PRODUCTION AND SUPPLIES OF 99MO: LESSONS LEARNT AND NEW OPTIONS WITHIN RESEARCH REACTORS AND NEUTRON SOURCES COMMUNITY

N. RAMAMOORTHY[†]
Bhabha Atomic Research Centre (BARC),
Trombay,
Mumbai,
India

Abstract

During the past few years, the research reactor (RR) topic has occupied the centre stage being the major factor in the crisis faced world over in the supplies of medical isotopes, molybdenum-99 in particular. It is therefore an important aspect for discussion at the quadrennial international conference on research reactors organised by the IAEA. The November 2011 IAEA conference at Rabat, Morocco comes at a time when the international availability of ^{99}Mo has fairly stabilised following the excellent technological efforts in terms of repairs done in the two large reactors, in Canada (NRU) and The Netherlands (HFR), serving the bulk of ^{99}Mo users. The author, who had led and coordinated the IAEA activities in addressing the various issues and extending support to international efforts and initiatives during the period until March 2011, shares in this article his professional analysis of the field of ^{99}Mo production, lessons and experience from the crisis as well as the aspects to be addressed to securing sustainable supplies of both ^{99}Mo and ^{99m}Tc in future. In line with the suggestion of the International Programme Committee of the IAEA Conference, the scope of coverage is confined to sourcing ^{99}Mo and ^{99m}Tc from RR and other neutron sources, while accelerator-based options are not included in this article.

1. HIGH IMPORTANCE OF ^{99m}Tc AND ^{99}Mo

Diagnostic imaging forms 90% of all nuclear medicine procedures (the rest 10% being radionuclide therapy) and out of this, over 80% involve the use of ^{99m}Tc (^{18}F accounts for 10% and all the rest 10%). With over 30 million studies reported per annum, there is practically one diagnostic imaging study performed every second using ^{99m}Tc. The medical use of ^{99m}Tc is growing particularly in countries expanding their healthcare programmes (2-5% per year), while it is expected to stabilise around 1-2% per annum in the long term. The excellent nuclear characteristics of ^{99m}Tc enable high quality images with low radiation doses to patients. Its chemical characteristics make it very versatile for attaching to different chemical substances, so that it can be used to target different organs and lesions required for different diagnostic procedures. The two major uses of ^{99m}Tc are in imaging myocardial perfusion in cardiac patients and imaging bone metastasis in cancer patients. Further, there are unique advantages of ^{99m}Tc imaging in certain other cases, as for example, in differential diagnosis of prosthetic infection from loosening of prosthesis, and sentinel lymph node imaging in breast cancer patients. It is expected that all the above applications of ^{99m}Tc will continue to be of high utility in future too, at least for the next 20-30 years. ^{99m}Tc continues to reign as the Queen of Nuclear Medicine and ^{99}Mo as the Queen Mother.

Fission-produced ^{99}Mo (f.p. ^{99}Mo) of very high specific activity and alumina column based ^{99m}Tc generators have remained the mainstay in the field as 'gold standard'. Reliable weekly availability of ^{99}Mo of high specific activity has thus been essential for uninterrupted supplies of ^{99m}Tc to serve patients. The technologically demanding process management and regular weekly supply services to users have been successfully handled, thanks to excellent

[†] Formerly Director of Division of Physical and Chemical Sciences (NAPC), IAEA, Vienna

efforts and reliable procedures and SOP in place among the limited number of industries and the RR managers responsible, for the commercial availability of fission-produced ^{99}Mo - mainly four major corporate sources located in Belgium, Canada, The Netherlands, South Africa. The estimated quantity of f.p. ^{99}Mo produced since 1980s would be over 50 kg with the recent level of weekly production being 80 to 100 kCi (~50 g) at the end of reactor irradiation (i.e. about 12000 '6-day Ci' per week). All of them therefore deserve very high appreciation and salutations on behalf of all the beneficiaries.

