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Update on IAEA Activities Supporting Non-HEU Production of ^{99}Mo & ^{99m}Tc

J. Dix and A. Borio di Tigliole
Department of Nuclear Energy
International Atomic Energy Agency, Vienna International Centre
PO Box 100, 1400 Vienna – Austria

and

J. A. Osso, D. Ridikas, and M. Venkatesh
Department of Nuclear Science and Applications
International Atomic Energy Agency, Vienna International Centre
PO Box 100, 1400 Vienna – Austria

ABSTRACT

Since 2008, the supply chain for ^{99}Mo/^{99m}Tc has experienced shortages due to unexpected shutdowns both at reactors and processing facilities. The possibility of future shortages remains, particularly as some of the key reactors producing ^{99}Mo cease operation, either permanently or for prolonged periods for maintenance and facility upgrades.

Realising the need to support Member States in mitigating the effects of a supply crisis of ^{99}Mo/^{99m}Tc in the future, the IAEA facilitates a number of activities, some of which will be presented in this paper. Those discussed include: (i) the ^{99}Mo HEU minimization project, (ii) the Coordinated Research Project on "Accelerator-based Alternatives to Non-HEU Production of Mo-99/Tc-99m", (iii) the Peaceful Uses Initiative project on "Supporting the Global Deployment of Mo-99 Production Capacity for Nuclear Medicine Applications without the Use of Highly Enriched Uranium (HEU)", (iv) the new Coordinated Research Project on "Sharing and Developing Protocols to Further Minimize Radioactive Gaseous Releases to the Environment in the Manufacture of Medical Radioisotopes, as Good Manufacturing Practice", and (v) a Round Robin exercise. The outcomes of these projects thus far as well as the activities planned for the future will be discussed.

1. Introduction

1.1 Role of ^{99m}Tc in Nuclear Medicine

While nuclear medicine applications encompass both diagnostic and therapeutic procedures, more than 90% of all nuclear medicine procedures are diagnostic imaging. The radionuclide ^{99m}Tc plays a particularly dominant role in nuclear medicine as its radiopharmaceuticals are employed in more than 80% of all diagnostic procedures worldwide. Over 30 million procedures with ^{99m}Tc radiopharmaceuticals are performed worldwide every year, with more than 50,000 procedures performed every day in the USA alone. Technetium-99m's physical decay characteristics, availability in the form of a radionuclide generator, and favourable chemistry make it an ideal medical radionuclide for these procedures.

Physical Decay Characteristics: Technetium-99m decays by isomeric transition to long-lived ground state ^{99}Tc. During this decay, a low energy photon (140 keV) is emitted without the emission of any other radiation. As a result of this and the short half-life of ^{99m}Tc (6 hours), the radiation dose to both medical staff and patients is minimized while providing excellent imaging properties.

Radionuclide Generators: Hospitals typically use the radionuclide generators for one to two weeks. The most employed generator is the chromatographic type based on alumina, which uses high specific activity ^{99}Mo and allows the elution of ^{99m}Tc with a high radioactivity concentration, suitable for labelling kits for the preparation of ^{99m}Tc radiopharmaceuticals.

Favourable Chemistry: The rich coordination chemistry of Tc, a transition metal element, enables ^{99m}Tc to form complexes with a variety of molecules, which in turn permits easy labelling of different molecules in various kit formulations. More than 20 different kits can be labelled with ^{99m}Tc and are routinely used [1, 2] to image various organs for structural as well as functional information. Myocardial perfusion imaging (MPI) and scanning of bone metastatic invasion as a side effect of cancers are among the most widespread applications.

1.2 Production Routes of ^{99}Mo

Although there are several ways of producing ^{99}Mo [3], the primary route involves neutron induced fission of ^{235}U, which has a large cross-section (~584 barns for thermal neutrons) and a high ^{99}Mo production yield of 6.1%. This route produces a high specific activity ^{99}Mo that is used in compact chromatographic ^{99}Mo/^{99m}Tc generators based on alumina. Most ^{99}Mo production that uses this route is produced in multipurpose high-power research reactors, as they have operational schedules and space available for irradiating multiple targets at high neutron fluxes (10^{13}–10^{14} $n.cm^{-2}.s^{-1}$). While historically ^{99}Mo has been produced using high enriched uranium (HEU) targets, the community is currently in the process of transitioning to non-HEU based technologies.

