EUROPEAN OBSERVATORY
on the supply of medical radioisotopes

Working Group 4 (WG4)

Capacity and Infrastructure Development

July, 2014

1. Overview

Radionuclides are used in nuclear medicine for the diagnosis and treatment of various diseases, such as cancer, cardiovascular diseases and brain disorders. Over 10,000 hospitals worldwide use radionuclides for the in vivo diagnosis or treatment of about 50 million patients every year, of which several million in Europe. Metastable technetium-99 (Tc-99m) is the most important radionuclide in nuclear medicine. It is used in more than 30 million diagnostic nuclear medicine procedures around the world each year, accounting for more than 20% of the global radiopharmaceutical market. Tc-99m is availed from its parent isotope Molybdenum-99 (Mo-99). The production of Mo-99 in large quantities is through the fission of Uranium-235, which is a complex process involving irradiation of uranium targets in nuclear reactors and separation of Mo-99 from the irradiated targets in specialised processing facilities. Since Tc-99m with a short half-life (6 hours) and the parent Mo-99 with a much longer half-life of 66 hours exist in equilibrium, it is possible to repeatedly separate Tc-99m from the parent Mo-99 for use. Short lived daughter nuclides such as Tc-99m where transport logistics could be challenging, are often availed from radionuclide generator systems containing the parent radionuclide, generally in immobilised form. In the case of Tc-99m, it can be repeatedly 'milked' from Mo-99 containing generator for several days, typically 1-2 weeks. Currently, in nearly all the Mo-99-Tc-99m generators Mo-99, the parent molecule, is adsorbed in a solid alumina phase and the Tc-99m is collected by saline elution and used for a week or up to a maximum of 2 weeks.

Most of the Mo-99 used in the world is produced by fission of highly enriched uranium targets in just a few research reactors in Europe, Canada, South Africa and Australia. Most of these reactors are old, and may be prone to discontinue their operation permanently, or suffer unforeseen temporary shutdowns. They also present additional drawbacks such as nuclear security implications of using highly enriched uranium, among others. The separation of the Mo-99 from those irradiated uranium targets is performed by a few processor facilities who then sell it to the generator manufacturers. The generators are then manufactured and sold by a number of companies to the end users.

The stability of supply for Mo-99 and the infrastructure which supports that supply is therefore critically important to the patients that rely on nuclear medicine.

In the current situation, the demand is met by the established infrastructure, especially after several measures were put in place by the different players to mitigate the risk of shortages. These measures include the coordination of the operating schedule of the reactors, the development of reserve capacity, the arrangements of some processors to be supplied by several irradiators, the upgrade of some processor facilities to operate round the clock the full 52 weeks of the year, and the more efficient use of Tc-99m by the healthcare end-users.

However, the current supply chain for Mo-99 is somewhat fragile, as the shutdown of one or more of the major irradiators or producers might cause a shortage of supply that the current infrastructure capacity might not cover. This situation could become worse in the short term, in a scenario under which a few irradiators, including two of the most important ones, are scheduled to be definitely or temporarily shutdown between 2015 and 2016. The situation in the longer term could become better, as several new projects are to be commissioned.

The nature of the supply chain allows decoupling the irradiation of the targets and their processing by industrial companies. Production then ceases to be seen as localised, or geographically attached to a particular reactor, making it very difficult to, perform a geographical analysis of the supply of Mo-99 based only on the location of the reactors or the producers. Although aware of these difficulties, an attempt was made by the Working Group to assess the sustainability of the European market of Mo-99, based on available data, assumptions on the flows (i.e. export from and import to Europe) of processed targets, and other information (i.e. information from the target manufacturing companies, processors, reactors, AIPES, etc).

The attempt failed due to several modelling difficulties: the actual flow of Mo-99 from the processors to the different regional markets, the use of reserve capacity, the impact of conversion from highly enriched uranium targets to low enriched uranium targets. Also, difficulties in assessing the viability of future projects (especially those under the private initiative) to produce Mo-99, and the difficulties in forecasting the demand, hindered any kind of sensible analysis, and these limitations were acknowledged by the Working Group in the Plenary meeting in January 2014.

