Technetium-99m – New Production and Processing Strategies to Provide Adequate Levels for SPECT Imaging

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Abstract: The most important radioisotope for use in Nuclear Medicine is ^{99m}Tc, supplied in the form of a ^{99}Mo/^{99m}Tc generator. After the supply crisis of ^{99}Mo starting in 2008 the availability of ^{99}Mo became a worldwide concern. The purpose of this work is to do a brief story of the availability of ^{99}Mo in the world followed by an overview of the production routes of ^{99}Mo and the generators technology.

Keywords: Fission of ^{235}U, Molybdenum-99, Nuclear Reactor, Particle Accelerator, Radioisotope generator, Technetium-99m.

INTRODUCTION

Nuclear medicine applications encompass both diagnosis and therapeutic procedures. More than 90% of all nuclear medicine procedures are diagnostic imaging and more than 80% of the images are still obtained with the use of technetium-99m (^{99m}Tc, $T_{1/2}$= 6.0h), the daughter of Molybdenum-99 (^{99}Mo, $T_{1/2}$= 66.0h) (Fig. **1**). This isotope emits a 140keV photon when it decays to the ground state, ^{99}Tc, and it is ideally suited for efficient detection by gamma scintigraphy.

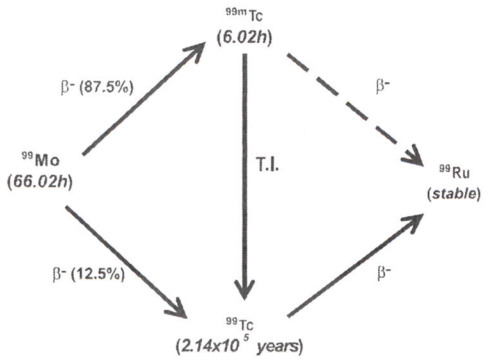

Fig. (1). Decay scheme of ^{99}Mo.

The ^{99}Mo/^{99m}Tc generator has been described in previous reviews [1-4].

Although ^{99m}Tc has been the most important radioisotope in nuclear medicine, its helpful properties were overlooked when it was initially detected as a trace contaminant during the development of a different generator at the U.S. Department of Energy's Brookhaven National Laboratory in the 1950s. Walter Tucker and Margaret Greene were refining the product ^{132}I, the "daughter" radioisotope generated from the "parent" ^{132}Te. They discovered that technetium was being generated by decay of its ^{99}Mo parent, which was following the decay chemistry of ^{132}Te. Noticing a similarity between the tellurium-iodine parent daughter pair and the molybdenum-technetium pair, Tucker and Greene developed the first ^{99}Mo/^{99m}Tc generator in 1958[5].

The generator consisted of the adsorption of ^{99}Mo, as molybdate, on an aluminium oxide column and further elution of ^{99m}Tc (as pertechnetate) in 0.1mol.L^{-1} HNO_3.

The first clinical use of the generator took place at the Argonne Cancer Hospital (Chicago, USA) and by the end of the 1960's commercial generators became available from Nuclear Consultants Inc. (St. Louis, latter Mallinckrodt) from Union Carbide Nuclear Corporation, in New York and from ER Squibb and Sons. These generators employed ^{99}Mo produced by the fission of ^{235}U and the clinical use of ^{99m}Tc started to become a reality. By this time the generator was eluted with 0.9% NaCl solution, and remains the same up to today. Several tissue-specific radiolabeling kits were being prepared and approved for instantaneous labeling with ^{99m}Tc and the first big breakthrough in nuclear medicine imaging was made possible. For more than 50 years ^{99m}Tc–labeled tissue-specific radiopharmaceuticals kits have been available for diagnostic studies of essentially all major organs.

As stated in the BNL website [5] "Though hundreds of thousands of generators have been produced since the very first one at Brookhaven, the Laboratory has never realized any monetary gain from this invention as it was never patented. But Richards and his colleagues have gained immeasurable satisfaction from the knowledge that their discovery, inventiveness and persistence have paid off so handsomely for patients around the world".

