotope Systems: beyond 2024 (12)
- Magneto-Inertial Fusion Technologies: beyond 2024 (12)
- Flibe Energy: beyond 2024 (12)

These projects in the United States are privately funded. The projects in Canada were funded through grants from the federal government with a payback formula based on revenues from successful implementation of the respective approaches (16). The American Medical Isotopes Production Act of 2012 contained a sunset provision to end the export of HEU from the United States for use in medical isotope production as of January 2, 2020 (12) (however, as of the writing of this review, the DOE has lifted the ban for 2 years to allow the IRE to complete its conversion of targets to LEU; see, e.g., 17).

5.1. ^{98}Mo(n,γ)^{99}Mo

The initial proponents supported by NNSA contracts to produce ^{98}Mo(n,γ)^{99}Mo reactions were NorthStar (Wisconsin) (18) and GE/Hitachi (9). NorthStar proposed using the Missouri

Figure 2

The NorthStar Radiogenix ^{99}Mo/^{99m}Tc generator system. Photo courtesy of James Harvey, NorthStar; reproduced with permission.

University Research Reactor (MURR) (**https://www.murr.missouri.edu**) as the neutron source. MURR is a multipurpose research reactor operated by the University of Missouri. However, MURR uses HEU fuel. Plans for conversion depend on finding a fuel configuration that will not degrade the reactor's operational mission. The GE/Hitachi proposal planned to use power reactors around the United States as the neutron source (9). This latter proposal was abandoned early because the proponents felt there was not enough strength in the market for their business model.

The (n,γ) approach was first used over three decades ago (19). It can be used with natural molybdenum where the abundance of ^{98}Mo is 24% (yield is 750 six-day Ci/week) or with enriched ^{98}Mo with >99% ^{98}Mo (yield is 3,000 six-day Ci/week—a potential fourfold increase in production). The biggest challenge with this approach is that the produced ^{99}Mo is low specific activity [typically 1–10 Ci/g; the medical isotope market uses curies as the measure of radioactivity (1 Ci = 37 GBq)]. This is in comparison to the existing supply chain using fission-produced ^{99}Mo, which has a specific activity >5,000 Ci/g. Thus, generators using fission ^{99}Mo would require a very small molybdenum retention column to retain the micrograms of molybdenum needed to provide clinical generators (1–20 Ci). To provide generators of comparable strength, several grams of low-specific-activity molybdenum would be required for the equivalent amount of radioactivity. With such a large amount of molybdenum and the subsequent column size, a proportionate large volume of eluant would be required. This large volume would cause the eluted ^{99}Mo/^{98}Mo mixture to be very dilute, which would not make it compatible with existing generator columns and the subsequent tracer kits to be labeled for diagnostic exams.

5.1.1. Northstar. NorthStar (18), the proponent of this approach, spent a great deal of effort to develop a generator system (Radiogenix) that captures the ^{99m}Tc from the ^{99}Mo stream and releases the ^{99m}Tc in a concentration similar to that provided by the high-specific-activity generators. The ^{99}Mo is stored for later use (see **Figure 2**). That said, the NorthStar generator is physically larger;

it has two columns and requires more time to recycle the ^{99}Mo for capture of the ^{99m}Tc. Also, when using enriched ^{98}Mo, the material will have to be saved and returned to the manufacturer for processing into new targets.

As of the writing of this article (2020), NorthStar has received approval from the US Food and Drug Administration for use of its Radiogenix system to supply ^{99m}Tc to the nuclear medicine community (12, 18). NorthStar has been able to supply a number of doses of ^{99m}Tc for clinical use. It is not clear whether the user community will be willing to adopt this approach since it involves a different generator system and new protocols for the nuclear medicine technologists to follow. However, this approach is the only new technology operating at the clinical level as of the start of 2020.