Therefore, instead of providing a quantitative analysis of the demand and supply of Mo-99 in Europe, the Working Group has decided to compile a qualitative assessment of the state of play of the infrastructure, and of the challenges that lay ahead to meet the demand for Mo-99 in the future.

2. Mission and objectives

The main objective of WG4 is to examine Mo-99 production capacity and infrastructure developments for both reactors and processing facilities. The team reviewed current and future demands compiled by the OECD/NEA. It also reviewed independent marketing data, data from the industry and other data looking at both current demand and forecasts of future demand.

The working group began by focusing on the Mo-99 demand and supply in Europe. After several attempts, and after discussing the complexity of Mo-99 supply and demand, the group agreed that breaking down the available data into geographical regions was impossible with the available information, and decided to focus its efforts on global demand and not limit itself to European demand. As this scope overlaps with the activity of OECD/NEA, the working group has decided as well not to replicate the results already available, but rather to comprehensively present a qualitative evaluation of the supply and demand for Mo-99, its evolution and challenges.

The group also examined new technologies being developed around the globe for the production of Mo-99 and Tc-99m. These efforts are in various stages of development and have varying degrees of technical and commercial feasibility, and a summary of them is included in this report.

3. Group Members

The WG4 is comprised of representatives of AIPES, the reactor operators, the Mo-99 processors, the fuel/target manufacturers, OECD/NEA, IAEA, EANM, and European Commission's Directorates General of Research and Innovation (DG RTD), and Joint Research Centre (DG JRC):

- Mr. Manuel Martín Ramos, DG JRC, leader of the WG4,

- Mr. Krzysztof Bańko, POLATOM, representing the reactor operators

- Mr. Roy Brown, Mallinckrodt Pharmaceuticals, representing the Mo-99 processors

- Mr. Pavel Peykov, OECD/NEA

- Mr. Franck Chopard, AREVA, representing fuel/ target manufacturers

- Mr. Jean-Michel Vanderhofstadt, AIPES

- Mr. Karim Berkouk, DG RTD

- Dr. Fred Verzijibergen, EANM

- Ms. Meera Venkatesh, IAEA

4. Meetings

The WG 4 had two formal meetings and two conference calls:

25 April 2012, Brussels, Belgium, with following conclusions:

1. A new version of the mandate was approved

2. The content of the 4 tasks of the WG4 was discussed. It was concluded that:

- the group's study should take into account the international context, but its recommendations should be focussed on the EU situation; one of the main output should concern the need for new infrastructures in Europe;

- the group's analyses would be based on existing data, reports or surveys by OECD/NEA, IAEA, EANM, but the WG4 members will bring their updated input based on their knowledge and judgement. This could modify some of the existing data, as for example related to the Tc-99m demand projection.

4 October 2012, Brussels, Belgium, with following conclusions:

1. A revision of the mandate was adopted (the previous Task 4 " Target standardization design, qualification and integration process" is moved to WG3, after agreement in the Observatory Plenary meeting in June 2012);

2. The first data on demand and infrastructure status and projections were discussed. The content of the group's report was defined.

10 January 2014, teleconference, with the following conclusions:

1. The difficulty to obtain reliable and independent data was acknowledged

2. The group agreed to present the main results of the analysis of supply and demand based on available data (provided by AIPES, reactors, industry and processors) and committed to finalise the WG4 report during the first quarter of 2014.

3. The report on alternative methods for production of radioisotopes was approved, subjected to the resolution of some comments.

16 May 2014, teleconference, with the following conclusions:

1. The working group is not in a position to break down the available data to estimate geographical demand or supply of Mo-99. The work should be based on a global approach.

2. Estimations of the current status and evolution of the global demand and supply of Mo-99 are published by OECD/NEA. The working group agreed that it should not

replicate the work of OECD/NEA in this field, nor will it be able to obtain better data or better models.

3. The working group commits to delivering and presenting its report in the next EU Observatory plenary meeting, although the scope of the report will be different.

4. The report will comprehensively describe the current status of the supply and demand of Mo-99, and a qualitative evaluation of its potential evolution and challenges in the mid-term. The report will incorporate the diverse views of its members (associations, industry, reactors, international organisations), but avoiding presenting quantitative estimations.