Over 30 million procedures with ^{99m}Tc radiopharmaceuticals are estimated to be performed worldwide every year, with more than 50,000 procedures in USA alone every day. The number of procedures with ^{99m}Tc is expected to steadily grow in the coming years (2.5-5%) due to the increase market in developing countries. The two main applications of ^{99m}Tc-radiopharmaceuticals are in imaging myocardial perfusion in cardiac patients and imaging bone metastasis in

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1874-4729/12 $58.00+.00

Table 1. ^{99m}Tc Kits for Nuclear Medicine Diagnostic Imaging [6]

Commercial Name	Imaging Procedure
Technetium Tc-99m Medronate (MDP)	Bone Scan
Technetium Tc-99m Albumin Aggregated (MAA)	Lung Perfusion
Technetium Tc-99m Pentetate (DTPA)	Kidney Scan and Function
Technetium Tc-99m Sulfur Colloid	Liver Scan, Sentinel Lymph Node Localization
Technetium Tc-99m Sestamibi	Cardiac Perfusion
Technetium Tc-99m Exametazime	Brain Perfusion
Technetium Tc-99m Mebrofenin	Gall Bladder Function
Technetium Tc-99m Etidronate	Bone Scan
Technetium Tc-99m Disofenin	Gall Bladder Function
Technetium Tc-99m Succimer (DMSA)	Kidney Scan and Function
Technetium Tc-99m Tetrofosmin	Cardiac Perfusion
Technetium Tc-99m Bicisate	Brain Perfusion
Technetium Tc-99m Red Blood Cell	Blood Pool Imaging
Technetium Tc-99m Sodium Pertechnetate	Thyroid, Salivary Gland, Meckel's Scan
Technetium Tc-99m Lidofenin	Gall Bladder Function
Technetium Tc-99m Mertiatide (MAG3)	Kidney Scan and Function
Technetium Tc-99m Oxidronate (HDP)	Bone Scan

NOTE: MAA = methacrylic acid, MDP = methylene diphosphonate, DTPA = diethylene triamine, Pentaacetic acid, DMSA = dimercaptosuccinic acid, MAG3 = mercapto acetyl triglycine, HDP= hydroxymethylene diphosphonate.
SOURCE: Extracted from the Food and Drug Administration approved pharmaceutical list, 2008.

cancer patients. Table **1** gives a list of some of the kits for labeling with ^{99m}Tc approved by the Food and Drug Administration (FDA) from the United States.

AVAILABILITY OF ^{99}Mo

The availability of the generators is directly related to the capacity for production of ^{99}Mo. Up to the middle of the 2000's the situation was very comfortable due a sufficient capacity was available to meet international needs. However, at the beginning of 2009 a global crisis in the supply of ^{99}Mo took place making it necessary for the development and evaluation of alternative technologies for the production of ^{99}Mo and ^{99}Mo/^{99m}Tc generators. The ^{99}Mo shortage drew the attention of the whole world and started several efforts aiming sustainability of supply.

The purpose of this paper is to provide a brief story of the availability of ^{99}Mo in the world followed by an overview of the production routes of ^{99}Mo and the generators technology.

The total world demand of ^{99}Mo is around 12,000 Ci per week with a 6-day pre-calibration (also known as 6 day ^{99}Mo) that totals nearly 600,000 Ci ^{99}Mo 6-day per year [7]. These numbers mean nearly 71,100 Ci of ^{99}Mo at the end of bombardment (EOB) per week and 3,600,000 Ci at EOB every year. More than 95% of the ^{99}Mo required is produced by the main route, the fission of ^{235}U targets (^{99}Mo fission yield: 6.1%). The remained comes mostly from domestic production by the neutron capture reaction, ^{98}Mo(n,γ)^{99}Mo.

The irradiated targets are then processed and the resulting purified ^{99}Mo solution subsequently distributed for use in the production of ^{99}Mo/^{99m}Tc generators.

Up to 2008 four reactors were primarily responsible for most of the world production of ^{99}Mo: the High Flux Reactor (HFR) in The Netherlands, National Research Universal (NRU) in Canada, Belgium Reactor (BR2) and Safari1 in Africa, as summarized in Table **2**. All used Highly Enriched Uranium (HEU) targets for the production of ^{99}Mo and were at the time at least 45 years old.

