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Non-HEU Production Technologies for Molybdenum-99 and Technetium-99m

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NON-HEU PRODUCTION TECHNOLOGIES FOR MOLYBDENUM-99 AND TECHNETIUM-99m

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INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2013

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FOREWORD

One of the IAEA's statutory objectives is to "seek to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world." One way this objective is achieved is through the publication of a range of technical series. Two of these are the IAEA Nuclear Energy Series and the IAEA Safety Standards Series.

According to Article III.A.6 of the IAEA Statute, the safety standards establish "standards of safety for protection of health and minimization of danger to life and property". The safety standards include the Safety Fundamentals, Safety Requirements and Safety Guides. These standards are written primarily in a regulatory style, and are binding on the IAEA for its own programmes. The principal users are the regulatory bodies in Member States and other national authorities.

The IAEA Nuclear Energy Series comprises reports designed to encourage and assist R&D on, and application of, nuclear energy for peaceful uses. This includes practical examples to be used by owners and operators of utilities in Member States, implementing organizations, academia, and government officials, among others. This information is presented in guides, reports on technology status and advances, and best practices for peaceful uses of nuclear energy based on inputs from international experts. The IAEA Nuclear Energy Series complements the IAEA Safety Standards Series.

The report was compiled in two consultancy meetings held in March 2010 and February 2011. The IAEA wishes to thank K. Crowley (USA), T.J. Ruth (Canada), C.W. Allen (USA) and G. Vandegrift (USA) for their contributions to this report. This work was made possible by financial and technical support provided by the Global Threat Reduction Initiative, managed by the United States Department of Energy, National Nuclear Security Administration. The IAEA officer responsible for this publication was E. Bradley of the Division of Nuclear Fuel Cycle and Waste Technology.

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CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

Technetium-99m (^{99m}Tc) is used in approximately 85% of nuclear medicine diagnostic imaging procedures worldwide. Almost all the ^{99m}Tc used for this purpose is obtained from the radioactive decay of molybdenum-99 (^{99}Mo), which is produced by processing irradiated uranium targets in Belgium (IRE), Canada (AECL/Nordion), the Netherlands (Covidien) and South Africa (NTP). After irradiation, the uranium targets are processed to extract ^{99}Mo, which in turn is purified for use in ^{99}Mo/^{99m}Tc generators that are shipped to radiopharmacies, hospitals and clinics. Demographic and medical trends suggest that, at least in the near future, global demand for ^{99m}Tc will grow at an average annual rate of 3–8% as these diagnostic imaging procedures expand to new markets, such as those in Asia [1].

The research reactors used to irradiate targets that produce most of the world's supply of ^{99}Mo are over 40 years old. Planned and unplanned shutdowns of some of these reactors have resulted in several recent ^{99}Mo/^{99m}Tc supply interruptions. These interruptions prompted international organizations and several government agencies to step up efforts to find both short and long term solutions to supply shortages. In response to a Canadian government initiative, the OECD/NEA established the High Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) with participation by the IAEA as an observer. Several Member States of the IAEA expressed concern about supply shortages during the 2009, 2010 and 2011 Board of Governors Meetings and IAEA General Conferences (GC). The 2009 Conference, in Resolution GC(53)/RES13, urged the Secretariat "to work cooperatively with other international initiatives ... to implement activities that will contribute to enhancing the molybdenum-99 production capacity, including in developing countries, in an effort to ensure the security of supplies of molybdenum-99 to users worldwide". These calls for action continued throughout 2012 in the work of the OECD and IAEA. In support of these efforts, the OECD published economic and technology studies on the ^{99}Mo supply chain [2, 3].

The IAEA convened a group of experts to initiate a new activity specifically aimed at supporting global efforts to improve ^{99}Mo/^{99m}Tc supply reliability and promoting the conversion of ^{99}Mo production from highly enriched uranium (HEU) to low enriched uranium (LEU). Three of the four facilities used to produce most of the world's supply of ^{99}Mo use HEU targets with ^{235}U enrichments of up to 93%. The remaining producer, NTP in South Africa, produces ^{99}Mo using 19.75% LEU and 45% HEU. Plans for converting South African production to LEU reached a major milestone in 2010 when LEU based ^{99}Mo was imported into the United States of America for use in patients. The Australian Nuclear Science and Technology Organization is routinely producing ^{99}Mo from LEU targets irradiated in the OPAL reactor. Efforts continue to ramp up production there.

The IAEA's focus on the conversion of ^{99}Mo production from HEU to LEU is part of a long standing effort to eliminate HEU use in civilian applications. This effort received a boost in 2009 when the US National Academy of Sciences concluded that the elimination of HEU in medical isotope production is technically and economically feasible [4]. The scope of all IAEA activities related to improving ^{99}Mo/^{99m}Tc supplies, including this publication, supports global efforts to eliminate the civilian use of HEU.

The reliability of ^{99}Mo/^{99m}Tc supply can be improved by increasing diversity and redundancy in all aspects of the supply chain. Smaller scale production (for domestic and regional use) and well distributed production facilities are important supplements for increasing supply reliability. Several alternative/supplementary technologies for producing ^{99}Mo/^{99m}Tc have been proposed. Some of them are not yet commercially proven and some are still in the early stages of development. International exchanges of information can hasten the development of technically and economically viable technologies and prepare them for deployment.

1.2. OBJECTIVES

The objectives of this report are to document current and novel ^{99}Mo/^{99m}Tc production technologies that do not involve the use of HEU and thereby facilitate international cooperation on ^{99}Mo supply and technology development. These technologies were compiled from information provided by consultants and participating Member States.

This report complements other related IAEA and international activities. They include the IAEA coordinated research project (CRP) on Small Scale Indigenous ^{99}Mo Production (2005 to 2011), a CRP on Accelerator Based Alternatives to Non-HEU Production of ^{99}Mo/^{99m}Tc, the Peaceful Uses Initiative (PUI) and technical cooperation projects on small scale ^{99}Mo production technology deployment, as well as robust studies, conducted, for example, in Canada, Europe, the USA and by the OECD/NEA [2, 3].

1.3. SCOPE

This report considers current and novel non-HEU ^{99}Mo/^{99m}Tc production technologies at all stages of the production process and on all scales (local to global) of supply. It considers improvements to existing technologies for producing ^{99}Mo involving fission and neutron activation, novel technologies for producing ^{99}Mo such as photofission and transmutation as well as technologies for the direct production of ^{99m}Tc. This report considers technologies at all stages of development. This approach ensured the most comprehensive review of existing and novel ^{99}Mo/^{99m}Tc technologies.

The focus of this report is on the technical readiness of ^{99}Mo/^{99m}Tc production technologies. Efforts to compile the report did not consider non-technical or business related issues such as manufacturing readiness, cost, supply demand or supply security. Although all of the production technologies considered in this report produce waste by-products, such production is a result of the application of a technology and not an attribute of technology development. The report does not consider specific waste management technologies. However, the expected waste and regulatory requirements associated with the different technologies are discussed.

1.4. INTENDED AUDIENCE

The IAEA cooperated with other international organizations — including the HLG-MR of the OECD/NEA — and with Member States throughout the supply crises and the project to produce this report. Specifically, the IAEA encouraged partnerships, cooperation and complementary implementation of ^{99}Mo/^{99m}Tc production and supply technologies among interested governmental, scientific and technical organizations. To achieve this end, this report has been developed for policy and decision makers within these governmental, scientific and technical organizations.

1.5. STRUCTURE

This report is broken into eight major sections and includes one appendix. The first three sections introduce the subject, provide background information on ^{99}Mo production and lay out the technical breakdown of the remaining discussion.

Section 4 discusses reactor based ^{99}Mo production. In general, this includes fission of heterogeneous uranium targets, fission of homogeneous uranium solution and activation of natural and enriched ^{98}Mo targets. The section also describes technologies to address low specific activity ^{99}Mo, a challenge specific to ^{98}Mo activation based production.

Section 5 considers accelerator based ^{99}Mo/^{99m}Tc production. Both fission and non-fission production technologies are described, as are target materials, chemistry, waste and post-production isotopic separation. Accelerator based production is receiving significant interest and investment, but remains in the development phase.

Section 6 describes ^{99}Mo/^{99m}Tc generator systems. Generator technology is an important aspect of the ^{99m}Tc supply chain. However, a given technology could apply to both reactor and accelerator based technologies. Therefore generator technology is considered in a separate section.

Section 7 includes technology readiness tables for technologies presented in sections 3 and 4. Generator technology is included within individual production methods. The tables reflect the outcome of an objective, evidence based review of the different production technologies.

Section 8 includes the conclusion. An appendix explains the technology readiness terminology beyond what was presented in Section 3. This is followed by a list of references, a glossary and a list of longhand terminology abbreviated throughout the report.

2. PRODUCTION OF ^{99}Mo/^{99m}Tc

Molybdenum-99 is a radioactive isotope that undergoes beta decay with about a 66 hour half-life (Fig. 1). About 88% of these decays result in the production of the metastable isotope ^{99m}Tc (Fig. 1), which subsequently decays to the ground state (^{99g}Tc) with about a 6 hour half-life.

The present 'gold standard' process for producing ^{99}Mo for medical isotope use involves the neutron fission of ^{235}U (i.e. ^{235}U(n,f)^{99}Mo) in multipurpose research reactors (Fig. 2). About 6.1% of the ^{235}U fissions produce ^{99}Mo. The cross-section for this reaction is large (~584 barns for thermal neutrons) compared with other production processes shown in Fig. 2. Multipurpose research reactors are especially well suited for ^{99}Mo production because they have space for irradiating multiple targets at high neutron fluence rates (typically in the order of 10^{13}–10^{14} neutrons per square centimetre per second ($n \cdot cm^{-2} \cdot s^{-1}$)).

Molybdenum-99 can be produced through a number of other schemes illustrated in Fig. 2:

- Fission of ^{235}U with neutrons produced in deuteron and proton accelerators through (D, n) and (p, n) reactions on heavy targets.
- Neutron activation of ^{98}Mo (i.e. ^{98}Mo(n,γ)^{99}Mo). This process is only practical for reactor based production owing to the small activation cross-section (0.13 b for thermal neutrons). Also, ^{99}Mo produced through this process has a lower specific activity than neutron fission produced ^{99}Mo.
- Photofission of ^{100}Mo (i.e. ^{100}Mo(γ,n)^{99}Mo). The energetic photons used in this production scheme are obtained by irradiating heavy targets with electron beams produced by linear accelerators.

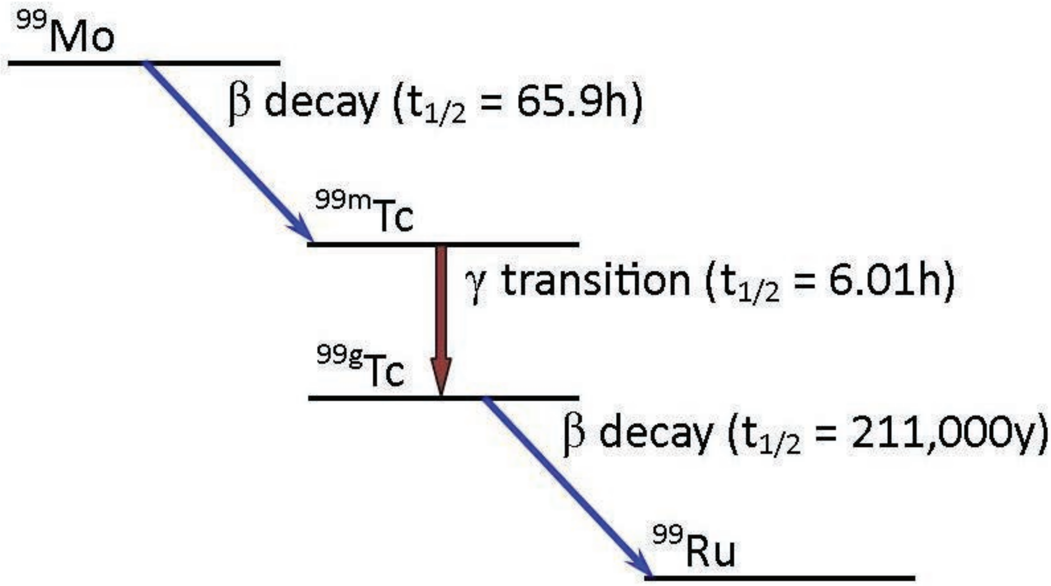

FIG. 1. ^{99}Mo decay.

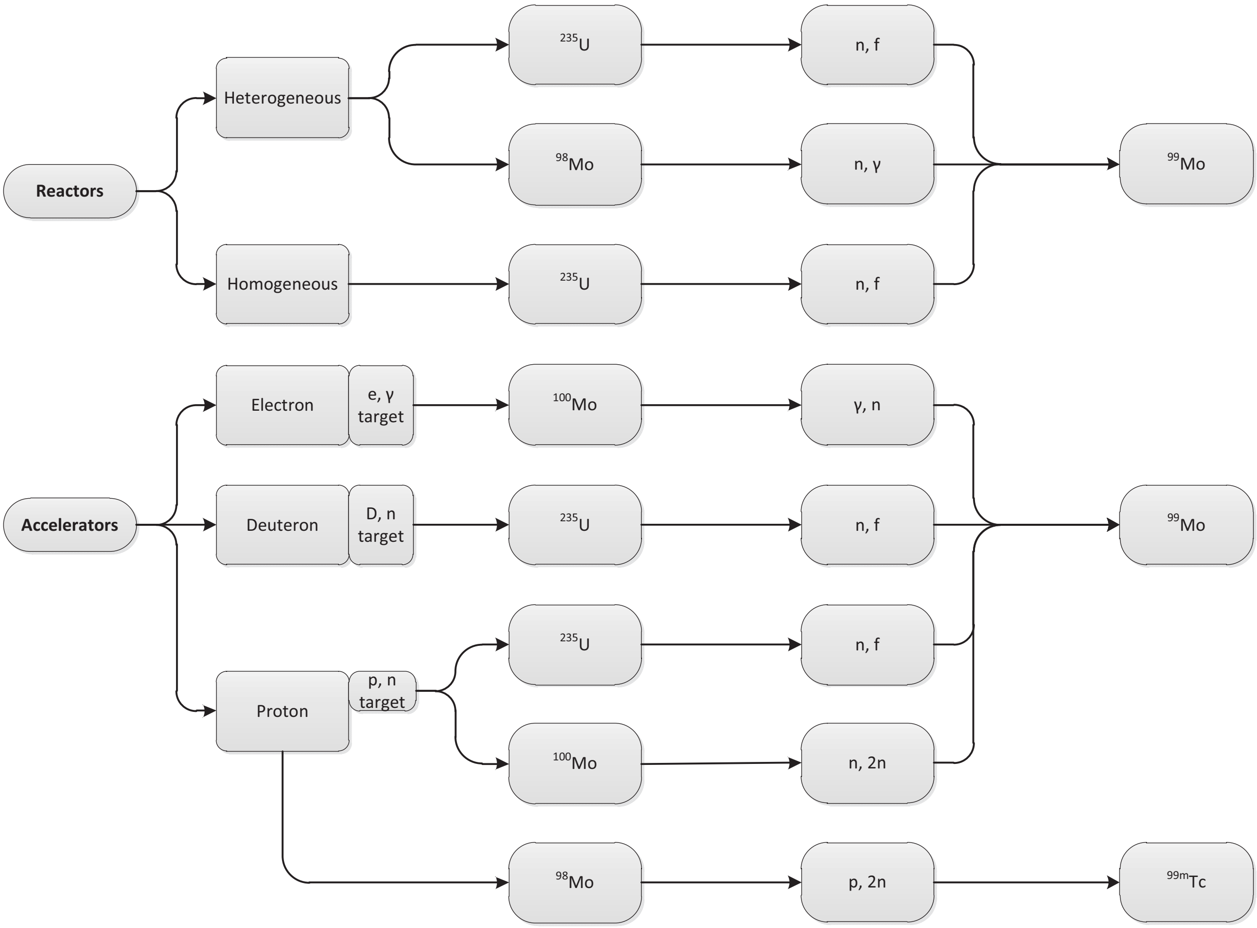

FIG. 2. Schemes for producing ^{99}Mo and ^{99m}Tc discussed in this report.

Technetium-99m can also be produced directly through (p, 2n) reactions on targets containing ^{98}Mo (Fig. 2). This production scheme eliminates the need for intermediate production steps involving the recovery and purification of ^{99}Mo. However, it is suitable only for short (e.g. city scale) supply chains because of the short half-life of ^{99m}Tc.

All the production schemes shown in Fig. 2 result in the production of by-product wastes. The major waste streams include off-gas generated during target processing and liquid and solid processing residues. Some key waste production characteristics for each production scheme are described in this report.

3. ORGANIZATION OF PRODUCTION TECHNOLOGIES

The discussion of ^{99}Mo/^{99m}Tc production technologies in this report is organized according to the production schemes shown in Fig. 2. Section 4 describes reactor based production schemes and Section 5 describes accelerator based production schemes. The following information is provided for each production scheme shown in Fig. 2:

- Description of the production scheme;
- Target materials and processing;
- Waste;
- Regulatory issues.

Section 6 describes technologies for concentrating and storing ^{99}Mo/^{99m}Tc produced from both reactor and accelerator based technologies.

Tables 6–14, which are included at the end of this report, provide estimates of technology readiness level (TRL) for each of the production schemes. Judgements on TRL were based on information supplied by technology developers, information available from the literature and also from extrapolations from other technologies. With respect to extrapolation, one can assume, for example, that processes for isolating ^{99}Mo from a uranium target will be similar regardless of whether the target was irradiated in a reactor or an accelerator. The TRLs shown in the tables are not judgements about the ability of any particular technology developers to implement a particular technology. In fact, implementation of any particular technology could require assistance from experienced technology developers and may entail the use of proprietary information.

4. REACTOR BASED PRODUCTION

4.1. FISSION BASED (n, f) PRODUCTION IN HETEROGENEOUS REACTORS

At present, most of the world's supply of ^{99}Mo for medical diagnostic imaging is produced by irradiating solid targets containing ^{235}U in heterogeneous reactors. After irradiation in the reactor, the target is digested in acid or alkaline solutions and ^{99}Mo is recovered through a series of extraction (separation) and purification steps.

As noted in Section 1, most current ^{99}Mo production utilizes targets containing HEU. However, LEU targets have been developed and are currently being used for small to medium scale[1] commercial ^{99}Mo production by several organizations:

(1) Targets containing uranium-aluminium dispersed in an aluminium matrix (commonly referred to as UAl_2 or UAL_x targets). The dispersion is clad between thin (nominally 0.3 mm) aluminium plates. These targets are currently being used by CNEA, ANSTO and NECSA[2] to produce ^{99}Mo. This target is described more fully in Section 4.1.1.1.

(2) Targets containing uranium metal foil. The foil is clad between aluminium tubes and is separated from the cladding by a recoil barrier; the barrier prevents the foil from bonding to the cladding. These targets have been successfully irradiated and processed on a trial basis at BATAN, CNEA and MURR [3]. This target is described more fully in Section 4.1.1.4.