5.1.2. BWXT. BWXT purchased some of the high-level radioisotope laboratories from Nordion in Canada with the aim of entering the production business by using the ^{98}Mo(n,γ)^{99}Mo reaction using natural molybdenum, which is ~24.3% ^{98}Mo (15), with a power reactor serving as the neutron source. BWXT is working with Ontario Hydro (Ontario, Canada) to use the Darlington Nuclear Generating Station, a power reactor supplying electricity to the Province of Ontario. BWXT has demonstrated the ability to insert and withdraw targets during hot operation of the power reactor; this means the reactor does not have to shut down to perform a target transfer. Thus, the production method can be run in parasitic mode. While this approach produces low-specific-activity ^{99}Mo, BWXT claims to have a separation and column chemistry that will allow the produced ^{99}Mo to be used directly in the existing generator systems without any modifications (15).

5.2. ^{100}Mo(γ,n)^{99}Mo

The proponents of this approach include NorthStar (9, 18) and a consortium in Canada that includes Canadian Isotope Innovations (20), a spinoff company at the Canadian Light Source (CLS), Canada's national synchrotron-based accelerator lab. While the approach has been demonstrated on a proof-of-principle basis (21, 22), it has not been demonstrated at the commercial scale. Because the cross section for photon interaction with the nucleus is several orders of magnitude lower than that for hadron interactions (cross section is 0.001 that of neutrons), the accelerator approach requires very high electron fluxes (milliamp or more) as well as multiple accelerators and efficient cooling systems associated with the heat dissipated by the conversion of the energetic electrons into photons (the Bremsstrahlung effect) (23).

In addition, because of the exponential decline in the flux of photons through matter, the energy of the production electrons must be higher than the giant resonance energy of about 16 MeV. Thus, machines capable of accelerating >35 MeV are typically used (see **Figure 3**) (23). As with the neutron capture approach, the produced ^{99}Mo will be of low specific activity (mixture of ^{99}Mo/^{100}Mo), requiring an alternative generator. NorthStar's RadioGenix system will work equally as well with this approach. That said, the target material is enriched ^{100}Mo (10% in natural molybdenum), which requires recovery and recycling. Each accelerator system is projected to produce 500 six-day Ci/week. NorthStar plans to bring its accelerator systems—multiple pairs of accelerators, with each pair sharing a common target station—online around 2023 (18). As of early 2020, NorthStar has ordered eight electron accelerators from IBA. While the CLS has demonstrated that it can produce ^{99}Mo via photon transmutation of ^{100}Mo, it has not taken further steps for commercialization.

5.3. Accelerator-Driven Fission

For a number of years, the possibility of using accelerators to generate neutrons for the fission of ^{235}U has been discussed. None of these accelerator approaches were being tested at the

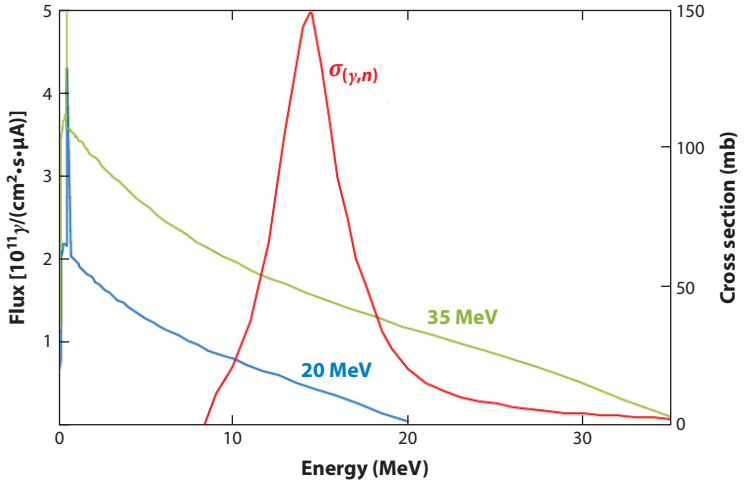


Figure 3

Comparison of Bremsstrahlung photon spectra for 20-MeV (*blue*) and 35-MeV (*light green*) electrons in a molybdenum target compared with the photonuclear cross section of ^{100}Mo (*red*) (23).

production scale because reactors were meeting the needs of the medical and research communities. However, with the shutdown of a couple of major producers in the 2008–2009 period, interest in replacing the aging fleet of reactors rose in importance. The following proponents are taking advantage of technological advances in a number of fields to explore various approaches to the use of accelerators to generate neutrons.

