The Indian pursuit of gel generator technology for $^{99m}$Tc was driven mainly by three considerations, namely, (i) well-established and ease of reliable production of (n, gamma)-based $^{99}$Mo in several tens of GBq quantities in the research reactors in Trombay/Mumbai, India, (ii) need for relatively low-cost alternate technology to replace the solvent (MEK) extraction generator system in use in India since 1970s and (iii) minimize dependency on weekly import of fission-produced $^{99}$Mo raw material required for alumina column generator. Extensive investigations on process standardisation for zirconium molybdate gel (ZMG) led to a steady progress, achieved both in terms of process technology and final performance of $^{99m}$Tc gel generators. The $^{99m}$Tc final product purity from the Indian gel system was comparable to that obtained from the gold-standard alumina column generators. Based on the feasibility established for reliable small-scale production, as well as satisfactory clinical experience with a number of gel generators used in collaborating hospital radiopharmacies, full-fledged mechanised processing facilities for handling up to 150 g of ZMG were set up. The indigenous design and development included setting up of shielded plant facilities with pneumatic-driven as well as manual controls and special gadgets such as, microwave heating of the zirconium molybdate cake, dispenser for gel granules, loading of gel columns into pre-assembled generator housing etc. Formal review of the safety features was carried out by the regulatory body and stage-wise clearance for processing low and medium level $^{99}$Mo activity was granted. Starting from around 70 GBq $^{99}$Mo handling, the processing facilities have since been successfully operated at a level of 740 GBq $^{99}$Mo, twice a month. In all 18 batches of gel have been processed and 156 generators produced. The individual generator capacity was 15 to 30 GBq with an elution yield of nearly 75%. 129 generators were supplied to 11 user hospitals and the estimated number of clinical studies done is well over 5000. The salient aspects of the Indian experience have been reported in many a forum and shared with the IAEA through the on-going CRP. The detailed process know-how is available for technology transfer from BRIT, India.

[Key-words: $^{99}$Mo-$^{99m}$Tc generator, $^{99}$Mo specific activity, $^{99m}$Tc gel generator, zirconium molybdate]

(* since October 2003, Director of the Division of Physical and Chemical Sciences of the IAEA)
Introduction

The year 2007 marks the golden jubilee of the serendipitous discovery of $^{99m}$Tc generator in 1957 at the Brookhaven National labs (BNL), USA. This discovery later on became the basic foundation for all the enormous progress achieved subsequently in in vivo imaging of physiological functions in humans to aid diagnostic decisions and managing treatment of millions of patients [1]. The widespread diagnostic imaging in nuclear medicine practised world over to day would not have attained such a pre- eminent status but for $^{99m}$Tc generator and $^{99m}$Tc labelled products. In order to sustain the nearly 20 million studies annually performed using $^{99m}$Tc, it is of utmost importance to assure access to appropriate technologies for continued, reliable availability of $^{99m}$Tc generators and in turn, that of the raw material radionuclide $^{99}$Mo required in extremely large quantities, estimated to be of the order of 10000 to 12000 Ci per week at reference time (usually 6 days after the end of reactor irradiation) and throughout the year [1].

The $^{99m}$Tc generator using a bed of acidic alumina column for column chromatographic separation of $^{99m}$Tc from $^{99}$Mo has remained the most popular procedure world over [1-3]. The capacity of alumina for taking up molybdate ions is limited (up to 20 mg Mo per g of alumina) necessitating the use of $^{99}$Mo of the highest specific activity available, as can be found in fission produced $^{99}$Mo (about $10^4$ Ci/g) [1-3].

The solvent extraction of the generator eluate using methyl ethyl ketone (MEK), initially used to improve the radionuclidic purity of $^{99m}$Tc [4], opened an independent avenue for meeting local needs of $^{99m}$Tc in centres that could access $^{99}$Mo from neutron activation of MoO$_3$ targets in their research reactors (RR), referred to as (n, gamma)$^{99}$Mo, of specific activity of 100-300 mCi per gram of Mo. Given the simplicity of producing (n, gamma)$^{99}$Mo by reactor activation of MoO$_3$ targets and the ease of adopting solvent extraction in radiochemical processing, the solvent extraction generator concept emerged gaining attention, commonly known as the MEK-based generator system. India was an early entrant thanks to its strong local capacity in reactor production of radioisotopes [5,6]. The utility and limitations of MEK method are too well-known to be repeated here.