2. ^{99}Mo PRODUCTION, SUPPLY CRISIS AND LESSONS

Well over 95% of the ^{99}Mo required for ^{99m}Tc generators is produced by the fission of uranium-235 targets (^{99}Mo fission yield 6.1%) in nuclear research reactors. The irradiated targets are processed involving several steps of radiochemical separation and purification (very high levels of radioactivity, remote handling equipment, heavily instrumented etc.). The resulting purified ^{99}Mo bulk solution is subsequently distributed to users in several countries across different regions (10-20 large-scale generator producers, 50-80 small to medium scale generator producers and others) for production of ^{99}Mo-^{99m}Tc generators (in turn shipped to many thousands of users, practically in every part of the world). Three methods are used in processing irradiated uranium-235 targets, one involving acidic dissolution of the targets, the second involving alkaline digestion of the targets (originating from KFK – Dr Sameh Ali; currently the most widely used), and the third (of Isotope Technologies – Dresden, ITD, Germany based on the former Rosendorf lab process) using a mixture of NaOH and $NaNO_3$ (which avoids hydrogen generation). All the processes require a series of radiochemical separation and purification steps that are very complex and require sophisticated technical skills and well-equipped hot cells. Purity requirements for ^{99}Mo are very high, and extensive quality controls are essential.

Almost all of the f.p ^{99}Mo is from the use of HEU targets (until the first large-scale producer's conversion in 2010 accomplished by South Africa). About 45 kg of HEU per year is used, with less than 5% of the original ^{235}U in the targets consumed during irradiation. Thus a large amount of HEU is left behind in the waste to be taken care of, over and above addressing all the nuclear security measures required to be in place for transfer, receipt, custody and handling of HEU. Strategies to address the reliability of ^{99}Mo supplies should therefore take into account international consensus efforts to shift from HEU to LEU to strengthen nuclear security.

An alternative to the fission-based production of ^{99}Mo is through neutron activation of MoO_3 targets in research reactors. This produces ^{99}Mo of relatively low specific activity, of the order of 0.2 to 1 Ci/g (7.4 to 37 GBq/g), depending upon the neutron flux, especially the epithermal profile (6.5 b cross-section versus 0.13 b for thermal neutrons alone). This product is popularly known as (n, gamma) ^{99}Mo and has been in limited use (1-2%) for producing ^{99m}Tc either through a process using solvent (MEK) extraction (e.g. in India and RF) or through a process known as zirconium molybdate – ^{99}Mo gel generator (e.g. in India and Kazakhstan).

There are currently four large-scale facilities for processing the irradiated uranium-235 targets after they are removed from the reactors. A new facility at ANSTO, associated with Australia's OPAL reactor, and available since 2010, the first large-scale ^{99}Mo producer to use LEU targets with a production capacity of over 1000 Ci per week, was built by INVAP, Argentina using the technology developed by CNEA, Argentina (adopted for regular medium-scale production in the CNEA plant in Ezeiza near Buenos Aires). In Russian Federation, a project is underway in Dimitrovgrad for large-scale fission-based ^{99}Mo production, which is based on German industrial technology (GSG-ITD). Other new facilities recently commissioned are at PINSTECH, Pakistan (supplied by ITD-Germany) and EAEA, Egypt (supplied by INVAP, Argentina). A project for setting up an f.p. ^{99}Mo facility is on the anvil in Mumbai, India.

From around the end of 2007, the production and supplies of fission-based ^{99}Mo were severely and repeatedly affected due to both planned and unplanned shutdown of the two large producing reactors (NRU, Canada; HFR-Petten, NL), causing worldwide concerns. This led to calls for international efforts to address the security of supplies of ^{99}Mo and ^{99m}Tc. Various initiatives and analytical reviews during the past two years, including at the IAEA and OECD-NEA (High-level Group on the Security of Supply of Medical Radioisotopes, HLG-MR), have revealed a number of issues and lessons learnt.

The managers of research reactors (RR) and their governments serving ^{99}Mo-^{99m}Tc industry face several challenges, technological, regulatory and economical among others, besides the fact that the RR are not dedicated to isotopes production. For addressing the crisis, enhancing the base of RR deployed for irradiation of uranium-235 targets was necessary. Thanks to some excellent collaboration and follow-up actions including with regulatory bodies, production from the MARIA reactor in Poland based on the irradiation of HEU targets (for Covidien, Petten, NL) was begun in March 2010. In May 2010, similar irradiation of HEU targets began at the Rez reactor in the Czech Republic for production at IRE's facility in Fleurus, Belgium. The FRM-II reactor in Germany is also progressing on a project to produce ^{99}Mo via HEU target irradiation by 2013 (for IRE, Fleurus, Belgium). Many other countries (including Brazil, India Japan, ROK) affected badly have announced, or intend to plan, building back-up domestic production capacity (partially at least) for sustenance of supplies and patient services.