5.3.1. Shine Medical Technologies. Shine (Wisconsin) is pursuing an alternative approach to high-specific-activity fission ^{99}Mo (24). The company plans to produce neutrons via the D(T,*n*)^{3}He reaction. The produced neutrons would then interact with ^{235}U in a salt solution form, operating at below criticality (i.e., when the accelerator shuts off, the reactor also shuts down). The produced ^{99}Mo would be extracted periodically and processed as in other fission-based approaches. Shine's process system is shown schematically in **Figure 4**.

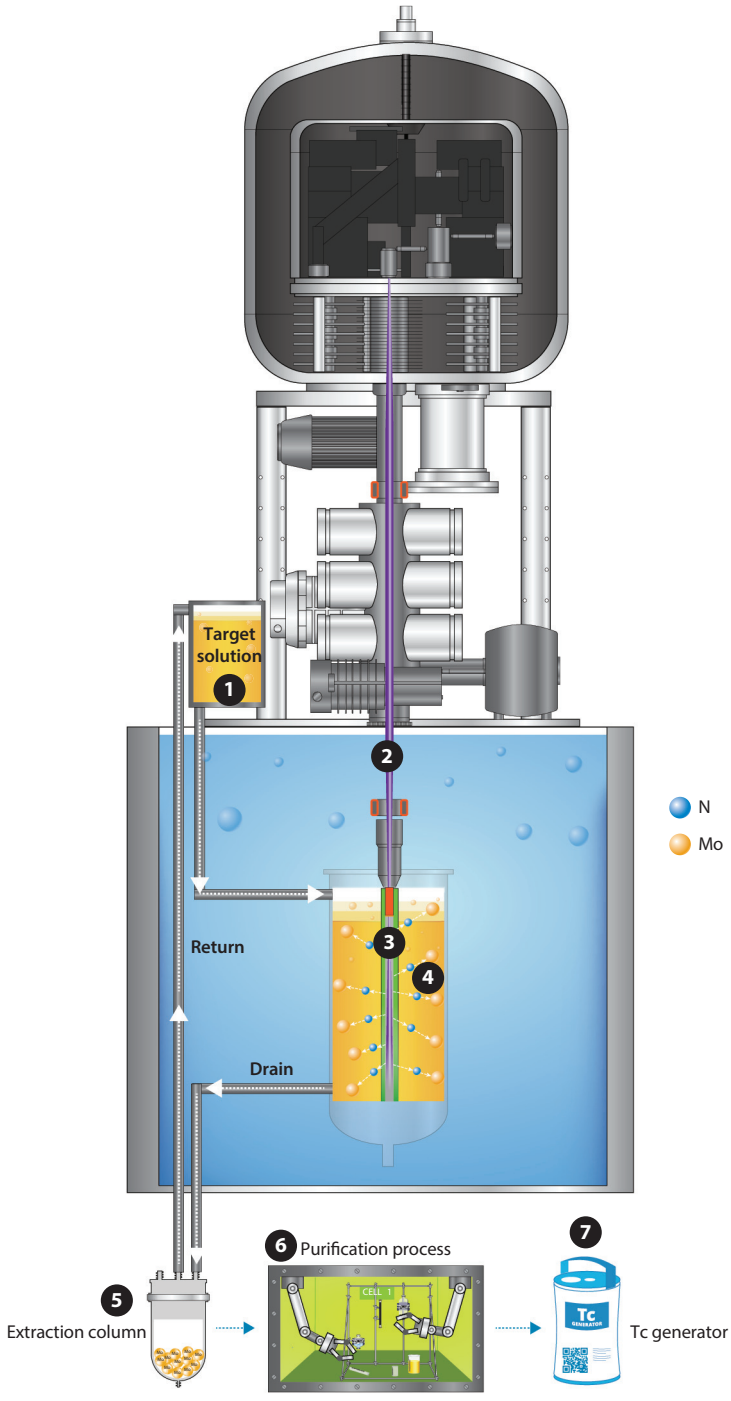
The challenges with this system include having a reliable tritium recycling system—an accelerator with enough power to supply the requisite neutrons to the liquid reactor. The tritium target must be in a windowless gas cell requiring a sophisticated differential pumping system to contain the tritium with high vacuum on the accelerator side and a high-powered deuteron accelerator. Each of the components has been tested separately, and a test facility with all parts functioning together has been demonstrated. Construction of the first of eight production systems has begun, and supply is scheduled for 2021. Shine has a supply agreement with Lantheus Medical Imaging, a generator manufacturer in Massachusetts.

