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# Sustained Availability of $^{99m}$Tc: Possible Paths Forward

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The availability of $^{99m}$Tc for single-photon imaging in diagnostic nuclear medicine is crucial, and current availability is based on the $^{99}$Mo/$^{99m}$Tc generator fabricated from fission-based molybdenum (F $^{99}$Mo) produced using high enriched uranium (HEU) targets. Because of risks related to nuclear material proliferation, the use of HEU targets is being phased out and alternative strategies for production of both $^{99}$Mo and $^{99m}$Tc are being evaluated intensely. There are evidently no plans for replacement of the limited number of reactors that have primarily provided most of the $^{99}$Mo. The uninterrupted, dependable availability of $^{99m}$Tc is a crucial issue. For these reasons, new options being pursued include both reactor- and accelerator-based strategies to sustain the continued availability of $^{99m}$Tc without the use of HEU. In this paper, the scientific and economic issues for transitioning from HEU to non-HEU are also discussed. In addition, the comparative advantages, disadvantages, technical challenges, present status, future prospects, security concerns, economic viability, and regulatory obstacles are reviewed. The international actions in progress toward evolving possible alternative strategies to produce $^{99}$Mo or $^{99m}$Tc are analyzed as well. The breadth of technologies and new strategies under development to provide $^{99}$Mo and $^{99m}$Tc reflects both the broad interest in and the importance of the pivotal role of $^{99m}$Tc in diagnostic nuclear medicine.

**Key Words:** $^{99m}$Tc; $^{99}$Mo production; reactor production; accelerator production; aqueous homogeneous reactor (AHR)

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Obtained from $^{99}$Mo/$^{99m}$Tc generators, $^{99m}$Tc is the most commonly used medical radioisotope, accounting for an estimated 30 million diagnostic procedures performed annually worldwide, with approximately 50% in the United States (*1–3*). Roughly twenty $^{99m}$Tc-labeled tracers are routinely used (*4*), and the demand for $^{99m}$Tc is estimated to increase at an annual rate of 3%–5% (*5,6*). A constant and reliable supply of $^{99m}$Tc is thus crucial to provide the diagnostic benefits of $^{99m}$Tc-based imaging. Reactor-produced $^{99}$Mo (Fig. 1) has been the only source of $^{99m}$Tc, which is mainly made by irradiation of high enriched uranium (HEU) targets. Because a transition from using HEU to low enriched uranium (LEU) is being implemented to minimize potential proliferation issues (*7*), other $^{99}$Mo and $^{99m}$Tc production strategies must become available. Evaluation of a variety of strategies reflects the great importance of continual availability of $^{99m}$Tc for nuclear medicine applications. [**Fig. 1**]

Table 1 summarizes information concerning the designation of uranium with respect to fissile $^{235}$U isotope content. Until 2011, more than 95% of the $^{99}$Mo required for nuclear medicine applications had been primarily produced in 7 research reactors. With the exception of the new Opal Reactor in Australia, research reactors that have been major $^{99}$Mo producers have used HEU targets (Table 2) (*7,8*). A few other reactors also produce fission-based molybdenum (F $^{99}$Mo) in small amounts, mainly to meet local and, at times, regional needs. [**Table 1**] [**Table 2**]

The irradiated HEU targets are processed at radiochemical laboratories that are not necessarily part of the reactor complex and in some cases are even located in different countries. The purified $^{99}$Mo solution is often shipped abroad to manufacturers for fabrication of $^{99}$Mo/$^{99m}$Tc generators. The most recent global disruption of $^{99}$Mo supplies began in 2007 and had wide publicity, which sensitized governments, international bodies, policy makers, physicians, patients, and the general public about the crucial role $^{99m}$Tc plays in health care. Although the supply chain has stabilized for the time being, the vulnerability of depending on aging reactors for $^{99}$Mo production is expected to continue. Except for Opal, all of the reactors used for the production of $^{99}$Mo are approaching the end of their useful operational lifetimes.

Approximately 85 kg of weapon-grade HEU is used annually in targets for $^{99}$Mo production (*9*). Because only a small portion (~2%–3%) of the HEU is actually involved in target fission, the current practice of not recycling targets after the removal of $^{99}$Mo means that most of the HEU remains. The proliferation risk increases over time after irradiation, because spent HEU targets can be handled more easily after the radioactive content is reduced and the shielding requirements are decreased. Minimizing the use of HEU for $^{99}$Mo production is the current target, but

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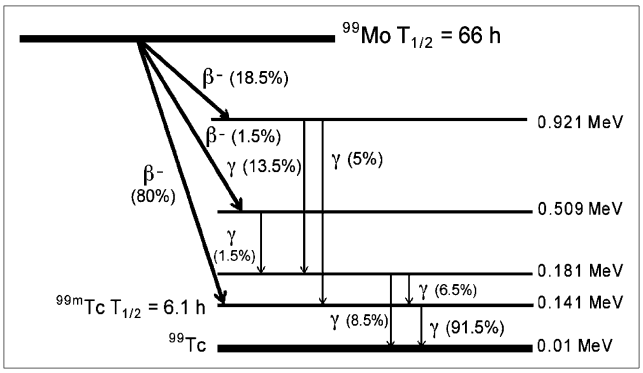


**FIGURE 1.** Decay scheme of $^{99}$Mo and $^{99m}$Tc. $T_{1/2}$ = half-life.

comprehensive abolition of the use of HEU for $^{99}$Mo production is essential to preclude potential misuse.

The U.S. Department of Energy (DOE) initiated the Reduced Enrichment for Research and Test Reactors program in 1978 to address conversion from the use of HEU as a nuclear fuel to the use of LEU (*10*). The Energy Policy Act of 1992 required that foreign producers of medical radioisotopes who received HEU from the United States cooperate in converting to LEU-based production (*10,11*) and limits U.S. export of HEU to only facilities that meet specific conditions. In 2004, the Global Threat Reduction Initiative (GTRI) was announced by U.S. Energy Secretary Spencer Abraham at the International Atomic Energy Agency headquarters in Vienna. The initiative aims to minimize as quickly as possible the amount of available weapons-usable nuclear material. The GTRI also mandates assistance for the $^{99}$Mo production facilities to help in establishing a reliable $^{99}$Mo supply network without the need for HEU (*12*).

The Burr amendment to the U.S. Energy Policy Act was then passed in July 2005, which permitted the export of U.S.-origin HEU to Europe and Canada for $^{99}$Mo production without any precondition for conversion to LEU (*10*). The 2005 Energy Act also included a provision enabling the National Academy of Sciences to ascertain "the feasibility of procuring supplies of medical isotopes from commercial sources that do not use HEU" (*13*). As part of its mandate, GTRI provides technical expertise, on a nonproprietary basis, to all global radioisotope producers to promote $^{99}$Mo production processes without HEU.

In January 2009, GTRI's efforts were validated by a National Academy of Sciences report entitled "Medical Isotope Production without the Use of Highly Enriched Uranium" (*14*). According to this study, large-scale production of $^{99}$Mo by non-HEU methods is economically feasible. In April 2009, U.S. President Barack Obama announced a new international effort to secure all vulnerable global nuclear material within 4 y (*15*), which was accepted for consideration by 47 government heads of state in 2010 (*16*). In November 2011, the U.S. Senate passed S.99, the American Medical Isotopes Production Act of 2011 (*17*), intended to end U.S. reliance on foreign sources of F $^{99}$Mo. The S.99 legislation recognizes the need for stability in the supply of $^{99}$Mo for medical use and allows for domestic reactor production using LEU rather than HEU. In addition, the DOE is directed to establish a program to make LEU available, through lease contracts, for $^{99}$Mo production and retain responsibility for the final disposition of waste created by the irradiation, processing, or purification of leased uranium. Finally, this legislation makes provision to prohibit HEU exports within 7–13 y, depending on the state of the U.S. supply at that point (*18*).