5. Methodology and scope of the report

The Working Group bases its analysis on data publicly available, plus information and other input provided by its members. Initially, the working group started to analyse the demand and supply of Mo-99 in Europe. However, focusing the analysis in Europe proved to be impossible, due to the following reasons:

- The Mo-99 market is global, and extracting the information of a particular region in an isolated manner would yield inaccurate results.

- Actual commercial flows among regions are considered proprietary information, and were not made available to the working group. Estimations for such flows are very difficult to produce and justify, as the flows change quite dynamically to adapt to different market situations.

- Availability and use of reserve capacity were either not available, or very difficult to estimate and justify.

- Estimations of the impact of the conversion of targets to low enriched uranium were not available, or very difficult to estimate and justify.

- Information on the state of development of new Mo-99 production projects, especially those under private sponsorship, was not available.

During the debate among the members of the Working Group, it was decided to present a qualitative report on the supply and demand of Mo-99, with the points of view of the different players represented, conclusions and recommendations rather than a quantitative analysis which is regularly produced by the OECD/NEA.

From the side of demand, the report will present an overview of current demand of medical radioisotopes, in particular of Mo-99, including information on potential alternatives and potential evolution with time. When possible, specific information on relevant regions of the world, and especially on Europe will be presented.

From the side of supply, the report will describe the current state of play of the infrastructure that is today meeting the Mo-99 demand worldwide. The report will provide the latest information on capacities, expected lifetime span, and any other relevant information on the current irradiators and producers. The report will identify the most important projects with the up-to-date relevant information, and will assess their impact in the current supply state of play.

The report will also briefly describe alternate methods for the production of Mo-99, with advantages and disadvantages, and will identify those projects in the pipeline. The report will assess the potential impact of these alternate methods in the Mo-99 supply state of play.

The report will end with a list of conclusions and recommendations regarding the supply and demand of Mo-99.

5. Findings

5.1 Demand for Mo-99

The production of radionuclides for medicine and other applications is one of the most important applications of nuclear chemistry and the nuclear industry. Tc-99m (T1/2=6.0 h) is the most important radionuclide in single photon emission computed tomography (SPECT), the widest used nuclear imaging technique. The worldwide number of exams in nuclear medicine was estimated as follows by DG SANCO[1]:

- cardiac imaging (12 million/year; mainly Tc-99m, some with Thallium-201);

- bone scintigraphy, including tumour metastases (10 million/year; mainly Tc-99m);

- lung investigation (5 million/year ; mainly Tc-99m);

- thyroid imaging and function analysis (5 million/year ; Tc-99 or Iodine-123/-131);

- kidney function analysis (Tc-99m);

- tumour staging (PET, 18F-FDG).

Around 35 million in vivo procedures are performed annually in the World, including 20 million in the USA, 9 in Europe, 3 in Japan and 3 in the rest of the World[2].

European diagnostic procedures, for example in cardiac imaging, are expected to rise over the next decades, to slowly match the number of procedures done in the US[2]. The growing trend is nevertheless hampered by conflicting tendencies, contributing to the stabilisation or slight decrease in the number of exams performed. The latter include the loss of procedures to other modalities and pre-authorisation requirements, which in the US made nuclear medicine more vulnerable to economic concerns.

As stated above, the two most widely used nuclear medicine studies (and the largest consumers of Tc-99m) are bone scintigraphy and myocardial perfusion imaging. The alternatives for Tc-99m for these more frequently used imaging techniques were reviewed by Ballinger (2010).

A PET alternative for bone scintigraphy is the 18F-fluoride, but that would require PET scanner capacity which is currently not in place. For myocardial perfusion imaging, Tl-201, produced by cyclotron, can be used, as it was before Tc-99m was widely adopted 15–20 years ago. The quality of Tl-201 images has improved owing to advances in gamma camera design and performance, but there is a lack of training of nuclear medicine experts for this technology. There is also a PET technique using Rb-82, but it is expensive to implement and has the same PET capacity issues as bone scintigraphy.