A 2009 report from the USA National Academy of Sciences concluded that "LEU targets that could be used for large scale production of ^{99}Mo have been developed and demonstrated." The expert committee that authored this report also concluded that it saw "no technical reasons that adequate quantities (of ^{99}Mo) cannot be produced from LEU targets in the future" [4]. While the present IAEA report was being developed, ANSTO demonstrated large scale production of ^{99}Mo, although it has not yet implemented routine production on a large scale.

The following sections describe LEU target materials and processing methods that could potentially be used for the production of ^{99}Mo on small to large scales.

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[1] NECSA has reported that production will be increased following non-nuclear regulatory approvals in customer countries.

[2] NECSA successfully demonstrated their capability to produce ^{99}Mo from LEU targets in 2010. As of the final edit of this report, NECSA was continuing to work toward routine production and a complete process conversion to LEU.

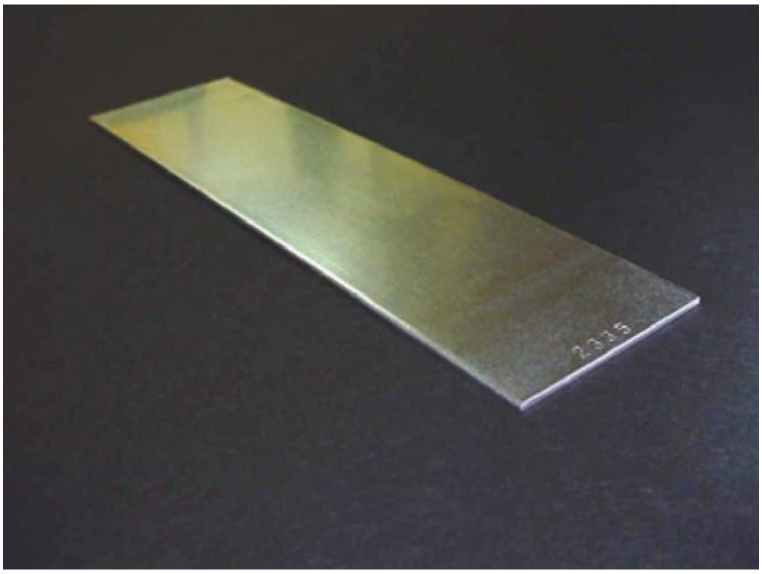

FIG. 3. CNEA's LEU-aluminium dispersion targets. These targets have been used since 2002 to produce ^{99}Mo in Argentina. The target is 13.0 cm in length and 3.5 cm in width [5].

4.1.1. Targets and processing methods

4.1.1.1. UAl$_x$ dispersion targets

Uranium-aluminium (UAl$_x$) dispersion targets comprised of HEU and LEU are currently being used to produce ^{99}Mo worldwide. These targets are manufactured to MTR fuel specifications by both CERCA and CNEA and are qualified to moderate burnup (i.e. >30%). This burnup is typically several times greater than that experienced during target irradiation for ^{99}Mo production. Historically, multiple thousands of HEU dispersion targets have been safely irradiated and processed to produce ^{99}Mo of high quality and purity.

The uranium density (also referred as uranium loading) of an LEU dispersion target is in the range of 2.5–3.0 gU/cm^3. In contrast, the maximum uranium density of HEU dispersion targets now in use is ≤1.6 gU/cm^3. In comparison, uranium metal targets have a density of 19.0 g/cm^3. An LEU dispersion target manufactured by CNEA is shown in Fig. 3.

LEU Al$_x$ dispersion targets are currently being irradiated on a routine basis to produce ^{99}Mo in Argentina, Australia and South Africa. Both Covidien and IRE currently use HEU Al$_x$ dispersion targets manufactured by CERCA to produce ^{99}Mo. CERCA is currently manufacturing LEU Al$_x$ dispersion targets for NECSA. ANSTO has used LEU Al$_x$ dispersion targets supplied by both CERCA and CNEA.

LEU dispersion target fabrication begins with LEU UAl$_2$ particles matrixed with pure aluminium powder. The UAl$_2$ to UAl$_3$/UAl$_4$ phase transformation is inherent to the fabrication process used to manufacture these targets. (The various steps of the fabrication process convert UAl$_2$ to UAl$_3$ /UAl$_4$.) The ratio of UAl$_3$ to UAl$_4$ in a finished target will vary from manufacturer to manufacturer depending on the processes and heat treatments that are used in fabricating the powder, core compacts and target plates [6].

All current ^{99}Mo producers who use LEU Al$_x$ targets use an alkaline digestion chemical process. Multiple targets are digested in a dissolver unit containing sodium hydroxide (NaOH), or, in the case of IRE and PINSTECH, NaOH and NaNO$_3$. The molybdenum in the dissolution liquor is then recovered and purified by a series of processing steps. The number of purification steps, typically four or five, varies from producer to producer. The process used by both Covidien and CNEA and subsequently marketed by the Gamma–Service Group International (GSG) and INVAP is based on technology developed by A.A. Sameh at KfK [7–9]. The alkaline digestion based chemical processing scheme for LEU Al$_x$ dispersion targets has been successfully demonstrated with LEU targets in Australia, Argentina and South Africa.

GSG is also marketing a chemical digestion processes called ROMOL99 [10]. The process involves the dissolution of UAl$_x$ dispersion targets in a closed system under reduced pressure conditions (and without generation of H_2) including a NH_{3-} and iodine removal process step. The process is being operated using semiautomated process control. This process is currently being used with HEU targets by PINSTECH and in Dimitrovgrad (Russian Federation) with a production capacity of 200–250 6 day Ci (7400–9250 GBq).

4.1.1.2. U_3Si_2-Al dispersion targets

U_3Si_2 has been successfully used as research reactor fuel for many years. This fuel is manufactured to established and industry accepted MTR fuel specifications [11]. It has been qualified to a uranium loading of 4.8 g/cm^3 for research reactors [12]. For use as a ^{99}Mo production target, a uranium loading of 6.0 g/cm^3 is achievable [13].

In October 1988 the US Nuclear Regulatory Commission (NRC) approved the use of U_3Si_2-Al dispersion fuel in its licensed plate type reactors at densities of up to 4.8 gU/cm^3 and up to power densities and ^{235}U burnup values typical of fuels tested in the 30 MW Oak Ridge Research Reactor at the Oak Ridge National Laboratory. Since that time regulatory authorities in many other countries have approved the use of U_3Si_2-Al plate type fuel.

The French research reactor fuel fabricator (CERCA) announced in 1992 that it could provide U_3Si_2-Al dispersion fuels up to a density of 6.0 gU/cm^3 [14]. Five fuel plates with uranium densities of 5.8 and 6.0 gU/cm^{3}were irradiated at the Siloé reactor in Grenoble, France, to a burnup of 55% in 1995 to 1997 and two 5.8 gU/cm^3 fuel assemblies were irradiated in Osiris to a burnup of 74% in 1997 and 1998. These irradiations produced very good results [13].

These manufacturing developments and irradiations have shown that higher density U_3Si_2-Al dispersion fuel can be manufactured reliably and perform well under irradiation. By the definition of 'qualified fuel' presented in Ref. [15], 6.0 gU/cm^3U_3Si_2-Al dispersion fuel can be considered to be qualified for use under conditions that do not exceed those of the test irradiations described above.

Uranium silicide-aluminium (U_3Si_2) dispersion targets have been evaluated for use to produce ^{99}Mo [16]. Dissolution of 4.8 gU/cm^3 U_3Si_2-Al targets by a process has been demonstrated on a laboratory scale. The mechanism and rates for dissolution of the aluminium cladding, aluminium in the fuel matrix and the silicide particles are understood. Irradiated silicide has a slow dissolution rate owing to the bonding of silicide particles during irradiation. A chemical method to break up the fused silicide particles before or during dissolution is required to successfully process these targets.

The use of alloyed aluminium cladding (e.g. Al type 6061) necessitates a solids separation step following cladding dissolution. Hydroxide precipitates of alloying elements are suspended in the spent cladding dissolver solution. Separation of this low density precipitate from the high density U_3Si_2 is possible.

U_3Si_2 cannot be readily dissolved by sodium hydroxide (NaOH) solutions or NaOH solutions containing sodium nitrate ($NaNO_3$). Therefore, the cladding and aluminium powder in the fuel matrix are dissolved in one step using potassium hydroxide (KOH) and a second step is required using a more powerful reagent, such as hydrofluoric acid, to dissolve the U_3Si_2. Because some of the ^{99}Mo is lost to the aluminium matrix due to fission recoil, it must be recovered during both dissolution steps to maximize the ^{99}Mo yield of a production batch.

The dissolution and chemical processing of a U_3Si_2 target containing greater than 4.8 gU/cm^3 has not yet been demonstrated.

GSG is marketing a further developed version of this process as the Karlsruhe Sameh Silicide (KSS) process.

4.1.1.3. Uranium nitride (UN) dispersion targets

Uranium nitride MTR fuel plates have been developed and fabricated on a laboratory scale [17]. Uranium nitrides are denser, more stable and conduct heat better than mixed uranium–plutonium oxide reactor fuels — properties that suggest these fuels could run cooler in power reactors to generate more thermal energy.

In the mid-1980s, a method to create a discrete compound of uranium nitride was discovered. The compound is uranium nitrid important because its ceramic state, uranium mononitride, was identified as a candidate for reactor nuclear fuel.

Published reactor fuel characteristics, for alloy in an aluminium matrix, identify the uranium loading of the dispersed phase as approximately 13.5 g/cm^3. When fabricated to the requirements of MTR fuel specifications, the maximum uranium loading of a UN fuel plate (or target) is 7.0 g/cm^3.

4.1.1.4. Uranium foil targets

Argonne has developed an LEU foil target for ^{99}Mo production (Fig. 4). The uranium loading of the LEU foil is approximately 19 g/cm^3. This is much higher than the uranium loading of HEU or LEU dispersion targets, which typically contain no more than 1.6 gU/cm^3 and between 2.5 and 3.0 g U/cm^3, respectively, as noted previously.

The target consists of a thin (typically 100–150 μm thick) uranium foil sandwiched between 15 μm thick nickel or 40 μm thick aluminium fission recoil barriers. The foil barrier sandwich is contained in a tubular aluminium cladding. The fission barrier prevents the LEU foil from bonding with the aluminium cladding during irradiation.

After irradiation, the foil is removed from the aluminium cladding for chemical processing and the cladding is discarded as low activity solid waste. The removal of the foil from the cladding prior to chemical processing reduces the processing time and the volume of processing waste compared to LEU dispersion targets. The target has been chemically processed using the LEU Modified Cintichem process developed by Argonne, which involves dissolution in nitric acid (HNO_3).

LEU foil targets have a limited irradiation history. Targets have been successfully irradiated in Argentina, Indonesia, Australia and the USA. Approximately thirty LEU foil targets have been irradiated worldwide to date.

Furthermore, LEU foil targets are not currently manufactured to an industry accepted standard or specification. Such a standard or specification must be developed and a corresponding target qualification programme must be implemented before this target can be adopted for widespread use.

Additionally, LEU foil targets have not been industrially adapted to the alkaline target dissolution processes used by many current ^{99}Mo producers. Argonne has developed two front end options for using LEU foil targets in alkaline based processes for use with these targets. It is anticipated that they will be demonstrated on a production scale in 2013 [18].

A small scale ^{99}Mo producer (BATAN in Indonesia) planned to convert to LEU foil targets after exhausting its inventory of HEU. (At the time of this report, BATAN was not producing LEU foil target based ^{99}Mo.) Consequently, for small scale ^{99}Mo production, target fabrication and chemical processing of LEU foil targets is not yet fully mature.

Work is in progress by the University of Missouri, Argonne and B&W Y-12 to develop LEU foil annular target specifications, a manufacturing method for high volume target production and quality control test criteria [19, 20]. Work is also in progress to transition the annular design to a plate (flat or curved) geometry as an option [21, 22]. Thin uranium metal foils manufactured by B&W Y-12 and KAERI are shown in Figs 5 and 6, respectively.

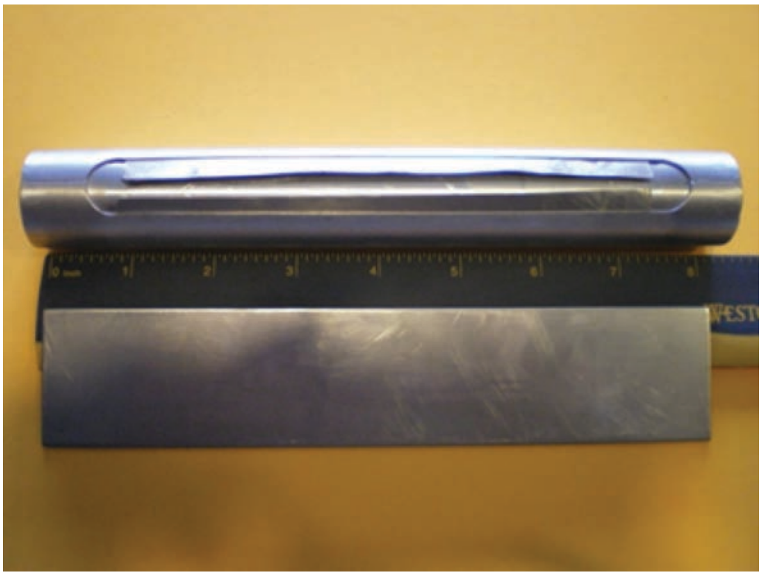

FIG. 4. LEU foil annular target comparison to a typical HEU dispersion target. Annular target shown with nickel wrapped 24 $gU_{(LEU)}$ foil exposed. A typical HEU dispersion target contains ~5 $gU_{(HEU)}$. Both targets yield about the same activity of ^{99}Mo if irradiated with the same thermal neutron flux and irradiation time.

FIG. 5. Uranium metal foil fabricated on a trial basis by B&W Y-12. The thickness of the foil is ~115 µm.

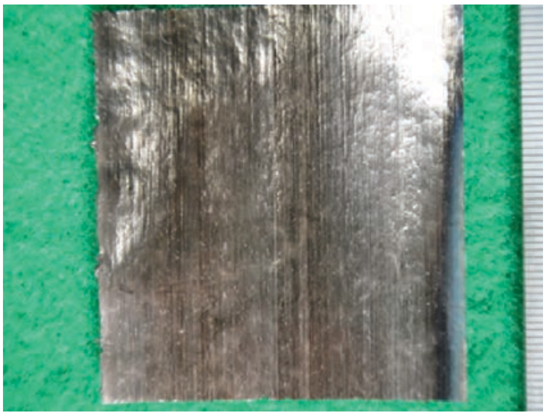

FIG. 6. Uranium metal foil fabricated by KAERI using their cooling roll casting method. The average thickness of the foil is ~140 µm.

4.1.1.5. Uranium metal targets

The concept of uranium metal targets is by no means new. Natural uranium metal slugs electroplated with nickel (~7 µm in thickness) and clad in aluminium (1.27 mm in thickness) were used to produce plutonium in the Savannah River reactors [23]. Thousands of these slugs were routinely irradiated and chemically processed over a period of about fifty years.

CINR Rossendorf routinely irradiated and processed natural uranium metal pellet targets to produce ^{99}Mo from 1963–1980 [24]. The target material was dissolved in HCl and ^{99}Mo was separated from the dissolution liquor using an alumina column. Commercially available 5% enriched uranium metal in the form of pellets, disks or strips could be used in lieu of natural uranium target material for ^{99}Mo production. GSG developed a processing system concept, LITEMOL, which aims to provide a small scale ^{99}Mo production capability to those institutions operating research reactors with moderate neutron flux densities ($1–5 \times 10^{13}$). The chemistry of the LITEMOL concept is identical to that used at CINR. However, this processing concept has not yet been demonstrated using the commercially available 5% enriched uranium metal disks or strips.

4.1.1.6. Uranium oxide (UO_2) targets

ANSTO routinely irradiated 1.8% enriched UO_2 pellets to produce ^{99}Mo in the early 1980s. The enrichment of the pellets was later increased to 2.2%. The density of UO_2 in a dispersed phase was approximately 9.7 g/cm^3. The pellets were irradiated for up to 7 days in a double encapsulated aluminium can configuration. The small gap between the fuel pellets and the aluminium irradiation can was filled with magnesium oxide (MgO) to enhance heat dissipation.

Following irradiation, the pellets were separated from the MgO powder by sieving, followed by dissolution in concentrated nitric acid. The solution was passed through an alumina column, which sorbed the ^{99}Mo. The remainder of the solution, which contained uranium and most of the fission products, passed through the column. The alumina column was then washed in sequence with nitric acid, purified water and a dilute ammonia solution to remove traces of contaminants.

The purified ^{99}Mo was eluted from the column with concentrated ammonia solution, followed by boiling the solution to remove residual traces of iodine and ruthenium. The alumina column separation was repeated to produce ^{99}Mo of the specified purity [25].

The EOB yield of a target batch was approximately 135 Ci (5,000 GBq). Up to five production runs were performed on a weekly basis, totalling 675 Ci (25,000 GBq) at EOB. Technetium-99m generator production was spread out over the entire week. ANSTO continued to produce ^{99}Mo using the UO_2 pellets until late 2006, when it began transitioning to LEU UAl_x targets.

JAERI also produced ^{99}Mo in 1977 using UO_2 pellets (2.6% enrichment) as a target material. JAERI irradiated 120 g of pellets in the JRR-2 or JRR-3 reactor for up to 7 days at a maximum neutron flux of 3×10^{10} $n \cdot cm^{-2} \cdot s^{-2}$. A batch of about 20 Ci (740 GBq) of ^{99}Mo per week was routinely shipped to a local ^{99}Tc generator manufacturer [26].

AECL designed an HEU UO_2 powder annular target for irradiation in the MAPLE reactors. The UO_2 powder was vibra-packed between two concentric cylinders made from zirconium and hot isostatic pressed to seal the target and provide good thermal contact between the target meat and cladding. These targets were fabricated by B&W but were never used.

From the early 1970s to 1989, the Cintichem reactor facility prepared targets using HEU electroplated from a uranyl oxalate system onto the inside surface of a stainless steel tube [27]. After electroplating, the tubes were heated to convert the uranium to UO_2 and their tops and bottoms were welded shut. After irradiation, the tubes served as dissolver vessels.

4.1.1.7. Uranium aluminide alloy targets

The target is fabricated from U–Al alloy rods clad with aluminium. This target is manufactured by AECL using HEU and is of the same basic construction as the HEU fuel rods that were used in the NRU reactor before its conversion.

LEU based targets of the same general design and dimensions would yield less ^{99}Mo activity than the HEU targets they replace. The amount of decrease would depend on the density of ^{235}U in the LEU target compared to the HEU target.