**TABLE 1**
Designations for Uranium Enrichment

| Uranium grade | Designation | $^{235}$U content (%) |
|---|---|---|
| NU | Natural uranium | 0.7 |
| LEU | Low enriched uranium | ≤20 |
| HEU | High enriched uranium | ≤20 |
| HEU | Weapons-grade uranium | ≥85 |

It can be inferred that it is only a matter of time until another $^{99}$Mo crisis occurs because either U.S. HEU is curtailed to $^{99}$Mo producers or some aging reactors are shut down before alternatives are in place, or both. Although overwhelming efforts by the international community are directed toward substituting HEU with LEU for target irradiation, several other emerging options deserve serious consideration (Table 3). The production of $^{99}$Mo or $^{99m}$Tc without the use of HEU will not be a trivial process and would be expected to pose formidable technical, economic, regulatory, and political challenges. [**Table 3**]

## REACTOR-BASED $^{99}$MO PRODUCTION

### Fission Production of $^{99}$Mo from LEU Targets

No scientific reasons preclude the use of targets from LEU instead of HEU; however, there are technical and economic implications because of the differences in both target design and chemical processing. Conversion to LEU would reduce the $^{99}$Mo yield per mass of uranium target to approximately 20% that from HEU, but this loss is partially offset by the use of denser uranium foil targets compatible with both acidic and alkaline dissolution processes (*19,20*). The commercial availability of LEU foils is one of the challenges for widescale deployment of this strategy. A change in the target composition is also associated with the change in the $^{99}$Mo processing procedure, because of the higher production of unwanted $^{239}$Pu by neutron capture by $^{238}$U, which is present in 80% isotopic abundance. Although the quantity of $^{239}$Pu produced from the irradiation of LEU is still relatively small in absolute amounts, its impact on the processing of $^{99}$Mo is a point of concern. In this context, use of the Cintichem process (*21,22*) merits continued attention. Argentina began commercial production of $^{99}$Mo from LEU targets as early as 2002 and acquired expertise to undertake turnkey manufacturing contracts (*11*). With DOE assistance, South African Nu-



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**TABLE 2**
Operating Research Reactors Used for Large-Scale $^{99}$Mo Production

| Country | Reactor name | Power ($MW_t$) | Thermal neutron flux ($n \cdot cm^{-2} \cdot s^{-1}$) | Target type |
|---|---|---|---|---|
| Canada | NRU | 135 | $4.0 \times 10^{14}$ | HEU |
| Netherlands | HFR | 45 | $2.7 \times 10^{14}$ | HEU |
| Belgium | BR-2 | 100 | $1.0 \times 10^{15}$ | HEU |
| South Africa | Safari-1 | 20 | $2.4 \times 10^{14}$ | HEU |
| France | OSIRIS | 70 | $1.7 \times 10^{14}$ | HEU |
| Poland | MARIA | 30 | $3.5 \times 10^{14}$ | HEU |
| Australia | OPAL | 20 | $3.0 \times 10^{14}$ | LEU |

clear Energy Corporation, in South Africa, achieved the world's first large-scale production of $^{99}$Mo in 2010 by use of LEU targets (*23*). Batan, in Indonesia, is also pursuing an LEU-modified Cintichem process for $^{99}$Mo production with support from Argonne National Laboratory. New LEU-based $^{99}$Mo commercial-scale production facilities have also been constructed in Egypt by Invap, S.A. (Argentina), and Pinstech in Pakistan has plans to produce $^{99}$Mo from LEU targets in a facility purchased from GSG, formerly Isotope Technologies, in Dresden, Germany (*24*).

Although the efforts by smaller $^{99}$Mo producers have been fruitful and have drawn widespread praise as a step in the right direction, devising an effective strategy to remove HEU from major $^{99}$Mo producers is challenging because of concerns about logistical difficulties and economics. Modifications to existing facilities require temporary shutdowns for decontamination, which in turn require that new processing facilities be available to ensure the $^{99}$Mo supply during the transition period. A key point is that any research and techniques funded by the GTRI cannot be patented by the current major $^{99}$Mo manufactures. Modifications and overhaul of the back-end processing would have to be developed independently by the manufacturers. Such options are not only expensive but also time-consuming. The fear of market share loss during significant periods of operational downtime may be another reason for the slow reaction of some $^{99}$Mo manufacturers to shift from HEU to LEU targets.

*Aqueous Homogeneous Reactor Using LEU.* In concept, a compact aqueous homogeneous reactor (AHR), or solution reactor, consists of $^{235}$U (LEU) in solution form as the core contained in a shielded tank or vessel. This concept precludes the need for targets; rather, at periodic intervals $^{99}$Mo can be recovered from aliquots of fuel solution removed at optimal intervals. Babcock & Wilcox Co., in association with Covidien, is currently exploring this technology for $^{99}$Mo production using a uranyl nitrate–based AHR (*25*). The conceptual plan consists of a 200-kW system that is estimated to yield approximately 40.7 TBq (1,100 Ci) of $^{99}$Mo per 6-d week (*25*). The advantages are a less complex structure, ensured inherent nuclear safety features of negative reactivity coefficients, and relatively lower costs for installation and operation. Although these positive aspects are appealing, several other equally important technologic challenges include separation process details, corrosion, uranium fuel cleanup, and waste handling. These challenges need to be addressed to ensure the technical viability of the approach. Although the AHR

**TABLE 3**
Key Strategies for $^{99}$Mo and $^{99m}$Tc Production

| Production method | Target | Product | Comment |
|---|---|---|---|
| Reactor-based strategies | | | |
| HEU | $^{235}$U | $^{99}$Mo | Current commercial technology |
| LEU | $^{235}$U | $^{99}$Mo | Transition for routine production |
| $^{98}$Mo | $^{98}$Mo | $^{99}$Mo | Low-specific-activity product |
| Use of power reactors | $^{98}$Mo | $^{99}$Mo | Low-specific-activity product; under consideration |
| Aqueous homogeneous reactor–based technology | $^{235}$U | $^{99}$Mo | Under development as major alternative |
| Accelerator-based strategies | | | |
| Photo-fission | $^{238}$U | $^{99}$Mo | All are under development as major alternatives |
| Photo transmutation of $^{100}$Mo | $^{100}$Mo | $^{99}$Mo | |
| Direct production of $^{99m}$Tc | $^{100}$Mo | $^{99m}$Tc | |
| Subcritical hybrid intense neutron emitter | LEU | $^{99}$Mo | |
| ADS | LEU | $^{99}$Mo | |



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concept may come to fruition in the near future, this technology may be of utility in meeting long-term requirements.

*Target Fuel Isotope Reactor Concept.* Investigators at the U.S. Sandia National Laboratories have developed a compact 2-MW open-pool reactor fueled by LEU oxide, designated as the target-fuel isotope reactor. The proposed reactor may represent one of the lowest-risk options from the standpoints of regulatory approval and business risk and would be dedicated solely to the production of $^{99}$Mo (*26*). In this approach, the reactor fuel pins act as the targets for $^{99}$Mo production. The quantity of $^{99}$Mo that could be produced is directly proportional to the power attainable in the fuel pins. At periodic intervals, a chosen number of fuel pins can be withdrawn for $^{99}$Mo recovery, while simultaneously replacing with the same number of fresh fuel pins. The technology used in the concept is proven and is based on current and past research reactors and light water reactor fuel used in commercial power reactors. The safety–control system is available off the shelf from research reactor providers. The recovery of $^{99}$Mo could be accomplished with a well-known oxide dissolution process and separation procedures (*27–30*).