The possibility to incorporate $^{99}$Mo into an inorganic ion exchanger matrix cited in an old literature [7], in place of loading $^{99}$Mo on an a small bed of a column material, was probably the origin of molybdenum gel column based generators for $^{99m}$Tc, reported by the Australian group for the first time in 1982 [8]. Their concept of preparing zirconium molybdate – $^{99}$Mo gel (ZMG) seemed very attractive as it would use (n, gamma)$^{99}$Mo and at the same time offer the convenience of column based separation system. The developments over the last two decades however have shown that it has not been easy to take full advantage of the early promises.

The International Atomic Energy Agency (IAEA, also into its 50th year in 2007 having been founded on July 29, 1957), has been involved for well over three decades in fostering developments in $^{99m}$Tc generator systems [1] through (i) implementation of a number of CRPs, including an on-going one related to the production of $^{99}$Mo using LEU targets, (ii) arranging

---

1 L.G.Stang et al. in 1st UNESCO Intnl Conf, 1957; W.D.Tucker et al. USAEC Report BNL-3746 (1958)
topical reviews by experts through Technical/Consultancy Meetings and (iii) publication of various technical documents [9-11], e.g. IAEA-TECDOC: 515 (1989), 852, (1995) and 1065 (1999). The IAEA has also supported a number of its interested Member States (MS) in establishing and/or operating $^{99m}$Tc generator production facilities, as for example in Bangladesh, China, Indonesia, Iran, Pakistan and Syria [1].

The present report is a narration of gel generator technology development and adoption in India, interspersed with the IAEA’s role and contributions in the gel generator area.

**Indian Scenario**

Thanks to the early availability RR for isotope production in India, the Isotope Division of BARC was already handling in the 60s products such as $^{198}$Au, $^{131}$I etc and towards the later part of that decade, produced (n, gamma)$^{99}$Mo to meet the demands for $^{99m}$Tc from its nuclear medicine wing and thus was born the Indian MEK extraction generator system for $^{99m}$Tc, popularly known as ‘Trombay Technetium Cow’ [5]. This manually operated, open system required certain operational facilities at the user end and training of the operators, but has been in extensive use in India [5,6]. There was a period of time when as many as 60 to 70 centres regularly used up to 40-50 Ci $^{99}$Mo per week [12]. Presently there are still about 30 centres handling MEK process at the hospital end, while the typical quantity of (n, gamma)$^{99}$Mo supplied now is only about 15 Ci per week.

India has all along been participating in the IAEA’s efforts towards development of alternate technologies for $^{99m}$Tc generators, due to its preference to retain the option of (n, gamma)$^{99}$Mo. The gel generator concept of Australia was one of the keenly pursued routes since mid-80s. The R&D level pursuits in gel method - parts of which were done under two CRP of the IAEA during 1985-89 and 1991-94 [10] - moved up to technical feasibility studies upon the closure of the alumina column production trials carried out for some months in 1994 and subsequent considerations of unfavourable cost implications on one side and permanent dependency on imports of fission product $^{99}$Mo on the other side. There has been consequently steady pursuit in India on the gel generator option [12-17] through process optimization, process gadgets development, small-scale production, demonstration of clinical utility, technology considerations for larger scale gel handling, design and installation of shielded plant facilities with mechanized processing systems, regulatory clearances and commencement of operations for periodic production of gel generators. This was supported further by India’s vast experience in the various aspects involved in reactor irradiation of MoO$_3$ in large quantities (a few hundred grams), purity of targets, radionuclidic impurity burden in $^{99}$Mo and their fate through the separation techniques for obtaining $^{99m}$Tc for medical use [5,6,12].