4.1.1.8. Uranium metal particle aluminium matrix dispersion targets

This target design is being developed by KAERI. An atomization process produces 50–150 μm uniform spherical uranium metal particles, which are incorporated into an aluminium metal matrix to produce the target meat. A uranium volume fraction is anticipated of up to 50% (approximately 9.0 gU/cm^3) in the target meat with these small particle sizes.

Small amounts of silicon, chromium, iron or other elements can be alloyed with the uranium metal and/or a small amount of silicon can be alloyed with the pure aluminium matrix to retard the interaction with uranium metal particles [28].

4.1.2. Waste

Uranium fission production schemes generate higher volume and activity waste compared with other production schemes described in this report. Uranium fission production also requires substantially higher shielding for targets, processing and waste handling. The liquid processing wastes must be solidified and stored until a permanent disposal pathway becomes available.

Production of ^{99}Mo using LEU targets will generate waste with the same characteristics as that produced from HEU targets. However, waste volumes could be different (larger or smaller) depending on target design.

4.1.3. Regulatory issues

Regulatory approvals will be needed before new target designs can be irradiated on a routine basis and also before ^{99}Mo produced from these targets can be used in medical procedures.

The safety aspects of target use are evaluated in a manner consistent with the evaluation of reactor fuel. Thermohydraulic considerations will dictate the maximum thermal power (kW) of the targets, their uranium mass and the requirements for their positioning in the reactor. Also, a target failure in containment analyses must be performed as part of the safety case for target irradiation. Historically, targets fabricated from the same material as the reactor fuel material have been easiest to qualify and license. The safety aspects of target processing must also be addressed.

The production of ^{99}Mo using LEU targets is almost identical to the present ‘gold standard’ process for producing ^{99}Mo using HEU, and chemical processing is in many cases almost identical. In some cases, however, chemical processing might have to be modified to accommodate larger masses of LEU target material. The LEU based production process and products will have to be validated and approved by regulatory bodies, but past experience suggests that this will be a straightforward process when carried out in close coordination with regulators.

4.2. FISSION BASED (n, f) PRODUCTION IN HOMOGENEOUS REACTORS

A pseudo-prototype system, ^{99}Mo production and recovery from an aqueous homogeneous reactor (ARGUS), has been demonstrated on a pilot scale in the Russian Federation. The Kurchatov Institute, in collaboration with Argonne and Technology Commercialization International, a private company from the USA that is no longer in business, developed an LEU uranyl sulphate based aqueous homogeneous reactor at ARGUS to produce ^{99}Mo. The concept never progressed beyond laboratory scale development, but a similar concept is now being pursued by CJSC Resources and Technologies [29] and ROSATOM.

Babcock and Wilcox has developed a conceptual design for a 200 kW aqueous homogeneous reactor and recovery system to produce ^{99}Mo, called MIPS. The reactor fuel solution, which contains LEU salt dissolved in water and acid, is also the target material for ^{99}Mo production. The reactor would be operated to allow the buildup of ^{99}Mo in the fuel solution. The reactor would then be shut down and the fuel solution pumped through a recovery column that preferentially sorbs molybdenum. Molybdenum-99 would be recovered by stripping (i.e. eluting) the recovery column and subsequently conditioned by one or more purification steps.

Babcock and Wilcox estimate that a single 200 kW MIPS is capable of producing about 10 000 Ci (370 000 GBq) of ^{99}Mo at the EOB (5 day irradiation). The expected yield from sorbent extraction is 90%. Assuming a 10 hour processing time, approximately 8000 Ci (~1700 6 day Ci) (296 000 GBq or ~62 900 6 day GBq) can be produced on a weekly basis[3]. A comprehensive description of the MIPS concept is presented in IAEA-TECDOC-1065 [30].

A key technical challenge in utilizing solution reactor technology for the production of ^{99}Mo is the development of an efficient method for extracting or separating the product isotope from the irradiated fuel solution. Specifically, the effects of radiation and fission product buildup on the separation of ^{99}Mo by an adsorbent media must be determined. Several different adsorbent media have been evaluated: Termoxid 52 (T52), Termoxid 5M (T5M), titanium dioxide (TiO_2) and alumina (Al_2O_3) [31]. Because of the relatively high uranium nitrate or uranium sulphate concentration of the fuel solution, alumina has insufficient sorption properties for use in the molybdenum recovery system.

4.2.1. Fuel/target solutions

Two types of aqueous fuel solutions have been considered for ^{99}Mo production using an AHR: (1) uranium nitrate [$UO_2(NO_3)_2$] and (2) uranium sulphate [UO_2SO_4]. Some characteristics of these solutions are described in the following sections.

4.2.1.1. Uranyl nitrate fuel solution

Uranyl-nitrate solutions have superior chemical properties for the separation of Mo and for waste treatment relative to uranyl-sulphate solutions. However, the radiolytic decomposition of an aqueous uranyl-nitrate solution is far more complex than that of the sulphate salt. In addition to the radiolysis production of H_2 and O_2 from water, nitrate is reduced forming nitrite, nitrogen and nitrogen oxide (NO_x) gases and ammonium ions are also generated from the radiolytic decomposition of the fuel solution. A subsystem to remove the NO_x gases may be required in the design of the off-gas system to prevent degradation of the charcoal filters (if charcoal is chosen as a sorbent for fission gas removal).

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[3] This information was reported by Babcock and Wilcox in a ^{99}Mo production R&D survey submitted to the IAEA.

4.2.1.2. Uranyl sulphate fuel solution

Uranyl sulphate's main advantage is that only H_2 and O_2 are formed by the radiolytic decomposition of the fuel solution. These gases can be recombined to water using a catalyst bed (recombiner) and the condensed water can then be returned to the fuel solution. Its disadvantages are related to the chemistry of sulphate and its salts. This is the concept pursued by the Kruchatov Institute at the ARGUS reactor.

4.2.2. Waste

The operation of homogeneous reactors will produce off-gas wastes and liquid waste streams, primarily the reactor fuel/target and process wastes from ^{99}Mo purification steps. The reactor fuel/target solutions will have to be periodically replaced or replenished. The waste will have to be solidified and stored until a disposal pathway becomes available.

4.2.3. Regulatory issues

Regulatory concern is expected to focus on the stated subcritical nature of the system and design features that will assure that it will remain subcritical. There may also be regulatory issues regarding the disposition of process wastes from these systems.

Over time, fission products will accumulate in the solution as discussed above. Changes to the solution may have to be addressed to satisfy non-nuclear/pharmacoepeia regulatory requirements.

4.3. NEUTRON ACTIVATION PRODUCTION (n, γ) IN HETEROGENEOUS REACTORS

Neutron activation based ^{99}Mo production (i.e. ^{98}Mo (n, γ) ^{99}Mo) is a viable and proven technology that dates back to the 1960s. As an example, MURR began producing low specific activity neutron activation for the USA by irradiating pressed sintered metal natural ^{98}Mo targets in 1967. MURR continued producing ^{99}Mo by this method into the early 1980s. Production was suspended because neutron capture based ^{99}Mo could not compete economically with the high specific activity fission product ^{99}Mo produced domestically at the Cintichem reactor facility (see Section 4.1.1.6).

The production of neutron activation based ^{99}Mo is being carried out in several countries on a routine basis, including India, Japan, Kazakhstan, Peru, the Russian Federation and Uzbekistan.

4.3.1. Targets

Several types of ^{98}Mo target can be used to produce ^{99}Mo through the (n, γ) scheme. These are described in the following sections.

4.3.1.1. Molybdenum metal/molybdenum trioxide (MoO_3) powder

There are 35 known isotopes of molybdenum, 7 of which occur naturally with atomic masses of 92, 94, 95, 96, 97, 98 and 100. Of these naturally occurring isotopes, 6 are stable, with atomic masses from 92 to 98.

Molybdenum-100 is the only naturally occurring isotope that is not stable. Molybdenum-100 has a half-life of approximately 8.0×10^{18} years and undergoes double beta decay into ^{100}Ru. All unstable isotopes of molybdenum decay into isotopes of niobium (Nb), technetium (Tc) and ruthenium (Ru). Molybdenum-98 is the most common isotope, comprising 24.1% (natural abundance) of all molybdenum on Earth. In comparison, the natural abundance of ^{100}Mo is only 9.6%.

High specific activity ^{99}Mo cannot be produced using natural Mo targets because the thermal neutron cross-section for ^{98}Mo neutron capture reaction (n, γ) is only about 0.13 barn (b); this is a factor of about 4400 times less than the ^{235}U thermal fission cross-section, which is about 584 b. Irradiation of natural Mo targets in an epithermal neutron flux of $\geq 1 \times 10^{13}$ n/cm^2-s would produce higher specific activity ^{99}Mo because the epithermal neutron cross-section for the ^{98}Mo neutron capture (n, γ) reaction is about 6.7 b. This is a factor of about 50 times greater than the thermal neutron capture cross-section but still well below the ^{235}U fission cross-section. However, a marked increase in production rate is not seen due to the reduction in the thermal neutron flux available for ^{98}Mo when other natural Mo nuclides are present. These have much higher thermal cross-sections (0.34 b, 13.4 b, 0.5 b, 14.4 b and respectively for $^{94, 95, 96}$ and ^{97}Mo) and hence capture neutrons that would otherwise be available for ^{98}Mo. Most of these have much higher epithermal cross-sections as well.

Although the enriched ^{98}Mo would have four times the ^{98}Mo atoms compared to the natural Mo, much higher production rates are often observed due to the (a) high epithermal neutron captures as well as (b) availability of the neutrons otherwise lost to the competing reactions from other Mo isotopes. The actual increase seen will depend upon the epithermal neutron flux available.

For the purpose of relative comparison, the specific activity of ^{99}Mo produced using the neutron capture (n, γ) versus fission product (n, f) method is presented below:

(1) Neutron capture (n, γ) production
High thermal neutron flux irradiation (EOB):
Natural isotopic abundance target ~1 Ci (37 GBq) ^{99}Mo/g of Mo irradiated
Highly enriched ^{98}Mo target ≥4 Ci (148 GBq) ^{99}Mo/g of Mo irradiated
(2) Fission product (n, f) production (EOB):
Reactor irradiation >10,000 Ci (370,00 GBq) ^{99}Mo/g of total Mo

However, scientists at the Delft University of Technology in the Netherlands developed a methodology to increase the specific activity of neutron activated ^{99}Mo by a factor of more than 1000 by chemical separation of ^{99}Mo from the Mo target using Szilard–Chalmers chemistry, rendering a specific activity level in the order of that produced via fission ^{99}Mo [32–34]. The methodology can be applied to both natural and ^{98}Mo enriched targets. This process is currently in the stage of being scaled up towards demonstration of commercial production feasibility. The target material is to be recycled.

Two types of natural Mo target material are typically used to produce (n, γ) ^{99}Mo: molybdenum trioxide and molybdenum metal. These target materials are shown in Fig. 7.

FIG. 7. Natural abundance and high purity pressed sintered metal Mo targets (32 g) once irradiated at MURR shown with molybdenum trioxide powder for comparison.

The crystalline density of molybdenum trioxide (MoO_3) is about 4.7 g/cm^3; the loose packed powder density would be about half that. MoO_3 powder can be easily dissolved in sodium hydroxide (NaOH). The density of pressed sintered metal targets is 30%–95% of the theoretical density of 10.3 g/cm^3 (i.e. about 3.1 g/cm^3 to 9.8 g/cm^3). Granulated Mo metal can also be used as a target material.

High density pressed sintered natural Mo metal targets are commercially available. They are typically manufactured in the range of about 70%–95% of theoretical density. Molybdenum metal targets can be dissolved in alkaline hydrogen peroxide (H_2O_2) or electrochemically.

The metal form takes more time to dissolve than the powder form. However, the advantage of using metal is that more natural Mo can be irradiated per target, producing a greater yield of ^{99}Mo per unit volume of irradiation space and making more effective use of irradiation space.

The purity of the natural Mo target material should be >95% and should contain no detectable tungsten (W). The irradiation of tungsten produces ^{188}Re (rhenium) by the radioactive decay of ^{188}W, which is difficult to separate from ^{99m}Tc because it has similar chemical properties.

4.3.1.2. Enriched molybdenum-98

The use of ^{98}Mo target material (powder or metal) with an enrichment of >95% offers the advantage of increased ^{99}Mo production yield. The purity of the enriched ^{98}Mo target material should be >95% with no detectable tungsten (W) for the reasons described previously. However, because of the relatively high cost of highly enriched target material, it might be necessary to recover the unused irradiated ^{98}Mo in a purified chemical form suitable for new target production. This material is radioactive and must decay for at least 30 days before it can be classified as non-radioactive.

4.3.2. Waste

Since neutron activation does not involve the presence of mixed fission products, the dose considerations for production and waste handling and storage are significantly less. Shielding requirements through the whole process are much less than for fission product ^{99}Mo. The other activation products present in the waste streams decay within a reasonable period of time such that both solid and liquid wastes can be removed from the cell environment as low activity waste after about 6 months.

4.3.3. Regulatory issues

Neutron activation based production involves no fissile material. Nuclear regulatory/safety approvals are anticipated to be of similar complexity as the irradiation of other, non-fissile material.

5. ACCELERATOR BASED PRODUCTION

5.1. FISSION BASED (n, f) PRODUCTION USING ACCELERATORS

The use of accelerators — as opposed to reactors — to generate high fluxes of thermal neutrons (neutrons of energy ~0.02 eV) for stimulating ^{235}U fission has been proposed for a number of years, initially using HEU. More recently, yield calculations have been performed for LEU targets.

Two accelerator based production schemes are described in this report: The first uses a proton accelerator to produce neutrons through the (p, n) reaction. The second uses a deuteron accelerator to produce neutrons through the (D, n) reaction. These production schemes are illustrated in Fig. 2 [35].

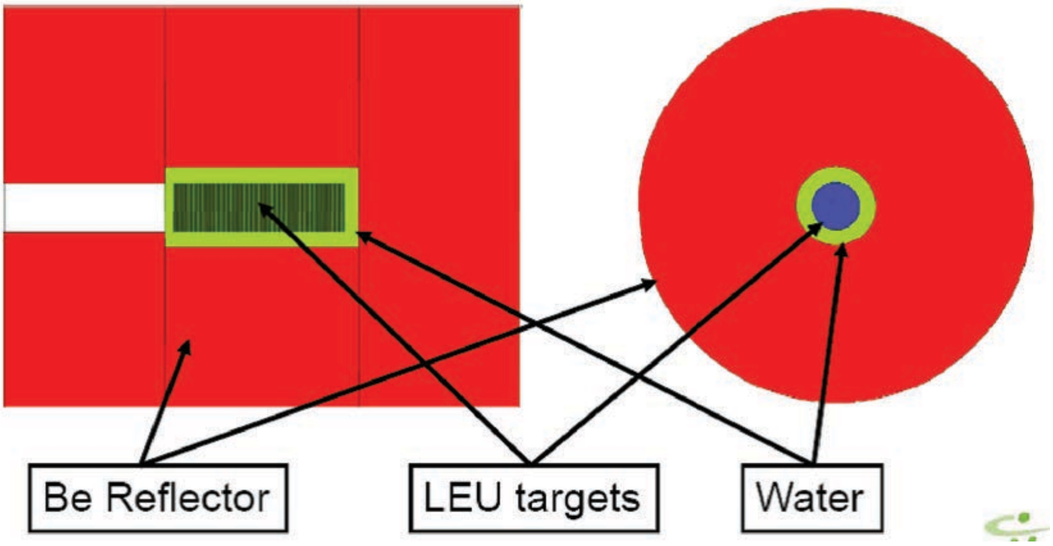

FIG. 8. Subcritical reactor schematic using LEU target assembly with moderator and beryllium reflector [35].

5.1.1. Proton accelerator production

The driver for producing high energy protons has generally been a linear accelerator with high power, with the combination of proton energy and beam current usually in the range of 150–500 MeV with up to 2 milliamps of beam current (~10^{16} particles/s). The goal is to produce an order of magnitude more secondary neutrons inside the target from ^{235}U fission.

As an example, the schematic system shown in Fig. 8 [35] consists of a target made of 0.5 mm thick metallic LEU foils with a radius of 5 cm separated by 1 mm thick water channels for cooling. A target assembly containing 142 foils would generate nearly 5000 6 day Ci/week (185 000 6 day GBq/week) using a proton beam of 350 MeV with a flux of 1 mA. In other words, this scheme would be suitable for large scale ^{99}Mo production.

5.1.1.1. Targets

The target(s) for this approach will consist of a series of LEU discs surrounded by a beryllium reflector to enhance neutron interaction with the target material as well as a water moderator for thermalizing the neutrons.

5.1.1.2. Waste

The waste issues associated with accelerator based fission processes are essentially the same as for reactor based fission processes. Both processes would produce liquid waste containing uranium fission products. However, current reactor based processes utilize uranium–aluminium dispersion targets, which have a greater mass than the uranium foil targets that would be used in the accelerator based process. Consequently, the accelerator based process might produce smaller volumes of waste than current reactor based processes. Specific waste stream volumes would not be known until the target configuration and design have been developed.

5.1.1.3. Regulatory issues

The fission based accelerator production methods are closest to the present ‘gold standard’ of reactor based thermal neutron fission of HEU; thus, the chemical processing would be identical. However, chemical processing might have to be modified to account for the final target configuration discussed above. The LEU based production process and products will have to be validated and approved by regulatory bodies.

5.1.2. Deuteron accelerators

Low energy accelerators can be used to produce neutrons via the D,T reaction or the photon induced breakup of D_2O. These neutrons can be directed to a target composed of a solution of uranyl nitrate or sulphate similar to the solution reactor.

A high intensity neutron source with a very high neutron yield and efficiency has been developed at Phoenix Nuclear Laboratory (PNL) [36]. The source was created by directing a collimated deuterium ion beam into a tritium gas target in an aluminium container. This process produces yields consistent with those predicted by theoretical calculations. The neutrons are produced via the low energy (300 keV) acceleration of deuterons on a tritium target.

Based on current yield estimates, this scheme could be used for medium scale production of ^{99}Mo to meet regional needs. A cluster of devices could achieve large scale production.

The final design will require beam currents in the order of 50 mA, which have been exceeded in reliable, high intensity light ion injectors by groups at LANL and LBNL. The lifetime of the ion source also must be increased from several hours to months. The next generation prototype neutron source will incorporate higher voltage, advanced pumping and improved beam focusing resulting in higher neutron output.

5.1.2.1. Targets

The target material is almost identical to aqueous homogenous reactor fuel consisting of a few kg of ^{235}U. There are plans to study separation methods on both uranyl sulphate and uranyl nitrate target solutions. Questions remain regarding the number of times that the solution can be recycled and reused due to waste product buildup.

The chemical processing of the solution reactor will follow established fission product chemistry. After about five days of operation, the solution will be run through a chromatographic column to recover Mo from other fuel components. This will be followed by the stripping of a Mo product from the column and further purification steps.

5.1.2.2. Waste

The waste produced is that associated with fission of ^{235}U. One challenge with this unit as well as with solution reactors is how to deal with off-gas releases during operation (see Section 4.1.2).