None of the five major reactors that produce ^{99}Mo is entirely dedicated to the production of ^{99}Mo. They were financed and built with government/state support to provide multiple services to multiple users and not based on a viable business model designed to serve the ^{99}Mo industry-market. Over the years, as the industry has grown, appropriate adjustment to moving away from the paradigm of 'radioisotopes being bi-products' of government-owned/supported RR has not taken place. There is yet another ironical situation, namely, f.p. ^{99}Mo producer country ends up being the sole agency requiring to manage the nuclear waste (national) burden arising from the weekly large-scale production activities meant to supply users most of whom are located outside the producer country. The economics of the supply chain, especially at the front end of the chain, is unsustainable (full cost recovery principle seldom considered/applied) and is a major concern to industry and discourages investments in the front end. The cost of ^{99}Mo is however only a very small fraction of the cost of the final radiopharmaceutical dose administered to the patient (about 0.1%). Thus, raising the price of ^{99}Mo, which would help strengthen the business case in building more buffer capacity in ^{99}Mo production, should be possible without significantly adding to the cost of the final radiopharmaceutical (about 1%).

The OECD-NEA report 'The supply of medical radioisotopes: An economic study of the Molybdenum-99 supply chain' highlights all these aspects. Six policy principles and allied recommendations have also been released by NEA's HLG-MR. This calls for coordinated actions by industry and governments involved in ^{99}Mo business (sort of a self-imposed code of conduct in running the ^{99}Mo business), advocates full cost recovery operations, and urges to avoid direct financial/resource support by governments. These are necessary to both ensure the reliability and long term sustainability of ^{99}Mo supply, while how much of this scheme can be enforced in actual practice will depend on several factors and policies and attitudes of stakeholders involved. Government role is necessary to achieve international, non-proliferation goals related to the minimization of HEU use in civilian applications.

On the demand side, scope for considerable improvements and adjustments for very highly optimised utilisation of all ^{99}Mo and ^{99m}Tc produced was identified and in place. One generator producer intimated up to 25% reduced demand of ^{99m}Tc generator activity post-crisis!

The overall conclusion is that changes including price increases must occur for supply to be secure over the long term. There is a need for a paradigm-shift in understanding and accepting the techno-economic reality of ^{99}Mo–^{99m}Tc supply chain and instituting changes required. Also, support has to be mobilised for ensuring the availability of medium to high flux RR services beyond the life span of the current fleet of RR. The projects of JHR, France and Pallas, The Netherlands are relevant in this context, while many other new RR proposals are also on the cards (as national sovereign decision), as for example in Argentina, Brazil, and Republic of Korea. NRU, Canada has recently received license renewal for its operations until October 2016. Furthermore, it is worth reiterating the point that there are several important radioisotopes (apart from ^{99}Mo–^{99m}Tc) required for applications in medicine (e.g. ^{131}I, ^{177}Lu, ^{192}Ir, ^{60}Co), industry (e.g. ^{82}Br, ^{192}Ir, ^{60}Co) and research (e.g. $^{32/33}$P, $^{125/131}$I) and role of RR will continue to be of significant value in future.

Towards long term security and sustainability of ^{99}Mo supplies, LEU target conversion aspects need to be addressed, since HEU for civilian use is expected to be phased out in 7-10 years. South Africa completed LEU conversion tasks in 2010 and is the first large-scale producer to convert to using LEU targets. There is however no apparent incentive to industry in the LEU conversion (endorsed by also the NEA's economic study of ^{99}Mo industry) and political role cum support would be necessary to foster adoption of LEU technology by the other major producers. The IAEA has been providing a forum for stakeholders interactions in this context, while it revived such activities in Q3 2010 following the stabilisation of ^{99}Mo supplies.

3. ALTERNATE TECHNOLOGY OPTIONS

The ^{99}Mo crisis has led to an increased focus on alternate technologies for production of ^{99}Mo and ^{99m}Tc. Among the options proposed - that range from purely conceptual stage, to proof of principle demonstrated, to proven potential, to limited deployment - including through non-fission and non-reactor based methods, those based on reactor or neutron sources are outlined below. One or more of these options are expected to mature in to deployable technologies and can provide 'additional supplementary sources' to complement the f.p. ^{99}Mo supplies.

Fission-based options under investigation/development:

— Aqueous homogeneous reactors (^{235}U salt solution fuelled) (Babcock & Wilcox, USA): This development involves the off-line separation of fission product ^{99}Mo from an aliquot of the LEU fuel solution at periodic intervals. This approach under the charge of a US company is the recipient of one of the four technology development support grants of NNSA-DOE. The IAEA is also running a CRP related to this approach to assess the feasibility and requirements.