**Gel Technology Option for $^{99m}$Tc Generators**

The zirconium molybdate gel (ZMG) concept enables one to avail advantages of column operation while yet using the (n,$\gamma$)$^{99}$Mo of specific activity 10-37GBq/g. However, the processing is quite complex due to several factors influencing the gel characteristics and in turn its final performance [8,13-17]. The processing of the $^{99}$Mo gel poses many challenges and the early promise of gel system was not easily realizable for a long time. The developments in
automated modules for radiochemical processing and better understanding of the gel manufacture process led to a re-look at this technology option for countries like India having research reactors (RR) with suitable features such as adequate neutron flux and number of irradiation positions and regular weekly operational schedules. Attaining reliably high specific activity of the order of 12-37GBq/g is necessary to effectively utilize (n, gamma)⁹⁹Mo through ZMG strategy.

The international scenario of the gel (ZMG) systems reveals mixed trends [1]. In China nearly 25% of ⁹⁹ᵐTc needs are reported to be met by (ZMG) gel generators produced in a facility at Chengdu. The Chinese technology along with equipment was availed by Egypt under an IAEA Technical Cooperation (TC) project. New facilities are still under construction in Egypt and thanks to their new RR, the scope for adopting the ZMG system would appear good. Full-fledged plant and processing facilities are set up in IPEN, Sao Paolo, Brazil for (ZMG) gel generators and is slated to go on production stream after their reactor upgrade so that ⁹⁹Mo of higher specific activity can be availed locally. In Almaty, Kazakhstan, regular production of ZMG from a centralized facility and ⁹⁹ᵐTc distribution to local centers is an on-going activity. They are presently interested in developing portable gel generators for supply to other parts of their country. In Bucharest, Romania there are plans to explore the gel route in view of the suitability of the operational features of the research reactor in Pitesti for the production of (n, gamma)⁹⁹Mo of specific activity 800 mCi/g (~30 GBq/g). In India, BRIT is handling 740 GBq lots of (n, gamma)⁹⁹Mo twice a month in their facility in Navi Mumbai [17]. India, Kazakhstan and Romania are participating in the IAEA CRP cited in this paper.

Gel Generator Technology Development in India [13-17]

The need for a simple user-friendly column based generator that uses (n, gamma)-produced ⁹⁹Mo of medium specific activity, prompted Indian research efforts in exploring the gel generator route in the mid-eighties [6,10,12]. While the initial studies held promise, a major deterrent to the ready adaptation of the zirconium molybdate-⁹⁹Mo gel generator technology, was the requirement of elaborate remote handling facilities for carrying out the complex radioactive gel processing steps involving precipitation, filtration, optimal drying of gel cake and conversion to granules serving as a suitable column matrix. Later on, in view of the potential for accessing higher specific activity (n, gamma)⁹⁹Mo from Dhruva reactor, efforts at BRIT were intensified in the mid nineties in terms of optimization of the preparatory conditions, setting up of pilot plant/small scale facilities equipped with features for handling the complex processing steps, design of a prototype generator[13,14], generator performance evaluation in local hospitals and use in patients. At that time, 14 generators, containing up to 18.5 GBq ⁹⁹Mo, were supplied to two local hospitals, Radiation Medicine Centre (RMC) of BARC and Nair Hospital, Mumbai, for evaluation and used to satisfaction in over 200 patient investigations [13,14].

The salient aspects demonstrated at the conclusion of the small scale production feasibility studies were:

a) need for a 2-column generator system comprising a primary ZMG column and secondary acidic alumina column for holding up ⁹⁹Mo co-eluted during ⁹⁹ᵐTc elution;

b) need for controlled drying of gel cake to avoid structural damage and consequent reduction in ⁹⁹ᵐTc elution efficiency;
c) 99mTc elution efficiency of 60–80% in 10ml normal saline for a 6 g gel bed (i.e. ~2 g Mo) coupled to a 2 g acidic alumina column as purification trap;
d) need for replacing the alumina column after a few elutions;
e) compatibility for formulation of all 99mTc radiopharmaceuticals.