### Neutron Activation Production of $^{99}$Mo

An alternative to LEU or HEU fission-based production of $^{99}$Mo is through neutron activation of molybdenum, referred to as $(n,\gamma)^{99}$Mo production. This early established technology strategy for $^{99}$Mo production was mostly abandoned when F $^{99}$Mo became widely available (*31,32*). The approach provides low-specific-activity $^{99}$Mo, with specific activity ranging from 7.4 to 130 GBq/g (0.2 to 3.5 Ci/g), from reactors that have thermal neutron flux values of $5 \times 10^{13}$ to $1 \times 10^{15}$ neutrons·cm$^{-2}$·s$^{-1}$. Thermal neutrons have an energy range that allows facile interaction with target nuclei, and the neutron flux is the cross-sectional number of neutrons available for unit time. Table 4 provides a comparison of fission and neutron activation production of $^{99}$Mo. The overwhelming preference for the F $^{99}$Mo production route results from the high $^{235}$U fission cross-section (586 barn) and the 6% fission yield production of $^{99}$Mo, which together yield high $^{99}$Mo activity levels at the end of irradiation using relatively small $^{235}$U targets. [**Table 4**]

Despite these advantages for F $^{99}$Mo production, the merits of further considering the neutron activation production route are considerable. The International Atomic Energy Agency database, which provides a summary of 236 research reactors currently in operation worldwide (*33*), indicates that approximately 50 of these research reactors have thermal neutron flux capabilities more than $1 \times 10^{14}$ n·cm$^{-2}$·s$^{-1}$ and that the thermal fluxes of an additional 85 reactors range from $1 \times 10^{12}$ to $1 \times 10^{14}$ n·cm$^{-2}$·s$^{-1}$. Seventy-eight of these reactors are already involved in radioisotope production, and their geographic distribution is good. Many could be used for $^{99}$Mo production by the $(n,\gamma)^{99}$Mo route. Facilities for irradiation and postprocessing are much less technically and financially demanding than required for production of F $^{99}$Mo. The process is waste-free, and the $^{99}$Mo solution is free from fission products and actinides. Because of the better geographic distribution of

**TABLE 4**
Comparison of Fission and Neutron Activation Production Routes for $^{99}$Mo

| | Fission $^{99}$Mo | $(n,\gamma)^{99}$Mo |
|---|---|---|
| Target | $^{235}$U (HEU or LEU); enriched $^{235}$U in the form of uranium–aluminum alloy, foil, or pellet | $^{98}$Mo (natural or enriched) in the form of $MoO_3$, molybdenum metal, or pellet |
| Nuclear reaction | $n + {}^{235}U \rightarrow {}^{99}Mo + F.P. + 2.5\ n$; $\sigma_{fission} = 586$ b; fission yield of $^{99}$Mo = 6% | $n + {}^{98}Mo \rightarrow {}^{99}Mo$; $\sigma_{th} = 0.14$ b |
| Availability of target | Limited producers/suppliers | Widely available |
| $^{99}$Mo specific activity | High (185–370 TBq/g); independent of reactor neutron flux | Low (7.4–130 GBq/g) depending on the reactor neutron flux |
| Postirradiation process | Complex chemical process consists of a series of precipitation and ion exchange procedures | Simple dissolution of the irradiated solid targets |
| Processing facility | Expensive | Economical |
| Radioactive waste | Significant amount of radioactive waste including fission products, uranium, and plutonium | Negligible |
| Security and nonproliferation concerns | High | Negligible |
| Production capability | Restricted to few countries | Widely distributed |
| Cost of production | High | Low |
| Quality of $^{99m}$Tc | No carrier added; suitable for nuclear medicine applications | No carrier added; suitable for nuclear medicine applications |



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such production facilities, decay loss and freight costs will be less, making the $^{99}$Mo more economical.

### Use of Enriched $^{98}$Mo

The use of enriched $^{98}$Mo would be a positive step because target enrichment of 96% or greater augments the production yield and the specific activity of $^{99}$Mo by a factor of approximately 4. The low-cross-section nuclear reaction (thermal neutron cross section = 0.13 barn), however, coupled with the high cost of enriched target and the difficulties in recovering and recycling $^{98}$Mo targets, makes this route difficult to readily adapt. Maintaining a large $^{98}$Mo inventory and collecting the spent generators for recovery of enriched molybdenum targets would complicate the task, because the $^{99}$Mo/$^{99m}$Tc generators have a wide geographic distribution.

### Power Reactor Production of $^{99}$Mo

Neutron irradiation of $MoO_3$ in a power reactor pressure tube may also be a promising new strategy for irradiation of Mo targets. The neutron flux available in power reactors is much higher than that in research reactors. For this reason, the $^{99}$Mo produced in power reactors will have sufficient specific activity even while using natural Mo targets. Although this strategy is technically challenging compared with the use of research reactors, this option has merit because of the good distribution of power reactors throughout the world, and its potential has been assessed (*34*). GE Hitachi Nuclear Energy had entered into a cost-sharing cooperative agreement with the DOE's National Nuclear Security Administration. After more than 2 y, however, GE Hitachi Nuclear Energy has recently decided not to proceed with the project, indicating that $^{99}$Mo production is not economically feasible at this time because it would compete with power generation (*35*). The principal challenges for widespread pursuit of (n,γ)$^{99}$Mo are that the specific activity values are much lower than for fission-produced $^{99}$Mo and are dependent on the neutron flux and isotopic composition of the target used for irradiation. Furthermore, the separation methods are not as user-friendly as the column chromatography used for low-specific-activity $^{99}$Mo.

In addition to the use of traditional alumina-adsorption–type chromatographic generators, a variety of other effective methods for obtaining $^{99m}$Tc from $^{99}$Mo have also been developed; these are summarized in Table 5. [**Table 5**]

*Methyl Ethyl Ketone (MEK) Extraction of $^{99m}$Tc from $^{99}$Mo Solution.* The classic method of separating $^{99m}$Tc from molybdate solution by solvent extraction using MEK is simple and capable of providing high radiochemical and radionuclidic purity and a high radioisotopic concentration of $^{99m}$Tc. The MEK extraction method was abandoned in favor of alumina column generator technology when fission-produced $^{99}$Mo was available on the world market at favorable prices. This method can be quickly revived is well described (*36*). The concept has been implemented successfully in the Russian Federation, where it is currently used to produce 4.44 TBq (120 Ci) of $^{99m}$Tc for distribution to 21 diagnostic centers in St. Petersburg (*37*). Using similar technology, the Medradiopreparat plant in Moscow regularly produces the $^{99m}$Tc supply for various local clinics, and the Atommed Center in Moscow has developed a computer-controlled semiautomatic $^{99m}$Tc delivery system based on MEK extraction of $^{99m}$Tc followed by ion-exchange purification. The system, capable of handling 296 GBq (8 Ci) of $^{99}$Mo (*38*), includes individual small-scale units that can be operated safely at central pharmacy facilities.

*Solid-Phase Column Extraction.* On a similar theme, the possibility of adsorbing $^{99}$Mo on a chromatographic column containing solid-phase adsorbent followed by subsequent elution of $^{99m}$Tc with MEK has also been explored (*39–42*). This concept, an extension of the MEK extraction procedure, is attractive as it would use (n,γ)$^{99}$Mo and at the same time offer the convenience of column-based separation. This strategy thus far has been confined to laboratory-scale investigation but probably could be readily deployed for practical use.

*Thermoseparation of $^{99m}$Tc from $^{99}MoO_3$ by Sublimation.* This strategy to obtain pure $^{99m}$Tc from bulky masses of (n,γ)$^{99}$Mo by sublimation takes advantage of the differences in the volatilization properties of oxides of molybdenum and technetium. The option has already been investigated by some institutions (*43*). Such generators were in use in Australia and could produce multicurie quantities of $^{99m}$Tc activity but with only 20%–25% yields. Subsequent refinement efforts in Hungary increased $^{99m}$Tc

**TABLE 5**
Methods for Obtaining No-Carrier-Added $^{99m}$Tc from Low-Specific-Activity $^{99}$Mo

| Method | Status/comments |
|---|---|
| Extraction from methyl ethyl ketone | Established/high-yield technology |
| Postelution concentration | Widespread verification |
| Solid-phase column extraction | Promising technologies but only small-scale experimental verification |
| Zirconium-molybdate gel | |
| High-binding adsorbents | |
| Electrochemical generator | |

yields to approximately 50% (*44*). Sublimation technology can be adapted for centralized production of $^{99m}$Tc; however, the need to perform high-temperature operations on a regular basis with high levels of radioactivity raises safety concerns.