5.3.2. Niowave. Niowave (Michigan) (25) has built a superconducting electron linear accelerator that will be used to generate neutrons from a liquid PbBi eutectic, which generate x-rays and neutrons that will in turn interact with an LEU assembly. The fission products will be chemically extracted in a closed loop system in which the uranium will be captured and recycled into target pellets for further use.

The components have been assembled, and the system, including the PbBi convertor, has operated at 10 kW on a natural uranium assembly. Full operation would be at the 100-kW power level.

Figure 4

Schematic of the production system being developed by Shine Medical. The top section is the deuteron accelerator and tritium recycling system; the lower section shows the liquid solution reactor and separation systems. Parts include (❶) target solution reservoir, (❷) beam line, (❸) tritium target, (❹) low enriched ^{235}U salt solution, (❺) ^{99}Mo extraction column, (❻) hot cell for ^{99}Mo purification, and (❼) final product ^{99}Mo in ^{99m}Tc generator. Figure courtesy of Katrina Pitas, Shine Medical; adapted with permission.



A 100-kW electron device could generate 10^{14} *n*/s, while a 400-kW accelerator would produce 10^{15} *n*/s. The higher-power system would produce approximately 1,500 six-day Ci/week. A Drug Master File has been registered, and an Active Pharmaceutical Ingredients document will be filed in 2020.

5.4. ^{100}Mo(*p*,2*n*)^{99m}Tc

There were two consortia in Canada that pursued the cyclotron approach. The first consisted of TRIUMF, BC Cancer Agency, the University of British Columbia, Lawson Health Research Institute, and the Center for Probe Development and Commercialization in Ontario (26–28); the second consisted of the University of Alberta, Université de Sherbrooke, and Advanced Cyclotron Systems, Inc. (29, 30). This approach is based on the 1971 report from Beaver and Hupf (31) that indicated that although direct production had possibilities, high-specific-activity fission product ^{99}Mo for use in generators was developing rapidly, and there was not a cyclotron base from which to pursue this approach.

Following the 2009–2010 isotope shortage crisis involving a lack of available ^{99}Mo, the Government of Canada requested proposals that were not based on reactors or HEU. In addition to the cyclotron consortia, there were two groups (20, 32) that pursued the photon transmutation of ^{100}Mo as described above. At the time (2010–2012), there was a growing cyclotron base within Canada and throughout the world. The direct approach was modeled on the successful distribution of ^{18}F produced on low-energy cyclotrons. Because ^{99m}Tc has a half-life three times longer than that of ^{18}F, it seemed like this approach could work on a regional basis. The concept was tested on three types of medical cyclotrons (27, 28) (see **Table 1**).

The cyclotrons covered an energy range of 16.5–24 MeV (see **Figure 5**). The steps required included updating the cross-sectional data to determine the optimal production conditions that maximized yield while minimizing the impurities—primarily the other isotopes of technetium. The concern regarding isotopic purity recognized that there were two issues to be aware of: (*a*) the radiation dose to the patient due to long-lived technetium isotopes such as ^{96}Tc ($t_{1/2}$ = 4.3 days) and (*b*) the quantity of ^{99g}Tc ($t_{1/2} = 2.13 \times 10^5$ years). The issue of ground-state ^{99}Tc impacts the ability to label certain radiopharmaceutical kits that are sensitive to the total amount of technetium present. The optimal energy range is between 16 and 24 MeV. Purity is highest at the low-energy region, while yields are highest at the upper end at the expense of increasing amounts of technetium impurities, depending on the isotopic mixture of the ^{100}Mo target (33).