Having successfully completed the feasibility demonstration studies, technology development for regular production was then undertaken. Allocation of funds under the Government’s IX-Plan and constitution of a multidisciplinary core team comprising chemists and engineers working in mission mode enabled successful completion of the project. The technology development entailed four major aspects: (i) adaptation of chemical process to automation, (ii) erection of a production facility with adequate shielding, (iii) design/fabrication/installation of operation specific gadgets, and (iv) design of a compact, portable, generator assembly.

There were a number of chemical process related aspects addressed in undertaking a process upscale. Presently, it is feasible to convert up to 75 g of neutron irradiated MoO₃ (i.e. 50 g Mo) to ZMG granules in about 4.5 hours adopting the optimized process. The production process entails the various steps shown in Fig. 1. Three major issues addressed are described below.

1) Process time reduction: This was achieved by reducing the time required for preparing ZMG granules. The multi-step process in turn had two critical rate determining steps: filtration of the thick, viscous, gelatinous precipitate which undergoes rapid sedimentation and forms an impervious barrier preventing further filtration and drying of ZMG cake.

At the end of the filtration stage, the gel-cake contains about 85% water, which needs to be removed in a controlled manner taking care to retain ‘structural water’ necessary to enable 99mTc elution from the matrix. Use of a domestic microwave oven for drying at a controlled intensity to prevent structural damage provided the solution [15]. The optimization of the microwave drying conditions and its adaptation to gel processing is a major breakthrough from Indian efforts paving the way for process upscale [14,15].

2) Process refinement for improving gel characteristics: A thorough optimization of preparatory conditions was found essential to consistently obtain gels having the desirable characteristics of high 99mTc release and minimal 99Mo breakthrough; e.g. reactant concentration, alkalinity/acidity of reactant solution, mixing time and temperature, pH of gel formation, filtration rate, controlled dessication of gel cake etc [14,16]. Process refinement was attempted with a view to (i) reduce the inter batch variations observed in 99mTc elution efficiency, viz. 60-80% in the earlier studies, and (ii) minimize the breakthrough of 99Mo in the eluates to deploy a single alumina column as purification trap during the entire useful period of the generator. Significant improvements in gel characteristics were observed under two conditions [14,16].

a) When gels were prepared using reactant mole ratio [Zr]:[Mo]:: 1.25:1 and 1.5:1, the release of 99Mo in the eluates was reduced by an order of magnitude as compared to when using a reactant mole ratio [Zr]:[Mo]:: 1:1. 99mTc elution efficiency of ~75% was obtained consistently, while elution profile studies showed a relatively sharper profile for gels prepared with [Zr]:[Mo]:: 1.25:1.
b) The co-elution of $^{99}$Mo in trace amounts from gel columns were compared for two different eluents, normal saline and water. The release of $^{99}$Mo in normal saline was found to be significantly less than in water. This observation was used to advantage in the gel dispersion stage after drying (Fig.1), where normal saline was used instead of water.

(3) Process adaptation to automation in shielded facility: Special process apparatus were designed and fabricated to suit operational requirements for slurry filtration, collection of filtered cake and granule collection post drying. Solution/slurry transfers were effected using peristaltic pumps. For filtration, an oil-free, moisture–free diaphragm type vacuum pump was used. After filtration, the gel-cake was discharged into a collection vessel and dried in a domestic microwave oven rendered amenable for remote operations. The cake collection dish and granule receiver were moved from one station to another by pneumatically operated actuators [17]. Special ducting was connected to the oven to exhaust the moisture laden air during drying of the gel cake [17]. The dried lumps were transferred into another vessel and rendered into granular form using a shower arrangement for spraying normal saline. The granules were converted into free flowing form by drying under an infra-red lamp.

The indigenous design and development thus included setting up of shielded plant facilities with pneumatic-driven as well as manual controls and special gadgets such as, microwave heating of the zirconium molybdate cake, dispenser for gel granules, loading of gel columns into pre-assembled generator housing etc.