It can be seen there has been no recent contribution from the US in the production of ^{99}Mo. Prior to 1989, Cintichem, Inc. produced ^{99}Mo for the U.S. market using a 5 MWt (megawatt thermal) research reactor located in Tuxedo, New York. This reactor was shut down when tritium contamination of surface waters adjacent to the reactor site was confirmed. A decision to decommission the reactor was subsequently made after a risk-benefit study carried out by Cintichem's parent company, Hoffman-LaRoche, determined that its continued operation was not justified.

In the past, ^{99}Mo shortages happened as fast as they disappeared, however the shortage in 2009 had a direct impact in the use of ^{99m}Tc in the clinics and also led to several actions in different countries in order to improve the availability of ^{99}Mo and to nationalize its production. Table **3** describes a timetable of the main events concerning the supply of ^{99}Mo.

Table 2. Principal Large-Scale and Regional Producers of ^{99}Mo [6]

^{99}Mo Producer	Country	Primary Supply Regions	Percent of World Supply of ^{99}Mo	Percent of U.S. Supply of ^{99}Mo
MDS- Nordion	Canada	North America, South America, Europe, Asia	40	60
Mallinckrodt	United States, Netherlands	North America, Latin America, Europe, Middle East	25	40
IRE	Belgium	Europe	20	0
NTP	South Africa	Africa, Australia	10	0
Other	Argentina, Australia, Russia	South America, Pacific-Asia, Russia	5	0

Source: Medical Isotope Production without Highly Enriched Uranium

Table 3. Timetable of ^{99}Mo Worldwide Supply

Year	Events
1989	Permanent shut down of the Cintichem Reactor in New York, USA, ending the U.S. domestic supply of ^{99}Mo;
1982	The U.S. Department of Energy (DOE) begins an effort to produce ^{99}Mo in its reactors;
1995	Strike of Canadian air-flight personnel led to a reduction in the supply of ^{99}Mo;
1995-1997	Shutdown of the BR2 reactor (21 months) for major refurbishment;
1997	Shutdown of the NRU reactor (5 days) because of a strike; Definitive shutdown of the SILOE reactor (Grenoble, France) which produced ^{99}Mo;
1999	The U.S. DOE ends its efforts to produce ^{99}Mo due to the lack of economical interest;
2001	The terrorist attacks on USA soil in 11th of September interrupt the delivery of ^{99}Mo by air;
2002	Shut down of the HFR Reactor for 42 days due to reactor operation safety concerns;
2005	Shut down of the Mallinckrodt facility for production of ^{99m}Tc generators in the USA from November 2005 until April 2006;
2006	Shut down of the NRU reactor for 6 days and permanent shut down of the FRJ-2 reactor (Jülich, Germany);
2007	Shut down of the NRU reactor for 24 unplanned days by the Canadian regulatory body due to safety concerns. Recall of ^{99}Mo/^{99m}Tc generators by COVIDIEN (1month);
2008	Shut down of the HFR Reactor due to problems in the cooling system from August 2008 until February 2009. Shut down of the IRE Reactor due to ^{131}I release from August to November. Shutdown of the NRU reactor in December 2008 for several days extended for several additional days;
2009	Shut down of the NRU Reactor for 12 months for repairs starting in May 2009 [8];
2010	NRU Reactor is back in operation in 18 August 2010. Shut down of the HFR Reactor for repairs from February until September 2010.

This summary illustrates the complexities involved in ^{99}Mo supply from fission in nuclear reactors and the complexities in the ^{99}Mo supply chain.

After the ^{99}Mo supply crisis several actions were put in motion [7,9,10]. The Osiris Reactors in France and Maria in Poland were allowed to irradiate U targets for the major producers. In the case of Poland, the US FDA gave approval for use of the irradiated targets as raw material for the production of ^{99}Mo in a record fast time. At the same time the new Opal Reactor and the new ^{99}Mo production installation in Australia started their operation using LEU targets in 2010, using the technology developed in Argentina, that had been producing ^{99}Mo using LEU targets since 2002. Its production capacity increased and started to supply ^{99}Mo to the neighboring country, Brazil, in 2009. Latter, the OSIRIS Reactor in France and LVR-15 in Czech Republic also started to irradiate HEU targets for the main producers.