To take advantage of the cross section for the (*p*,2*n*) reaction, each installed cyclotron had to be modified to operate a beam current >100 μA. For example, the PETTrace was modified to operate at 130 μA, and the TR19 was modified to operate at 300 μA while the TR24 was designed

Table 1 Energy ranges, beam currents, and end-of-bombardment yields of ^{99m}Tc for various cyclotron types

Cyclotron	Energy thickness of target (MeV)	Average beam current (μA)	Yield
PETTrace[a]	16.5–10[d]	130	4.7 Ci (174 GBq)
TR19[b]	18–10	240	13.9 Ci (514 GBq)
TR24[b]	24–10	400	26.8 Ci (993 GBq)
TR24[c]	24–10	450	39 Ci (1.44 TBq)

All irradiations were for 6 h.
[a]PETTrace cyclotron manufactured by GE (28).
[b]ACSI cyclotrons nominal 19 MeV (28).
[c]ACSI cyclotrons nominal 24 MeV (29).
[d]An energy level of 10 MeV is the point at which the desired (*p*,2*n*) reaction does not significantly contribute to the yield of ^{99m}Tc.

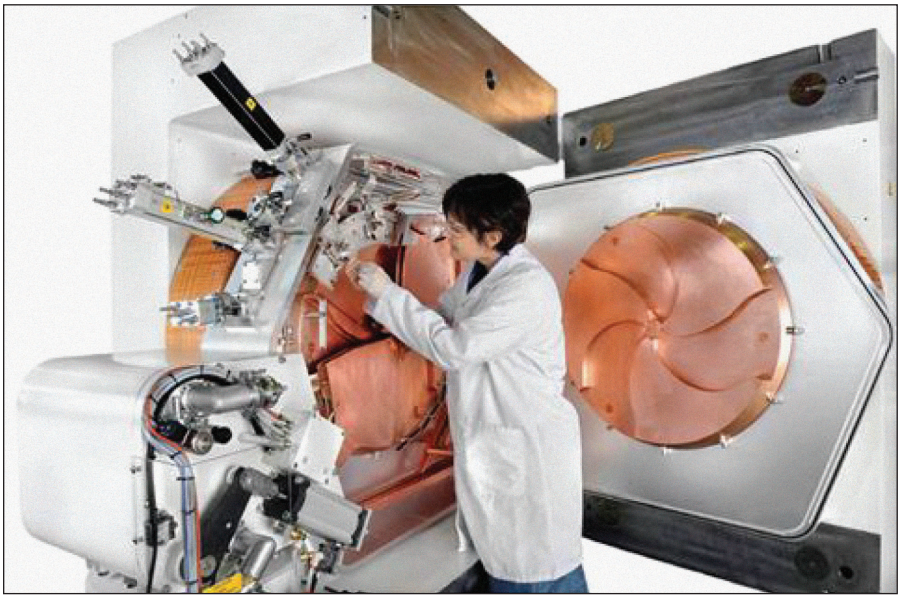


Figure 5

The GE PETTrace (16.5 MeV, 130 μA protons) cyclotron at Lawson Health Research Institute (LHRI), London, Ontario, Canada. The yield for this cyclotron is 4.7 Ci in 6 h. Photo courtesy of M. Kovacs (LHRI) and P. Schaffer (ARTMS); reproduced with permission.

to operate at 500 μA. Based on these modifications, targets had to be designed to withstand this high beam power. The targets as well as target transfer systems had to be designed and built to reduce the technicians' radiation exposure. A spinoff company, ARTMS, has been formed to prepare targets and transfer systems as well as target dissolution systems (34).