— Target-fuelled isotope (production) reactor (TFIR) concept is based on using fuel element itself as irradiated target for recovery of fission-product ^{99}Mo (Sandia labs, US). The approach involves withdrawing a chosen number of fuel elements for reprocessing and recovery of ^{99}Mo, while simultaneously replacing with the same number of fresh fuel elements. The proponents, who have completed the physics design aspects, have been looking for funding support.

— Low energy (300-350 keV) deuterium accelerators for D-T reaction and making use of neutrons produced for fission of LEU salt solution (sub-critical system) for amplification of D-T neutrons as well as production of fission-product ^{99}Mo is the scheme called 'sub-critical hybrid intense neutron emitter, SHINE. This is being promoted by SHINE Medical Technologies, USA in collaboration with a few academic groups and is the recipient of one of the four technology development support grants of NNSA-DOE. Being a sub-critical system, the promoters expect (relatively) less stringent licensing requirements compared to a new reactor concept.

— A German company (GSG-ITD, Germany) has developed and offered technology and equipment support for small-scale production of ^{99}Mo by fission of LEU or natural uranium targets. This supplements the already available LEU technology support for production of ^{99}Mo of CNEA, Argentina (commercially provided by INVAP, Argentina) and ROMOL technology of ITD (offered now commercially by GSG – Germany).

In the case of all the above, it is to be noted that the methodology is still 'fission-based' with all its associated aspects and issues to be considered.

Activation-based options under investigation/development:

— A consortium (Eurasia Isotopes Coalition, EIC) has proposed to use enriched ^{98}Mo targets for neutron activation making use of four RR s (thermal and epithermal neutrons) in Central Asia and Eastern Europe and process in Budapest for supplies to ^{99m}Tc generator manufacturers (building on the proven experience of INP, Tashkent, Uzbekistan)

— There is an industrial scale approach involving utilization of commercial BWR power reactors (at least 35 available in US) for Mo metal target activation and making use of traversing in-core probe (TIP) like system (GE-Hitachi, USA). The scheme envisages 6-day irradiation cycle and a manufacturing facility in US east coast for subsequent use in a new concept gel generator system for ^{99m}Tc. This scheme is also the recipient of one of the four technology development support grants of NNSA-DOE.

— There is a revived interest as well as good scope to use neutron activation (thermal and epithermal neutrons) of natural ^{98}Mo targets along with adoption of appropriate methods of separation of ^{99m}Tc (described further in the next section).

— One proposal from a group in South Africa is to utilise isotopic separation of ^{99}Mo (enrichment) for obtaining enhanced specific activity after producing activation ^{99}Mo (e.g. from natural ^{98}Mo targets' neutron activation)

— Use of intense neutron sources (e.g. SNS) for fast neutron induced (n,2n) reaction on enriched ^{100}Mo targets is a potential option to produce ^{99}Mo in medium-term future. The intense fast neutron source facility such as for example the proposed IFMIF (International Fusion Materials Irradiation Facility), meant to support fusion materials development, would be of interest in this context.

Potential and prospects of established and/or emerging methods of radiochemical separation to utilising (neutron) activation-based ^{99}Mo:

— MEK extraction extensively used in Russian Federation and India is the basis for an automated plant module developed and offered by Atommed, RF.

— The technology of zirconium molybdate gel based generators (25% Mo content) regularly deployed in India (over 220 batches and 2300 generators handled) and Kazakhstan is available for replication.

— Multi-column ion-exchange chromatography is based on Indian work to adsorb sub micro molar level of ^{99m}Tc (no-carrier-added, nca) on tiny ion-exchange column (developed for post-elution concentration of pertechnetate from large-bed alumina column generators) , recover ^{99}Mo for subsequent use and then re-elute pure ^{99m}Tc. This has been developed further by Northstar, USA into an automated module and can be in principle deployed for production of ^{99m}Tc from activation. The process involves oxidative dissolution of Mo metal target and subsequent separation of pertechnetate and molybdate.

— The use of high affinity adsorbent for molybdenum pursued in Australia, India and Japan could help overcome the limitation of alumina capacity of 20 mg Mo per gram of alumina. Polymeric zirconium compound (PZC) has been explored under FNCA led by Japan. Poly-titanium oxochloride (PTC) investigated in Vietnam-Australia and India (BARC) have shown useful results and a capacity of 80 mg Mo/g of PTC. BARC's recent work involving nano zirconia (140 mg Mo/g capacity) and nano-ceria hold further potential for development and deployment.