5.1.2.3. Regulatory issues

Since ^{99}Mo will be produced from fission of ^{235}U, there are expected to be minimal regulatory hurdles for the use of ^{99m}Tc in radiopharmaceutical applications. The ^{99m}Tc product is expected to meet USP specifications and be of high specific activity so that it can be used directly in existing commercial generator systems (no new generator needed).

Over time, fission products will accumulate in the solution as discussed above. Changes to the solution will have to be addressed to satisfy non-nuclear/pharmacopoeia regulatory requirements.

5.1.3. Subcritical liquid LEU target for accelerator driven production of fission ^{99}Mo

The Advanced Medical Isotope Corporation (AMIC) is developing a ^{99}Mo production technology whereby a tank of heavy water (deuterium oxide, D_2O) is bombarded by photons (gamma rays) with energies of at least 2.224 MeV. Neutrons in the nucleus of the deuterium atoms in the heavy water are ejected from the deuterium nucleus. Such a process results in a field of neutrons generated inside the tank. By dissolving uranium salts homogeneously in the heavy water, the target material (the uranium) is directly held within the neutron source (the deuterium nuclei). The neutrons generated by the photon bombardment cause some of the uranium atoms to fission, producing useful fission products and extra neutrons that provide a boost to the neutron flux in the system.

The resulting fission product ^{99}Mo can then be extracted from the system and used. The uranium target material is returned to the tank and can be used many times over. This system can run efficiently on LEU.

5.1.3.1. Targets

The target material is almost identical to aqueous homogenous reactor fuel consisting of a few kg of ^{235}U. There are plans to study separation methods on both uranyl sulphate and uranyl nitrate target solutions. Questions remain regarding the number of times that the solution can be recycled and reused due to waste product buildup.

The chemical processing of the solution reactor will follow established fission product chemistry although in a continuous extraction mode. The approach will require the development of column approaches in a semicontinuous or batch mode.

5.1.3.2. Waste

The waste produced is that associated with fission of ^{235}U. One challenge with solution reactors is how to deal with off-gas releases during operation (see Section 4.1.2).

5.1.3.3. Regulatory issues

Since ^{99}Mo will be produced from fission of ^{235}U, there are expected to be minimal regulatory hurdles for use of ^{99m}Tc in radiopharmaceutical applications. The ^{99m}Tc product is expected to meet USP specifications and be of high specific activity so that it can be used directly in existing commercial generator systems (no new generator needed).

Over time, fission products will accumulate in the solution as discussed above. Changes to the solution will have to be addressed to satisfy non-nuclear/pharmacopoeia regulatory requirements.

5.2. PHOTON BASED (γ, n) PRODUCTION USING ELECTRON ACCELERATORS

The photon based (γ, n) production scheme uses a high powered electron accelerator (see Fig. 9) to irradiate a high Z converter target such as liquid mercury or water cooled tungsten. High energy photons (known as bremsstrahlung radiation) are produced by the electron beam as it interacts and loses energy in the converter target. The photons are then used to irradiate another target material placed just behind the convertor, in this case ^{100}Mo, to produce ^{99}Mo via the reaction ^{100}Mo(γ, n)^{99}Mo. Table 1 [38] illustrates the photonuclear cross-sections for the

FIG. 9. High power electron accelerator manufactured by Mevex, Stittsville, Ontario, Canada [37].

TABLE 1. PHOTONUCLEAR CROSS–SECTION FOR PARTICLE EMISSION [38]

$\gamma + {}^{100}Mo$									
Abundance (%)	Threshold Energies (MeV)								
	γ,n	γ,p	γ,t	γ,He-3	γ,α	γ,2n	γ,np	γ,2p	γ,3n
9.63	8.29	11.15	15.53	18.17	3.17	14.22	18.02	19.48	22.86

Note: ‘Abundance’ refers to the natural abundance of ^{100}Mo.

TABLE 2. PRODUCTION OF ^{99}Mo BY A 50 MeV ELECTRON BEAM

Target mass (g of ^{100}Mo)	Ci/100 kW (GBq/100 kW) at saturation	Specific activity (Ci ^{99}Mo/g of Mo) (GBq ^{99}Mo/g of Mo)	Power deposited in target (kW)
0.29	100 (3 700)	360 (13 320)	2.2
1.0	210 (7 770)	20 (740)	4.8
2.3	300 (11 100)	147 (5 439)	11.4
9.1	518 (19 116)	57 (2 109)	16.4
70.6	900 (33 300)	12.8 (474)	29.0

Note: The saturated yield of ^{99}Mo for ^{100}Mo targets of various sizes irradiated by a 100 Kw electron beam incident on a converter target is shown [39]. The columns provide the total activity, the specific activity and the actual power that is deposited in the production target.

production of various particles such as neutrons, protons and alphas. A separate convertor is not necessarily required; the conversion can also be the front section of the Mo targets.

Based on theoretical data, estimated production yields can be determined as shown in Table 2 [39]. The quantity of ^{100}Mo required for the production levels shown in the table is based on the following assumptions, taken from Ref. [39] and representing an example developed to look at a scenario where production would be geared to a regional market and which is not necessarily optimized):

- Target enrichment >98 %;
- Target material is recycled;
- Two targets irradiated daily to produce 180 Ci (6660 GBq) of ^{99}Mo per target;
- Recycle time set by decay: 10 mCi (0.37 GBq) can be handled with modest shielding, which requires 40 days for decay before reusing the Mo;
- Need (2 × 15) [g/day] × 40 [days] = 1200 g of Mo target material as basic stock;
- Nine cycles per year: losses per cycle expected to be small: estimated at 4 %;
- Need 430 g per year to replace ^{100}Mo losses.

Under these assumptions and with the anticipated yields shown in Table 2, this production scheme could be used for medium scale production of ^{99}Mo for regional markets. Obviously, multiple units could produce ^{99}Mo on larger scales.

5.2.1. Target materials

Molybdenum-100 is used as the target material for this production scheme (see Fig. 2). Enrichments of at least 99% are preferable to minimize possible side reactions that result in the production of unwanted technetium and molybdenum isotopes with long half-lives. These isotopes are problematic for waste disposal and result in increased radiation doses in patients. ^{100}Mo is available from European (including Russian Federation) centrifuges with enrichments >92%.

Solid targets usually consist of the target material and an optional support (substrate or target holder assembly). The target material needs to be firmly attached to the substrate[4] to ensure mechanical stability and good surface contact for heat removal, which is commonly achieved by water cooling of the support plate (helium gas cooling can also be used).

The target material can be an element (metal) or a compound. Generally, metallic targets are preferable to compounds because they are of higher density and have higher thermal conductivity (and can therefore be irradiated at a higher beam power). Technetium has been produced from molybdenum metal (foils, fibres) as well as molybdenum trioxide targets [40–43]. Target fabrication methods are currently under investigation. The most likely method would involve some type of sintering of molybdenum metal powder.

5.2.2. Recycling of target materials

Recycling of the ^{100}Mo target material is essential because of its high cost. After processing, the residual ^{100}Mo will be mixed with the ^{99}Mo that was not removed during chemical processing. This material will have to be stored until the level of ^{99}Mo and other co-produced radioactive species decay sufficiently to allow for handling. Additionally, the other co-produced isotopes such as ^{95}Nb can contaminate the ^{99}Mo produced in the next cycle. The level of contamination is related to the level of other molybdenum isotopes present in the original enrichment of ^{100}Mo. For example, ^{95}Nb is predominately formed from the ^{98}Mo(p,α) reaction and thus the amount of ^{98}Mo in the ^{100}Mo target material will be reflected as a final contaminant in the recycled ^{100}Mo. The separation of molybdenum and niobium is possible but such chemical separation steps can result in the loss of ^{100}Mo.

A process will need to be developed to recover the ^{100}Mo in a physical state suitable for new target preparation (i.e., metal powder). This process will probably need to be carried out in a facility able to handle radioactive waste. Similar processes are already in place for the production of other radionuclides used in nuclear medicine such as the ^{203}Tl(p,3n)^{201}Pb → ^{201}Tl reaction system.

5.2.3. Waste

The production cycle produces very little process waste. No fission product waste is present and because the bulk of Mo target material is recovered for recycling into targets, there would be very little radioactive waste generated from routine production. However, the flux of high energy neutrons generated during ^{99}Mo production will activate surrounding components and facility walls.

5.2.4. Regulatory issues

The primary regulatory issue for this production method is associated with the generator system for the delivery of the ^{99m}Tc: The specific activity of ^{99}Mo is too low for use in existing commercial generator systems that use alumina columns. The existing columns are designed to capture multiple curies (gigabecquerels) of ^{99}Mo with a specific activity of greater than 5000 Ci/g (185 000 GBq/g). The ^{99}Mo produced by the above method yields a specific activity of less than 10 Ci/g (370 GBq/g). A number of alternative generator systems have been proposed, but none is proven to routinely deliver ^{99m}Tc of specific purity and also allow recycling of ^{100}Mo. Thus, there are health and safety related issues as well as nuclear safety issues that must be addressed. These issues include the impact on the quality of the ^{99m}Tc as produced by this method (breakthrough of the ^{99}Mo from a different generator

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[4] This may be generally true but is not true for the NorthStar target material. The sintered metal disks need no support; they are loosely held in a frame to keep the spacing between the thin disks constant to allow cooling by a stream of pressurized He gas.

system) and the challenges of moving significant quantities of ^{100}Mo contaminated with ^{99}Mo from the site of use back to the production site. Any new generator would be considered as a new drug that would need approval from regulators (i.e. a market authorization or new drug application).

5.3. NEUTRON INDUCED PROCESS ^{100}Mo(n,2n)^{99}Mo [44]

This process is a variation of the process discussed above in that the target and product will be essentially the same. The neutrons used for the production of ^{99}Mo are derived by the D(T,n) reaction yielding neutrons of 14 MeV. The proposed (n,2n) reaction has a cross-section of approximately 1.5 b in this energy range. The major challenge for this approach will be in producing sufficient flux of neutrons to be viable.

5.3.1. Target materials

Please refer to the discussion in Section 5.2.1 of this report.

5.3.2. Recycling of target materials

Recycling of the ^{100}Mo target material is essential because of its high cost. After processing, the residual ^{100}Mo will be mixed with the ^{99}Mo that was not removed during chemical processing. This material will have to be stored until the level of ^{99}Mo and other co-produced radioactive species decay sufficiently to allow for handling.

A process will need to be developed to recover the ^{100}Mo in a physical state suitable for new target preparation (i.e. metal powder). This process will probably need to be carried out in a facility able to handle radioactive wastes.

5.3.3. Waste

Please refer to the discussion in Section 5.2.3 of this report.

5.3.4. Regulatory issues

Please refer to the discussion in Section 5.2.4 of this report.

5.4. DIRECT PRODUCTION OF ^{99m}Tc USING PROTON ACCELERATORS

Beaver and Hupf first reported the feasibility of producing ^{99m}Tc by proton irradiation of ^{100}Mo via the (p,2n) reaction (Fig. 2), with theoretical yields of 15 Ci/h (555 GBq/h) using 22 MeV protons at 455 μA [45]. More recently, Scholten and colleagues demonstrated that a peak cross-section of 200 mb achieved at approximately 17 MeV, with a peak production of 102.8 mCi/μA (3.80 GBq/μA) at saturation. They suggested that the use of a >17 MeV cyclotron could be considered for regional production of ^{99m}Tc [46]. Takacs et al. found a peak cross-section of 211 ± 33 mb at 15.7 MeV [47]. Higher energy cyclotrons can produce a higher total yield of ^{99m}Tc because the protons can more deeply penetrate the targets [48, 49].

The direct production of ^{99m}Tc from proton irradiation of ^{100}Mo via the (p, 2n) reaction (Fig. 2) has also been performed using natural and enriched ^{100}Mo metal foils. Using ^{100}Mo at an enrichment of 97.46% (^{100}Mo is now available at greater than 99.5% enrichment), Lagunas-Solar obtained greater than 99.99% radionuclidic purity at the end of processing in his experiments [48]. According to these authors, however, robust systems have not been reported in the literature for plating and recovering ^{100}Mo from a solid support to create reusable targets at low cost while maximizing ^{100}Mo recovery.

^{99}Mo is co-produced directly during the production of ^{99m}Tc via the ^{100}Mo(p,pn) reaction. However, such production requires higher energy cyclotrons and offers much lower yields than direct ^{99m}Tc production [46, 48].

The yield and expected radionuclidic impurities of proton reactions on selected isotopes of Mo have recently been presented along with the measured quantities of $^{99m/g}$Tc co-produced. As an example, Table 3 lists sample isotopic compositions of ^{100}Mo that are commercially available. The supply and cost of enriched ^{100}Mo would need to be evaluated to determine the commercial feasibility of this production system.

5.4.1. Target materials

5.4.1.1. Electro-deposition/aqueous aolution

Electroplating of metals from aqueous solutions is a standard industrial process. There are unique characteristics associated with metallic coatings for use as targets for cyclotron bombardment that must be taken into account (see for example the IAEA's report on Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides (Technical Report Series No. 432)) .It is often the method of choice for target preparation because many metals can be deposited on target substrates as well adhering, uniform layers. Refractory metals such as molybdenum cannot easily be deposited from aqueous solutions due to their high affinity for oxygen [50]. However, Fink describes the electroplating of tungsten, thorium, aluminium and molybdenum from particular alkaline solutions [51]. His publication focuses mainly on tungsten plating, but the process could be applied for molybdenum as well. A similar method is described in Ref. [52]. Typically this approach results in a mixture of Mo metal and Mo oxide.

5.4.1.2. Non-aqueous solution

Ionic liquids have been developed as solvents for the electroplating of metals that cannot be deposited from aqueous media. Ionic liquids are purely ionic, salt-like materials, which are by definition liquid below 100ºC. They typically consist of organic cations, such as imidazolium, pyridinium, or pyrrolidinium, and an organic or inorganic anion (e.g. tosylate, alkyl sulphate, tetrafluoroborate). Ionic liquids are thermally and electrochemically stable. About 300 ionic liquids are commercially available. While thick coats can be achieved, the high temperatures and water sensitive molybdenum salts require significantly more complex and specialized equipment [53, 54].

Recently, a description of a successful means for electroplating Mo metal has been published [55]. However the thickness of this plate is generally not sufficient to be used in the preparation of thick targets.

5.4.1.3. Metal foils

^{100}Mo is currently available in foil form up to enrichments of >97% to 99%. For high current targets (500 µA), the estimated amount of molybdenum needed is 1g; lower current targets can probably be designed with as little as 100 mg of foil with proper backing material. Unused foils could be sent back after decay for recycling and repurification, preferably to a central processing facility for scaling economy.

5.4.2. ^{99m}Tc pertechnetate yields and purity

The major radioisotope produced as a contaminant for the ^{100}Mo(p,2n) reaction is ^{99g}Tc. As shown in Table 3, the only other significant Mo isotope present in the target material is ^{98}Mo, which can lead to the production of ^{98}Tc

TABLE 3. TYPICAL CERTIFICATES OF ANALYSIS FOR >97% ^{100}Mo[a,b]

Isotope	92	94	95	96	97	98	100
%	0.005	0.005	0.005	0.005	0.01	2.58	97.39
%	0.06	0.03	0.04	0.05	0.08	0.47	99.27

[a] For example, as found on the web sites of Trace Sciences (http://www.tracesciences.com/) and Isoflex (http://www.isoflex.com/).

[b] It should be noted that the enrichment of ^{100}Mo determines the relative yield, while the percentage abundances of the lighter molybdenum isotopes reflects the isotopic purity of the ^{99m}Tc.

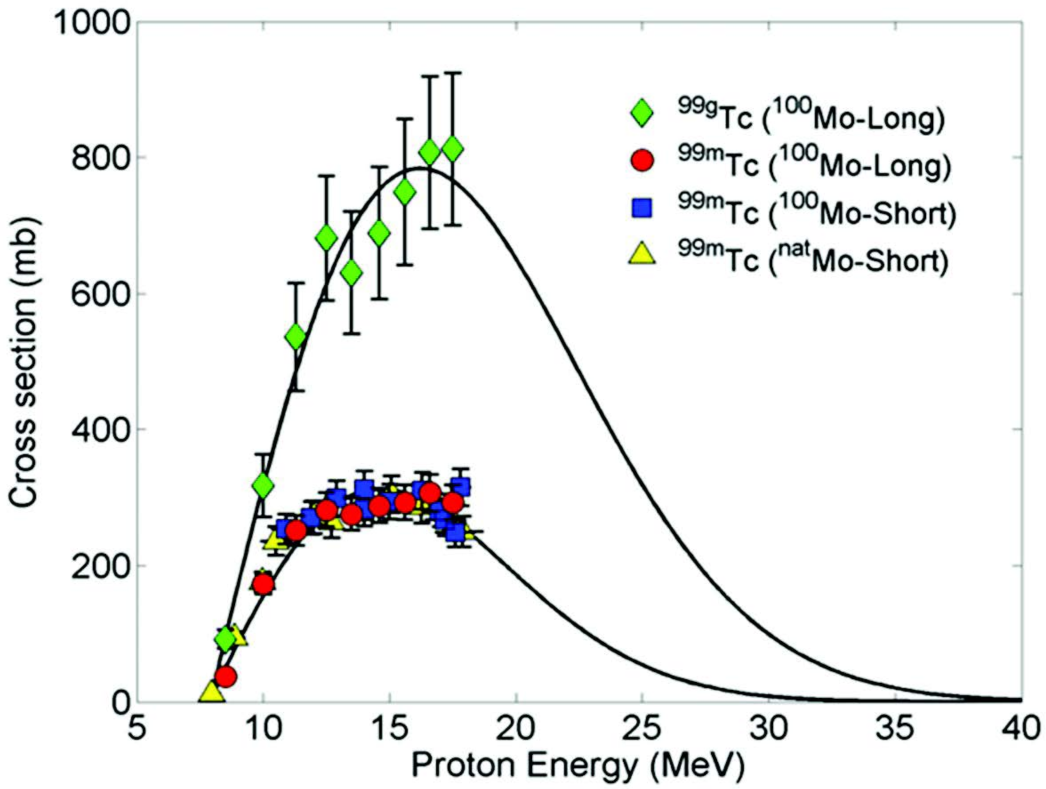

FIG. 10. Experimental excitation function for the ^{100}Mo(p,2n)^{99g}Tc and ^{100}Mo(p,2n)^{99m}Tc reactions. The 'Short' designation refers to irradiations of 1 μA for 600 seconds while the 'Long' indicates irradiations lasting 10 hours at 20 μA. The ^{100}Mo had an enrichment of 97.5% while natural Mo was of natural composition — enrichment of ^{100}Mo=9.63%. [58].

and ^{97}Tc through (p,n) and (p,2n) reactions [48, 56]. Although both of these radioisotopes are long lived (2.6 and 4.2 million year half-lives, respectively), they contribute little to the activity in a ^{99m}Tc batch (and therefore little to patient dose) or the total mass of the Tc (thus lowering its specific activity) because their production rate is orders of magnitude lower than that for ^{99m}Tc.