Chemistry systems for dissolving the molybdenum target and isolating the desired ^{99m}Tc had to be constructed to provide a final product suitable for labeling the radiopharmaceutical kits. The process steps include dissolving the enriched ^{100}Mo target in H_2O_2 and then making the solution basic with NaOH. The resulting basic solution is added to the solid-phase extraction column, which extracts the technetium isotopes from the target solution, allowing the ^{100}Mo target and non-technetium isotopes generated during irradiation to pass through into a waste vial. The ^{100}Mo is extracted from the waste at a later time for recycling into MoO_3 suitable for target manufacturing. The purification efficiency for ^{99m}Tc was >93% during this process, and the ^{100}Mo recovery efficiency was >95%.

Although these particular cyclotrons were chosen because they were associated with existing positron emission tomography (PET) programs in the consortia, the application of this technique to other platforms is straightforward and has already been demonstrated with IBA cyclotrons (18 MeV). **Figure 6** illustrates the cyclotron base around the world with standard operational characteristics that can be used with this approach (28). The one major drawback from this approach is the challenge of receiving multicenter regulatory approval. However, this has been achieved for PET tracers such as ^{18}F-FDG.

All of these steps have been completed within the two separate consortia, and clinical trials have been undertaken to demonstrate that cyclotron-produced ^{99m}Tc (CPTc) is clinically equivalent to fission-produced ^{99m}Tc. Submissions to Health Canada have been made (2019) with the expectation that approval would be given sometime in 2020 (34). The final step in this process,

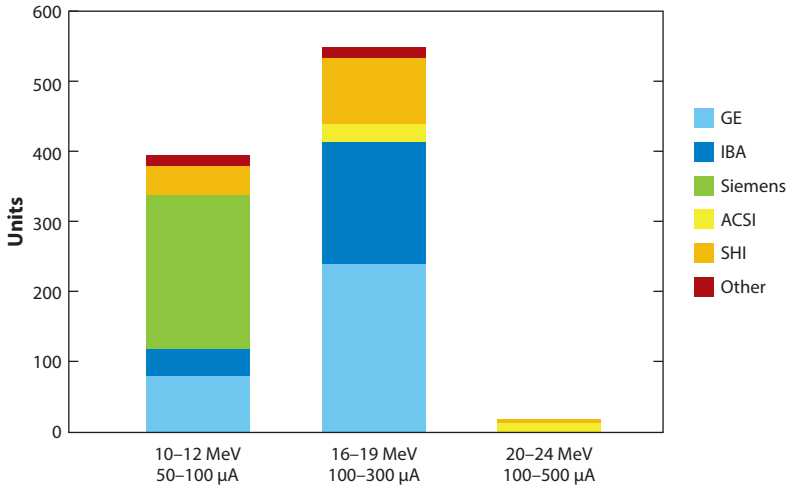


Figure 6

Estimated positron emission tomography cyclotron numbers by manufacturer [with data from ACSI, GE, IBA, and Siemens; Sumitomo (SHI) data estimated]. Figure courtesy of Paul Schaffer, TRIUMF and ARTMS; adapted with permission.

for Canada, will be for the Provincial Health Services Authority to adopt CPTc for at least part of its clinical requirements. The individual provinces in Canada are responsible for procurement of radiopharmaceuticals. In addition, some jurisdictions in Europe (35, 36) have expressed interest in adopting this approach. In some instances, a single cyclotron could meet a country's needs. For smaller markets, it makes sense to have their ^{99m}Tc supply under their total control.

5.5. New Special Reactors

While some of the major producers have plans to replace their aging reactors (see **Table 2**), a number of proposals have been developed that make use of the traditional approach of using reactors as the neutron source. In some ways, these proposals are similar to the MAPLE project (see Section 2.3) in that the reactors are relatively small (~2–10 MW), single-purpose systems dedicated to ^{99}Mo production. Below is a brief description of the proposals that have been described at public forums.

5.5.1. Northwest Medical Isotopes. NWMI is based out of Oregon but is building a processing facility near MURR in Columbia, Missouri (37). This would enable NWMI to irradiate targets at MURR and process them at its own facility. This facility would also extract LEU following chemical extraction of the ^{99}Mo. The LEU targetry and processing are a proprietary system developed at Oregon State University. Operations are to begin in 2023.