Alternative well known approaches for diagnosis employing radiopharmaceuticals prepared with other radioisotopes than ^{99m}Tc were further promoted and introduced primarily, including the use of ^{201}Tl chloride and ^{82}Rb for cardiac perfusion and ^{18}F-flouride for bone scan. These alternatives were advertised and analyzed by societies such as The American Society of Nuclear Medicine (SNM) that even published surveys of the effect of the supply crisis in the clinics [11].

The needs that have arisen from the crisis have met the efforts of the Global Threat Reduction Initiative (GTRI) led

Table 4. Alternative ^{99}Mo Production Processes and their Cross Sections [33,34]

Alternatives	Reaction	Cross Section (barn)	Targets
Reactor	$n + {}^{235}U \rightarrow {}^{99}Mo + FP + 2n$	586 x 6% = 35.16	LEU, HEU
	$n + {}^{98}Mo \rightarrow {}^{99}Mo + \gamma$	0.14	Natural Mo, enriched ^{98}Mo
Accelerator	$\gamma + {}^{100}Mo \rightarrow {}^{99}Mo + n$	0.16	enriched ^{100}Mo
	$\gamma + {}^{238}U \rightarrow {}^{99}Mo + FP + 2n$	0.16 x 6%= 0.96	^{235}U
	$p + {}^{100}Mo \rightarrow {}^{99m}Tc + 2n$	0.20	enriched ^{100}Mo
	$p + {}^{100}Mo \rightarrow {}^{99}Mo + p + n$	0.15	enriched ^{100}Mo
	$n + {}^{100}Mo \rightarrow {}^{99}Mo + 2n$	1.5	enriched ^{100}Mo

FP = Fission Product

by the U.S. and the National Nuclear Security Administration (NNSA) that aims to convert research reactors and radioisotope production facilities from the use of highly enriched uranium (HEU) to low enriched uranium (LEU) [12-14]. On October 15, 2010, the NNSA awarded Necsa/NTP Radioisotopes funding to minimize and eliminate the use of HEU in the production of ^{99}Mo in South Africa. On December 6, 2010, Lantheus Medical Imaging received the first shipment of FDA-approved LEU-produced medical isotopes from NTP Radioisotopes in South Africa. Since then NTP has been commercializing large-scale quantities of LEU-produced ^{99}Mo [15,16].

In 2009 the Organization for Economic Cooperation and Development from the Nuclear Energy Agency's (OECD-NEA) [17-23] created the High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) with the purpose of developing a policy approach on Full-cost recovery and Outage Reserve Capacity to facilitate a reliable market for ^{99}Mo. The Association of Imaging Producers and Equipment Suppliers (AIPES) [24] with SNM and the European Association of Nuclear Medicine (EANM) to define measures that should be taken to secure the ^{99}Mo supply in the short, medium and long term [6,25,26].

The International Atomic Energy Agency (IAEA) has also been acting in several approaches to find a solution for the ^{99}Mo worldwide availability [27-31]. Several Coordinated Research Projects (CRP) and Consultancy Groups were created, which include the following:

- Conversion Planning for ^{99}Mo Production from HEU to LEU
- Small-Scale Indigenous Production Using LEU Targets or Neutron Activation
- Current and Novel, Non-HEU-Based Isotope Production and Supply Technologies for ^{99}Mo and ^{99m}Tc
- Feasibility Evaluation of the Use of Low Enriched Uranium Fuelled Homogeneous Aqueous Solution Nuclear Reactors for the Production of Short Lived Fission Product Isotopes
- Progress with the Production of ^{99}Molybdenum using Neutron Activation
- Supporting a Sustainable Increase in the Use of Research Reactors in the Latin American and Caribbean Region

Some countries made important decisions about the supply of ^{99}Mo. The Canadian government renewed the operation license for the NRU Reactor and the ^{99}Mo production facility until 2016. No additional fission moly will be produced after this date and the project of producing ^{99m}Tc directly in Cyclotron received the necessary funds to be completed.