Using 99.5% enriched ^{100}Mo produces very pure ^{99m}Tc. The major contaminants include ^{99g}Tc and ^{99}Mo. Trace amounts of ^{95}Nb are produced from the ^{98}Mo(p,α) reaction, the amount being dependent upon the amount of ^{98}Mo present in the target material. With a 19 MeV proton beam irradiating for 6 hours at 200 μA the ^{99m}Tc produced represents 99.6% of the total technetium radioactivity at end-of-bombardment (with the proviso that all of the long lived species such as $^{97,\,98,\,99g}$Tc are considered stable) [57]. The major radioactive contaminants are ^{96}Tc and ^{95}Tc, each accounting for less than 2 mCi (0.07 GBq).

In terms of trace metal contaminants, the major concern will be with respect to metal ions that could interfere with Tc labelling of radiopharmaceuticals. The metals present in the target material that act as contaminants include baluminium, iron and tungsten, all of which are trace elements in the Mo target material. The quantities of impurities are in the order of ppm as indicated on the certificate of analysis[5] from the vendor.

As a means of determining the amount of ^{99g}Tc produced by direct production from the ^{100}Mo(p,2n) reaction, it has been measured directly by liquid scintillation which will be cross calibrated via ICP-MS. Results are shown in Fig. 10 [58] and Table 4.

Table 5 shows calculated ^{99m}Tc yields for various proton energies, beam currents and irradiation times. Based on the half-life of ^{99m}Tc and the predicted yields for production at various energies, the direct production route is viewed as small scale.

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[5] A certificate of analysis is a factsheet from the supplier indicating the chemical content of all materials present as determined by chemical analysis. It is considered an official document of purity.

TABLE 4. EXPECTED MASS RATIO OF THE META-STABLE TO GROUND STATE OF ^{99m}Tc UNDER DIFFERENT IRRADIATION CONDITIONS

Energy (loss in target) MeV Ein → Eout	1 hour irradiation		3 hour irradiation		6 hour irradiation	
	Ratio (%)	99mTc yield (MBq/μA)	Ratio (%)	99mTc yield (MBq/μA)	Ratio (%)	99mTc yield (MBq/μA)
18 → 10	28	543	25	1458	21	2490
20 → 10	26	661	24	1774	20	3029
22 → 10	25	747	23	2006	19	3425
24 → 10	24	804	22	2158	19	3685

TABLE 5. ESTIMATED PRODUCTION YIELDS FOR ^{99m}Tc BASED ON MEASURED CROSS–SECTION DATA [58].

Cyclotron	Energy (MeV)	Current (mA)	Irradiation time (h)	Theoretical activity at EOB (Ci)
CP42	18	0.2	3	7.6
	18	0.2	6	13
	18	0.2	12	19.5
	22	0.2	3	9.8
	22	0.2	6	16.7
	22	0.2	12	25.0
TR19	18	0.2	3	7.6
	18	0.2	6	13
	18	0.2	12	19.5
	18	0.5	3	19.1
	18	0.5	6	32.5
	18	0.5	12	48.8
GE PET trace	16.5	0.08	3	2.4
	16.5	0.08	6	4.2
	16.5	0.08	12	6.3
	16.5	0.16	3	4.9
	16.5	0.16	6	8.4
	16.5	0.16	12	12.5

Note: Thick target yields are for the proton energy range from beam on target down to 10 MEV where the excitation function is too low to provide any additional product. The energy bite defines the stopping power (areal density) of the target material.

5.4.3. Waste

This production scheme produces very little waste when the bulk of Mo target material is recovered for recycling. As with any accelerator production facility there will be activation of beam line components and target holders. While the concrete shielding walls will become radioactive, this can be minimized by using low sodium content concrete which is standard for constructing such facilities. The above bulk waste is generally low level while the components directly hit by the proton beam will be high level but generally small in volume.

5.4.4. Regulatory issues

In the direct production and distribution of ^{99m}Tc, a new product or process that will need approval from the health agencies (market authorization) and each manufacturing site should be GMP compliant (similar to PET cyclotron centres for commercial distribution). Labelling the efficiency of each cold kit with the new ^{99m}Tc solution will require validation, at least internal validation from the technetium supplier or external validation with health agencies.

The use of recycled ^{100}Mo should also be validated and the purity level of the ^{99m}Tc produced with the recycled Mo target checked with quality procedures.

6. ^{99}Mo/^{99m}Tc GENERATOR SYSTEMS AND CHEMISTRY

6.1. HIGH SPECIFIC ACTIVITY (FISSION PRODUCT) GENERATORS

6.1.1. Principles of generator operation

A ^{99}Mo/^{99m}Tc generator, or ‘technetium generator’, is a device used to recover and concentrate technetium from ^{99}Mo. A conventional generator consists of an alumina (Al_2O_3) column about the size of a short pencil; associated tubing, valves and filters for extracting technetium; and lead shielding for radiation protection (see Fig. 11.)

The column is loaded with ^{99}Mo at the generator manufacturing facility before shipment to a hospital, radiopharmacy or clinic. The ^{99}Mo in the column decays to technetium with about a 66 hour half-life. About 88.6% of the ^{99}Mo decays to ^{99m}Tc; the remainder decays directly to ^{99}Tc. Technetium is extracted (eluted) by passing a saline solution through the column.

The half-life of ^{99}Mo is about 10 times longer than that of ^{99m}Tc. Approximately 50% of the steady state activity is reached within one ^{99m}Tc half-life and approximately 75% within two half-lives. Therefore, ^{99m}Tc can be

FIG. 11. External and cutaway view of LMI’s TechneLite® ^{99}Mo/^{99m}Tc generator. Photos used with permission from Lantheus Medical Imaging, Inc. All rights reserved.

eluted from the generator to obtain patient dose quantities as often as every 6 hours. The useful life of a generator is between three and five times the half-life of ^{99}Mo (i.e. 8–14 days). As a consequence, generator users typically purchase at least one generator per week, or order several on a staggered basis throughout the week.

The elution efficiency is an important factor when evaluating the performance of various sorbent materials in ^{99}Mo/^{99m}Tc generator systems. All practical generator designs exhibit good elution efficiency. Additionally, all ^{99m}Tc generator systems, regardless of type, must be manufactured to the requirements of an established GMP programme.

6.1.2. Chemistry of alumina column based generator and technetium cows

Most commercial ^{99}Mo/^{99m}Tc generators use column chromatography, in which ^{99}Mo in the form of molybdate (MoO_4^{2-}) is adsorbed onto acidified alumina (Al_2O_3). A typical column contains 2–3 g of alumina (Fig. 11). When the ^{99}Mo decays it forms pertechnetate (TcO_4^-), which because of its single charge is less tightly bound to the alumina. Passing a normal (0.9%) saline solution through the column elutes sodium pertechnetate. The sodium pertechnetate can then be added in an appropriate concentration to the organ specific pharmaceutical or can be used directly for specific procedures.

The two most important factors for the design of an alumina column based ^{99m}Tc recovery system are high elution efficiency (typically 85%) and minimal Mo breakthrough. Fission product based technetium generators manufactured in the USA are commercially available in activity ranges of 1–18 Ci (37–666 GBq) at the manufacturer's stated time of calibration[6].

Uzbekistan currently uses enriched ^{98}Mo oxide targets to produce (n, γ) ^{99}Mo for use in standard size alumina column generators. POLATOM is supplying the materials necessary for Uzbekistan to manufacture their own line of low specific activity alumina column ^{99}Mo/^{99m}Tc generators. A typical alumina column supplied by POLATOM to Uzbekistan is shown in Fig. 12.

IPEN routinely manufacturers about 320 alumina column generators weekly to meet Brazil's domestic need. The activity of the generators range from 250 mCi to 2 Ci (9.25–74 GBq). The fission product ^{99}Mo used in these generators is imported from Argentina, Canada and South Africa [59]. The sodium molybdate supplied to IPEN by both Argentina and South Africa is produced from LEU. A typical ^{99}Mo/^{99m}Tc generator manufactured by IPEN is shown in Fig. 13.

CNEA LEU based ^{99}Mo production satisfies the Argentine national demand, which is approximately 200 Ci (7400 GBq) (calibrated to 3 days). ^{99}Mo/^{99m}Tc generators are manufactured by two private Argentine companies. The size of the generators range from 500 mCi to 2 Ci (18.5–74 GBq). CNEA exports LEU based ^{99}Mo to Latin America, including neighbouring Brazil.

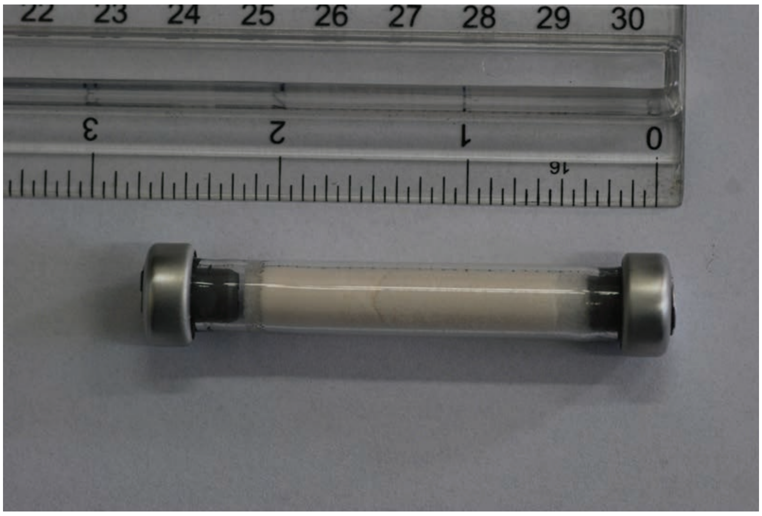

FIG. 12. Typical alumina column manufactured by POLATOM.

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[6] Designated on the paperwork by the manufacturer.

FIG. 13. ^{99}*Mo/*^{99m}*Tc generator manufactured by IPEN.*

6.2. LOW SPECIFIC ACTIVITY ^{99}Mo/^{99m}Tc RECOVERY METHODS

6.2.1. Chemistry

As a point of reference, the production of ^{99}Mo from thermal neutron induced fission of ^{235}U typically generates material with a specific activity greater than 5000 Ci/g (>185,000 GBq/g). This level of specific activity permits the extraction of the ^{99m}Tc daughter nuclide using adsorption chromatography, which exploits the relative immobility of the MoO_4^{2-} anion relative to the TcO_4^- anion on alumina. Modern Tc generators contain alumina columns loaded with ^{99}Mo. These columns are washed (eluted) with saline solutions to obtain ^{99m}Tc.

Production of ^{99}Mo from photonuclear or proton reactions on enriched Mo targets produces material with a lower specific activity. Extraction of ^{99m}Tc from this material requires larger volumes of alumina to accommodate the non-activated molybdenum. This results in high elution volumes and ultimately low Tc concentrations, too low for radiopharmaceutical production [60–64].

Alternative methods for the extraction of ^{99m}Tc from enriched molybdenum target material have been reported and reviewed [45, 65]. These methods fall into three general categories: (a) *adsorption chromatography* (as discussed above but with Mo being incorporated into the support material rather than being adsorbed on it (zirconium or titanium molybdate gels) or columns where Tc is sorbed on the column material and Mo passes through unadsorbed, (b) *liquid–liquid extraction* and (c) *sublimation*.

Tc isolation via sublimation, or thermochromatographic separation, involves heating irradiated Mo followed by recovery of the technetium activity from various adsorption zones within the cooling apparatus. $NaTcO_4$ is isolated by rinsing the apparatus with a hot 0.1 mM NaOH solution followed by purification on alumina. Conventional heating of a MoO_3 target was reported to yield ~70% of the Tc in the sample in approximately 20 min [66, 67], which is not quite as efficient as adsorption based generators which typically yield ^{99m}Tc at 85% efficiency. The radiochemical purity of Tc isolated using sublimation is typically >99% and Mo breakthrough is below detectable limits [65]. Bigott et al. reported an improved method that combines purification and concentration into one step, thereby decreasing the amount of time needed to complete the process [67].

6.2.2. Liquid–liquid generator concept

Liquid–liquid extraction begins with the dissolution of solid molybdenum target material in an acidic medium (HCl, H_2O_2 mixture), which transforms Mo into a cationic species (MoO_2^{2+}) and Tc into TcO_4 by the addition of ammonia. Ammonium pertechnetate can be extracted from the aqueous solution of ammonium molybdate by methyl ethyl ketone (MEK) as ammonium pertechnetate [43, 68]. Once the MEK is evaporated, the ammonium pertechnetate can be dissolved in saline solution.

MoO_3 targets, on the other hand, necessitate the use of a different method. MoO_3 is dissolved in ammonia and dissolved in 30% H_2O_2. The Tc is then extracted into MEK as discussed in the previous paragraph. Radiochemical yields of 60% have been reported with overall isolation times of approximately 1 hour [42, 69].

In either case, sodium hydroxide can be used instead of ammonia to increase the pH of the solution. Below is a more detailed description of a specific MEK generator system.

A standard approach to separating ions is through liquid–liquid extraction where there is a polar and non-polar solvent and the ions to be separated have a different affinity for the two solvents. The degree of separation is directly related to the solubility of the different ionic species in the respective solvents. For separating molybdenum and technetium ions a mixture of methyl ethyl ketone 1% aqueous hydrogen peroxide added to the NaOH/^{99}Mo solution is used.

The Mo is dissolved in 5.0 N NaOH and transferred via vacuum to an extraction reservoir (ER). Sufficient 5.0 N NaOH solution is used to wash the transfer vessel and lines and fill the ER to the extraction volume. The extraction volume is specific for each unit and is determined by the placement of the extraction tube located approximately midway in the ER.

The extraction cycle consists of adding a mixture of methyl ethyl ketone 1% aqueous hydrogen peroxide to the NaOH/^{99}Mo solution and mechanically stirring the ER contents to selectively remove the ^{99m}Tc from the aqueous layer into the organic layer. Hydrogen peroxide is added to keep the ^{99}Mo and ^{99m}Tc in the appropriate oxidation state. After the suspension is allowed to separate, the upper MEK layer is removed by vacuum draw and transferred to a 20 mL syringe filled with acidic alumina (~15 mL). The MEK–^{99m}Tc solution is passed through the alumina column to remove any ^{99}Mo that may be transferred with the MEK solution. Since the hydrogen peroxide is added as an aqueous solution, there is a small increase in the aqueous volume after each MEK addition. However, this small aqueous volume that is removed with each MEK extraction thus inadvertently removes a small amount of ^{99}Mo that is trapped by the alumina column and lowers the overall amount of ^{99}Mo for future extractions.

The MEK–^{99m}Tc solution eluted through the alumina column is transferred to a stainless steel evaporation vessel (EV). The EV is heated to ~70 C and subjected to a slight vacuum to hasten evaporation of the MEK. After the MEK has been removed, sterile saline is added to the EV to dissolve the ^{99m}Tc. The sterile saline is then transferred through a sterilizing filter into a sterile vial for further processing into radiopharmaceuticals after appropriate QC (e.g. Mo, hydrogen peroxide, alumina and MEK breakthrough, pH). Several alternatives for liquid–liquid extraction of pertechnetate have also been reported [70–72].

6.2.3. Low cost/high efficiency wet extraction using an automated unit

An example of the adsorption column approach where technetium is adsorbed and Mo is not is detailed below. Recently, Chattopadhyay and co-workers reported a method to extract ^{99m}Tc from (n,γ) activated ^{98}Mo [73]. Using inexpensive and commercially available strong base anion exchange Dowex 1 × 8 resin (25 mg, 1 mm × 14 mm), the authors report the ability to selectively trap and separate [^{99m}Tc]TcO_4^- from a low specific activity Mo solution after transient equilibrium has been achieved. Na^{99m}TcO_4 wasn recovered from the Dowex 1 × 8 column using tetrabutylammonium bromide (TBAB) in CH_2Cl_2 and purified by immobilization on a neutral alumina column. This column was washed with water and Na^{99m}TcO_4 was isolated by flushing with physiological saline. Subsequent quality control revealed no significant levels of trace metal contaminants or organic components. Tc recovery yields of greater than 90% were demonstrated and radiochemical purity was consistently over 99%.

As with the liquid–liquid extraction, the Mo target containing Tc will be dissolved in 5M NaOH and passed through the Dowex 1 × 8 resin. The resin will be washed with saline and the Tc recovered using 0.2 mg/mL solution of TBAB. This eluate (containing the Mo) will be applied to a neutral alumina column, dried, flushed with water and the [$^{99m}TcO_4^-$] will be eluted from the column using 3–5 mL of physiological saline. This process can be easily automated.

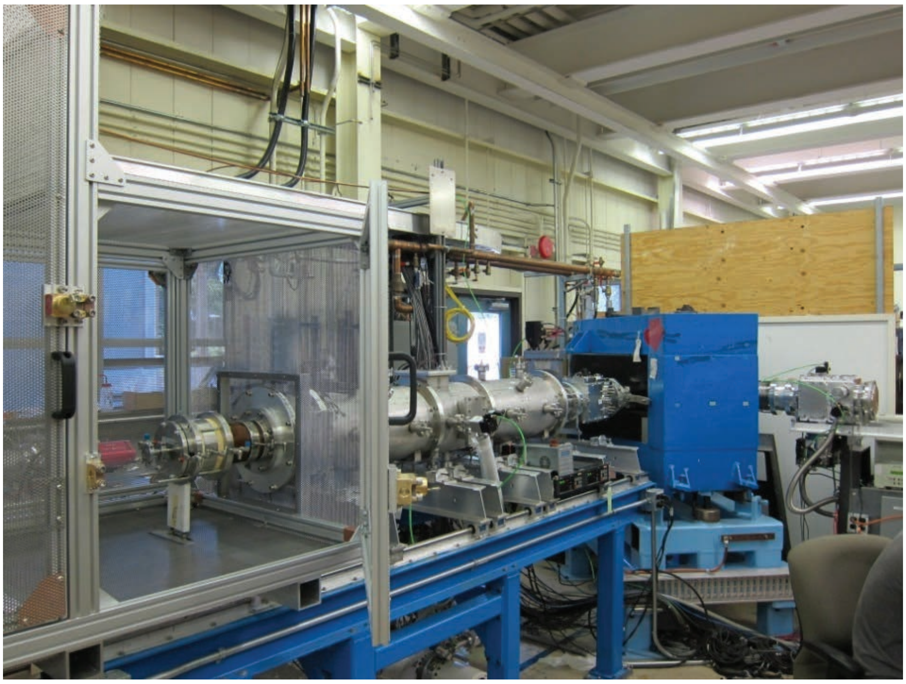

FIG. 14. Ion source test stand showing ion source in the Faraday cage on the left, the beam line with analysing elements, the blue analysing magnet and the collection Faraday cup on the far right. (Courtesy of Ruth, T., TRIUMF/AAPS).