In addition to these most frequent exams, there are a number of other important studies where nuclear medicine provides unique clinical information and no practical alternatives exist. Examples of these techniques include lung ventilation/perfusion imaging of some groups of patients (including pregnant women) with a suspected pulmonary embolism; sentinel lymph node localization; pediatric studies, especially renal and bone; and localisation of parathyroid adenoma. Most of these require lower amounts of Tc-99m and can be prioritised in times of production shortage.

In 2009-2010, the protracted shutdown of the NRU reactor in Canada coincided with the shutdown of the Netherlands reactor, decreasing Mo-99 production by 60 to 70 percent leading to Mo-99 shortages, when the global demand peaked at approximately 12,000 Ci per week (6-days). As a result of those shortages Tc-99m users worldwide adopted a series of efficiency measures, which have reduced the demand for Mo-99. Examples of the efficiencies adopted are multiple generator elutions per day and scheduling patients throughout the day rather than concentrating them in the morning hours for imaging studies. These behavioural changes have led to a drop in the requirement for Mo-99, and allow for the coverage of the same number of patients with a smaller quantity of radio-isotope, and the ordering of smaller Tc-99m generators. Current global demand for Mo-99 is estimated to be between 9,500 and 10,000 Ci per 6-day week (OECD/NEA 2012). Although some nuclear medicine procedures may have been temporarily lost to other modalities, such as ultrasound, during the 2009-2010 shortages, it is generally felt that the nuclear medicine modality has regained these patient procedures. This is due largely to the superior images generated by nuclear medicine for cardiac and other procedures compared to competing imaging modalities such as ultrasound.

Based on an analysis of the available information and reports, the demand of Mo-99 is:

- current (2012 estimate) global demand for Mo-99 is estimated at 9,500 - 10,000 Ci per week (6-day); 500,000 per year.

- the future trend is estimated to fluctuate between two lines, the lowest being a zero growth maintaining the current value, and the highest being a straight line starting at the current value and increasing at a rate of 2.1 % per year until 2020 and 0.5 %/year thereafter, corresponding to the average estimate increase rate in [2] "The Path to Reliability" (OECD/NEA, 2011)

Available data shows that for Europe:

- The current (2012) demand is about 25 % of the global demand, reaching 125,000 Ci per year (6-day).

The future trend is estimated to lay between a line with a 0% growth, and a line that reflects a growth of 1.8 % per year between 2012 and 2020, and of 0.41 % from 2020 to 2030. [2]

5.2 Current supply of Mo-99

There are currently eight reactors producing the majority of the global supply of Mo-99. There are other local indigenous producers operating on a small scale (probably around 5% of the total global volume). Table 1 below summarizes data from these eight major Mo-99 producing reactors.

These eight reactors routinely supply irradiated targets to Mo-99 processors, that distribute it to Tc-99m generator manufactures in Europe, the United States, Asia, South Africa, South America, and Australia. Over the last years the reactors have developed outage reserve capacity in order to cover times when one or more of the other reactors are down for scheduled or unscheduled (however for a limited time) maintenance or repair, and the operators have agreed to coordinate their operating schedules to contribute to the security of supply. Although this has normally worked well, this was not the case when both the NRU reactor in Canada and the HFR reactor in the Netherlands were shutdown for unscheduled repairs for an extended length of time in 2009-2010, when the world capacity was reduced by 60-70%. During these outages, there were regions of the world that experienced shortages in Tc-99m generator supply: procedures were postponed or cancelled, patients were given different radioisotopes, or the procedures were changed to non-nuclear procedures such as CT, magnetic resonance imaging (MRI) or ultrasonography.

Reactor	**Location**	Comm. Date	**Target Type**	**Capacity (Ci–6 day)/y**	**Reactor Operator/Mo-99 Producer**	**Expected shutdown date**
NRU	Chalk River,	1957	HEU	187,200	AECL/	2016

	Canada				Nordion	
HFR	Petten, Netherlands	1961	HEU*	187,200	NRG/Mallinckrodt and IRE	2024
BR2	Mol, Belgium	1961	HEU*	156,000	SCK-CEN/Mallinckrodt and IRE	2026
OSIRIS	Saclay, France	1966	HEU	62,400	CEA/ IRE	2015
SAFARI	Pelindaba, S. Africa	1965	HEU/LEU*	130,700	South African Nuclear Energy Corporation / NTP	2030
MARIA	Otwock-Swierk, Poland	1974 1993 (rebuilt)	HEU	66,000	IAE-Polatom/ Mallinckrodt	2030
LVR-15	Rez, Czech Republic	Mid 1950's 1989 (rebuilt)	HEU	84,000	Czech Nuclear Research Institute/IRE	2028
OPAL	Lucas Hts, Australia	2007	LEU	42,900	ANSTO	2055