— BARC's development of an electrochemical method of separation of ^{99m}Tc is the other attractive option for consideration, especially due to the commercial availability of an automated electrochemical cell module (developed for ^{90}Y thanks to an IAEA CRP and based on the work of BARC scientists).

Many of the above separation procedures are equally applicable for accelerator activation product ^{99}Mo but are not described here due to the design of the scope of the article. In the context of developments of the past decade in automation of radiochemical processes, and launch of easy-to-use modules with compact shielding compatible for GMP compliance, the scope to deploy one or more of the above procedures appears very bright. The successful model of ^{18}F-FDG production and distribution established very effectively in a large number of centres across the world provides an additional motivation to propose adoption of alternate chemistry-based solutions for delivering ^{99m}Tc and/or providing new ^{99m}Tc delivery systems to medical users.

The IAEA is implementing several activities as well as supporting other international efforts (e.g. NEA's HLG-MR) to address the shortages in ^{99}Mo supplies and meeting domestic and regional needs of its Member States. The CRP on the use of LEU targets or neutron activation for small-scale domestic ^{99}Mo production scheduled for completion this year, as well as the recent initiative to facilitate conversion to LEU targets, are relevant for long-term sustainable supplies of ^{99}Mo-^{99m}Tc. The IAEA is also proposing a new CRP on non-HEU technologies as well as projects under Technical Cooperation for delivering direct support to interested Member States, including through funds envisaged from the US Peaceful Uses Initiative (PUI) support extended through the IAEA.

4. PATH FORWARD—SOME (PERSONAL) PROFESSIONAL THOUGHTS

Even as most of the stakeholders are intensely engaged in debating and addressing various issues towards ensuring reliable and sustainable supplies in future, it is worth considering the question, 'whether one-size fits all, and that too, at all times?'. The paradigm of f.p. ^{99}Mo and alumina column generator as the singular source of ^{99m}Tc warrants to be challenged. Diversified sourcing of ^{99}Mo and ^{99m}Tc, and adopting aptly suited separation schemes for using more widely and easily producible 'activation-based' ^{99}Mo should be given serious consideration to complement the praiseworthy industrial efforts and contributions of f.p. ^{99}Mo (that is still very important).

One can draw an analogy with the energy scenario. There is no single source of electrical energy possible for meeting the entire needs of all the population of the world. Just as thermal power remains a major source of electricity world over, f.p. ^{99}Mo can continue to serve a large fraction of the end medical users to the extent possible and wherever possible. 'Activation-product ^{99}Mo' can simultaneously hold an independent place in serving a finite segment of end medical users, in a manner similar to that of nuclear power making contributions to the electricity grid in countries and regions choosing to deploy the nuclear option (estimated average 14%; varying from a few percentage share in many countries, to 20-25% in many industrialised countries, and to as high as nearly 80% in France). In this context, the prospects of the 'accelerator based activation approaches' need to be treated (almost) at par with the 'neutron-based activation methods' discussed earlier.

It is also deemed pertinent to take note of the reactions and decisions by certain countries as a follow-up action arising from the unfortunate natural twin disasters that struck Fukushima – Dai-ichi in March 2011, and which consequently led to a series of incidents of nuclear and radiological significance at the Dai-ichi nuclear power plants. So, what happens if some or all such countries decide to renounce 'nuclear fission' altogether? Will they move away from using 'RR-based medical isotopes' altogether or at least give up using 'fission-based medical isotopes'? One cannot perhaps rule out such a move, as well as the consequent likely demands for 'non-fission routes' for vital isotopes like ^{99}Mo, ^{99m}Tc.

The principles applicable in building up nuclear safety incorporate the elements of redundancy, defence in depth as well as diversity. For analogous reasons, the adoption of 'activation-product ^{99}Mo' is deemed highly warranted in the case of ^{99}Mo-^{99m}Tc field, especially due to the tremendous advances available today in commercial automation of (radio)chemical processing – modules and compact shielded facilities. The push to consider moving along such a sustainable path (while the f.p. ^{99}Mo can continue as a 'toll highway') has come from the recently faced crisis of ^{99}Mo supplies, although such an option has been sitting on the shelves all along. It will be a sadly missed opportunity if the ^{99}Mo-^{99m}Tc community will shun away from entering this additional greener avenue of peaceful co-existence. It is imperative that all stakeholders come together to help sustain the well-established and value-based status of technetium-99m and nuclear medicine being synonymous for the past several decades.

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