6.2.4. Post-production isotopic separation [74, 75]

The use of a high throughput, high efficiency, rapid off-line isotope separators to extract ^{99}Mo of high specific activity that had been produced via ^{98}Mo(n,γ) and/or ^{100}Mo(γ,n) routes would allow for introduction of the ^{99}Mo into existing supply chains.

A high power ion source coupled to a high resolution dipole magnet would be used to generate beams of molybdenum ions and separate the respective isotopes with the aim of producing ^{99}Mo with a specific activity of greater than 1000 Ci/g (37 000 GBq/g). The feedstock for the separator system will be low specific activity ^{99}Mo generated from the thermal neutron capture of ^{98}Mo or the photon induced neutron emission of ^{100}Mo. This approach does not require HEU or LEU targets and could generate commercial quantities of ^{99}Mo suitable for use in existing commercial technetium generators.

Preliminary proof of principle experiments have demonstrated the capability for generating intense Mo ion beams. A test stand incorporating all of the elements of the separator system is underway with the expectation that a beam current and ionization efficiency can be achieved that will make it possible to use this device for producing commercial quality and quantities of ^{99}Mo. This test stand is shown in Fig. 14.

This separation system has several advantages: the ^{99}Mo produced can be directly used in existing commercial generators; there is no need for uranium targets and it can be used to generate the required target material (^{98}Mo/^{100}Mo) during the separation process. In addition, the system can be used in conjunction with neutron or photon sources to create a distributed delivery system.

Each separator is designed to handle approximately 100 6 day curies (gigabecquerels) per week. A cluster of separators would be required to obtain regional supply and would be classified as a medium scale production capability.

6.2.4.1. Waste management

The waste associated with electromagnetic separators will depend on the efficiency of the ion source. The waste will be composed of whatever ^{99}Mo does not get injected into the separator. There will inevitably be losses of ^{99}Mo in the separator system and in the collection process itself. Nevertheless, the only radioactive contaminants associated with this process are ^{99}Mo and the ^{99g}Tc that grows in from the decay of ^{99}Mo, either in storage or in situ with the separator.

As with any accelerator production facility there will be activation of beam line components and target holders. While the concrete shielding walls will become radioactive, this can be minimized by using low sodium content concrete which is standard in constructing such facilities. The above bulk waste is generally low level while the components directly hit by the proton beam will be high level but generally small in volume.

6.2.4.2. Regulatory issues

The goal of this approach is to prepare ^{99}Mo with chemical, radionuclide and specific activity specifications that are equivalent to ^{235}U fission. There should be no significant challenges to regulatory approval if such specifications can be achieved.

6.2.4.3. Stable isotopes

The phototransformation and direct production routes require high purity enriched ^{100}Mo as target materials. The proponents of the separator project have proposed using their device for the production of ^{100}Mo (and ^{98}Mo).

6.2.5. Solvent extraction

Solvent extraction technology is the most common method for separating ^{99m}Tc from low specific activity ^{99}Mo. Generators based on MEK extraction of TcO_4^- from alkaline aqueous molybdate solutions have been widely used for the production of ^{99m}Tc [76]. The solvent extraction method can produce, under well controlled conditions, ^{99m}Tc of high purity comparable to that obtained from a high specific activity alumina column generator. This extraction method is used routinely in India, Peru and the Russian Federation.

^{99m}Tc can be eluted from a zirconium/titanium molybdate gel type generator column (so called solid solvent extraction) using a volatile solvent such as acetone. As reported in Ref. [77], a ^{99m}Tc elution yield of 80% has been achieved by acetone extraction of ^{99m}Tc from a titanium molybdate gel column, followed by evaporation of acetone and recovery of the pertechnetate with saline. India routinely produces a limited number of gel generators and supplies. Kazakhstan also produces gel generators.

6.2.6. Sublimation extraction

A process has also been developed to extract and recover ^{99m}Tc through sublimation using a sublimation process. An irradiated Mo oxide target or Mo metal target (the latter after dissolution and calcining to MoO_3) is heated in a furnace in a stream of oxygen between 600°C and 750°C. The Tc sublimes to Tc_2O_7 [78– 80]. NorthStar Medical Radioisotopes, LLC has an exclusive licence from INL for this technetium recovery technology. Additional information about this technology is provided in section 3.6 and annex IV of Ref. [96].

6.2.7. Post-elution concentrator

Some of the processes described above produce lower than required concentrations of ^{99m}Tc. In principle, there is no impediment to in-line concentration of low activity concentration ^{99m}Tc solutions using simple post-elution concentration technologies. Methods for effective concentration of saline generator eluents have in fact been widely used in clinical practice to obtain ^{188}Re from the ^{188}W/^{188}Re generator system [81, 82]. The specific activity of reactor produced ^{188}W is low (<8–10 Ci (296–370 GBq) ^{188}W/g ^{186}W target material) and requires large (high mass) generators.

In a $^{188}W/^{188}Re$ generator system, a normal saline eluent is first passed through a small silver nitrate impregnated column which traps the chloride anion converting the solution to a nitrate media and allowing perrhenate to be loaded onto a second (anion exchange column). The perrhenate can be subsequently stripped from this column with a small volume of normal saline, making it ready for 'kit' radiolabelling. The concentration factors in this technique can be as high as 10–20. Many generator prototypes using this concept of post-elution dual column purification/concentration have been reported [83].

Another dual column purification/concentration process was developed recently to separate ^{99m}Tc from the low specific activity ^{99}Mo based on pertechnetate ion selective columns. A special generator system based on this process has been developed (see Fig. 15). An alkaline Mo solution is fed into a column specifically designed to adsorb pertechnetate. Once the column is loaded, it is washed to remove any absorbed molybdate. Following the wash, technetium is stripped from the column with normal saline solution, which is passed through an alumina guard column to remove any impurities (primarily Mo). The eluate is then passed through dual 0.22 μm sterility filters [30, 31].

A single column process for purification/concentration of dilute solutions of ^{99m}Tc was developed a long time ago [84] but has been improved recently by automated operation [85]. This process is based on the selective adsorption of ^{99m}Tc eluted from a ^{99}Mo column onto a significantly smaller sorbent column. In the following step the technetium is stripped from the column with a small volume of saline solution suitable for injection. Optionally, the sorbent column can be washed prior to stripping. The automated purification/concentration unit coupled radionuclide generator shown in Fig. 16 is a versatile system which can be used for the production, for example, of ^{99m}Tc, ^{188}Re, ^{90}Y and ^{68}Ga, producing solutions of high radioactive concentration.

6.3. LOW SPECIFIC ACTIVITY GENERATOR TYPES

6.3.1. Technetium selective separation system

A new generator system based on technetium selective separation (aqueous biphasic extraction chromatographic, or ABEC) has been developed [86, 87] that can be used with low specific activity ^{99}Mo (Fig. 15). The technetium is eluted from the ABEC column using normal saline and is passed through an alumina guard column. The volume activity of ^{99m}Tc produced by this system is comparable to that of an alumina column generator loaded with fission product (i.e. high specific activity) ^{99}Mo. This new generator system is currently in

FIG. 15. Newly developed automated chemical separation unit (TechneGen) from NorthStar Medical Radioisotopes, LLC.

FIG. 16. Automated chemical separation unit (ARSII) developed by NorthStar Medical Radioisotopes.

the process of being validated for nuclear pharmacy use through a new drug application on file with the US Food and Drug Administration.

A commercial system based on technetium selective separation is the commercially available Automated Radionuclide Separator (ARSII) chemical separation unit [88–90]. This system was developed by NorthStar Medical Radioisotopes and is the predecessor system to the TechneGen device shown in Fig. 15. The ARSII unit (Fig. 16) is being used in a clinical trial involving other radioisotopes [91, 92].

6.3.2. Jumbo alumina column generator

Researchers at BRIT have developed a means for using low specific activity ^{99}Mo (0.2–0.4 Ci/g or 7.5–15 GBq/g) ^{99}Mo in a large (jumbo) alumina column generator. They have developed a simple procedure for the concentration of ^{99m}Tc eluates using a small Dowex 1 column for trapping $[^{99m}TcO_4]^-$. The primary column contains 60 g of alumina [84].

6.3.3. Gel moly generator

The concept for the ^{99m}Tc chromatographic gel generator was developed by Evans et al. [93] in the mid-1980s. The technical maturity of this gel based system has advanced significantly since then. Recent advances in radiopharmaceutical diagnostic applications (e.g. ^{99m}Tc sestamibi for myocardial perfusion studies) require pertechnetate of moderate to high ^{99m}Tc activity concentration. A gel moly generator, which is used exclusively with low specific activity ^{99}Mo, can provide the necessary post-elution ^{99m}Tc activity concentration. Typically if a gel generator is prepared using (n, γ) ^{99}Mo alone, its strength is ~270 mCi (10 GBq) /generator and upon elution with 10 mL saline, it will give ^{99m}Tc at ~20 mCi/mL (0.74 GBq). Post-elution concentration can provide ^{99m}Tc at ~100–140 mCi/mL (3.7–5.2 GBq/mL) (typically 5–7 times concentrated).

Loading low specific activity ^{99}Mo in a traditional alumina column technetium generator requires a large alumina column. This is because the capacity of alumina to adsorb Mo is limited (~20 mg Mo/g of alumina). Large eluent volumes are required to obtain patient dose quantities of ^{99m}Tc from these columns. These eluent volumes contain unacceptably low concentrations of pertechnetate for most radiopharmaceutical diagnostic procedures. A post-elution concentration column is required to increase the activity concentration.

In 1999, it was reported that low specific activity gel moly generators were used to satisfy more than 30% of China's domestic ^{99m}Tc demand [16]. It has been demonstrated that ^{99m}Tc can be effectively eluted from a gel based recovery system in exactly the same manner and with identical quality to that obtained from a fission based technetium generator [94].

FIG. 17. The Geltech ^{99m}Tc generator, manufactured by BRIT, is a dual column system comprised of a primary zirconium molybdate ^{99}Mo gel column and a secondary purification acidic alumina column.

A gel moly generator contains ^{99}Mo in the form of an insoluble zirconium or titanium molybdate hydrous gel with a pH of 2–9.

The dried gel contains about 25% by weight of molybdenum and has the characteristics of a cation exchanger. The passage of an aqueous eluent (typically either purified water or normal saline) through a column of molybdate gel releases ^{99m}Tc. However, an additional mini-column of alumina is required to remove impurities (e.g. ^{99}Mo, Zr, Ti) in the eluate. A typical gel moly generator is shown in Fig. 17.

An example of a gel generator for low specific activity ^{99}Mo is the technetium generator system shown in Fig. 17, which can be used for the production of high specific activity solutions containing several radioisotopes (e.g. ^{99m}Tc, ^{188}Re, ^{90}Y and ^{68}Ga) [85, 95]. In the system developed for Mo/Tc separation, this device is based on the selective adsorption of ^{99m}Tc eluted from the ^{99}Mo column onto a significantly smaller sorbent column. In the following step, the technetium is stripped from the smaller column with a small volume of injectable saline solution. Optionally, this small sorbent column can be washed to remove any impurities that may have sorbed onto the column. Following the wash, the ^{99m}Tc nuclide is stripped from the column with a small volume of solution suitable for injection or for investigational purposes.

Elution of ^{99m}Tc from the generator followed by eluate purification/concentration is performed using a low cost automated bench top system [85]. This system was designed based on the timing sequence of seven processing steps without feedback control. The variable flow rate of eluents used for elution/purification also ensure the optimization of operating times with respect to the different adsorption/desorption kinetics of daughter radionuclide ion species, which is controlled by the sorbent and ion exchange resin used in the generator and the purification columns.

The conditions under which the zirconium or titanium molybdate is prepared will modify the cavity sizes in the gel, its diffusion properties and thus the generator's performance. Factors such as pH, the molar ratios of zirconium (or titanium) to molybdenum, solution concentrations, the order of reactive agent addition and the drying temperature of the final product must be properly controlled to consistently reproduce the properties of the gel.

As is the case for an alumina column recovery system, the radiochemical purity of ^{99m}Tc eluted from a gel moly generator can be impacted by radiolysis, changes in temperature or pH and the presence of reducing or oxidizing agents. Finished product quality control testing clearly demonstrates that the radiochemical purity is equivalent to that of the traditional alumina column technetium generator.

The most important characteristics of a high quality gel moly generator system are: (1) high elution efficiency and (2) minimal Mo breakthrough. These two characteristics can only be achieved when the gel has a uniform particle size. The gel can withstand thermal (wet steam) autoclaving; consequently, the generator can be provided to radiopharmacies as a terminally sterilized finished product.

A more comprehensive description of gel moly generator system types and other technetium recovery systems that use low specific activity ^{99}Mo is presented in Ref. [96].

6.3.4. High adsorption capacity column generator

Another form of generator takes advantage of the high capacity for molybdate ion on a new class of sorbents, such as polymeric oxides of zirconium (PZC) [77, 97–100] and titanium (PTC) [3, 77, 85].

Research is in progress at ANSTO [101] and in the Dalat Nuclear Research Institute (DNRI) on the use of PTC and/or PZC as sorbent materials for radionuclide generator column loading [77]. The high adsorption capacity of PTC and PZC sorbent for ^{99}Mo (270–275 mg Mo/g) makes it suitable for obtaining ^{99m}Tc in patient dose quantities with small columns and small eluate volumes. PZC/PTC sorbents (i.e. Nano-crystalline ZiSORB, TiSORB, ZT-11 and ZT-31), when modified by further physicochemical treatments, can be used for different radionuclide generator systems (e.g. ^{188}W).

A PZC/PTC based integrated radioisotope generator system is shown in Fig. 18 [102]. It consists of a PZC/PTC sorbent column (housed in a lead container in the lower part of the system, behind the green sign);

FIG. 18. The integrated radioisotope generator system, recently developed at MEDISOTEC and ANSTO, is a radionuclide generator system coupled with an automated purification/concentration unit [102].

FIG. 19. Covidien's kit for the preparation of ^{99m}Tc sestamibi injection.

a concentration/purification processing unit with a nuclide selective sorbent column (ZiSorb or ion exchange resin) and eluent vials (upper part of the system); and a programmable control unit (bottom right). The programmable electronic control unit allows the operator to specify the operating conditions for different integrated generator systems for producing different radioisotopes such as ^{68}Ga, ^{99m}Tc and ^{188}Re [102].

6.3.5. Technetium radiolabelling

Technetium-99m radiopharmaceuticals are typically formulated from radiolabelling kits prepared in manufacturing facilities that have an established GMP program. A cold kit contains: (1) the ligand to which ^{99m}Tc is to be complexed, (2) a quantity of reducing agent, (3) a buffer to adjust the pH to suit the labelling conditions and (4) stabilizing agents and excipients. The radiolabelling kits are prepared in a freeze dried state and have a shelf life ranging from several months to years depending on the specific kit. There are 23 different radiolabelling kits currently in use [103]. A typical cardiac perfusion imaging kit is shown in Fig. 19.

The compounding of ^{99m}Tc radiopharmaceuticals using radiolabelling kits in a hospital radiopharmacy is routine. It involves the addition of $[^{99m}TcO_4]^-$ eluted from a generator, usually at room temperature, but at times with heating.

The use of a chromatographic technique such as paper chromatography, ITLC, or HPLC is performed to determine the radiochemical purity of the final product before it is administered to patients.

7. TECHNOLOGY READINESS TABLES

7.1. REACTOR BASED TECHNOLOGIES

Tables 6–9 present the technology readiness levels (TRL) for reactor based technologies.

TABLE 6. TRLs[7] FOR QUALIFICATION OF LEU AND MOLYBDENUM TARGETS

(n, f) target material	TRL	Production scale applicability	Comments
LEU in the form of dispersion mix, oxide, or metal			
UAl_x (2.6– 3.0 gU/cc)	9	S, M, L[a]	• Targets currently manufactured by CERCA and CNEA; • Irradiated in Argentina, Australia, Egypt and South Africa.
U_3Si_2 (4.8 gU/cc)	6/7	S, M, L	• Qualified fuel type for material and test reactors; • Evaluated by the NRC [12].
U_3Si_2 (6.0 gU/cc)	6	S, M, L	• Capability to fabricate has been demonstrated by CERCA; • Not qualified as a fuel type for material and test reactors (U-Loading > fuel qualification limit of 4.8 gU/cc)
U foil (19.0 gU/cc)	8	S, M	• Targets for small scale productionfabricated on-site by BATAN; • CERCA produced prototype targets for ANSTO.
	5	L	• Targets not yet manufactured commercially; • Target qualification documentation does not yet exist; • Not yet irradiated to the burnup that is representative of a current major ^{99}Mo producer.
U nitride (7.0 gU/cc)	5/6	S, M, L	• Has been manufactured into mini-plates by CERCA; • No test irradiations performed to date.
U metal pellets/discs	8	S	• Targets have been fabricated using natural uranium and irradiated to produce ^{99}Mo at CINR from 1963 to 1980 [24];
U oxide pellets/powder	8	S. L	• Pellets once used as target material (2.2% enrichment) to produce ^{99}Mo at ANSTO; • Pellets used as target material (2.6% enrichment) to produce ^{99}Mo at JAERI in 1977; • AECL developed HEU oxide powder (MAPLE reactor targets); • Original Cintichem process used HEU oxide targets.

[a] *S = small, M = medium, L = large.*

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[7] The TRLs are defined in Appendix B.

TABLE 6. TRLs[7] FOR QUALIFICATION OF LEU AND MOLYBDENUM TARGETS (cont.)

(n, f) target material	TRL	Production scale applicability	Comments
LEU in the form of an aqueous solution (solution reactor fuel)			
Uranyl nitrate ($UO_2(NO_3)_2$	5	L[a]	• Several experimental solution (HEU) reactors have been operated for several minutes to several hours; not yet demonstrated at steady state operation for long periods of time.
Uranyl sulphate (UO_2SO_4)	4–5	L	• Solution reactor technology not yet demonstrated using LEU fuel.
Molybdenum-98 oxide (MoO_3)			
Natural abundance (~24%)	9	S	• Currently in use throughout the world (e.g. India, Kazakhstan, Vietnam).
Enriched >95%	9	S	• 97% enriched material used in Uzbekistan; • Available in limited/small quantities at present.
Molybdenum-98 Metal			
Natural abundance (~24%)	8	S	• Once used routinely prior to the advent of fission produced ^{99}Mo.
	4	M, L	• Demonstration trials in progress at MURR.
Enriched >95%	4	S	• Available in limited/small quantities at present.