The American Medical Isotopes Production Act of 2011 (S.99) was approved by the U.S. Congress to promote the production of ^{99}Mo in the United States, and to condition and phase out the export of HEU for the production of medical isotopes [32]. The U.S. government, through the NNSA decided to support the following existing commercial projects to meet at least 100% of the U.S. demand of ^{99}Mo produced without HEU [13]:

- Neutron Capture, with a Cooperative Agreement to General Electric-Hitachi together with Missouri University Research Reactor (MURR);
- LEU Solution Reactor Technology, with a Cooperative Agreement to Babcock and Wilcox (B&W);
- Accelerator Technology, with a Cooperative Agreement to NorthStar Medical Radioisotopes, LLC and to Morgridge Institute for Research.

PRODUCTION ROUTES FOR ^{99}Mo

Table **4** highlights the possible production routes for ^{99}Mo *via* irradiations in nuclear reactors and particle accelerators.

Reactor: Fission of ^{235}U

The most employed ^{99}Mo production route is the fission of ^{235}U with thermal neutrons in a nuclear reactor, especially in the case of the large-scale commercial producers. The most significant advantage is the high specific activity of ^{99}Mo that allows the preparation of the ever reliable and widely used chromatographic-type ^{99}Mo/^{99m}Tc generator system.

This generator provides sodium pertechnetate ($Na^{99m}TcO_4$) by elution with saline and uses high specific activity no-carrier-added ^{99}Mo, which is adsorbed on aluminium oxide. In this case, aluminium oxide acts as an anion exchanger having the following adsorption order for these anions: $MoO_4^{2-} > Cl^- > TcO_4^-$. When the generator is first loaded onto the column, MoO_4^{2-} is strongly adsorbed, ^{99}Mo decays to ^{99m}Tc in the form of TcO_4^-, and when saline is percolated through the column the chloride ions replace the

TcO_4^- ions, assuring the total elution of the desired radioisotope. The elution process is fast, with high elution yield (>98%) and high elution efficiency (>95%), with a elution volume of 6 mL for a typical generator containing 9,25-518 GBq of ^{99}Mo, providing ^{99m}Tc with high radioactivity concentration. Glass flasks in vacuum are used for the elution of ^{99m}Tc in this generator. The ^{99}Mo breakthrough values must be <0.5kBq/MBq^{99m}Tc (>0.5μCi/mCi) (USP/NF 1995).

The drawbacks for the fission route are the large number of radionuclidic impurities produced in addition of ^{99}Mo, that leads to necessary complex chemical separations, a high level waste management, the need of a dedicated and well shielded hot cell and the need for proper shielding when transporting the irradiated target from the reactor to the hot cell. It is clear that such process will be expensive to maintain and operate.

It is mandatory that enriched targets of ^{235}U are used for obtaining high activities of ^{99}Mo. There are two types of ^{235}U concerning its enrichment, LEU (< 20% ^{235}U) and HEU (≥ 20% ^{235}U). LEU targets require approximately five times more uranium than HEU targets and approximately 25-times more ^{239}Pu is produced in a LEU target. Despite the fact that most of the ^{99}Mo is produced in the world uses HEU, this material is considered to be weapons-grade and its transport is a worldwide concern that will eventually end its use for both reactor fuels and targets (GTRI/DOE efforts) [35,36].

Producers using HEU employ targets in the form of Uranium aluminide/aluminum-alloy dispersion; Uranium aluminum alloy in aluminum-cladding; UO_2 deposited on the inside surface of a stainless-steel closed cylinder; and compacted UO_2 powder. On the other hand those using LEU employ targets of UAlx dispersion targets; metallic U foil target and the proposed U_3Si_2 dispersion targets.

There are two general approaches for chemically processing targets to recover ^{99}Mo: alkaline dissolution and acidic dissolution [37]. The processes can be used on both HEU and LEU targets. The ^{99}Mo separation and purification process depends on the target and the kind of dissolution.

Reactor: Fission of ^{235}U: Solution Reactor (Homogeneous) Production

The idea behind this route is to use a solution containing LEU-based nitrate or sulphate salt dissolved in water and acid that is at the same time the reactor fuel and the target material for ^{99}Mo production. The reactor would be operated in batch mode to produce ^{99}Mo and would be shut down and the fuel solution containing ^{99}Mo pumped through a recovery column that would preferentially adsorb molybdenum. After removal from the column ^{99}Mo would go through purification steps.