1.3 Supply & Demand of ^{99}Mo/^{99m}Tc

At present, there are five large-scale producers of ^{99}Mo: Nordion (Canada), the Institute for Radioelements (IRE) (Belgium), Covidien/Mallinckrodt (the Netherlands), NTP Radioisotopes (South Africa) and the Australian Nuclear Science and Technology Organisation (ANSTO) (Australia). The National Atomic Energy Commission (CNEA) in Argentina was the first ^{99}Mo producer to use low enriched uranium (LEU) targets for small-scale, primarily national production (as of 2002). Since 2010, both ANSTO and NTP Radioisotopes have been producing large scale quantities of ^{99}Mo using LEU targets.

According to the 2014 estimates made by the OECD-NEA, the weekly global demand for ^{99}Mo is approximately 10,000 6-day Ci,[1] with the annual growth rate of ^{99}Mo in mature markets (North America, Europe, Japan and the Republic of Korea) assumed to be 0.5%, and in emerging markets 5%. [4]

Since 2007, the supply of ^{99}Mo has experienced disruptions for various reasons, primarily stemming from the ageing fleet of reactors. As some of the key reactors producing ^{99}Mo cease operation, either permanently or for prolonged periods for maintenance and facility upgrades, the supply of ^{99}Mo will need to be closely monitored.

1.4 Role of IAEA in Supporting the Production of ^{99}Mo and/or ^{99m}Tc

Realising the need to support the Member States in mitigating the effects of a supply crisis of ^{99}Mo/^{99m}Tc in the future, the IAEA has initiated the following main activities:

- **(i)** the HEU minimization project, aimed at the transition of ^{99}Mo production away from the use of HEU;
- **(ii)** the Coordinated Research Project on “Accelerator-based Alternatives to Non-HEU Production of Mo-99/Tc-99m”, aimed at the direct production of ^{99m}Tc through the reaction ^{100}Mo(p,2n)^{99m}Tc using cyclotrons;
- **(iii)** the Peaceful Uses Initiative (PUI) project on “Supporting the Global Deployment of Mo-99 Production Capacity for Nuclear Medicine Applications without the Use of Highly Enriched Uranium (HEU)”, aimed at assisting small-scale, national-level producers in setting up their production capability using LEU fission or the ^{98}Mo(n,γ)^{99}Mo reaction;
- **(iv)** the new Coordinated Research Project on “Sharing and Developing Protocols to Further Minimize Radioactive Gaseous Releases to the Environment in the Manufacture of Medical Radioisotopes, as Good Manufacturing Practice”, aimed at mitigating emissions from medical isotope production; and
- **(v)** the Round Robin exercise, aimed at providing experimental results on production capabilities of the participating research reactors of ^{99}Mo based on the ^{nat}Mo(n,γ)^{99}Mo reaction for supply to local users.

2. Activities Supporting the Transition Away from HEU

As part of the IAEA's continuing involvement to address security of supply as well as minimize the use of HEU in civilian applications, the IAEA held a series of Technical Meetings on Conversion Planning for Molybdenum-99 Production Facilities from 2010-2015. These meetings provided a forum for representatives of the major ^{99}Mo producers and related stakeholders to identify issues associated with the conversion of existing isotope production facilities to LEU targets and to help develop a plan to address these challenges.

[1] The activity of ^{99}Mo is traditionally mentioned in curies after decay correction for 6 days, to indicate the activity a user will get when the generator is shipped and arrives about 6 days later at the hospital or radiopharmacy.

ANSTO (Australia) and NTP Radioisotopes (South Africa) continue to be the major suppliers of non-HEU ^{99}Mo. In 2014, ANSTO broke ground on its new ^{99}Mo production facility, which is expected to increase its LEU-based ^{99}Mo production to 3,500 6-day Ci. NTP Radioisotopes is continuing to convert its processes to the exclusive use of LEU. IRE (Belgium) and Mallinckrodt (the Netherlands) have initiated efforts to support the conversion of their commercial-scale production processes from HEU to LEU targets. In October 2016 Canada's NRU reactor will cease regular isotope production. However, in February 2015, the Canadian Government announced its intention to extend operations of the NRU reactor until 31 March 2018 to support the global medical isotope supply in the case of any major unexpected shortages. After March 2018, the NRU reactor will shut down.

Given the progress of the major ^{99}Mo producers in their conversion activities, it was decided that the meeting as originally established fulfilled its mission and that a forum dedicated to its specific discussion was no longer necessary. However, given continuing interest in addressing future activities that will assist the producers following initial conversion, the IAEA is in the process of developing new meetings on global capabilities for targetry, with the possibility of addressing issues ranging from methods of manufacture to harmonization/optimization. The first of these new meetings with be a Technical Meeting on Global Capabilities for the Production and Manufacture of Molybdenum-99 Targets, which will be held on 20-21 October 2015 in Vienna, Austria.