*Zirconium Molybdate Gel Concept.* Conversion of irradiated (n,γ)$^{99}$Mo directly into a gel form as zirconium molybdate and loading the gel after processing into a column, followed by elution of $^{99m}$Tc, is also an option (*45*). This widely evaluated strategy involves many intricate steps, such as dissolution, precipitation, filtration, drying, gel fragmentation, and column packing, which necessitate significant handling of radioactive material (*46*). The requirement for technically intense operations in a hostile radiation environment, coupled with unfavorable cost implications, has been a major pitfall for the successful use of this technology.

*Preparation of Alumina-Based Generator Using (n,γ)$^{99}$Mo Integrated with Postelution Concentration.* Because of the limited adsorption capacity of alumina (optimal maximum, ~20 mg of molybdenum per gram), the use of low-specific-activity $^{99}$Mo produced from $^{98}$Mo in a typical alumina-based chromatographic generator would need large-size columns to adsorb sufficient $^{99}$Mo activity. The radioactive concentration of $^{99m}$Tc eluted from such columns is too low for the formulation of freeze-dried technetium kits. A postelution concentration can be used to enhance the $^{99}$Mo radioactive concentration. This strategy was originally developed to concentrate $^{188}$Re obtained from alumina-based $^{188}$W/$^{188}$Re generators (*47*) and was successfully adapted for $^{99}$Mo/$^{99m}$Tc generators in the early 1990s (*48*).

*High-Capacity Sorbent-Based Column Generator.* High-capacity sorbents capable of stabilizing much larger quantities of Mo for use in column-based chromatographic systems have been developed and include a poly zirconium compound (*49*) and a poly titanium oxychloride (*50*). Synthetic alumina functionalized with a sulfate moiety (*51,52*) was another strategy to prepare column-based generators using (n,γ)$^{99}$Mo. In recent years, nanoscale materials have caught the attention of radiopharmaceutical scientists. Because of the high surface area and intrinsic surface reactivity, nanomaterial-based sorbents possess much higher sorption capacity than conventional sorbents. Three different nanomaterial-based sorbents have been successfully exploited for the preparation of chromatographic radionuclide generators using (n,γ)$^{99}$Mo (*53–55*). Preparation of a 13-GBq (350-mCi) generator using $^{99}$Mo with a specific activity of 14.8 GBq (400 mCi)/g was recently demonstrated (*56*). This strategy could be especially useful for producers having access to medium- to high-flux research reactors, wherein $^{99}$Mo of a specific activity of up to 111 GBq (3 Ci) can be obtained with natural $^{98}$Mo targets. The shielded generator assembly and the elution procedure are identical to those for existing alumina-based generators.

*Electrochemical Generator.* Electrochemical separation has been successful for the preparation of $^{90}$Y, $^{188}$Re, and $^{99m}$Tc (*57–60*). Using electrochemistry for routine production of $^{99m}$Tc is appealing because the electrochemical process provides separation and concentration in 1 step. This technology is adaptable even when the specific activity of $^{99}$Mo is low (3.7 GBq/g [100 mCi/g]). A fully automated system is available for the separation of clinically useful $^{90}$Y from $^{90}$Sr (*61*), and the technologic adaptation for making a $^{99}$Mo/$^{99m}$Tc generator is not expected to be difficult.

## ACCELERATOR-BASED PRODUCTION OF $^{99}$MO AND $^{99M}$TC

As a major technologic alternative to the use of reactors, use of accelerators represents a promising approach for the production of $^{99}$Mo without the requirement for HEU targets. Various accelerator-based nuclear reactions that could be used to produce $^{99}$Mo (and $^{99m}$Tc), along with their corresponding reaction cross-sections, are shown in Table 6. [**Table 6**] Technologic advances in the use of accelerator routes may allow the success of this concept, even though several issues related to the practical limits of irradiation volumes and the low cross-sections of the reaction routes need careful assessment. The following sections elaborate some of the accelerator options currently being considered.

### Photo-Fission of Uranium Targets

Significant research effort has been expended on producing $^{99}$Mo using $^{238}$U targets to exploit the photo-fission process (*62*). In this process, a high-intensity beam (0.5–2 MW) of electrons is allowed to impinge on a converter target to

**TABLE 6**
Accelerator Production of $^{99}$Mo and $^{99m}$Tc

| Process | Nuclear reaction | Fission cross-section, σ (barn)* |
|---|---|---|
| Photo-fission† | $\gamma + {}^{238}U \rightarrow {}^{99}Mo +$ fission products + 2n | 0.16 |
| Photo-transmutation | $\gamma + {}^{100}Mo \rightarrow {}^{99}Mo + n$ | 0.16 |
| Proton-induced reaction | $p + {}^{100}Mo \rightarrow {}^{99}Mo + p + n$ | 0.15 |
| Direct production of $^{99m}$Tc | $p + {}^{100}Mo \rightarrow {}^{99m}Tc + 2n$ | 0.20 |

*1 barn = $10^{-24}$ cm$^2$.
†Fission yield of $^{99}$Mo = 6%.



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produce bremsstrahlung photons. The photon beam is focused on the $^{238}U$ target to promote fission (*63*). After irradiation, the uranium target is processed in the same manner as in the HEU route to recover $^{99}Mo$. According to a 2008 study by TRIUMF, in Canada, the photo-fission accelerator technique holds promise as a viable approach that has several key advantages (*64*). However, the extremely low cross-section of the reaction route coupled with the expense and challenges in the development of a high-power machine are major challenges for the success of this proposition (*65*). Nordion, also in Canada, and TRIUMF have signed an agreement to develop a technology called ZEUM (zero-enriched uranium Mo-99) to produce $^{99}Mo$ by the photo-fission route. The arrangement involves state-of the-art technology to build a high-power electron accelerator, an effort that will be pursued by TRIUMF, whereas the target chemistry and analysis will be performed by Nordion (*66*).

### Photon-Induced Transmutation by $^{100}Mo(\gamma, n)^{99}Mo$ Reaction

The use of high-intensity photons to initiate the $^{100}Mo(\gamma,n)^{99}Mo$ nuclear reaction to produce $^{99}Mo$ is another strategy (Fig. 2) under consideration (*65*). The reaction cross-section of this path is approximately 0.1 barn at neutron energies of $12 \leq$ neutron energy $\leq 17$ MeV, which is much larger than with the photo-fission route and yields correspondingly increased $^{99}Mo$ production. The maximum attainable specific activity of $^{99}Mo$ produced through this route is estimated to reach several hundred curies of $^{99}Mo$ per gram, provided very high-power accelerators are used for this purpose. TRIUMF is also evaluating the prospect of using this concept in collaboration with the National Research Council of Canada and Mevex Corp. (*65*). In the United States, the National Nuclear Security Administration's GTRI has signed a cooperative agreement with North Star Medical Radioisotopes, LLC, to develop this technology to produce $^{99}Mo$ and will include an operational plan, business model, and time lines (*67*). Although the method holds promise, some issues need to be addressed. The high-energy electron accelerators with high-power beams required for this route are currently not widely available. The enormous estimated cost for the huge inventory of enriched $^{100}Mo$ that is expected to be required might be a barrier to commercialization. Substantial research and development is also necessary to develop methods to recover or recycle the $^{100}Mo$ from spent generators as a means to reduce the cost of the $^{99}Mo/^{99m}Tc$ generators.