*Conversion to LEU underway

Table 1. Major Reactors Producing Mo-99 (6)

However, the irradiation capacity in the short term will be reduced, as the license of OSIRIS expires at the end of 2015, the BR-2 reactor will undergo a major refurbishing programme in 2015 and the first quarter of 2016, and the NRU will be definitively shut down for ^{99}Mo irradiations in 2016.

In the longer term, HFR will cease operation in 2024, BR-2 in 2026, LVR-15 in 2028 and MARIA and SAFARI in 2030.

The irradiated targets are treated in processing facilities listed in Table 2.

Procesor	Target	Capacity (Ci per week)	Capacity (Ci per year)
AECL/NORDION	HEU	4,680	187,200
ANSTO HEALTH	LEU	1,000	52,000
MALLINCKRODT	HEU	3,500	182,000
IRE	HEU	3,500	182,000
NTP	HEU/LEU	3,500	182,000

Table 2. Major Mo-99 processors

The global processing capacity will decrease as the Nordion facility will stop receiving supply from AECL in 2016.

During the last years, IRE and MALLINCKRODT have diversified the suppliers of irradiated targets and have upgraded their facilities and procedures to operate round the clock 52 weeks per year. Even though the processing companies compete in the open market to increase their share, they have established fluent communication that allows flexible arrangements among irradiators and producers to cope with the demand in cases of unanticipated shutdowns of any facility of the supply chain, thus contributing to ensure the supply of Mo-99.

5.3 Future supply of Mo-99

The future supply of Mo-99 will be based upon the current capacity, plus the capacity brought by existing reactors and processors that supply regionally or locally, but that could enter the global supply chain, new reactors and new processors, and other facilities that will produce Mo-99 or Tc-99m by alternate, non-fission means.

The majority of the reactors supplying Mo-99 are approaching the end of their lifespan. In many cases, these reactors have suffered unanticipated shutdowns, or have had extended outages for significant refurbishment, to solve aging problems or other failures. It is also probable that they might need refurbishments or modifications in order to continue operation. This would certainly imply important expenses that unless recovered by the commercialization of the isotopes, might compromise the continuation of the operation, and jeopardise the security of supply.

The extended outages of the HFR in the last years due to aging and other problems have shown on the one hand the fragility of the supply structure (the difficulty to backup the production of such a large contributor), and on the other hand the effectiveness of the measures taken by the rest of the reactors and processors to ensure to the extent possible the security of supply. During the period of the HFR shutdown the risk of Mo-99 shortages was very high, because should another large reactor had shut down at the same time, shortages would have occurred like in 2009-2010.

Thus, new capacity needs to be foreseen to replace the production of the current capacity as it is being taken out of the market when the corresponding reactors are shut down. The replacement can be done through Mo-99 produced by fission in new or existing research reactors (which can be adapted), or by other alternate means. As discussed in Section 5.4 below, even though a number of projects are under way, the alternate means have not yet demonstrated the potential at industrial or commercial level to replace the production of Mo-99 through fission. Moreover, there is a high uncertainty with regard to the feasibility of some of these new projects, both because of the difficulty to finance complex and expensive infrastructure, and the doubts on the feasibility of obtaining a commercial return considering that the current prices of Mo-99 lay below the full-cost recovery levels.

Recognising that the feasibility of the new non-fission alternate methods is not yet known, the members of the Working Group believe that the reactors to be shut down in the short term will be replaced by existing reactors that start producing Mo-99 (or making it available globally and not only locally), or new reactors.