5.5.2. Eden Radioisotopes. Eden Radioisotopes has licensed nuclear technology from Sandia National Laboratories with plans to build a small (2 MW) single-purpose reactor capable of operating 22 h/day, 7 days/week, every week (13). With this schedule, Eden expects to produce 10,000 six-day Ci/week, meeting the world demand for ^{99}Mo. The company will start with a configuration capable of producing 4,500 six-day Ci/week before moving to the final design. The plans include

Table 2 Existing European reactors producing ^{99}Mo (38)

Reactor (country)	Commissioned year	Thermal power (MW)	Operating weeks/year	Expected available ^{99}Mo capacity (six-day Ci/week)	Estimated end of operations
BR2 (Belgium)	1961	60	21	7,800	2026
HFR (Netherlands)	1961	45	34	6,200	2024
LVR-15 (Czech Republic)	1957	10	30	3,000	2028
Maria (Poland)	1974	30	36	2,700	2035
FRM II (Germany)	2005	20	32	2,100	2054
JHR (France); start-up planned for 2022	2021	70–100	24	4,800	2081

Abbreviations: BR2, Belgian Reactor 2; FRM II, Forschungsreaktor München II; HFR, High Flux Reactor; JHR, Jules Horowitz Reactor.

producing other radioisotopes (e.g., ^{131}I, ^{133}Xe, ^{177}Lu), with a goal of being in full operation by 2024.

5.5.3. Coquí RadioPharmaceuticals. Coquí RadioPharmaceuticals is a Puerto Rico–based company that plans to build two 10-MW reactors using designs from the Argentinian nuclear engineering company INVAP (14). INVAP designed and built the OPAL reactor in Australia. The facility will be built on an island adjacent to Oak Ridge National Laboratory in Tennessee. Each of these reactors would be capable of meeting all of the US demand. Production is projected to begin in 2025.

6. EUROPE

While Canada and the United States were pursuing alternative production routes without the use of HEU, the existing reactors in Europe were in the process of converting their targets from HEU to LEU and, in some cases, increasing capacity (38). In addition, through the Association of Imaging Producers and Equipment Suppliers' Security of Supply Working Group, coordination of schedules has allowed for the maximum number of facilities to be in operation to alleviate situations in which reactors and/or processing facilities are down for maintenance. There are also backup agreements from the various entities to try to mitigate any unexpected disruptions caused by unplanned outages.

The companies are also in the process of upgrading their processing facilities to increase overall capacity. It should be pointed out that the production capacity (irradiation of targets) at the reactors listed in **Table 2** (38) represents a comfortable margin including an over-capacity rate of 35% (11). The uncertainty lies in the limited number of processing facilities: There are four worldwide at this point (Curium, IRE, NTP, and ANSTO) (11, 39).

In addition to the efforts to increase production and reliability of ^{99}Mo, new reactors have been proposed. Principally, the multipurpose Jules Horowitz Reactor (JHR) in France is due to come online in 2022. Plans to replace the HFR with the PALLAS reactor and the BR2 with the

MYRRHA reactor are advancing and should be online before the respective reactors close (see **Table 2**).

In 2016, the European Pharmacopoeia Commission issued a monograph defining the characteristics and metrics for supplying CPTc (40). There is not an equivalent document in the United States.

7. REST OF WORLD

Both SAFARI-1 in South Africa and OPAL in Australia are upgrading to increase production and processing capacity (39). Both use LEU targets for production, and a backup agreement between these two sites is in place. Several facilities are in the process of being built or upgrading existing facilities to meet the needs of the countries or regions in which they are located. These include Russia, South Korea, Argentina, Brazil, and Egypt.

While Russia is in fact in Europe, the plans to increase production will be limited in the short term because their reactors are fueled by HEU and their targets are manufactured from HEU. The elimination of HEU-based ^{99}Mo production could hinder Russia's ability to penetrate the market if restrictions are imposed on HEU-generated ^{99}Mo. In addition, the major producers are concerned that any effort to insert HEU-based ^{99}Mo into the market would be disruptive since it is cheaper to produce using HEU and could potentially undercut the existing pricing structure.