[**Fig. 2**]

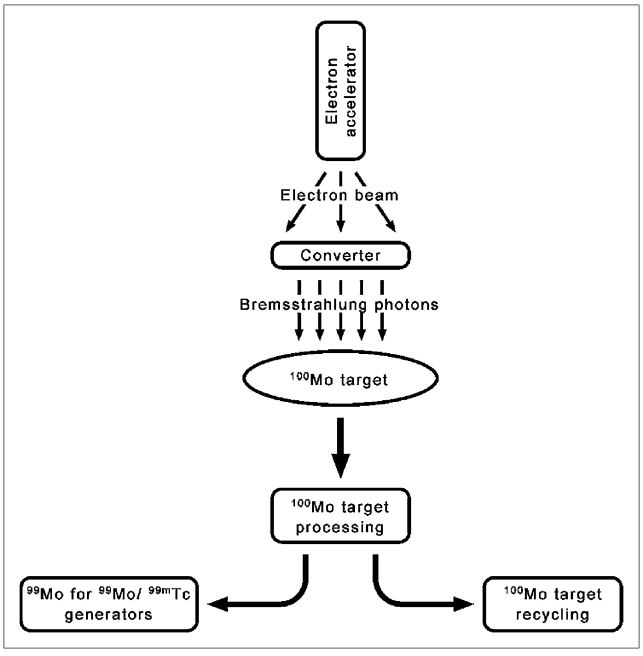


**FIGURE 2.** $^{99}Mo$ production by $^{100}Mo(\gamma,n)^{99}Mo$ photon-induced reaction.

### Direct Cyclotron Production of $^{99m}Tc$

The direct production of $^{99m}Tc$ from a cyclotron beam of energetic protons using the $^{100}Mo(p,2n)^{99m}Tc$ nuclear reaction may make possible the local distribution of $^{99m}Tc$. This concept was initially described in 1971 (*68*) and has subsequently been corroborated by several researchers (*69–73*). Feasibility demonstration studies to produce $^{99m}Tc$ have been proven experimentally. It is possible to avail 2,590 GBq (70 Ci) of $^{99m}Tc$ in two 6-h bombardments using a high-current medium-energy (500 μA, ~24 MeV) cyclotron (*70,74,75*). Direct $^{99m}Tc$ production using cyclotrons thus holds promise as a viable approach, even though there are issues related to the long-term availability and cost of enriched $^{100}Mo$. In addition, the requirement of a large number of cyclotrons to meet world demand and the research and development requirement associated with target design and $^{100}Mo$ recycling are yet to be addressed. The coproduction of other long-lived technetium isotopes (i.e., mass dilution decreases specific activity of $^{99m}Tc$) in this proposed route may require the reformulation of radiopharmaceutical kits. Although about 40 of the existing medical cyclotrons in the world could produce $^{99m}Tc$ by this strategy, most of these machines do not currently handle solid targets, as would be required for this route (*76*). The $^{99m}Tc$ produced by this route could meet local needs but could be distributed only regionally. Separating $^{99m}Tc$ from the irradiated $^{100}Mo$ solid target is more complex than separating $^{99m}Tc$ from low-specific-activity $(n,\gamma)^{99}Mo$. Automated modules are under development for the separation of $^{99m}Tc$ from the molybdenum target obtained after irradiation (*77*). Once the complete technology is well developed, we estimate that about 200–300 geographically well-distributed cyclotrons could satisfy world demand for $^{99m}Tc$.

### Accelerator-Driven Subcritical Assembly (ADS)

Another possible strategy for producing $^{99}Mo$ is with an ADS, which is a unique combination of an accelerator and a subcritical nuclear reactor. The system basically consists of a proton accelerator that delivers its beam to a high-mass

spallation target such as lead, tantalum, tungsten, and uranium to produce a high-intensity spallation neutron flux, which in turn is coupled to a subcritical fast core cooled with liquid metal. The spallation target is surrounded by a subcritical assembly consisting of secondary $^{235}U$ (LEU) targets. Within this subcritical assembly, one can tailor the neutron spectrum of these irradiation fields for production of $^{99}Mo$. Each collision of a proton results in up to 20–30 fast neutrons (with energies mainly between 1 and 10 MeV) that in turn are moderated to produce epithermal neutrons that can be captured by $^{98}Mo$ to produce $^{99}Mo$.

With this concept, it is possible to obtain $(n,\gamma)^{99}Mo$ of a relatively higher specific activity because of the reactor availability of the epithermal neutron flux profile, since the activation cross-section with epithermal neutrons is nearly 50 times higher than the thermal cross-section. In addition, $^{99}Mo$ can be obtained from the chemical processing of $^{235}U$ (LEU) targets of the subcritical assembly. The ADS possesses a higher level of safety because the accelerator can be turned on and off without any consequences. Joint research on this method has been undertaken by the Kharkiv Institute of Physics and Technology, in the Ukraine, and by the Belgian Nuclear Research Center. The ADS system MYRRHA in Belgium may be an alternative for nuclear reactors (*78*). Although the production of $^{99}Mo$ using ADS may not materialize in the near future, it is of interest and utility and could eventually pave the way for a new paradigm of $^{99}Mo$ production to meet future demands.

#### SHINE (Subcritical Hybrid Intense Neutron Emitter)

Investigators at the Morgridge Institute for Research and Phoenix Nuclear Labs, in Madison, Wisconsin, are developing a compact, relatively inexpensive system consisting of an aqueous pool of LEU nitrate or LEU sulfate solution in a subcritical assembly driven by a single deuterium-tritium beam line. Beryllium surrounding the pool provides neutron reflection and multiplication. In this system, deuterium gas is first ionized by microwaves. A low-energy (300–350 keV) DC accelerator then pushes the ions toward a target chamber containing tritium gas to produce high-energy neutrons through the D-T reaction. The neutrons then enter an aqueous LEU solution, where they [**Fig. 3**] multiply subcritically (Fig. 3). Uranium concentration in the solution can be controlled to maintain a subcritical pool. Unlike a reactor, this system does not create a self-sustaining nuclear chain reaction. $^{99}Mo$ produced from fission of the uranium in solution can be recovered periodically (*79*). The advantages include lack of nuclear criticality, minimizing the chance of a criticality accident; low heat, eliminating the chance of a meltdown; and reduced nuclear waste generation. The conceptual plan of SHINE cites a 250-kW fission power system that can yield about 92,500 TBq (2,500 kCi) of $^{99}Mo$ per 6-d week. The $^{99}Mo$ separation in this case is identical to that from reactor-based fission routes, and a facility is expected to be completed by late 2014 (*80*). This option has many favorable characteristics that portend a promising future, but it has yet to reach full technologic maturity and acceptance by regulators and the user community.

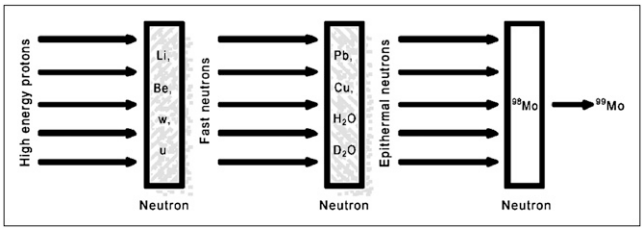


**FIGURE 3.** Schematic view of ADS concept for $^{99}Mo$ production.

## CONCLUSIONS AND FUTURE PERSPECTIVES

With a sensible strategy, adequate resources, and sustained determination, the goal of producing $^{99}Mo$ without the use of HEU targets can be achieved. Although the AHR, photo-fission, target-fuel isotope reactor, and ADS routes hold promise as innovative approaches for $^{99}Mo$ production, the routine implementation of these technologies would be expected to be years away. These approaches are balanced on a fine line, with technical breakthroughs on the one hand and long-term economic viability on the other. In the medium term, accelerator production of $^{99}Mo$ or $^{99m}Tc$ and the SHINE concept for producing fission $^{99}Mo$ may hold special promise. Among the accelerator- and cyclotron-based options, direct production of $^{99m}Tc$ may be the most feasible and the most readily adaptable. Given the short half-life of $^{99m}Tc$, however, supplying it is more akin to supplying [$^{18}F$]-FDG, requiring immediate transport to the locale of use. As a result, a network of cyclotrons would need to be located proportionally to the demand, which could be synergistic with PET radionuclide production. Although most of these PET machines are in the 9- to 18-MeV range and not optimal for large-scale production of $^{99m}Tc$, the existing PET cyclotrons can be upgraded to undertake large-scale production of $^{99m}Tc$ by use of solid targets.