In Europe, four new reactors are scheduled to enter into service and could replace the Mo-99 production of the OSIRIS, HFR, and BR-2 reactors: FRM-II (Germany) with a capacity of 72,000 Ci (6 days)/y available from 2017, and JHR (France) with a capacity of 151,000 Ci (6 days)/y available from 2019, in the short and mid-term; and reactors PALLAS (The Netherlands), with a capacity of 312,000 Ci (6 days)/y since 2024, and MYRRHA (Belgium), with a capacity of 212,000 Ci(6d-week)/y since 2023 in the longer term. These last two reactors are still in the design phase.

Worldwide, the OPAL reactor in Australia is currently able to supply the domestic Mo-99 needs by the irradiation of LEU targets. ANSTO is engaged in a project to increase its processing capacity from 1,000 to 3,600 6-day Ci/week in 2016 which will allow for exporting Mo-99 outside Australia.

The South African SAFARI reactor is assumed to run until 2030. A project for SAFARI-2 exists but no decision has been taken yet.

New or modified reactors are scheduled or planned in Russia, South Korea, China, India, Brazil, and Argentina. These are at different levels of development.

"Medical Isotope Supply in the Future: Production Capacity and Demand Forecast for the 99Mo/99mTc Market, 2015-2020"[5] and "A Supply and Demand Update of the Molybdenum-99 Market"[3,] both OECD/NEA reports, comprehensively analyse different scenarios in which the global Mo-99 demand is confronted with different assumptions of availability of additional capacity. The conclusion of the studies is that the processing capacity in the short term might be insufficient to cope with the current demand although this would be quickly overcome with the planned additional capacity. The study also warns against the possible shortage of capacity in the longer term (>2025) in the most pessimistic scenarios, and the possible excess capacity in the most optimistic ones. The available information does not allow performing a similar analysis focusing on Europe.

5.4 Potential for New Technology Impact on Capacity

There are numerous efforts underway utilizing new technologies for the production of Mo-99 and Tc-99m. These include nuclear reactors for neutron enrichment of Mo-98, accelerators to produce spallation neutrons for enrichment of Mo-98, linear accelerators for the fission of U-238 or the Mo-100(g,n)Mo-99 reaction, and the direct production of Tc-99m through the Mo-100(p,2n)Tc-99m reaction. Recent reports defend that high power electron accelerators are an attractive option for producing Mo-99 as the final product may be clinically equivalent to the current fission-Tc-99m supply, and this technology will significantly reduce the amount of radioactive waste, and be able to recycle it and hence the cost associated waste management[7]. Many of these efforts are sponsored by the U.S. and Canadian governments. Although these technological options were previously described by the OECD/NEA[8], the latest report focused largely on the technologies themselves and not on the practical feasibility of the projects.

By developing alternative methods of producing Tc-99m, the industry may be able to avoid shortages of the isotopes due to reactor shutdowns. The accelerator-based isotope production has the potential to back-up the reactor-produced Mo-99. The production of Tc-99m requires high current medium energy (500 μA, ~24 MeV) cyclotrons, therefore some of the currently installed medical cyclotrons, mainly with beam energies in the 20-30 MeV range would be able to fulfil the task. One of the challenges is to optimize the irradiation conditions, as well as the chemical isolation of cyclotron-produced Tc-99m, to demonstrate that it is of sufficient purity for use in medical imaging procedures. Similarly, the technology for recovering and recycling of the expensive enriched Mo-100 targets requires development to demonstrate the economic viability of this process. The principle advantage of accelerator-produced radionuclides is the high specific activities that can be obtained and the smaller amount of radioactive waste is generated from the charged particle reactions in comparison to reactor production. Nevertheless, a large number of adequately-located, high-current medium energy cyclotrons would be necessary for securing Tc-99m supply, as this supply would have to be in close proximity to the end users because they would be producing the short-lived radionuclide directly.

A report has recently been drafted by the EC – DG RTD on alternative methods to produce Tc-99m. The scope of this document is the review of the worldwide status and consideration of the feasibility of potential other methods of Tc-99m production. The main conclusions of this report regarding the alternative methods were that cyclotrons might be a good alternative for Tc-99m supply from an economic and environmental point of view, with the limitation of the local or regional supply due to this radioisotope's short half-life. Linear accelerators might be a good alternative having into consideration investments in R&D for development of all steps.

Despite some successes with low-current irradiations, the implementation of a robust production system for routine, large-scale production of Tc-99m has remained elusive to date.