3. Coordinated Research Project on "Accelerator-based Alternatives to Non-HEU Production of Mo-99/Tc-99m

An alternative procedure for producing ^{99m}Tc that is presently under investigation is the use of medical cyclotrons, which are commonly employed in the routine production of ^{18}F and ^{11}C radiopharmaceuticals for positron emission tomography (PET). An IAEA coordinated research project (CRP) on "Accelerator-based Alternatives to Non-HEU Production of Mo-99/Tc-99m" was launched in 2011, with the aim of demonstrating the routine, reliable, commercial-scale production of ^{99m}Tc via the ^{100}Mo(p,2n) reaction [5]. The final meeting of this CRP was held 22-26 June 2015.

The studies performed under the CRP included building a high-efficiency target, finding the proper irradiation conditions (incident proton energy, target thickness and duration of irradiation), implementing automated methods to extract and purify ^{99m}Tc in the chemical form of pertechnetate, recycling of the enriched ^{100}Mo target, performing quality control of ^{99m}Tc and in particular its radionuclidic purity, assessing the suitability of the technetium radioisotope for eventual human use, performing dosimetry calculations to estimate radiation dose to the patient from potential radionuclidic impurities, and comparing the image quality of standard ^{99m}Tc radiopharmaceuticals prepared using cyclotron-produced pertechnetate with commercial generator-produced ^{99m}Tc through animal imaging studies.

Most of the technical issues have been resolved and now the challenges relate to regulatory approval, distribution logistics and the guaranteed supply of enriched ^{100}Mo for target preparation. Recently, one of the CRP participants (TRIUMF) issued a press release stating the achievement of the production of 34 Ci of ^{99m}Tc in one irradiation and that clinical trials were initiated with cyclotron produced ^{99m}Tc [6].

The overall conclusion of the CRP is that the cyclotron production route of ^{99m}Tc introduces one possible solution to supply issues while also addressing the proliferation concerns associated with the current HEU-based method of ^{99}Mo production.

4. Peaceful Uses Initiative Project on "Supporting the Global Deployment of Mo-99 Production Capacity for Nuclear Medicine Applications without the Use of Highly Enriched Uranium (HEU)"

In 2005, the IAEA launched a CRP on "Developing Techniques for Small Scale Indigenous Molybdenum-99 Production Using LEU Fission or Neutron Activation." The aim of this CRP was to support interested Member States in adopting non-HEU technologies for the small-scale, national level production of ^{99}Mo through LEU fission or (n,γ) routes. The expected output of the CRP was that the Member States would acquire an understanding of the available technologies and be in a position to make a sound decision on whether to proceed with domestic production of ^{99}Mo or to look for alternative options to satisfy domestic demand. Fourteen Member States participated in this CRP, which concluded in December 2011. In January 2015, the IAEA published Technical Report Series No. 478, *Feasibility of Producing Molybdenum-99 on a Small Scale Using Fission of Low Enriched Uranium or Neutron Activation of Natural Molybdenum* [7], which summarizes the activities and results of this CRP.

This CRP and a 2013 IAEA publication *Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m* [3] served as the basis for the Peaceful Uses Initiative project on "Supporting the Global Deployment of Mo-99 Production Capacity for Nuclear Medicine Applications without the Use of Highly Enriched Uranium (HEU)", which was initiated in 2013. The project is aimed at strengthening the supply of ^{99m}Tc in developing countries by assisting small-scale, national level producers in setting up a production capability. This is achieved by (i) developing human resources and skills related to target irradiation and handling, radiochemical processing, ^{99m}Tc generator production, supply logistics, and waste management; and (ii) the direct, coordinated, multi-regional deployment of demonstrated, non-HEU based ^{99}Mo production technologies.

This project and supporting activities are implemented using PUI funding from Japan and are jointly managed by the IAEA's Department of Nuclear Energy and Department of Nuclear Sciences and Applications. To achieve the objective, the following activities have taken place:

- Detailed fact-finding missions to facilities in participating Member States. These missions evaluated the status of the currently available $^{99}Mo/^{99m}Tc$ production infrastructure, taking into account research reactor capabilities, radioisotope production facilities, waste management and overall logistics, including commercialization aspects. Production infrastructure fact-finding missions were completed to Mexico, Morocco, Peru, Poland and Romania. Similar missions were conducted in Egypt (2010) and Malaysia (2011). Comprehensive mission reports, including recommended infrastructure improvements for various production options, were prepared following each mission and shared with the counterparts.