B&W has developed the "MIPS" conceptual design for a 200kW Aqueous Homogenous Reactor (AHR) and recovery system to produce ^{99}Mo.

Besides the pros and cons evaluated for the fission of ^{235}U, other challenges still have to be resolved. The reduction of the pH and the radiolysis effects during the irradiation can reduce the solubility of the salts and further deposition, reducing the recovery yield of ^{99}Mo.

Reactor: Neutron Activation ^{98}Mo(n,γ)^{99}Mo Reaction

The production of ^{99}Mo via the neutron activation of Mo targets is a traditional and attractive alternative to the fission of ^{235}U. The main disadvantage is the low specific activity of ^{99}Mo (37-370 GBq/g Mo) that can be increased with the use of highly enriched ^{98}Mo targets and high neutron fluxes. The advantages are the generation of very low level of radioactive wastes generated during the simple chemical processing of the targets and the use of rather simple hot cells. Targets commonly used are MoO_3 and metallic Mo. The later is better considering the total number of Mo atoms but it is very difficult to dissolve and also contains one major impurity, W, that can produce ^{188}W during the neutron irradiation leading to a ^{188}Re impurity in the ^{99m}Tc eluate. Compressed or molten MoO_3 targets have been successfully employed [38].

The traditional chromatographic-type ^{99}Mo/^{99m}Tc generator system based in alumina cannot be generally used with low specific activity ^{99}Mo. The adsorption capacity of acidic alumina for molybdate ions is limited (maximum of 20 mg Mo per g of alumina at pH 3-4), which in turn requires increased volumes of the saline eluant, resulting in decreased activity concentration of ^{99m}Tc.

However, some attractive alternatives for the use of (n,γ)^{99}Mo are as follows:

- Generators based on methyl ethyl ketone (MEK) extraction of $^{99m}TcO_4^-$ from alkaline aqueous molybdate solutions. This alternative is appropriate for batch production of ^{99m}Tc and is currently being employed in Peru, Chile, India, Russia and Brazil [39];
- Generators based on the sublimation of Tc_2O_7 when MoO_3 is heated at high temperatures [40];
- Electrochemical generator based on the ^{90}Sr/^{90}Y generator developed in India [41];
- A new generator concept developed by NorthStar;
- The 'gel-type' generator approach involves preparation of molybdenum-zirconium gel. The use of preformed and post-formed gels is two strategies for preparation of the gel generator. In the preformed technique ^{99}Mo is produced by neutron activation of Mo in the trioxide or metal form and the gel is then prepared. The preformed technique provides easier generator assembly and involves less handling of radioactivity but has the disadvantages of producing more chemical and radionuclidic impurities, resulting from radiolysis of the gel during irradiation. The post-formed technique provides a generator with better performance quality and the generator can be assembled either wet or dry. With elution in about 12 mL of saline, the wet generator has a higher ^{99m}Tc elution efficiency (>85%) than the dry system (>80%). It is more difficult to load reproducible levels of ^{99}Mo during fabrication of the wet generator, however, since the wet gel cannot be weighed. In the dry technique the gel can be loaded by weight. India and Kazakshtan have routine production of gel type generators [42-47];
- Post elution concentration of the eluate coming from the gel type generator or large alumina column generators. The technique employs an anion-exchange column in tandem with the Al_2O_3 generator column, similar to that

developed for the $^{188}W/^{188}Re$. Or a cationic resin in the Ag form followed by an anionic. In both cases the first column retains Cl^- and the second TcO_4^- that is further eluted with low volume of saline solution [48-50];

- The development and use of materials that have high capacity for Mo by Australia, Japan, Vietnam, Korea and India. Polymeric zirconium compound (PZC) [51], polytitanium oxochloride (PTC- 80mg Mo/g), nano-zirconia (140mg Mo/g) nano-titania (>100mg Mo/g) and nano-ceria are some examples of this kind of material [52];
- Irradiation of Mo metal targets in commercial BWR power reactors [53, 54]. In February 2012 this alternative was abandoned due to economic costs [55];
- The isotopic separation of ^{99}Mo from the irradiated target by laser ablation techniques in order to improve the ^{99}Mo specific activity. This method has yet to be proven reliable and economic and technically viable [56].