Facility Operations and Production Status

Concurrent to process technology development, a lead-shielded facility comprising 4 interconnected cells was erected, operation-specific gadgets as stated above were designed, fabricated and installed (Fig. 2). Formal review of the safety features was carried out by the regulatory body and stage-wise clearance for processing low and medium level $^{99}$Mo activity was granted. Starting from around 70 GBq $^{99}$Mo handling, the processing facilities have since been successfully operated at a level of 740 GBq $^{99}$Mo, twice a month. In all 18 batches of ZMG have been processed and 156 generators (Fig. 3) produced till July 2007. The individual generator capacity was 15 to 30 GBq with an elution yield of nearly 75% in 10 ml normal saline. Higher capacity generators of 37 GBq was also shown to be feasible by spiking indigenous (n,γ)$^{99}$Mo with imported fission-produced $^{99}$Mo. 129 generators were supplied to 11 user hospitals and the estimated number of clinical studies done is well over 5000. The detailed process know-how is available for technology transfer from BRIT, India.

It is essential to reduce the time period between the end of reactor irradiation (EOI) and completion of processing of gel generators in order to avail maximum generator capacity, being a function of the specific activity of $^{99}$Mo used, which, in turn, depends on the neutron flux available for reactor irradiation. It has been found feasible to increase the generator capacity further by using a larger gel bed (3-4 g Mo). To effectively deploy larger gel bed generators in hospitals, a simple procedure for concentration of $^{99m}$Tc eluates post elution has been developed [18,19] as described later in this paper. The adaptation of the generator design for the concentration procedure to make it a user-friendly, closed system operation at the user end is being addressed.
IAEA CRP on the use of LEU targets and (n,g)\(^{99}\)Mo for gel technology [20-23]

The IAEA is currently implementing a CRP to assist countries interested in initiating indigenous, small-scale production of \(^{99}\)Mo to meet local requirements. The CRP formulated following consultations since late 2004 aims to provide interested MS with access to non-proprietary technologies and methods to produce \(^{99}\)Mo using LEU foil (ANL/USA method of annular target) or LEU mini-plate (CNEA/Argentina method of dispersion target) targets. The CRP also aims to foster the utilization of (n, gamma) \(^{99}\)Mo through the use of gel (ZMG) generators. There are currently 14 participants, 7 agreement holders (Argentina, India, Indonesia, Poland, Republic of Korea, two groups from USA) and 7 contract holders (Chile, Egypt, Kazakhstan, Libya, Pakistan and two groups from Romania). The Missouri University Research Reactor (MURR) entered the CRP in 2006 to share its experience in attempting to establish regulatory compliance of \(^{99}\)Mo of LEU origin as an active (radio)pharmaceutical ingredient (API) augmenting the regular production experience of CNEA at the level of 700-800 Ci per week. The CRP thus brings together the expertise of (as Research Agreement (RA) holders) ANL-USA, CNEA-Argentina and MURR-USA for the LEU route, as well as that of India for the ZMG system and is progressing well in transferring know-how to the other participants (as Research Contract (RC) holders).

Under this CRP, 3 work-shops were held, one in May 2005 in Buenos Aires, the second in Serpong/Indonesia in March 2006 and the third in Vienna in Nov 2006, as well as 2 research coordination meetings (RCM), the first RCM in Vienna in Dec 2005 and the second RCM in Bucharest in April 2007. These led to useful discussions on the various issues to be addressed and sharing/exchange of relevant technical information. Supplies of materials and some scientific visits to facilitate transfer of technical know-how are also envisaged under the CRP. The Indian experience and technology expertise in ZMG system is currently an important contribution to the on-going CRP of the IAEA. The CRP team scientists from Kazakhstan and Romania are expected to visit the gel processing plant facilities in India.