Of the several non-HEU reactor options discussed, the prospect of using $(n,\gamma)^{99}Mo$ still offers appeal for its utility to address shortages of $^{99}Mo$ in the immediate future. From technical and economic perspectives, the global demand for $^{99}Mo$ could readily be met using $(n,\gamma)^{99}Mo$ produced in existing research reactors. These reactors would require few design changes, and they have good geographic distribution around the world. As discussed, $^{99m}Tc$ can be separated from $(n,\gamma)^{99}Mo$ by methods that are inexpensive, realistic, implementable in a short time frame, and capable of producing pharmaceutical-grade $^{99m}Tc$.

Ensuring reliable $^{99}Mo$ production without HEU is thus an evolving process in which government, manufacturers, suppliers, regulators, and users together have specific but complementary and overlapping roles and responsibilities. It is important to ensure the commercial success of non-HEU–based $^{99}Mo$ production technologies to provide



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$^{99}$Mo or $^{99m}$Tc of required quantities and quality for nuclear medicine. Otherwise, the current suppliers will move to more financially successful programs, a move that is already on the horizon as seen from their enthusiasm in developing PET-based alternatives to replace $^{99m}$Tc radiopharmaceuticals (*81*).

Both economic strategies and regulatory aspects are intimately involved in the production of $^{99}$Mo and $^{99m}$Tc. Beyond specific scientific and technical obstacles, substantial economic, political, and security issues are inhibiting the transition to non-HEU–based options for $^{99}$Mo production. The outlook for the $^{99}$Mo economy is still ill-defined in light of government subsidies and the government support of the research reactors in which target irradiations are performed. Many processing facilities that were originally funded by governments had been commercialized by the 1980s and 1990s, but they are continuing to operate with government subsidies. Over the years, even though $^{99}$Mo production technology has grown significantly and matured into a self-sustaining industry, an appropriate costing mechanism has not evolved. Such subsidies are a major hindrance, causing new entrants to doubt the economic viability of capital-intensive alternate technology to produce non-HEU–based $^{99}$Mo or $^{99m}$Tc and resulting in slow HEU cleanout. All sovereign entities should relinquish the current practice of subsidies, which would alleviate the current stalemate and create new benchmarks.

Although expeditious response is needed to ensure the future availability of $^{99m}$Tc, implementation of any new $^{99}$Mo or $^{99m}$Tc production technologies will require approval from national regulatory agencies. Obtaining such approvals is essential, time-consuming, and expensive, but the commercial and strategic success of new production approaches depends on it. It is obligatory to ensure that any change in production strategy does not deleteriously affect radiopharmaceutical purity, efficacy, or safety.

It has been estimated that the current price of irradiating $^{99}$Mo may significantly increase in the medium term to allow new entrants to build sustainable businesses requiring investment in new non-HEU–based production facilities and to open the market to investment. An increase in the cost of $^{99}$Mo is expected to only fractionally increase the cost of $^{99m}$Tc generators. The increased cost of $^{99m}$Tc generators is likely to have only a marginal effect on the overall cost of diagnostic investigation because the costs of kits, scintigraphic imaging, and staff support constitute the major cost of investigations. For third-party reimbursement of typical $^{99m}$Tc imaging procedures, analyses and speculations are quite clear and generally agree that any increase in the $^{99}$Mo reactor production costs, for example, would only marginally affect the total reimbursement costs for typical $^{99m}$Tc imaging procedures. The $^{99}$Mo production costs represent only a small fraction of the radiopharmacy costs of $^{99m}$Tc radiopharmaceutical preparations (*82*). Sufficient information is not yet available with regard to the accelerator production of either $^{99}$Mo or $^{99m}$Tc to provide a similar analysis. For these reasons, the sustained reliable availability of $^{99m}$Tc eclipses any issue regarding the total costs.

## DISCLOSURE

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## REFERENCES

1. Verbeek P. *Report on Molybdenum-99 Production for Nuclear Medicine 2010–2020. State of the art*. AIPES Report. November 2008. Available at: http://www.oecd-nea.org/med-radio/docs/200902_AIPESMolySupplyReport.pdf.
2. Technopolis Group. *Radioisotopes in Medicine, Foresight of the Use of Reactor Isotopes until 2025*. Technopolis Report. December 2008. Available at: http://www.technopolis-group.com/resources/downloads/life_sciences/EN_Radioisotopes_in_Medicine_final.pdf.
3. Eckelman WC. Unparalleled contribution of technetium-99m to medicine over 5 decades. *JACC Cardiovasc Imaging*. 2009;2:364–368.
4. International Atomic Energy Agency. *Technetium-99m Radiopharmaceuticals: Manufacture of Kits*. Technical Report Series 466. 2008. Available at: http://www-pub.iaea.org/MTCD/publications/PubDetails.asp?pubId=7867.
5. Lantheus Medical Imaging, Inc. *$^{99}$Mo and $^{99m}$Tc: Radioisotopes Critical to Nuclear Medicine*. 2009. Available at: http://www.lantheus.com/SupplyUpdate/pdf/Moly-FactSheet-v3_07Oct10.pdf.
6. International Atomic Energy Agency. *IAEA Helps to Close Radioisotope Production Gap*. Staff Report. 2011. Available at: http://www.iaea.org/newscenter/news/2011/prodgap.html.
7. Bonet H, David B, Ponsard B. In: *9$^{th}$Int. Topical Meeting on Research Reactor Fuel Management (RRFM)*. Hungary. 2005. Available at: http://www.euronuclaer.org/pdf/RRFM2005.Session1.pdf.
8. Von Hippel FN, Kahn LH. Feasibility of eliminating the use of highly enriched uranium in the production of medical isotopes. *Sci Global Security.* 2006;14:151–162.
9. Department of Homeland Security Nuclear Assessment Program. *Nuclear Smuggling.* Available at: www.exportcontrol.org/library/conferences/1379/005_Proliferation_Threat_Brief-Nuclear_Smuggling_Zachary_K.pdf.
10. Loukianova A, Hansell C. Leveraging US policy for a global commitment to HEU elimination. *Nonproliferation Rev.* 2008;15:159–183.
11. Hansell C. Nuclear medicine's double hazard imperiled treatment and the risk of terrorism. *Nonproliferation Rev.* 2008;15:185–208.
12. U.S. National Nuclear Security Administration. *Office of Global Threat Reduction.* Available at: http://www.nnsa.energy.gov/mediaroom/pressreleases/mo99noheu61512.
13. Summary of Section 630, Medical isotope production, under Title VI, Nuclear Matters, Subtitle B, General Nuclear Matters. Available at: www.ne.doe.gov/energypolicyact2a.html.
14. Committee on Medical Isotope Production Without Highly Enriched Uranium, National Research Council. *Medical Isotope Production Without the Use of Highly Enriched Uranium*. January 2009. Available at: http://www.nap.edu/catalog.php?record_id=12569#description.