Proton Accelerator, Secondary Particle Beam: Fission of ^{235}U

Accelerator can also be the source of neutrons, that are used in order to produce fission in a blanket of ^{235}U surrounding the neutron source. This neutron flux can be generated by proton irradiation of heavy nucleus targets such as Pb, Ta, W and U. Very high fluxes are required and would be difficult to achieve the necessitated geometry in order for this method to be competitive with reactor-generated neutrons. Moreover, such an accelerator would be expensive to build and operate, although it would be less expensive than a new reactor. All the issues associated with fission of ^{235}U in a reactor are also encountered by this route.

Proton Accelerator, Secondary Particle Beam: $^{98}Mo(n,\gamma)^{99}Mo$ Reaction

The concept of generating a secondary beam of neutrons is the same as discussed earlier, but in this case enriched ^{98}Mo targets are irradiated with the same irradiation drawbacks mentioned before. In addition ^{99}Mo is only produced with low to medium specific activity, compared with NCA ^{99}Mo recovered from reactor fission products.

Proton Accelerator: $^{100}Mo(p,n)^{99m}Tc$ Reaction

This route is unique in accelerator production route that provides the direct production of ^{99m}Tc, and is then considered decentralized [57]. This solution requires the use of cyclotrons located near hospitals, by which the delivery of radiopharmaceuticals to patients could be easy and secured. It requires the use of enriched ^{100}Mo targets and several groups have been extensively studying this route. Recently Canada announced the development of the technology for producing ^{99m}Tc in cyclotrons. At a special session at the 2011 annual meeting of the American Association for the Advancement of Science, a team led by TRIUMF (Canada) announced the successful production of multi-Ci quantities of ^{99m}Tc on cyclotrons already available in Ontario and British Columbia [58,59].

Three aspects are very important for this technology: (i) the development of a metallic enriched ^{100}Mo targets that withstand high proton beam currents, with electrodeposition being one of the best choices, (ii) the efficient recovery of the expensive enriched target after the chemical processing and (iii) the choice of the best proton beam energy range to minimize the radionuclidic impurities ^{97}Tc, ^{98}Tc, ^{99}Tc all with half-lives higher than 10^5 years and decrease the specific activity of the desired ^{99m}Tc. Based on excitation function studies the Canadian group found that the best energy range is between 19 and 16 MeV.

In 2012 IAEA will initiate a CRP concerning the accelerator-based alternatives to non-HEU production of $^{99}Mo/^{99m}Tc$.

Proton Accelerator: $^{100}Mo(p,pn)^{99}Mo$ Reaction

The same targets can be used compared with the previous strategy, with the advantage of producing ^{99}Mo, but with a major setback coming from the low cross section for this reaction. This leads to a very low specific activity of ^{99}Mo.

Deuteron Accelerator, Secondary Particle Beam: $^{100}Mo(n,2n)^{99}Mo$ Reaction

High energy neutron beams are generated by the bombardment of natural carbon foil targets with high energy deuterons. This approach is also considered expensive and provides low activity ^{99}Mo compared to the $^{98}Mo(n,\gamma)^{99}Mo$ reaction.

Electron Accelerator, Secondary Particle Beam: Fission of ^{235}U

This approach requires the use of a high powered electron beam to generate high-intensity photons known as bremsstrahlung radiation which in turn would be used to initiate the desired nuclear reaction. The electron beam irradiates a high-Z target, also called the converter, such as liquid mercury or water-cooled tungsten. The interaction and loss of energy of the electron beam with the converter target generates the high-energy photons. This technique would require multiple machines since the fluxes of photons would not be sufficiently high to be competitive. Moreover, the expected very high cost of building and operation of multiple machines would have to be considered.

When the fission of ^{235}U is considered by the photon activation reaction, apart from all the issues related to fission, another disadvantage is the low cross section of the reaction.