Prospects of post-elution concentration of pertechnetate (PEC)

The concept to concentrate the primary generator eluate in a relatively larger volume into an acceptable small volume of 5-8 ml and in a chemical composition to suit pharmaceutical use, is a spin-off outcome from another independent development at ORNL, USA [24]. There was a need to have very high radioactive concentration (RAC) of sodium perrhenate - \(^{188}\)Re, as an essential pre-requisite for use in liquid filled balloons meant for intravascular radiation therapy following balloon angioplasty in cardiac patients. This led to the development and use of ion-exchanger cartridges to trap ‘no-carrier-added (nca)’ levels of Re, and by analogy of Tc, from their respective radionuclide generators and subsequent re-elution in a few ml of normal saline [18,24,25]. This scheme called post-elution concentration (PEC) of pertechnetate would help to enhance the prospects to utilize (n, gamma)\(^{99}\)Mo along with larger beds of ZMG columns [18,19].

The Indian work has shown that the purification trap column of alumina contained in the ZMG system can be used for the dual purposes of purification and concentration [18,19]. Use of de-
ionised water as primary eluent, after carefully applying pre-treatment procedures on ZMG granules, is compatible to trapping traces of $^{99}$Mo and all the $^{99m}$Tc eluted; subsequent elution of the alumina trap bed with a few ml of normal saline releases pure $^{99m}$Tc in quantitative yields. The critical requirement is to ensure absence of macroscopic anionic load in the primary eluate. Other related conditions necessary have also been worked out [19] in terms of the medium preferred for gel disintegration and washings. The prospects of adopting such a scheme, especially in a central radiopharmacy setting, appear promising in future in interested countries having operational research reactors (RR) with suitable features cited earlier.

**Conclusion**

The important details available from the Indian experience, as well as their comprehensive technical know-how, would be of considerable value for other producers and countries planning to pursue the gel generator strategy. It is feasible to obtain (n, gamma)$^{99}$Mo of specific activity in the range of 10 – 30 GBq/g at end of reactor irradiation (EOI), and in turn, gel generators of capacity 12 – 36 GBq at calibration time (taken as 48 hours from EOI). It is envisaged that the gel technology option would thus serve as a good complement to ensuring the availability of $^{99m}$Tc in countries with low to medium requirements and local reactor production capability for (n, gamma)$^{99}$Mo, even as alumina column chromatographic generators based on the use of fission product $^{99}$Mo continue to remain the main source of $^{99m}$Tc for most of the large-scale production needs.

**Acknowledgements**

_The authors thank all their technical colleagues for their active involvement and contributions during the various stages of the project and later in regular operations, the Reactor Group, BARC, for the irradiations of molybdenum trioxide, the Radiopharmaceuticals Division, BARC, for supplying $^{99}$Mo radiochemical and the Chemical Engineering Division, BARC, for their inputs in planning facilities for gel processing. Parts of the work reported here also constitute Indian contributions under a Research Agreement in the on-going CRP of the IAEA._
Preparation of zirconium molybdate gel (ZMG) for $^{99m}$Tc generator

1. Preparation of zirconium molybdate gel (ZMG) for $^{99m}$Tc generator
   - $\text{Na}_{99}\text{MoO}_4$ Solution
   - Mixing with $\text{ZrOCl}_2$ solution (GEL)
   - Vacuum Filtration (CAKE)
   - Drying of gel cake (LUMPS)
   - Dispersion (GRANULES)
   - Drying (FREE FLOWING GRANULES)
   - Transfer to columns, sealing, bed washing
   - Placement in Generator assembly
   - QC testing, External packaging, HP certification
   - Despatch to users
Fig. 2: ZMG Processing Plants in BRIT labs, BARC Vashi Complex, Navi Mumbai, India
Fig. 3: ZMG-based $^{99m}$Tc generator - Geltech of BRIT
References

4) Radiopharmaceuticals from generator produced radionuclides, STI/PUB/294, IAEA, (1971)
7) Radioisotopes Production and Quality Control, STI/DOC/10/128, IAEA (1971)
11) Production technologies for $^{99}$Mo and $^{99m}$Tc, IAEA-TECDOC-1065 (1999)