5.5. Conclusions and recommendations

Over 10,000 hospitals worldwide use radionuclides for the in vivo diagnosis or treatment of about 50 million examinations every year, of which several million in Europe. Mo-99 is the most important radionuclide in nuclear medicine. It is used to produce Tc-99m generators which are used in more than 35 million diagnostic nuclear medicine procedures around the world each year accounting for more than 20% of the global radiopharmaceutical market.

The supply of medical radioisotopes is a global matter, together with the supply chain and can be completely unpaired from the irradiation of targets and their processing by industrial companies. Production cannot be seen as localised, or geographically attached to a particular production centre, making it very difficult to, based on the location of the reactors or the producers, and without access to the relevant information on commercial flows to perform a regional analysis of the supply of Mo-99.

The current supply structure is constituted by a network of a few research reactors and processors that is currently able to supply Mo-99 to meet the demand in normal conditions, especially after several measures were put in place by the different players:

a) the operators of the reactors have agreed since many years to the coordination and adaptation of the operating schedules with the objectives of ensuring a smooth global supply, by covering the outage periods of one or more of the reactors by the operation of the others, even increasing production if necessary.

b) The industry has developed increased capacity by establishing arrangements with diverse suppliers, upgrades of the facilities, and reorganisation of their activity to operate round the clock 52 weeks of the year.

c) The users have reduced the demand for Tc-99m by using alternative radioisotopes or alternative techniques and by better distributing the procedures over the day in their services, more efficient use of Tc-99m, etc.

However, the structure is fragile as in case of extended outages or unanticipated shutdowns of large reactors or facilities, the risk of shortage of Mo-99 becomes high.

This situation might become worse in the short term, in which a few irradiators are scheduled to be definitely (NRU and OSIRIS) or temporarily (BR-2) shutdown between 2015 and 2016. Part of the lost production would be compensated by the commissioning of new projects (FMR-II and JHR). Other projects to bring Mo-99 involving existing or new reactors and processors are scheduled in several countries (Argentina, Russian Federation, Republic of Korea, Brazil, and China), but the information available does not allow to estimate any sensible prospective evaluation on capacity.

Two reports drafted by the OECD/NEA analyse the demand and supply of Mo-99 in the short and mid-term (up to 2020) and in the long term (up to 2030). In these reports, it is concluded that the processing capacity in the short term (2016) might be insufficient to cope with the current demand although this might potentially be overcome with the planned additional capacity. The study also warns against the possible shortage of capacity in the longer term (>2025) in the most pessimistic scenarios (i.e. HFR and BR-2 are not replaced by PALLAS and MYRRHA), and the possible excess capacity in the most optimistic ones. The available information still has significant uncertainties, especially in the longer term. Moreover, the information as presented does not allow performing a supply and demand analysis focusing on Europe.

A number of projects on the production of Mo-99 by alternate means are underway worldwide. These projects, however, have not yet demonstrated the potential at industrial or commercial level to replace the production of Mo-99 through fission in research reactors. Moreover, there is a high uncertainty with regard to the feasibility of some of these new projects, both because of the difficulty to finance complex and expensive infrastructure, and the doubts on the feasibility of obtaining a commercial return considering that the current prices of Mo-99 lay below the full-cost recovery levels.

The Working Group proposes the following **recommendations**:

The existing network of reactors is fundamental to ensure the supply of medical radioisotopes to the market in the foreseeable future. The current capacity should be maintained encouraging the necessary investments to both refurbish the current fleet if appropriate, or to replace the capacity that will be lost as the operating reactors reach the end of their lifespan.

Many new projects and alternatives to guarantee the supply of radioisotopes have been recently published. These are very welcome, but the Working Group believes that a majority of these announcements do not provide sufficient evidence to be considered as a credible industrial alternative to the current fleet of reactors. More information on the technical details, budget, financial arrangements, schedules, licenses, etc. is needed to assess the viability of these projects.

The Mo-99 market is a global market. It is thus fundamental that any potential distortions are identified and avoided. The EU shall ensure, (within the scope of its competences), and promote that the market conditions do not hinder the commercial flows between the different regions.

6. References

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