Electron Accelerator, Secondary Particle Beam: $^{100}Mo(\gamma,n)^{99}Mo$ Reaction

All the issues discussed for the previous strategy must be taken into account for the photo activation of enriched ^{100}Mo targets. The cross section for the reaction is comparable to the $^{98}Mo(n,\gamma)^{99}Mo$ reaction and will produce low to medium ^{99}Mo specific activity. The one advantage when compared to the proton activation of Mo targets is the heat generated in the target during the irradiation is lower, and consequently more simple metallic Mo targets can be employed [60].

In November 2011, the U. S. Department of Energy's National Nuclear Security Administration (NNSA) announced that it has signed a cooperative agreement with NorthStar Medical Radioisotopes LLC to further develop-

ment of ^{99}Mo production capability in the United States. The NNSA and NorthStar will evenly share the costs of the work under the agreement, which is reported to be valued at $4.6 million [61]. NorthStar is proposing to construct a facility in Beloit, Wisconsin, U.S., to produce ^{99}Mo using multiple linear accelerators, with the aim of providing 50 percent of the U.S. requirement of ^{99}Mo by the end of 2014. In the shorter term, NorthStar has partnered with MURR to produce ^{99}Mo from the ^{98}Mo(n,γ)^{99}Mo reaction, starting in the second quarter of 2012 [62].

^{99}Mo/^{99m}Tc Generator for low Specific Activity

Most of the alternative ^{99}Mo production routes described generally provide only low specific activity ^{99}Mo. Some options for generators have also been discussed, such as the gel and electrochemical generators, or even the use of post concentration unities or the isotopic enrichment on ^{99}Mo of the irradiated target.

NorthStar Medical Radioisotopes LLC recently developed a new generator, the NorthStar's Technegen™ Generator System [63].

A point of curiosity is to compare this new generator concept with the first small ^{99}Mo/^{99m}Tc which had been developed initially. The NorthStar generator can be used with any source of low specific activity ^{99}Mo. The Mo containing target is dissolved in alkaline solution that is fed then to a specific column where ^{99m}Tc is adsorbed. The ^{99m}Tc is stripped from the column using low volumes of saline solution, and subsequently passed through an alumina column to remove any Mo left and finally through a 0.22 micron sterile filter. The ^{99}Mo solution is maintained in a proper lead shield to allow ^{99m}Tc to grow and the process is repeated. The elution efficiency is > 90%, and the quality of the $^{99m}TcO_4^-$ solution is reported to meet the Pharmacopeia requirements. Another advantage is that the generator is computer controlled.

CONCLUSIONS

There are no questions about the past, present and future role and importance of ^{99m}Tc in nuclear medicine and the secure supply of ^{99m}Tc and its parent ^{99}Mo became a worldwide concern. This is particularly important after the failures of supply of ^{99}Mo starting in 2008 and the ageing of the main reactors that have traditionally produced ^{99}Mo. Also, the ^{99m}Tc activity levels administered to patients per dose have decreased and there has been a more important efficient overall use of the generators, together with the development new SPECT machines with higher resolution and efficiency. Lessons in general were well learned after the crisis.

Several countries started or implemented projects aiming the production of ^{99}Mo or directly producing ^{99m}Tc, especially after the decision of the Canadian government to end the production of fission based ^{99}Mo in 2016.

Some countries are pursuing the fission route, using nuclear reactor, improving already existing facilities, such as Argentine, Australia, Belgium, Chile, Czech Republic, Egypt, France, Germany, Indonesia, Pakistan, Poland and South Africa, or planning new Reactors, as Argentine, Brazil, France and Netherlands. It is important to note the importance of efforts to use LEU targets in the new installation or the conversion to LEU in the existing facilities.

Alternative production routes for ^{99}Mo are also being studied and funding by private companies and/or governments. In this particular point it is relevant to mention the breakthrough of the technology of producing ^{99m}Tc by proton irradiation of ^{100}Mo targets made by Canada and the technology of producing ^{99}Mo by the photon activation of ^{100}Mo targets by NorthStar in the U.S. Together with MURR and its new generator technology, NorthStar claims to supply half of the U.S. demand of ^{99}Mo by the end of 2014.

All the efforts are being helped or supported by important actions coming from IAEA, DOE, NSSA, GTRI, AIPES, HLG-MR, OECD-NEA, SNM, EANM among others.

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CONFLICT OF INTEREST

Declared none.

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