15. Remarks by President Barack Obama. White House website. Available at: http://www.whitehouse.gov/the_press_office/Remarks-By-President-Barack-Obama-In-Prague-As-Delivered. April 5, 2009.
16. Participating States. *Work Plan of the Washington Nuclear Security Summit, Statements and Releases from the Washington Nuclear Security Summit*. Washington, D.C., April 12–13, 2010. Available at: http://www.whitehouse.gov/the-press-office/work-plan-washington-nuclear-security-summit.
17. US House of Representatives Subcommittee on Energy and Environment. *American Medical Isotopes Production Act of 2009, Section by Section Summary.* Available at: http://energycommerce.house.gov/Press_111/20090908/hr3276_%20sectionbysection.pdf.
18. *American Medical Isotopes Production Act of 2011*. Civic Impulse. Available at: http://www.govtrack.us/congress/billtext.xpd?bill=s112-99.
19. Vandegrift GF. Mo-99 production. In: *Progress in Chemical Processing of LEU Targets for Mo-99 Production – 1997.* Proceedings of 1997 International Meeting on Reduced Enrichment for Research and Test Reactors. Jackson Hole, WY, Oct. 1997. Lemont, IL: Argonne National Laboratory; 2009.
20. Vandegrift GF, Conner C, Hofman GL, et al. Modification of targets and processes for conversion of $^{99}$Mo production from high- to low-enriched uranium. *Ind Eng Chem Res.* 2000;39:3140–3145.
21. McDonald MJ, Carson SD, Naranjo GE, et al. Challenges of extracting and purifying fission-produced molybdenum-99. *Ind Eng Chem Res.* 2000;39:3146–3150.
22. Vandegrift GF. Facts and myths concerning $^{99}$Mo production with HEU and LEU targets. International Meeting on Reduced Enrichment for Research and Test Reactors, RERTR Meeting 2005. Available at: http://www.rertr.anl.gov/RERTR27/Abstracts/S8-1_VandeGrift.html.
23. Podvig P. South African company delivers $^{99}$Mo produced with LEU. International Panel on Fissile Materials; Aug. 25, 2010. Available at: http://www.fissilematerials.org/blog/2010/08/south_african_company_del.html.
24. International Atomic Energy Agency. *CRP on Production of Mo-99 from LEU or Neutron Activation*. Available at: www.iaea.org/OurWork/ST/NE/NEFW/nfcms_researchreactors_Mo99.html.
25. International Atomic Energy Agency. *Homogeneous Aqueous Solution Nuclear Reactors for the Production of Mo-99 and Other Short Lived Radioisotopes*. IAEA TECDOC Report 1601. Vienna, Austria: IAEA; September 2008.
26. Parma EJ, Coats RL, Dahl JJ. *Sandia National Laboratories Medical Isotope Reactor Concept*. Report SAND 2010-1816. Albuquerque, NM: SAND; 2010.
27. Taylor RF, Sharratt EW, de Chazal LEM, et al. Dissolution rates of uranium dioxide sintered pellets in nitric acid systems. *J Appl Chem.* 1963;13:32–40.
28. Shabbir M, Robins RG. Kinetics of the dissolution of uranium dioxide in nitric acid I. *J App Chem.* 1968;18:129–134.
29. Nishimura K, Chikazawa T, Hasegawa S, et al. Effect of nitrous acid on dissolution of $UO_2$ powders in nitric acid; optimal conditions for dissolving $UO_2$. *J Nucl Sci Technol.* 1995;32:157–159.
30. Woignier T, Duffours L, Phalippou J, et al. Kinetic study on dissolution of $UO_2$ powders in nitric acid. *J Nucl Mater.* 1995;224:266–272.
31. Pillai MRA, Knapp FF Jr. Overcoming the Tc-99m shortage: are options being overlooked? *J Nucl Med.* 2011;52:15N–16N, 28N.
32. Pillai MRA, Knapp FF Jr. Molybdenum-99 production from reactor irradiation of molybdenum targets, a viable strategy for enhanced availability of technetium-99m. *Q J Nucl Med Mol Imaging.* In press.
33. International Atomic Energy Agency. *Operation Research Reactors in the World* [database]. Available at: www.naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/foreword_home.html.
34. GE Hitachi Nuclear Energy to deliver life-saving medical isotope molybdenum-99 using alternative to highly enriched uranium. Press release, GE-Hitachi, 25 January 2010. Available at: www.ge-energy.com/about/press/en/2010_press/012510.htm.
35. Forrest W. GE Hitachi puts molybdenum-99 project on ice. http://www.auntminnie.com/index.aspx?sec=sup_n&sub=mol&pag=dis&ItemID=98224.
36. Chattopadhyay S, Das SS, Barua L. A simple and rapid technique for recovery of 99mTc from low specific activity (n,γ) 99Mo based on solvent extraction and column chromatography. *Appl Radiat Isot.* 2012;68:1–4.
37. Khlopin Radium Institute. Research and production section for radiopharmaceuticals fabrication on the basis of reactor nuclide. Available at: http://www.khlopin.ru/english/radiopharm_fabricating.php.
38. Semi-automatic $^{99m}$Tc solvent extraction system. Available at: http://www.rcrusia.com.ar/espanol/cooperacion/pub4.pdf.
39. Braun T, Imura H, Suzuki XN. Separation of $^{99m}$Tc from parent $^{99}$Mo by solid-phase column extraction as a simple option for a new $^{99m}$Tc generator concept. *J Radioanal Nucl Chem Lett.* 1987;119:315–325.
40. Muddukrishna SN, Narasimhan DVS, Desai CN. Extraction of $^{99m}$Tc into MEK from large quantity of molybdate retained on alumina column. *J Radioanal Nucl Chem.* 1990;145:311–320.
41. Chattopadhyay S, Das S, Barua L, Das MK. A novel method of separation of $^{99m}$Tc from (n,γ) $^{99}$Mo of low/medium specific activity based on solid phase column extraction technique: suitability for use in diagnostic radiopharmaceuticals. *J Nucl Med.* 2009;509(suppl 2):397P.
42. Chattopadhyay S, Das SS, Das MK, Goomer NC. Recovery of $^{99m}$Tc from $Na_2[^{99}Mo]$ $MoO_4$ solution obtained from reactor-produced (n,γ) $^{99}$Mo using a tiny Dowex-1 column in tandem with a small alumina column. *Appl Radiat Isot.* 2008;66:1814–1817.
43. Christian JD, Petti DA, Kirkham RJ, Bennett RG. Advances in sublimation separation of technetium from low-specific-activity molybdenum-99. *Ind Eng Chem Res.* 2000;39:3157–3168.
44. Gerse J, Kern J, Imre J, Zsinka L. Examination of a portable $^{99}$Mo/$^{99m}$Tc isotope generator: SUBLITECH. *J Radioanal Nucl Chem.* 1988;28:71–79.
45. Boyd RE. The gel generator: a viable alternative source of $^{99m}$Tc for nuclear medicine. *Appl Radiat Isot.* 1997;48:1027–1033.
46. International Atomic Energy Agency. *Alternate Technologies for $^{99m}$Tc Generators*. Report IAEA-TECDOC-852, Vienna, 1995. Available at http://www-pub.iaea.org/MTCD/publications/PDF/te_852_prn.pdf.
47. Knapp FF Jr, Beets AL, Guhlke S, et al. Development of the alumina-based tungsten-188/rhenium-188 generator and use of rhenium-188-labeled radiopharmaceuticals for cancer treatment. *Anticancer Res.* 1997;17:1783–1795.
48. Blower PJ. Extending the life of a $^{99m}$Tc generator: a simple and convenient method for concentrating generator eluate for clinical use. *Nucl Med Commun.* 1993;14:995–997.
49. Tanase M, Tatenuma K, Ishikawa K, et al. A $^{99m}$Tc generator using a new inorganic polymer adsorbent for (n, [gamma]) $^{99}$Mo. *Appl Radiat Isot.* 1997;48:607–611.
50. So LV, Nguyen CD, Pellegrini P, Bui VC. Polymeric titanium oxychloride sorbent for $^{188}$W/$^{188}$Re nuclide pair separation. *Sep Sci Technol.* 2009;44:1074–1098.
51. Lee JS, Lee JS, Park UJ, et al. Surface-modified alumina as a high capacity material of $^{99}$Mo/$^{99m}$Tc generator column. In: *Proceedings of 2007 AIChE Annual Meeting*, Nov. 4–9, 2007, Salt Lake City, Utah. Available at: http://aiche.confex.com/aiche/2007/preliminaryprogram/abstract_93290.htm.
52. Lee JS, Han HS, Park UJ, Son KJ, Shin HY, Hong SB, Jang KD Lee JS, inventors; Korea Atomic Energy Research Institute, assignee. Adsorbents for Radioisotopes, Preparation Method Thereof, and Radioisotope Generators Using the Same. US patent 2009/027788 A1. November 12, 2009.
53. Chakravarty R, Shukla R, Gandhi S, et al. Polymer embedded nanocrystalline titania sorbent for $^{99}$Mo-$^{99m}$Tc generator. *J Nanosci Nanotechnol.* 2008;8:4447–4452.
54. Chakravarty R, Shukla R, Ram R, et al. Practicality of tetragonal nano-zirconia as a prospective sorbent in the preparation of $^{99}$Mo/$^{99m}$Tc generator for biomedical applications. *Chromatographia.* 2010;72:875–884.
55. Chakravarty R, Shukla R, Ram R, et al. Exploitation of nano alumina for the chromatographic separation of clinical grade $^{188}$Re from $^{188}$W: a renaissance of the $^{188}$W/$^{188}$Re generator technology. *Anal Chem.* 2011;83:6342–6348.
56. Chakravarty R, Ram R, Dash A, Pillai MRA. Preparation of clinical-scale $^{99}$Mo/$^{99m}$Tc column generator using neutron activated low specific activity $^{99}$Mo and nanocrystalline γ-$Al_2O_3$ as column matrix. *Nucl Med Biol.* In press.
57. Chakravarty R, Pandey U, Manolkar RB, et al. Development of an electrochemical $^{90}$Sr/$^{90}$Y generator for separation of $^{90}$Y suitable for targeted therapy. *Nucl Med Biol.* 2008;35:245–253.
58. Chakravarty R, Dash A, Venkatesh M, Pillai MRA. A novel $^{188}$W/$^{188}$Re electrochemical generator with potential for medical applications. *Radiochimica Acta.* 2009;97:309–317.
59. Chakravarty R, Dash A, Pillai MRA. Electrochemical separation is an attractive strategy for development of radionuclide generators for medical applications. *Curr Radiopharm.* 2012;5:271–287.
60. Chakravarty R, Dash A, Venkatesh M. A novel electrochemical technique for the production of clinical grade $^{99m}$Tc using (n,γ) $^{99}$Mo. *Nucl Med Biol.* 2010;37:21–28.
61. International Atomic Energy Agency. *Annual Report 2009*. 2009:55. Available at: www.iaea.org/Publications/Reports/Anrep2009/anrep2009_full.pdf.
62. Ruth T. Accelerating production of medical isotopes. *Nature.* 2009;457:536–537.
63. Freeman T. Medical isotope supplies: a game plan for the future. Editorial. Medical Physics website. December 8, 2008. Available at: http://medicalphysics-web.org/cws/article/opinion/36974.