- Training course on the production of ^{99}Mo by the (n,γ) reaction. This training course took place in Mumbai, India from 22-27 June 2015 with 15 participants from 12 Member States. The course had lectures and laboratory demonstrations related to the following topics: production and supply of ^{99}Mo; all aspects related to (n,γ) production; preparation of generators with low specific activity ^{99}Mo (gel generator); solvent extraction separation of ^{99m}Tc and regulatory issues.

5. Coordinated Research Project on "Sharing and Developing Protocols to Further Minimize Radioactive Gaseous Releases to the Environment in the Manufacture of Medical Radioisotopes, as Good Manufacturing Practice"

In 2014, following a request from Australia, Belgium, the Netherlands, the Republic of Korea, and the USA, the IAEA launched a CRP on "Sharing and Developing Protocols to Further Minimize Radioactive Gaseous Releases to the Environment in the Manufacture of Medical Radioisotopes, as Good Manufacturing Practice". The overall objective of this CRP is to formulate a roadmap to guide the international community of medical radioisotope producers on how to address and reduce the emission of radioactive gases resulting from medical isotope production, in particular ^{99}Mo. The first research and coordination meeting of this CRP will take place from 17-21 August 2015 and is expected to include eight participants and ten observers.

6. Round Robin Exercise

In 2014 the IAEA initiated and carried out a Round Robin exercise known as "Inter-Comparison related to Mo-99 Production Rates by Irradiation of Mo-nat Samples". This exercise was intended to explore and quantify national capabilities of ^{99}Mo production through the (n,γ) pathway from natural or enriched ^{98}Mo targets. The IAEA sent questionnaires to a number of research reactor institutes to invite them to participate in the exercise, to receive expressions of interest and to select participating institutions. Eighteen (18) laboratories covering a wide range of reactor types and powers signed up to participate and perform exploratory experiments. Each participant received a package containing two pieces of metallic molybdenum (one $10\times10\times1$ mm^3, one $50\times10\times1$ mm^3) and a high-density polyethylene plastic capsule containing about 1 gram of molybdenum oxide. In December 2014, the samples were shipped to the participating laboratories, packaged in heat-sealed polyethylene foil and a padded envelope. At the same time the samples were shipped, the IAEA sent an email containing the irradiation and measurement protocol and the reporting form, as well as an announcement on the shipment of the specimens.

All experimental data from participants that was received prior to May 2015 (13 facilities) was included in the draft analysis report. It is intended that the experimental data from the remaining five facilities, when received, will be included in the final analysis report. These activities were coordinated and supported by the Reactor Institute Delft (the Netherlands) in its role as the IAEA Collaborating Centre for Neutron Activation Based Methodologies of Research Reactors.

The IAEA will conduct a follow up meeting in December 2015 to finalise the analysis report related to this inter-comparison exercise and provide some quantitative estimates for the local production capacity of ^{99}Mo. A comparison among different reactor types, power levels, neutron energy spectra, irradiation volumes, experimental details, analysis methodology, etc. will be made. This activity will also serve as a platform for networking in the area of local ^{99}Mo production capabilities using non-fission pathways. Lessons learned and good practices from the Round Robin exercises will also be beneficial to the countries that were not able to join the initiative this time.

7. Conclusions

The IAEA, through a variety of activities, continues to support actions aimed at securing a reliable, non-HEU supply of ^{99}Mo and/or ^{99m}Tc. In addition to the efforts mentioned previously in this paper, the IAEA is pursuing new actions to assist in this goal. Upcoming activities include:

- A Technical Meeting on "Regulatory aspects of radiopharmaceutical production". This meeting is expected to bring together regulators and producers from developed and developing countries to discuss the difference between conventional pharmaceuticals and radiopharmaceuticals and different approaches of the regulations for radiopharmaceuticals around the world. It is expected to occur in December 2015.
- A Technical Meeting on "New Ways of Producing ^{99m}Tc and ^{99m}Tc Generators". This meeting is expected to discuss novel materials/technologies for preparation of ^{99}Mo-/^{99m}Tc generators using low specific activity ^{99}Mo and novel routes for producing ^{99m}Tc other than the established ones and is expected to take place in the first quarter of 2016.

8. References

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