[a] *S = small, M = medium, L = large.*

TABLE 7. TRLs FOR DISSOLUTION OF DISPERSION MIX, OXIDE AND METAL LEU TARGETS

	Dissolution Process							
Fission production target material	Conventional alkaline	Conventional acidic	LEU modified Cintichem	Alkaline w/ acidic front end	Alkaline w/ electrochemical front end	Alkaline w/ fluoride front end	Pyro-processing	Comments
UAl$_x$ (2.6–3.0 gU/cc)	9							Currently used by Argentina, Australia, Egypt and South Africa.
U$_3$Si$_2$ (4.8 gU/cc)						6		Demonstrated at Karlsruhe, Germany.
U$_3$Si$_2$ (6.0 gU/cc)						2		Not yet demonstrated to work with uranium loading of 6.0 gU/cc.
U foil (19.0 gU/cc)		4	8	4	3		x[a]	LEU Modified Cintichem process was developed to produce ^{99}Mo at small scale (BATAN); Cintichem used a similar process with HEU on a large scale.
U nitride (7.0 gU/cc)	2							
U metal pellets/discs		x	x	8	x		1	Alkaline with acidic front end used in the 1980s for dissolving irradiated natural uranium (NU) pellets for small scale moly production at CINR.
U oxide pellets/powder		8	x					Once used at ANSTO (2.2% enrichment); AECL developed a process for dissolving HEU oxide powder (MAPLE reactor targets); Cintichem process used HEU oxide targets.

[a] x = potentially applicable but untried process

TABLE 8. TRLs FOR DISSOLUTION OF LEU AQUEOUS SOLUTION TARGETS

	Dissolution process				
Solution reactor target material	^{99}Mo recovery	^{99}Mo purification (Cintichem)	^{99}Mo purification (conventional alkaline)	^{99}Mo purification (Kurchatov) process	Comments
$UO_2(NO_3)_2$	4	4	4	x	INVAP is developing this technology.
UO_2SO_4	x	x	x	4	Kurchatov demonstrated conventional acidic process for HEU.

TABLE 9. TRLs FOR DISSOLUTION, SEPARATION AND POST-ELUTION CONCENTRATION OF MOLYBDENUM TARGETS

		Target Material				
Process		Oxide (MoO_3)		Metal		Comments
		Natural	Enriched	Natural	Enriched	
Dissolution	Alkaline	9	9	3	3	
	Acidic	x	x	x	x	
	Peroxide			3	3	• See Ref. [41]
	Electrochemical			3	3	• See Ref. [40]
^{99m}Tc generator	Electrochemical	2				• See Ref. [104]
	Recoil	1	1	x		• Based on Delft Papers/patent using organometalic target compounds.
	Sublimation	8	x	x	x	• Performed in Australia and Hungary.
	$ZrMoO_4$ gel	9	9	x	x	• Performed in China, Kazakhstan, Uzbekistan and Vietnam.
	$TiMoO_4$ gel	2	x	x	x	• R&D in India and Vietnam.
	PZC	6	x	x	x	• R&D in Australia, Japan and Vietnam.
	PTC	3	x	x	x	• R&D in Australia, India and Vietnam.
	Ion exchange	4	x	4	4	• For natural MoO_3. Based on Ref. [105] and the agreed potential application of Northstar's development work.
	Solvent extraction	9	9	9	9	• Performed in Australia, India and Vietnam [106].
	Post-elution concentrators	6	6	6	6	• R&D in Australia, India, USA and Vietnam.

7.2. ACCELERATOR BASED TECHNOLOGIES

Tables 10–14 present the TRLs for accelarator based technologies. The levels are based on information supplied, on what has appeared in the literature as well as extrapolation from what has been achieved in other areas that can be directly applied to the present problem. For example, where one of the technologies produces ^{99}Mo via fission of ^{235}U, one can assume that the technology for isolating the ^{99}Mo from the LEU target mix would be identical to that being used in the reactor facilities. However, this does not mean that the proponents for the particular approach have the necessary skill sets to implement such approaches without the input from experienced partners that may include proprietary information. TRLs are defined in Appendix A.

No attempt has been made to determine the technology readiness of any particular proponent, since this will in all likelihood be a constantly changing metric as efforts move forward with greater or lesser efficiency throughout the world.

TABLE 10. PHOTONEUTRON, (γ,n), TRANSFORMATION OF ^{100}Mo
(classified as medium capacity for a single device)

Technology	TRL	Comment
Accelerator	6	Concept well established, requires development for high power
Targetry	3	Enriched target, development work needed
Processing	5	Prototype exists, in clinical trials for other radioisotopes
Production of ^{99m}Tc generators	5	See above
Waste management	4	Minimal waste, although tracking of ^{99g}Tc and non-moly isotopes required
Regulatory approval:		
— Nuclear	7	Extensive testing required
— Health	5	

The technology is rated overall as 4.

TABLE 11. DIRECT PRODUCTION OF ^{99m}Tc VIA ^{100}Mo(p,2n) REACTION
(classified as small capacity for a single device)

Technology	TRL	Comment
Accelerator	8–9	Use of existing cyclotrons; proposed new cyclotron not field tested
Targetry	4	Under development
Processing	4	Working at lab scale
Production of ^{99m}Tc generators	n/a	Not used; the ^{99m}Tc is distributed directly from the cyclotron centre
Waste management	4	Minimal, tracking of ^{99g}Tc required
Regulatory approval:		
— Nuclear	9	Cyclotrons have been reviewed by nuclear regulatory authorities for this process
— Health	5	Extensive testing required to validate the quality of ^{99m}Tc produced

The technology is rated overall as 5.

TABLE 12. HIGH ENERGY PROTON FISSION OF ^{238}U

(classified as large capacity for a single device)

Technology	TRL	Comment
Accelerator	2	CW high energy driver (200 MeV, 100 kW); ideas are well documented; theoretical calculations have been performed and are available. However, no confirmation is available regarding laboratory prototype testing which demonstrates proof of principle.
Targetry	2	Target composition is still being evaluated. Even if composition of the target will be similar to the standard LEU reactor fuel, there is no available report on laboratory prototype testing which demonstrates proof of principle of this concept.
Processing	4	Most of the U type materials have been tested in dissolution processes but not all are related to ^{99}Mo production. Therefore information is available but it may not be complete.
Production of ^{99m}Tc generators	9	Assuming that the processing of the U target is fully developed and the ^{99}Mo contamination profile and specific activity follows the current standard specification for fission ^{99}Mo, the current alumina based ^{99m}Tc generators can be used without any modification or licence change.
Waste management	2	Management of the processing waste streams may be known but has not yet been tested on the laboratory scale to demonstrate proof of principle for this type of ^{99}Mo technology.
Regulatory approval:		
— Nuclear	1	This technology is new for the regulators, since there is no operational device currently running. The regulatory approval process must first be developed and will be lengthy.
— Health	7–8	The ^{99}Mo contamination profile and specific activity follows the current standard specification for fission ^{99}Mo. The product would only need to be tested in three production runs to confirm the repeatability of final product quality. In some States the final product quality can be related to both nuclear isotopes: ^{99}Mo, Tc$^{99m}/^{99g}$Tc.

The technology is rated overall as 2.

TABLE 13. LOW ENERGY PRODUCTION OF NEUTRONS VIA (d,t) OR D(γ,n)H REACTIONS FOLLOWED BY FISSION USING LEU

(production capacity rating: medium — single device or a cluster of devices would meet national needs)

Technology	TRL	Comment
Accelerator		
(D,T)	3	Under development, prototypes exist
(γ,n)	6	Concept well established, requires development for high power
Targetry	6	Production targets for both methods exist but need development
	3	Would use LEU targets
Processing	5	Similar to existing fission process
Production of ^{99m}Tc generators	3	Product is expected to meet USP specifications and be of high specific activity so that it can be used directly in existing commercial generator systems
Waste management	3	Extensive, similar to existing fission process
Regulatory approval:		
— Nuclear	5	A representative model or prototype system has been tested (ARGUS). Regulatory concern will focus on the stated subcritical nature of the system and system design features which will assure that it will remain subcritical.
— Health	6	Product is expected to meet USP specifications based on ARGUS experience if these results can be confirmed.

The technology is rated overall as 4.

TABLE 14. POST-PRODUCTION ENRICHMENT OF ^{99}Mo VIA OFF-LINE ISOTOPE SEPARATOR
(classified as medium capacity for a single device)

Technology	TRL	Comment
Accelerator	4–5	Prototype exists
Targetry	n/a	Supplied from existing systems
Processing	4–5	Minimal changes to the chemical form of the collected material required
Production of ^{99m}Tc generators	9	Uses existing technology
Waste management	4	Minimal, track ^{99g}Tc
Regulatory approval:		
— Nuclear	4	Operation of separator with large quantities of radioactivity will require development of remote handling systems
— Health	8	Expected to be straightforward

The technology is rated overall as 5.

8. CONCLUSION

The information in this report, including Tables 6–14 and the cited references, gives an indication as to the TRL for each of the technical approaches described in the preceding sections. Determinations of TRLs were based on information supplied by technology developers, information available from the literature and also from extrapolations from other technologies. With respect to extrapolation, one can assume, for example, that processes for isolating ^{99}Mo from a uranium target will be similar regardless of whether the target was irradiated in a reactor or an accelerator. The TRLs shown in the tables are neither judgements nor endorsements of any particular technology developing organization.

Appendix A

TECHNOLOGY READINESS LEVELS (TRLs) AND THEIR DEFINITIONS

The following list describes the various technology readiness levels and descriptions from a systems approach for both hardware and software.

Technology readiness level (TRL) description

TRLs are used in private industry and in many government agencies to guide technology investment, development and deployment. Examples of several TRL systems used in various applications are provided in Refs [107–109]. The TRL definitions used in this report were tailored from Refs [108] and [109].

Industry recognized product development methodologies are used to some extent in all major industries. They are used to ensure that the technology required to deploy a product to market is consistent with the product's business development model. These methodologies provide a common language to describe the extent to which the product design is complete. They also provide a guide for the designers of a manufacturing or production process to follow, allowing them to focus only on the tasks defined for a given development level. This prevents superfluous studies that do not contribute to the advancement of the product's technology. Furthermore, it provides assurance that the product's business development model is both practical and economically viable. The rationale for TRLs is that they provide a metric for measuring technical maturity and communicating readiness of the product for each phase of a project. In summary, a technology readiness assessment simply establishes the 'maturity' of a specific technology.

Numerous studies performed in the USA for both private industry and the federal government have concluded that the insertion of immature technologies and/or immature manufacturing systems increases risk and cost and significantly decreases the likelihood of successful implementation.

For the purpose of this document, a TRA has been performed using established TRL requirements or milestones. Each non HEU ^{99}Mo production technology is evaluated against the TRL requirements. The established TRL scale ranges from 1 to 9 and is presented in Fig. 20. The TRLs progress from research and development activities to design validation in a production environment. The TRL assignment is a snapshot of where the maturity of the technology is at a given point of time. It should represent the highest level of TRL for which all the exit criteria are satisfied.

It should be noted that there is an associated methodology that defines manufacturing readiness levels [110]. A manufacturing readiness assessment is performed in conjunction with a TRA to make a final determination of the overall readiness level of a non HEU ^{99}Mo production technology. Manufacturing readiness assessment is a critical prerequisite of a project, but is beyond the scope of this report. A more comprehensive explanation of TRLs 1–9 is presented below.

TRL definitions and Exit Criteria

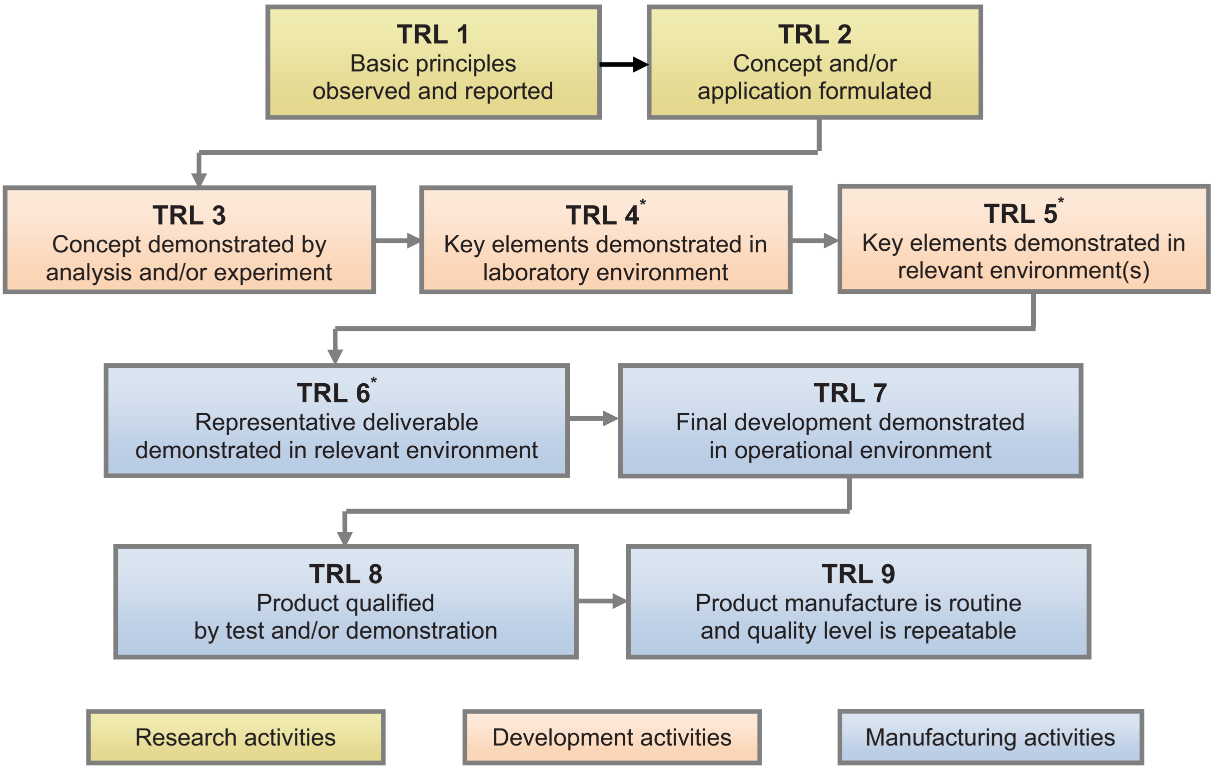
TRL 1 Lowest level of technology readiness. Scientific research begins to be translated into a concept for a technology.

Exit Criteria (1) A fundamental concept, innovation or scientific principle has been identified.

TRL 2 Practical applications are beginning to be identified or developed. There is no proof or detailed analysis to support assumptions. The step up from TRL 1 to TRL 2 moves the concept from pure to applied research. Experimental work is designed to corroborate the basic scientific observations made during TRL 1 work. The filing of a patent is under consideration.

Exit Criteria (1) Potential practical applications for this research and/or innovation are identified. An R&D plan has been developed.

TRL 3 Active research and development (experiments, simulations) is initiated to validate key elements of the technology. The results of this work should constitute proof of concept validation of the applications and concepts formulated at TRL 2. Examples include the study of separate elements of the technology that are not yet integrated or representative. At TRL 3 the work has moved beyond the paper phase to experimental work that verifies the concept as anticipated. Components of the technology are validated, but there is no attempt to integrate



** TRLs 4– 6 represent the bridge from scientific research to process design development.*

FIG. 20. TRL element identification and activity type.

the components into a complete system. Modelling and simulation may be used to complement physical experiments.

Exit Criteria (1) Key elements of the technology have been identified and proof of concept has been demonstrated for each. Individual elements are not necessarily integrated at this technology readiness level.

TRL 4 The key elements of the technology are integrated (i.e. elements will function together) in the laboratory. TRL 4 is the first step in determining whether the individual components will work together as a system.

Exit Criteria (1) A laboratory validation establishes that key elements function together; validation in a laboratory environment can be made with mock material and (2) performance metrics for the laboratory prototype have been defined and met.

TRL 5 Key elements of the technology are integrated with applicable supporting elements so that the system can be tested in a simulated or somewhat realistic environment. The major difference between TRL 4 and 5 is the increase in the fidelity of the system and environment to the actual application. The system tested is almost prototypical.

Exit Criteria (1) Validation in a simulated or somewhat realistic environment establishes that the key elements function together and (2) performance metrics have been defined and met.

TRL 6 A system or subsystem prototype is demonstrated in a high fidelity, simulated or actual environment. This represents a major step in a technology's demonstrated readiness.

Exit Criteria (1) A prototype has been created and successfully demonstrated in a high fidelity, simulated or actual environment and (2) the metrics for successful performance in an actual environment have been refined, met and documented. TRL 6 begins true engineering development of the technology as an operational system. The major difference between TRL 5 and 6 is the step up from laboratory scale to engineering scale and the determination of scaling factors that will enable design of the operating system.

TRL 7 Demonstration of an actual system prototype in an operational environment. In almost all cases, TRL 7 coincides with the end of development.

Exit Criteria (1) An actual system prototype has been demonstrated in an operational environment and (2) the metrics for successful performance in operational environments have been refined, met and documented.

TRL 8 The actual system has been proven to work in its final form under expected conditions based on certification and qualification activities to validate that it meets design requirements, product definition and quality requirements.

Exit Criteria (1) A manufacture system has been certified/qualified.

TRL 9 The system is implemented in its final form. The system is fully developed and currently operational. TRL 9 does not consider ongoing or planned product improvement, or scale up to larger production volumes.

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GLOSSARY

6 day curie (Ci) (gigabecquerels - GBq). The quantity of ^{99}Mo available for sale from an irradiated target is much less than the total quantity of ^{99}Mo produced in the target because of radioactive decay and process losses. Standard industry practice is to sell bulk ^{99}Mo on the basis of a calibrated ‘6 day curie,’ which is nominally the quantity of ^{99}Mo remaining 6 days after the ^{99}Mo leaves the producer’s facility. ^{99}Mo has a 65.94 hour half-life. To have one curie (37 gigabecquerels) remaining after six days of decay, a producer must ship 4.54 Ci (168 GBq). The production cycle of ^{99}Mo illustrating growth during irradiation followed by losses due to chemical processing and radioactive decay is presented below.