jnm110338-pm ■ 12/19/12

64. Fong A, Meyer TI, Zala K. *Making Medical Isotopes, Report of the Task Force on Alternatives for Medical isotope Production*. Vancouver, Canada: TRIUMF; 2008. Available at: www.triumf.ca/report-medical-isotope-production.
65. Committee on Medical Isotope Production Without Highly Enriched Uranium. *Medical Isotope Production Without Highly Enriched Uranium*. Report 14. January 2009. Washington, DC: National Academy of Sciences; 2009.
66. Securing a Supply of Critical Medical Isotopes for Canada Using ZEUM Technology, an Expression of Interest Submitted to the Expert Review Panel on Medical-Isotope Production. July 31, 2009. Available at: http://www.triumf.ca/sites/default/files/ZEUM-Panel-Submission-vFINAL.pdf.
67. NNSA Signs Cooperative Agreement to Produce Molybdenum-99 in the United States Without the Use of Highly Enriched Uranium. Press release. November 1, 2011. Available at: http://nnsa.energy.gov/mediaroom/pressreleases/norhtstarmo99.
68. Beaver J, Hupf H. Production of $^{99m}$Tc on a medical cyclotron: a feasibility study. *J Nucl Med.* 1971;12:739–741.
69. Lagunas-Solar MC. Accelerator production of $^{99m}$Tc with proton beams and enriched 100 Mo targets. In: *Production Technologies for Molybdenum-99 andTechnetium-99m*. IAEA-TECDOC-1065. Vienna, Austria: International Atomic Energy Agency; 1999:87–112.
70. Lagunas-Solar MC. Cyclotron production of NCA $^{99m}$Tc and $^{99}$Mo, an alternative non-reactor supply source of instant $^{99m}$Tc and $^{99}$Mo/$^{99m}$Tc generators. *Int J Rad Appl Instrum A*. 1991;42:643–657.
71. Scholten B, Lambrecht RM, Cogneau M, et al. Excitation functions for the cyclotron production of $^{99m}$Tc and $^{99}$Mo. *Appl Radiat Isot.* 1999;51:69–80.
72. Takacs S, Szucs F, Tarkanyi F, et al. Evaluation of proton induced reactions on $^{100}$Mo: new cross sections for production of $^{99m}$Tc and $^{99}$Mo. *J Radioanal Nucl Chem.* 2003;257:195–201.
73. Targholizadeh H, Raisali G, Jalilian AR, et al. Cyclotron production of technetium radionuclides using a natural metallic molybdenum thick target and consequent preparation of [Tc]-BRIDA as a radio-labelled kit sample. *Nukleonika.* 2010;55:113–118.
74. Takacs S, Tarkanyi F, Sonck M, Hermanne A. Investigation of the $^{nat}$Mo(p, xn)$^{96mg}$Tc nuclear reaction to monitor proton beam: new measurements and consequences on the earlier reported data. *Nucl Instrum Methods Phys Res B.* 2002;198:183–196.
75. Guérin B, Tremblay S, Rodrigue S,. Cyclotron production of $^{99m}$Tc: an approach to the medical isotope crisis. *J Nucl Med.* 2010;51:13N–16N.
76. International Atomic Energy Agency. *Directory of Cyclotrons Used for Radionuclide Production in Member States: 2006 Update*. Report IAEA-DCRP/2006. Vienna, Austria: IAEA; 2006. Available at: www-naweb.iaea.org/napc/iachem/cyclotrons/PDF/DCRP.pdf.
77. Morley TJ, Dodd M, Gagnon K, et al. An automated module for the separation and purification of cyclotron-produced $^{99m}TcO_4^-$. *Nucl Med Biol.* 2012;39:551–559.
78. Abderrahim HA, Baeten P, Bruyn DD, et al. MYRRHA, a multipurpose hybrid research reactor for high-end applications. *Nucl Phys News.* 2010;20:24–28.
79. Piefer GR, Pitas KM, Van Abel EN, et al. Mo-99 production using a subcritical assembly. In: *1st Annual Molybdenum-99 Topical Meeting (Mo-99 2011)*, Dec. 4–7, 2011. Available at: theltemes.net/cv/publications/nonreviewed/.
80. Clark BE. Financial support, backing from leaders helped Janesville win $85 million factory. Available at: http://www.wisbusiness.com/index.iml?Article=264341.
81. Hillman BJ, Frank RA, Rodriguez GM. New pathways to Medicare coverage for Innovative PET radiopharmaceuticals: report of a Medical Imaging & Technology Alliance (MITA) Workshop. *J Nucl Med.* 2012;53:336–342.
82. Seeverens HJJ. The economics of the molybdenum-99/technetium-99m supply chain. *Dutch J Nucl Med.* 2010;32:604–608.