8. CONCLUSIONS

Several issues affect the availability of ^{99}Mo in the present and in future situations with the full array of production possibilities. Over the past 15 years, the demand for ^{99}Mo has been in decline (from 12,000 to 9,000 six-day Ci/week) (2).

If all of the proposed facilities were to come online shortly after 2020, the processing capacity would be more than 15,000 six-day Ci/week, with the irradiation capacity even higher (11). What does this say about the ability of new commercial ventures to compete in a shrinking market with established providers meeting the basic demand? During 2018, several outages occurred because one or more of the four processing facilities were offline. With a limited number of providers, the likelihood of shortages would still exist.

By 2030 (38) (see **Table 2**), the following scenarios need to be considered:

- Several changes in the European reactor inventory could occur: BR2, Maria, LVR-15, and HFR will have reached the ends of their operating lives and will be permanently shut down; JHR (France), a reactor currently under construction, could start production of ^{99}Mo in 2022; and/or the new reactor PALLAS (the Netherlands) could start producing ^{99}Mo around 2026.
- SAFARI-1 in South Africa could stop producing ^{99}Mo when its current operating license expires in 2030.
- Several new projects could be completed, and producers in Argentina, Brazil, China, Egypt, India, Japan, and South Korea could start producing ^{99}Mo for domestic and regional supplies.

The projected growth in demand for ^{99}Mo/^{99m}Tc comes from the very sector that is seeing a potential increase in supply in these regions, but the balance between supply and demand is unknown. In addition, with time, will PET scan studies supplant single-photon emission computerized tomography, and will the demand for ^{99}Mo/^{99m}Tc further decline? All of these conflicting situations

make it difficult to predict what will happen globally and regionally for the supply–demand for ^{99}Mo/^{99m}Tc. With profit margins being small, new entities without a track record could find themselves with no path forward for a business model to succeed.

In addition, as discussed, there is an agreement among the OECD countries that the industry must move toward FCR (11, 41). While all of the countries have signed on to this concept, the implementation has not been as successful. Thus, it is unclear where this leaves new proponents who have to raise funds for construction and obtain regulatory approval.

And finally, the efforts to establish new supply routes face a steep challenge in moving from proof-of-principle to full commercial production on a routine basis. Historically, this is extremely challenging. Many of the new projects discussed above have seen their schedules slide by 2 years or more; this is true both for those receiving funds from the DOE and for those funded through the private sector.

There are two major issues not addressed in this review, each of which will have an impact on new initiatives. First are the regulatory issues, from getting approval to construction and finally receiving approval to market new products. Since each jurisdiction is different, it is hard to predict what challenges the new entities will face. Secondly, the issue of waste has not been addressed. Again, each jurisdiction has different requirements and resource needs. A new project costs between a quarter million and half a billion US dollars or more and takes at least 5 years to complete (and more likely longer).

Finally, the success of any new endeavor will be related to the ability to respond when there is a sustained shortage. With the various agreements in place among the existing suppliers, it will be difficult to be positioned to respond on an ad hoc basis. How long can a new entity wait to break into the club?

DISCLOSURE STATEMENT

The author is one of the principal proponents of the cyclotron approach to the direct cyclotron production of ^{99m}Tc. In addition, the author has served on multiple reviews by the US National Academy of Sciences and the Subcommittee of the Nuclear Science Advisory Committee to the US Department of Energy. The author, to the best of his abilities, has maintained confidentiality regarding proprietary information received from these briefings. The references below associated with the ^{99}Mo Topical Meetings on Technology Development in September 2018 in Knoxville, Tennessee (**https://mo99.ne.anl.gov/2018/pdfs/**), and in September 2019 in Chicago, Illinois (**https://mo99.ne.anl.gov/2019stakeholders/**), are from public presentations by the various proponents and have not been peer-reviewed for content. The reader is referred to the websites for content not shared in this review. The opinions presented in this article are the author's and do not reflect those of any one individual or institution with whom the author is associated.

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