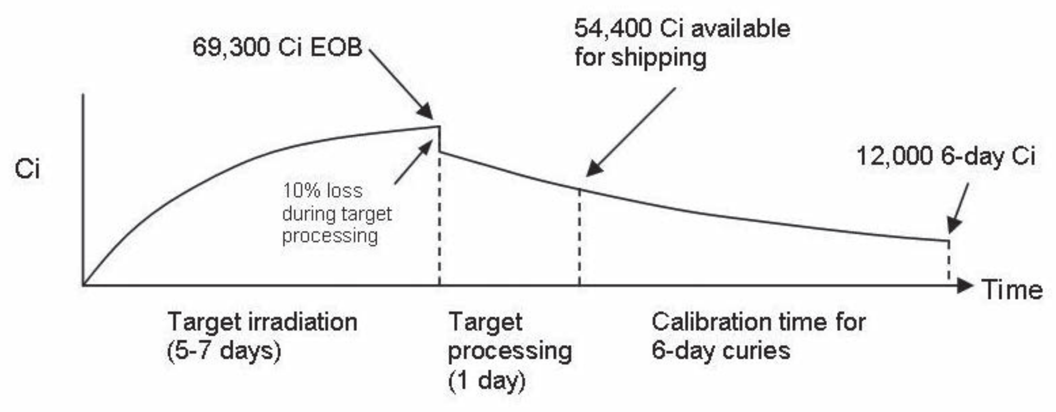

Figure G-1. ^{99}Mo production and decay timeline (typical).

activity concentration (also called radioactivity concentration). For technetium-99m (^{99m}Tc), it is the activity of ^{99m}Tc in a sample expressed in Ci (GBq) divided by the volume expressed in millilitres (mL) of the sample at a specified reference calibration date and time.

barn. Symbol (b), is a unit of measurement. The neutron interaction with the nucleus of a target material can be quantitatively expressed in terms of the nuclear cross-section, which is a measure of the probability that the given reaction takes place. The unit of cross-section is a barn (1 barn = 10^{-24} cm^2). The value of the cross-section varies with the energy of the neutrons and from nucleus to nucleus. In general, the slower the neutron, the greater the probability for the reaction to occur.

bequerel. Symbol (Bq), is the SI derived unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second. The Bq unit is therefore equivalent to s^{-1}. 1 Bq $\cong 2.70 \times 10^{-11}$ curie. A gigabecquerel (GBq) is a billion becquerels. 1 GBq = 10^9 Bq $\cong 2.70 \times 10^{-2}$ curie.

burnup. The amount, expressed in percent (%), of the ^{235}U atoms in a target that fission during irradiation. For targets irradiated at a thermal neutron flux of greater than 2.0E14 n/cm^2-s and irradiated for 200 hours or more, burnup will be in the range of 9–12%.

chromatographic recovery of ^{99m}Tc. The method of eluting ^{99m}Tc from a chromatographic column. The column material is traditionally made of alumina (Al_2O_3). Column materials other than alumina can be used, such as titanium dioxide or zirconium dioxide. Column chromatography in chemistry is a method used to separate an individual compound (or isotope) from a mixture of compounds (or isotopes).

curie. Symbol (Ci), is a older unit of radioactivity, defined as the radioactivity in 1g of pure radium 226. 1 Ci = 3.7×10^{10} decays per second (= 3.7×10^{10} Bq).

eluate. The effluent exiting a chromatographic bed when elution is performed.

eluent (or eluant). The liquid or gas entering a chromatographic bed that is used to effect a separation by elution. For the recovery of ^{99m}Tc, the eluent is normal saline.

elution efficiency. The fraction, expressed in percent (%), of ^{99m}Tc on the column at the time of elution that is stripped from the column by the eluent. For conventional generators this is typically about 85%. Elution efficiency is also referred to as 'recovery efficiency'.

epithermal neutron. A neutron having an energy in the range of 1.0–10 keV. Refer to **thermal neutron** for comparison.

half-life. The time required for a quantity of radioactive material to decay to one half of its original value.

heterogeneous reactor. A nuclear reactor in which the fuel is separated from the moderator.

homogeneous reactor. A nuclear reactor in which the fuel is mixed with the moderator or coolant. An example of a liquid homogenous reactor is uranium sulphate in water.

key elements. Components/pieces of a technology that are integrated into a process so that the technology meets the customer requirements agreed upon. Identification of key elements involves understanding the functional aspects of a technology as well as how they will be developed.

large scale producer.[1] Has the processing capability to produce greater than 1000 6 day curies (37 000 6 day gigabecquerels) per week of ^{99}Mo on a routine basis. A large scale producer has the necessary shipping infrastructure in place to transport the finished product internationally on a routine basis.

liquid–liquid extraction. Chemical separation method used to recover ^{99}Mo. Also known as solvent extraction. It is a method to separate compounds based on the relative equilibrium concentrations of two different immiscible liquids in contact, usually water and an organic solvent. It is the extraction (recovery) of a substance from one liquid phase into another liquid phase.

medium scale producer.[2] Has the processing capability to produce in the range of 200 to 1000 6 day curies (7400 to 37,000 6 day gigabecquerels) per week of ^{99}Mo on a routine basis. A medium scale producer typically supplies a specific regionally based market and has the necessary shipping infrastructure in place to transport the ^{99}Mo finished product to its established regional market. 'Regionally based' includes neighbouring countries.

molybdenum-99/technetium-99m production cycle. Regardless of the mode of production of ^{99}Mo, the relative quantities of ^{99}Mo and ^{99m}Tc remain the same for any particular production cycle and decay period during processing and shipment. The 6 day curie concept is schematically illustrated in Figure G-1, which shows the buildup and decay of ^{99}Mo during target irradiation, processing and shipping. During the 5–12 day period of irradiation in the reactor (left side of figure), ^{99}Mo builds up in the target and eventually approaches a maximum as ^{99}Mo production is balanced by ^{99}Mo loss to radioactive decay. ^{99}Mo continues to be lost to radioactive decay after the targets are removed from the reactor and some additional losses are incurred during target processing because of process inefficiencies (middle of figure). The amount of ^{99}Mo available

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[1] Magnitude established by the National Research Council of the National Academies (COMMITTEE ON MEDICAL ISOTOPE PRODUCTION WITHOUT HIGHLY ENRICHED URANIUM, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, Medical Isotope Production Without Highly Enriched Uranium, The National Academies Press, Washington DC (2009)).

[2] Definition should not be construed as being absolute. The purpose of defining production scale levels in this document is to qualitatively compare the manufacturing capability of the various production technologies under development or currently deployed to produce ^{99}Mo. In essence, the definition is used for the benchmarking of a one producer's production capability against another's.

for sale as 6 day curies (right side of figure) is only a fraction of the isotope present in the targets at the end-of-bombardment (EOB) by neutrons during irradiation in the reactor. ^{99}Mo 6 day curies represent the number of curies present in a shipment of ^{99}Mo 6 days after it leaves the producer's facilities.

natural molybdenum (Mo). Of all the stable molybdenum isotopes, ^{98}Mo is the most abundant, comprising 24.1% of all natural molybdenum. As such, ^{98}Mo is said to have a natural abundance (NA) of 24.1%. The other stable isotopes of natural molybdenum are: (1) ^{92}Mo; 14.8% NA, (2) ^{94}Mo; 9.3% NA, (3) ^{95}Mo; 15.9% NA, (4) ^{96}Mo; 16.7% NA, (5) ^{97}Mo; 9.5% NA and (6) ^{100}Mo; 9.6% NA. Because ^{100}Mo has an extremely long half-life (>10^8 years), it is considered to be a stable isotope of natural molybdenum.

polymeric titanium-oxychloride or polymeric titanium compound (PTC). Sorbent material developed and proposed for use in neutron activation (n-gamma) ^{99}Mo based ^{99m}Tc generators [3, 77, 85]. This titanium based inorganic polymer exhibits both excellent ^{99}Mo adsorption capacity and ^{99m}Tc elution. The main constituents of this sorbent material are titanium, oxygen and chlorine. The adsorption capacity of PTC for ^{99}Mo is reported to be higher than that of conventional alumina.

polymeric zirconium-oxychloride or polymeric zirconium compound (PZC). Sorbent material used in neutron activation (n-gamma) ^{99}Mo based ^{99m}Tc generators. This zirconium based inorganic polymer exhibits both excellent ^{99}Mo adsorption capacity and ^{99m}Tc elution [77, 95, 97]. The main constituents of this sorbent material are zirconium, oxygen and chorine. The adsorption capacity of PZC for ^{99}Mo is reported to be higher than that of conventional alumina.

post-elution concentrator. Used for low specific activity ^{99}Mo. The eluate of the technetium recovery system is passed through a chromatography column (i.e., concentrator). The concentration column is then stripped using normal saline. This two stage recovery process increases the final activity concentration of the ^{99m}Tc.

production strategy. The high level sequence of steps that will be used to produce an item. The production strategy is intended to be of sufficient detail to be able to develop a cost and schedule.

readiness level. A measure of technology and manufacturing system maturity.

small scale producer. Has the processing capability to produce up to 200 6 day curies (7400 6 day gigabecquerels) per week of ^{99}Mo on a routine basis to a geographically local ^{99m}Tc generator manufacturer.

specific activity. For molybdenum-99 (^{99}Mo), it is the activity of the ^{99}Mo in a sample expressed in curies (Ci) (gigabecquerels–GBq) divided by the total mass, expressed in grams, of the elemental molybdenum in the sample at a specified reference calibration date and time.

solvent extraction (or recovery). See liquid–liquid extraction.

sublimation. Is the transition of a substance from the solid phase to the gas phase without passing through an intermediate liquid phase.

target. For fission product ^{99}Mo, this consists of a target meat that is encapsulated by a cladding. For neutron activation (n-γ) ^{99}Mo consists of encapsulated molybdenum trioxide (MoO_3) powder or a pressed sintered molybdenum metal wafer. For accelerator produced ^{99}Mo, targets consist of molybdenum metal disks. For direct production, metal foils or plating of enriched Mo on various substrate materials is being explored.

target cladding. Serves to protect the reactive uranium metal or alloy target meat and provides the barrier that prevents the release of solid and gaseous fission products produced during target irradiation. The target cladding material is typically aluminium.

target meat. The uranium bearing material in a fission product ^{99}Mo production target. The target meat can be in the form of U-Al alloy, UAl_x-Al dispersion matrix, UO_2, or U metal.

Technology readiness assessment (TRA). An industry recognized method used to assess the technology readiness of a product under development. It is formal, systematic and metric based. The metrics are defined by the TRLs. A TRA: (1) provides a common language to communicate the maturity of a technology, (2) enables a disciplined approach to evaluate technology readiness and (3) provides an effective tool and metrics to assess technology risk. It is simply an analysis for determining the technology maturity with respect to meeting product realization goals.

Technology readiness level (TRL). A metric used for describing technology maturity. It is a measure to assess the maturity of evolving technologies (materials, components, devices, etc.) prior to incorporating that technology into a system or subsystem. TRLs focus on a technology's maturity and are designed to measure it and indicate what has been accomplished in the development of that technology.

thermal neutron. A neutron having an energy of about 0.025 eV at 20°C. Refer to **epithermal neutron** for comparison.

UAl_x dispersion target. For HEU Al_x dispersion targets, the target meat begins as a blend of UAl_x powder made of UAl_2, UAl_3 and UAl_4 intermetallics and pure aluminium powder. For LEU Al_x dispersion targets, the target meat begins as a blend of UAl_2 and pure aluminium powders. During the hot rolling and annealing steps in fabricating a ^{99}Mo production target, all of the UAl_2 reacts with aluminium in the target meat matrix to form UAl_3 and some of the UAl_3 reacts with aluminium to form UAl_4. Thus, the target meat of a finished target contains both UAl_3 and UAl_4. The actual fractions of UAl_3 and UAl_4 in a finished dispersion target will vary from manufacturer to manufacturer depending on the processes and heat treatments that are utilized in fabricating the powder, core compacts and target plates.

Uranium loading. The mass of uranium per cm^3 of the target meat. It is sometimes referred to as U density.

US Pharmacopeia (USP). Is the official pharmacopoeia of the United States, published dually with the National Formulary (NF) as the USP-NF. It establishes written (documentary) and physical standards for medicines, food ingredients, dietary supplement products and ingredients. These standards are used by regulatory agencies and manufacturers to help to ensure that products are of the appropriate identity, as well as strength, quality, purity and efficacy. Many other countries use the USP-NF instead of issuing their own pharmacopoeia, or to supplement their government pharmacopoeia.

ABBREVIATIONS

ABEC	aqueous biphasic extraction chromatographic
AECL	Atomic Energy of Canada Limited
AHR	aqueous homogeneous reactor
AMIC	Advanced Medical Isotope Corporation
ANSTO	Australian Nuclear Science and Technology Organisation
AREVA/CERCA	Compagnie pour l’etude et la réalisation de combustibles atomiques, France
Argonne	Argonne National Laboratory, USA
ARI	ANSTO Radiopharmaceuticals and Industrials, Australia
BARC	Bhabha Atomic Research Centre, India
BATAN	National Nuclear Energy Agency, Indonesia
BRIT	Board of Radiation and Isotope Technology, Mumbai, India
BR2	Belgian Reactor-2, SCK•CEN Centre, Belgium
B&W Y-12	Babcock & Wilcox, USA
CCHEN	Chilean Nuclear Energy Commission
CEA	French Alternative Energies and Atomic Energy Commission
CINR	Central Institute for Nuclear Research Rossendorf, Germany
CNEA	National Atomic Energy Commission, Argentina
DNRI	Dalat Nuclear Research Institute, Vietnam
EOB	End of Bombardment (synonymous with End of Irradiation (EOI)
FDA	Food and Drug Administration, USA
GMP	good manufacturing practices (also cGMP, *current* good manufacturing practices)
GSG	Gamma-Service Group International
HEU	high enriched uranium, uranium enriched in the isotope ^{235}U to 20% or more
HLG-MR	High-level Group on Security of Supply of Medical Radioisotopes
HPLC	high performance liquid chromatography
ICP-MS	inductively coupled plasma mass spectrometry
INL	Idaho National Laboratory, USA
INR	Institute for Nuclear Research — Pitesti reactor facility, Romania
INVAP	Investigaciones Aplicadas S.E. INVAP, Argentina
IPEN	Nuclear and Energy Research Institute, Brazil
IRE	Institute for Radioisotopes, Belgium
ITLC	instant thin layer chromatography
JAEA	Japan Atomic Energy Agency
JAERI	Japan Atomic Energy Research Institute
JRR	Japan Research Reactor
KAERI	Korea Atomic Energy Research Institute
KfK	Institut für Radiochemie Kernforschungszentrum Karlsruhe, GmbH, Germany
LANL	Los Alamos National Laboratory, USA
LBNL	Lawrence Berkeley National Laboratory, USA
LEU	low enriched uranium, uranium enriched in the isotope ^{235}U to less than 20%
LMI	Lantheus Medical Imaging, Massachusetts, USA
MAPLE	Multipurpose Applied Physics Lattice Experiment reactor, Canada
MEK	methyl ethyl ketone
MIPS	medical isotope production system
MTR	materials testing reactor
MU	University of Missouri, USA
MURR	University of Missouri Research Reactor, USA
NA	natural abundance
NAS	National Academy of Sciences, USA

NDA	new drug application
OECD/NEA	OECD Nuclear Energy Agency
Necsa-NTP	Nuclear Energy Corporation of South Africa — Nuclear Technology and Products division
NRC	Nuclear Regulatory Commission, USA
NRG	Nuclear Research and Consultancy Group, Netherlands
NRU	National Research Universal reactor, Canada
NU	natural uranium
OPAL Reactor	Open Pool Australian Light Water Reactor
ORNL	Oak Ridge National Laboratory, USA
PINSTECH	Pakistan Institute of Nuclear Science and Technology
PNL	Phoenix Nuclear Laboratory, USA
POLATOM	Institute of Atomic Energy, Radioisotope Centre, Poland
PUI	Peaceful Uses Initiative (IAEA)
RERTR	Reduced Enrichment for Research and Test Reactors program
ROSATOM	State Atomic Energy Corporation “Rosatom”, Russian Federation
SCK·CEN	Belgian Nuclear Research Centre
TRIUMF	TRI-University Meson Facility, Canada
USP	United States Pharmacopeia

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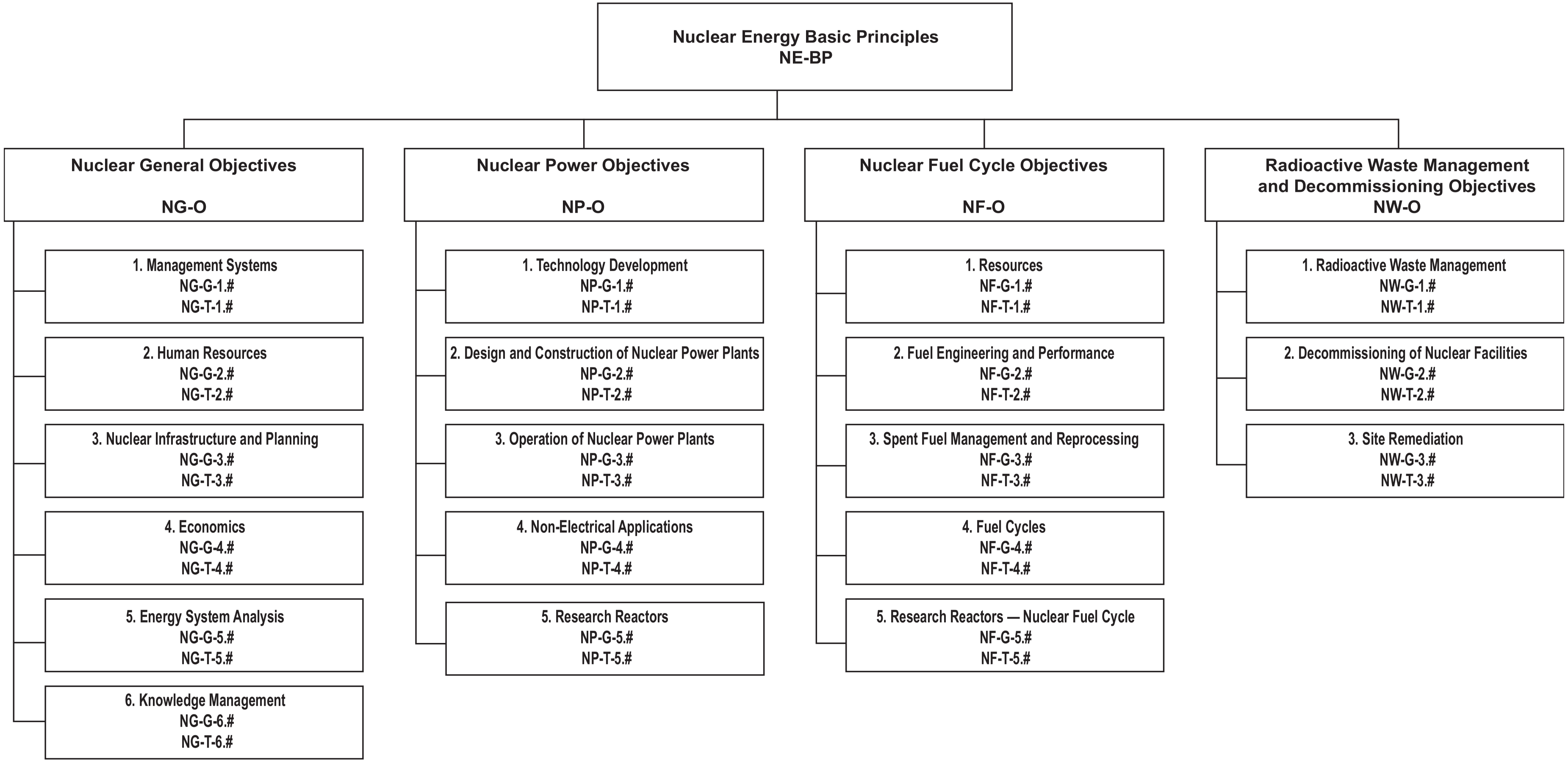

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